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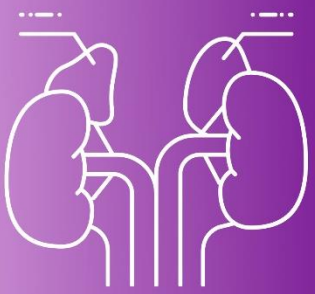

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Editorial Board InaJEMD

ORIGINAL ARTICLE

Comparison of Anti Thyroid Drugs, Radioactive Iodine and Surgery for Graves' Disease: a Systematic Review and Meta-Analysis

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ABSTRACT

Selection of therapy for Graves' Disease (GD) has always been a puzzling decision to be taken by both the patient and physician. This is due to the three modalities (Anti Thyroid Drug (ATD), Radioactive Iodine (RAI) and surgery) in with each one being just as established as the other two in being an effective treatment strategy. Therefore, this study was conducted in purpose to compare ATD, RAI and surgery for GD. The author searches from several databases such as PubMed, Directory of Open Access Journals (DOAJ), and Science Direct as well as registers, such as Cochrane Central Register of Controlled Trials (CENTRAL). The systematic review was incorporated to all of seven studies and six studies has been selected to be included in the analysis. ATD has higher risk of relapse compared to RAI (RR 2.77, 95% CI 0.99-7.75); p=0.05) and surgery (RR 6.60, 95% CI 3.76-11.58); p<0.00001). In comparison to surgery, RAI has higher risk of relapse (RR 2.52, 95% CI 0.66-9.67); p 0.18). ATD has lower success rate compared to RAI (RR 0.47, 95% CI 0.35-0.63); p<0.00001) and surgery (RR 0.44, 95% CI 0.34-0.58); p<0.00001). ATD has lower risk of hypothyroid compared to RAI (RR 0.08, 95% CI 0.02-0.27); p<0.0001) and surgery (RR 0.09, 95% CI 0.02-0.40); p=0.001). ATD has the highest risk of relapse compared to RAI and surgery. RAI and surgery did not differ significantly in risk of relapse and hypothyroid.

Keywords: *Thyroid hormone, hyperthyroid, methimazole, iodine*

INTRODUCTION

Hyperthyroid happens to 1.2% population. The three top leading causes of hyperthyroidism are Graves' Disease (GD), toxic multinodular goitre, and toxic adenoma.[1] Graves' disease, also known as toxic diffuse goiter, is an autoimmune condition where the circulation of the Thyroid-Stimulating Hormone (TSH) caused an unregulated stimulation to the thyroid that leads to overproduction of thyroid hormones.[2] It was first described in 1835 as exophthalmic goiter due to its pathognomonic feature of ophthalmopathy. Untreated GD has a negative impact towards the quality of life and puts one at crucial risk of psychosis, tachyarrhythmia and cardiac failure.[3] cardiovascular disease is the most prominent factor causing the death of patients with hyperthyroidism, and an effective control of hyperthyroidism is known to lower cardiovascular mortality.[4] Therefore, one must select with care but still decide quickly on which effective treatment to take.

According to American Thyroid Association Guidelines 2016, patients with overt Graves' hyperthyroidism should be treated with any of the following modalities, such as Anti Thyroid Drug (ATD), Radioactive Iodine (RAI) and surgery.[5] Selection of therapy has always been a challenge for both patient and physician because these three modalities have been established as an effective treatment strategy. These three modalities have not shown any differences in quality of life.[6] Multiple countries showed different preferences in therapy. In the United States of America (USA), RAI is the preferred therapy, but in Europe, Latin America and Japan, ATD is the preferred therapy.[7,8] Each of the modalities has its own risks and benefits. Graves' disease is known as a remitting and relapsing disease. ATD was associated with high relapse rate compared to other modalities and hypothyroid was more common in patients undergone RAI and surgery. Effectiveness and side effect of therapy should be taken into consideration in managing patients as periods of hyperthyroidism and hypothyroidism are detrimental and lead to higher mortality risk.[9]

Due to high prevalence of GD and prompt and effective treatment is needed, studies regarding the most effective modality in managing GD is important. The aim of this study, without prejudice, was to compare ATD, RAI and surgery for adult GD patients.

METHODOLOGY

Eligibility Criteria

The authors compiled all studies analyzing different modalities of therapy in adult GD patients (>18 years). The authors excluded studies that were not in English.

Study Search And Selection Strategy

This meta-analysis is based on the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement.[10] This study was registered in PROSPERO (CRD42023467907). The author has sourced from several databases such as PubMed, Directory of Open Access Journals (DOAJ), and Science Direct as well as registers, such as Cochrane Central Register of Controlled Trials (CENTRAL) with the search words: ((antithyroid drug) OR (methimazole) OR (carbamazepine) OR (propylthiouracil)) AND (radioactive iodine) AND (thyroidectomy) AND (Graves' disease). This study is still being reviewed in PROSPERO. There were no limitations applied for the year of study in the search. The authors conscientiously reviewed the obtained articles and resolved any disagreements through consensus among themselves.

Data Extraction

The Microsoft Excel program was utilized by the author to carry out data extraction. The data sought were the country, author, year, study design, number of samples, duration of ATD therapy, mean dose of RAI, type of surgery, follow-up duration and research outcomes. The quality of studies was gauged with NOS (Newcastle-Ottawa quality assessment scale), with grading details as such; Poor (score 0-3), Fair (score 4-6) or High (score 7-9).[11]

Analysis using Review Manager 5.4.1 (Copenhagen: The Cochrane Collaboration,

2020). To compare and asses the efficacy of using ATD, RAI and surgery in managing GD, analysis of risk ratio (RR) on relapse and success was performed. The Mantel-Haenszel Formula was employed to compute the dichotomous variables. The risk ratio, along with its 95% confidence interval (CI), indicates statistical significance when $p < 0.05$.

Assessment to deduce heterogeneity was conducted with the I2 test, which examines variation between studies. A result where I2 is greater than 50% suggests significance, urging the usage of a random-effect model. A qualitative assessment for publication bias was conducted through funnel plot analysis, with an asymmetrical shape indicating the presence of publication bias.

RESULTS

Baseline Characteristics

Seven studies were compiled in our conscientious review and six studies was selected to be statisticaly analyzed (Figure 1). Four thousand and five subjects were given ATD, 2,586 subjects were managed with RAI and 513 subjects undergone surgery (Table 1). Most studies were cohort and female dominant. All studies were comparing subjects that were given ATD or RAI or surgery. Most of the surgery were subtotal thyroidectomy, with one study[12] using subtotal thyroidectomy and three studies using total and subtotal thyroidectomy.[13-15] All of the studies compiled were studies of good quality.

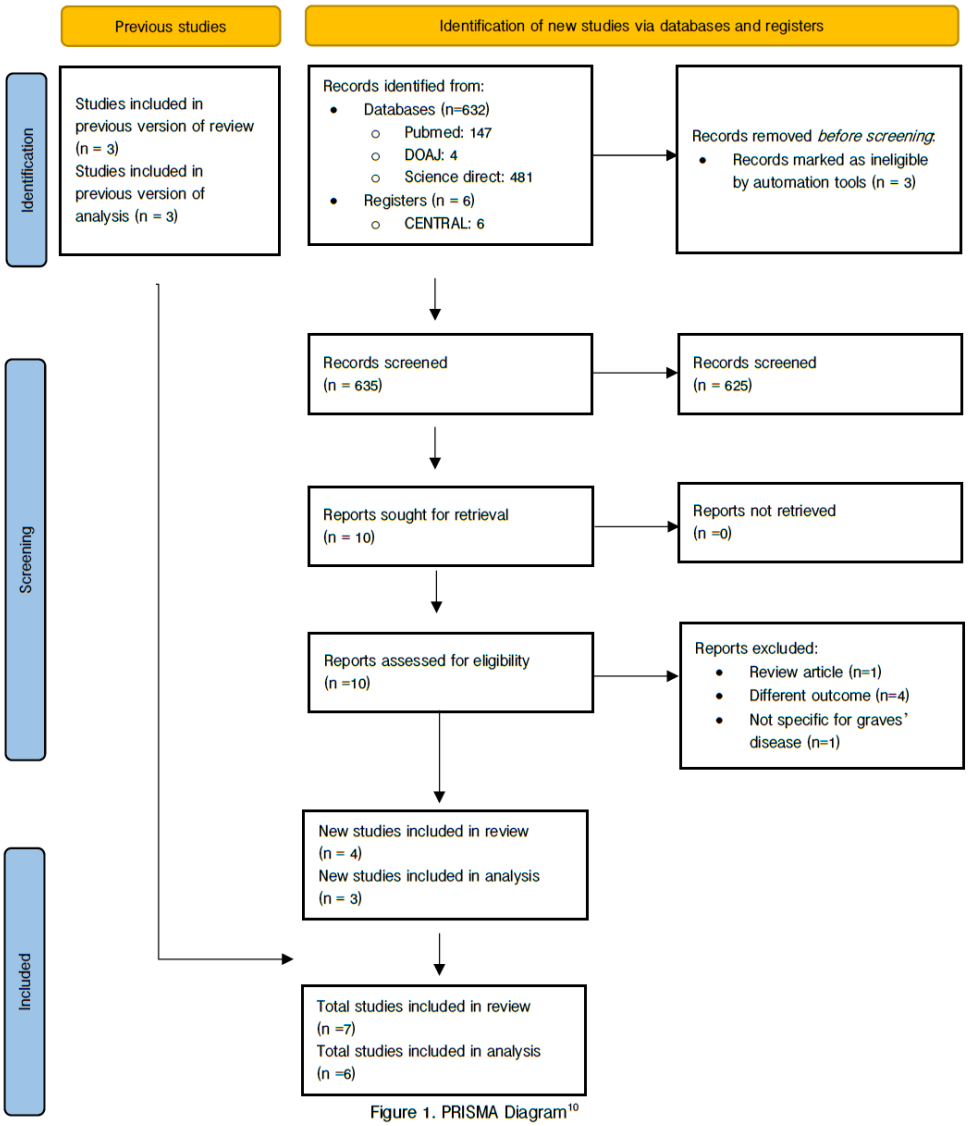

Figure 1. PRISMA Diagram[10]

Table 1. Baseline Characteristics

Author (year)	Country	Design	Age (years)	F (%)	ATD			RAI			Thyroidectomy			Outcome
					Total	Duration of therapy (mo)	Follow-up duration	Total	Mean dose of RAI	Follow-up duration	Total	Follow-up duration	Type of surgery	
Berglund et al. [16] (1991)	Sweden	Cohort	Mean 52 (14 -88)	170 (80.2)	83	Median 20 (7-54)	108 (2-192) mo	106	6.7 mCi (1.75-43.8)	108 (2-192) mo	23	108 (2-192) mo	Subtotal thyroidectomy	Relapse: ATD (43%) vs RAI (9%) vs surgery (5%)
Torring et al. (old cohort) (1996)[6]	Sweden	Cohort	ATD 45 ± 6; RAI 45 ± 5; surgery 45 ± 6	100 (84.0)	35	18	30	39	6.8 mCi	48	37	42	Subtotal thyroidectomy	Relapse: ATD (42%), vs RAI (21%) vs surgery (3%)
Torring et al. (young cohort)[6] (1996)	Sweden	Cohort	ATD 29 ± 4; Surgery 29 ± 4	49 (81.7)	25	18	30	N/A	N/A	N/A	28	48	Subtotal thyroidectomy	Relapse: ATD (34%) vs surgery (8%).
Leary et al.[17] (1999)	Ireland	Cohort	Mean 37 (9-76)	107 (84)	74	Median 24	10.5 (2.3-18) y	72	7.5 mCi (5-10)	10.5 y (2.3-18 y)	26	10.5 y (2.3-18 y)	Subtotal thyroidectomy	Relapse: ATD (68%) vs surgery (19%).
Sundaresh et al. (2017)[13]	USA	Cohort	Mean 49.3 (14.9)	552 (76.7)	118	>12	1.5 (2.2) y	543	16.5 mCi; 200 µCi/g	3.8 (3)	19	4.3 (3.1)	Subtotal and total thyroidectomy	ATD had an overall failure rate of 48.3% compared with 8% for RAI and 100% for surgery.
Conaglen et al. [12] (2018)	Australia	Cross-sectional	Median 50 ± 16	101 (82)	79	>12	N/A	13	N/A	> 6	31	> 6	Total thyoroidectomy	Patient satisfaction with therapy and quality of life does not differ between treatment
Brito et al. [15] (2019)	USA	Cohort	Mean 48 (14)	3,709 (79.6)	2817	Median 213.94 (148) days	4.5 (2.1) y	1549	N/A	4.7 (2.3) y	295	4.5 (2.1) y	Subtotal and total thyroidectomy	Surgery was most effective (99%), followed by RAI (93%), and ATD (50%).
Sjolin et al.[14] (2019)	Sweden	Cohort	Mean 46.9 (14.4)	973 (82)	774	12-18	8 ± 0.9 y	264	N/A	8 ± 0.9 y	54	8 ± 0.9 y	Subtotal and total thyroidectomy	Remission rate for ATD (43%) is lower than RAI (81.5%)and surgery (96.3%).

ATD, antithyroid drug; RAI, radioactive iodine; USA, United States of America; N/A, not available.

Relapse rate

ATD has higher risk of relapse compared to RAI (RR 2.77, 95% CI 0.99 - 7.75); *p = 0.05*) and surgery (RR 6.60, 95% CI 3.76 - 11.58); *p < 0.00001*). In comparison to surgery, RAI has higher risk of relapse (RR 2.52, 95% CI 0.66 - 9.67); p 0.18), but it is not statistically significant (Figure 2).

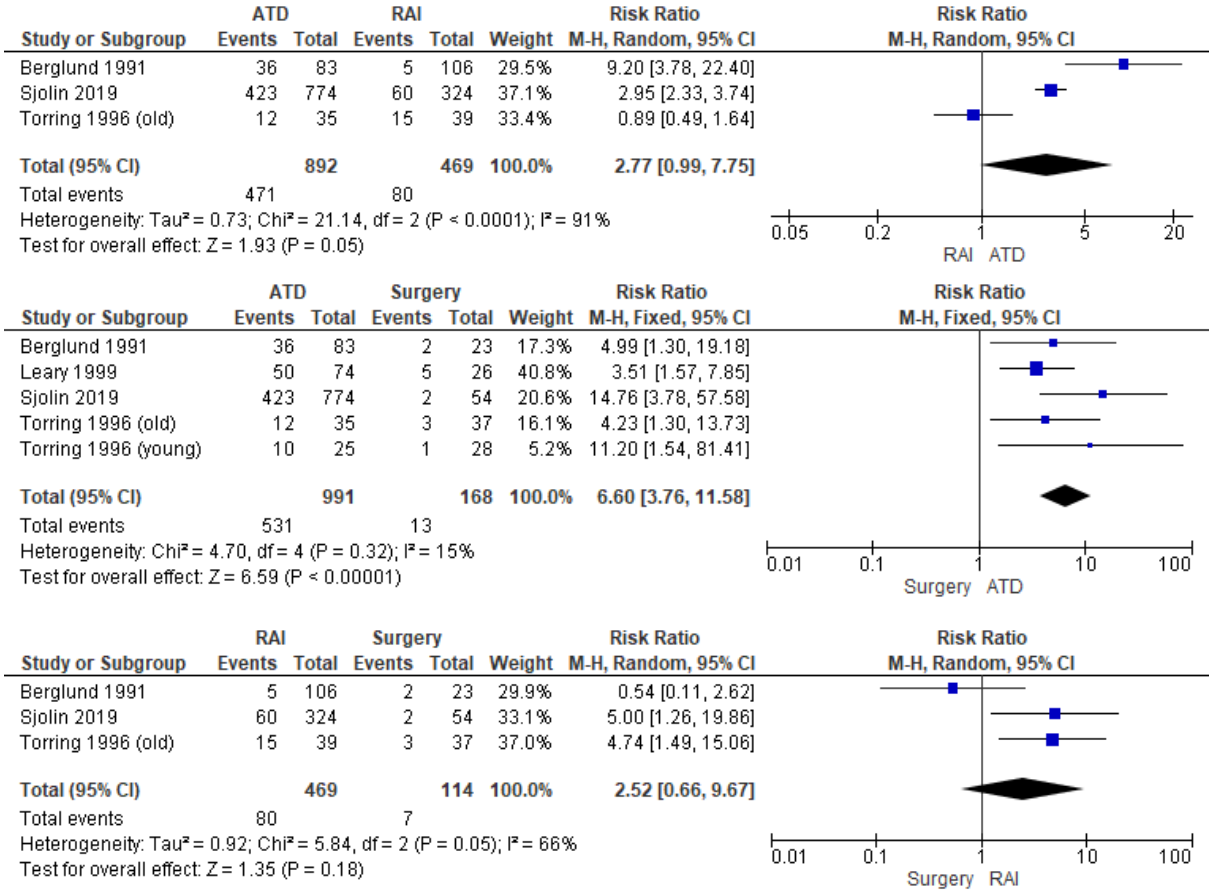

Figure 2. Risk Ratio of Relapse in GD Patients

Success rate

ATD has lower success rate compared to RAI (RR 0.47, 95% CI 0.35-0.63); *p<0.00001*) and surgery (RR 0.44, 95% CI 0.34-0.58); *p<0.00001*). In comparison to surgery, RAI has lower success rate (RR 0.97, 95% CI 0.94-0.99); *p=0.0009*) (Figure 3)

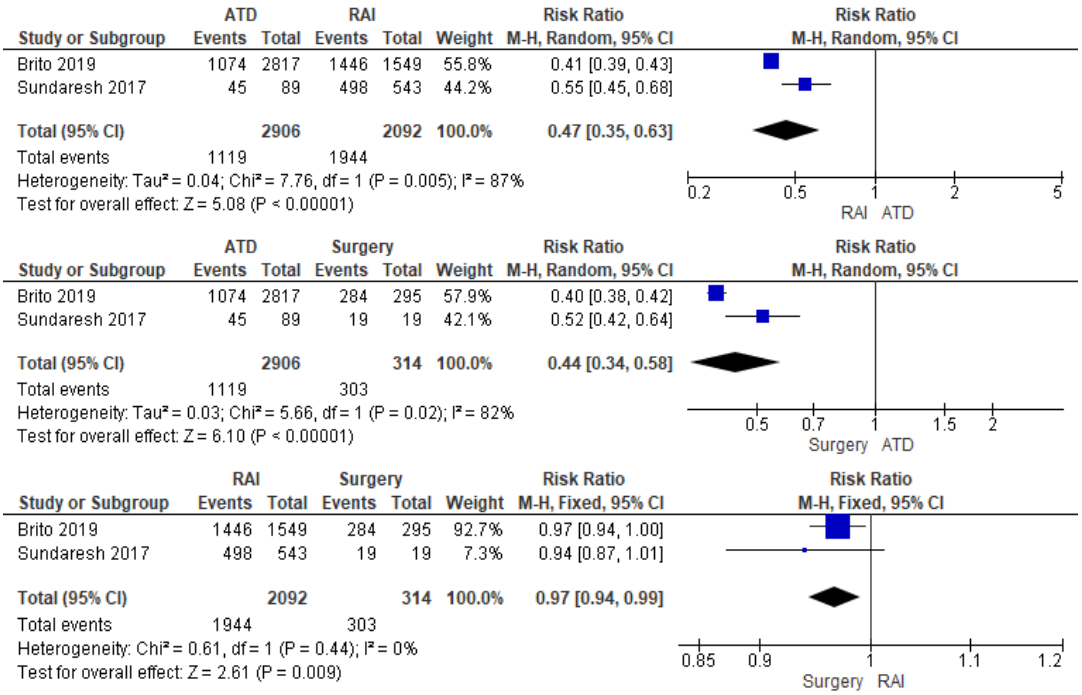

Figure 3. Success Rate in GD Patients

Hypothyroid

ATD has lower risk of hypothyroid compared to RAI (RR 0.08, 95% CI 0.02-0.27); *p<0.0001*) and surgery (RR 0.09, 95% CI 0.02 - 0.40); *p = 0.001*). RAI has higher risk of hypothyroid compared to surgery (RR 1.04, 95% CI 0.66 - 1.62); p = 0.87), but it is not statistically significant (Figure 4).

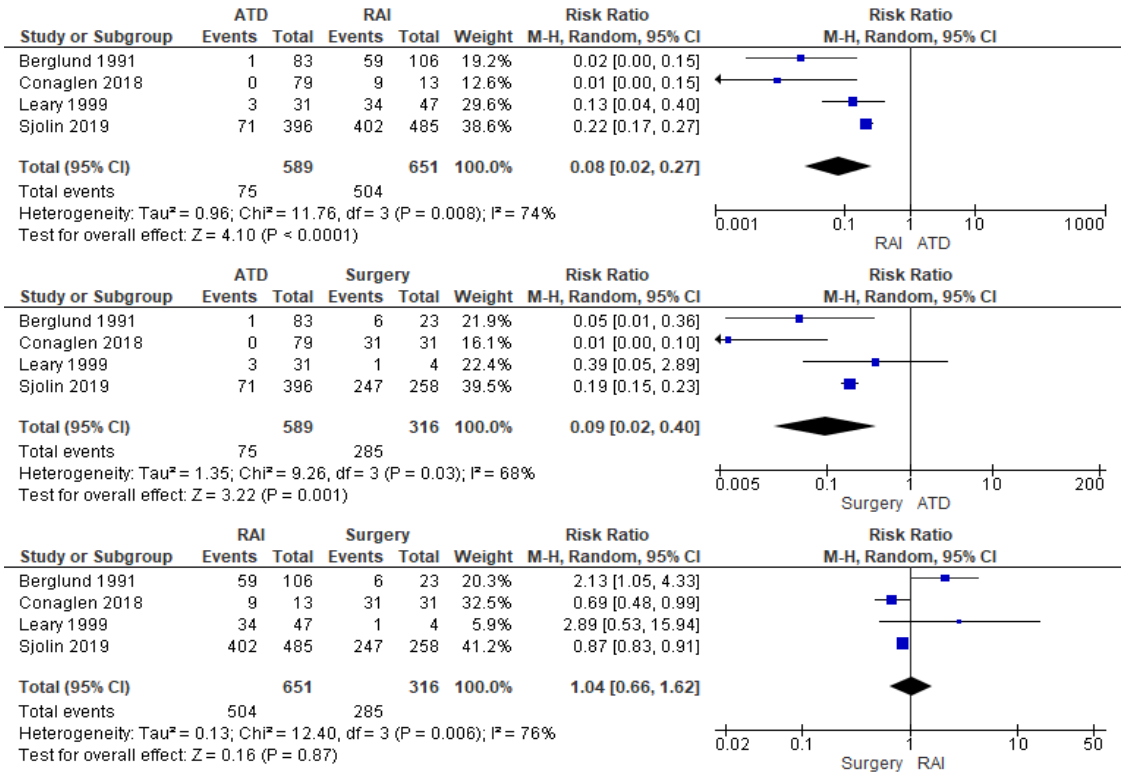

Figure 4. Risk Ratio of Hypothyroid in GD Patients

Publication bias

Due to the limited number of studies that amount to less than 10, there were no qualitative assessment for publication bias performed using the funnel plot analysis.

DISSCUSION

Total 7,104 participants were included with 56.4 % were given ATD, 36.4 % were given RAI and 7.2 % were done surgery. In our study, we found that ATDs have highest relapse rate compared to RAI and surgery, with the other remaining two modalities having no noticeable difference in relapse rate. This result is like previous meta-analysis.[13] Anti thyroid drugs work by decreasing thyroid hormone synthesis. Radioactive iodine and surgery work by reducing the amount of thyroid tissue.[18] A higher relapse rate is anticipated in the ATD group since the latter two modalities induce hypothyroidism in patients, often requiring lifelong thyroid hormone replacement. Anti-thyroid drugs offer the advantage of enabling the thyroid to return to normal functioning. We also analysed success rate of these three modalities and found that ATD has lower success rate compared to RAI and RAI has lower success rate compared to surgery. The 2018 European Thyroid Association Guideline for the Management of Graves' Hyperthyroidism, suggest that patients who are newly diagnosed with GD to be medically treated with methimazole (MMI) as the preferred drug for 12-18 months,[18] but as per the 2019 guidelines from the National Institute for Health and Care Excellence (NICE), RAI stands as the primary treatment choice due to its superior balance of advantages and costs compared to surgery (total thyroidectomy) and its greater cost-effectiveness over ATD.[19]

In patients whereas patients prefer ATDs or in condition where RAI and surgery are contraindicated, long-term ATD treatment is recommended.[20] In order to lower failure rate of ATD, it is advised to be given minimum one year. Longer ATD breaks was also associated to treatment failure (90 days versus 120 days).[15] One study found that when ATD was given for more than 60 months, it has the highest remission rate.[20]

Dosage of RAI in this study range from 6.7 mCi to 16.5 mCi. Dosing was based on thyroid size and iodine uptake. In iodine-deficient countries, participant tend to have higher RAI uptake, resulting in lower doses of RAI. Jeong et al. stated that thyroid volume has significant effect on the outcome of RAI in GD patients, with optimal fixed RAI dose for Korean GD patients with $\geq$ 33 mL thyroid volume should be at least 15mCi.[21] Higher baseline 999m technicium (99m Tc) uptake, male gender, body mass index (BMI) and higher baseline free thyroxine (fT4) level predicted treatment failure following RAI.[22]

Patient and physician should have thorough discussion regarding adverse effect of each modality. Hypothyroid is the most common adverse effect of RAI and surgery. We found ATD has lower risk of hypothyroid compared to RAI and surgery. It should also be taken into consideration, while ATD have lower risk of hypothyroid, ATD have other adverse effects, such as rash in MMI and hepatic involvement in propylthiouracil (PTU).[13] For RAI's adverse effects, new or worsened Graves' ophthalmopathy may arise in 15-33% patients, especially for smokers and radiation thyroiditis in 1% of patients.[23,24] Complications of thyroidectomy is recurrent laryngeal nerve injury.[25]

One study assesses quality of life following treatment of GD. 123 patients with Graves' disease underwent treatment, with 64% receiving only ATD, 11% undergoing RAI, and 25% opting for total thyroidectomy. Additionally, there were 18 untreated patients newly diagnosed with GD. The primary considerations in treatment selection included impacts on daily activities, apprehensions regarding radioiodine usage, potential for depression and anxiety, and recommendations from doctors. Most patients expressed satisfaction with their treatment and its results. Quality of life was higher in treated patients compared to untreated patients.[12] This showed the three modalities for GD did not have different quality of life.

LIMITATIONS

Our study has several limitations, such as 1) our included studies are observational study, therefore it contributes to higher risk of bias. 2) Most of the studies did not include thyroid size

and laboratory results, such as Thyroid Stimulating Hormone (TSHS), thyroxine, and Thyroid-Stimulating Hormone Receptor Antibodies (TRAb), therefore effect of this factors could not be analysed in this meta-analysis.

CONCLUSION

ATD has the highest risk of relapse compared to RAI and surgery. RAI and surgery did not differ significantly in risk of relapse and hypothyroid. This should be taken into consideration in managing GD patients.

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CASE REPORT

Secondary Hypogonadism in Recurrent Adamantinomatous Craniopharyngioma: Fertility Evaluation and Management

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ABSTRACT

Craniopharyngioma is an intracranial tumor with pituitary hormone deficiencies and affects 40% of gonadotropins deficiency. Gonadotropin deficiency causes secondary hypogonadism and male infertility which need to investigation for male infertility therapy options. A 22-year-old man presented with history of intermittent headaches, visual impairment, mild left-side hemiparesis, and developed erectile dysfunction. On clinical examination, there was abnormal penile and testicular size. The radiological examination showed a solid intrasellar mass with cystic lesion. The histological diagnosis was adamantinoma Tous craniopharyngioma. The hormonal evaluation showed low testosterone level, LH and FSH, and semen analysis showed azoospermia. The human chorionic gonadotropin stimulation test showed testosterone increase times from baseline, but evaluation semen test remained azoospermia. Craniopharyngioma morbidity is associated with tumor related and or treatment-related risk factors such as hormone deficiencies. Pituitary hormone deficiencies have been reported in 54-100% of patients that affect secretion of growth hormone, gonadotropin, TSH and ACTH. Gonadotropin deficiency associated with infertility in men. In this case, gonadotropin deficiency was due to the tumor because the symptoms had developed before surgery. Hypogonadism in this case occurs after puberty and he willing to have offspring. The hormonal therapy is effective in restoring spermatogenesis relates to the regulatory of the hypothalamic pituitary gonadal axis. The administration of HCG alone or combined with FSH, restores spermatogenesis of patients with hypogonadotropic hypogonadism, with reported pregnancy rates of up to 65%. Gonadotropin stimulation therapy will be planned after ruling out seminal tract obstruction and testicular fibrosis. Infertility in secondary hypogonadism can be managed with hormone therapy, but a complete investigation is required before starting treatment to determine therapy options.

Keywords: *Secondary hypogonadism, craniopharyngioma, male infertility*

INTRODUCTION

Craniopharyngioma (CP) is a rare solid or mixed cystic epithelial tumor in the sellar and suprasellar region. CP constitutes 1.2-4.6% of all intracranial tumours, accounting for 0.5-2.5 new cases per 1 million population per year globally. There are two clinicopathological forms of craniopharyngiomas, which are papillary squamous type and adamantinomatous craniopharyngioma (ACP). ACP has a bimodal age distribution with peak incidences in children aged 5-15 years and adults aged 45-60 years. In the childhood and adolescent age group, the APChistological type with cyst formation is the most common. It has poor prognosis when compared to papillary craniopharyngioma. Endocrine deficiencies such as impaired sexual function, clinical manifestations of increased intracranial pressure (such as headache) and hypothalamic syndrome (such as disruptions in body temperature regulation, growth and water balance) are major symptoms of CP in adults. Although CPs are typically of low histological gonadotropins secretion (40% of patients), thyroid-stimulating hormone secretion (25% of patients) and ACTH secretion (25% of patients). Gonadotropin deficiency associated with hypogonadism and male infertility. The clinical features of male hypogonadism depend upon the age of onset, severity of testosterone deficiency, and whether there is a decrease in one or both two major functions of the testes (sperm and testosterone production).

Hormonal therapy has been integral to male infertility treatment options. The rationale of this approach relates to the critical regulatory role of the hypothalamic pituitary gonadal (HPG) axis on spermatogenesis and the common knowledge that hormonal abnormalities are potentially treatable causes of male infertility. The use of hormonal therapy, exogenous human chorionic gonadotropin alone or combined with exogenous follicle-stimulating hormone (FSH), to treat specific endocrine disorders is well-established and evidence based. Before starting the therapy, needed complete investigation for choosing therapy options.

grade, the prognosis and outcomes of patients are frequently impaired owing to the hypothalamic-pituitary location of the CP and tumour-related and/or treatment-related injury to these areas.[1,2]

Long-term morbidity is associated with tumour related and/or treatment-related risk factors such as progressive disease with multiple recurrences, cerebrovascular disease and chronic neuroendocrine deficiencies. The standardized overall mortality varied from 2.88-fold to 9.28-fold in previous studies. The best treatment for CP is that which leads to the least long-term morbidity. Treatment may include surgery alone, irradiation alone or, more commonly, a combination of the two. Surgery alone implies gross total resection and is, therefore, appropriate for tumours that may be completely resected without neurovascular injury and visual impairment.[1,2]

Pituitary hormone deficiencies have been reported in 54-100% of patients that affect growth hormone secretion (75% of patients).

CASE ILLUSTRATION

A 22-year-old man presented with history of intermittent headaches and tinnitus for more than 6 months. He had noticed gradual onset of visual impairment, progressive narrower of visual field, and mild left-side hemiparesis. He also developed erectile dysfunction, fatigue and decrease of his libido. On clinical examination his height was 166 cm, weight 58 kg, with normal arm span (162 cm). His stretch penile length was 8 cm, right testicular volume was 8 ml, left testicular volume was 6 ml Tanner stage 3 of pubic hair.

On October 2021 radiological examination showed a solid intrasellar mass with cystic lesion (6.2x6.1x7.3 cm) that extends to the left suprasella, left cerebellopontine angle and intraventricular III, causing non-communicating hydrocephalus. Then in December 2021, the patient underwent a craniotomy and Ommaya reservoir insertion, followed by radiotherapy with total doses 54 Gy. One year after surgery, the patient complained of general weakness and disorder of

balance. Imaging evaluation showed fluid collection occupying intrasellar-suprasellar, the the fluid aspirated from Ommaya.

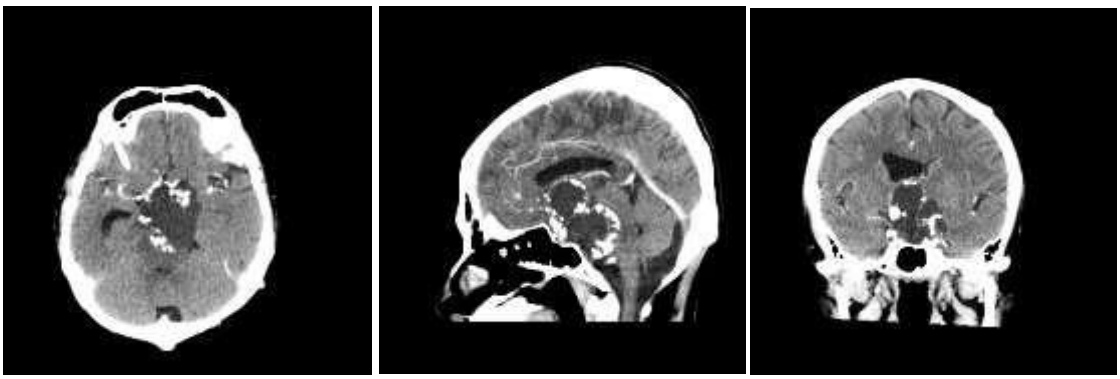

Figure 1. Coronal (A), axial (B) and sagittal (C) views of the contrast-enhanced CT scan (after craniotomy procedure) showing a heterogeneously enhancing mass with calcifications and fluid collection occupying intrasellar-suprasella. The mass pressing on the pons and mesencephalon tothe left side. The histological diagnosis was adamantinoma Tous craniopharyngioma. Following surgery, treatment continued with 30 times external beam radiotherapy.

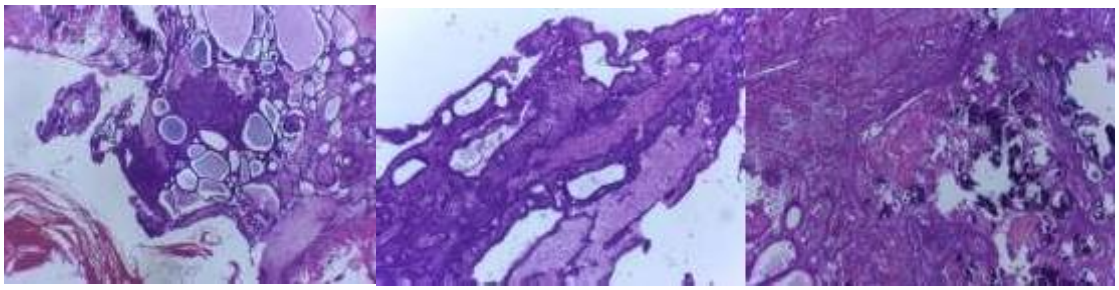

Figure 2. H&E-stained sections at 40x magnification showing tumor cells trabecular arranged(A). H&E-stained sections at 100x magnification showing tumor cells are palisaded on the peripher and stellate reticulum is visible (B). H&E-stained sections at 100x magnificationshowing tumor cells with wet keratin and calcifications (C).

The hormonal evaluation showed low testosterone level (7.26 nmol/L), low luteinizing hormone level (< 0.09 mIU/mL) and low follicle-stimulating hormone level (0.19 mIU/mL), and semen analysis showed azoospermia. The ultrasound showed small bilateral testicular mass densitometry showed low bone mass. The patient then underwent human chorionic gonadotropin (HCG) stimulation test for evaluation of testicular function with a single dose of HCG injection atdose of 5000 iu intramuscular. After test evaluation, testosterone showed increase 2.6 times frombaseline (7.26 to 18.75 nmol/L) but evaluation semen analysis remained azoospermia.

DISCUSSION

About 40% of craniopharyngioma patients have gonadotropin deficiency. These imbalances of reproductive hormones are associated with hypogonadism and male infertility. A well-conducted andrological evaluation is critical to evaluate the causes of male infertility and then to choose the treatment. It includes a detailed medical and reproductive history of the patient, a physical examination, and routine semen analysis. The second-line investigations (such as hormonal assessment, sperm functional tests, genetic analysis, and imaging studies) might be necessary and are based on the clinical and semen analysis findings.[3]

Hypogonadism in a male is a clinical syndrome that results from failure of the testis to produce physiological concentrations of testosterone and/or a normal number of spermatozoa due to pathology at one or more concentrations of the hypothalamic-pituitary-testicular axis. These abnormalities can result from disease of the testes (primary hypogonadism) or disease of the pituitary or hypothalamus (secondary hypogonadism). The patient has primary hypogonadism if his serum testosterone concentration and/or sperm count are low and/or his serum LH and FSH concentrations are high, and the patient has secondary hypogonadism if his serum testosterone concentration and/or the sperm count are low and/or his serum LH and FSH concentrations are inappropriately normal or low, which would be inappropriate if gonadotroph cell function were normal. In this patients, serum testosterone, LH and FSH concentrations are low and azoospermia from semen analysis, in accordance with secondary hypogonadism.[3,4]

The clinical features of male hypogonadism depend upon the age of onset, severity of testosterone deficiency, and whether there is a decrease in one or both two major functions of the testes: sperm production and testosterone production. When testosterone deficiency first occurs after completion of puberty, symptoms may include a decrease in energy and libido that occurs within days to weeks. However, sexual hair, muscle mass, and bone mineral density usually do not diminish to a significant degree for several years, although profound deficiency may cause a more rapid decline. Adults may also present with infertility. Hypogonadism in this case occurs after puberty with erectile dysfunction symptom, abnormal penile and testicular size, and low bone mass as seen in bone mass densitometry, but before managing the infertility we need evaluate the testicular function. The evaluation of testicular function can be investigated with a reliable dynamic test called human chorionic gonadotropin stimulation test.[5]

Human chorionic gonadotropin (HCG) is a hormone that mimics the action of luteinizing hormone which is normally produced by the pituitary gland. HCG stimulation is an important test to determine Leydig cell function and testosterone secretion. The normal response indicates a normal Leydig cell function and possible presence of viable testicular tissues. The HCG stimulation test requires an intramuscular injection of 5000 IU, with blood test on days 1 before injection and on day 4 after injection and semen analysis evaluation on week 4 after injection. In this case, after HCG stimulation test, the testosterone level showed increase 2.6 times from baseline (7.26 to 18.75 nmol/L) but evaluation semen analysis remained azoospermia. It means that the body is producing testosterone in response to the injections but need evaluation of factors that affect azoospermia, such as the seminal tract obstruction and testicular fibrosis.[5,6]

Hormonal therapy has been integral to male infertility treatment options. The rationale of this approach relates to the critical regulatory role of the hypothalamic pituitary gonadal (HPG) axis on spermatogenesis. The pulsatile secretion of gonadotropin-releasing hormone (GnRH) from the hypothalamus stimulates the release of pituitary FSH and LH. The number of spermatogonia modulates pituitary FSH secretion, when spermatogonia is absent or their number is markedly reduced, the endogenous FSH levels increase. In this case, FSH levels are low, typically observed in male

with hypogonadotropic hypogonadism due to primary pituitary dysfunction. Indeed, the use of hormonal therapy to treat specific endocrine disorders (such as hypogonadotropic hypogonadism and hyperprolactinemia) is well-established and evidence based.[7,8]

The administration of exogenous HCG, alone or combined with exogenous follicle-stimulating hormone (FSH), restores spermatogenesis to varying degrees in up to 90% of patients with hypogonadotropic hypogonadism, with reported pregnancy rates of up to 65% (natural or assisted). HCG has the biologic activity of LH but a longer half-life in the circulation, it stimulatesthe Leydig cells of the testes to synthesize and secrete testosterone. HCG always replaced before FSH because HCG stimulates the Leydig cells to secrete testosterone, which results inan intratesticular testosterone concentration 100 times that in the peripheral circulation, a concentration essential to stimulate spermatogenesis; HCG alone maybe sufficient for stimulation of spermatogenesis, but FSH alone is not effective; HCG preparations are considerably less expensive than exogenous FSH preparations. After HCG administration, the serum testosterone concentration is measured every one to two months and, if it is not between 400 and 800 ng/dL (13.87 to 27.7 nmol/L) within two to three months, the dose is increased accordingly by using lower volumes of diluent. Some patients require as much as 10,000 units per dose. On rare occasions, the serum testosterone concentration fails to respond to hCG, even to 10,000 units threetimes a week. This problem is suspected to be due to antibodies to hCG, that hCG stimulation test is needed before giving hCG. The sperm count is measured every one to three months once the serum testosterone concentration is 400 to 800 ng/dL, but the value is not used to adjust the hCG dose. An increase in testicular volume is usually associated with an increase in sperm count.[9]

Follicle-stimulating hormone (FSH) is given for cases where the sperm count has not reached5 to 10 million/mL and/or pregnancy has not occurred six months after serum testosterone reached the target. Recombinant human follicle-stimulating hormone (rhFSH) has not been compared directly with Human menopausal gonadotropins (a preparation used for its FSH but also containsLH), but its efficacy when added to hCG in stimulating spermatogenesis in men with hypogonadotropic hypogonadism seems similar, but the cost of rhFSH is almost double than human menopausal gonadotropins (hMG). The effect of FSH is probably exerted via the Sertoli cells of the seminiferous tubules. FSH appears to be necessary for the initiation of spermatogenesis, but not for its maintenance or reinitiation.[9]

The sperm count is measured once every one to three months. The reason for such frequent measurement of the sperm count is that individual values fluctuate considerably, so that many samples are needed to detect a trend. Men treated with both hCG and hMG achieve sperm in approximately 6 to 10 months, but the time to pregnancy is longer. If pregnancy does not occur spontaneously within 12 to 24 months of achieving any sperm in the ejaculate, can be suggested to assisted reproductive technologies, such as intrauterine insemination, IVF, and, as a last resort, intracytoplasmic sperm injection. Cryopreservation of sperm can be offered, especially if the sperm count is normal, for possible future attempts to achieve pregnancy. When the couple does not wish to have more children, virilization can be maintained by continuing hCG alone or by using testosterone.[9]

CONCLUSION

Infertility in secondary hypogonadism can be managed with hormone therapy, but acomplete investigation is required before starting treatment to determine therapeutic options.

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CASE REPORT

Approach to Diagnosis and Management of An Elderly Female Patient with Recurrent Hypocalcemia

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ABSTRACT

Disorders of calcium metabolism are common in the everyday clinical setting. Although hypocalcemia is not as common as hypercalcemia, it can be life-threatening if not properly recognized and treated promptly. Causes of hypocalcemia can be divided into three broad categories, such as parathyroid hormone (PTH) deficiency, high PTH levels, and other causes. There is no literature that specifically discusses the incidence and prevalence of hypocalcemia in general. In general, renal failure is the most common cause of hypocalcemia. This condition is followed by vitamin D deficiency, magnesium deficiency, acute pancreatitis, and others. The clinical presentation of hypocalcemia can vary widely, from asymptomatic to life-threatening. In an emergency, unrecognized or poorly managed hypocalcemia can cause significant morbidity or mortality. Symptomatic patients with classic clinical findings of acute hypocalcemia require immediate resuscitation and evaluation. However, most cases of hypocalcemia are found based on clinical suspicion as well as appropriate laboratory testing. Treatment of hypocalcemia depends on the presence and severity of symptoms, degree of hypocalcemia, and etiology of hypocalcemia. Most cases of hypocalcemia are clinically mild and require only supportive treatment and further laboratory evaluation. Oral calcium absorption may be indicated for outpatient treatment in mild cases. In cases of severe hypocalcemia leading to seizures, tetany, refractory hypotension, or arrhythmias, a more aggressive approach may be required, including intravenous calcium infusion.

***Keywords**: Calcium, hypocalcemia, parathyroid hormone, vitamin D*

INTRODUCTION

Hypocalcemia is one of the most diagnosed electrolyte disturbances and requires careful management and evaluation. Epidemiological studies of hypocalcemia compared with other electrolyte abnormalities have not been carried out. For the past 20 years, laboratory tests that included serum levels of calcium, ionized calcium, and parathyroid hormone (PTH) allow diagnosis to be easier. Hypocalcemia has been reported to occur due to genetic disorders or acquired from several organ and organ system disorders. Diseases that interfere with the physiology of the parathyroid glands, bones, intestines, and kidneys, which are all responsible for regulating serum calcium levels, can cause hypocalcemia.[1-3] The incidence of ionized hypocalcemia is difficult to measure. In intensive care patients, the reported rates range from 15-88%. A systematic review and meta-analysis of hypocalcemia after thyroidectomy found that the average incidence of transient hypocalcemia was 27% (range 19-38%) and permanent hypocalcemia was 1% (range 0-3%). In a series of 500 postoperative thyroidectomy patients who were operated on for hyperparathyroidism, 2% developed permanent hypocalcemia.[2]

Patients with hypocalcemia may be present with a variety of signs and symptoms. Low serum calcium levels have the potential to affect nearly all organs and organ systems. New-onset hypocalcemia can be life-threatening and requires immediate medical intervention. Meanwhile, in cases of chronic hypocalcemia, patients sometimes appear asymptomatic or have mild symptoms. Identification, clinical assessment and management of hypocalcemia are key points that need to be addressed simultaneously and carried out as soon as possible. The focus of this case report is to update the evidence on the diagnostic assessment and clinical management of hypocalcemia according to an algorithm that is useful for everyday clinical practice.[1,2]

CASE REPORT

A 72-year-old female patient came with her family to hospital, in conscious state with the main complaint of shortness of breath. Shortness of breath has been felt since the last 1 month and got worse 3 days before entering the hospital. Shortness of breath that feels like fatigue after undergoing heavy exercise, with fast and short breaths, chest feels heavy, accompanied by cold sweat. Since the last 3 days, the shortness of breath has been felt continuously with increasing intensity when carrying out normal daily activities and aggravating when lying down. Shortness of breath is felt to decrease if the patient is at rest and in a sitting position. Over the past 1 month, complaints of shortness of breath have gotten worse and more frequent. When shortness of breath occurs, the patient feels nausea, fatigue, difficulty speaking, and coughing.

Complaints of nausea have also been felt by the patient since the last 3 days after starting with aggravating complaints of shortness of breath. Nausea is not accompanied by vomiting and decreases if shortness of breath improves. Cough has also been felt since the last 2 days. Cough complaints come and go, beginning with the desire to get rid of phlegm. Cough worsens if tightness increases. Cough with thick yellow phlegm and hard to cough up. Cough and shortness of breath are reduced when given oxygen while on Triage. Apart from shortness of breath and coughing, the patient also complained of decreased appetite since the last 3 days due to the aggravating tightness. Patients can eat up to 1/2 portion but can still drink as much as 500-1,000 ml/24 hours.

The patient also complained of stiffness in the fingers of the limbs but felt the heaviest in the fingers of both hands, difficult to control, painless, difficult to move, intermittent, and one attack lasted less than 5 minutes. Complaints of stiffness have been felt since the last 1 month. Currently, for stiff complaints, attacks are less common. When an attack occurs, the fingers grip, the wrist is slightly flexed, and the upper arm is slightly extended. Consciousness

remains full during an attack. There are no conditions that exacerbate or alleviate these stiff complaints.

Other complaints such as fever, tremors, cold sweat without preceded by shortness of breath, heat intolerance, convulsions, decreased consciousness, liquid stools, decreased frequency of urination, and significant weight loss were denied by the patient. There is no problem regarding defecation. Urinate in an average of at least 1,000 cc per 24 hours, yellow, not frothy, not painful. Complaints of frequent thirst have been noticed by the patient since the last 1 month.

The patient was undergoing treatment at our hospital with complaints of pain in the right shoulder area. The patient was diagnosed with a closed fracture with dislocation of the third proximal of the right humerus. In patients, Open Reduction and Internal Fixation (ORIF) +bone graft on 5 July 2022 and discharged on 6 July 2022. History of untreated subclinical hyperthyroidism and blood calcium deficiency recognized during previous hospitalization (25 June 2022). Prior history of diabetes mellitus was denied.

The patient has a history of hypertension and congestive heart failure since the last 5 years and is taking regular medication from the heart polyclinic at Kasih Ibu Hospital in Tabanan with drugs namely candesartan 1x8mg and bisoprolol 1x5mg. The patient also had a history of goiter and had surgery in 1975. The patient said that an incision was made on the right and left side of the neck. The incision scars are still visible. There were no complaints of palpitation, cold sweat, tremor, and weight loss at that time.

There is no history of family members having similar complaints. History of hypertension, heart disease, kidney disease, thyroid gland disease, diabetes mellitus and liver disease in the family was denied by the patient. The patient works as a housewife. Everyday patients rarely consume milk. The patient does not smoke, does not consume alcohol, and has never taken herbs and pain medications.

A follow-up physical examination was carried out when the patient had moved to the Lely Room on 7/22/2022. From the physical examination, the patient's weight was 55 kg, height 160 cm, body mass index (BMI) 21.48 kg/m^2 with compos mentis awareness. Vital signs obtained: blood pressure 130/80 mmHg, pulse 89 times per minute, respiratory rate 28 times per minute and axillary temperature 37.8^{O}C, visual analog score (VAS) 0/10 and oxygen saturation was 97% in room air. On examination of the neck, it was found that there were multiple lumps in the right and left coli areas, which appeared to be more significant in the left coli region with a size of ± 3x3x4 cm. The lumps also move when swallowing, there are incision marks on the anteroinferior side of the right and left coli, and on auscultation no bruits are heard. On cardiac examination, the left heart border was enlarged, the S1 and S2 heart sounds were normal, regular, and there were no additional heart sounds. Examination of the lungs, abdomen and extremities showed no abnormalities.

On laboratory examination, there was a decrease in serum calcium and intact PTH level. The results of other laboratory tests are shown in tables 1 and 2.

Table 1. Laboratory Results of The Patient's Current Hospitalization Period

Types of Laboratory Examination	Results (Date, July 2022)				Reference	Unit
	16	17	18	20		
Whole Blood						
Leucocytes	14,7				4,1-11,0	$10^3/\mu L$
Neutrophils	12.64				2.50-7.50	$10^3/\mu L$
Lymphocytes	1.6				1.00-4.00	$10^3/\mu L$
Hemoglobin	10.1				13,5-17,5	g/dL
Hematocrite	32				41-53	%
MCV	84.7				92.20	fL
MCH	26.7				29.31	Pg
Platelets	465				150-440	$10^3/\mu L$
Blood Sugar						
RBS	208				70-140	mg/dL
HbA1C	7.3				<6.5	%
Inflammatory Markers						
Procalcitonin	2.65				<0.15	ng/mL
Liver Function Test						
SGOT	43.5				11-33	U/L
SGPT	30.8				11-34	U/L
Albumin	3.59		3.29		3.4-4.8	g/dL
Kidney Function Test						
BUN	11.4		14.9	15.6	8-23	mg/dL
Creatinine serum	1.19		1.3	1.18	0.5-0.9	mg/dL
Coagulation Test						
PPT	14.1				10.8-14.4	second
APTT	31.9				24-36	second
INR	0,99				0.9-1.1	
Serum electrolytes						
Natrium	143	144		137	136-145	mmol/L
Kalium	5.85	3.51		2.98	3,5-5,1	mmol/L
Calcium	4.4		5.2	5.1	8.4-9.7	mg/dL
Corrected calcium	4.7		5.8	5.7	8.4-9.7	mg/dL
Blood Gas Analysis						
pH	7.44					
pCO2	34				35-45	mmHg
pO2	121				80-100	mmHg
BE	-1.1				-2-2	mmol/L
HCO3	23.1				22-26	mmol/L

Table 1. Laboratory Results of The Patient's Current Hospitalization Period (Continuation)

Types of Laboratory Examination	Results					Reference	Unit
	21	23	25	26	27		
Whole Blood							
Leucocytes	7.58					4,1-11,0	10^3/µL
Neutrophils	4.97					2.50-7.50	10^3/µL
Lymphocytes	1.9					1.00-4.00	10^3/µL
Hemoglobin	9					13,5-17,5	g/dL
Hematocrit	27.5					41-53	%
MCV	84.1					92.20	fL
MCH	27.5					29.31	Pg
Platelets	353					150-440	10^3/µL
Kidney Function Test							
BUN		12.9		13.2		8-23	mg/dL
Creatinine serum		0.9		1.05		0.5-0.9	mg/dL
Serum electrolytes							
Natrium	135	139		139		136-145	mmol/L
Kalium	3.19	3.7		4.85		3,5-5,1	mmol/L
Calcium		5.7	6.6	6.9		8.4-9.7	mg/dL
Corrected calcium		6.3	7.2	7.5		8.4-9.7	mg/dL
Magnesium			1.47			1.6-2.6	mg/dL
Hormones							
Intact PTH					5.83	10-65	pg/mL
Urinary electrolytes							
24-hour urine's K				48.57		25-100	mmol/24 hour
24-hour urine's Na				273.6		30-300	mmol/24 hour
24-hour urine's Ca				2.93		2.5-8.0	mmol/24 hour
Urine osmolality				214.5		500-800	mOsm/kg H2O

MCV (mean corpuscular volume); MCH (mean corpuscular hemoglobin); RBS (random blood sugar); HbA1C (glycosylated haemoglobin); SGOT (serum glutamic oxaloacetic transaminase); SGPT (serum glutamic pyruvic transaminase); PPT (plasma prothrombin time); APTT (activated Partial Thromboplastin Time); BE (base excess); Na (sodium); K (potassium); PTH (parathyroid hormone)

Table 2. Laboratory Results of Patients In The Previous Hospitalization Period

Types of Laboratory Examination	Results	Reference	Unit
	June 27, 2022		
Reticulocyte %	1.58	0.76-2.21	%
Reticulocyte#	0.06	0.03-0.1	10^6µL
TSHs	0.15	0.27-4.2	uIU/mL
FT4	1.19	0.7-1.48	ng/dL
Albumin	3.04	3.4-4.8	g/dL
Calcium	3.8	8.4-9.7	mg/dL
ALP	98	42-98	U/L
CRP	124.4	<5	mg/dL
Vitamin D,25-OH Total	26.9	30-100	ng/dL

TSHs (thyroid stimulating hormone); FT4 (free thyroxine); ALP (alkaline phosphatase); CRP (C-reactive protein)

Furthermore, an anteroposterior (AP) plain chest X-ray examination was carried out and showed that in the lung there was bilateral consolidation on upper to middle zone of the lungs, perihilar treasure in both lung fields, increasing of vascular pattern, and cephalization. Furthermore, on the heart, it is enlarged in size, the left border is covered with opacities, and there is aortic knob calcification. Then, installed plate and screw internal fixation on the proximal third of the right humerus is found. The impression on this chest X-ray is cardiomegaly with aortosclerosis, pulmonary edema, bilateral pleuropneumonia, and installed plate and screw internal fixation on the proximal third of the right humerus.

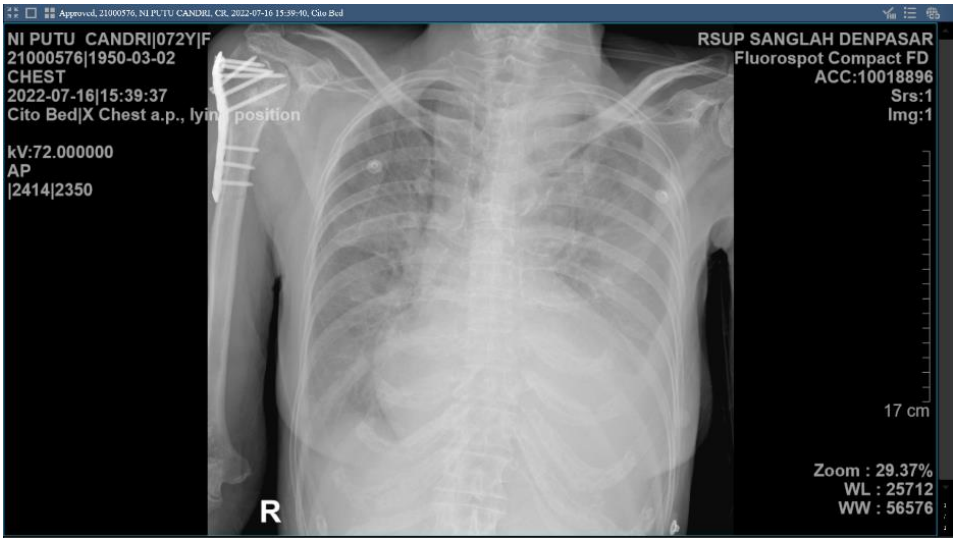

Figure 1. Photo of the patient's chest upon admission to the hospital

Bedside echocardiography also performed and showed the results of dilatation of the left atrium and left ventricle, left ventricle hypertrophy, ejection fraction 25%, mild mitral regurgitation, mild tricuspid regurgitation, low probability of pulmonary hypertension, estimated right atrial pressure (eRAP) 15 mm Hg, as well regional wall motion abnormality (RWMA). The patient also underwent cytopathological examination fine needle aspiration biopsy (FNAB) of the thyroid gland (25/7/2022) which showed a cytomorphological impression of a predisposition to a benign follicular nodule.

The patient also had a history of hospitalization. Several examinations were carried out such as plain photos of the humerus and AP/lateral shoulder, ultrasonography (ultrasound) of thyroid gland, as well head magnetic resonance imaging (MRI). Thyroid ultrasound results (30/6/2022) showed the impression of a solid lobulated mass on the left thyroid to left thoracic inlet, according to Thyroid Imaging Reporting & Data System (TIRADS)-5 (Highly Suspicious), a solid lobulated mass on the right thyroid to right thoracic inlet according to TIRADS-4 (Moderately Suspicious), a solid mass with a cystic component on isthmus TIRADS-4 compliant (Moderately Suspicious), as well as multiple nonsuspicious lymphadenopathy on right and left coli, submental, and left submandibular regions.

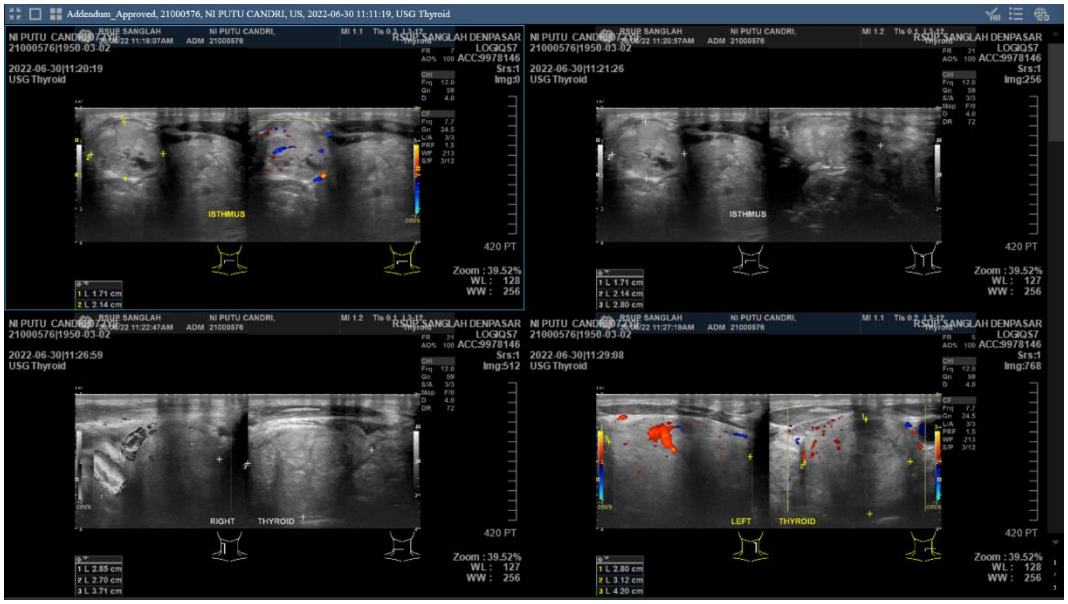

Figure 2. Result of thyroid ultrasound

Because clinically there were repetitive spastic involuntary movements, symptomatic epilepsy was suspected, an MRI of the head was performed. Head MRI results axial, sagittal, and coronal slices without contrast show an impression of small vessel ischemic changes on the right and left lateral periventricular (Fazekas 2), Pansinusitis, and mesial temporal sclerosis is not visible.

Figure 3. MRI of the head

The patient also underwent plain AP/lateral humeral photos before and after surgery. Plain radiographs before surgery show a complete displaced fractur on right anatomical neck os humerus accompanied with soft tissue swelling surroundings and osteopenia. Later, plain radiographs after surgery showed fracture attached on right anatomical neck os humerus attached with plate and internal fixation screw with good standing and apposition, accompanied with soft tissue swelling surroundings and osteopenia.

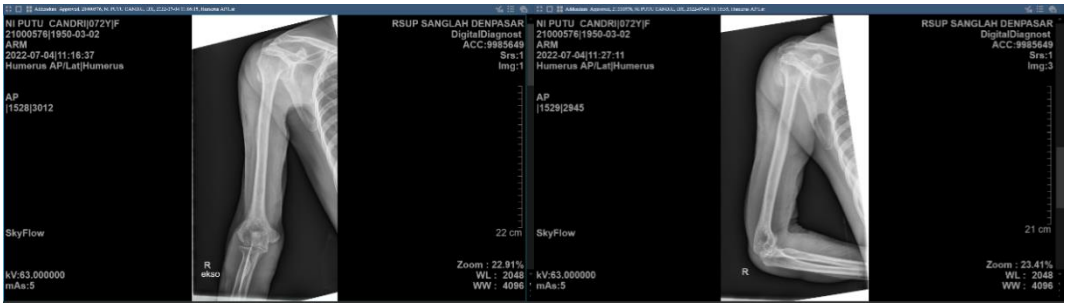

Figure 4. Photo of AP/Lateral humerus before surgery

Figure 5. Photo of AP/Lateral humerus after surgery

The patient is being treated in the intermediate ward of Penyakit Jantung Terpadu (PJT) before finally being transferred to our hospital. In intermediate ward of PJT, the patient was diagnosed with acute decompensated heart failure (ADHF) profile B; type 2 diabetes mellitus (DM); hypokalemia; acute on chronic kidney disease (ACKD) et causa prerenal on chronic kidney disease (CKD) et causa diabetic kidney disease (DKD); multiple thyroid nodule suspect malignancy, subclinical hyperthyroidism; hypocalcemia; community acquired pneumonia (STAMP). Meanwhile, in the Lely Room, the patient was diagnosed with ADHF profile B (improved); DM type 2; ACKD et causa prerenal on CKD et causa DKD (improved); benign multiple thyroid nodule; subclinical hyperthyroidism; suspect hypoparathyroidism; hypocalcemia; CAP (improved).

Therapy given in intermediate ward of PJT is an infusion of 0.9% NaCl 8 drops per minute, furosemide 3x20mg iv, insulin glulisine 3x3 units sc, insulin glargine 1x8 units sc, ceftriaxone 1x2gr iv, levofloxacin 1x750gr po, spironolactone 1x25mg po, acetosal 1x80 mg po, candesartan 1x8 mg po, bisoprolol 1x2.5 mg po, simvastatin 1x20mg po, acetylcysteine 3x200mg po, calcitriol 1x0.25mg po, lansoprazole 1x30mg iv, calcium gluconate 3x1 gram iv. Meanwhile, the therapy given in the Lely Room was an infusion of 0.9% NaCl 8 drops per minute, CKD diet nutrition 1900 kcal/day + 48 gr protein/day, calcium gluconate 3 x 1 gram IV, insulin glulisine 3 x 3 units SC, insulin glargine 1 x 8 units SC. , furosemide 40 mg IV (if there are signs of congestion), acetosal 1x80 mg po, candesartan 1x8 mg po, bisoprolol 1x2.5 mg po, spironolactone 1x25 mg po, simvastatin 1x20 mg po, calcitriol 1 x 0.5 mg po, KSR 3x600 mg po , and lansoprazole 1x30mg po. Monitoring blood sugar is done by examining fasting blood sugar and 2 hours after eating. Electrolyte monitoring is also carried out by checking natrium, kalium and calcium every 72 hours. Evaluation of kidney function was also carried out by assessing blood urea nitrogen (BUN) and serum creatinine every 72 hours and urine output in 24 hours.

DISCUSSION

Definition

Hypocalcemia is defined as a total serum calcium concentration <8.8 mg/dL (<2.20 mmol/L) in the presence of a normal plasma protein concentration or a serum ionized calcium concentration <4.7 mg/dL (<1.17 mmol/L). The reference range for serum calcium varies with age and sex.[2] Hypocalcemia is one

of the most common electrolyte disturbances and requires careful diagnosis and management. Calcium homeostasis in the body is a complex interaction between several different hormones and other factors. The main factors that regulate calcium homeostasis in the body are the PTH hormone, vitamin D, fibroblast growth factor 23 (FGF23), and calcitonin.[3]

The serum calcium concentration is maintained within a very narrow range. About 45% of body calcium is bound to plasma proteins, especially albumin. About 15% is bound to small anions such as phosphate and citrate. About 40% is in the free or ionized state. Most laboratories report total serum calcium concentrations ranging from 8.5 to 10.5 mg/dL (2.12 to 2.62 mmol/L). Ionized calcium can also be measured by some laboratories, where the normal range is 4.65 to 5.25 mg/dL (1.16 to 1.31 mmol/L). Any level below this range is considered hypocalcemia.[3]

In this case, the patient's total calcium level at admission was 4.4 mg/dL, with a total calcium level of 4.7 mg/dL after corrected with plasma albumin levels. Hence, the patient was diagnosed with hypocalcemia.

Epidemiology

There is no literature that generally addresses the incidence and prevalence of hypocalcemia. A systematic review and meta-analysis of hypocalcemia after thyroidectomy showed that the mean incidence of transient hypocalcemia was 27% (range, 19-38%) and that of permanent hypocalcemia was 1% (range, 0-3%).[4] In a series of 500 postoperative patients for hyperparathyroidism, as many as 2% of patients also reported having permanent hypocalcemia.[2]Hypocalcemia occurs in chronic kidney disease and acute kidney injury, vitamin D deficiency, magnesium deficiency, acute pancreatitis, hypoparathyroidism, pseudohypoparathyroidis, severe degree corona virus disease-19 (COVID-19) infections, as well as the use of calcium-free phosphate, citrate, or albumin infusions. The underlying disease causing the hypocalcemia has a greater impact on morbidity than the hypocalcemia itself.[2,6]

Etiology

Disorders causing hypocalcemia can be divided into PTH-mediated and non-PTH-mediated. The first group includes all cases of impaired parathyroid gland function resulting in reduced or overproduction of PTH. Meanwhile, in the second group are organs and other organ systems that are involved. Kidney, liver, bone, intestine, and vitamin D metabolism play a major role in this case, which is generally associated with a secondary increase in PTH levels (Table 3).[1]

Table 3. Causes of hypocalcemia

PTH-mediated causes	
Genetic disorders	**Acquired disorder**
Familial isolated hypoparathyroidism Hypoparathyroidism-associated syndrome, namely: 22q11.2deletion (DiGeorge) syndrome; Hypoparathyroidism, Sensory Neural Deafness, Renal Dysplasia Syndrome (HDR); Kearns-Sayre syndrome; Kenny-Caffey syndrome type 1 and 2; Mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes (MELAS) syndrome; Sanjad Sakati syndrome (SSS); Mitochondrial trifunctional protein (MTP) deficiency syndrome; Autosomal Dominant Hypocalcemia (ADH) 1 and 2; Pseudohypoparathyroidism 1A and 1B; Wilson's disease; hemochromatosis	Postoperative hypoparathyroidism Hypomagnesemia Hypermagnesemia Autoimmune polyendocrine syndrome type 1 (APS1) Blood transfusion (hemosiderosis) Radiation therapy Metastasis sclerotic "Hungry bone" syndrome Vitamin D deficiency Chronic kidney disease

Table 3. Causes of hypocalcemia (continued)

Causes not mediated by PTH	
Genetic	**Got**
Vitamin D dependent rickets (VDDR) types 1 and 2 Hypocalcemia vitamin D-resistant rickets (HVDRR) Osteopetrosis Maternal hyperparathyroidism	Malabsorption End stage liver disease Critical illness Acute pancreatitis Osteoblastic metastases Citrate (blood transfusion) Drugs: loop diuretics; phosphate; foscarnet; anti-convulsant; magnesium sulfate; calcitonin, bisphosphonates, denosumab; cinacalcet

PTH deficiency (low or low normal serum of PTH)

This occurs because of decreased PTH secretion (hypoparathyroidism), which can be caused by destruction of the parathyroid glands (postoperative or autoimmune), abnormal regulation of PTH production and secretion, or abnormal development of the parathyroid glands. Postoperative procedures are the most common cause of hypoparathyroidism.

Post surgery

Postoperative hypoparathyroidism is the most common form of this condition. This surgery can include parathyroidectomy thyroidectomy, laryngectomy, or radical neck surgery.[7] This condition can be temporary, that is, it heals in the first days-months after surgery. However, this condition can be permanent if it lasts more than 6 months after surgery.[3,8] Normal parathyroid glands consist of about 30% capillary cells. This makes the parathyroid glands very sensitive to interruption of the arterial blood supply or venous drainage, which can result from mechanical, thermal, or electrical injury during a thyroidectomy procedure. In this context, early measurement of serum calcium and PTH levels after neck surgery is a good predictor of permanent postoperative hypoparathyroidism.[1]

In addition, in other cases such as severe hyperparathyroidism with significantly elevated PTH levels before surgery and cases of tertiary hyperparathyroidism in renal disease, a sudden decrease in PTH levels after surgery can lead to severe hypocalcemia. This is due to excessive osteoblast activity, causing significant calcium uptake into the bones. This condition is called hungry bone syndrome.[3,9]

Hypomagnesemia day Hypermagnesemia

Hypomagnesemia is a relatively common cause of functional hypoparathyroidism, whereas hypermagnesemia is less common in everyday clinical practice. Magnesium deficiency causes hypocalcemia by interfering with PTH end-organ action and/or by inhibiting its secretion. Both disorders can cause a decrease in PTH secretion by the parathyroid glands, which is thought to be through stimulation of the Calcium Sensing Receptor (CaSR).[1,7,8]

Autoimmune

Hypoparathyroidism can occur because of an autoimmune process. Autoantibodies against the parathyroid glands are the main cause of autoimmune hypoparathyroidism which can be a manifestation of autoimmune polyendocrine syndrome 1 (APS1). The APS1 associated with hypoparathyroidism may be affected by other endocrinopathies or immune system-mediated disorders, such as Addison disease, mucocutaneous candidiasis, Graves' disease, hypogonadism, vitiligo, malabsorption (steatorrhea), pernicious anemia, and diabetes mellitus.[7]

Abnormal Parathyroid Gland Development

X-linked or autosomal recessive hypoparathyroidism causes abnormal development of the parathyroid glands. This condition can be associated with complex congenital syndromes such as the DiGeorge syndrome, Kearns-Sayre syndrome, Kenny-Caffey syndrome type 1 and 2, and others.[1,7]

Parathyroid gland destruction

This condition can also be caused by other, rare causes, namely infiltrative diseases of the parathyroid glands such as granulomatous disease, hemochromatosis, Wilson disease, or radiation impact. Human immunodeficiency virus (HIV) infection is also a rare cause of symptomatic hypoparathyroidism. Finally, mutation activation of calcium-sensing receptors (CaSR) can decrease the set point ofCaSR, thus causing hypoparathyroidism and hypocalcemia.[3]

High PTH levels

Absolute or relative vitamin D deficiency

Vitamin D deficiency can be caused by decreased intake or malabsorption, inadequate sun exposure, liver disease, kidney disease, and decreased conversion to its active metabolite (1,25-dihydroxy vitamin D). This can lead to decreased intestinal calcium absorption and bone resorption. The resulting hypocalcemia causes a compensatory increase in PTH secretion (secondary hyperparathyroidism). Severe vitamin D deficiency results in hypocalcemia, which is commonly associated with hypophosphatemia and high serum PTH levels.[1,3]

Chronic kidney disease

Chronic kidney disease (CKD) causes impaired excretion of phosphate and impaired hydroxylation of 25-hydroxyvitamin D to 1,25-dihydroxy vitamin D. This encourages PTH secretion, causing secondary hyperparathyroidism. However, due to impaired vitamin D metabolism and high phosphate levels, serum calcium will remain low even though PTH levels have increased.[3] Elevated phosphate levels result in hypocalcemia by complicating serum calcium and depositing it in bones and other tissues. Meanwhile, impaired vitamin D metabolism results in hypocalcemia by reducing calcium absorption in the digestive tract.[7]

Pseudohypoparathyroidism

Pseudohypoparathyroidism (PHP) is a genetic disorder characterized by unresponsiveness of target organs to PTH. This condition mimics a form of hypoparathyroidism due to hormone

deficiency (hormone-deficient forms of hypoparathyroidism). This condition is characterized by hypocalcemia and hyperphosphatemia, but PTH levels are increased.[1,3,7]

OTHER CAUSES

Pseudo hypocalcemia

Serum calcium is generally bound to proteins in the blood, especially albumin. Therefore, low albumin status can provide information that the total serum calcium level is also very low. In this state, ionized calcium levels are usually normal. Thus, a correction of adding 0.8 mg/dL to the serum calcium level for every 1 gram decrease of serum albumin below normal (4 g/dL) is recommended.[3]

Acidosis/alkalosis

The binding of calcium to albumin is dependent on serum pH. Thus, in conditions of severe acidosis, ionized calcium will increase and vice versa will decrease in conditions of severe alkalosis. There is no reliable correction factor to estimate this shift in ionized calcium levels. This is why direct measurement of ionized calcium is recommended in these cases to guide therapy.[3]

Acute pancreatitis

Hypocalcemia can be induced by disruption of the PTH-vitamin D axis in several conditions, such as acute pancreatitis. This condition occurs due to calcium deposition in the abdominal cavity because of ongoing inflammation. There is a process of saponification of calcium from the released fatty acids in acute pancreatitis.[1,3]

Severe sepsis/critical illness

Severe sepsis can cause hypocalcemia through mechanisms that are not clear. Impaired PTH secretion, dysregulation of magnesium metabolism, and impaired vitamin D (calcitriol) secretion have been identified as potential mechanisms of this condition. More recent reports have also shown hypocalcemia to be associated with severe COVID-19 infection.[3]

Drugs

All drugs that inhibit bone resorption used to treat hypercalcemia (eg, calcitonin, intravenous bisphosphonates, receptor activator of nuclear factor kappa B (RANK) or the RANK-L inhibitor denosumab) and calcimimetics cinacalcet or etelcalcitide Drugs used to treat hyperparathyroidism can also cause hypocalcemia.[7] Bisphosphonates and denosumab can inhibit osteoclastic bone resorption, which can lead to severe hypocalcemia in some cases. Simultaneously, taking these drugs can reduce vitamin D levels, which can also cause hypocalcemia. Patients taking this drug should check their calcium and vitamin D levels regularly.[3]

Cinacalcet is a calcimimetic agent that works by stimulating CaSR, thereby reducing PTH secretion. This drug is used in the treatment of primary and secondary hyperparathyroidism. Cisplatin, a chemotherapy drugs can also cause hypocalcemia via hypomagnesemia state. Foscarnet can also cause hypocalcemia by forming complexes with ionized calcium, thereby reducing ionized calcium levels.[3]

Massive citrate blood transfusion

Excessive transfusion of citrate blood products causes an acute and transient depletion of ionized calcium. This is because calcium binds to citrate, which is used as an anticoagulant in stored blood.[3,7]

Osteoblastic metastasis

As in the case of prostate cancer, metastatic processes can also cause hypocalcemia, through increased osteoblastic activity.[3,7] In this case, the patient had a history of goiter surgery in 1975. There were incision marks on the right and left sides of the neck. The patient's low PTH level (5.83 pg/mL) was suspected to be due to the removal of the parathyroid glands during the surgical removal of the goiter that year. This condition is temporary in most cases, but can become permanent if all 4 glands are removed without parathyroid gland autotransplantation.[3,9] In this case, it is predicted that the removal of the parathyroid glands will not be total, so that

at the start there is no significant decrease in PTH levels which causes a decrease in total calcium levels, or there is still a decrease in total calcium levels but there are no symptoms.

Impaired production and secretion of PTH from the remaining parathyroid glands can be caused by age-related decline in parathyroid cell function. In elderly patients, occurs impaired parathyroid cell function, decreased provitamin D production by the liver, impaired renal response to vitamin D activation, and increased osteoclast activity, resulting in hypocalcemia. In addition, patients have been found to have decreased magnesium levels which contribute to lower total calcium levels through decreased PTH secretion.

DIAGNOSIS

Clinical manifestations

Clinical manifestations of hypocalcemia can range from no symptoms to life-threatening symptoms such as seizures, heart failure or laryngospasm. In addition, clinical manifestations also depend on the degree of progression of hypocalcemia and its chronicity. The history and physical examination of the hypocalcemia patient should focus on identifying the symptoms present. This is because some symptoms may not be seen in some patients. In addition, it is also important to carry out provocation checks. Symptoms of hypocalcemia include[1,3,11] seizures, tetany, paresthesia, psychiatric manifestations (anxiety, depression or emotional lability), carpopedal spasms (Trousseau sign), tail sign, prolongation of the QTc interval on the ECG which in advanced circumstances can cause severe ventricular tachycardia (Torsades de pointes).[3,11]

Seizure is a life-threatening condition in association with severe hypocalcemia. A mechanism associated with the pathogenesis of seizures is that low calcium levels, through a modulatory effect mediated by CaSR signaling, can shift channels and surface charges. This can increase the influx of sodium through voltage-gated sodium channels and produce glutamate release with a secondary increase in neuronal cell activity, which may enhance epileptogenesis.[12,13]

Paresthesia is the most common clinical manifestation of chronic hypocalcemia, especially postoperative chronic hypoparathyroidism. Low serum calcium and PTH levels are hallmarks of this condition. Lack of PTH can increase urinary calcium excretion and high calcium x phosphate products can lead to ectopic calcification. Report from Underbjerg et al demonstrated that patients with postoperative hypoparathyroidism have a 4-fold increased risk of renal complications related to kidney calcification or injury.[15] Brain calcifications can also develop during chronic hypocalcemia states. This condition can play a role in the process of epileptogenesis.[16]

Table 4. Clinical manifestations of hypocalcemia.[1]

Organs/Systems	Acute	Chronic
Cardiovascular	QTc interval prolongation 2:1 atrioventricular block or atrioventricular block $2^{nd}/3^{rd}$ degree Hypotension Cardiomyopathy Heart failure	
Respiration	Laryngeal stridor, bronchospasm	
Nerves	seizures paresthesia (Tail sign and Trousseau sign) Tetanus Coma	Extrapyramidal disorders (Fahr's disease) Pseudotumor of the brain Neuropsychiatric manifestations
Kidney	Hypercalciuria	Decreased renal filtration rate Nephrocalcinosis
Ophthalmology		Cataract Corneal calcification Papilledema
Tooth		Changes in tooth morphology Tooth enamel hypoplasia
Dermatology		Alopecia Xeroderma

In this case, the patient experienced repetitive stiffness of the extremity muscles that could not be controlled by consciousness, as well as a history of fractures due to minor trauma. On physical examination found carpopedal spasm, without symptoms of severe hypocalcemia.

Supporting examination

Most cases of hypocalcemia are found based on clinical manifestations and appropriate laboratory tests. Examination of albumin, liver function, and coagulation parameters should be performed to assess for liver dysfunction and hypoalbuminemia. Examination of BUN and serum creatinine should also be done to determine kidney dysfunction.[2]

Other necessary laboratory tests are serum phosphate and magnesium. Impaired renal function is generally associated with increased serum phosphate levels. Assessment of serum magnesium is necessary in these patients because hypomagnesemia is a frequent cause of reduced PTH secretion.[1] In patients with hypocalcemia, measurement of serum albumin is essential to differentiate true hypocalcemia, which involves a reduction in serum ionized calcium with factitious hypocalcemia, which is defined as a decrease in total serum calcium, but not serum ionized calcium.[2] PTH levels should also be checked as early as possible. Vitamin D levels should also be measured if a deficiency is suspected. In patients with PTH deficiency, alkaline phosphatase levels tend to be normal or slightly decreased. However, these serum levels are often elevated in patients with osteomalacia and rickets. If a diagnosis of osteomalacia is suspected, a bone biopsy can determine the final diagnosis.[2] Other biomarkers can also

provide information such as serum lipase examination in suspected acute pancreatitis.[3] An ECG examination must be carried out to determine whether there is a QTc interval prolongation. If there is, then it is a risk factor for malignant arrhythmias.[3]

Necessary imaging studies include x-ray or computed tomography (CT) scan. On x-ray examination, abnormalities associated with rickets or Looser Zone on osteomalacia may be found, which is highly pathognomonic and can be observed on the pubic ramus, upper femoral bone, and ribs. X-ray examination may also reveal osteoblastic metastases from certain tumors (eg: breast, prostate, lung cancer). CT scan of the head may show calcification of the basal ganglia, which is associated with extrapyramidal neurologic symptoms.[2]

In this case, decreased levels of total calcium, magnesium, PTH, and total vitamin D,25-OH were found, without impaired liver and kidney function. On radiological examination, also found the impression of osteopenia which is suspected of being the cause of the patient's previous fracture. The overall results strengthen the patient's diagnosis, that the hypocalcemia that occurs is mainly due to decreased PTH levels.

Hypocalcemia Diagnostic Algorithm

Assessment of medical history, family, pharmacology, as well as physical examination, is very important in patients with hypocalcemia (Figure 6). Identification of drugs that induce hypocalcemia is also important to know. In this context, careful evaluation needs to be carried out on each patient. Below is an algorithm for diagnosing hypocalcemia.

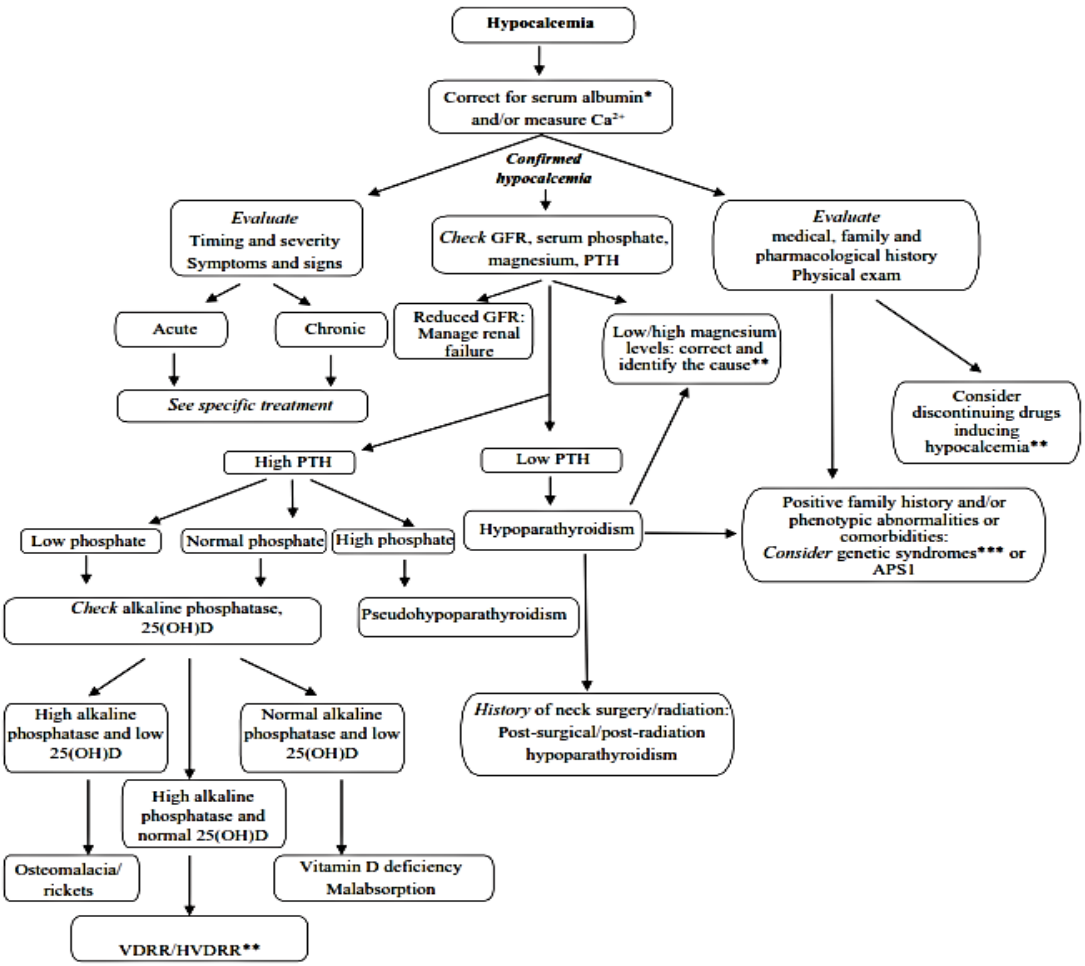

Figure 6. Diagnostic flowchart and differential diagnosis of hypocalcemia

In this case, the flow of diagnosis begins with an exploration of the signs and symptoms experienced by the patient. Patients with a history of fracture due to minor trauma, accompanied by recurrent muscle rigidity, direct the clinician to check the total calcium level. Total calcium levels were found to be low even after corrected with serum albumin levels. No impaired liver, kidney, and urinary calcium function was found, and an impression of osteopenia was found on radiological examination, causing plasma magnesium, vitamin D, and intact PTH levels to be examined. Low PTH levels with a history of thyroidectomy and low vitamin D levels suggest hypoparathyroidism as the diagnosis.

Treatment

Treatment of hypocalcemia can vary based on the severity, degree, and underlying cause of hypocalcemia. In acute and chronic hypocalcemia, the goals of treatment are to increase serum calcium within the normal range and to treat or minimize symptoms. Identifying the etiology of hypocalcemia is critical to establishing optimal management (Table 5).[3,17]

Table 5. Treatment options for hypocalcaemia.[17]

Agent	Dosage Information	Notes
Acute Management		
Parenteral Calcium Infusion		
Calcium chloride	10 mL ampoule (272 mg elemental calcium) diluted in 200 mL 5% dextrose in water given intravenously over 30-90 minutes	CaCl solutions can irritate adjacent tissues if extravasation occurs, so these agents should be administered via a central venous catheter, if possible.
Calcium gluconate	10 mL ampoule (93 mg elemental calcium); 1-3 ampoules diluted in 200 mL of 5% dextrose or normal saline given intravenously over 30-90 minutes	Therapy should be individualized and guided by frequent determinations of serum ionized calcium
Calcium gluconate infusion	10 ampoules (930 mg elemental calcium) diluted in 1 L dextrose 5% in water	The infusion rate should be 1-3 mg/kg/hour to maintain serum calcium levels within the targeted range
Long Term Management		
Calcium Supplements		
Calcium carbonate	40% elemental calcium by body weight	Best absorbed in small doses, multiple doses with food, and on an acidic stomach.
Calcium citrate	21% elemental calcium by body weight	The preferred option for patients with achlorhydria
Vitamin D Preparation		
D_2 (ergocalciferol) D_3 (cholecalciferol)	2000-100,000 IU once a day; onset action 10-14 days; offset action 14-75 days	The wide dosage range reflects the use of these agents in a variety of disorders. Careful attention to serum levels of calcium, phosphorus and creatinine is required for safe use
25-Hydroxyvitamin D_3 (calcifediol)	20-200 µg daily; onset action 5-10 days; offset action 14-75 days.	This drug is used in cases of liver failure when renal function is intact to ensure 1-alpha hydroxylation is available to activate this metabolite.
Dihydrotachysterol	0.2-1 mg once a day; onset action 4-7 days; offset action 7-21 days	Active D metabolite that does not require renal conversion
1α(Alpha)-hydroxyvitamin D_3 (alfacalcidol)	0.5-3 µg daily; onset action 1-2 days; offset action 5-7 days.	Converts rapidly to active 1,25-dihydroxyvitamin D3live

● 1,25-Dihydroxyvitamin D_3 (calcitriol)	● 0.25-1 µg once or twice daily; onset of action 1-2 days; offset action 2-3 days	● Active D metabolite that does not require renal conversion - agent of choice
● Thiazide diuretic		
● Hydrochlorothiazide ● Chlorthalidone	● 25-100 mg daily ● 25-100 mg daily	● Administered concomitantly with a low sodium diet (80-100 mmol per day) to increase renal calcium retention. Hypokalemia and hyponatremia are side effects of using this drug.

In this case, the patient was given calcium gluconate 3 x 1000 mg IV and vitamin D supplementation with calcitriol 1 x 0.5 mg po. The target of intravenous calcium supplementation is to pass through the acute phase during hospitalization, and it is planned to continue with the administration of 3x500mg po calcium carbonate as a long-term treatment. Calcitriol supplementation is given by monitoring total vitamin D, 25-OH levels periodically every 3-6 months. Because the patient's hypoparathyroidism is permanent, the provision of supplementation is not time-limited, only based on periodic monitoring for dose adjustments.

Parenteral administration of calcium is recommended for patients with severe symptoms, evidence of QTC prolongation, or in asymptomatic patients who have had acute hypocalcemia for a short time. Parenteral infusion of calcium gluconate or calcium chloride is indicated when rapid correction of serum calcium levels is required. Although calcium chloride provides nearly four times more elemental calcium than an equivalent amount of calcium gluconate, calcium gluconate is the salt of choice most often for administration in the peripheral vein. This is because calcium chloride can cause tissue necrosis if local extravasation occurs. Initially, 1 g calcium chloride (272 mg calcium) or up to 3 g calcium gluconate (279 mg calcium) may be given over 30-90 minutes to control symptoms (Table 3). However, a single intravenous injection of calcium is generally only effective for a few hours. Continuous calcium gluconate infusions will be necessary to fully control symptoms and achieve a safe and stable ionized calcium level, which is usually above 1.0 mmol/L.[17]

In patients receiving parenteral calcium replacement, serum ionized calcium levels should be measured every 1-2 hours until the patient's condition stabilizes. Then, these serum levels should be measured every 4 to 6 hours for monitoring of therapy. Recurrence of symptoms of hypocalcemia requires an increase in the infusion rate, but it should always correlate with the ionized calcium level. The rate of infusion should not exceed 1-2 mg/min because of the potential risk of cardiac arrhythmias associated with rapid calcium infusion. Alkaline solutions such as those containing bicarbonate and phosphorus should be avoided in the same infusion stream to prevent precipitation of calcium salts. Oral calcium and vitamin D should be started as soon as possible, and the intravenous calcium infusion should be tapered off slowly (over 24-48 hours or longer), while oral therapy should be further adjusted.[3,17]

If the symptoms of hypocalcemia are mild such as paresthesia or are asymptomatic, then oral calcium supplementation can be given. Calcium carbonate (40% elemental calcium) or calcium citrate (21% elemental calcium) are the most used calcium preparations. The aim of this preparation is to provide 1500 to 2000 mg of elemental calcium daily in 2 to 3 divided doses. Calcium carbonate requires an acidic medium for its absorption, so administration of this drug should be avoided in patients taking this class of proton pump inhibitor (PPIs) drugs. Vitamin D supplementation is often recommended to be given together with calcium to promote better absorption.[3]

Treatment of chronic hypocalcemia must be adjusted to the underlying etiology and almost always relies on oral calcium supplements, vitamin D, and (sometimes)

thiazide diuretics. Although calcium supplementation of all types can be used for hypocalcemia, the most efficient supplementation is in the form of carbonate or citrate salts. A reasonable initial dose that can be given is 0.5-1 g of elemental calcium, two or three times daily. Subsequent doses may be adjusted based on patient compliance, side effects, and clinical goals. Calcium carbonate should be taken during or after meals to ensure optimal absorption. Calcium carbonate can interfere with the absorption of other drugs, for example L-thyroxine, so special instructions should be given to the patient in this case. Calcium citrate also has the advantage of optimal absorption regardless of food intake.[1,17] Vitamin D deficiency is common in most clinical scenarios leading to hypocalcemia conditions. Vitamin D supplementation should be given in this condition. In subjects with good renal function, ergocalciferol (vitamin D_2) or cholecalciferol (vitamin D_3) can be selected to give. Patients who choose to avoid consumption of animal products should be aware that cholecalciferol is an animal product. The recommended regimen to achieve a 25-hydroxyvitamin D concentration of 25-30 ng/mL is giving 50,000 IU vitamin D weekly for 8-12 weeks. Ergocalciferol 50,000 IU daily can be administered safely for 5 days at the start of therapy in patients with severe vitamin D deficiency. Because of its long-term storage in fat, this form of vitamin D has a long tissue half-life (up to months) and toxicity may be difficult to anticipate and/or correct quickly. Hypercalcemia (if it occurs) can persist for weeks after vitamin D supplementation is discontinued. For this reason, administration of calcitriol (although the cost is greater than vitamin D), this drug is preferred by many doctors because its fast onset and offset work.[1,3,17]

Serum calcium, phosphorus, and creatinine along with measurements of urinary calcium excretion should be monitored regularly to avoid toxicity from calcium and vitamin D therapy. In patients with hypercalciuria (urine excretion of calcium > 300 mg/day), thiazide diuretics (along with a low salt diet) can be used to increase urinary calcium retention. The effective dose of hydrochlorothiazide is generally between 50 and 100 mg/day. Patients should be monitored for changes in serum kalium, natrium and magnesium. Soft tissue calcification and nephrocalcinosis can be prevented by keeping the serum calcium phosphate product below 55 mg/dL. Hyperphosphatemia can be managed by reducing the patient's intake of phosphate-rich foods (eg, meat, eggs, and dairy products) and if necessary, by oral phosphate binders (oral phosphate binders).[17]

Most patients will develop hypocalcemia following a thyroidectomy or parathyroidectomy due to hyperparathyroidism, which is usually transient. Prophylactic treatment with calcium after surgery is recommended. Administration of calcium can prevent severe symptomatic hypocalcemia in most cases. Calcium levels should be monitored closely after surgery and the calcium dose gradually reduced as indicated.[3]

Hypocalcemia in CKD is generally the result of a lack of vitamin D. This condition can be corrected by supplementing it with vitamin D or its active metabolite, calcitriol. Patients with significant vitamin D deficiency should be given ergocalciferol 50,000 units weekly for 8 to 12 weeks followed by cholecalciferol at a lower dose, ie, 1000 to 5000 units daily.[3]

PTH Linked to Vitamin D Metabolism

Calcium is important for many physiological processes, including blood clotting, platelet adhesion, neuromuscular activity, endocrine and exocrine secretory functions, and bone metabolism. The adult human body contains about 1000 g of calcium. About 40-50% of calcium in the blood is bound to plasma proteins, especially albumin. An equivalent amount is ionized or "free" and the remainder is complexed into phosphate, citrate, bicarbonate, and other ions. Only free calcium is physiologically active. Thus, it is a better indicator of the functional status of calcium metabolism than the total calcium level. The

normal range for ionized serum calcium concentration is 1.20-1.30 mmol/L.[17]

Regulation of ionized calcium concentration can be achieved mainly by the coordinated action of PTH and calcitriol at the three main sites of calcium transport, namely intestine, bone, and kidney (Figure 7). PTH and Vitamin D play important roles in calcium and phosphate homeostasis and the development and maintenance of healthy bones. PTH is the main stimulator of vitamin D synthesis in the kidney, while vitamin D provides negative feedback on PTH secretion. The main function of PTH is to maintain serum calcium within the normal range. PTH has a reciprocal effect on phosphate metabolism. Conversely, vitamin D has a stimulatory effect on calcium and phosphate homeostasis, which plays a key role in providing sufficient minerals for normal bone formation.[18]

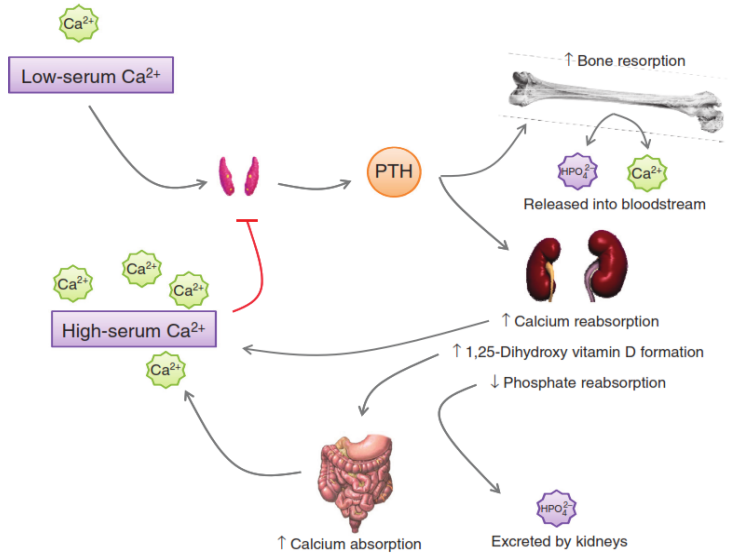

Figure 7. Regulation of Serum Calcium by PTH.[18]

Calcium-sensing receptors on the parathyroid cell surface constantly influence the extracellular ionized calcium concentration. Figure 7 describes the levels of Ca^{2+} Low serum levels will stimulate the synthesis and release of PTH from the parathyroid glands. PTH exerts effects on several target organs. The first organ is the skeleton, in which PTH enhances osteoclast-mediated bone resorption. This will lead to the release of Ca^{2+} and $HPOs_4^{2-}$ into the bloodstream. The next organ is the kidney, where PTH will increase Ca reabsorption^{2+} into the extracellular space of the distal convoluted tubule and decrease HPO_4^{2-} reabsorption from the proximal convoluted tubule. In addition, PTH also increases the activity of renal 1α-hydroxylase, which increases the conversion of 25-hydroxyvitamin D to its active form (calcitriol). Vitamin D is activated in the kidney by 1α-hydroxylase, causing increased Ca absorption^{2+} from the intestines. Ca^{2+} The recovered serum provides a negative feedback signal to the parathyroid glands, which stops PTH release.[17,18]

Vitamin D can be synthesized in the skin by breaking down the B ring of cholesterol through the medium of ultraviolet (UV) light. Animal sources of vitamin D are D3, and plant sources of vitamin D are D2. The two forms are basically equivalent in terms of biological activity. The clinical consequences of vitamin D deficiency are rickets/osteomalacia (lack of adequate minerals and osteoid), osteoporosis (reduced bone mass, reduced mineral and osteoid), secondary hyperparathyroidism, as well as muscle pain, weakness, bone pain, and fractures.[17]

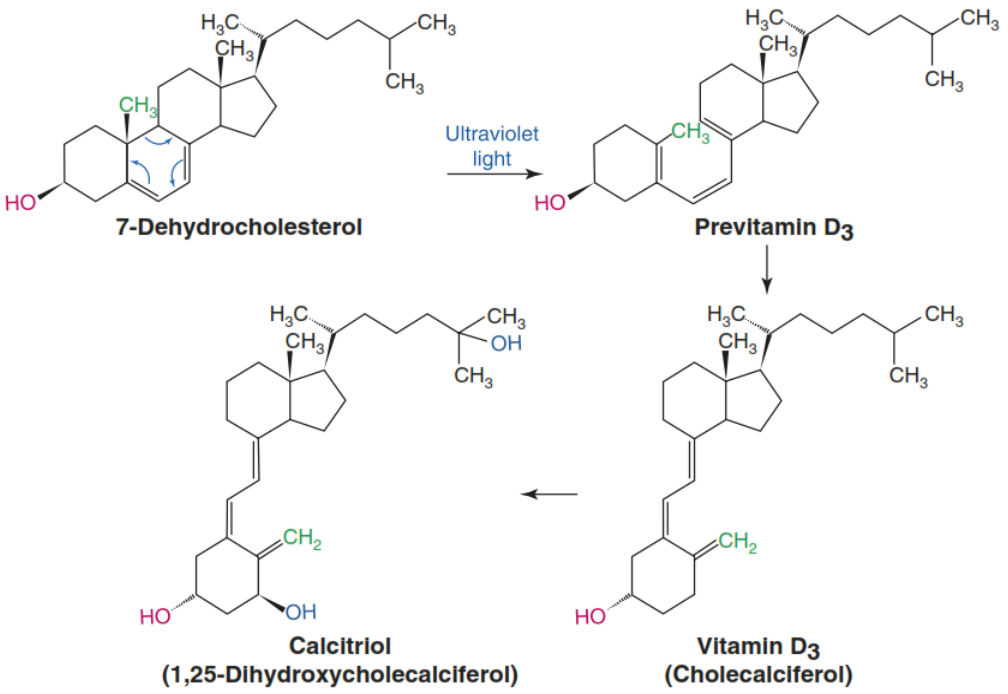

Figure 8. Vitamin D synthesis[19]

CONCLUSION

Hypocalcemia is one of the most common electrolyte disturbances and requires careful diagnosis and management. Some of the main factors that regulate calcium homeostasis in the body are PTH and vitamin D. Postoperative procedures on the neck (specifically: goiter) are the most common cause of hypoparathyroidism. In addition, autoimmune diseases and abnormal development of the parathyroid glands can be causes of hypoparathyroidism. Severe vitamin D deficiency results in hypocalcemia, which is associated with hypophosphatemia and hyperparathyroidism. Treatment of hypocalcemia can vary based on the severity and the underlying cause. The goal of treating hypocalcemia is to increase serum calcium within the normal range and to treat or minimize the symptoms it causes. Identifying the etiology of hypocalcemia is critical to establishing optimal management.

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CASE REPORT

Adrenal Cortical Adenoma Resulting from Congenital Adrenal Hyperplasia Managed with Unilateral Laparoscopic Adrenalectomy: a Case Report

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ABSTRACT

Congenital adrenal hyperplasia (CAH) is an autosomal recessive disorder resulting from mutations in genes encoding enzymes involved in cortisol biosynthesis. Over 90-95% of cases are caused by 21-hydroxylase deficiency, with an incidence of 1:10,000-1:20,000 among Caucasians. This condition leads to cortisol deficiency, causing a loss of negative feedback in the pituitary gland and subsequently increased secretion of adrenocorticotropic hormone (ACTH), which in turn stimulates the production of adrenal androgens and adrenal hyperplasia. We report a 31-year-old female with classic CAH of the simple virilizing subtype and a history of genital reconstruction due to external genital ambiguity. She received glucocorticoid therapy and spironolactone to block androgen receptors. As a result, hirsutism decreased, and MRI evaluation of the adrenal glands revealed a reduction in size compared to pre-treatment (bilateral adrenal gland enlargement). No disturbances due to mineralocorticoid receptor blockade from spironolactone administration were found. In the fourth-year MRI evaluation, the left adrenal gland was larger than normal, while the right was within normal limits. A functional left adrenal gland tumor T1N0M0 was concluded, and a left laparoscopic adrenalectomy was decided upon. The patient consented to the procedure one year later. Laparoscopic adrenalectomy of sinistra was successfully performed with histopathologic examination revealed adrenal cortical adenoma. Monitoring and evaluation of clinic visits, we concluded that unilateral adrenalectomy cannot replace routine medication, but can reduce the dose requirement. Currently, the patient is still under regular control and supervision to evaluate the long-term results of the procedure whether there is a risk of adrenal crisis, whether it can overcome the effects of hyperandrogenism, and whether there is an adrenal rest tumor.

Keywords: *Congenital adrenal hyperplasia, hyperandrogenism, functional adrenal tumor, laparoscopic adrenalectomy, adrenal cortical adenoma*

INTRODUCTION

Congenital adrenal hyperplasia (CAH) comprises a group of seven inherited autosomal recessive disorders, resulting from mutations in genes encoding enzymes involved in the cortisol biosynthesis pathway, including 21-hydroxylase (21OH), 11β-hydroxylase (11βOH), 17α-hydroxylase (17OH), 3β-hydroxysteroid dehydrogenase type 2 (3βHSD2), steroidogenic acute regulatory protein (StAR), P450 cholesterol side-chain cleavage enzyme (SCC), and P450 oxidoreductase (POR).1 Over 90-95% of CAH cases are caused by 21-hydroxylase deficiency, with an incidence of 1:10,000-1:20,000 in the Caucasian population.[1,2]

Deficiency of 21-hydroxylase leads to cortisol deficiency, resulting in the loss of negative feedback in the hypothalamus-pituitary-adrenal axis, thereby increasing adrenocorticotropic hormone (ACTH) secretion, which in turn stimulates adrenal androgen production and causes adrenal hyperplasia.3 CAH patients face two main issues: adrenal insufficiency and androgen excess. Adrenal insufficiency can lead to life-threatening adrenal crises, while androgen excess can cause genital abnormalities in 46 XX neonates, abnormal growth patterns (tall children, short adults), precocious puberty, virilization in females, and infertility in both males and females.[2,3,4]

CAH management involves glucocorticoid therapy aimed at reducing androgen excess and avoiding iatrogenic glucocorticoid excess. The challenge lies in balancing glucocorticoid dosages; insufficient glucocorticoid dosages pose a risk of adrenal crisis, while excessive dosages can result in short stature, obesity, hypertension, metabolic syndrome, osteoporosis, and Cushing's syndrome.[3]

Bilateral adrenalectomy can reduce the risk of virilization in females and potentially allow for a reduction in glucocorticoid dosage; however, the 2018 European Endocrine Society guidelines do not recommend this procedure due to the risk of adrenal crisis and adrenal rest tumors.[5] In this case report, we present a case of CAH with unilateral adrenalectomy, aiming to investigate whether this intervention can reduce glucocorticoid dosage and whether it poses a risk of adrenal crisis.

CASE ILLUSTRATION

A 31-year-old female patient was scheduled for a left laparoscopic adrenalectomy by the urology department. According to the patient's mother, she exhibited no abnormalities at birth and appeared as a typical female infant. However, during second grade, abnormalities in her genitalia began to manifest, including the appearance of an enlarging mass and fusion of the labia, resulting in an increasingly male-like appearance. Karyotype analysis confirmed her as a female (46 XX), and corrective surgery was performed during her third grade. Subsequently, her voice began to deepen, and her body stature was larger than her peers. By middle school, her voice resembled that of an adult male, and during high school, she developed excessive body hair, facial hair requiring routine shaving, and hair loss in the frontal region of the scalp, leading to partial baldness. The patient had never experienced menstruation.

Further examinations were conducted after she completed her college education and began working (around 2018/2019). She was diagnosed with congenital adrenal hyperplasia and was prescribed hydrocortisone (20 mg twice daily) and spironolactone (100 mg twice daily). While the frequency of shaving facial hair decreased after commencing medication, the patient did not experience menstruation. An evaluation of the MRI revealed a reduction in adrenal size compared to the pre-medication MRI, although the left adrenal remained larger than the right. The patient consulted the obstetrics and gynecology department for primary amenorrhea and was prescribed a combination of cyproterone acetate (2 mg) and ethinyl estradiol (0.035 mg). Following two months of medication, the patient experienced menstruation once but discontinued the medication during the COVID-19 pandemic, resulting in the cessation of menstruation. The

2022 MRI evaluation revealed a larger left adrenal gland compared to the right, and the urology department diagnosed the patient with a functional left adrenal tumor T1N0M0. The patient initially declined the laparoscopic adrenalectomy but consented to the procedure in early 2023.

Physical examination showed the patient in generally good health and fully conscious, exhibiting obesity, a BMI of 35.9 kg/m2, and a male-like body stature and voice. Blood pressure was 130/80 mmHg, pulse 90 beats/min, respiratory rate 20 breaths/min, and body temperature 36.6°C. Alopecia was noted in the fronto-occipital region, facial hair was not dense (routinely shaved), and moon face was absent. No thyroid or lymph node enlargement was observed in the neck. Heart and lung examinations were within normal limits, and no pink striae or organomegaly were detected in the abdomen. The extremities examination was within normal limits.

Routine blood tests, liver and renal function tests, blood glucose, and electrolyte levels were within normal limits. Chest X-ray revealed no pulmonary metastases and a normal-sized heart. Lower abdominal ultrasound showed uterine hypoplasia, and contrast-enhanced abdominal MRI indicated a larger left adrenal gland in comparison to the right.

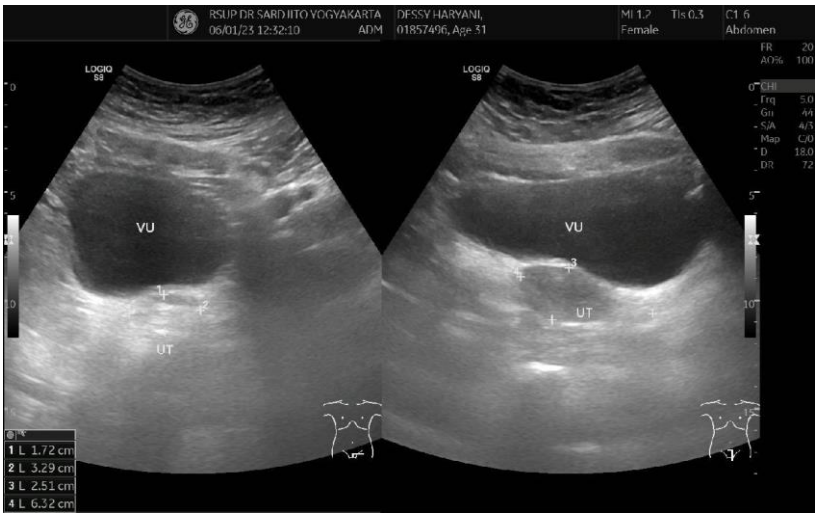


Figure 1. Ultrasound examination of the lower abdomen

Obtained uterine hypoplasia with an anteroposterior x lateral x craniocaudal diameter of 1.72 x 3.29 x 6.32 cm. The normal echo structure did not show a mass.

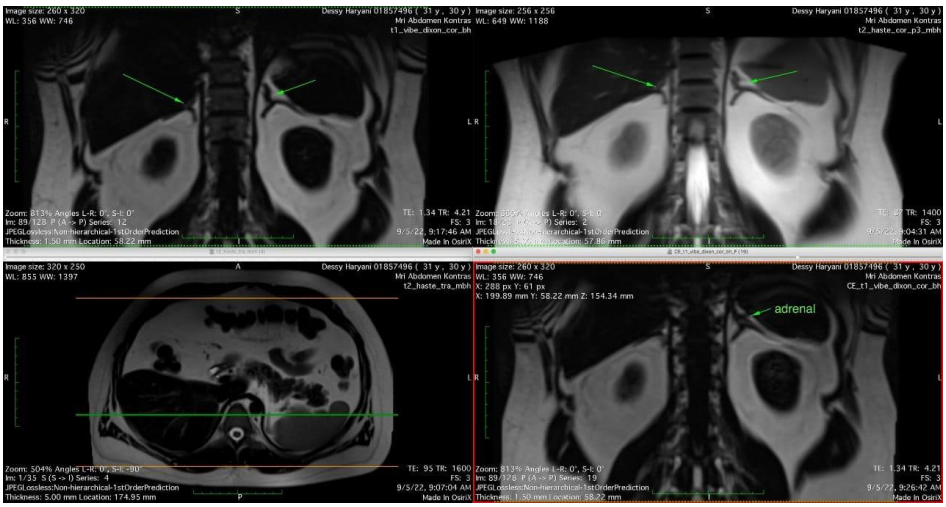


Figure 2. Abdominal MRI examination with contrast

The laterolateral and anteroposterior sizes of the left adrenal were larger than normal, and the size of the right adrenal was within normal limits. Left adrenal: length CC 3.08 (N:4-6 cm), x LL 4.18 (N:2-3 cm), x AP 3.30 (N:3 cm), thickness (limb thickness) 0 .4 (N:<0.6 cm) and normal location, no iso/hypo/hyperintense lesions seen. Right adrenal: length CC 3.3 (N:4-6 cm), x LL 2.62 (N:2-3 cm), x AP 2.2 (N:3 cm), thickness (limb thickness) 0 .9 (N:<0.79 cm) and normal location, no iso/hypo/hyperintense lesions seen.

Monitor evaluation of 17-OHP (17-hydroxyprogesterone) examination results at diagnosis of 13.88 ng/mL (4/12/2018), then successively 138.89 ng/mL (12/6/2019), and 10.14 ng/ mL (6/7/2020) with normal range values for the follicular phase <1.85 ng/mL, and the luteal phase <2.85 ng/mL. A summary of laboratory examination results from August 2018 to November 2022 can be seen in the following table.

Table 1. Summary Of Hormone And Biochemical Test Results

Lab	31/8/18	3/9/18		13/8/18	25/9/18	12/11/18	21/11/18	4/12/18	12/2/19	19/3/19	16/4/19	28/5/19	4/2/19	17/2/20	27/5/20	6/7/20
Testosteron	6,0			6,17		5,85			3,73	4,59	3,76	0,65	0,03	1,12	0,99	
Progesteron	2,3														4,2	1,1
Estradiol	65,73														48,54	44,92
LH	3,1						4,9									
FSH	2,6						4,2									
BUN		8				12		12,7								
Cr		1,07				1,07		0,7								
Prolactin					1,3		19,6									
fT4						2,29										
TSH						2,3										
Na								137					138			
K								4,76					4,4			
Cl								105					103			
GDS										89						
Cortisol														5,2	16,4	
Lab	19/10/20	21/1/21		15/4/21	1/7/21	3/11/21	6/12/21	12/1/21	27/1/22	16/3/22	20/5/22	17/6/22	29/7/22	29/8/22	2/9/22	30/11/22
Testosteron	1,63	1,34		1,51	0,41	2,33		2,48		2,66	2,45	2,41	2,88	1,15		1,10
Progesteron														13,8		
Estradiol		63,06		66,61	32,0											
LH																
FSH																
BUN		9,3							5,72						8	
Cr		1,0							0,96						0,93	
Prolactin																
fT4																
TSH																
Na						137										130
K						4,44										4,2
Cl						106										98
GDS		158														90
Cortisol							5,9									

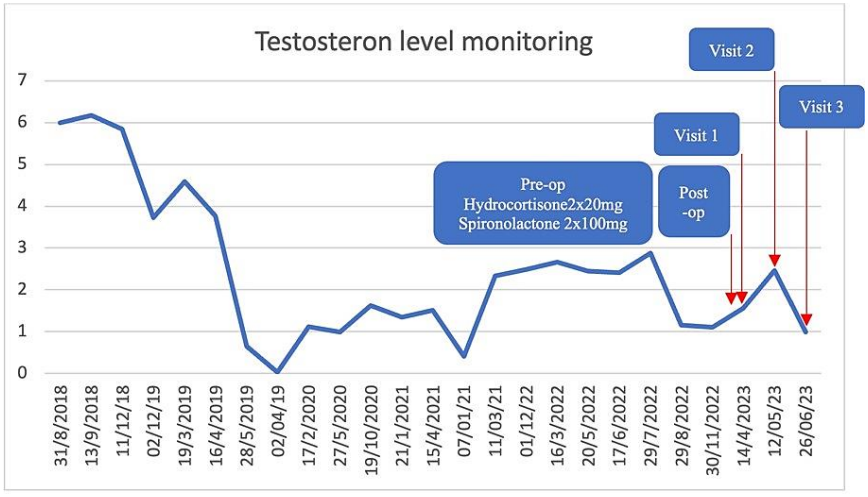
FSH 4-25 IU/L mid cycle peak, LH 10-75 IU/L mid cycle peak, prolactin < 20 ng/mL (425 µg/L), TSH 0,5-5,0 mIU/L, fT4 0,7-1,9 ng/dL, cortisol pagi 3,7-19,4 sore 2,9-17,4 µg/dL, testosterone 0,08-0,60 ng/mL, progesterone 0,2-2,7 ng/mL, estradiol 12,0-4300,0 pg/mL.

A summary of the radiological findings included the following: Lower abdominal ultrasound (6/8/2018) revealed uterine hypoplasia; contrast-enhanced head CT (6/9/2018) showed no signs of micro- or macroadenomas in the pituitary gland; cerebral MRI with contrast (14/11/2018) revealed a normal pituitary gland and sella turcica; contrast-enhanced pelvic MRI (11/12/2018) showed a smaller than normal uterus in an anteflexed and anteverted position, with normal-sized and normal-volume ovaries; abdominal MRI (11/12/2018) revealed bilateral adrenal gland enlargement, predominantly on the left side; contrast-enhanced abdominal MRI (28/1/2022) showed a reduction in adrenal gland size compared to pre-therapy, with the left gland larger than the right; contrast-enhanced abdominal MRI (5/9/2022) indicated an increased laterolateral and anteroposterior size of the left adrenal gland compared to the normal range, with the right adrenal gland size within normal limits.

The patient was diagnosed with a functional left adrenal tumor T1N0M0 resulting from congenital adrenal hyperplasia with hyperandrogenism and was treated with hydrocortisone (20 mg twice daily) and spironolactone (100 mg twice daily). A clinical conference held on February 28, 2023, involving the urology surgery department, internal medicine endocrine division, obstetrics and gynecology endocrine division, and radiology department, decided to perform a left laparoscopic adrenalectomy.

The left laparoscopic adrenalectomy was successfully performed, and histopathological examination revealed an adrenal cortical adenoma. The patient was stable postoperatively, showing improved conditions, with electrolyte and blood glucose levels within normal limits. The patient was discharged with hydrocortisone and spironolactone was discontinued.

At the time of the first clinic visit, two weeks after surgery, she reported that one week postoperatively, had spontaneous menstruation without the need for medication, and laboratory evaluations three weeks postoperatively revealed testosterone levels of 1.56 ng/mL, estradiol levels of 45.7 pg/mL, and progesterone levels of 1.46 ng/mL. At the second clinic visit, one and a half months after surgery, testosterone levels increased sharply compared to before, amounting to 2.46 ng/mL. So we decided to re-administered the routine medication but at a lower dose which were hydrocortisone 2x10mg and spironolactone 2x75mg. At the third clinic visit, one month after the second visit, we found testosterone levels decreased to 0.99ng/mL. We continued the routine medication at lower dosage. So we found that unilateral adrenalectomy in this case was not able to replace the routine medication, but was able to lower the dose requirement.



Post-op to visit 1: hydrocortisone/spironolactone stop; Visit 2and 3: hydrocortisone 2x10mg, spironolactone 2x75mg

Figure 3. Summary of testosterone levels (ng/mL) pre- and post-procedure

DISCUSSION

The clinical presentation of congenital adrenal hyperplasia (CAH) can generally be divided into three categories: classic CAH, non-classic CAH, and cryptic CAH. Classic CAH is further divided into salt-wasting and simple virilizing subtypes. Mutations in the CYP21A2 gene, which encodes the 21-hydroxylase enzyme, cause a blockade in cortisol and aldosterone synthesis. This blockade leads to increased secretion of ACTH, resulting in the accumulation of cortisol precursors, which are then converted to adrenal androgens. The cardinal sign of classic CAH or severe virilizing in female infants is the abnormal development of external genitalia, characterized by virilization.

Complete mutations that inactivate the CYP21A2 gene result in salt-wasting classic CAH, causing severe aldosterone deficiency and even life- threatening adrenal crisis within two weeks post-birth if not detected and managed properly. This condition accounts for 75% of classic CAH cases. In simple virilizing CAH, there is still 1-2% residual activity of CYP21A2, which is sufficient to maintain aldosterone production, thus avoiding crisis. This condition comprises 25% of classic CAH cases. In non-classic CAH, CYP21A2 activity is approximately 50%, preventing adrenal crisis, and only causing a partial glucocorticoid deficiency without external genital abnormalities in female patients. Mild hyperandrogenism with mild or no symptoms is observed. Cryptic CAH is asymptomatic and can only be detected by genetic testing.[1,5] According to this classification, the patient in this case, falls under classic CAH, simple virilizing subtype, as there is external genital ambiguity without adrenal crisis, and karyotype examination confirms the patient as female (46 XX).

Deficiency in the 21-hydroxylase enzyme activity encoded by CYP21A2 results in a decrease in glucocorticoid and mineralocorticoid synthesis, leading to an increase in the precursor 17-OHP. The increased precursor levels are used for diagnostic confirmation. Genotype testing is not performed as a first-line diagnosis due to the complexity of the CYP21A2 locus. A 17-OHP level above 1000 ng/dL (>30 nmol/L = 10 ng/mL) confirms CAH.1,4,5 The patient's 17-OHP level was 13.88 ng/mL (=1388 ng/dL), confirming CAH.

CAH patients face two problems: adrenal insufficiency and androgen excess. Therefore, the aim of therapy is to replace the deficient hormones and manage androgen excess. The current standard therapy for CAH is glucocorticoid therapy, with a target 17-OHP level of < 36 nmol/L (1200 ng/dL). The challenge lies in determining the appropriate glucocorticoid dosage to achieve a balance between cortisol replacement and androgen excess control. Insufficient glucocorticoid dosage can lead to adrenal crisis and symptoms of chronic cortisol deficiency (fatigue, weakness, nausea, loss of appetite, dizziness, hypotension, weight loss), as well as uncontrolled androgen excess effects (hirsutism, acne, menstrual disorders, baldness, infertility, precocious puberty, clitoromegaly).

Excessive glucocorticoid dosage poses risks of developing a cushingoid appearance, weight gain, central obesity, metabolic syndrome, osteoporosis, insomnia, and increased appetite. Additionally, patients are prone to mental health disturbances such as anxiety, depression, alcohol abuse, and even suicide risk.[3,4,5] The patient in this case received routine hydrocortisone and spironolactone therapy. The addition of spironolactone was due to its ability to block androgen receptors.[6] After initiating the routine therapy, the patient reported a decrease in the frequency of shaving facial hair, a reduction in testosterone levels, and a decrease in adrenal gland size on MRI compared to pre-treatment. However, spironolactone also has anti-aldosterone effects by blocking mineralocorticoid receptors in addition to androgen receptor blockade.[6] As a result, patients need to be monitored for adrenal crisis and electrolyte imbalances (hyponatremia, hyperkalemia). In this patient, there was no concern regarding the blockade of mineralocorticoid receptors, as electrolyte levels remained within normal limits.

Testosterone levels tended to decrease compared to pre-treatment levels but still fluctuated. Although the 17-OHP evaluation initially met the target within the first two years of routine therapy, subsequent evaluations could not be performed due to financial constraints, making it unclear whether the 17-OHP target was maintained in the past three years. MRI evaluation of the adrenal glands showed a reduction in size compared to pre-treatment; however, the left adrenal gland was larger than normal. The patient's weight also increased (BMI 39.5 kg/m^2), suspected to be due to excessive glucocorticoid dosage, though no signs of Cushing's syndrome were present. Therefore, the decision was made to perform a left laparoscopic adrenalectomy (unilateral). According to the 2018 European Endocrine Society recommendations, bilateral adrenalectomy is not recommended. While short-term improvements have been demonstrated, long-term problems may arise, such as the risk of adrenal crisis if the patient is non-compliant with glucocorticoid replacement therapy and the inability to fully address hyperandrogenism due to the occurrence of adrenal rest tumors in the testes, ovaries, or retroperitoneal region.[5]

Authors found that unilateral adrenalectomy in this case was not able to replace the routine medication, but was able to lower the dose requirement. The patient continues to attend routine follow-up appointments and remains under observation to evaluate the long-term outcomes of the surgery, including the risk of adrenal crisis, the management of hyperandrogenism effects, and the possibility of adrenal rest tumor occurrence.

CONCLUSION

We found that unilateral laparoscopic adrenalectomy in the case of adrenal cortical adenoma resulting from congenital adrenal hyperplasia was not able to replace the routine medication, but was able to lower the dose requirement. Long-term evaluation is still needed to evaluate the outcomes of the surgery, including the risk of adrenal crisis, the management of hyperandrogenism effects, and the possibility of adrenal rest tumor occurrence.

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CASE REPORT

A 59-year-old man with Riedel's Thyroiditis, Initial Suspicion of Thyroid Cancer and Improved with Tamoxifen and Corticosteroid Therapy

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ABSTRACT

Riedel's thyroiditis is a rare fibrotic condition involving damage to the thyroid gland and infiltration of surrounding structures. Synonyms of Riedel's thyroiditis include Riedel's goiter, fibrous goiter, ligneous goiter, or chronic invasive fibrous thyroiditis. The inflammatory thyroid condition of Riedel's thyroiditis is a local manifestation of a systemic fibrous or autoimmune process and chronic sclerosis or productive thyroiditis. A 59-year-old man came to the Endocrinology Clinic at Wahidin Sudirohusodo Hospital and was consulted by an oncology surgeon colleague with complaints of a lump in his neck for 2 years before coming to the hospital. Initially the lump was the size of a marble then it got bigger, felt hard, and not painful. The patient had a history of biopsies by surgical colleagues 2 times, the first in May 2022 Fine Needle Aspiration Biopsy with Malignancy (Papillary) results at Bhayangkara Hospital, then the patient was referred to a surgical oncology colleague at Wahidin Sudirohusodo Hospital and a 1-month incision biopsy was performed before going to the endocrine polyclinic with the results of Riedel's Thyroiditis. The patient was then given therapy with Tamoxifen 20 mg per 24 hours orally, and Methylprednisolone 16 mg per 8 hours orally with tapering doses every 7 days. In the treatment during control there were no complaints but complaints of a lump in the neck tended to shrink so the treatment was continued for 2 months then the patient returned to control with a clinical lump in the neck shrinking (Improvement). Riedel's thyroiditis is a disease characterized by an overgrowth of connective tissue that can invade surrounding structures. This connective tissue growth may extend into the recurrent laryngeal nerve. This thyroid inflammatory condition is suspected as a local manifestation of a systemic fibrotic process or an autoimmune process. Commonly used therapies such as glucocorticoids and immunosuppressant agents such as tamoxifen. Steroid treatment is usually given at a dose of 100 mg of prednisolone daily.

***Keywords**: Riedel's thyroiditis, tamoxifen, prednisolone*

INTRODUCTION

Riedel's thyroiditis is a rare fibrotic condition involving damage to the thyroid gland and infiltration of surrounding structures. Synonyms of Riedel's thyroiditis include Riedel's goiter, fibrous goiter, ligneous goiter, or chronic invasive fibrous thyroiditis.[1,2] The inflammatory thyroid condition of Riedel's thyroiditis is a local manifestation of a systemic fibrous or autoimmune process and chronic sclerosis or productive thyroiditis. This condition is characterized by progressive overgrowth of fibrous connective tissue that can invade structures around the thyroid so it most often presents with obstructive symptoms such as dyspnea, dysphagia, and hoarseness. Riedel thyroiditis may also present with manifestations of hypothyroidism, hypoparathyroidism, or Horner's syndrome.[2,3]

Riedel's thyroiditis is an extremely rare condition with an estimated incidence of 1.06 per 100,000 population and approximately 0.06% thyroidectomy.[3] In a meta-analysis it was stated that the average age of Riedel Thyroiditis patients was 47 years with the majority being women (81%). The most common ethnicity found was Caucasian followed by Asian. The majority of patients had experienced hypothyroidism (46%) or euthyroidism (44%). The remainder had hyperthyroidism (7%), subclinical hypothyroidism (2%), or subclinical hyperthyroidism (1%).[4]

The cause of Riedel's thyroiditis is not known. This disease is associated with systemic fibrotic processes and autoimmune diseases. It was recently stated that Riedel's thyroiditis is associated with high levels of immunoglobulin G type 4 (IgG4).[2,3,5,6] The diagnosis of Riedel's thyroiditis usually requires histopathological confirmation that there is a fibroinflammatory process of the thyroid with extension to the surrounding tissues. Inflammatory infiltrate, lymphoid follicles, granulomatous changes. Treatment of Riedel's thyroiditis is primarily aimed at reducing inflammation. Drugs such as steroids and immunosuppressant agents such as tamoxifen and mycophenolate mofetil are used to treat Riedel's thyroiditis. Surgery is sometimes needed for cases with obstructive symptoms.[4,5]

CASE REPORT

A 59-year-old man came to the Endocrine Clinic at Wahidin Sudirohusodo Hospital and was consulted by an oncology surgeon colleague with complaints of a lump in his neck 2 years before coming to the hospital. Initially, the lump was the size of a marble then it got bigger, felt hard, no pain. No fever, no history of fever. No weight loss. Weakness does not exist. There is no swallowing pain, no difficulty swallowing, no coughing and shortness of breath. There is no hoarseness. No chest pain, no abdominal pain. no nausea and vomiting. Urinate smoothly, clear yellow, no pain, no blood, smooth defecation, soft solid consistency, brownish, no blood. There is a history of hypothyroidism 2 years ago and had received levothyroxine 100mcg/24hours/oral but stopped because thyroid function tended to be normal in the last 1 month. History of biopsy by surgeon colleagues for the first 2 times in May 2022 Fine Needle Aspiration Biopsy with Malignancy (Papillary) results at Bhayangkara Hospital then the patient was referred to an oncology surgeon colleague at Wahidin Sudirohusodo Hospital and an incision biopsy was performed 1 month before going to endocrine polyclinic with Riedel Thyroiditis results. There was no history of hypertension and diabetes mellitus. There is no family history of similar complaints. There was no history of smoking or consumption of alcoholic beverages.

On physical examination, the general condition looked moderately ill, with adequate nutrition, compost mentis. Blood pressure 120/70 mmHg, pulse 72 times/minute, regular and lifting strength, respiratory rate 20 times/minute, axillary temperature 36.70 C. Body weight 64 kg and height 169 cm with body mass index 22.4 kg/m^2.

On physical examination of the head, it was found to be normocephalic, partly gray hair, not easily removed. The conjunctiva is not pale, the sclera is not icteric. There is no palpebral edema. The neck looks like a surgical scar,

palpable thyroid mass measuring about 11x6x12cm, feels hard, immobile, not hyperemic, with no tenderness, no warmth. Palpable multiple enlargement of supraclavicular and paracervical lymph nodes, average size of about 0.5x0.5cm, painless, rubbery consistency. On thoracic examination, venous dilatation was seen, symmetrical, right and left vocal fremitus were the same, right and left resonant percussion, vesicular breath sounds, no crackles and wheezing, no stridor. On examination, the ictus cordis was not visible and could not be felt, the heart border was normal. Single regular first and second heart sound, no murmurs. On abdominal examination, the abdomen looked flat, followed by breathing movements, and normal peristalsis. The liver was not palpable, the spleen was not palpable, there was no tenderness. There are no ascites. On examination of the warm acral extremities, edema is absent.

Based on the history and physical examination, the patient had clinical symptoms of Riedel's thyroiditis, so further examination was carried out. Patients underwent laboratory investigations, radiological and histopathological examinations.

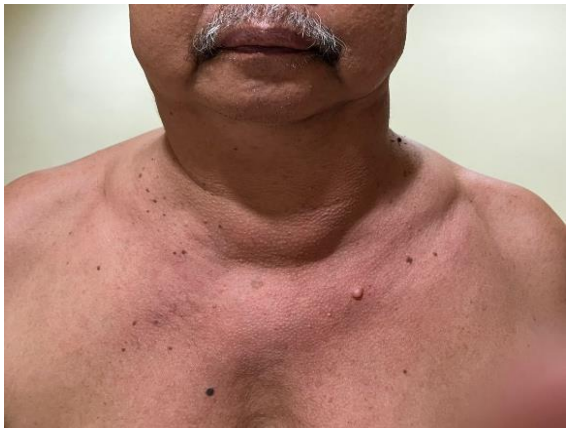

Figure 1. Clinical photo of the patient before treatment

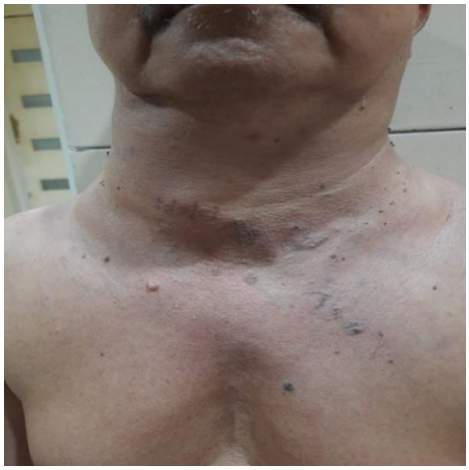

Figure 2. Clinical photos of the patient after treatment with methylprednisolone and tamoxifen

Soft tissue density is seen in the colli region bilaterally which has entered the superior thoracic aperture. Soft tissue density in the paratracheal area is well defined, the edges are regular, form an obtuse angle to the lungs, and a is within clean houtte sign to the ascending aorta. The heart normal CTR, dilated aorta. Both sinuses and diaphragm are good, and bones are intact. From this examinations, we found bilateral soft tissue masses in the neck a superior mediastinal mass presumed to be a thymoma, and aortic dilatation.

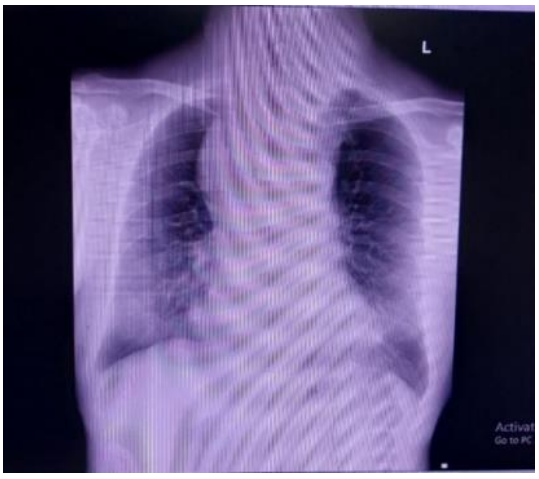

Figure 3. Photo of the patient's chest

Table 1. Laboratory Examination Results at Wahidin Sudirohusodo Hospital

Routine Blood	03-06-2022	Reference Value
WBC	6,000	4-10 x 103/ul
Neutrophils	61.2	52-75 %
Lymphocytes	27.1	20-40 %
Monocytes	5.8	2-8 103/ul
Eosinophils	5.4	1-3 103/ul
Basophils	0.5	0-0.1 103/ul
Hemoglobin	14.3	12-16 gr/dl
MCV	94	80-97 fL
MCH	30	26.5-33.5 p.m
PLT	271,000	150-400 x 103/dl
PT	10,7	10-13 sec
APTT	24.8	25-35
INR	1.03	<1.10

Blood Chemistry	03-06-2022	Reference Value
SGOT	24	<37 U/L
SGPT	18	<42U/L
UREUM	22	10-50 mg/dl
creatinine	1.14	<1.3 mg/dl
GDS	87	<110 mg/dl
Albumin	3.6	3.8 - 5.1 g/dl
FT4	1.45	0.93 - 1.71 ng/dl
TSHs	2.28	0.27 - 4.20 mIU/ml
Sodium	143 mmol/ltr	136-145 mmol/ltr
Potassium	4.0 mmol/ltr	3.5-5.5 mmol/ltr
Cloride	106 mmol/ltr	94-110 mmol/ltr

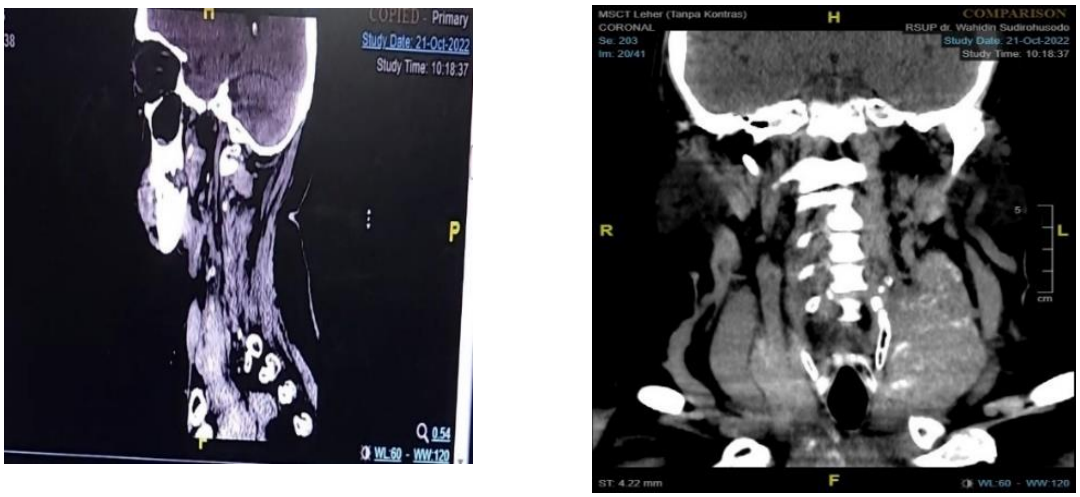

Figure 4. MSCT of the patient's neck

The right thyroid was enlarged with irregular margin, and increased and heterogeneous tissue density, along with multiple calcifications in the parenchyma. The left thyroid showed an enlarged size with irregular margin, increased tissue density, and heterogeneous, multiple calcifications in the parenchyma. There were multiple enlargements accompanied by calcification in the lymph nodes in the submandibular region level IIa, level IIb, level III and IV paracervical region, level V supraclavicular region, and bilateral thoracic level paratracheal. Bilateral parotids were enlarged, especially on the right, with irregular edges, and decreased parenchymal density. The nasopharynx area appeared symmetrical, the parapharyngeal space and larynx appeared normal. The fossa of Rossenmuller was good. Both piriform sinuses appeared normal. The scanned paranasal sinuses and mastoid air cells were within normal limits. Scanned cerebral parenchyma within normal limits, without any impaired bores. The imaging reveled features consistent with chronic thyroiditis, accompanied by multiple lymphadenopathies in the submandibular region (levels IIa and IIb), paracervical region (levels III and IV), supraclavicular region (level V), and bilateral paratracheal regions within the thorax. Additionally, a bilateral thyroid mass is observed, along with suspected bilateral parotid gland enlargement.

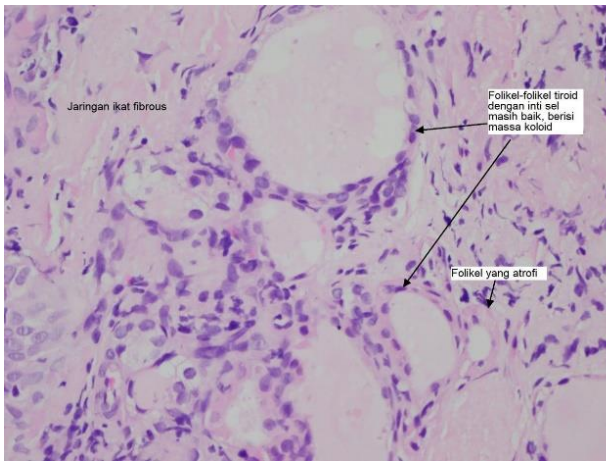

Figure 5. Histopathology

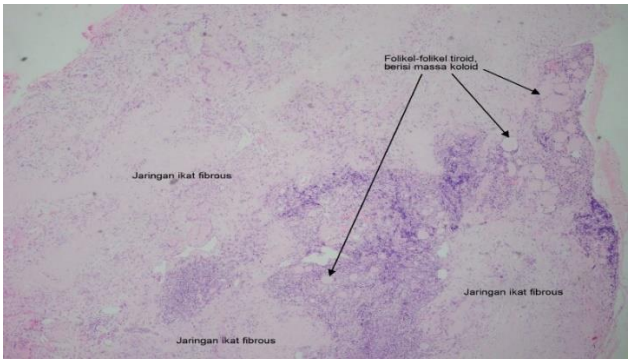

Figure 5. Histopathology

Examination of the thyroid revealed brownish-white tissue with a dense, and chewy consistency macroscopically. Microscopely, atrophic thyroid follicles with distinct nuclei were observed, some contained collards, and were surrounded by inflammatory lymphocytes and fibrous connective tissue.

The patient was diagnosed with Riedel's Thyroiditis. The patient was given therapy with Tamoxifen 20 mg per 24 hours orally, and Methylprednisolone 16 mg per 8 hours orally with tapering doses every 7 days. In the treatment during control there were no complaints but complaints of a lump in the neck tended to shrink so that treatment was continued for 2 months then the patient returned to control with a clinical lump in the neck shrinking.

DISCUSSION

A 59-year-old man with Riedel's Thyroiditis was consulted by a surgical oncology colleague with a diagnosis of Riedel's Thyroiditis, complaints of tumor et regio colli which tended to get bigger for 2 years before going to the hospital, hard consistency but not painful. Riedel's thyroiditis is a disease characterized by an overgrowth of connective tissue that can invade surrounding structures. This connective tissue growth may extend into the recurrent laryngeal nerve. This thyroid inflammatory condition is suspected as a local manifestation of a systemic fibrotic process or an autoimmune process.[5,7] It has recently been recognized that Riedel's thyroiditis may occur as part of a systemic disease associated with IgG4. IgG4-associated systemic

disease is defined as IgG4 plasma cell infiltration and fibrosis.[5,8]

The hallmark of Riedel's thyroiditis is the replacement of thyroid tissue with dense fibrotic tissue. Fibrosis can involve extrathyroidal structures, including the trachea, parathyroid glands, neck muscles, laryngeal nerves, and blood vessels. Clinically, the physical examination revealed a thyroid tumor with a firm consistency.[1]

Radiological examination can be used in making the diagnosis of Riedel's Thyroiditis. Computed Tomography (CT) scan and nuclear magnetic resonance (NMR) show extensive fibrosis of the thyroid parenchyma in the form of a heterogeneous appearance, either hypodense or isodense. This patient was found to be enlarged in size, with irregular margins, with increased tissue density and heterogeneous, with multiple calcifications in the parenchyma. The advantage of CT and NMR is that they can assess the extent of the spread of Thyroiditis to surrounding tissues, including the possibility of vascular invasion.[5,9,10]

Most patients have normal thyroid function, and both TSH and Free T4 are normal in most of those affected. However, many patients are also reported to have hypothyroidism. In a meta-analysis, 46% of individuals had experienced a phase of hypothyroidism before the disease process.[4,5]

This patient has a history of hypothyroidism and has received therapy for 2 years but currently the results of thyroid function tests are within normal limits. The diagnosis can be confirmed on histological examination. The results of fine needle aspiration (FNAB) cannot be used as a benchmark and surgical biopsies are more reflective of the histological results of Riedel's thyroiditis. The histopathological diagnosis is confirmed by the characteristic features of a fibroinflammatory process in the thyroid with extension into the surrounding tissues, an inflammatory infiltrate that does not contain giant cells, lymphoid follicles, oncocytes, or granulomas, evidence of occlusion; and no evidence of thyroid malignancy.[4,5,10] In this case, an incisional biopsy was performed by a surgical oncology colleague and an evaluation of the confirmation of histopathological results was carried out by an anatomical pathology colleague, with the same results as the histopathological diagnosis of Riedel's Thyroiditis.

Currently, there are no guidelines or large-scale clinical studies that discuss the optimal management of Riedel's thyroiditis. This is due to the low incidence of Riedel's Thyroiditis. Therapy should aim to treat hypothyroidism in those who present it and manage life-threatening fibrosclerotic manifestations such as airway compression.[5] Commonly used therapies such as glucocorticoids and immunosuppressant agents such as tamoxifen. Steroid treatment is usually given at a dose of 100 mg of prednisolone daily.

A rapid response to steroid treatment is found in most cases. However, relapse of symptoms is also common and may occur when the dose is reduced. In addition to steroids, tamoxifen is also used in monotherapy or as an adjunct when steroids fail. Tamoxifen has an anti-inflammatory role through the induction of autocrine secretion that converts growth factor β1. These drugs can relieve symptoms and reduce the size of the mass. The dose of tamoxifen used is between 10 and 20 mg daily. Mycophenolate mofetil has also been reported to have been used to treat Riedel's thyroiditis in cases resistant to steroids and tamoxifen.[4,10] This patient was given therapy with Tamoxifen 20 mg/24 hours orally, and Methylprednisolone 16 mg/8 hours orally with tapering doses every 7 days. In the treatment during control there were no complaints but complaints of a lump in the neck tended to shrink so the treatment was continued for 2 months later the patient returned to control with a clinical lump in the neck shrinking.

Definitive treatment with surgical management is sometimes required in cases complicated by obstructive symptoms. In this case, surgical management was not carried out because it did not yet show obstructive symptoms. The prognosis of most patients improves or remains stable with medical and

surgical management. In a meta-analys is also found a better prognosis, with 90% having improvement or resolution of symptoms but needing an average monitoring of 12 months.[4,11]

CONCLUSION

A case of Riedel's thyroiditis was reported in a man aged 59 years. Complaints improved after getting Tamoxifen and methylprednisolone therapy for 2 months.

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CASE REPORT

Parathyroid Carcinoma with Hungry Bone Syndrome Complication After Parathyroidectomy: a Case Report

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ABSTRACT

Parathyroid carcinoma is one of the causes of primary hyperparathyroidism, and the most effective treatment is parathyroidectomy. It is important to acknowledge the occurrence of Hungry Bone Syndrome following parathyroidectomy, as it could lead to higher death rates and longer hospital stays. In this report, we provide a case of a 27-year-old male who presented with repeated occurrences of bone fractures. The physical examination revealed a mass in the right thyroid region and deformities in the humerus and femoral regions. The laboratory analysis revealed increased calcium levels and significantly raised parathyroid hormone levels. The imaging findings revealed widespread bone lytic lesions and a mass in the right parathyroid region. The patient was diagnosed with primary hyperparathyroidism and underwent a parathyroidectomy, and the pathology results revealed the presence of a parathyroid carcinoma. On the fourth day following parathyroidectomy, the patient reported symptoms of tingling and muscle cramping. We noticed a decline in the calcium levels, which raised the possibility of Hungry Bone Syndrome. We implemented calcium correction and rigorous monitoring to prevent potentially lethal occurrences.

Keywords: *Hungry bone syndrome, parathyroid carcinoma*

INTRODUCTION

Parathyroid carcinoma is the least common cause of primary hyperparathyroidism, representing approximately 1 to 2% of cases.[1] Individuals diagnosed with parathyroid carcinoma typically experience a greater number of symptoms, including renal and skeletal complications, neck masses, and notable elevations in calcium and parathyroid hormone (PTH) concentrations.[2]

Surgery is the most effective and reliable treatment for parathyroid carcinoma, achieving a success rate of 95%.[3,4] Hypocalcemia commonly occurs briefly and transiently following parathyroidectomy, but there is a possibility of developing Hungry Bone Syndrome (HBS), which can lead to prolonged and potentially life-threatening hypocalcemia.[5] Patients with parathyroid carcinoma who have extremely high levels of parathyroid hormone (PTH) and skeletal abnormalities are at an increased risk of developing hungry bone syndrome (HBS) after undergoing parathyroidectomy.

The rarity of parathyroid carcinoma and the potentially life-threatening HBS syndrome led us to select this case. To avoid negative outcomes, it is critical to promptly identify and effectively manage this condition.

CASE ILLUSTRATION

A 27-year-old male patient experienced repeated occurrences of bone fractures. The patient had confirmed hematuria one month before hospital admission, and further examination revealed the presence of renal calculi. During the last two years, the patient has encountered a sequence of falls, leading to fractures in the right femur, as well as fractures in the left femur and right humerus. There is a lack of symptoms such as increased urine (polyuria), increased thirst (polydipsia), problems with bowel movements (constipation), abdominal discomfort, feelings of illness (nausea), vomiting, or changes in mental state. There is a lack of visual impairments and neurological issues. There is no evidence of any medical records within the family that show the existence of neck tumors, fractures, or kidney stones.

The physical examination revealed a firm and immobile mass measuring 3x3 cm in the right thyroid region. There were no detectable swollen lymph nodes in the neck. The abdominal bowel sounds were normal. Upon inspection of the limbs, abnormalities were observed in the right upper arm and right thigh regions.

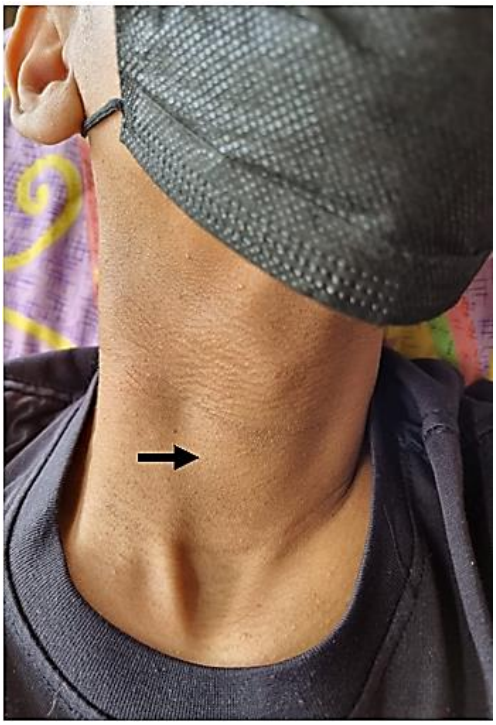

Figure 1. Mass in the right thyroid region (black arrow)

From the laboratory examination, the calcium level was found to be elevated at 8.58 mg/dL (normal range: 4.5 - 5.6 mg/dL). There was a significant increase in parathyroid hormone levels, measuring 1720 pg/mL (normal range: 15 - 65 pg/mL). Alkaline phosphatase levels were elevated at 2166 U/L (normal range: 46 - 116 U/L). Phosphate levels were decreased at 1.99 mg/dL (normal range: 2.5 - 4.9 mg/dL). Additionally, vitamin D levels were found to be decreased at 6.8 mg/dL (normal range: 30 - 100 mg/dL).

The right femoral X-ray revealed a malunion fracture with an accompanying plate

screw. The X-rays revealed malunion fractures and reduced bone density in the left femoral and right humerus. Radiographs of the thorax and pelvis revealed a reduction in bone density throughout all skeletal areas. The abdominal ultrasonography revealed the presence of multiple nephrolithiasis in both kidneys. An ultrasound of the neck revealed a heterogeneous hypoechoic mass with anechoic components, well-defined borders, irregular edges, and calcifications, measuring 3.65 x 2.08 x 4.41 cm. The mass originates from the right parathyroid gland and exerts pressure on the right thyroid gland. The ultrasound image was validated by a CT scan of the neck, which revealed a tumor in the right parathyroid gland and enlarged lymph nodes at levels IIA and IIB, with the largest measuring 1.82cm. The patient also had a Technetium-99m sestamibi parathyroid scan, which revealed evidence of a parathyroid adenoma located in the midpole lobe of the right thyroid. This finding was consistent with the Perrier Type D classification. Based on the available supporting investigations, it may be determined that this is a case of primary hyperparathyroidism with a possible diagnosis of parathyroid carcinoma.

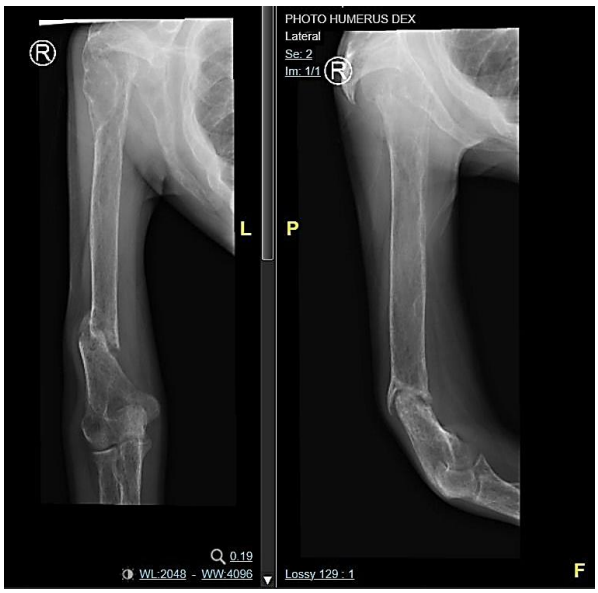

Figure 2. Right humerus X-Ray. There were fractures and lytic lesions of the bones.

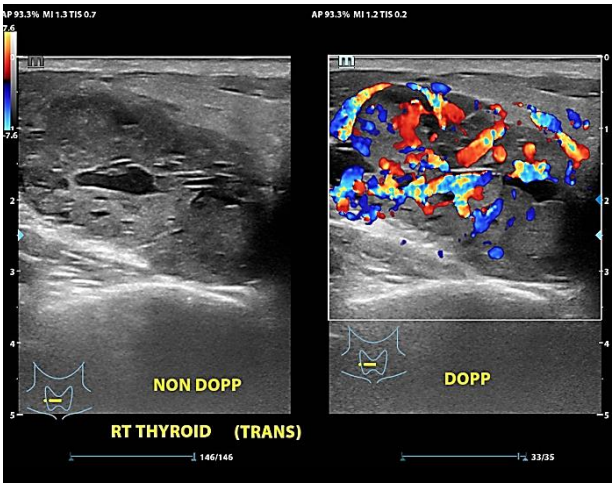

Figure 3. Right thyroid ultrasound. There was a mass pressing against the right thyroid, suspecting a parathyroid tumor.

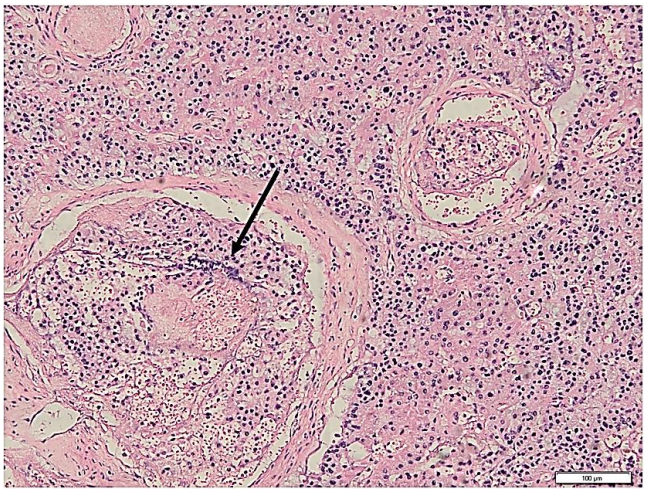

Figure 4. Histopathological analysis showing the tumor cells invaded the lymph vascular vessel (black arrow)

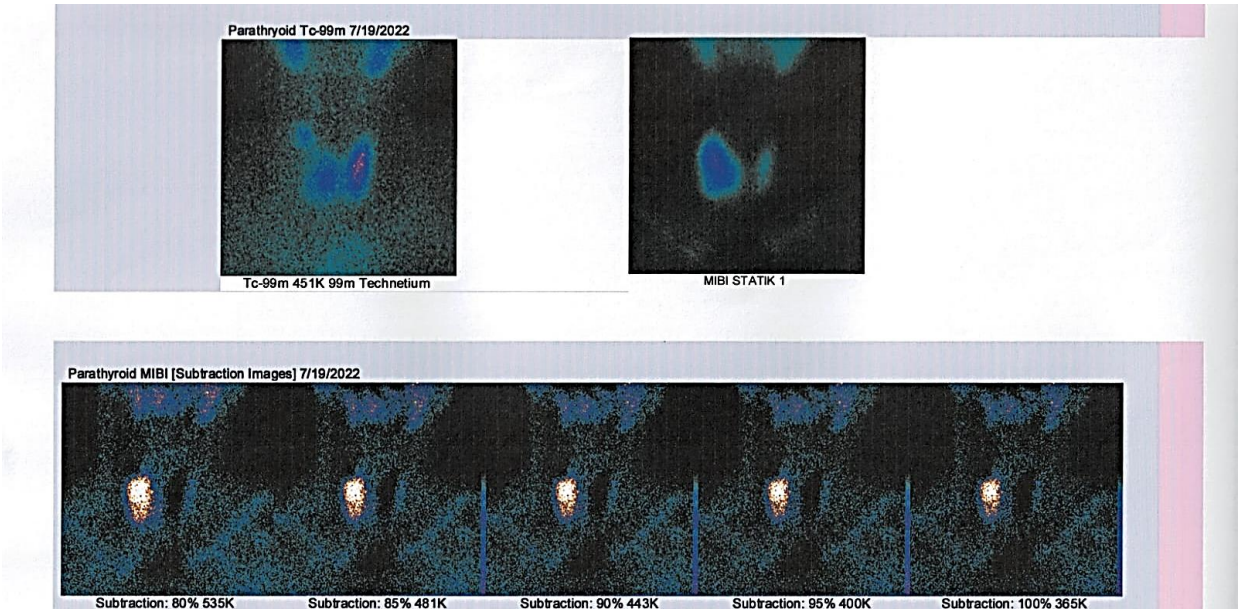

Figure 4. A Technetium-99m scan of Sestamibi showed parathyroid enlargement in the midpole of the right thyroid lobe.

Therapeutic Intervention

The patient had preoperative preparations for parathyroidectomy surgery, which included hydration with a 0.9% sodium chloride solution, administration of zoledronic acid, and a single dose of 5000 units of vitamin D. An oncology surgeon performed surgery on the patient, resulting in the extraction of a tumor measuring 6 x 4.5 x 3 cm. The histopathological analysis revealed the presence of hyperplastic oval round cells, forming the trabecular structure. The cell nucleus displayed pleomorphism, hyperchromatism, and the presence of mitosis. Additionally, the tumor cells had invaded the lymph vascular vessels, leading to the diagnosis of parathyroid carcinoma. Following the procedure, the patient was treated with a 1-gram intravenous bolus of calcium gluconate, followed by a 4-gram intravenous drip. We monitored calcium levels at 6-hour intervals for a total of 72 hours after the operation. The patient had measurements of parathyroid hormone levels both during and after the surgery. Additionally, the patient was prescribed a daily dose of 0.5 mg of calcitriol twice a day and a daily dose of 5000 units of vitamin D.

Continuing monitoring until the fourth day after the surgery, calcium levels returned to the normal range, and both the intraoperative and 4-hour postoperative parathyroid hormone (PTH) levels were within the normal range. However, on the fifth day after the surgery, patients experienced sensations of tingling and muscle cramping, but did not have seizures. The patient's vital signs were steady during the physical examination, nevertheless, Chvostek's Sign and Trousseau's Sign yielded favorable findings. The ECG study revealed no extended QTc or arrhythmia. The laboratory tests indicate a notable reduction in calcium levels, as depicted in the chart.

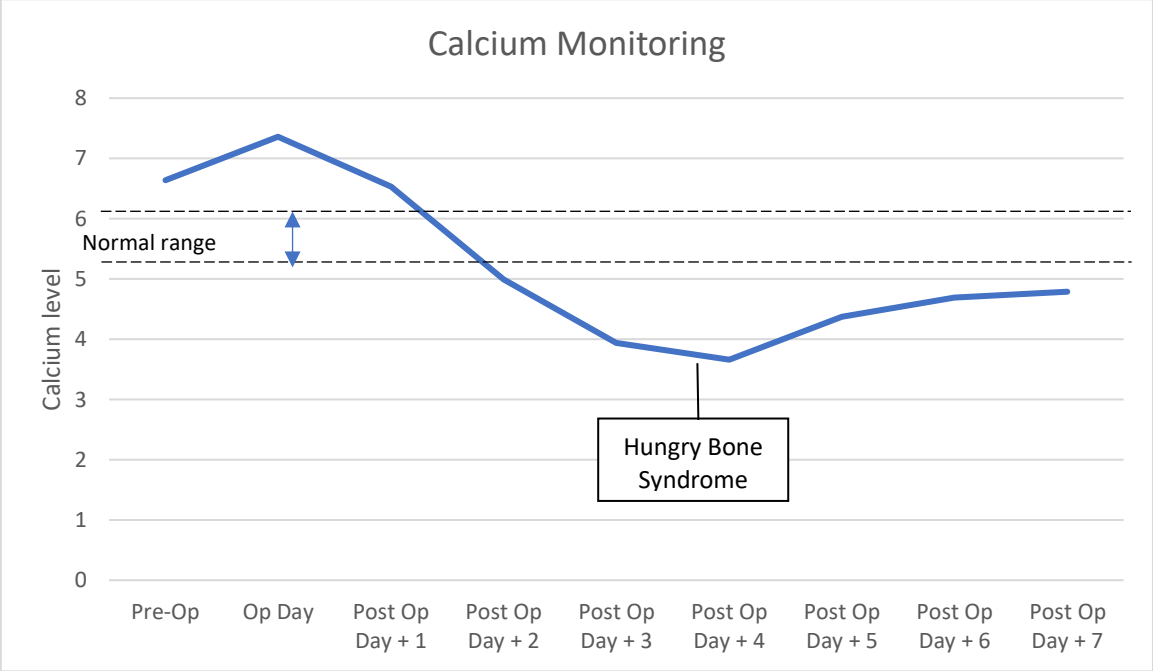

Figure 6. Calcium monitoring

The patient received a diagnosis of Hungry Bone Syndrome following the parathyroidectomy. To correct the low calcium levels, the patient received periodic intravenous administration of calcium gluconate, and the dose of calcitriol was increased to 4x0.5 mg. This treatment resulted in a positive therapeutic response. On the seventh day after surgery, the patient was discharged and prescribed home medications, including calcium carbonate 1x1000 mcg, calcitriol 2x0.5 mg, and vitamin D 1x5000 units. Three months later, there were no reports of hypocalcemia, and the laboratory examination showed normal calcium levels.

DISCUSSION

Primary hyperparathyroidism is a condition characterized by the parathyroid glands overproducing parathyroid hormones. When the PTH Levels increase, the kidneys enhance the reabsorption of calcium, leading to an increased excretion of phosphorus in the urine. This results in the production of more 1,25-dihydroxy vitamin D and an accelerated breakdown of the bone tissue. This condition will result in elevated levels of calcium in the blood (hypercalcemia), low levels of phosphate in the blood (hypophosphatemia), reduced bone density, excessive calcium in the urine (hypercalciuria), and other long-term illnesses associated with high levels of calcium in the blood. The etiology of primary hyperparathyroidism includes parathyroid adenomas (75 - 80%), parathyroid hyperplasia (20%), and parathyroid carcinoma (<1 - 2%).[2]

Parathyroid carcinoma is the least common kind of primary hyperparathyroidism. The incidence rate is equal among both males and females, with an average age ranging from 44 to 54 years. Parathyroid carcinoma can arise due to genetic anomalies, either in the familial form, such as hyperparathyroidism-jaw tumor syndrome, or in the nonfamilial (sporadic) type. Parathyroid carcinoma is exceptionally uncommon in cases with multiple endocrine neoplasia.[2] No malignancy was detected in the patient's jaw area, and there was no reported family history of similar concerns.

The primary manifestations of parathyroid carcinoma typically include neck masses (34 - 52%), skeletal abnormalities (34 - 73%), and renal abnormalities (32 - 70%). Metastases can form in lymph nodes or spread to distant sites, such as the liver. The average calcium laboratory values range from 14.6 to 15.9 mg/dL, whereas the levels of parathyroid hormone are

typically 5 to 10 times higher than the upper limit of normal. Parathyroid carcinoma should be suspected in patients presenting with recurrent hypercalcemia, elevated PTH levels, a neck mass, or hoarseness.[6-8] Carcinomas are typically considered during surgery when there is evidence of local invasion into surrounding tissue.[2,6,7,9] The presence of pathological fractures, nephrolithiasis, neck masses, and significantly raised PTH levels in this patient support the suspicion of parathyroid carcinoma.

The imaging techniques used to locate the mass in the parathyroid glands include cervical ultrasound, sestamibi scan, or CT scan. An ultrasound examination is the most economically efficient procedure when conducted by a skilled operator. Combining sestamibi scan and ultrasound can improve the examination's precision and sensitivity.[9] An ultrasound examination and sestamibi scan revealed an expansion of the parathyroid glands in the midpole of the patient. Additionally, a cervical CT scan showed an enlargement of the lymph nodes.

Trabecular patterns, mitotic features, fibrosis bands, and signs of vascular or capsular invasion are common histological features of parathyroid carcinoma. A definite diagnosis is established when lymph node metastases or distant metastases are present.[10,11] Our patient's histopathological findings reveal lymph vascular invasion, corroborated by the CT scan's observation of enlarged lymph nodes. These results validate the diagnosis of parathyroid carcinoma.

Surgery remains the most effective treatment for primary hyperparathyroidism, including cases of parathyroid carcinoma. The surgical success rate is 95%.[3] Postoperative hypocalcemia is usually mild and transient, occurring on days 2 or 3 postoperatively. Some patients can develop prolonged hypocalcemia after parathyroidectomy with normal PTH results, this phenomenon is called Hungry Bone Syndrome (HBS). Although there is no consensus definition of HBS, some literature states that it occurs when there is severe hypocalcemia on day four or more postoperatively.[12] This phenomenon can arise because of the discontinuation of bone resorption followed by bone formation and subsequent remineralization after parathyroidectomy. Hypocalcemia may present with moderate symptoms such as muscle cramps or tingling, more severe symptoms like tetany or seizures, or life-threatening signs such as cardiac arrhythmias.

The prevalence of HBS in primary hyperparathyroidism following parathyroidectomy varies between 8.6% and 59%. The occurrence of the condition is higher when bone abnormalities are detected in radiology, as compared to when there are no bone abnormalities (25 - 90% vs. < 6%). Elevated pretreatment levels of PTH and alkaline phosphatase (ALP) can serve as indicator for the development of HBS following parathyroidectomy.[13] Low vitamin D levels as a predictor of HBS remain controversial.[5]

The primary approach in HBS treatment is to replenish calcium levels in the bones. Following intravenous calcium administration, oral calcium supplementation and the active form of vitamin D (calcitriol) should be initiated right away. The recommended daily dosage for calcium supplementation might range from 6 to 12 grams. Phosphate supplementation is not generally indicated for correcting hypophosphatemia due to the potential to worsen hypocalcemia, unless there is notable weakness and heart failure.[14]

There are several methods to prevent HBS after parathyroidectomy, including the preoperative use of cholecalciferol, calcitriol, and bisphosphonates.[14] Researchers suggest cholecalciferol to enhance blood levels of vitamin D, but the evidence for its use in preventing HBS is debatable.[14,15] Calcitriol has been found to be effective in enhancing calcium levels, but, research investigations have not demonstrated favorable outcomes in terms of preventing HBS. Administration of bisphosphonates, such as clodronate, alendronate, pamidronate, zoledronate, or ibandronate, has demonstrated efficacy in

preventing HBS. However, their effectiveness is limited in individuals with severe and long-lasting bone abnormalities.[14]

The patient exhibited persistent hypocalcemia on days 3 and 4 after surgery, while having normal levels of PTH, which provides evidence for HBS. Patients had modest symptoms associated with hypocalcemia but did not show any abnormalities in the electrocardiogram (ECG) attributable to arrhythmia. Treatment for hypocalcemia involved administering calcium gluconate intravenously and calcium carbonate orally at a dosage of 1000 mg. Additionally, calcitriol and cholecalciferol were given. We closely monitored calcium levels and electrocardiogram (ECG) readings during the treatment. The radiography reports indicated that our patient has been experiencing significant bone anomalies for an extended period. Despite the administration of cholecalciferol, calcitriol, and bisphosphonates as preventive measures, our patient still suffers from HBS. The therapeutic intervention yielded favorable outcomes, leading to the patient's discharge with a notable improvement in calcium levels.

CONCLUSION

Parathyroid carcinoma should be considered a potential cause of primary hyperparathyroidism, particularly in patients who have bone lesions, nephrolithiasis, and significantly elevated levels of parathyroid hormone. Parathyroidectomy is the primary treatment option for parathyroid carcinoma. It is important to evaluate the occurrence of Hungry Bone Syndrome following parathyroidectomy in patients with parathyroid carcinoma, since they have a higher likelihood of developing this complication due to severe and prolonged hypocalcemia.

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CASE REPORT

Adult-Onset Nesidioblastosis (Non-Insulinoma Pancreatogenous Hypoglycemia Syndrome): a Rare Case

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ABSTRACT

Finding the etiology of hypoglycemia in adult patients can be challenging because of the wide variety of etiologies. Ninety percent of endogenous hyperinsulinemic hypoglycemia is caused by insulinoma, the rest are caused by insulin antibodies and pancreatic β cell dysfunction (nesidioblastosis) which indicates neoformation of nesidioblasts (stem cells that form the islets of Langerhans). A 28-year-old female complained of neuroglycopenia and adrenergic symptoms that improved with drinking sugar, so she had weight gain. The 72 hours of prolonged fasting test results are C-peptide ≥0.2 mmol/L, insulin ≥21 pmol/L, insulin to C-peptide molar ratio ≤1, and negative insulin antibody. Imaging tests were normal and there is no evidence of malignancies. When blood glucose falls, the first defense mechanism to prevent hypoglycemia is decreased in insulin secretion. When this mechanism fails, insulin and C-peptide levels remain high in circulation. Confirmation of Whipple's triad is required, followed by insulin tests in hypoglycemic conditions. Imaging tests, biomarkers, and hormonal malignancies were done to rule out differential diagnoses. Nuclear diagnostics, SACST, biopsy, and histopathology are currently in capable of being carried out. The diagnosis of adult-onset Nesidioblastosis/NIPHS in this patient was made through the diagnosis of exclusion, namely by eliminating all diagnostic appeals because several examination modalities cannot be carried out. The gold standard for diagnosing Nesidioblastosis/NIPHS is SACST and histopathological examination of pancreatic tissue. The patient is well-controlled with Amlodipine 2.5 mg.

Keywords: *Hypoglycemia, hyperinsulinemia, nesidioblastosis, non-insulinoma pancreatogenous hypoglycemia syndrome (NIPHS)*

INTRODUCTION

Hypoglycemia is a life-threatening condition that can occur in various circumstances. Establishing an etiological of hypoglycemia in adult patients can be a challenge, because of the wide variety of causes such as the effects of diabetes treatment (insulin, insulin secretagogue), alcohol consumption, critical illness (sepsis, liver failure, kidney failure), endocrine diseases (adrenal insufficiency, pituitary), a tumor that produces insulin like-growth factor (IGF) or insulin, and endogenous hyperinsulinemia.[1-7]

Ninety percent of hyperinsulinemic endogenous hypoglycemia in adults is caused by insulinoma. In contrast, the rest is caused by the presence of antibodies to insulin (Hirata's disease) and pancreatic β cell dysfunction. Insulinoma is a tumor originating from the islets of Langerhans β cells of the pancreas. Hirata's disease is a disease caused by antibodies to insulin. Meanwhile, dysfunction of pancreatic β cells is the presence of inappropriate secretion of endogenous insulin, which is called nesidioblastosis, which shows the origin of the cells, namely neoformation of nesidioblasts, the stem cells that form the islets of Langerhans.[1-7]

Nesidioblastosis is characterized by focal or diffuse hypertrophy, hyperplasia, and hyperfunction of the β cells of the pancreatic islets of Langerhans without any abnormalities found in pancreatic cells. Nesidioblastosis began to be termed non-insulinoma pancreatogenous hypoglycemia syndrome (NIPHS) by Service et al. in 1999.[7-9]

The following is a rare case reported, namely adult-onset NIPHS in a 28-year-old woman with problems in diagnosis and management.

CASE ILLUSTRATION

A 28-year-old woman came to the Endocrine metabolic diabetes polyclinic with the main complaint felt suddenly weak and getting worse for 3 years ago. Additional complaints were dizziness, cold sweat, muscle aches, palpitations, and intense hunger even after eating. To get rid of the feeling of weakness, she drank a sugar solution or syrup. She checked herself at the community health center and found that his blood sugar value without fasting at that time was 90mg/dL. She ate larger portions than usual to prevent her body from becoming weak. She had weight gain from 57 kg to 78 kg in the past 3 years.

Previous medical history did not reveal a history of hypertension, diabetes, kidney disease, tumors, or a history of surgery or taking medication or herbal medicine. Family history revealed diabetes in her biological mother and older siblings. Eating habits revealed eating patterns as follows when she woke up, immediately drink 1 glass of water plus 3 tablespoons of granulated sugar, around 7 breakfasts: 2 cups white rice, side dishes, vegetables, around 10 o'clock have a snack: fried food or fruit, around 12 lunches: 2 cups white rice, side dish, vegetables, around 15 o'clock have a snack: fried food or fruit, around 18 o'clock dinner: 2 cups white rice, side dish, vegetables, around 20 o'clock have a snack: fried food or fruit, before going to bed, drink 1 glass of water plus 3 tablespoons of sugar

General physical examination revealed weight: 78 Kg, Height: 160 cm with BMI: 30.4 (obesity 1). The organ-specific examination did not reveal any abnormalities.

Figure 1. Clinical picture

From the history, physical examination, and blood sugar examination, it was concluded that the Whipple's Triad criteria for Hypoglycemia in this patient had been confirmed so that it could be included in the Hypoglycemia diagnosis algorithm as in Figure 2.

Routine blood screening, liver function, and kidney function showed normal results. Adrenal function screening through morning Cortisole examination and Pituitary function through TSH examination showed normal results. Screening for diabetes with HbA1C examination resulted in 5.7%, comparable to an average blood sugar of 110 mg/dL, and screening for hyperinsulinemia through C-Peptide examination with high result 5.19 mmol/L (normal 0.26-1, 72 mmol/L).

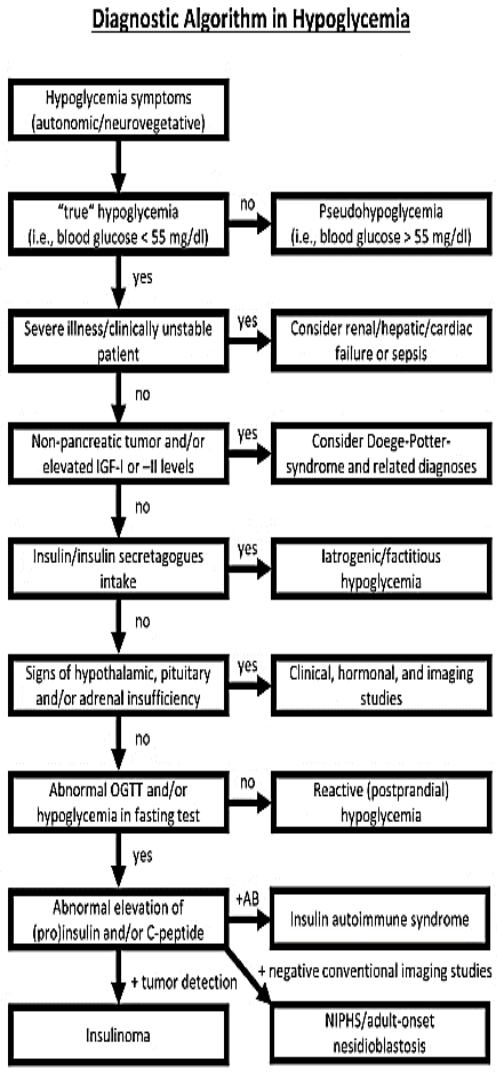

Figure 2. Diagnostic Algorithm of Hypoglicemia

The 72 hours prolong fasting test, a hypoglycemia provocation test, was carried out (figure 3) and the results showed that C-peptide ≥0.2 mmol/L and insulin ≥21 pmol/L which means that still increased although the patient's blood sugar was 53 mg/dL at the 53rd hour of fasting (Figure 3).

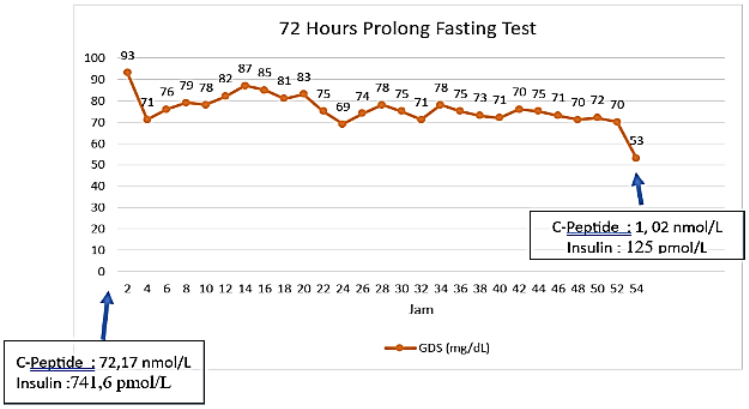

Figure 3. 72 Hours Prolong Fasting Test

We performed the calculation of the Insulin: C-peptide molar ratio that obtained a value of ≤1 which corresponds to endogenous hyperinsulinemic Hypo-glycemia (Table 1). Next, an insulin antibody test was carried out with negative results.

Table 1. Dynamic Test Result

Test	Pre-Test	Post Test	Normal Value
C-Peptide	72,17	1, 02	0,26 - 1,72 nmol/L
Insulin	741,6	125	34,7 - 69,4 pmol/L
Insulin: C-peptide molar ratio (pmol/L)	0,01	0,12	≤ 1 Hiperinsulinemic Hypoglicemi Endogen > 1 Hiperinsulinemic Hypoglicemi Eksogen/ Insulin autoantibody

CT scan of the abdomen with contrast and MRI of the abdomen with contrast did not reveal an intra-abdominal mass. Thoracic imaging examination, thyroid, and parathyroid ultrasound as well as biomarkers of malignancy, namely intact PTH, Calcium, CEA, Cyfra 21-1, and CA 19-9 to rule out insulin-secreting NET and MEN-1 syndrome, showed normal results.

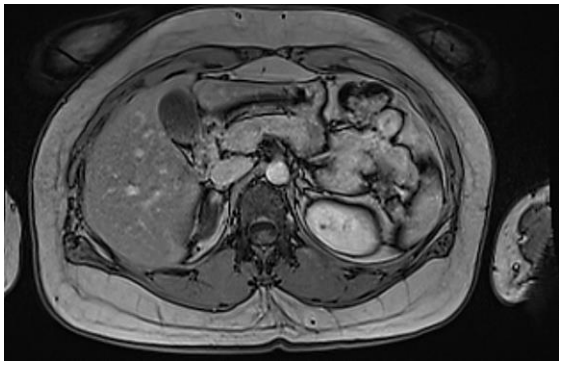

Figure 4. Abdomen contrast MRI

The β-OHB examination cannot be carried out, so it is not carried out, but the β-OHB examination is needed only if insulin levels are low. Blood and urine sulfonylurea screening examinations were not carried out because the patient had no history of consuming drugs or herbs. The insulin receptor antibody examination was not carried out because the physical examination and supporting examinations did not reveal any manifestations of severe insulin resistance. Examination of mutations in the gene that forms the K-ATP channel protein is not yet possible because it cannot be done if there is only 1 patient sample. Meanwhile, the diagnosis of Congenital Hyperinsulinemi (CHI) and Familial Hyperinsulinemia (FHI) usually occurs at birth and in childhood.

To establish a definite diagnosis of adult-onset NIPHS, a Selective Arterial Calcium Stimulation Test (SACST) or histopathology of the pancreas gland is required. To date, the SACST examination has never been carried out in the vascular surgery department but theoretically, it can be carried out, while pancreatic gland biopsy can be carried out in the digestive surgery department, but these two invasive examinations are hampered because the patient is not yet willing to undergo surgery. After eliminating all differential diagnoses, the patient was diagnosed with Suspected Adult-Onset NIPHS.

Patients are given non-pharmacological therapy in the form of diet modification in consultation with a clinical nutritionist. Diet modification with complex carbohydrates, low glycemic index, high fiber, and diet frequency every 2-3 hours, wake up and eat complex carbohydrates, for example, boiled corn, boiled sweet potatoes, at 8 breakfasts: 1.5 cups white rice, side dishes, a larger portion of vegetable, at 10 o'clock have a snack: 1 large piece of fruit, 12 o'clock lunch: 1.5 cups white rice, side dishes, a larger portion of vegetables, at 15 o'clock have a snack: fruit, 18 o'clock dinner: 1.5 cups white rice, side dishes, a larger portion of vegetables, at 20 o'clock have a snack: fruit, before going to bed, don't eat or drink sugar water anymore, if symptoms of hypoglycemia appear (cold sweat, body weakness, dizziness, palpitations) you can drink sugar water, diet will be monitored every week

At 2 weeks of follow-up with diet modification, it was found that blood sugar was stable, and the frequency of hypoglycemia events began to decrease. Diet modification therapy was continued. In the 3rd month of follow-up, the incidence of hypoglycemia decreased but when woke up she still drank 1.5 tablespoons of sugar water, and her weight increased by 1 kg. Amlodipine therapy was given 5 mg at night before bed. After 2 weeks of amlodipine administration, the symptoms of hypoglycemia did not appear, but the systolic blood pressure dropped to 100 mmHg, and the dose was reduced to 1x 2.5 mg at night. The prognosis of this patient is poor due to the requirement for lifelong treatment and monitoring.

DISCUSSION

Hypoglycemia is a decrease in blood sugar levels low enough to cause symptoms and signs to appear. Blood sugar concentration is normally maintained within a narrow range of 72-144 mg/dL through a balance between glucose entry (exogenous glucose intake and endogenous glucose production) and glucose output (glucose utilization by insulin-sensitive tissues such as muscle and insulin-insensitive tissues such as the brain). Hypoglycemia occurs due to an imbalance between the entry and exit of glucose either due to an increase in the rate of glucose clearance from the circulation, a lack of glucose delivery into the circulation, or both.[8]

Under physiological conditions, insulin secretion from pancreatic β cells is precisely regulated in response to changes in glucose concentration in the blood. The increase in post-prandial blood glucose and the release of glucagon-like peptide 1 (GLP-1), an incretin hormone from the intestine, will stimulate the synthesis and secretion of insulin from pancreatic β cells. Insulin secretion will return to basal levels around 2-4 hours after eating. [5.8]

When blood glucose falls, the first defense mechanism to prevent hypoglycemia is decreased insulin secretion. When blood sugar falls below 3.8 mmol/L (68.4 mg/dL), there is a rapid increase in glucagon and epinephrine secretion to prevent hypoglycemia. If hypoglycemia continues, the secretion of cortisol and growth hormone increases as a further counter-regulatory response. All these effects aim to suppress insulin secretion, induce hunger, increase glucose levels, reduce peripheral glucose uptake and provide alternative fuel when blood glucose falls, the first defense mechanism to prevent hypoglycemia is a decrease in insulin secretion. When blood sugar falls below 3.8 mmol/L (68.4 mg/dL), there is a rapid increase in glucagon and epinephrine secretion to prevent hypoglycemia. If hypoglycemia continues, the secretion of cortisol and Growth Hormone increases as a further counterregulatory response. All these effects aim to suppress insulin secretion, induce hunger, increase glucose levels, reduce peripheral glucose uptake, and provide alternative fuel for the brainl for the brain.[5,8]

Insulin secretion is completely suppressed at blood sugar levels of 3 mmol/L (54 mg/dL). Post-prandial hypoglycemia occurs when insulin secretion fails to be suppressed due to falling glucose concentrations and there is a blunting of the response to glucagon and epinephrine. Excessive insulin will suppress the processes of glycogenolysis and gluconeogenesis so that hypoglycemia occurs because of a decrease in glucose production compared to an increase in utility. Meanwhile, suppression of the lipolysis process will reduce ketogenesis so that there is no alternative fuel for brain metabolism which is dangerous for the brain.[5,8]

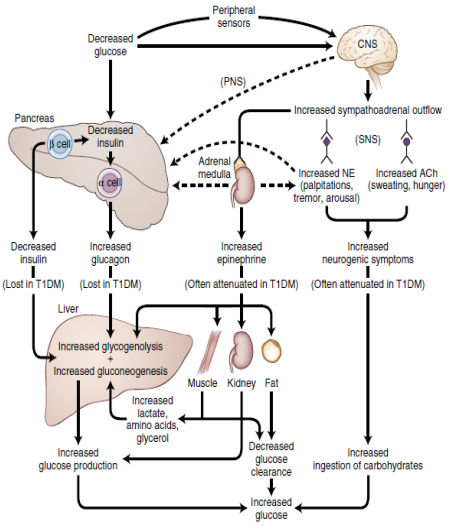

Figure 5. Physiological and behavioral defenses against hypoglycemia.[8]

Hypoglycemia in non-diabetic individuals is rare. It is important to explore the history of Whipple triad (neuroglycopenic symptoms, low blood sugar, improvement of symptoms after glucose administration) in non-diabetic individuals who are suspected of having hypoglycemia before starting further tests. The etiology of hypoglycemia can be seen in Tables 2 and 3. DM drugs are currently still the most common cause of hypoglycemia.[5,8]

Spontaneous hypoglycemia in apparently normal individuals may occur in a single episode or subacute neuroglycopenic symptoms. The clinical history should assess whether hypoglycemia occurred during fasting or postprandially, the nature of symptom onset (e.g., cold sweats, anxiety, tremors, palpitations, intense hunger, and tingling), and the resolutions of symptoms after ingesting sugar. Family history should be explored for transient symptom, such as hemiplegia, strabismus, hypothermia, hyperthermia, seizures, and involuntary movements.[5,8] Additionally, document, any history of medication, supplement, herbs, alcohol use, and prior gastric surgery.

In this patient, after anamnesis and initial examination, Whipple's Triad was confirmed, namely the presence of

neuroglycopenic symptoms, low blood sugar below 3.0 mmol/L (54 mg/dL), and improvement in symptoms after administration of glucose. Next, an assessment is carried out as to whether the patient is experiencing a critical illness condition through a thorough physical examination and supporting examinations. From the anamnesis, there were no complaints that indicated a sign of malignancy such as weight loss, lumps, persistent pain, or changes in urination and defecation patterns. On physical examination, the patient was found to be in stable condition, only the BMI was increased and there were no signs of other diseases.

Table 2. Etiology of Hypoglycemia

Ill or Medicated Individual
Drugs
Insulin or insulin secretagogue
Alcohol
Others (see Table 38.8)
Critical Illnesses
Hepatic, renal, or cardiac failure
Sepsis
Inanition
Hormonal Deficiency
Cortisol
Glucagon and epinephrine (in insulin-deficient diabetes mellitus)
Non–Islet Cell Tumor
Seemingly Well Individual
Endogenous Hyperinsulinism
Insulinoma
Functional beta-cell disorders (nesidioblastosis)
Noninsulinoma pancreatogenous hypoglycemia
Post–gastric bypass hypoglycemia
Autoimmune hypoglycemia
Antibody to insulin
Antibody to insulin receptor
Insulin secretagogue
Other
Accidental, Surreptitious, or Malicious Hypoglycemia

The next diagnostic step is to look at insulin levels in a fasting condition with a 72-hour long fasting test. The principle of the 72-hour prolonged fasting test is that when blood sugar conditions drop, the body's first response is to reduce insulin/C-peptide secretion to prevent hypoglycemia (Fiigure 3). In conditions of hyperinsulinemic endogenous hypo-glycemia, this suppression mechanism fails, so that insulin to C-peptide ratio levels remain high in the circulation and cause hypoglycemia. The examination procedure is that the patient is installed with intravenous access and then fasted from food and drinks that contain calories. Peripheral blood sugar is checked every 2-4 hours then every 1 hour if blood sugar is below 70 mg/dL. The test is stopped, and insulin and C-peptide samples are taken before adding glucose. These conditions include 72 hours have been reached, patients without symptoms of hypoglycemia but GDS < 2.5 mmol/L (45 mg/dL), and symptoms of hypoglycemia appear even though the capillary GDS is > 2.5 mmol/L (45 mg/dL).[7]

In this patient, after carrying out a 72-hour prolonged fasting test, the patient's glucose level was 53 mg/dL at the 53rd hour of examination and a high insulin level was found, namely 18 µU/mL (>3 µU/mL/ 18 pmol/L), C - peptide 1.02 nmol/L (>0.2 nmol/L) and Insulin to C-peptide molar ratio < 1. These results support a state of endogenous hypoglycemic hyperinsulinemia (Table 3).[6-8]

Insulinoma, although rare, is the most common Neuroendocrine Tumor (NET) in the gastrointestinal tract with an annual incidence of around 0.5 - 1 per 1 million population per year. Insulinoma occurs more often in women. It can occur at any age but especially in middle age (mean age 47 years in sporadic cases and 23 years in MEN1 syndrome cases). [7,8]

To rule out the differential diagnosis of insulinoma, MEN1 syndrome, and insulin-secreting NET, the patient underwent an imaging examination to localize the tumor using Computer Tomography (CT) with a sensitivity of 70% and Magnetic Resonance Imaging (MRI) with a sensitivity of 80% for the diagnosis of insulinoma. Biomarker examination of malignancy also yielded positive results normal so that MEN1 syndrome and insulin-secreting NETs can be ruled out.[1,5,7,8]

If there is no intra-mass image, the next examination is the SACST to confirm the diagnosis of NIPHS. In this patient, imaging examination did not reveal an insulinoma. Meanwhile, the SACS test was not yet able to be carried out, so it was not carried out. This patient has never had surgery on the stomach and intestines so the differential diagnosis of Post Gastric By-Pass Surgery (PGBH) can be ruled out. Meanwhile, Congenital

Hyperinsulinemia (CHI) and Familial Hyperinsulinemia (FHI) have onset from birth to childhood. The examination of insulin auto-antibodies in this patient was negative. After ruling out all differential diagnoses a diagnosis of adult-onset NIPHS can now be established.[5,6,11-13]

Table 3. Patterns of findings after fasting test

Patterns of Findings During Fasting or After a Mixed Meal in Normal Individuals[a] and in Individuals With Hyperinsulinemic (or IGF-Mediated) Hypoglycemia or Hypoglycemia Caused by Other Mechanisms

Symptoms, Signs, or Both	Glucose (mg/dL)	Insulin (μU/mL)	C-Peptide (nmol/L)	Proinsulin (pmol/L)	β-Hydroxybutyrate (mmol/L)	Glucose Increase After Glucagon (mg/dL)	Circulating Oral Hypoglycemic Agent	Antibody to Insulin	Diagnostic Interpretation
No	<55	<3	<0.2	<5	>2.7	<25	No	No	Normal
Yes	<55	≫3	<0.2	<5	≤2.7	>25	No	Neg (Pos)	Exogenous insulin
Yes	<55	≥3	≥0.2	≥5	≤2.7	>25	No	Neg	Insulinoma, NIPHS, PGBH
Yes	<55	≥3	≥0.2	≥5	≤2.7	>25	Yes	Neg	Oral hypoglycemic agent
Yes	<55	≫3	≫0.2[b]	≫5[b]	≤2.7	>25	No	Pos	Insulin autoimmune
Yes	<55	<3	<0.2	<5	≤2.7	>25	No	Neg	IGF[c]
Yes	<55	<3	<0.2	<5	>2.7	<25	No	Neg	Not insulin- or IGF mediated

Epidemiologically, the etiology of endogenous hyperinsulinemic hypo-glycemia in adults is the most common cause by insulinoma which is 90%, while adult-onset NIPHS only occurs in around 0.5-5% of cases of endogenous hyperinsulinemic hypo-glycemic.[1,2,4,7]

Epidemiological research in Japan by Yamada et al., which was launched in 2020, regarding the incidence of endogenous hyperinsulinemic hypoglycemia in 2017-2018, resulted in 447 CHI patients, 205 insulinoma patients, 111 NIPHS patients, and 22 insulin autoimmune syndrome patients. The incidence of adult-onset NIPHS is estimated to occur in 1: 10,000,000 people per year aged 28-63 years with an average age of 48 years.[14]

The physiological mechanism of insulin secretion begins with the entry of glucose into pancreatic β cells through glucose transport proteins (GLUT) 1 and 3. Glucose is phosphorylated by glucokinase (GCK) to form Glucose-6-phosphate, and then the glycolysis process occurs in the Krebs cycle and the oxidative phosphorylation chain which ultimately forms adenosine triphosphate (ATP). Increasing ATP concentration will increase the ATP to ADP ratio. ATP inhibits K-ATP channel activity resulting in a decrease in the efflux of potassium ions (K+) which causes an increase in cell membrane potential. If the membrane potential limit is reached, calcium ions (Ca2+) channels open, resulting in an influx of calcium which stimulates the fusion of vesicles containing insulin at the plasma membrane and stimulates insulin secretion. [1.8]

In patients who experience NIPHS, there is a change in mechanism. GCK gene mutations cause excessive GCK enzyme activity. This increases the oxidative metabolic pathway increased in an increase in the ATP to ADP ratio which will cause KATP channel inhibition so that K+ ions cannot exit which causes a higher resting membrane potential and causes greater Ca2+ channel opening. Apart from that, NIPHS patients also found increased insulin synthesis and storage. Likewise, the basal rate of insulin secretion is higher than in normal cells. So, it was concluded that in NIPHS patients there was increased insulin secretion from pancreatic B cells, resulting in hyperinsulinemic hypoglycemia which was associated with clinical symptoms. [1.8]

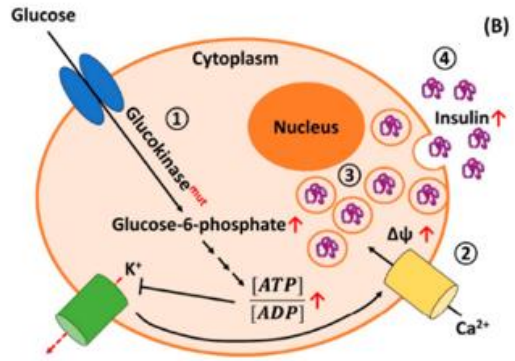

Figure 6. Insulin secration in Nesidioblastosis/ NIPHS

Apart from conventional diagnostic modalities, there are other diagnostic modalities:

1. **68Ga-DOTATE PET/CT and 68Ga-DOTA-Extendine-4 PET/CT**

Pancreatic neuroendocrine cells express the high-affinity somatostatin receptor (SSTR). 68Ga-DOTATE specifically binds SSTR type 2 which is in high concentration in pancreatic islet B cells, so imaging based on SSTR is an option to confirm the diagnosis of NIPHS. The latest guidelines recommend that SSTR PET/CT examination should be used as the main modality to diagnose NIPHS with a sensitivity of 80-90% and a specificity of 82-90%. The newest is 68Ga-DOTA-Extendine-4 PET/CT where the target is cells that express GLP-1 with an accuracy of 93.9%. In NIPHS, tracer capture is diffuse, whereas in insulinoma the tracer capture is localized.

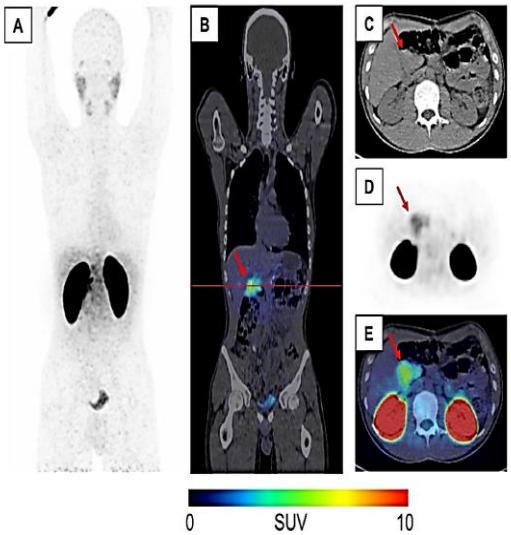

Figure 7. ^{6,8}Ga-DOTA-Extendine-4 PET/C[1]

NIPHS Clinically and biochemically, cannot be differentiated from insulinoma, especially insulinomas < 1 cm in size that cannot be detected using imaging techniques. In this case, the SACST can be used to differentiate them.

With SACST is since calcium will stimulate insulin secretion from hyperfunctioning pancreatic B cells, but not from normal pancreatic B cells. A positive result occurs if there is a twofold increase in hepatic vein insulin concentration after calcium injection in the pancreatic artery. Thompson et al., research found in NIPHS increased insulin concentration is diffuse whereas in insulinoma patients it is more localized.[1-3,10,15,19]

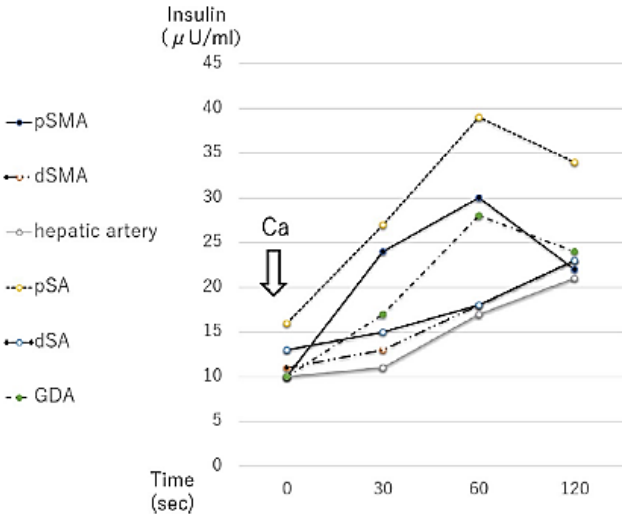

Figure 8. Sample of SACST

2. Histopathology of the Pancreatic Gland

The gold standard for the diagnosis of NIPHS is a histopathological picture with pancreatic B cells in the form of enlarged nuclei and cytoplasm throughout the pancreas. There were no abnormalities in somatostatin cells, glucagon cells, and pancreatic polypeptide cells, and an increase in the number of ductuloinsular complexes. Table 4 shows the histopathological criteria of nesidioblastosis.[20-22]

The terminology nesidioblastosis was first described by George F Laidlaw (1938) from the Greek "nesidion" which means island and

"blastos" which means stem cell (germ). It is characterized by hypertrophy and hyperplasia of B cells of the islets of Langerhans, enlarged and hyperchromatic cell nuclei, and neoformation of pancreatic islets from the ductal epithelium.[3,16,20]

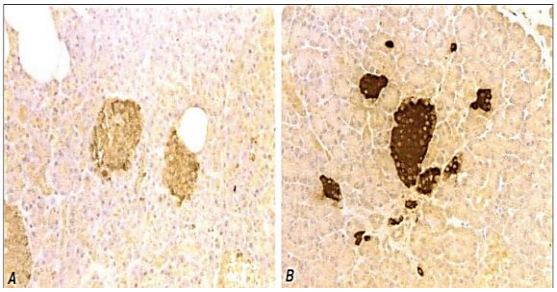

Figure 9. Comparison of Islets of Langerhans cells using insulin immunohistochemical staining. Images of a normal person (A) and a NIPHS patient (B). NIPHS patients show hypertrophic nuclei and brighter cytoplasm, clusters of islets with varying sizes and shapes, and contain more insulin. [20]

Table 4. Histopathological Criteria for NIPHS[1,2]

MAJOR CRITERIA	MINOR CRITERIA
-Exclusion of an insulinoma by macroscopic, microscopic, and immunohistochemical examination	-Irregular shape and occasional enlargement of islets
-Multiple b-cells with an enlarged and hyperchromatic nucleus and abundant clear cytoplasm	-Increased number of islets
-Islets with normal spatial distribution of the various cell types	-Lobulated islet structure
-No proliferative activity of endocrine cells	-Macronucleoli in b-cells

3. Genomics

Various genetic mutations are responsible for pancreatic B cell hyperplasia. Two genes encoding the proteins ABCC8 (formerly known as SUR1) and KCNJ11 (formerly known as Kir6.2) which form K-ATP channels in the membrane of pancreatic B cells, are the main genetic defects causing diffuse NIPHS. This gene mutation is located on chromosome 11p14-15.1, causing changes or inactivation of the K-ATP channel. Inactivation of K-ATP channels cause the closure of potassium channels so that calcium ions enter the cell, resulting in depolarization of the cell membrane which causes continuous insulin secretion.[1,2,4,23,24]

Normal production of K-ATP channel proteins includes transcription of the ABCC8 and KCNJ11 to produce pre-mRNA which then becomes mRNA (mature RNA). The mRNA exits the nucleus and is translated into protein in the ribosomes embedded in the endoplasmic reticulum. Next, the polypeptide is folded into a tertiary structure and enters the Golgi Apparatus for post-translational modification. Vesicles containing the assembled K-ATP channel protein are then expressed on the plasma membrane. In CHI there is a defect in the regulation, biogenesis and movement of K-ATP channel proteins which results in ineffective K-ATP channel degradation in lysosomes (Figure 10) [23,24]

Apart from that, defects were also found in the Glucokinase (GCK), Hexokinase (HK), Glutamate Dehydrogenase type-1 (GLUD-1) genes causing changes in insulin secretion as explained in Figure 6.[1, 2, 4, 23, 24]

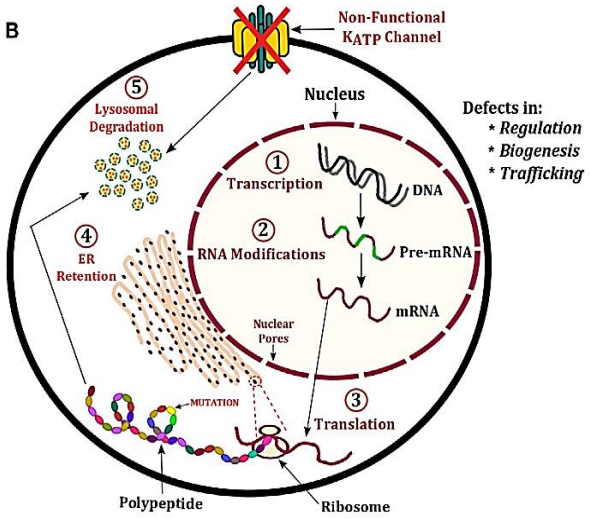

Figure 10. KATP channel protein gene mutations in the pathophysiology of hyperinsulinemia.[23]

Table 5. Gene Mutations in Familial Hyperinsulinemia[24]

Gene	*ABCC8*	*KCNJ11*	*GCK*	*GLUD1*	*HADH1*	*SLC16A1*	*HNF4A, HNF1A*	*UCP2*
Protein	**SUR1** ATP-binding cassette, subfamily C; sulfonylurea receptor	**Kir6.2** inwardly rectifying potassium channel	**GCK** glucokinase	**GLUD1** glutamate dehydrogenase	**SCHAD** 3-hydroxyacyl-CoA dehydrogenase	**SLC16A1/ MCT1** Solute carrier family 16 member 1/ monocarboxylate transporter 1	**HNF4A, HNF1A** hepatocyte nuclear factors 4α and 1α	**UCP2** mitochondrial uncoupling protein 2
Function	Subunits of the β-cell ATP-dependent potassium channel		β-cell glucose metabolism	Amino acid-stimulated insulin secretion	Enzyme involved in fatty acid oxidation	Plasma membrane pyruvate transporter	Nuclear transcription factor	Mitochondrial uncoupling protein
Autosomal mutations	— recessive: • severe form of neonatal hypoglycaemia [48, 49] • diffuse FHI** [6] — dominant: • milder form [48, 49] • focal FHI — caused by a paternal mutation of one of the genes and a specific loss of maternal alleles [8]		Dominant, activating [10, 14–16]	Dominant, activating [4, 19] Relatively mild FHI, may escape recognition in infancy [20]	Recessive, loss of function [4, 25–28]	Dominant, increased expression [29]	Dominant, loss of function [35] Also associated with MODY1 (HNF4a) and MODY3 (HNF1a) [35]	Dominant, loss of function
Characteristic	Large birth weight [4] Increased risk of diabetes in adulthood [4]		Normal birth weight [15]	Hyperammonaemia [21] Leucine-dependent protein- stimulated hypoglycaemia [4]	Elevated urinary 3-hydroxyglutaric acid excretion [4] Leucine-dependent protein-stimulated hypoglycaemia [25]	hypoglycaemia after intensive exercise [29]	Large birth weight [34] Evolution of neonatal hyperinsulinism to diabetes later in life [34, 35]	
Diazoxide treatment effective-ness	–* [4]		– or + Depending on the mutation [10, 14–16]	+ [4, 20]	+ [4, 28]	Partial response [50, 51]	+ [32, 34, 35]	+ [42]

*Cases with dominant KATP mutations may be responsive to diazoxide [48, 49]. **Most cases. Dominant diffuse FHI is also being observed [6]

Therapeutic options for adult-onset NIPHS currently remain limited. Because the pathophysiology of this disease is not yet fully understood, interventions aimed at treating the causes of impaired pancreatic β-cell function do not yet exist. The first step is a low-carbohydrate diet with a low glycemic index to reduce the strong stimulation of insulin secretion. Furthermore, existing pharmacological therapies are α-glucosidase inhibitors (Acarbose), K-ATP channel agonists (Diazoxide), calcium channel antagonists (Amlodipine), and somatostatin analogs (Octreotide, Lanreotide, Pasireotide)[1,25-30] and some cases, glucocorticoids, β-blockers, antipsychotics/antiepileptics such as phenytoin are also used as therapy for NIPHS through effects that cause hyperglycemia. Everolimus, a nuclear cell signaling inhibitor, was also tried in the treatment of NIPHS but failed to maintain euglycemic conditions.[1]

Refer to Table 6 for comprehensive details on therapy options and their respective mechanisms for adult-onset NIPHS.[1] In some patients, total/subtotal pancreatectomy is still an option to control symptoms. Current resection limits are still a matter of debate, some limit it to 50-60%, and some suggest 80-95%. Surgical intervention is associated with increased postoperative morbidity, and type 3C diabetes mellitus (exocrine pancreatic insufficiency) can occur.[1]

Because current management options are unsatisfactory, a less innovative strategy is needed invasive. Boss et al conducted experimental studies on the GLP-1 receptor. Exendin-4 paired with a photosensitizer will carry out internal irradiation to selectively kill the GLP1 receptor. Therefore, this therapy may be promising in reducing pancreatic β-cell mass without surgery.

Table 6. Treatment Modalities for Nesidoblastosis/NIPHS[1]

Therapeutic Principle	Mechanism of Action [1]	Therapeutic Effect Based on the Current Literature [1]
Low carbohydrate diet/diet with low glycemic index	Limits insulin secretion postprandially due to low slope of glucose increase after food intake	Low but non-invasive
α-glucosidase inhibitors (Acarbose, Voglibose)	Slows down glucose resorption through inhibition of carbohydrate-digesting enzymes in the intestines	Low but non-invasive; few adverse effects
Diazoxide	Activates ATP-dependent potassium channels in β-cells → stabilizes resting membrane potential → inhibits insulin secretion	Sometimes effective; may have severe adverse effects (fluid retention, angina pectoris)
Calcium-channel antagonists (Verapamil, Amlodipine, Nifedipine)	Inhibit voltage-dependent calcium channels → inhibit depolarization of β-cells → inhibit insulin secretion	Sometimes effective; may have severe adverse effects (hypotension)
Somatostatin analogs (octreotide, lanreotide, pasireotide)	Stimulate somatostatin receptors (G-protein coupled receptors) on β-cells → inhibit insulin secretion	Sometimes effective; may lead to increased frequency/intensity of hypoglycemia (due to inhibition of glucagon; depends on receptor specificity)
Glucocorticoids	Induce gluconeogenesis and glycogenolysis in the liver; augment effects of glucagon; induce peripheral insulin resistance	Sometimes effective; long-term treatment associated with severe adverse effects
β-blockers (e.g., propranolol)	Mechanism not entirely clear (β1-adrenoceptor-mediated inhibition of insulin secretion?)	Rarely effective; β-blockers also tend to precipitate hypoglycemia (especially through inhibition of β2-adrenoceptor-dependent glycogenolysis)
Antipsychotics/Antiepileptics (e.g., phenytoin)	Probably through insulin insensitivity	Rarely effective; may have severe adverse effects
Everolimus	Inhibition of mammalian target of rapamycin (mTOR) signaling, which is involved in the regulation of insulin secretion	Rarely effective (more likely to be effective in the pediatric population [409])
(Sub)total pancreatectomy	Surgical removal of the islets of Langerhans	Effective, if enough endocrine tissue is removed; considerable morbidity and mortality
Receptor-targeted photodynamic therapy	Selective destruction of GLP-1 receptor-expressing cells	Experimental treatment (animal model)

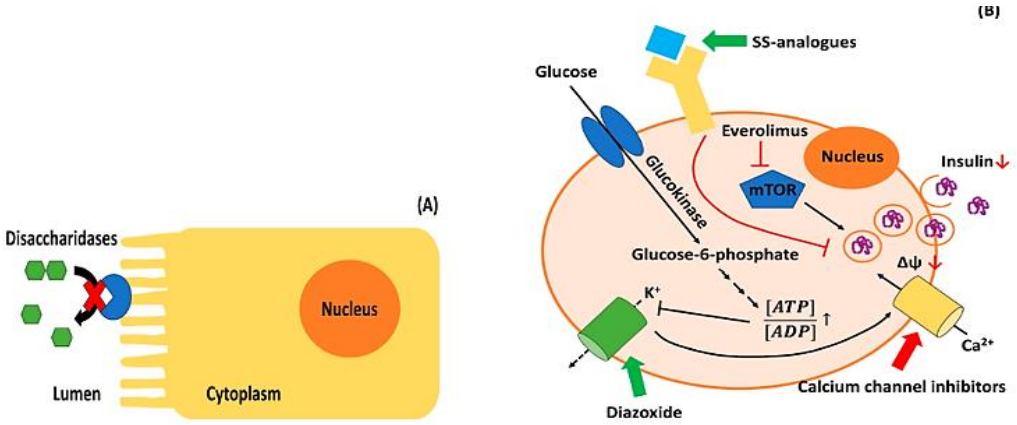

Figure 11. Mechanism of action of anti-hypoglycemia drugs[1]

This patient was given amlodipine therapy 1x 2.5 mg at night with consideration effectiveness and low side effects.[27,31]

CONCLUSION

A rare case of adult-onset NIPHS in a 28-year-old woman with recurrent clinical hypoglycemia has been reported. The diagnosis of adult-onset NIPHS in this patient was made through a diagnosis of exclusion, namely by eliminating all differential diagnoses because several examination modalities were not yet capable. The gold standard for diagnosis of adult-onset NIPHS is a histopathological examination of pancreatic tissue. The patient is currently still well controlled with conservative management and will continue to be monitored to see if alternative therapy or more progressive measures are needed.

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CASE REPORT

Paraparesis and Bipolar Affective Disorder Episodes of Depression in Graves' Disease with Thyroid Cancer Patient

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ABSTRACT

Thyroid nodules in Graves' disease raise awareness of thyroid cancer. Thyrotoxicosis in patients with thyroid cancer suggests extensive metastases or large tumours. Hyperthyroidism or thyrotoxicosis can exacerbate symptoms of anxiety, depression, mood lability, and insomnia in patients with bipolar disorder. We present a rare case, a 29-year-old woman with a history of Graves' variant nodule and bipolar affective disorder since the age of 17, was admitted to the hospital for paraparesis within a month. Patients also complain of sleeplessness, hopelessness, and fatigue. The patient has been taking Thiamazole 10 mg twice daily, Propranolol 20 mg twice daily, Alprazolam 0.5 mg trice daily, Haloperidol 5 mg nightly, Trihexyphenidyl 2 mg daily, Lamotrigine 100 mg twice daily but not routinely. History of partial thyroidectomy 10 years ago with pathology results was said to be benign. Neurological examination: bilateral lower extremity motor weakness with a value of 2/5 muscle function. MRI of the spine with contrast: changes in signal intensity in the vertebral bodies C.2, C.4, C.5, Th.2 - tend to bone metastases. Thyrotoxicosis thyroid function test results (free T4 = 66.71 pmol/L (N = 10.6 - 19.4); TSHs < 0.05 ulU/mL (0.51 - 4.94 ulU/mL) and thyroid scintigraphy showed toxic multinodular goiter (cold nodule) with high thyroid uptake. A total thyroidectomy was performed, and the pathology result revealed papillary thyroid cancer. Thyroid cancer can occur together with Graves' disease. Graves' disease-associated cancers were more often metastatic to distant sites such as spinal metastases that significantly increases morbidity and mortality. Thyrotoxicosis was associated with regional metabolic changes of limbic structures that mediate affect in patients with bipolar affective disorder.

Keywords: *Graves' disease, thyroid cancer, bipolar disorder*

INTRODUCTION

Thyroid nodules are frequently found in patients with Graves' disease. The presence of these nodules raises concern about co-existent thyroid carcinoma.[1] The reported incidence of nodules in Graves' disease varies from 12,8% to 33.6%. Around 10-15% of nodules associated with Graves' disease are reported to be thyroid cancers with papillary thyroid cancer being the commonest histopathology.[1] During the past few years, there has been growing recognition that thyroid-stimulating antibodies (TSAbs) may enhance the growth and function of differentiated malignant thyroid cells.[2] Increased aggressiveness of thyroid cancers in patients with coexistent Graves' disease and suggested that, in these patients, monitoring (and attempting to lower) TSAbs may be as important as suppressing the release of thyrotropin by the pituitary.[2,3]

Thyrotoxicosis in patients with thyroid cancer was of patients with extensive metastatic involvement or a large tumor. The bone is the second most common location to which thyroid cancer is known to metastasize, affecting 3% of patients with thyroid cancer.[4] Neuropsychiatric symptoms, such as mood disturbances and cognitive impairment, are very common among patients with thyroid disorders.[5] Hyperthyroidism or thyrotoxicosis is usually associated with symptoms such as anxiety, depression, mood lability, and insomnia in patients with bipolar disorder. However, overt psychiatric disorder is rare and occurs in only about 10% of the patients.[6]

CASE PRESENTATION

A 29-year-old woman was admitted to the hospital complaining of progressive loss of muscle strength in the lower limbs. Within a month of evolution, this case had recently been followed by paraparesis. The patient already partially cared dependent. Patients also complain of sleeplessness, hopelessness, and fatigue. Her past medical history was Graves' variant nodule and bipolar affective disorder since the age of 17. The patient has been taking Thiamazole 10 mg twice daily, Propranolol 20 mg twice daily, Alprazolam 0.5 mg trice daily, Haloperidol 5 mg nightly, Trihexyphenidyl 2 mg daily, Lamotrigine 100 mg twice daily but not routinely. History of partial thyroidectomy 10 years ago with pathology results was said to be benign.

On neurological examination, there was bilateral lower extremity motor weakness with a value of 2/5 muscle function. On mental status examination determined that she was alert and oriented, fairly groomed in an appropriate dress with good eye contact, and polite and cooperative with the interview and exam. Her speech was not pressured, loud, or rapid. She denied auditory and visual hallucinations, suicidal ideation and homicidal ideation. However, she did sleeplessness, hopelessness, and fatigue. Her thought processes were linear, no looseness of associations or ideas of reference. Her cognition and memory were intact. It was established the diagnosis of bipolar affective disorder episodes of depression and the patient received treatment with Alprazolam 0,5 mg twice daily and Lamogritine 100 mg nightly. An MRI of the spine with contrast was performed and revealed changes in signal intensity in the vertebral bodies C.2, C.4, C.5, Th.2 - tend to bone metastases (Figure. 1).

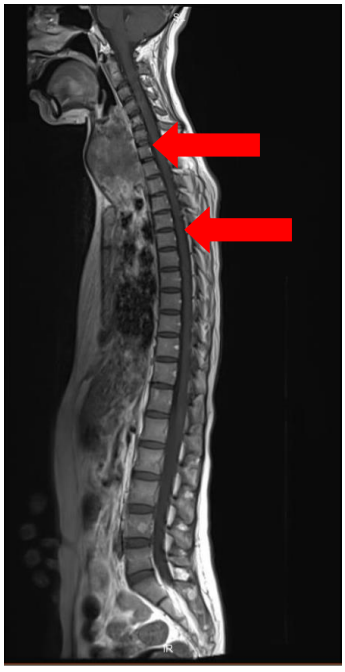

Figure 1. Spinal MRI - notice changes signal intensity

Thyrotoxicosis thyroid function test results (free T4 = 66.71 pmol/L (N = 10.6 - 19.4); TSHs < 0.05 uIU/mL (0.51 - 4.94)) and thyroid scintigraphy showed toxic multinodular goiter (cold nodule) with high thyroid uptake. The patient was then referred to the Division of Oncology Surgery. Interdisciplinary consultation recommended total thyroidectomy as a therapeutic approach. The patient was prepared psychologically for the accomplishment of total thyroidectomy with full acceptance. During the surgical procedure, it was noticed that the lobes had an irregular shape and had a multinodular structure (Figure. 2). Thyroid pathological examination revealed a papillary thyroid carcinoma.

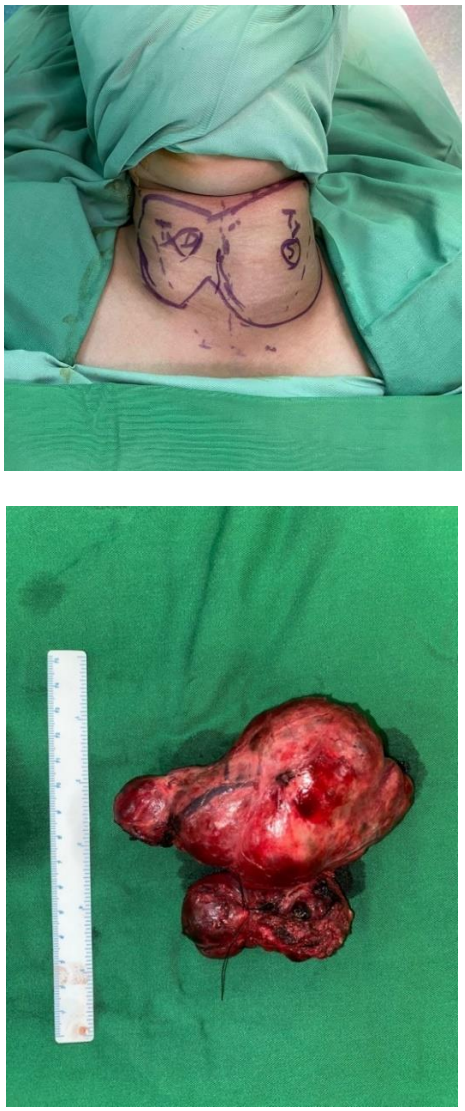

Figure 2. Macroscopic aspect of thyroid after excision - irregular shape and a multinodular structure.

DISCUSSION

The only clinical feature that initially distinguished this patient's thyroid from that of Graves' disease was the firm nodule within the right and left thyroid gland. Thyrotoxicosis in patients with thyroid cancer were of patients with extensive metastatic involvement or a large tumor. These tumors have almost always been follicular carcinomas or occult papillary carcinoma.[7] Thyroid cancer was detected in patients with Graves' disease with a frequency 2.5-fold that among patients with autonomous thyroid nodules, and the Graves' disease associated cancers were more often multifocal, locally invasive, and metastatic to lymph nodes or distant sites (10-fold) than were the cancers in patients with autonomous thyroid nodules.[8] We suspect that the growth and function of the tumor in our patient were modulated by thyroid-stimulating autoantibodies.

Among all the variants of thyroid carcinomas, follicular thyroid carcinoma (FTC) is the most likely to present with distant metastasis or metastasize during the disease.[9] It is estimated that metastatic disease develops in 7-23% of FTC cases and its initial presentation occurs in 1-4%. When present, it normally leads to a worse prognosis and constitutes the main mortality factor.[9] Bone and lung are the most likely locations for metastatic disease in FTC.[10] In a series of 444 patients with thyroid carcinoma and distant metastasis, 44% of them had bone involvement, and among these, 36% were diagnosed with FTC. According to the literature, over 80% of bone metastasis of all tumors are mainly located in the axial skeleton, namely vertebrae, ribs and basin.[11] Metastasis of thyroid carcinomas is preferentially osteolytic, being in pain is the most common manifestation found at its presentation, followed by pathological fractures[11], and rarely, medullary compression symptoms[12], as in this clinical case.

In this case, the patient was diagnosed with bipolar affective disorder episodes of depression. Hyperthyroidism is frequently associated with irritability, insomnia, anxiety, restlessness, fatigue, and impairment in

concentrating and memory, these symptoms can be episodic or may develop into mania and depression.[13] However, overt psychiatric disorder is rare and occurs in only about 10% of the patients.[14] Thyrotoxicosis and attendant psychological symptoms were associated with regional metabolic changes of limbic structures that mediate affect. Psychiatric symptoms in hyperthyroidism, such as anxiety or mania, appear to be mediated by beta-adrenergic hyperactivity.[15]

CONCLUSION

Thyroid neoplasms usually have an indolent behavior and patients are commonly asymptomatic. Metastatic disease is uncommon as an initial manifestation but, when present, it assumes a later stage of the disease along with a worse prognosis. Paraparesis is a rare form of presentation of thyroid carcinoma. Hyperthyroidism or thyrotoxicosis is usually associated with symptoms such as anxiety, depression, mood lability, and insomnia in patients with bipolar disorder; early treatment of the hormone or metabolic alteration can minimize the morbidity of a secondary psychopathology.

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CASE REPORT

Dengue Fever and Graves' Disease Complicated with Guillain-Barré Syndrome: a Case Report

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ABSTRACT

GBS is a rare neurological autoimmune disorder in which a person's immune system mistakenly attacks part of peripheral nervous system and the network of nerves that carries signals from the brain and spinal cord to the rest of the body. GBS is not commonly found alongside Graves' disease or dengue fever. 35-year-old woman who have been previously diagnosed with Graves' disease with dengue fever and GBS. On the fifth day of treatment, she showed signs of poor respiratory function, weak neck muscle power, paralyzed and was indicated for intubation. The cerebrospinal fluid analysis showed a consistent finding of GBS of albumin cytological dissociation with an increased level of protein of 80 mg/dL, glucose 50 mg/dL, and a normal lymphocytes cell count of 4/cmm without polymorphs. She was ventilated for three days and began to receive the treatment of intravenous immunoglobulins (IVIG) of 0.4 g/kg/day for a total of five days and remarkable recovery and was extubated on day 3 of IVIG. The case study theorises those endogenous factors, such as gangliocytes and ICAM-1, as well as exogenous factors such as bacterial and viral infection, may play a part in the simultaneous presentation of GBS and Graves' disease. Antibodies that formed from these factors have an affinity to GM1 and GT1A gangliosides which are typically exposed on the plasma membrane and can cause molecular mimicry as well as cytokine stimulation which is the main feature of GBS. Furthermore, it is thought that preceding infection of dengue virus may also lead to the development of GBS. Intravenous immunoglobulin therapy shows a promising result on treating a simultaneous case of GBS presenting in patient with Graves' disease and dengue fever.

Keywords: *Guillain barre syndrome, dengue fever, graves' disease*

INTRODUCTION

Graves' disease and Guillain-Barré syndrome (GBS) are both autoimmune disorders, but the pathomechanisms are very different. Graves' disease is an autoimmune disease that affects thyroid gland, and the symptoms are a result of antibodies binding to receptors on the thyroid causing over-expression of thyroid hormone.[1]

GBS is a rare neurological disorder in which a person's immune system mistakenly attacks part of the peripheral nervous system and the network of nerves that carries signals from the brain and spinal cord to the rest of the body. GBS usually starts a few days or weeks following a respiratory or gastrointestinal bacterial or viral infection.[2] One of the most common risk factors for GBS is infection with the bacteria *Campylobacter jejuni*, SARS-COV-2, Zika, Cytomegalovirus, or Epstein-Barr viruses. Although rare, few cases of GBS have been causally linked to serologically confirmed dengue illness in the medical literature. Etiopathogenesis of GBS following dengue is not yet fully described, but the molecular mimicry causing an immune attack on myelin and axons, and pro-inflammatory cytokines such as tumor necrosis factor (TNF), the interleukins, and complements participating in immune response are postulated as possible mechanisms.[3]

CASE ILLUSTRATION

A 35-year-old woman was admitted in February 2024 with a 4-day history of fever with arthralgia, myalgia, headache, and generalized malaise. She had a no difficulty in breathing and coughing. She denied recent diarrheal or respiratory illness. She was previously apparently well, but she had previous history of Graves' disease with no significant comorbidities. For 3 years she received antithyroid drug, but 1 month before being admitted to the hospital she was given radioactive iodine therapy at a dose of 5 milli curies. On examination, she was moderately ill, conscious, rational, and had normal vital parameters. Cardiovascular, respiratory, abdominal, and extremity examinations were normal. On skin examination, there were no spontaneous petechiae, but the Rumpel Leede result was positive.

The complete blood count on admission showed a white cell count of 2.2 × 10^6/μL, Platelets of 46 × 10^3/μL, and a hematocrit of 40%. Her nonstructural protein 1 (NS1) antigen result was positive. With the compatible history, positive dengue antigen, leukopenia, and thrombocytopenia, a diagnosis of dengue fever was made. Laboratory examination of thyroid function showed free T4 0.78 ng/dL and TSHs 1.2 uIU/mL during treatment with antithyroid drug, thiamazole 5 mg a day.

On the 5th day of treatment, the patient complained of shortness of breath and a feeling of bloating in his stomach. Lung rales and ascites were found on physical examination. Limb examination revealed hypotonia and reduced power in the bilateral lower limbs. Her upper limbs were normal, but lower limb tendon reflexes were absent with reinforcement and her upper limb reflexes were diminished. All her sensory modalities were intact. Although she had a good cough reflex, her neck muscle power was reduced. A cranial nerve examination was normal. Laboratory examination results showed an increase in WBC of 12.3 × 10^6/μL and platelets of 96 × 10^3/μL and decrease in hematocrit of 38% and albumin 2.4 g/dL. Brain and spine MRI revealed no abnormalities. Initially, to this was thought to be thyrotoxicosis related to neuropathy. Antithyroid thiamazole was stopped, and propylthiouracil with propranolol and methylprednisolone injections were initiated, but her symptoms rapidly progressed with ascending weakness of lower extremities and deteriorated neurologically. She was having poor respiratory effort with low neck muscle power. She was electively paralyzed and intubated. Brain and spine MRI revealed no abnormalities. A cerebrospinal fluid study showed albumin cytological dissociation; protein 70 g/dL, cell count lymphocytes 5/cumm, and no polymorphs, consistent with diagnosis of GBS.

Our patient was started on intravenous immunoglobulins (IVIG) 0.4 g/kg/day (20 g in this 50 kg weighing woman). She was ventilated for

3 days, and intravenous immunoglobulins were administered for a total of 5 days. She made a remarkable recovery and was extubated on day 3 of IVIG. She was able to walk without support on discharge.

The dengue illness of our patient followed an uncomplicated course without clinical or ultrasonic evidence of hemoconcentration. The lowest thrombocytopenia noted was 22 × 10^3/μL on the eighth day of her illness. Transaminases were significantly elevated, AST 364 U/L and ALT 240 U/L. Both dengue virus-specific immunoglobulin M (IgM) and immunoglobulin G (IgG) were positive on the ninth day of his illness. On discharge, she was fully recovered neurologically.

DISCUSSION

Dengue is an arboviral infection commonly presenting with fever, arthralgia, headache, and rashes. It is a major global public health challenge. Neurological manifestations of dengue fever are rare but have been reported in the medical literature. Guillain-Barré Syndrome, also known as GBS, is a rare neuromuscular disease that affects the peripheral nervous system.[4]

There has been a suggestion that the inflammatory cytokines produced from the dengue infection may lead to the development of GBS. It is thought that the dengue virus was able to increase the permeability of the blood-brain barrier, allowing the antibody to present itself to the cellular membranes. A case study in 2023 conducted by Lim et al., shows a patient showing signs of GBS after being previously diagnosed with Dengue Haemorrhagic Fever (DHF). The patient initially showed the typical symptoms of DHF with fever, arthralgia, and diarrhoea. The patient started to experience weakness and numbness in the lower limb after the second day of fever. The neurological examination showed a reduced muscle power distally and an absent deep tendon reflex as well as plantar reflexes.

The nerve conduction study reveals a bilateral asymmetrical mixed sensory and motor demyelinating polyneuropathy which is a common finding in GBS. It is unlikely that the two cases coincidentally occur as the symptoms have been presented in the early phase of dengue.[4]

According to the study conducted by Global Burden of Diseases in 2019, there was an increase of prevalence of GBS between the year 1990-2019 of around 6.4% per 100,000 population. The global number of cases had risen from 90,249 in 1990 to 150,095 in 2019. GBS is seen to be more prevalent in the young and the elderly with the highest number of cases found in the 5-9-year age group. The rising prevalence was also associated with an increase in terms of GBS related disability. In Indonesia, the prevalence of GBS is found between 1 to <1.25 per 100.000 population.[5] Patients with GBS are at risk of developing respiratory distress, cardiovascular dysfunction, as well as progressive weakness. It can occasionally occur after 1-2 days since the onset of the disease and may reach maximum severity at 2-4 weeks. The causes of death are often the result of cardiac arrest or acute respiratory distress syndrome. Symptomatic treatments, such as assisted ventilation, are needed in one quarter of the patients. Tracheostomy might be needed if there is a prolonged need for mechanical ventilation. It is necessary that most patients are admitted for observation of respiratory, autonomic, and motor function.[6]

The gold standard treatment of GBS lies in plasma exchange therapy and IV Immunoglobulin (IVIG) therapy. Immediate therapy is needed in patients with signs of respiratory distress, mobility problems, as well as reduction in vital signs. Plasma exchange allows plasma from cells to be separated from cells using filtration or centrifugation while the cells are re-infused back into the patient with GBS. Albumin is then used to maintain volume and osmotic equilibrium. IVIG is easier and safer compared to plasma exchange therapy however the efficacy between the two therapies was found to be similar. According to the American Society for Apheresis guideline for the

use of therapeutic apheresis, a therapeutic plasma volume (TPV) of 1-1,5 TPV is recommended over the course of 5-6 therapies over 10-14 days. A case study conducted by Stoian et al., reveals a significant improvement in patient with GBS undergoing four routine plasma exchange therapy with alternate doses between 0,5-1,2 TPV. Respiratory symptoms have improved after the first plasma exchange therapy.[6]

The developed of GBS alongside Graves' disease is rarely reported. A rare case study in 2019 by Majumder et.al shows a patient who develop Graves' disease alongside GBS.[1] The case study theorises those endogenous factors, such as gangliocytes and ICAM-1 as well as exogenous factor, such as bacterial and viral infection, may play a part in the simultaneous presentation of GBS and Graves' disease. Antibodies formed from these factors have an affinity to GM1 and GT1A gangliosides which are typically exposed on the plasma membrane of the peripheral nerves in the nodes of Ranvier and can cause molecular mimicry as well as cytokine stimulation which is the main feature of GBS. Simultaneously, these factors may also lead to the development of thyroid receptor antibodies (TRAb), which is the main factor in the development of Graves' disease. It is important to note, however, that the bacterial and viral infection that preceded each disease are different and more studies are needed to find a common infective ethology for both diseases.[7]

CONCLUSION

This case illustrates the importance of high clinical suspicion of GBS when a patient with Graves' disease and dengue fever infection develops GBS pattern neuropathy. Graves' disease is known to cause neuropathies, but the association between GBS and Graves' disease is less clear. Both are autoimmune disorders and can have common mechanisms or predisposing factors, but elevated thyroid hormones seem to be independently associated with nerve damage through increased oxidative stress. GBS begins suddenly and can increase in intensity over a period of hours, days, or weeks until certain muscles cannot be used at all. Some cases of GBS are very mild and only marked by brief weakness. Others cause nearly devastating paralysis, leaving the person unable to breathe on their own. In these cases, the disorder is life-threatening, potentially interfering with breathing, blood pressure, and heart rate. The patient was treated with IVIG with clinical improvement. Fortunately, most people eventually recover from even the most severe cases of GBS. After recovery, people may continue to have some weakness.

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CASE REPORT

Diffuse Toxic Goiter Hyperthyroid with Atrial Fibrillation in Type 2 Diabetes Patient

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ABSTRACT

Goiter is an enlargement of the thyroid gland which can occur in euthyroid, hyperthyroid, or hypothyroid. Hyperthyroidism can cause symptoms, such as palpitations, fatigue, sleep disturbances, weight loss, and heat intolerance. There are various complications and symptoms of hyperthyroidism, one of which is cardiac arrhythmia. Thyroid dysfunction can coexist with type 2 diabetes, so special attention is needed. Male, 43 years old, complaining of palpitations in the chest since 2 days ago. Complaints were accompanied by weakness, hand tremors, and lack of appetite. Patient also complained there was a lump in the neck that moved when swallowing since 5 months ago. Patient has a history of type 2 diabetes and regularly takes metformin. Physical examination found diffuse enlargement of the thyroid gland, soft consistency, indistinct borders and irregular heart rhythm. Electrocardiography showed atrial fibrillation. Ultrasound examination revealed bilateral diffuse goiter. Free T_4 result is elevated. Therapy given is infusion, methimazole, beta-blockers, digoxin, and metformin. Thyroid hormones have significant effects on the heart, which include increasing resting pulse rate, blood volume, stroke volume, cardiac muscle contractility, and ejection fraction. Thyroid also causes sinus rhythm disturbances. Early thyroid treatment has a better prognosis for improvement. Treatment of hyperthyroidism can affect the condition of diabetes, so monitoring blood sugar is necessary. Early diagnosis and prompt treatment of hyperthyroidism can resolve complaints and prevent complications. Thyroxine concentrations higher than normal are more at risk of experiencing atrial fibrillation. Hyperthyroidism can occur together with type 2 diabetes so it needs special attention.

***Keywords**: Goiter, hyperthyroid, atrial fibrillation, type 2 diabetes*

INTRODUCTION

Goiter is an enlargement of the thyroid gland.[1] The normal size of thyroid gland is 4 to 4.8 centimeters in The sagittal plane, 1 to 1.8 centimeters in the transverse plane, and 0.8 to 1.6 centimeters in anteroposterior dimension.[1] Goiters can occur in euthyroid, hyperthyroid, or hypothyroid.[1] The most common cause of goiter is iodine deficiency, with a prevalence of around 2.2 billionpeople worldwide.[1] Iodine is the main ingredient for the formation of thyroid hormone so iodine deficiency can cause a lack of thyroid hormone synthesis.[1]

Hyperthyroidism is characterized by increased synthesis and secretion of thyroid hormone from the thyroid gland.[2] The prevalence of hyperthyroidism is 0.8% in Europe and 1.3% in the United States.[2] The most common cause of hyperthyroidism is Graves' disease.[2] Graves' disease is triggered by an autoimmune process due to the presence of autoantibodies that bind to the TSH receptor thereby stimulating follicular cells to continue producing thyroid hormone.[2] Hyperthyroidism can affect various organ systems in the body.[3]

The most commonly complained symptoms are palpitations, fatigue, tremors, anxiety, sleep disturbances, and heat intolerance.[3] Physical examination can reveal tachycardia, tremors in extremities, and weight loss.[3] Graves' disease should be suspected in cases with symptoms of hyperthyroidism accompanied by clinical chemical findings of hyperthyroidism, such as decreased TSH level and free thyroxine (T4) level or increased triiodothyronine (T3) level.[4] Serum TSH level needs to be done first because it has higher sensitivity and specificity in diagnosing thyroid disorders.[2] Ultrasonography (USG) and TSH-receptor autoantibodies (TRAb) examinations can also be performed to support the diagnosis.[2]

Hyperthyroid therapy options are divided into three, namely anti-thyroid drugs, radioactive iodine ablation, and surgery (thyroidectomy).[5] Anti-thyroid drug therapy is preferred in cases of Graves' disease, except in America which prefers radioactive iodine ablation.[5] Methimazole is the main choice of anti-thyroid drug, except for first-trimester pregnant women, propylthiouracil (PTU) is the main choice.[5] Giving beta-blockers drugs, such as propranolol,is also needed to reduce patient complaints regardless of the cause of hyperthyroidism.[5] Complications and symptoms that arise in patients with hyperthyroidism vary.[2] Older patients show fewer symptoms than younger people but have a greater risk of cardiovascularcomplications.[2] When compared with elderly people without hyperthyroidism, elderly patients with hyperthyroidism have 3 times greater risk of experiencing atrial fibrillation.[2] Thyroid disorders can also be found in patients with type 2 diabetes related to insulin resistance.[6] Another condition that can be experienced in hyperthyroid patients is blood disorders because the thyroidalso plays an important role in hematopoiesis.[7]

CASE ILLUSTRATION

A male, 43 years old, came with chest palpitations 2 days ago and had been getting worse since this morning. Complaints accompanied by weakness, tremors in both hands, nausea without vomiting, and decreased appetite. Since 5 months ago, a lump appeared on the patient's neck. The lump enlarged and moved when swallowing. Complaints of weight loss were also recognized, but the amount of weight loss was not measured. The patient had a history of diabetes and routinely took metformin twice a day. History of similar disease in the family was denied. Examination of the patient's vital signs showed full awareness, blood pressure 135/88 mmHg, pulse rate 79 times per minute, respiratory rate 20 times per minute, and body temperature 37.5°C . Physical examination of the neck showed diffuse enlargement of the thyroid gland, soft consistency, with indistinct boundaries. Physical examination of the heart revealed single irregular 1st and 2nd heart sounds, without murmurs or gallops. An electrocardiography examination of the

patient showed atrial fibrillation. Ultrasound examination of the thyroid was also performed and found bilateral diffuse goiter suggestive of hyperthyroidism. Thyroid function examination showed increased levels of free thyroxine hormone (T4). A complete blood count examination showed an increase in hemoglobin, erythrocyte count and hematocrit parameters. Random blood sugar was increased. Treatment was given with ringer lactate infusion 28 drops per minute, methimazole 20 milligrams every 12 hours orally, propranolol 20 milligrams every 12 hours orally, digoxin 0.25 milligrams every 24 hours orally, and metformin 500 milligrams every 12 hours orally. After being treated for four days, the patient's complaints were reduced and the condition was stable.

DISCUSSION

Goiter is an enlargement of the thyroid gland.[1] Goiter can occur in euthyroid, hyperthyroid, or hypothyroid.[1] Hyperthyroidism is characterized by increased synthesis and secretion of thyroid hormone from the gland.[2] The most common symptoms complained by patients with hyperthyroidism are palpitations, fatigue, tremors, anxiety, sleep disturbances, and heat intolerance.[3] Physical examination can find tachycardia, tremors in extremities, and weight loss.[3] A 43-year-old male patient complained of a lump was the neck which had enlarged since 5 months ago. The lump is felt to move when swallowing, accompanied by weight loss and atrial fibrillation. Physical examination of the neck revealed diffuse enlargement of the thyroid gland, soft consistency, with indistinct boundaries.

Serum TSH level needs to be done first in cases with suspected hyperthyroidism because it has higher sensitivity and specificity in diagnosing thyroid disorders.[2] Ultrasound examination and TSH-receptor autoantibodies (TRAb) can also be performed to support the diagnosis and determine the etiology of hyperthyroidism.[2] Early screening and treatment of thyroid disorders with arrhythmias is important because it can affect long-term prognosis.[7] Normal levels of free hyroxine (fT4) in the blood are 11-25 pmol/L or 0.85-1.94 ng/dL.[9] T4 concentrations that are higher than normal have a higher risk of experiencing atrial fibrillation, especially in young patients.[9] The patient was then examined for free thyroxine hormone levels and found an increase in free T4 with a result of 4.86 ng/dL (normal: 0.89 - 1.72 ng/dL). The patient also underwent an ultrasound examination, which obtained bilateral diffuse goiter suspicion of hyperthyroidism with a right thyroid size of 5 centimeters x 2.9 centimeters x 2.99 centimeters, left thyroid size of 6 centimeters x 2.9 centimeters x 2.8 centimeters; irregular surface; parenchymal echotexture looks more hypoechoic inhomogeneous; no nodules or cystic lesions were seen; no calcification is seen.

Thyroid hormones have significant effects on cardiac function, both genomic and non- genomic.[10] Hyperthyroidism is characterized by an increase in resting pulse rate, blood volume, stroke volume, heart muscle contractility, and ejection fraction.[10-11] Atrial fibrillation can occur due to various mechanisms, such as an increase in right atrial pressure which can increase right ventricular workload and impaired ventricular relaxation, ischemia due to increased resting heart rate, and increased ectopic atrial activity.[11] Atrial fibrillation can also occur due to disturbances in sinus rhythm caused by suppression or replacement of sinus mechanism by a diffuse and irregular rhythm.[8] In this case, the patient complained of chest palpitations. This complaint was related to atrial fibrillation. Physical examination of the patient's chest revealed single but irregular in both first and second, heart sounds. The patient then underwent an electrocardiogram examination and atrial fibrillation was found with a pulse rate of 92 beats per minute.

In this case, the patient also had a history of diabetes mellitus and routinely consumed 500 milligrams of metformin twice a day. The patient was randomly checked for blood sugar and the result was 245 mg/dL

(normal: <200 mg/dL). Diabetes mellitus an thyroid disorders are endocrine disorders that are often found and can occur together.[12] Both of these endocrine disorders can increase the risk of heart disease.[12] Thyroid disorders are more common in type 1 diabetes than type 2.[12] This is related to the autoimmune process that underlies thyroid disorders and type 1 diabetes[12], whereas type 2 diabetes is associated with insulin resistance.[6]

Anti-diabetic drugs can affect thyroid function and anti-thyroid drugs can interfere with glycemic control.[12] Hyperthyroidism is associated with poor glycemic control, characterized by hyperglycemia and insulinopenia.[12] Thyroid hormone can increase gastrointestinal motility and increase glucose absorption in the gastrointestinal tract.[13] An increase in the process of gluconeogenesis also occurs in the liver due to the effects of thyroid hormones.[6,13] Thyroid hormone also increases the process of lipolysis in adipose tissue.[6] Diabetes can interfere with thyroid function by affecting TSH hormone levels and interfering with the conversion of T_4 to T_3 in peripheral tissues.[14]

Thyroid hormone plays an important role in hematopoiesis so blood disorders often occur in patients with thyroid disorders.[7] Thyroid hormone can have a direct effect on blood by stimulating erythrocyte precursors and indirectly by increasing erythropoietin production.[7] The study conducted by Ahmed et al. demonstrated that thyroid disorders can affect all blood parameters except platelets.[7] Anemia often occurs in patients with thyroid disorders, especially hypothyroidism.[7] Another study conducted by Liu et al. showed the presence of erythrocytosis in hyperthyroid patients with Graves' disease.[15] This result is associated with an increase in hypoxia-inducible factor-1-alpha (HIF-1α) which causes an increase in erythropoietin.[15] Polycythemia can occur in cases of hyperthyroidism. A case report by Souresho et al., explainedthat patients with a history of hyperthyroidism and hypertension experienced polycythemia with a hemoglobin level of 16.4 g/dL and a hematocrit of 52.1%.[16] However, there was no examination of erythropoietin or JAK2 cell mutations to confirm the cause of erythrocytosis.[16]In this case, the patient underwent a complete blood count, obtained a hemoglobin level of 18.6g/dL (normal: 11.5-16.2 g/dL), erythrocytes 6.76 million/uL (normal: 4.00-5.90 million/µL), hematocrit 53.1% (normal: 35-45%), leukocytes 7.24 thousand/uL (normal: 4.50-11.00 thousand/µL), and platelets 181 thousand/uL (normal: 150 450 thousand/µL). Patients experiencing erythrocytosis or polycythemia are characterized by an increase in erythrocytes, hemoglobin, and hematocrit. Relative polycythemia can occur due to lack of intake. To rule out the differential diagnosis, patients can be planned for examination of erythropoietin and JAK2 hormone levels.

Management of hyperthyroidism depends on the etiology, severity, age, comorbidities, and treatment options. The main options for therapy are beta-blockers and anti-thyroid drugs, namely propylthiouracil and methimazole.[8] Beta-blockers, such as propranolol, are used to control adrenergic symptoms.[8] Early screening and thyroid treatment are important because they can affect long-term prognosis.[8] Patients were given methimazole 20 milligrams every 12hours orally and propranolol 20 milligrams every 12 hours orally to reduce thyroid hormone levels in the blood and overcome complaints.

Treatment of atrial fibrillation patients with hyperthyroidism aims to prevent symptoms by controlling heart rate and rhythm and preventing complications, such as heart failure and stroke.[8] A study in 1982 showed that 62% of patients with atrial fibrillation were able to return to sinus rhythm after the first three to four months of thyroid treatment.[8] Patients with early thyroid treatment can experience improvement in heart rhythm after two to three months.[17] Cardioversion, both electrically and pharmacologically, can be given if atrial fibrillation has not improved.[17] Patients are given digoxin 0.25 milligrams every 24 hours orally as a therapy tocontrol heart rate and rhythm.

Diabetic patients on metformin treatment have smaller thyroid volumes and a smaller risk of developing thyroid nodules compared to controls.[18-19] Metformin is known to have the effect of lowering TSH levels, reducing thyroid nodule volume, and preventing the development of thyroid carcinoma.[18] Giving sulfonylureas should be avoided in diabetic patient with thyroid disorders because they can increase the risk of thyroid carcinoma.[20] Metformin medication which was taken by the patient continues. Anti-thyroid drugs can also cause hypoglycemia, related to insulin autoimmune syndrome which can make insulin ineffective due to binding with insulin autoantibodies.[12]

Cases of erythrocytosis or polycythemia can be divided into relative and absolute polycythemia.[16] Relative polycythemia occurs in patients with low plasma volume due to insufficient intake or excessive output.[16] While absolute polycythemia occurs in patients with polycythemia vera, a mutation in the JAK2 gene which causes an increase in the number of erythrocytes, and patients with increased levels of erythropoietin, a hormone that can stimulate the production of erythrocytes.[16] Patients were given a ringer lactate infusion of 28 drops per minute to increase intake.

CONCLUSION

A 43-year-old male, came with complaints of chest palpitations since 2 days ago and had been getting worse since this morning. Complaints accompanied by weakness, tremors in both hands, nausea, and decreased of appetite. Since 5 months ago, a lump appeared on the patient's neck. The lump enlarged and moved when swallowing. Complaints of weight loss was recognized by the family but was not measured. Patient has a history of diabetes and routinely takes metformin 500 milligrams twice a day. Physical examination of the neck showed diffuse enlargement of the thyroid gland, soft consistency, with indistinct boundaries. Physical examination of the heart revealed single irregular first and second heart sounds. The result of the heart record examination showed atrial fibrillation. Ultrasound examination of the thyroid was also performed and found bilateral diffuse goiter suggestive of hyperthyroidism. Examination of thyroid function showed increased levels of free thyroxine (T_4) hormone. Complete blood count showed an increase in the parameters of hemoglobin, erythrocyte count, and hematocrit. Examination of random blood sugar of patients showed increased results. The treatment given was an anti-thyroid drug and beta-blockers to reduce thyroid levels and reduce complaints, an anti-diabetic drug in the form of metformin to control sugar levels, infusion of physiological fluids to treat polycythemia, and anti-arrhythmic drugs to control heart rhythm. After being treated for 4 days, the patient's complaints were reduced and his condition was stable.

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Review Article

The Comparison of X-ray Finding in Pulmonary Tuberculosis with and without Diabetes Mellitus

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ABSTRACT

Diabetes Mellitus patients are considered as a high-risk population for the development of Pulmonary Tuberculosis (PTB) by about three-fold. Diabetes Mellitus sufferers by glycated haemoglobin A1C (HbA1C) level. The relative risk(RR) of Tuberculosis (TB) was 3,1 (95% CI 1.6-5.9) for those with HbA1C ≥7%. There are several contradictory opinions regarding the radiological appearance of TBC sufferers with genuine effect of DM. Chest X-ray remains the primary investigation for the assessment of PTB. Pulmonary Tuberculosis is found predominantly in the lung apices. It is not clear whether DM can affect the presentation of TB. Thus, whether diabetic subjects present atypical radiological presentation of PTB is still controversial. There have been several studies with contradictory results regarding the differences in the radiological appearance of PTB patients with and without DM. Clinical studies have shown ambiguous results.Any other risk factors maybe associated with age, sex, smoking status, and nutrition status.

Keywords: *Tuberculosis, pulmonary tuberculosis, diabetes mellitus, chest x-ray, lesion.*

INTRODUCTION

Tuberculosis is a chronic infection disease caused by bacteria belonging to the Mycobacterium Tuberculosis (MTb) which usually infects lung parenchyma.[1] Tuberculosis has been a significant public health problem worldwide for the last 2 decades. Globally, in 2021, there were an estimated 1.5 million deaths among TB infection. Furthermore, World Health Organization (WHO) estimated 9.6 million people fell ill with TB worldwide in 2021. Currently, Indonesia is the second largest contributor to TB cases in the world, after India. Diabetes Mellitus is an important risk factor for TB development. World Health Organization reported, DM was associated with an increased risk of PTB infection 3 times higher in patients than in those without DM.[2] Diabetes mellitus is known caused immune dysregulation, adversely affecting neutrophil chemotaxis, macrophage function and phagocytic responses, decrease T-helper cells (Th)-1 cytokine, tumor necrosis factor (TNF)-α and TNF-β, interleukin (IL) such as IL-1 and IL-6.[3,4]

There are several contradictory opinions regarding the radiological appearance of TB sufferers with DM risk factors. Radiographic manifestations of PTB in patients with DM have previously been reported differently. Diabetes mellitus type 2 could increase the risk of advance lesion PTB as much as 5.25 times.[5] Radiologically, co-existing DM and TB may induce an increase of pulmonary atypical manifestation, including lower lobe lung opacity, occurrence of more lung lesions, cavity, and extensive parenchymal involvement. Whereas non-DM patients usually had upper lobe infiltrates.[6-9] However, the results reported by different researchers have not been consistent. Meanwhile, in several other studies, no differences were found in chest X-ray between PTB patients with and without DM. Two research from our hospital find no significant differences in the appearance of PTB lesions of DM compared to non-DM.[10-13] Additional research by Morris JT and Weaver RA there was no cavitary lesions on PTB with DM patients.[14-15]

EPIDEMIOLOGY OF TBC AND DM

Globally, TB is one of the 10 leading causes of death and the top cause from a single infectious agent. The World Health Organization estimated the global burden of TB in 2017 at 10 million incident cases, which is 90% of cases are adults (aged ≥15 years).[16] The higher MTb burden is associated with increasing number of DM cases.[17] Active PTB will appear more often in insulin-dependent DM patients (insulin dependent diabetes mellitus/IDDM) compared with non- insulin dependent DM patients (non-insulin dependent DM/NIDDM). Diabetes Mellitus subject with baseline glycated hemoglobin A1C (HbA1C) levels ≥7% higher prevalence of developing active PTB (adjusted hazard ratio [HR]: 3.11) with 95% confidence interval (CI) 1.6-5.9.[18] Hyperglycemia was strongly associated with worsen pulmonary radiographic manifestation in TB patients.

RADIOLOGICAL FEATURES OF PTB

Chest x-ray constitutes the main diagnostic support to identifying suspected PTB. Chest x-ray examination is relatively simple but can describe the severity of PTB, the status of active PTB, and evaluate the extent of lung lesions/damage. Serial chest radiographs are also used to monitor PTB therapy.[18] The location of the main lesion on chest radiograph was classified as typical and atypical lesion. Typical means the lesion is in the upper fields of the lung, while atypical means the lesion involves the lower fields of the lung. Primary TB parenchymal involvement can happen in any segment of the lung. Mostly, the lesions are in the apex area in accordance with bacterial predilection. Mycobacterium Tuberculosis is an aerobic bacterium and therefore proliferates higher oxygen tension and lower blood flow, i.e., a higher ventilation/perfusion (V/Q) ratio than the base lung fields.[19-20]

The sensitivity and specificity of infiltrate-fibro infiltrate on chest X-ray to presumptive TB was 87.5% and 82.5%, while the combination >3 lesions was 87.5% and 77.2%. This means that existing chest X-ray abnormalities can significantly diagnose

patients with PTB. Specificity rates of 82.5% in fibro infiltrate and 77.18% in combined abnormalities means that not finding these lesions on a chest X-ray can significantly rule out the diagnosis of the patient not suffering from PTB.[21-22]

The imaging appearances in PTB initially consists of cloud-like spots with unclear boundaries, then develop to various types of lesions. They can be grouped into lung parenchymal/infiltrate lesions (including consolidation, cavitation, miliary nodules, fibrosis, calcification, atelectasis), pleural lesions (including pleural effusion, pleurisy, pleural calcification), and mediastinal lesions (including hilar and mediastinal lymphadenopathy). The types of lesions in TB can imitate various other disease processes, furthermore TB is often called "the great imitator". For example, tuberculoma and consolidation as radiological finding in PTB is also often found in pneumonia, pulmonary mycosis, bronchial carcinoma, or metastatic carcinoma in the lung. Besides, a cavity picture is also present in lung abscesses.[19,23]

The extent of disease was estimated based on the sum of all areas of abnormality in which a boundary of abnormal opacity could be drawn. Minimal lesions were defined as an area less than that above a horizontal line across the 2nd chondrosternal conjunction of one lung. Whereas PTB with extensive lesion includes moderately advanced lesion and far advanced lesion. Moderately advanced lesions were defined as an area greater in size than the minimal lesions but smaller than that of one entire lung. Far advanced lesions were defined as an area equivalent to or greater than one lung. The size of the largest cavity was dichotomized into small and large by the median diameter.[24]

RADIOLOGICAL FEATURES IN PTB WITH DM

Diabetes Mellitus is also believed to affect radiological manifestations of PTB. It has been demonstrated in numerous studies that co-existing DM and TB conditions may induce an increased frequency of pulmonary atypical manifestation, including lower lobe lung opacity, occurrence of more lung lesions, cavity and extensive parenchymal involvement. Impaired immune response in diabetic patients will increase bacterial load and inflammation, thus leading to necrosis and bacterial dissemination. The site of PTB lesions is generally present in the upper lobes. Compared with those without DM, PTB patients with DM were significantly more likely to have lesions over lower lung fields. In DM, there is an increase in alveolar ventilation and decrease in perfusion due to thickening of the lung alveolar epithelium. This condition resulting in an increase in alveolar oxygen pressure in the lower part of the lung which representative lesions in the lower lung fields.[25] The characteristics of atypical lesions in PTB sufferers with DM have been proven by many studies, such as those conducted by Qazi, et al, Perez-Gusman, and Shaikh et al.[8-10]

Several studies reported that TB patients with DM had worsen radiological finding. According to Layali et al (2019), diabetic PTB patients have a significantly 15-fold higher risk of multiple cavitary lesions and 6,29-fold higher risk of having an atypical lesion appearance compared with those without. In another study, Utomo and Margawati also reported that DM have increased the risk of advance lesion PTB as much as 5.25 times. Based on the area of the lesion, the degree of severity that most found was far advanced lesion (61.9%), followed by moderately advanced lesion (28.6%), and the least was minimal lesions (9.5%). In addition, Ramzi showed the chest X-rays of diabetic PTB are the most performed extensive lesions (60%).[5,13,26] Thus, chest X-rays with extensive lesions was dominated by TB patients with DM.

Elevated levels of HbA1c can worsen infections caused by TB because HbA1c levels are directly proportional to blood glucose concentrations. Chronic hyperglycemia impairs the immune system, worsening the clinical appearance, and radiographic manifestations of PTB. This is in line with research by Chang JT et al, showed DM-TB patients with mean HbA1C 10.0 ± 2.6% results in more severe infections and higher mycobacterial loads. In fact, an increase of 1 unit in HbA1c indicates an

increased risk of 3 types of lung lesions (cavities, infiltrates, and fibroustracts) or ≥ 4 lung lesions in TB patients.[27,28]

CONTRADICTIVE RADIOLOGICAL FEATURES OF TBC WITH AND WITHOUT DM

There had been much debate concerning the atypical radiographic findings of TB with DM. Some authors have reported no major differences while others havereported a higher involvement of the lower lung fields. Pérez-Guzman et al. reported that TB patients with DM had cavity disease more frequently than patients without DM. It is known that DM causes the dysfunction of polymorphonuclear leukocytes and reduces bactericidal activity. Thus, cavity development may be more progressive in DM patients with pulmonary TB. However, decreased immunity may also be related to the lower frequency of cavitation in DM patients, as discussed above. It remains controversial whether DM has a positive or negativeimpact on cavity disease.[8]

Similarly, research conducted by Alavi et al, showed that in PTB patients with DM, lesions were more common in the upper lobes of the lungs (59%).[30] Otherwise, Layali found a relationship between DM and the location of the lesion. TB subjects with DM had a 6.29 times risk of having atypical lesions compared to TB without DM (P<0.01).[26] Diabetic PTB subjects who had HbA1c=7-8.9% increased 14.25 times risk of having atypical lesions compared to those with HbA1c <7gr% (P=0.024). This is in accordance with previous research conducted by Bokam et al, who found that HbA1c levels with an average of 8.87 had 59% lesionsin the lower lung fields.[31] Further examination revealed that pulmonary TB lesions in the lower lung fields were more common in the group of TBC-DM subjects (24.11%) compared to TBC without DM (6.35%) (P<0.0001).[32] Likewise, research by Chiang et al, who found that TB with DM had a risk of having lesions in the lower part of the lungs 1.37 times compared to TB without DM (OR=1.37; 95% CI=1.04-1.81).[15] In addition, Edwina examined the degree of severity which minimal lesions was found more common in PTB non-DM (40%).[33] We conclude that the patients with PTB and DM are more likely to present atypical and extensive lesions in radiographic manifestation. Tuberculosis lesions in DM often occur in the lower lung fields because the VA/Q and PaO2 ratios are high in the lower lung fields.[8] The number of mature alveolar macrophages increased in PTB patients, but there was no significant difference in the number ofT lymphocytes between PTB patients with and without DM. The lower proportion of mature alveolar macrophages in TB patients with DM may be responsible for the more severe expansion of lesions in the lung fields of pulmonary TB patients.[10]

FACTORS AFFECTING RADIOLOGICAL FINDING OF PTB

Besides the correlation with glycaemic index, other findings confirmed previous reports that age, sex, smoking, and nutritional status were associated with radiographic manifestation of pulmonary TB.

Age

The impact of age on the radiologic presentation of PTB is important because misinterpretation might delay appropriate diagnostic. Pulmonary Tuberculosis lesions in DM and elderly patients are often located in the lower lung fields. One possible explanation for this atypical presentation may be that in the elderly and diabetics increased alveolar oxygen pressure in the lower lobes promotes disease development in these areas. It is based on the concept that multiplication of MTb is favored by high oxygen tension. Aging leads to increased alveolar ventilation (VA) and reduced perfusion (Q), resulting in an increase in VA/Q miss-match and increases PaO2 in the lower lung fields. Therefore, age-induced changes should favor multiplication of Mycobacterium tuberculosis in lower lung zones. Furthermore, Guzman et al, found that the frequency of upper lung field lesions (with or without lower lung field lesions) was similar at all ages, suggesting that aging does not alter conditions in the upper lobes.[8,25,34] The proportion of patients with upper lung field

opacity did not differ by age group (p=0.380). Those aged ≥65 years were significantly more likely to have lower lung field opacity than those <65 years old (75.3% vs 68.6%, adjusted OR 1.42, 95% CI 1.09-1.85). In all age groups, the proportion of patients with upper lung field opacity was higher than those with lower lung field opacity. However, due to the increased proportion of patients with lower lung field opacity among those with DM in those aged <55 years old, the association between age group and lower lung field opacities was no longer statistically significant among DM (p=0.550). However, the frequency of cavitation in the TB group showed a negative correlation with age, from about 80% at age-periods 30-39 and 40-49, to less than 20% at age ≥80 (p<0.05). A higher proportion of both cavities and lower lung lesions was still observed in the diabetic group in all age categories (almost always more than 70%).Infiltrates were found to be the most common radiological finding in both younger (35.25%) and elderly (65.76%) patients. [15,25,35,36] The elderly are more likely to have lower lung field lesions and less likely to have cavities as compared with younger patients

Cavitation with infiltration was significantly associated with the younger age group. Due to impaired T-cell function and poor immunological status, the elderly are less prone to cavity formation. The proportion of patients with cavitary lesions was highest among those aged 35-44 years and decreased progressively with age. Diabetes did not obscure but aggravated the differential risks of cavitary lesions between the elderly and younger patients. Diabetes increased the risk of cavitary lesions, especially among younger patients, likely through a mechanism that is different from the one causing increased lower lung field involvement, and the risk of cavity among diabetes patients is driven by glycemic control.[25,35,36]

Sex

Radiographic manifestations of TB also differed by sex. Chiang reported males were significantly more likely to have any opacity on lung parenchyma (male 99.3% vs female 97.6%, p=0.019), opacity over upper lung field (male 95.8% vs female 86.9%, p<0.001). Females were significantly more likely to have isolated lower lung field opacity (male 3.5% vs female 10.7%), with an adjusted odds ratio 2.5 (95% CI 1.4-4.5). Males were significantly more likely to have far advanced parenchymal lesions (male 23.0% vs female 14.5%, p<0.001), any cavitary lesion (male 46.3% vs female 31.5%, p<0.001) and cavitary lesions over upper lung fields (male 43.2% vs female 28.7%, p<0.001) but not cavitary lesions over lower lung fields (male 10.0% vs female 6.9%, p=0.116).[15]

Isolated lower lung field TB without upper lung field involvement deserves attention as diagnosis of lower lung field TB can be difficult. Aktogu reported that 6.2% of PTB patients had isolated lower lung field TB and the proportion of patients with isolated lower lung field TB was higher among females (11.8% of female vs 4.4% of males, p<0.005) and diabetes (11% of diabetic patients vs 5.3% non-diabetic patients). Chang reported that 5.1% of PTB patients had isolated lower lung field TB and the proportion of patients with isolated lower lung field TB was 16.3% among females and 3.1% among males (p<0.005). That a higher proportion of diabetic patients had isolated lower lung field TB than non-DM has also been reported by Pérez-Guzmán (19% among DM vs 7% among non-DM) and Marais (29% among DM vs 4.5% among non- DM).[29,36,37,38] Our study confirmed that isolated lower lung field TB is more frequent among female than male but not more frequent among DM than non- DM.

Smooking

Although smoking and DM are both important risk factors for TB, it is unclear whether there is a differential influence of smoking on PTB between non-DM and DM patients. There is a significant relationship between smoking status and extensive PTB status. Research on the effects of nicotine has revealed that it may increase the risk of TB by reducing local TNF in the lungs. Tobacco smoke contains around 4.500 compounds that likely have active

biological effects. Anti- inflammatories and immunosuppressants were also found to be concentrated in the substance nicotine. An initial hypothesis was that nicotine is immunosuppressive because it activates hypothalamo pituitary adrenal axis (HPA axis) via nicotine receptors in the central nervous system. However, it waslater discovered that the HPA axis was only important for the acute effects of nicotine, while the chronic anti-inflammatory effects persisted after adrenalectomy. The body's resistance, especially in the lungs, decreases,causing TB lesions that were initially not extensive to become extensive.[24,39,40] By contrast, smoking reported was only associated with non-DM PTB patient. Smoking was increased frequency of bilateral lung parenchyma involvement (AdjOR 1.84, 95% CI 1.16-2.93) and far-advanced PTB (AdjOR 1.91, 95% CI 1.04-3.50) in non-DM PTB. Smoking was also significantly associated with an increased frequency of multiple, and large cavities in non-DM TB. However, smoking was not associated with cavitary lung parenchyma lesions in terms of the location, number, or size of cavitary lesions in DM TB patients.[24]

Nutrition status

Tverdal et al showed overweight reduced risk of PTB. Obese were believed to have a high nutritional intake of protein to produce energy, which is immunefunction is not disturbed. It has been used, the more BMI of a DM patients decrease (underweight), had a correlation the wider active PTB lesion on the chest X-ray. Of note, Sahin et al, found in non-DM TB patients that a decrease in BMI was associated with elevated inflammatory markers as well as a more advanced radiological manifestation. It is a well-recognized fact that weight loss in TB is evidently related to the acute phase response.[39,40]

CONCLUSION

Chest X-ray examination in PTB showed various forms (multiform). There are several contradictory opinions regarding the differences in the radiological appearance of PTB patients with and without DM. Some research suggested eitherno difference between the appearance of the lesions or severity of PTB. The factors summarised included age, sex, smoking, and nutrition status. Abnormalitiesseen on chest X-ray may be suggestive of but are never diagnostic of TB.

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Review Article

Tirzepatide: Dual GIP/GLP-1 Receptor Agonists, from Molecular to Clinical Practice for Treating Type-2 Diabetes and Obesity

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ABSTRACT

Tirzepatide is a promising drug with dual-acting glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide 1 (GLP-1) receptor activation that has revolutionized the treatment of type 2 diabetes mellitus (T2DM). In phase 3 clinical trials (SURPASS 1-5), tirzepatide has been shown to achieve better glycaemic control in terms of glycosylated hemoglobin reduction (HbA1c) and improved fasting, postprandial glucose levels and weight reduction as compared to placebo and active comparators. The SURPASS 4 clinical trial has shown positive cardiovascular outcomes in people with T2DM with elevated cardiovascular risk. Tirzepatide has acceptable side effects and is well tolerated, with a low risk of hypoglycaemia. Additionally, encouraging results from SURMOUNT trials and ongoing SURPASS-CVOT studies will shed more light on cardiovascular safety in the future. In this review, we have summarized the pharmacology, efficacy, safety, and clinical trials for potential impact for clinical treatment T2DM.

Keywords: *Dual agonist GIP/GLP-1, obesity, tirzepatide, type-2 diabetes*

INTRODUCTION

Diabetes mellitus (DM) remains a major global health problem, with 536.6 million people living with diabetes today.[1] Diabetic patients will spend more on healthcare than non-diabetics and have a 60% higher risk of premature death. Diabetes significantly increases the risk of comorbidities, including myocardial infarction, cardiovascular events, nephropathy, neuropathy, and retinopathy.[2] Obesity and particularly central adipocytes are risk factors for the occurrence of type 2 diabetes mellitus (T2DM), and weight loss can prevent or inhibit the worsening of diabetes, especially the occurrence of cardiovascular risk.[3,4]

Currently, many anti-diabetic drugs focus on weight loss in the diabetes mellitus population. Diabetes medications have advanced at the end of this decade. First, incretin-based, namely DPP4 inhibitors (DPP-4i, gliptins) and glucagon-like peptide-1 receptor (GLP-1Ras) agonists. Second, sodium-glucose cotransporter type 2 inhibitors (SGLT2is, gliflozins). GLP-1 receptor agonists have a special place in the treatment of T2DM patients. Treatment of DM with GLP-1 RA has been included in treatment guidelines by Europe[5], America[6], Indonesia[7], and the French Society of Diabetes (Société francophone du diabète: SFD), an important statement from SFD is that it has placed GLP-1 before insulin treatment after failure with oral drugs.[8]

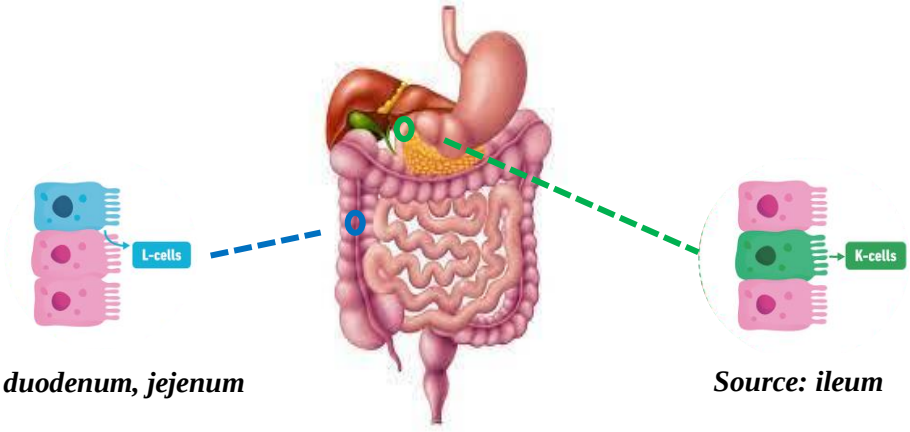
In recent years, GLP1 receptor and glucose-dependent insulinotropic polypeptide (GIP), known as the incretin hormone class, have attracted researchers. GIP can stimulate insulin after meals, lower blood sugar, and make the body more responsive to insulin.[9,10] Furthermore, it can also reduce weight by slowing gastric emptying.[11,12,13] The combination of GLP-1 and GIP has been proposed as a modern option for treating diabetes and obesity.[14] As the early product of dual GIP and GLP1 agonist ("twincretin"), tirzepatide (LY3298176, @ Mounjaro) has been approved by the US Food and Drug Administration since 13 May 2022 to medicate the DM patient, following to its diet and exercise treatment.[15]

This literature review aims to assess the role and clinical evidence of tirzepatide as a GIP/GLP1 dual in treating diabetes and obesity.

Mechanism of Action Tirzepatide for Glucose Haemostasis

Incretin Effect

Combining GIP and GLP-1 agonist in tirzepatide gives the GIP receptors a higher affinity, stabilizing normal glycemic state and weight loss in type 2 diabetes mellitus. Elrick et al, were the pioneers to report that plasma insulin concentration was significantly higher after oral glucose loading compared to parenteral therapy.[16] This phenomenon is known as the "incretin effect," it has been shown that insulin secretion from the pancreas is dominated by 65% of post-meal insulin secretion.[17] Incretin hormones include GLP-1 and GIP. Concentration levels of GLP-1 and GIP are deficient during fasting and increase 15-30 minutes after a meal.[18] Concentration levels of GLP-1 and GIP are deficient during fasting and increase 15-30 minutes after a meal.[19] Post-production, GIP and GLP-1 stimulate pancreatic cell receptors to activate the glucose-dependent insulinotropic response and increase the loss of proper carbohydrate and fat absorption. The incretin produces a brief effect, given that the activated hormones only last one to two minutes after the release before being terminated by the enzyme dipeptidyl peptidase-4 (DPP-4).[19] The effect of incretins is greatly decreased in T2DM patients compared to those without T2DM.[18] Decreased synthesis of incretin hormones in response to feeding (hyposecretion) and loss of insulinotropic action on beta cells[20] are two circumstances that illustrate the decreased effect of incretins in T2DM.[21]



GLP-1	Pancreatic and exopancreatic action	GIP
Appetie ↓ Food intake ↓ Nausea ↑	Brain	Appetie ↓ Food intake ↓ Nausea ↓
Insulin secretion ↑ Glucagon ↓	Pancreas	Insulin secretion ↑ Glucagon ↑
Gastric emptying ↓	Stomach	Gastric acid secretion ↓
Lipolysis ↑	Adipose tissue	Lipogenesis ↑ Lipid buffering capacity ↑
	Bone	Bone resoprtion ↓
Cardioprotection ↑	Heart	
Natriuresis ↑ Diuresis ↑	Kidney	

Figure 1. Mechanism of Action of glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide (GLP-1) in pancreatic and extra-pancreatic. *Adapted from* Rachel S 2023 (22) and André J. Scheena 2023[23]

Complementary effects of GIP and GLP-1

The complementary effects of GIP and GLP-1 can be seen in the illustration of Figure 1. GLP-1 is secreted mainly from L cells in the ileum and colon in response to food entry.[24] Exogenous infusion of GLP-1 persuades the action of lowering multiple glucose, including stimulation of glucose-induced insulin secretion, prolonging gastric emptying time, and inhibiting glucagon secretion in healthy individuals and T2DM patients.[25] Moreover, some reactions, such as decreased food consumption and appetite, are results of exogenous GLP-1 infusion, although it would not directly affect energy expenditure.[26] GLP-1 stimulates insulin secretion after a meal while inhibiting glucagon secretion, which both are sustained by glucose. It also improves satiety through two mechanisms: central (via the hypothalamus) and peripheral (via slow gastric emptying). This mechanism will improve glucose control in T2DM patients, thus bringing several advantages, such as inescapable hypoglycemia and losing weight. GLP1 also positively affects the cardiovascular system and may reduce liver steatosis.[26,27]

GIP is a peptide secreted by K cells in the duodenum and jejenum in response to post-food consumption. In non-diabetic people, GIP provokes insulin secretion without altering glucagon release during hyperglycemia, although GIP increases glucagon release without affecting insulin secretion during hypoglycemia.[28,29] In individuals with T2DM, GIP's ability to stimulate insulin secretion and improve glycemia is impaired, but GIP sensitivity can be regained after improving glycaemic control.[30,31] The central action of GIP may decrease appetite by increasing satiety, leading to weight loss.[32] However, the exact mechanism remains controversial, between the direct and indirect action of GIP through its ability to have an anorectic effect. In peripheral action, GIP benefits body fat and muscle tissue.[33] It can increase lipid storage in white fat tissue and decrease ectopic fat storage in muscle, improving insulin sensitivity.[34]

Tirzepatide: GIP/GLP-1 original unimolecular

The developed dual (or triple) receptor agonist's originality lies in its unimolecular structure, displaying the technological advancement in the field of peptide biotechnology.[35] The chemical structure of tirzepatide is LY3298176. The GIP/GLP-1R unimolecular dual agonist, tirzepatide, is a multifunctional peptide based on the native GIP peptide sequence, designed to bind to both receptors. GIP and GLP-1 combined effect on food consumption and expand in energy expenditure results in body weight loss.[34] tirzepatide is a linear peptide of 39 amino acids conjugated to the fatty diacid moiety C20 through a linker chained to a lysine residue at position 20.[35]

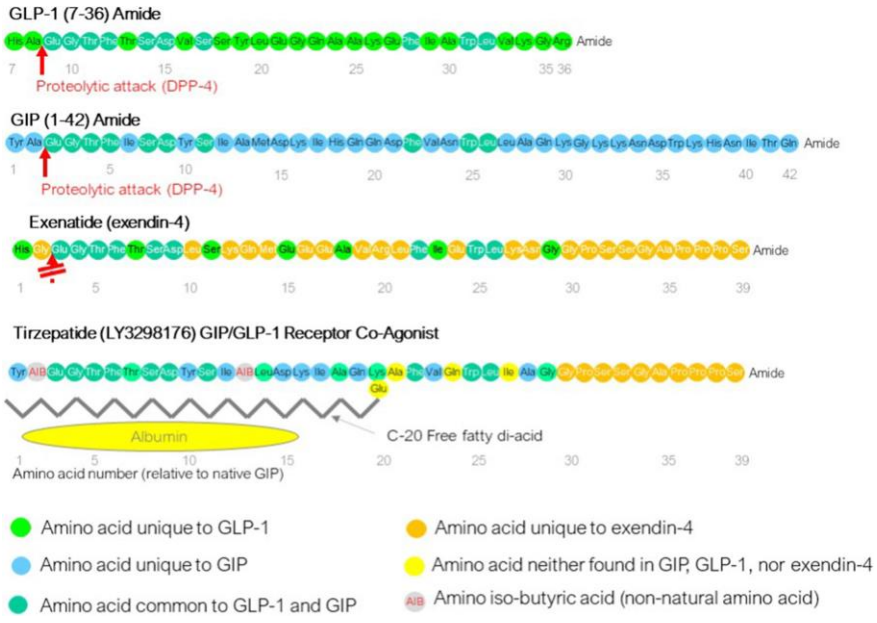


Figure 2. Amino acid sequences of the incretin hormones GLP-1 (glucagon-like peptide-1) and GIP (glucose-dependent insulinotropic polypeptide), the GLP-1 receptor agonist exenatide, and tirzepatide, a GIP/GLP-1 receptor co-agonist.

Colours indicate amino acids in the peptide sequence of tirzepatide which correspond to amino acids in the original primary structure of GLP-1 (green), GIP (blue), shared by both GLP-1 and GIP (blue-green), exenatide (orange). Amino acids not related to any of the parent peptides are shown in yellow. Amino-iso-butyric acid (AIB), a non-natural amino acid, is shown in grey with red letters. The primary amino acid sequence of tirzepatide has been taken from (35); the sequences for human GIP, mammalian GLP-1, and exenatide for comparison are from (36-37).[34]

Figure 2 shows the tirzepatide peptide sequence also accommodates two noncoding amino acid residues at positions 2 and 13 (Aib, a-amino isobutyric acid), and a C-terminus in the center.[38,39] The acylation approach with fatty acids is well known in the field of diabetes as it has been successfully used to extend the duration of insulin and GLP-1 activity, allowing the peptide to bind to albumin, increasing the biological half-life, estimated to be around 116 hours. Therefore, tirzepatide can be used once a week for subcutaneous injection in humans. The molecular weight of tirzepatide is 4810.52 Da.[23]

Clinical Trials for Tirzepatide

Tirzepatide was initially tested in patients with T2DM with lifestyle changes (diet and exercise) or with metformin in phase-2 trials. These trials assessed the effectiveness and safety of increasing doses of tirzepatide from 5 to 15 mg once weekly versus placebo for 12 weeks.[40] and compared to placebo or dulaglutide, a pure GLP-1 analogue, in 26 weeks.[41]

Promising early results in this trial have demonstrated that tirzepatide has been tested in a large study called SURPASS in T2DM patients uncontrolled with various sugar-lowering therapies,[42] including lifestyle alone (SURPASS-1)[43], metformin monotherapy (SURPASS-2)[44], metformin with or without SGLT2i inhibitors (SURPASS-3)[45], combined metformin, SGLT2i and/or sulfonylurea therapy (SURPASS-4)[46], insulin glargine with or without metformin (SURPASS-5)[47] and SURPASS-6[48] (unpublished study). All clinical trials of tirzepatide are reviewed in table 1.

Effects on Glycaemic Outcome

HbA1c effect

The main goal was the HbAc1 level's modification from baseline values. Tirzepatide showed greater dose-dependent reductions in

HbA1c values than placebo, basal insulin, and semaglutide in all SURPASS experiments, even with other glucose-lowering treatments.[23]

In new T2DM subjects, treated only with diet and exercise (SURPASS-1), tirzepatide 5 - 15 mg can increase HbA1c from 1.87% to 2.07% compared to an increase of 0.04% in the placebo group.[43]

In the SURPASS-2 study, subjects with T2DM were treated with tirzepatide 5-15 mg for 40 weeks, and HbA1c successfully dropped from 2.09% to 2.46% compared to the semaglutide 1 mg group at 1.86%.[44] Likewise, In SURPASS-3, tirzepatide 5-15 mg for 52 weeks resulted in HbA1c dropping from 1.93% to 2.37% as opposed to 1.34% drop with insulin degludec.[45] In patients with long-standing T2DM, or more than ten years, and increased cardiovascular risk (SURPASS-4), the use of tirzepatide 5-15 mg can also reduce HbA1c by 2.24% to 2.58% compared to the insulin glargine which boost the HbA1c by 1.44% at 52 weeks.[46]

In the SURPASS-5 study, when tirzepatide was added to those who had received daily glarine insulin, it was found that HbA1 decreased from 2.23% to 2.59% compared to placebo 0.93%, the improvement of HbA1c will be very influential in improving glycemia in insulin use.[47]

Fasting serum glucose (FSG) was lower in the tirzepatide group at all doses and studies (-43.6 to -74.4 mg/dL or -2.4 to -4.1 mmol/L) compared to previous baseline data and compared to placebo, semaglutide 1 mg, and dulaglutide 0.75 mg (J-mono) (Table 1). In the SURPASS-3 study, the depletion in FSG in the tirzepatide group was more significant than that in the insulin degludec; however, in the SURPASS-4 study, only in the tirzepatide 15 mg group was there a significant reduction in fasting blood sugar compared to the insulin glargine group.[45,46]

Constant glucose observation in a subgroup of subjects from the study in SURPASS-3 showed that at all doses of tirzepatide (5, 10, and 15 mg) increased time in range (TIR, 70 to 180 mg/dL or 3. 9 to 10 mmol/L) (TIR increased from 32% to 40% from baseline, attaining an overall 85% to 91% TIR) compared to insulin degludec (TIR increased 22% from baseline, achieving an overall 75% TIR) for 52 weeks after randomization. (A5.70) The tirzepatide group also showed a shorter time below range (<70 mg/dL or <3.9 mmol/L) than the insulin group and reduced glycemia variability.[48]

Effects on Body Weight

Changes in body weight could be seen in the groups in all SURPASS studies.[43-49] In subjects with new-onset T2DM, a 40-week course of 5 to 15 mg of tirzepatide resulted in a weight loss of 7 kg to 9.5 kg compared to a 0.7 kg loss in the placebo group.[44]

In subjects with T2DM, larger body weight was attained in the tirzepatide 5 mg, 10 mg, and 15 mg group (-7.8, -10.3, and -12.4 kg) compared to semaglutide 1 mg (-6.2 kg) in the SURPASS-2 study.[44] In the SURPASS-3 study, the insulin-initiated degludec group lost 2.3 kg after 52 weeks, while the tirzepatide 5-15 mg group lost weight from 7.5 kg to 12.9 kg.[45]

In subjects with long-standing T2DM, subjects who were already on glucose-lowering medications and initiated on insulin glargine (SURPASS-4) were seen to achieve a weight loss of 1.9 kg after 52 weeks compared to a weight loss of 7.1 kg to 11.7 kg in the tirzepatide group.[46] In the SURPASS-5 study, all subjects in the insulin basal glargine and terzipatide group achieved a weight loss of 6.2 to 10.9 kg compared to 1.7 kg in the placebo group.[47]

Table 1. Summary of completed randomized controlled of Tirzepatide versus comparators

Study	Sample size, duration, study design, study site	Participant(s)	Intervention(s)	A1c change from baseline	Body weight change from baseline	Secondary outcome(s)
Rosenstock et al 2021, (SURPASS-1)[43]	N = 478, 40 weeks (between June 2019 and Oct2020) Double blind Placebo controlled (phase 3), 52 sites in 4 countries	≥18 years with type 2 diabetes. HbA1c 7.0-9.5, BMI≥23 kg/m2, and stable weight (±5) during the previous 3 months, uncontrolled with diet and exercise alone (naive to injectable T2DM meds, no oral T2DM meds for prior 3 months)	Tirzepatide 5 mg	-1.75%	-6.3 kg	FSG changes from precedent (5 mg) -39.6 mg/dL, (10 mg) -39.8 mg/dL, (15 mg) -38.6 mg/dL, (placebo) +3.7 mg/dL. Fasting lipids change from precedent cholesterol (15 mg) -8.4%, triglycerides -21%, LDL -12.4%, VLDL -19.8%, HDL +7.5%
			Tirzepatide 10 mg	-1.71%	-7.0 kg	
			Tirzepatide 15 mg	-1.69%	-7.8 kg	
			Placebo once weekly	0.09%	-1,0 kg	
Frías et al 2021 (SURPASS-2)[44]	N = 1,879, 40 Weeks (between July2019 and February, 2021), open label, phase 3, 128 sites in 8 countries	T2DM, mean age = 56.6 years, HbA1C = 7.0% to 10.5%, treatment with metformin for ≥3 months (≥1,500 mg per day), stable body weight ≥3 months, BMI of ≥25 kg/m2	Tirzepatide 5 mg	-2.01%	-7.6 kg	Hypoglycemia less than 54 mg/dL in (5 mg) 0.6%, (10 mg) 0.2%, (15 mg) 1.7%, (semaglutide) 0.4% Fasting lipids change from precedent (15 mg) triglycerides -24.8%, VLDL -23.7%, HDL +7.1%
			Tirzepatide 10 mg	-2.24%	-9.3 kg	
			Tirzepatide 15 mg	-2.30%	-11.2 kg	
			Semaglutide	-1.86%	-5.7 kg	
Ludvik et al 2021 (SURPASS-3)[45]	N =1,444, 52 Weeks (between April 2019 and Jan2021) open label, phase 3, 122 sites in 13 countries	T2DM, ≥ 18 years, insulin naive, HbA1C = 7.0 - 10.5%, stable metformin (≥1,500 mg/day) or metformin and SGLT-2 inhibitor treatment ≥3 months, stable body weight ≥3 months, BMI of ≥25 kg/m2	Tirzepatide 5 mg	-1.85%	-7.0 kg	Hypoglycaemia less than 54 mg/dL in (5 mg) 1.4%, (10 mg), 1.1%, (15 mg) 2.2%, (insulin degludec) 7.3%
			Tirzepatide 10 mg	-2.01%	-9.6 kg	
			Tirzepatide 15 mg	-2.14%	-11.3 kg	
			Insulin degludec	-1.25%	+1.9 kg	
Battelino et al (SURPASS-3 CGM)[48]	Sub-study of SURPASS-3. Interstitial glucose values collected via CGM at baseline, 24 weeks, and 52 weeks	313 patients of SURPASS-3 with normal wake-sleep cycle.		n/a		Proportion of time of CGM values in tight target range (71-140 mg/dL) at 52 weeks: 60%, 72%, 73% vs 48%. Estimated treatment difference of 12%, 24%, and 25% ($P < 0.05$ for all)

Study	Sample size, duration, study design, study site	Participant(s)	Intervention(s)	A1c change from baseline	Body weight change from baseline	Secondary outcome(s)
Gastaldelli et al (SURPASS-3 MRI)[43]	Sub-study of SURPASS-3 MRI at baseline and 52 weeks	296 patients of SURPASS-3 with fatty liver index of at least 60		n/a		For the pooled tirzepatide 10 and 15 mg group compared with insulin degludec, there was a significant reduction in liver fat content ($P <$ 0.0001
Del Prato et al 2021 (SURPASS-4)[46]	N= 2,002, 104 weeks, (between Nov, 2018 and April, 2021) Open label, phase 3 187 sites in 14 countries	T2DM, HbA1C = 7.5% to 10.5%, ≥1-month stable treatment, three oral antihyperglycemic drugs (Metformin, SGLT-2 inhibitors, sulfonylureas), ≥3 months stable treatment, ≥3 months stable body weight, BMI ≥ 25 kg/m2, increased risk of cardiovascular events	Tirzepatide 5 mg	-2.11%	-6.4 kg	+Fasting lipids change from precedent (15 mg) cholesterol -5.6%, triglycerides -22.5%, VLDL -21.8%, HDL +10.8%
			Tirzepatide 10 mg	-2.30%	-8.9 kg	
			Tirzepatide 15 mg	-2.41%	-10.6 kg	
			Insulin glargine	-1.39%	+1.7 kg	
Dahl et al 2022 (SURPASS-5)[47]	N = 475, 40 weeks (between August 2019 and January, 2021) Double-blind, phase 3, 45 sites in in 8 countries	T2DM, 7.0% to 10.5% HbA1C, ≥3 months treatment of insulin glargine U100 (>20 IU/d or >0.25 IU/kg/d) once daily with or without metformin, stable body weight ≥3 months, BMI of ≥23 kg/m2	Tirzepatide 5 mg	-2.11%	-5.4 kg	Hypoglycaemia less than 54 mg/dL in (5 mg) 15.5%, (10 mg) 19.3%, (15 mg) 14.2%, (placebo) 12.5%
			Tirzepatide 10 mg	-2.40%	-7.5 kg	
			Tirzepatide 15 mg	-2.34%	-8.8 kg	
			placebo	-0.86%	+1.6 kg	

Study	Sample size, duration, study design, study site	Participant(s)	Intervention(s)	A1c change from baseline	Body weight change from baseline	Secondary outcome(s)
Inagaki et al 2022 (SURPASS-Jmono)[50]	N = 636, 52 weeks (between May, 2019 and March 2021) Double-blind, phase 3, Japan	T2DM ≥20 Years, HbA1C between 7.0% and 10.0% if OAD is naive, HbA1C = 6.5% to 9% if currently on OAD, BMI of ≥23 kg/m2, stable body weight ≥3 months with no exercise/intensive diet for body weight reduction	Tirzepatide 5 mg	-2.37%	-5.8 kg	FSG changed from precedent (5 mg) -57.9 mg/dL, (10 mg) -64.6 mg/dL, (15 mg) -67.6 mg/dL, (dulaglutide) -31.9 mg/dL. Fasting insulin changes from precedent (5 mg) -1.07 mU/L, (10 mg) -1.87 mU/L, (15 mg) -2.00 mU/L, (dulaglutide) 1.4mU/L. Fasting Cpeptide change from precedent (5 mg) -0.25 ug/L, (10 mg) -0.39 ug/L, (15 mg) -0.37 ug/L, (dulaglutide) 0.01 ug/L
			Tirzepatide 10 mg	-2.55%	-8.5 kg	
			Tirzepatide 15 mg	-2.82%	-10.7 kg	
			Dulaglutide 0,75 mg	-1.29%	-0.5 kg	
Kadowaki et al (SURPASS-Jcombo)[51]	N = 442, 52 weeks, Open label	T2DM, HbA1C between 7.0% and 11.0%, with ≥3 months metformin, sulfonylureas, thiazolidinediones, glinides, SGLT-2 inhibitor or alpha glucosidase inhibitor, BMI of ≥23 kg/m2, stable body weight ≥3 months with no exercise/ intensive diet for body weight reduction	Tirzepatide 5 mg	Not reported ≥1 SAE in patients	-3.8 kg	FSG changed from precedent (5 mg) -58.6 mg/dL, (10 mg) -71.2 mg/dL, (15 mg) -74.4 mg/dL. Fasting insulin changes from precedent (5 mg) 6.2 pmol/L, (10 mg) -4.8 pmol/L, (15 mg) -7.7 pmol/L. Fasting C-peptide change from precedent (5 mg) -0.12 ug/L, (10 mg) -0.28 ug/L, (15 mg) -0.34 ug/L
			Tirzepatide 10 mg		-7.5 kg	
			Tirzepatide 15 mg		-10.2 kg	
			Oral antihyperglycemic oral		-0.5 kg	
Jastreboff et al 2022 (SURMOUNT-1)[52]	N = 2,539, 72 weeks, double blind placebo controlled, phase 3, 119 sites in 9 countries	≥18 years old, BMI ≥ 30 kg/m^2, or ≥27 kg/m^2, or more and at least one weight-related complication. Comorbidities: hypertension, dyslipidemia, obstructive sleep apnea, and cardiovascular disease. History of at least one unsuccessful dietary effort to lose body weight	Tirzepatide 5 mg	Not applicable	-15%	Change in waist circumference from precedent (5 mg) -14.0 cm, (10 mg) -17.7 cm, (15 mg) -18.5 cm. Percentage weight reduction of ≥20% (5 mg, not controlled for type 1 error) 48%, (10 mg) 67%, and (1 5mg) 71% (placebo) 9%
			Tirzepatide 10 mg		-19.5%	
			Tirzepatide 15 mg		-20.9%	
			Placebo, weekly SC		-3.1%	

Outcomes Cardiovascular and Effect of Renal Function

In over two years, tirzepatide's safety and effectiveness were reviewed by comparing it with insulin glargine in subjects at high cardiovascular risk with advanced T2DM.[53] Cardiovascular outcomes were evaluated using four MACE-4 Composites (cardiovascular death, myocardial infarction, stroke, and hospitalization for unstable angina) as the secondary outcome. The tirzepatide group did not have an increased rate of MACE-4 events compared to insulin glargine (hazard ratio [HR], 0.74; 95% confidence interval [CI], 0.51 to 1.08).[53]

In a post-hoc analysis of SURPASS-4 data, a randomized study comparing tirzepatide with insulin glargine in T2DM patients and high cardiovascular risk, it was found that tirzepatide slowed down the decrease in glomerular filtration rate and lowered the ratio of urinary creatinine albumin compared to insulin glargine, after a median of 85 weeks.[54]

Tolerance and Side Effects of Tirzepatide

Hypoglycaemia. The incidence of hypoglycaemia episodes (blood glucose < 70 mg/dL) with tirzepatide has been compared and observed with placebo and GLP-1 Ras. The incidence of hypoglycaemia was lower with 8% to 14% tirzepatide than with insulin 48% degludec, but the same compared with placebo and insulin glargine.[3,42,55]

Gastrointestinal side effects. Nausea was more frequently reported as an adverse effect of tirzepatide compared with placebo (especially at the maximum dose of 15 mg: OR 5.60; 95% confidence interval, 3.12-10.06), followed by vomiting (OR 5.50; 95% CI, 2.40-12.59) and diarrhea (OR 3.31; 95% CI, 1.40-7.85). The incidence of gastrointestinal adverse events was also compared between tirzepatide and two GLP-1 RAs, dulaglutide and semaglutide, except that the incidence of diarrhea was higher at the 10 mg dose of tirzepatide. Note that treatment discontinuation due to intolerance was more frequent at the 15 mg Ttrzepatide dose than the other comparators.[42] Tirzepatide 15 mg was discontinued due to adverse events at 7% versus 3% with placebo in the SURPASS-1 study,[43] 10.8% versus 2.5% with placebo in the SURPASS-5 study,[47] 5.7% versus 2.8% with semaglutide 1 mg in the SURPASS-2 study,[44] 11% versus 1% with insulin degludec in the SURPASS-3 study,[45] and 11% versus 5% with insulin glargine in the SURPASS-4 study.[46]

The incidence of pancreatitis was no more than 1%, and progression to diabetic nephropathy was no more than 2% in all treatments with the tirzepatide group.[41,45,46] This study reported no risk for the above two conditions despite using GLP-1 receptor agonists.

Dosing and Administration

Tirzepatide, mounjaro, is produced as a colourless to slightly yellow transparent solution in an automatic syringe, is used in single doses, and is available in 6 doses, which are 2.5 mg; 2.5 mg; 5 mg; 7.5 mg; 10 mg; 12.5 mg and 15 mg. It is recommended to start this medication at 2.5 mg, subcutaneously (SC) in the abdomen, thigh, or upper arm, and the site should be rotated with each dose. Dose SC once weekly for four weeks to reduce gastrointestinal effects such as nausea and vomiting. The dose may be increased to 5 mg once a week.[52]

Like other GLP-1 agonists, tirzepatide can be administered regardless of meal timing. Dosing can be tolerated if it is as late as four days, but dosing should be skipped if it is more than four days. Patients can also change the day of the week for tirzepatide administration if desired, if the doses are spaced at least three days apart. It is recommended to store tirzepatide-filled syringes in their original containers and the refrigerator, but they can be kept at room temperature for up to 21 days.[52]

Table 2. Tirzepatide Studies Continue to be Carried Out and are Widely Reviewed

Study	Study design	Participant(s)	Start date	Completion date	Primary outcome
SUMMIT (NCT04847557)	Phase 3 study, comparator: placebo	N=700, BMI ≥ 30 kg/m2, diagnosis of stable heart failure (NYHA class II-IV) with LVEF ≥ 50%	April 2021	November 2023	i) A hierarchical composite of all-cause mortality, heart failure event, 6-minute walk test distance (6MWD) and Kansas City Cardiomyopathy Questionnaire Clinical Summary Score ii) Change from baseline in exercise capacity as measured by 6MWD at 52 weeks
SINERGT-NASH (NCT04166773)	Phase 2 study, comparator: placebo	N=196, BMI between 27 and 50 kg/m2 and histologic diagnosis of NASH with stage 2 or 3 fibrosis by liver biopsy	November 2019	December 2023	% of participants with absence of NASH with no worsening of fibrosis on liver histology at 52 weeks
SURMOUNT-OSA (NCT05412004)	Phase 3 study, comparator: placebo	N=412, without diabetes, BMI ≥ 30 kg/m2 and moderate to severe sleep apnoea at the trial screening	June 2022	February 2024	% change from baseline in apnoea-hypopnea index at 52 weeks
SURPASS-SWICTH (NCT05564039)	Phase 4 study, comparator: placebo	N=250 T2DM, BMI ≥ 25 kg/m2 and being on dulaglutide 0.75 mg or 1.5 mg once weekly	December 2022	September 2024	Change from baseline in HbA1c at 40 weeks
SURPASS-CVOT (NCT04255433)	Phase 3 study, comparator: Dulaglutide	N=13.299 with T2DM, BMI ≥ 25 kg/m2 and confirmed atherosclerotic CV disease	May 2020	October 2024	Time to first occurrence of death from CV causes, myocardial infarction or stroke
SURMOUNT-MMO (NCT045556512)	Phase 3 study, comparator: placebo	N=15.000 without diabetes aged ≥ 40 with established CV disease or ≥ 50 (for women ≥ 55) with multiple CV risk factors	October 2022	October 2027	Time to frost occurrence of any composite event of composite (all-cause death, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization or heart failure events)

Table 2. Selected ongoing clinical trials with tirzepatide: (a) SURPASS program and SURMOUNT program; (b) SUR¬MOUNT-MMO, A Study of tirzepatide on the Reduction on Morbidity and Mortality in Adults With Obesity; c) SURPASS-CVOT, A Study of tirzepatide Compared With Dulaglutide on Major Cardiovascular Events in Participants With Type 2 Diabetes; (d) SURPASS-SWITCH, A Study of tirzepatide in Adult Participants With Type 2 Diabetes Switching From Dulaglutide; HbA1c, glycosylated hemoglobin; (d) SYNERGY-NASH, A Study of tirzepatide (LY3298176) in Participants With Nonalcoholic Steatohepatitis (NASH); (e) SURMOUNT-OSA, Obstructive Sleep Apnea Master Protocol GPIF: A Study of tirzepatide in Participants With Obstructive Sleep Apnea; (f) SUMMIT, A Study of tirzepatide in Participants With Heart Failure With Preserved Ejection Fraction and Obesity; NYHA, New York Heart Association; LVEF, left ventricular ejection fraction. CV, cardiovascular; T2DM, type 2 diabetes mellitus; BMI, body mass index, NASH, non-alcoholic steato-hepatitis. *adapted from* Rachel S 2023 (22)

CONCLUSION

Tirzepatide, a uni-molecular dual receptor agonist of GIP/GLP-1, has been subjected to extensive trials in several studies involving large populations, SURPASS, and SURMOUNT. tirzepatide will be one of the future treatments that will be favoured and used as clinical practice guidelines for treating T2DM. tirzepatide has been shown to lower A1c more than other glucose-lowering drugs, more significant weight loss, and similar gastrointestinal incidence as semaglutide. In the future, tirzepatide may become the primary treatment for obesity, including metabolic liver disease, with minimal gastrointestinal effects and at a lower cost.

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Ethical Statement

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001-Research

Relationship of Clinical Factors and NTproBNP Levels with Asymptomatic Left Ventricular Diastolic Dysfunction in Type 2 Diabetes Mellitus Without Prior Known Cardiovascular Disease in Indonesia

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Abstract

Left Ventricular Diastolic Dysfunction (LVDD) often diagnosed late in Type 2 Diabetes mellitus (T2DM), therefore early detection is recommended. Aim of this study is to determine the association of clinical factors and NTproBNP levels in T2DM patients with asymptomatic LVDD in Indonesia. This study was cross-sectional, using secondary data from the 30th follow-up of the Bogor Non-communicable Diseases Cohort Study. Subjects under 65 years of age who are diagnosed with T2DM during observation and met the inclusion criteria were recruited. Diastolic dysfunction was defined using ASE/EACVI 2016 recommendations, NTproBNP levels were measured using the electrochemiluminescence immunoassay method. Bivariate tests were performed using chi-square and multivariate tests using multiple regression tests. The NTproBNP cutoff points were determined using Receiver Operating Characteristics. Ninety-one participants were included. The proportion of subjects with LVDD was 48.4%. NTproBNP level >62.5 pg/ml was significantly associated with the incidence of LVDD with Adjusted PR 2.587 (95% CI; 1.554 - 4.645; p: <0.0001) and Area under curve (AUC) 0.76. No clinical factors were significantly associated with the incidence of diastolic dysfunction. Diastolic dysfunction among T2DM in Indonesian populations is associated with a much lower cut-off point of the NTproBNP level than currently reported.

Keywords: Type 2 diabetes mellitus, diastolic dysfunction, NTproBNP, Indonesia, heart failure

002-Research

Correlation between the Ratio of FGF 21 to Klotho with the Incidence and Severity of Diabetic Retinopathy in Type 2 DM Patients

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Abstract

Diabetes Mellitus (DM) is a chronic metabolic disorder characterized by increased blood sugar levels due to impaired insulin secretion, insulin action, or combination of both. Diabetic retinopathy (DR) affects 50-60% of individuals with DM, leading to blindness in 2.6% of cases. In DR, FGF21 levels increase while Klotho levels decrease, resulting in a higher ratio of serum FGF21 levels to serum Klotho levels. To determine the correlation between FGF21 and Klotho ratio with the incidence and severity of DR in type 2 DM patients. This cross-sectional study was conducted at Wahidin Sudirohusodo Hospital and Hasanuddin University Hospital in Makassar from December 2023 until January 2024. The study included type 2 DM patients aged over 18 years. The analysis using descriptive methods and statistical tests, with $p<0.05$ considered to show statistical significance. The study included 88 patients with an average age of 52.41±11.32 years old. Thirty-nine subjects (44.3%) had no DR, 24 subjects (27.3%) had NPDR, 25 subjects (28.4%) had PDR. There was a significant correlation between increase serum FGF21 levels and the incidence and severity of DR ($p=0.005$). The optimal cut-off point for the ratio of serum FGF21 levels to serum Klotho levels with the incidence and severity of DR was found to be 4.1

(p=0.009; OR 3,24). This study discovered a correlation between high ratio of serum FGF21 levels to serum Klotho levels and the incidence and severity of DR in patients with type 2 DM.

Keywords: Type 2 DM, diabetic retinopathy, FGF21, klotho

003-Research

Correlation among Faecal Short Chain Fatty Acid, Serum Glucagon Like Peptide-1, and Body Mass Index of Type-2 Diabetes Mellitus Patients in Mohammad Hoesin General Hospital Palembang

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Type 2 Diabetes mellitus (T2DM) is a major health problem worldwide, both due to its increasing prevalence over the years and the progressiveness of the disease. Among the environmental factors that play a role in the development process of T2DM, there is the role of the gut microbiota. The gut microbiota will produce metabolites: SCFAs that play a role in blood glucose and energy homeostasis. Changes or dysbiosis of the gut microbiota will also cause changes in the metabolites produced. These changes are thought to play a role in the occurrence of insulin resistance which is the main pathogenesis of T2DM. In vitro and in vivo studies showed that SCFA are potent secretagogues for glucagon-like peptide-1 (GLP-1) that increase satiety feeling through the gut-brain axis, thus could modulate body mass index (BMI). To describe faecal SCFA concentration and its correlation to serum GLP-1 concentration and BMI in patients with T2DM in Mohammad Hoesin General Hospital Palembang. The study was a cross-sectional observational study in the population of T2DM who sought treatment at the Internal Medicine Outpatient Clinic of RSMH Palembang in the period of August-December 2022. Faecal SCFA was measured GCMS method and GLP-1 was measured using ELISA. Spearman correlation test was conducted to obtain the correlation coefficient. The p-value < 0.05 was significant. All data were analyzed using SPSS 26.0 for windows program. There were 40 participants with a median age of 52 (40-59) years. They were 20 male and 20 female. The median BMI was 24.97 (20.20-33.20) kg/m2. Mean or median of faecal SCFA, acetate, propionate, and butyrate were 13.78±4.95 mg/mL, 6.87±2.62 mg/mL, 3.12 (1.10 - 7.0) mg/mL, and 6.50 (±2.62) mg/mL respectively. The median of fasting GLP-1 (fGLP-1) and 1hour postprandial GLP-1 (1hGLP-1) were 0.909 (0.5-4.4) pg/L and 1.56 (69 - 4.62) pg/L respectively. There was insignificant positive correlation between total faecal SCFA and GLP-1 concentration (fGLP-1 r=0.050, p=0.758, 1hGLP-1 r=0.152, p=0.350). There was insignificant negative correlation between faecal SCFA and BMI (r=-0.006, p=0.969). There was also insignificant positive correlation between acetate, propionate, butyrate and BMI (acetate r=0.045, p=0.784, propionate r=0.069, p=0.671, butyrate r=0.153, p=0.346). In current study, there was no correlation among total faecal SCFA, acetate, propionate, butyrate levels, serum fasting and prandial GLP-1, and BMI.

Keywords: Type 2 DM, faecal SCFA, GLP-1, Body Mass Index

004-Research

Lower Serum Albumin Levels and Higher Serum Urea Levels as Determinants of Intravenous Insulin Therapy Success in Intensive Care Unit: A Cross-Sectional Study

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Abstract

Studies on the determinants of successful insulin therapy in critical care settings are limited. The present study aimed to explore the determinants of successful intravenous insulin therapy in hyperglycemic patients admitted to intensive care unit (ICU). A cross-sectional study was conducted at Intensive Care Unit, Dr. Zainoel Abidin Hospital, Banda Aceh, Indonesia from January to July 2024. A

total sampling method was utilized, involving hyperglycemic patients admitted to ICU who received continuous intravenous insulin infusion. Rapid-acting insulin was administered at a starting dose of 0.05 - 0.1 IU/kgBW/hour, with titration adjustments based on hourly blood glucose monitoring, targeting a range of 140 -180 mg/dL. The primary outcomes of the present study were the time to first glucose within the target range and the length of stay in the ICU. The present study found that lower serum albumin levels significantly delayed glucose control (mean difference -0.444, 95% CI: -0.791 - -0.096, p = 0.014). Higher serum urea levels were also associated with a longer time to achieve target glucose range (mean difference 0.368, 95% CI: 0.008 - 0.728, p = 0.045). In conclusion, lower serum albumin and higher serum urea levels are associated with delayed glucose control in hyperglycemic patients. This present identified that effective glycemic control alone is insufficient; managing serum albumin and serum urea levels is also crucial for achieving target glucose levels more quickly.

Keywords: Hyperglycemia, critically ill patient, insulin, albumin, urea.

005-Research

The Correlation of Urine Bisphenol a (Bpa) Levels with C-Peptide Index and Homa-IR in Type 2 Diabetes Mellitus at RSMH Palembang

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Diabetes Mellitus (DM) remains a significant health problem worldwide due to its year-on-year increase prevalence and progresion of the disease. Other evidence indicates that non-traditional factors such as environmental chemicals or Endocrine Distrupting Chemicals (EDCs) such as Bisphenol A (BPA) cause of pancreatic β-cell dysfunction and insulin resistance. To determine the correlation of urine BPA levels with pancreatic β-cell function and insulin resistance in type 2 Diabetes Mellitus at dr. Mohammad Hoesin General Hospital Palembang. This is a cross-sectional observational analysis study in a group of type 2 Diabetes Mellitus who were treated at the Internal Medicine Polyclinic dr. Mohammad Hoesin General Hospital Palembang from August to December 2022. Urine BPA was measured using the LCMS method, C-peptide with CMIA. All data were analyzed using SPSS 26.0 for windows. There were 40 research subjects with an average age of 52 (40-59), 20 men and 20 womwn subjects, and average BMI 24.97 (20.20-33.20) kg/m2. The median HOMA-IR, fasting C-peptide, and OGTT 1-hour C-peptide was 9.09 (2.60-24.10)%, 0.93 (0.36-3.70) ng/mL, 3.93 (1.02-12.37) ng/mL respectively. The fasting C-peptide index (fasting CPI) and OGTT 1-hour C-peptide index median were 3.89 (0.61-19.00) x 10-6 and 13.66 (1.80-42.46) x 10-6. The mean urine Bisphenol A (BPA) level was 8.71±4.19 ng/mL. There was a significant, moderately negative correlation between urine BPA levels and the fasting C-peptide Index (CPI) (r = -0.579; p=0.001 n=40). A significant negative and robust correlation exists between urine BPA levels and 1-hour OGTT C-peptide index (1hICP) (r= -0.801; p=0.001; n=40). Where as a strong significant positive correlation exists between urine BPA levels and HOMA-IR (r = 0.668; p=0.001; n=40). In this study, there was a negative correlation between urine BPA levels and C-peptide index (CPI) and a positive correlation between urine BPA levels and HOMA-IR in type 2 Diabetes Mellitus patients at dr. Mohammad Hoesin General Hospital Palembang.

Keywords: Type 2 Diabetes Mellitus, urine BPA, C-peptide index, HOMA-IR

006-Research

Incidence and Risk Factors of Hypothyroidism in Drug-Resistant Tuberculosis Patients: A Multicentre Cohort Study at Drug-Resistant Tuberculosis Referral Hospitals in Jakarta

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Abstract

Drug-resistant tuberculosis (DR-TB) represents one of the most significant challenges to the global effort to eradicate TB, including in Indonesia. The treatment of DR-TB is confronted with several significant obstacles, including hypothyroidism, which may frequently unrecognised and underdiagnosed, even though it may potentially affect DR-TB treatment adherence and outcomes, due to its impaired drug pharmacokinetics and reduced quality of life. We aim to assess the incidence of hypothyroidism, and its respective risk factors (Sex, body mass index, HIV comorbidity, DR-TB drug regimen, anti-TPO), in DR-TB patients in health services for DR-TB in Jakarta. This was an ambispective cohort study conducted in four tuberculosis referral hospitals in Jakarta, Indonesia. Baseline data was retrieved from the national tuberculosis information system. Participants who had undergone DR-TB treatment for a period of 3 to 6 months were recruited for questionairre, physical examination and venous blood sampling (TSH and Anti-TPO). Participants with baseline thyroid problems were excluded. A total of 148 DR-TB subjects were included in this study. Hypothyroidism were observed 8 subjects (5.4%). While the incidence of hypothyroidism seemed to be more frequent among those with HIV (1/5, 20% vs 7/143, 4.9%), receiving ethionamide/PAS (3/28, 10.7% vs 5/120, 4.2%) and with positive anti-TPO (1/9, 11.1% vs 7/139, 5%). Our study observed no statistically significant relationship between sex (RR = 1.6, 95% CI 0.4 - 6.3), body mass index (RR = 0.7, 95% CI 0.2 - 3.0), HIV comorbidity (RR = 4.1, 95% CI 0.6 - 27.2), type of antituberculosis drugs (ethionamide/PAS) (RR = 2.6, 95% CI 0.6 - 10.1), anti-TPO (RR= 2.2, 95% CI 0.3 - 16.0) and hypothyroidism, which might be related to the relatively low incidence of hypothyroidism in our study. The incidence of hypothyroidism among DR-TB patients in Indonesia was relatively low in comparison to other countries. Larger study is needed to assess the contributing risk factors for the development of hypothyroidism among DR-TB patients.

Keywords: Drug Resistant Tuberculosis, Hypothyroidism, Indonesia, Risk Factors

007-Research

Factors Associated with Post-hospitalization Quality of Life in Patients with History of Diabetic Foot Ulcer: Ambispective Cohort study of Cipto Mangunkusumo Hospital Diabetic Foot Registry

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Abstract
Diabetic foot ulcer (DFU) is a chronic complication of diabetes that appear as foot ulceration and causing high morbidity and mortality. These cumulatively decreasing quality of life (QoL) of patients with DFU. Post-hospitalization QoL and its influencing factors has not been widely studied yet. This study aimed to evaluate factors associated with posthospitalizatio QoL in patients with history of DFU. This study was an ambispective cohort study in which baseline data was taken from The Diabetic Foot Registry of Cipto Mangunkusumo Hospital and QoL data were obtained through interview to all patients that had been discharged from hospital for at least six months Quality of life scores are measured using the Diabetic Foot Ucer Scale-Short Form (DFS-SF) questionnaire and were displayed in mean or median value. The association between determinant factors and QoL was analyzed using univariate, bivariate, and multivariate. A total of 131 subjects were included in this study. The overall mean of QoL score was 57.46. In bivariate analysis, length of observation, peripheral neuropathy, and total ulcer areas were associated with QoL. Multivariate analysis showed that length of observation was significantly related to overal QoL, physical health, worry about ulcers, and bothered by ulcers domain. Peripheral neuropathy was related to the leisure domain. Length of observation and peripheral neuropathy are directly related to quality of life.
Keyword: diabetic foot ulcer, DFS-SF, diabetes mellitus, quality of life, amputation, post hospitalization

008-Case Report

Non-Hodgkin's Lymphoma Coexistent with Papillary Thyroid Carcinoma and Ovarian Metastasis from Thyroid Carcinoma: A Case Report

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Abstract
Papillary thyroid carcinoma (PTC) is a type of thyroid cancer that falls under the category of differentiated thyroid cancer (DTC). It is the most prevalent form of thyroid carcinoma, representing up to 90% of all cases of thyroid malignancies. The occurrence of hematological cancer in connection with this condition is highly uncommon, with an incidence rate of about 7%. Metastatic illness is uncommonly linked to papillary thyroid cancer, and there are only a limited number of documented examples of ovarian metastasis in the literature. In this report, we describe a case of concurrent PTC and non-Hodgkin's Lymphoma (NHL), together with ovarian metastases from thyroid carcinoma. We also explore the potential challenges in diagnosing and treating this condition. A 53-year-old woman was presenting with menorrhagia, abdominal pain, and reduced body weight. In 2023, the patient experienced a pathological fracture in the distal region of the humerus. Anatomical pathology studies confirmed the presence of non-Hodgkin's lymphoma. This patient had a documented history of having undergone a total thyroidectomy in 2019 due to the PTC. A surgical procedure called total abdominal hysterectomy - bilateral salpingo-oophorectomy (TAH-BSO) was carried out. The anatomical pathology results indicated the existence of PTC metastases in the right ovaries. The core biopsy of the left iliac wing also revealed metastases of PTC. The bone scan results revealed the existence of osteoblastic metastases in particular regions.
The management of the simultaneous presence of advanced thyroid cancer and non-Hodgkin lymphoma (NHL) can be complex; however, employing a multidisciplinary approach can significantly enhance the patient's prognosis.
Keywords: non-Hodgkin lymphoma, papillary thyroid cancer, differentiated thyroid cancer, ovarian metastasis

009-Case Report

Outcome of Graves' Disease Patients Treated with Radioactive Iodine Therapy at RSCM: Preliminary Study

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Abstract

Graves' disease (GD) constitutes 60-80% of all cases of thyrotoxicosis worldwide, usually managed by anti-thyroid drugs (ATD) as first-line therapy. If patient failed to achieve remission after 18 months or had ATD allergy, can continue to choose radioactive iodine (RAI) as definitive therapy. There is few research on the use of RAI in GD in Indonesia, and the facilities also not widely distributed and available. To assess the outcome treatment of fixed dose RAI^{131} 10 mCi and evaluate the factors that play roles in it. This is an observational retrospective study on 10 GD patients who underwent RAI at RSCM by taking secondary data consecutively from patient medical records. The outcome of this study was the prevalence of hypothyroid conditions in the 3th and/or 6th month after RAI. Free T4, TSHs at baseline, 3, 6, and 12 months post RAI were checked. Inclusion criteria were GD patients who underwent RAI therapy at the Department of Nuclear Medicine RSCM. After 3 months follow up, 40% subject obtained hypothyroidism targets, 40% subclinical hyperthyroidism and 20% euthyroidism and for 6 months 80% subclinical hyperthyroidism, 10% worsening hyperthyroidism and 10% permanent hypothyroidism. RAI is effective and safe as definitive therapy in GD patients. However, good interdisciplinary collaboration is needed to maximize hypothyroidism achievement as RAI therapy goals.

Keywords: Graves' disease, hyperthyroidism, radio-active iodine

010-Case Report

Sagliker Syndrome in End-Stage Renal Disease Patient with Parathyroid Adenoma: A Rare Case Report

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Abstract

Sagliker syndrome or uremic leontiasis ossea is a very rare disorder that manifests in patients with advanced chronic kidney disease undergoing hemodialysis. The presence of parathyroid adenoma, which is the most frequent cause of primary hyperparathyroidism in patients with ESRD, is challenging, whether it is related to or a different disease. A 31-year-old woman felt changes in her face one year ago. The patient has been routinely undergoing hemodialysis for the past five years. Facial deformities were found in the jaw areas, and the body posture was shortened. Laboratory examination found high Parathyroid Hormone, high phosphate, and low calcium. The patient performed a biopsy on his jaw and obtained fibrous dysplasia on histopathology. A sestamibi scan showed the presence of hyperplasia/parathyroid adenoma on the bilateral thyroid lobe inferior. The patient underwent a subtotal parathyroidectomy. The Histopathology of parathyroid was Adenoma. It is well known that 40% of patients with chronic kidney disease develop secondary hyperparathyroidism without appropriate treatment. The incidence of Sagliker syndrome is about 0.5% in the population of chronic kidney disease patients currently undergoing hemodialysis. Most cases have been attributed to patients' delayed access to appropriate treatment for secondary hyperparathyroidism. Delayed diagnosis and inadequate treatment of secondary hyperparathyroidism may contribute to Sagliker Syndrome development. Parathyroidectomy can stop the progression of the disease, but the existing bone deformities cannot be reversed. Recognizing, diagnosing, and managing bone and mineral disorders in patients receiving Hemodialysis is crucial. Parathyroid adenomas found in Sagliker syndrome are usually sporadic but can be associated.

011-Case Report

Parathyroid Carcinoma with Hungry Bone Syndrome Complication After Parathyroidectomy: A Case Report

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Abstract

Complete Androgen Insensitivity Syndrome (CAIS) is a rare genetic disorder characterized by the body's inability to respond to androgens, leading to a female phenotype despite a 46,XY karyotype. We present the case of a 20-year-old patient who was referred to our clinic for primary amenorrhea. Physical examination revealed a well-developed female habitus with normal breast development but minimal pubic and axillary hair. Genital examination showed normal external female genitalia with a shallow vaginal pouch. Pelvic ultrasound identified the absence of a uterus and ovaries. Magnetic resonance imaging of the pelvis showed undescended testes at both inguinal parts. Karyotype test revealed 46,XY. Hormonal assays demonstrated elevated levels of luteinizing hormone (LH) with a normal male range of testosterone levels, which is consistent with CAIS. The patient and her family received counseling to understand the condition, its implications, and the importance of gonadectomy to prevent the risk of malignancy. Surgical removal of the testes and vaginal lengthening were performed. This case highlights the importance of considering CAIS in patients presenting with primary amenorrhea and minimal secondary sexual hair. Early diagnosis and appropriate management are crucial for optimal patient outcomes, including psychological support to address the challenges associated with the condition.

Keywords: Complete Androgen Insensitivity Syndrome, Primary Amenorrhea

012-Case Report

Navigating sexuality and Growth Challenges in Youth with Type 1 Diabetes: A Case-Based Approach

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Abstract

Insulin is crucial for growth, development, and sexuality. Poor management of Type 1 Diabetes Mellitus (DM) can disrupt insulin signaling, potentially affecting these processes. A 19-year-old male with Type 1 DM since ages 9, on rapid insulin therapy (6-6-6), had uncontrolled blood sugar (HbA1c 13.7%). He exhibited signs of delayed puberty (Tanner stage 2) and growth impairment (height and weight not appropriate for age and BMI 14.13, indicating malnutrition). A contrast head CT scan showed a mega cisterna magna, but his academic performance remained excellent. Inadequate insulin therapy in Type 1 DM can affect physical growth and sexual development in patients. Insulin receptors are present in the hypothalamus, testes, and Sertoli cells, and insulin also influences IGF-1, which impacts growth. In this case of growth failure and delayed puberty, insulinopenia is suspected, as the patient's blood sugar levels were uncontrolled and central examination did not reveal any pituitary dysfunction. There was a mega cisterna magna, but the patient did not exhibit any neurobehavioral disturbances. The patient was given nutritional therapy, mixed insulin at 1 unit/kg body weight, and testosterone therapy. A contrast head MRI, growth hormone, IGF-1 examination, and psychiatric consultation were planned to confirm the diagnosis. This case highlights the importance of comprehensive management for adolescents with Type 1 DM. Achieving optimal blood sugar control is essential for normal growth, development, and sexuality. The patient received a multi-faceted approach including insulin adjustment, nutritional therapy, testosterone therapy, and a comprehensive evaluation plan.

Keywords: Type 1 Diabetes Mellitus, Insulinopenia, Delayed Puberty, Growth Impairment, Malnutrition

013-Case Report

A 46-Year-Old Woman with Hirsutism Caused by Adrenocortical Carcinoma

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Abstract

Hirsutism is a pathognomonic clinical sign for endocrine disorders such as congenital adrenal hyperplasia, Cushing's syndrome, and polycystic ovary syndrome.[1] Rapidly progressive extensive hirsutism or virilising features should prompt further investigation for androgen-secreting tumours. A 46-year-old woman came to the hospital with right upper abdomen discomfort and abdominal distension since three months. She also complained of hirsutism along with male pattern baldness, greasy skin, and amenorrhea. blood pressure was 195/110 mmHg. Abdominal examination a non-tender left upper quadrant mass and hepatomegaly with liver span 19 cm. Laboratory examination : SGOT 274 (N = 15 - 34 U/L), SGPT 62 (N = 15 - 60 U/L), LDH 2657 (N = 120 - 246 U/L), afternoon cortisol >119.6 (N = 2.9 - 17.3 ug/dL), LH <0.10 (N = 0.2 - 6.5 mIU/mL), FSH <0.10 (N = 17 - 95 mIU/mL), testosterone 805.13 (N = 10.83 - 56.94 ug/dL), and DHEA-S >1,500 ug/dL (N = 56.2 - 282.9). MSCT Scan Abdomen: 6.1X4.8X5.2 cm left adrenal mass, 2.7X3.6X2.5 cm right adrenal mass, and hepatomegaly accompanied by partially solid masses with necrotic areas; for which she underwent lumbotomy biopsy. Hirsutism is an important sign of endocrine disorder. Although the cause is commonly benign, a more serious or life-threatening one should not be missed.[3] Co-secretion of cortisol and androgens is the most frequent pattern and is highly suggestive of adrenocortical carcinoma. The aetiology of hirsutism sometimes can be life-threatening, early detection and treatment is key to avoid detrimental consequences.

Keywords: Hirsutism, adrenal mass, adrenocortical carcinoma

014-Case Report

Simultaneous Presentation of Conn Syndrome and Subclinical Cushing Syndrome in Adrenocortical Carcinoma

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Abstract

Adrenocortical carcinoma (ACC) is a rare and highly fatal malignant epithelial tumour of the adrenal cortex. While most cases are sporadic, ACC can occur in various syndromic conditions. We present the unique case of a 42-year-old female patient with ACC who exhibited two hormonal disorders: Conn Syndrome and subclinical Cushing Syndrome. This case involves a 42-year-old woman who presented with a right upper abdominal lump, weakness, and headaches. She had a history of diabetes mellitus and uncontrolled hypertension. Laboratory examinations revealed high blood sugar and low potassium levels. A hormonal workup confirmed hyperaldosteronemia (Conn Syndrome) and subclinical Cushing Syndrome. Imaging studies identified a large, malignant-appearing suprarenal mass suggestive of ACC. A biopsy confirmed high-grade ACC with capsular invasion. The treatment included medications to manage diabetes and blood pressure, followed by a successful laparoscopic adrenalectomy. Post-surgery, the patient experienced significant improvements in blood pressure, potassium levels, and blood sugar control. Remarkably, she no longer required diabetes therapy, potassium supplementation, or most antihypertensive medications. In adrenocortical carcinoma (ACC), hypercortisolism occurs when tumor cells produce cortisol independently, bypassing the normal feedback regulation of the hypothalamic-pituitary-adrenal (HPA) axis. Mutations in TP53 and CTNNB1 (β-catenin) exacerbate this

unchecked cortisol production. Normally, cortisol is regulated by a CRH-ACTH feedback loop, but in ACC, this loop is bypassed, leading to persistently high cortisol levels. Similarly, tumor cells in ACC produce aldosterone autonomously, bypassing the Renin-Angiotensin-Aldosterone System (RAAS) regulation, due to mutations in KCNJ5, ATP1A1, and ATP2B3, causing unregulated aldosterone secretion, sodium retention, and hypertension. This case highlights the complexity of ACC presenting with overlapping hormonal disorders (Conn and Cushing Syndromes). It underscores the importance of a comprehensive workup, including imaging and biopsy, for accurate diagnosis. Ultimately, laparoscopic adrenalectomy proved crucial for resolving functional ACC and its associated complications, leading to significant improvement in the patient's condition.
Keywords: Adrenocortical Carcinoma (ACC), Cortisol, Aldosterone, Conn Syndrome, Cushing Syndrome.

015-Case Report

Diagnostic problem of Hyperandrogenism in Female Patient with Non-Classical Congenital Adrenal Hyperplasia (NCCAH) and Polycystic Ovarian Syndrome (PCOS)

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Abstract

The diagnosis of hyperandrogenism can be based on clinical symptoms and measurement of androgen serum. The most common symptom of hyperandrogenism in females is hirsutism. The most common cause of hyperandrogenism in females is polycystic ovarian syndrome (PCOS) and other less common cause is non-classical congenital adrenal hyperplasia (NCCAH). These two diagnoses are difficult to differentiate based on clinical symptoms. A test of 17-hydroxyprogesterone (17-OHP) can help to distinguish these two diagnoses. A 31-year-old female, came with complaints overgrowth of hair on her leg and arms compare to the other female, also have beard and moustache. The patient also complains her breast are smaller than other female and patient has not had menstruation from younger age. From the physical examination, we found overgrowth hair in arm, leg, beard and moustache, the smaller size of the breast, and enlargement of clitoris. From the laboratory test, we found the increased level of 17-OHP, testosterone and ACTH. In imaging studies, from whole-body MRI, conclude with adrenal hyperplasia and multiple simple functional ovarian cyst bilateral. NCCAH caused by 21-hydroxylase enzyme deficiency and makes disturbance conversion of 17-OHP to 11-deoxycortisol and progesterone. Blockage of steroid conversion cause deficiency of glucocorticoid and mineralocorticoid cause compensation increase of ACTH and also increase of androgen precussor. For the diagnosis of PCOS, this patient also fulfils the diagnosis criteria from the clinical symptomps, increasing of androgen hormone, anovulation, and cystic lesion in imaging examination. Some studies even report patients with congenital adrenal hyperplasia also have ovarium adrenal tumour, which hard to differentiate with ovarium polycystic. The most common cause of hyperandrogenism is PCOS and NCCAH is less common. This patient already fulfils the criteria of NCCAH and PCOS from the laboratory and imaging examination.
Keywords: Hyperandrogenism, Non-classical Congenital Hyperplasia, Polycystic Ovarian Syndrome

016-Case Report

A Rare Case: Adult-Onset Nesidioblastosis (Non-Insulinoma Pancreatogenous Hypoglycemia Syndrome)

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Abstract

Finding the etiology of hypoglycemia in adult patients can be challenging because of the wide variety of etiologies. Ninety percent of endogenous hyperinsulinemic hypoglycemia is caused by Insulinoma, the rest are caused by insulin antibodies and pancreatic β cell dysfunction (Nesidioblastosis)

which indicates neoformation of nesidioblasts (stem cells that form the islets of Langerhans). A 28-year-old female complained of neuroglycopenia and adrenergic symptoms that improved with drinking sugar, so she had weight gain. The 72 hours of prolonged fasting test results are: C-peptide ≥0.2 mmol/L, Insulin ≥21 pmol/L, Insulin: C-Peptide molar ratio ≤1, and negative Insulin antibody. Imaging tests are normal and there is no evidence of malignancies. When blood glucose falls, the first defense mechanism to prevent hypoglycemia is a decrease in insulin secretion. When this mechanism fails so insulin and C-peptide levels remain high in circulation. Confirmation of Whipple's triad is required, followed by insulin tests in hypoglycemic conditions. Imaging tests, biomarkers, and hormonal malignancies were done to rule out differential diagnoses. Nuclear diagnostics, SACST, biopsy, and histopathology are currently not capable of being carried out. The diagnosis of adult-onset Nesidioblastosis/NIPHS in this patient was made through the diagnosis of exclusion, namely by eliminating all diagnostic appeals because several examination modalities cannot be carried out. The gold standard for diagnosing Nesidioblastosis/NIPHS is SACST and histopathological examination of pancreatic tissue. The patient is well controlled with Amlodipine 2.5 mg

Keywords: Hypoglycemia, Hyperinsulinemia, Nesidioblastosis, Non-Insulinoma Pancreatogenic Hypoglycemia Syndrome (NIPHS)

017-Case Report

Challenges In The Management Of Kallmann Syndrome: A Case Report

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Abstract

Kallman syndrome is combined disorder of hypogonadotropic hypogonadism and anosmia. Incidence of congenital hypogonadotropic hypogonadism is 1-10:100,000 live births, and approximately 2/3 and 1/3 of cases are caused by Kallmann syndrome and idiopathic hypogonadotropic hypogonadism, respectively. We report a man, 35 years old, with complaints of small penis, small voice, impaired smell, gynecomastia, narrowing of visual field, mustache not growing, little pubic and armpit hair. Patient underwent surgery on both breasts with histopathological results of gynecomastia, no malignancy. Testicular ultrasound results showed bilateral testicular atrophy. Laboratory results showed karyotype 46XY, FSH 1.79 mIU/mL, LH 1.49 mIU/mL, testosterone <0.03 ng/mL, estradiol 5.0 pg/mL, prolactin 6.75 ng/mL and PSA 0.473 ng/mL. Head CT scan imaging showed bilateral otitis media, mastoiditis and sinusitis. Patient was diagnosed Kallmann syndrome, ADS chronic tubotympanic suppurative otitis media, sinusitis, ODS hemianopsia. Patient was treated with testosterone undecanoate injection 1000 mg IM every 3 months, levofloxacin 500 mg PO once daily, avamys nasal spray twice daily. Symptoms of Kallman syndrome can include absent or incomplete pubertal development, anosmia or hyposmia, and low sex steroid levels. KAL1 gene mutations cause GnRH deficiency, associated with Kallmann syndrome. Testosteron replacement is indicated for men who already have children or have no desire for children. Surgery should be considered as the last option in patients with considerable discomfort, psychological stress, cosmetic problems, long-standing gynecomastia (>12 months) and suspected malignancy. The aim of testosterone therapy is to reverse the symptoms of hypogonadism, and surgery is last option in patients with considerable discomfort.

Keywords: Kallmann syndrome, small penis, gynecomastia, testosteron undecanoate, surgery.

018-Case Report

dr. Martha Rosana, SpPD

Hashimoto's Thyroiditis with Goitrous Phenotype Accompanied by A Mass-Pressing Effect

019-Case Report

Hybrid TKI and RAI Therapy in Metastatic Differentiated Thyroid Cancer: A Case Report

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Abstract

Differentiated thyroid cancer is the most prevalent malignant endocrine tumor which can metastasize in 6-23% patients. Radioactive iodine (RAI) ablation therapy is the primary treatment, but some patients become resistant to RAI Lenvatinib, a multikinase inhibitor, is an alternative treatment option in situations where RAI therapy cannot be administered. A 57-year-old female was referred to the endocrinology clinic in January 2022 for thyroid cancer management with a chief complaint of headache two years prior to the admission. The patient was diagnosed with papillary thyroid carcinoma in 2015 and underwent total thyroidectomy and ablation but did not continue follow-up care. Seven years later, the patient developed lymph node metastases and distant metastases to the brain and vertebral bones. After a second RAI ablation and external radiation therapy, the brain metastatic lesion enlarged, preventing the patient from continuing RAI therapy due to the risk of post-ablation brain edema. Lenvatinib therapy was initiated. The patient experienced side effects throughout the treatment, including hypertension, diarrhea, decreased appetite, hand-foot syndrome, stomatitis, and proteinuria. After 8 months of lenvatinib therapy, the lesions in the head and bones decreased in size, and the patient was able to resume RAI therapy with adjusted lenvatinib dosing. In PTC patients, around 30% to 40% metastasize to regional lymph nodes and 1-4% metastasize to distant sites. RAI ablation is the standard treatment following thyroidectomy for patients with metastatic differentiated thyroid cancer (DTC), however, around 25-50% of those with locally advanced or metastatic disease eventually become unresponsive to this therapy. Lenvatinib is a multitargeted tyrosine kinase inhibitor (TKI) which was approved for the treatment of metastatic, progressive, and radioiodine-refractory differentiated thyroid carcinomas. Treatment with lenvatinib significantly extended progression-free survival compared to placebo, with the median for patients treated with lenvatinib was 18.3 months, compared to 3.6 months for those receiving a placebo. However, numerous side effects of varying severity were observed with lenvatinib therapy, including hypertension, diarrhea, fatigue or asthenia, decreased appetite, decreased weight, nausea, stomatitis, hand-foot syndrome, and proteinuria. Symptomatic treatment, dose adjustments, or even discontinuation of lenvatinib therapy may be necessary to minimize the patient's side effects. Lenvatinib represents a promising treatment option for thyroid cancer, particularly in cases where other therapies are ineffective, but it requires careful management of dosage and side effects to achieve optimal outcomes.

Keywords: lenvatinib, tyrosine kinase inhibitor, metastatic thyroid cancer

020-Case Report

Marine Lenhart Syndrome a Rare Aetiology of Persistent Hyperthyroid in Grave's Disease

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Abstract

Graves' disease with concomitant functional nodules, known as Marine Lenhart syndrome, is rare and causes persistence hyperthyroidism. The prevalence of Marine Lenhart syndrome in patients with Graves' disease is about 0.26- 2.7%. A 34-year-old female patient was diagnosed as grave's disease more than five years ago and treated with thiamazole. The dose of thiamazole was variable, she never got remission. On physical examination was found exophthalmos, there was an enlarged

thyroid gland and a palpable nodule in the right thyroid, this was also confirmed by ultrasound examination. Scintigraphy examination of the thyroid gland revealed a diffuse struma with a hot nodule component in the right thyroid. The patient undergoes iodine ablation treatment. Patients with Graves' disease should be evaluated for the existence of nodules and the functional status of them for achievement of optimal therapy. Radioactive iodine therapy and surgery are chosen for treatment of Graves' disease with autonomic functionally thyroid nodule (AFTN). Missed active nodules may result in the failure of achievement of euthyroid. In cases of Grave's disease that relapse quite early after cessation of oral anti-thyroid therapy, the possibility of coexistence of AFTN must be considered.

021-Case Report

A Patient with Thyrotoxicosis Periodic Paralysis

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Abstract

Thyrotoxicosis Periodic Paralysis (TPP) is a disorder characterized by reversible muscle weakness and paralysis, accompanied by hypokalemia, which usually accompanies hyperthyroidism, mostly caused by Graves' disease. If not managed properly, TPP can lead to fatal complications. Here we present a man, Mr. A, who is 29 years old. The patient complained that both lower limbs felt weak and could not be moved. The complaint was felt suddenly for six hours before being admitted to the hospital. Initially, the back muscles felt sore, and a few hours later, the thighs felt weak first, followed by the entire lower leg, which couldn't be moved. In his past medical history, the patient said that about a year ago he had felt weakness in his legs, but he could still walk. The patient, since February 2018, has been diagnosed with hyperthyroidism. Evaluation laboratory parameters showed potassium 1.7 mmol/L, FT4 7, 02 ng/dl (N: 0.89-1.76 ng/dl), and TSH 0.003µIU (N: 0.55-4.78 µIU). The triad of periodic paralytic thyrotoxicosis consists of hyperthyroidism, muscle paralysis, and hypokalemia in the absence of a total body potassium deficit. This distinguishes TPP from Guillain-Barre syndrome, myasthenia gravis, botulism, and transverse myelitis. The important role of the pumpNa + K + ATPase in the pathogenesis of TPP is supported by the finding that there is a significant increase in its activity in skeletal muscle. TPP is caused by a combination of three factors: genetic, environmental, and thyrotoxicosis. It has been reported that a 29-year-old male with Periodic Thyrotoxicosis Paralysis, ec Graves' Disease. The patient complained of sudden lower limb weakness while resting after coming home from work without complaints of decreased consciousness or respiratory problems. The patient was treated with 50 meq KCl premix infusion, KSR tablets, propranolol, and thyrozol.

Keywords: Hyperthyroidism, Graves' disease, TPP, Hypopotassium.

022-Case Report

Hashitoxicosis: Case Report

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Abstract

Hashimoto Thyroiditis with Grave's disease (Hashitixicosis) is found in some cases, snd this case repirt describes a case of a woman with Hashitoxicosis. A 27-year-old woman came to polyclinic on 18th March 2024 with complain of a lump felt, fatique, constipation and weight loss two month before she had weight gain later without any treatment. She was compomentis, BP 149/90 mmHg, HR 87x/i, Wayne index 0, Billewicz score -22. TSH 93.40 mcIU/mL and FT4 0.39 ng/dL, anti-TPO >1000

Iau/mL, TRAb 2.46 IU/L. Thyroid ultrasound showed toxic diffuse struma, thyroid scintigraphy revealed enlarge lobes with high and even distribution and capture of radioactivity with conclusion Toxic Diffuse Struma, and cytologic examination showed colloid goiter. Patient was diagnosed as Hashitoxicosis and has been treated with levothyroxine 100 mg once daily. This woman was diagnosed as Hashitoxicosis based on clinical features of hypothyroidism at admission to polyclinic following clinical features of hyperthyroidism initially without any treatment, with laboratory results showed hypothyroidism with the increased of antibody for Hashimoto Thyroiditis and Grave's disease. Treatment with levothyroxine 100 mg once daily showed the decrease of TSH and normal FT4 level. **Conclusion:** We report a case of Hashitoxicosis based on clinical features of hypothyroid following hyperthyroidism initially, laboratory, thyroid ultrasound thyroid scintigraphy, and cytologic examination result. Treatment with levothyroxine showed improvement.

Keyword: Hashimoto's Thyroiditis, Graves' Disease, Hashitoxicosis.

023-Case Report

dr. Faisal Rozi Sembiring, SpPD

Turner's Syndrome Mosaicism 46,XX/45,X with Hyperthyroid: A Case Report of 21-Year Old Woman

024-Case Report

Dengue Fever and Graves' Disease Complicated with Guillain- Barré Syndrome: A Case Report

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Abstract

GBS is a rare neurological autoimmune disorder in which a person's immune system mistakenly attacks part of peripheral nervous system and the network of nerves that carries signals from the brain and spinal cord to the rest of the body. GBS usually starts a few days or weeks following a respiratory or gastrointestinal bacterial or viral infection. GBS are not commonly found alongside Graves' disease or dengue fever. This case report shows a case of a 35-year-old woman who have been previously diagnosed with Graves' disease with simultaneous presentation of dengue fever and GBS. On the fifth day of treatment, she shows sign of poor respiratory function and weak neck muscle power. She was paralyzed and was indicated for intubation. The result of her brain and spine MRI revealed no signs of abnormalities. The cerebrospinal fluid analysis showed a consistent finding of GBS of albumin cytological dissociation with an increased level of protein of 80 mg/dL, glucose 50 mg/dL, and a normal lymphocytes cell count of 4/cmm and no polymorphs. She was ventilated for three days and begins to receive the treatment of intravenous immunoglobulins (IVIG) of 0.4 g/kg/day (20 g in this 50 kg weighing woman) for a total of five days. She made a remarkable recovery and was extubated on day 3 of IVIG. She was able to walk without support on discharge. In this clinical case, the concomitant presence of two rarely associated autoimmune disorders is demonstrated. The case study theorises that endogenous factors such as gangliocytes and ICAM-1 as well as exogenous factors such as bacterial and viral infection may play a part in the simultaneous presentation of GBS and Graves' disease. Antibodies formed from these factors have an affinity to GM1 and GT1A gangliosides which are typically exposed on the plasma membrane of the peripheral nerves in the nodes of Ranvier and are able to cause molecular mimicry as well as cytokine stimulation which is the main feature of GBS. Simultaneously, these factors may also lead to the development of the thyroid receptor antibodies (TRAb), which is the main factor in the development of Graves' disease. It is important to note however that the bacterial and viral infection that preceded each disease are different and more studies are needed to find a common infective aetiology for both diseases. The gold standard treatment of GBS lies in plasma exchange therapy and IV Immunoglobulin (IVIG) therapy. Immediate therapy is needed in patients with signs of respiratory distress, mobility problems, as well as reduction in vital signs. It is thought that the nerve damage caused by an increased oxidative stress in Graves' disease may lead to an increased risk of susceptibility to GBS. Furthermore, it is thought that preceding infection of dengue virus may also lead to the development of GBS through molecular mimicry mechanism which causes the activation of pro-inflammatory cytokines such as tumor necrosis factor (TNF), interleukins, and complements on myelin and axons. Intravenous immunoglobulin therapy shows a promising result on treating a simultaneous case of GBS presenting in patient with Graves' disease and dengue fever.

025-Case Report

Sequential Manifestation of Graves' Disesae and Resistance to Thyroid Hormone, A Rare Case Report

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Abstract

Graves' disease (GD) is an autoimmune disease that leads to a generalized overactivity of the entire thyroid gland (hyperthyroidism), 7-8 times more common in women than men. The hyperthyroidism of GD is caused by thyroid stimulating immunoglobulins (TSIs) that are synthesized by lymphocytes in the thyroid gland. The presence of TSH receptor antibody (TRAb) in patient with thyrotoxicosis implies the existence of TSI. The circulating immunoglobulin G antibodies bind to the G-protein-coupled TSH receptor, and increase thyroid hormone production, causing hyperthyroidism, shows elevated FT3 and FT4 with suppression of TSH to below the level of detection. Resistance to thyroid hormone (RTH) is an autosomal dominant disorder characterized by reduced responsiveness of variable tissues to thyroid hormone (3). The human thyroid hormone receptor (TR) is expressed by two genes, TRβ and TRα. TRβ1 is expressed in the liver, kidney, and brain, while TRβ2 is expressed in the anterior pituitary and hypothalamus and is mainly involved in the negative feedback regulation of Thyroid Stimulating Hormone (TSH) by thyroid hormone in the anterior pituitary. RTH is mainly caused by germline mutations of TRβ, localized to the ligand-binding domain. The syndrome of inappropriate secretion of TSH (SITSH) showing elevated serum levels of free thyroxine (FT4) and free triiodothyronine (FT3) with normal or slightly elevated TSH levels (non-suppressed TSH) is a hallmark of RTH.Here, we describe a rare case of sequential manifestation of Graves' Disesae and Resistance to Thyroid Hormone (RTH), makes the diagnosis and treatment complicated. An 18 years-old woman was referred to our hospital because of goiter with fatigue, palpitation, and sweating for several months. She reported that his mother had a thyroid nodule that had been operated on and had never been checked again. She was 157 cms in height and 40 kgs in weight. Her blood pressure was 110/70 mmHg, and his heart rate was 120 beats/minute, regular. Her body temperature was 36.3°C. The thyroid gland was slightly enlarged, non-tender, and softly elastic on palpation. Exophthalmos was not observed. Thyroid function test demonstrated elevated levels of FT3 and FT4, and suppression of TSH level. Serum anti-TSH receptor antibody (TRAb) was not examined at that time. Ultrasonography of the thyroid gland revealed diffuse enlargement without tumour lesions. The thyroid scan revealed diffuse enlargement of the right thyroid with high uptake hyperthyroid, 11,2%. These results indicated that Graves' disease was responsible for primary hyperthyroidism in this case. Methimazole (MMI) therapy was started at 15 mg/day. After 3 months, methimazole therapy was continued at 10 mg/day because the levels of FT4 were close to normal ranges, but 1 month later the TSH level increased and the levels of FT4 were within normal range, the MMI was stopped. Four months later (on December 2022), TSH levels were within normal range and FT4 levels were elevated, the MMI given in small dose (5mg/day). We suspected whether SITSH occurred in this patient. Titter results of TRAb were negative, indicated that Graves' disease was in remission. The symptoms of palpitations were still complaining. Magnetic resonance imaging (MRI) was performed for the differential diagnosis of TSH producing pituitary tumour and revealed no tumour lesions. Gene sequencing could be used to confirm diagnosis of RTH. Gene sequencing should have been checked but was not done because the test was not yet available and was expensive. RTH is a rare autosomal dominant disorder characterized by reduced responsiveness to thyroid hormone and is estimated to affect approximately 1 per 40,000 newborn infants. The syndrome is associated with germline mutations of TRβ. TRβ gene encodes two isoforms by alternative splicing, TRβ1 and TRβ2. TRβ1 is widely expressed, especially in the liver and kidney. TRβ2 is expressed in the anterior pituitary and hypothalamus, and mainly contributes to the negative feedback regulation of TSH by thyroid hormone in the anterior pituitary. RTH is associated with genetic mutations in the ligand-binding domain of TRβ, which is common between TRβ1 and TRβ2.

Thus, mutations of TRβ cause failure of this negative feedback regulation of TSH by thyroid hormone and can cause SITSH. Resistance to thyroid hormone is compensated by increased thyroid hormone levels. Here, we reported a woman with Graves' disease sequentially with RTH. In the onset of Graves' disease, her TSH values were suppressed below the limit of normal range. Furthermore, she showed the apparent features of hyperthyroidism, such as general fatigue, palpitation, and sweating. These observations indicated that peripheral tissues were responsive to excess thyroid hormone. Although her TRAb had been negative, we could not reduce the dose of MMI due to her elevated thyroid hormone levels. Looking back at her clinical course, she showed elevated serum TSH even though FT4 was elevated. In a patient with common Graves' disease taking anti thyroid drug for the treatment, serum TSH will originally start to elevate after the normalization of FT4. We consider that this finding was different between the present case and common Graves' disease, and it was important for the diagnosis of RTH during therapy of Graves' disease. A few cases of RTH with Graves' disease have been previously reported. The prevalence of overt Graves' disease in individuals with RTH is unclear. Further studies are required to clarify the relationship of a RTH patient and Graves' disease. The optimal therapy for this complex situation remains unknown. Treatment with anti-hyperthyroidism drug remains the primary choice for Graves' hyperthyroidism complicated by RTH. This disease can be well controlled by anti-hyperthyroidism drugs, but no unified criteria exist based on clinical signs and symptoms and thyroid function. The optimal treatment should only slightly increase FT3 and FT4 levels, normalize the TSH level, and avoid drug overdose. We reported a patient who was diagnosed as having RTH during treatment of Graves' disease. If serum TSH gradually begins to elevate eventhough thyroid hormone never decreases during therapy of Graves' disease, we should consider that the patient has associated RTH. Gene sequencing could be used to confirm diagnosis of RTH. It was a rare case and makes the diagnosis and treatment complicated.

026-Case Report

Herapeutic Management of Graves' Disease with Block and Replace Regimen

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Abstract

Graves' disease is an autoimmune disorder that affects the thyroid gland due to antibody stimulation of TSH receptors in thyroid follicular cells resulting in hyperthyroidism, which is a pathological condition due to excessive synthesis and secretion of thyroid hormones by the thyroid gland. The most common cause of hyperthyroidism is Graves' disease, and women are more at risk than men with a peak incidence of 30-60 years of age.We report a 42-year-old woman with Graves' disease who was treated with titration regimen (TR), but the thyroid hormone monitoring results were very fluctuating even after RAI therapy. She still often felt weakness when hypothyroid, and palpitations when hyperthyroid so, she agreed to use BRR. Since using the regimen, thyroid hormones are more stable and under control, and the patient feels more comfortable. Until now, the patient is still using the regimen, with thiamazole 1x5mg daily and levothyroxine 1x50mcg alternately daily, and no side effects have been found. The recurrence rate of BRR was 51% while TR was 54%, there was no statistically significant difference between the two regimens. However, the side effects of BRR were more than TR. The higher side effects of BRR without better effectiveness, thus TR was chosen as the first-line regimen. The 2016 ATA guidelines no longer recommend BRR, except in certain circumstances where thyroid hormone levels are uncontrolled with MMI and become hypothyroid when the minimum MMI dose is increased. Block and replace regimens are as effective as titration regimens, but have higher side effects, which may be considered when hormonal status fluctuates during therapy.

027-Case Report

Mitigating Hungry Bone Syndrome: Best Practices After Parathyroidectomy

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Abstract

Severe hyperparathyroidism caused by prolonged high levels of parathyroid hormone (PTH) can be managed by removing the gland. One of the critical complications related to parathyroidectomy is hungry bone syndrome (HBS), an emergency morbidity which may fatal if not promptly and adequately managed. HBS is defined by a rapid and profound decline in serum calcium levels following surgery, as the bones avidly uptake calcium and phosphate in the absence of high PTH levels. It may present as worsened bone pain, carpopedal spasm, severe hypocalcemia, hypophosphatemia, hypomagnesemia, and. This report highlights two patients who underwent parathyroidectomy and had different postoperative outcomes for HBS. The first case involves a 19-year-old male who had a history of recurrent fractures and bone pain. In 2019, he got a fracture from a fall, and in 2020, he experienced another fall leading to shoulder dislocation and further fractures. By late 2021, he was diagnosed with severe hyperparathyroidism due to parathyroid adenoma. Two days post-parathyroidectomy, he developed HBS. He was treated with calcium and vitamin D supplementation. Over two years of follow-ups, his bone density and mobility improved significantly. The second case involves a 46-year-old male with uncontrolled hypertension and chronic kidney disease stage 5 on hemodialysis, presenting with bone pain and deformities. This patient had a long-standing history of bone pain and fractures. He underwent a similar surgical intervention for tertiary hyperparathyroidism but and not develop HBS postoperatively. Careful perioperative monitoring of electrolytes, vigorous supplementation of calcium and vitamin D, and the use of antiresorptive therapies before surgery had been employed. These cases underline the variety in postoperative outcomes and the importance of tailored management strategies. Early intervention, appropriate surgical management, and aggressive postoperative supplementation is crucial to prevent and manage HBS in patients with severe hyperparathyroidism. Multidisciplinary approach and the utilization of various imaging modalities and intraoperative PTH monitoring is mandatory in managing such complex cases. Applying these approaches will reduce the risk of HBS while also guaranteeing excellent postoperative care for individuals following parathyroidectomy.

Keywords: Hyperparathyroidism; Calcium; Vitamin D; Chronic kidney disease; Parathyroid adenoma.

028-Case Report

Two-Year Follow-Up of Parathyroid Hormone, Calcium, and Vitamin D Serum Levels in Patient after Parathyroidectomy

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Abstract

Parathyroidectomy is the definitive treatment for primary hyperparathyroidism. Because of the hungry bone syndrome and prolonged hypocalcemia risk, we need to follow up on a patient's parathyroid hormone, calcium, and vitamin D serum after parathyroidectomy. In this case report, we reported a parathyroidectomy patient that we followed for two years and interestingly had elevated parathyroid hormone levels. A 35-year-old male patient diagnosed with left parathyroid tumor by laboratory and radiologic examination underwent parathyroidectomy and isthmolobectomy. The patient was treated with calcium, vitamin D, and levothyroxine supplementation. We diagnosed the patient with hungry bone syndrome on 4th day of post-parathyroidectomy. Then, we documented calcium, vitamin D, and PTH levels in the next two years. The calcium levels are 7.2 (June 2022), 8.2 (July 2022), 8.5 (September 2022), 7.8 (October 2022), 8.1 (June 2023), 9.7 (June 2024). The PTH levels are 244.2 (June 2022), 328.3 (July 2022), 306.5 (September 2022), 457.2 (October 2022), 163.3 (June 2023), 34.4 (June 2024). The Vitamin D levels are 34.4 (July 2022), 13.4 (March 2023), 35.2 (September 2023), 50.4 (April 2024). We found an increase in PTH levels in the six months; then, we increased the dose of calcium supplementation and vitamin D. The patient is now in good condition and has reached an normal level of these laboratory parameters in the second

year post-parathyroidectomy. We suggested an increased PTH level in this patient because of vitamin D deficiency. The PTH, calcium, and vitamin D serum are needed for follow-up in patients after parathyroidectomy. Normalize calcium and vitamin D serum are essential to maintain normal PTH level. Normal PTH, calcium, and vitamin D serum are the cure indications in this patient.

Keywords: parathyroidectomy, parathyroid hormone, calcium, vitamin D

029-Case Report

Heterozygous Familial Hypercholesterolemia with LDL-R Gene Mutation: A Case Report

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Abstract

Heterozygous familial hypercholesterolemia (HeFH) is an autosomal dominant monogenic disorder, with a prevalence of approximately 1:300 people worldwide. There are still challenges to diagnose at the genetic level and to optimize the management of HeFH in Indonesia. A 34-year-old female patient with a normal weight and no smoking history, whose father had hypercholesterolemia, was diagnosed with type 2 diabetes mellitus last year. Clinical examination revealed xanthelasma and thickening of the Achilles tendons. Laboratory tests showed elevated Low-Density Lipoprotein (LDL) cholesterol (296 mg/dL), total cholesterol (348 mg/dL), and triglyceride levels (161 mg/dL), with low High-Density Lipoprotein (HDL) cholesterol (39 mg/dL). Based on the Dutch Lipid Clinic Network criteria, she was diagnosed with 'probable familial hypercholesterolemia'. Genomic analysis revealed a HeFH with mutation in the LDL-receptor (LDL-R) gene on chromosome 19. Mutations in the LDL-R gene account for 80% of clinical familial hypercholesterolemia (FH) cases. A 10-year observation of the ASCVD incidence in FH patients with diabetes was about 30.8%, therefore the recommended LDL-C threshold is less than 55 mg/dL. In HeFH, statin monotherapy can reduce LDL-C by 30% to 60%, and combination therapy may achieve an additional 20% to 30% reduction. In this patient, management with high-intensity statin therapy and lifestyle modifications was insufficient to achieve the target LDL-cholesterol (LDL-C) levels, despite well-controlled glycemic levels. Genetic testing is pivotal in diagnosing HeFH and tailoring treatment. Comprehensive management is essential to reduce cardiovascular risk and optimize overall health.

Keyword: Heterozygous familial hypercholesterolemia, LDL-R gene mutation.

030-Case Report

The Common yet Uncommon Idiopathic Central Diabetes Insipidus, A Case Report

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Abstract

Diabetes Insipidus (DI) is a rare endocrine disorder hallmarked by hypotonic (uOsm < 300 mOsm/kg) and increased urine volume (>3 L/24 h or 50 cc/kg BW/hour). Approximately 30% of DI cases were idiopathic and gave debatable pathogenesis. A 20-year-old male, a non-smoker, was referred to our clinic due to polyuria. The patient also complains of polydipsia (water intake 8-10L/day), and frequent urination (20-30x, total 13 L) with subsequent nocturia. There was no history of trauma or malignancy noted. Laboratory examination showed: Na 141 mEq/L (35-145 mEq/L), K 4.3 mEq/L (3.5-5.1 mEq/L), ureum 9.9 mg/dL glucose 83 mg/dl, serum osmolality 288.3 mOsm/kg (285-295 mOsm/Kg), random copeptin: 2.5 pmol/L (1.7-11.25 pmol/L), urine specific gravity 1.010 (1.010-1.030), and low urine osmolality 72 mOsm/Kg (300-800 mOsm/Kg). Patient was diagnosed with central idiopathic DI and started on desmopressin intranasal spray 20 mcg/day and showed good clinical response. Arginine vasopressin peptide (AVP) deficiency remains the main pathology in DI resulting in underconcentrated urine and inability to retain water. In our case, a direct random copeptin test was done instead of an indirect water deprivation test (WDT) which requires careful and experienced observation. A very low random copeptin 2.5 pmol/L is sufficient to establish central DI or else stimulation with hypertonic saline is warranted. Patient management aimed to replace free water loss, correction of hypernatremia, and subsequent AVP replacement with desmopressin. Idiopathic central DI is a condition of AVP deficiency with unknown pathology. Recent study showed comparable accuracy of serum copeptin to diagnose

central DI, and desmopressin replacement for central DI showed good results.

Keywords: Diabetes Insipidus, Copeptin, Desmopressin

031-Case Report

Persisten postoperative Acromegali: A Case Report

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Abstract

Background: Acromegaly is a rare disease caused due to hypersecretion of growth hormone. Most of the case of acromegaly are caused by pituitary adenoma. A 33-year-old male, patient presented with classical presentation of acromegaly with chief complain coarse facial feature and progressive enlargement of hand and feet. There was also headache, weight gain and excessive sweating. On examination from head to toe showed prominent supraorbital ridges, prognathism, widening of teeth space, macroglossia, enlarged lips, ears and fleshy nose. The patient was diagnosed as a case of acromegaly due to macroadenoma of pituitary gland. From Magnetic Resonance Imaging (MRI) showed suggestive macroadenoma pituitary. From IGF1 level was 604ng/ml (41-246 ng/mL) and Growth hormone Basal was 13.50ng/mL (< 0,030-2.47ng/mL). The patient underwent transsphenoidal surgical resection of macroadenoma. After a surgical resection, the patient examined CT scan, and the result showed a mass in intrasellar region suggestive residual mass and IGF1 level after surgical was 827ng/ml and we continue the treatment with octreotide long-acting release (LAR). Most cases of acromegaly are caused by excessive secretion of growth hormone. Transsphenoidal surgical resection by an experience surgeon is the preferred primary treatment. Many medical options including somatostatin analogue, dopamine agonists, growth hormone receptor antagonists are available either alone or in combination. SRLs are preferred initial medical treatment for most patients with Acromegaly. Persistent disease after surgery is usually treated with medical therapy or Radiation therapy. Reoperation is less common in patients with Acromegaly.

Conclusion: Early recognition and management is a key to success in better prognosis and improve quality of life.

032-Case Report

A Previously Undiagnosed Pituitary Macroadenoma Presenting with Apoplexy: A Case Report

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Abstract

Pituitary apoplexy (PA) is a rare but severe medical emergency characterized by sudden hemorrhage or infarction in the pituitary. Central hypoadrenalism, which occurs in over 70% of cases, warrants rapid glucocorticoid administration and comprehensive endocrine evaluation. This case report highlights the acute management of PA in a previously undiagnosed pituitary macroadenoma. A 67-year-old male with a history of hypertension presented with a sudden, severe headache and visual impairment in the right eye. Physical examination revealed no cranial nerve palsies. Laboratory tests showed hyponatremia (126 mmol/L), central hypothyroidism (TSH 0.046 μU/mL, free T4 0.44 ng/dL), and severe hypocortisolism (<0.1 μg/dL). MRI with contrast identified a 26 mm pituitary adenoma with hemorrhage and compression of the optic chiasm. Immediate treatment with intravenous hydrocortisone was initiated, followed by an endoscopic endonasal transsphenoidal hypophysectomy (EETH). Pathological examination confirmed a pituitary neuroendocrine tumor (PitNET). Post-operatively, the patient was maintained on oral hydrocortisone and levothyroxine therapy. PA often presents with acute anterior pituitary hormone deficiencies, with central hypoadrenalism posing the most immediate threat. Prompt glucocorticoid

replacement is crucial, and levothyroxine therapy should only be initiated after or concomitantly with hydrocortisone to avoid precipitating an adrenal crisis. Early recognition and prompt treatment of PA with glucocorticoids and surgical intervention are critical for favorable outcomes. This case underscores the importance of timely diagnosis and management of endocrine complications, which are usually present in PA.

Keywords: pituitary apoplexy, macroadenoma, hypoadrenalism, transsphenoidal surgery, endocrine emergency

033-Case Report

Prolactinoma in Patients with Miscarriage and FetalHygroma Colli

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Prolactinoma is the most common pathological cause of hyperprolactinemia and the most found type of pituitary adenoma. It is associated with ovulatory dysfunction and fetal distress. Various approaches and therapeutic options are considered to manage women with prolactinoma in order to help them achieve pregnancy. The following is a case report of a 33-year-old woman who experienced miscarriage accompanied by hygroma colli in the fetus. Based on the patient's medical history, physical examination, and diagnostic tests conducted, it was found that she has a pituitoid macroadenoma + GII P1001 11/12 weeks. The patient underwent a contrast-free head MRI, which showed a well-defined solid mass in the intrasellar region extending into the suprasellar area, measuring approximately +/- 3.3 x 3.18 x 3.6 cm (previously measured at 2.27x2.25x2.9 cm). During the pregnancy, MRI examination was performed in August 2022, revealing the presence of an aforementioned extension, which had increased in size compared to the previous MRI scans. In this case report, a woman with a diagnosis of prolactunoma has been reported.

034-Case Report

Pituitary Apoplexy Complicated by Stroke Infarction in an Elderly Patient: Rare Case

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Abstract

Pituitary apoplexy (PA) is an acute, life-threatening clinical syndrome caused by pituitary gland infarction and/or hemorrhage.[1] The clinical presentation of PA varies widely and includes asymptomatic hemorrhage, classical PA and even sudden death.[2] PA can cause narrowing of intracranial vessels by mechanical obstruction due to mass effect or by vasospasm resulting in cerebral ischemia. We report a 62-year-old male with a known pituitary macroadenoma and stroke infarct who was admitted to our emergency department for treatment of acute gastrointestinal bleeding (GI) induced by aspilet. His CT scan showed PA and infarction of both hemispheres. This patient illustrates the difficulties of administering anticoagulative therapy to patients who have a known pituitary macroadenoma. Stroke is a rare PA complication.[3] The majority of incidents occur during the 5th decade of life, primarily in men. Some predisposing factors include arterial hypertension, anticoagulant treatment, and major surgery. The clinical picture frequently includes headaches, visual impairment, cranial nerve palsies, and hypopituitarism.[3] Patients treated with delayed surgery had a better prognosis and lower mortality rate than those treated with emergency surgery and conservative treatment. Pituitary function is compromised in most patients prior to apoplexy, and ACTH deficit is prevalent, necessitating glucocorticoid replacement in most cases.[4] Sellar imaging and endocrinological function should be reassessed frequently. PA rarely results in cerebral infarction, a serious illness with a poor prognosis that is more common in men. Delayed surgery and TSS

appear to improve the outcome in people with this disease.

Keywords: pituitary apoplexy, stroke infarction, delayed surgery

035-Case Report

A Rare Case: Craniopharyngioma Presenting with Panhypopituitarism and Diabetes Insipidus

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Abstract

Craniopharyngiomas are rare intracranial tumors that typically arise in the suprasellar area of the brain, extending to involve the hypothalamus, optic chiasm, cranial nerves, and major blood vessels. Endocrine deficiencies are common symptoms and postoperative complications of craniopharyngioma that severely affect the perioperative and long-term treatment effects of patients. A 32-year-old male patient with panhypopituitarism and diabetes insipidus secondary of craniopharyngioma had a craniotomy tumor removal. Patients are presented with decreased consciousness, shortness of breath, frequent urination and fever. Initially the patient complained of progressive chronic headaches 6 months ago, accompanied by vomiting, weakness and blurred vision. The results of the examination showed a decrease in levels of cortisol, TSH, FT4, FSH, LH and testosterone, while prolactin levels are still normal. Symptoms of craniopharyngiomas arise due to mass effect and hypothalamic or endocrine disorders caused by compression of the optic chiasm and pituitary gland. Acquired hypopituitarism can result from any damage to the pituitary gland and lack of all hormones (panhypopituitarism) leads to hypofunction of all target glands. Treatment is based on the removal of the primary pathology, along with hormone replacement of hypofunctioning target glands. Craniopharyngioma tumor resection can provoke diabetes insipidus due to vasopressin or antidiuretic hormone deficiency. Craniopharyngioma are rare benign brain tumors that may be associated with hypopituitarism at diagnosis and after treatment. The case underscores the complexity of managing these rare tumors and the importance of a multidisciplinary approach.

Keywords: craniopharyngioma, suprasellar tumor, panhypopituitarism, diabetes insipidus, replacement therapy

036-Case Report

A 22-Year-Old Man with Hypogonadism Hypogonadotropic Suspected of Kallmann Syndrome

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Abstract

Kallmann syndrome (KS), is a rare genetic disorder with incidence 1:10.000 in men, characterized by hypogonadotropic hypogonadism and anosmia/hyposmia due to abnormal migration of olfactory axons and gonadotropin-releasing hormone-producing neurons. A 22-year-old man was reported with clinical presentation of secondary sexual growth delay, gynecomastia, and anosmia. Physical examination revealed micro-penis, absence of facial, axillary and pubic hair with presence of gynecomastia and anosmia. Laboratory examination revealed decrease of testosterone, LH and FSH level with normal prolactin levels. Genetic examination revealed normal male karyotype. Testicular ultrasound revealed bilateral micro-testis. Brain MRI and CT scan with no abnormality. Bone survey showing bone age approximately 13 years 6 months. Patient was diagnosed with hypogonadotropic hypogonadism suspected of KS. He was given 500 mcg/IM/month of testosterone therapy and experienced clinical and laboratory improvement after 1 year treatment. Diagnosis of KS in adult was depending on the co-existence of anosmia with sign of hypogonadotropic hypogonadism. Testosterone or gonadotropin therapy were used for the improvement of secondary sexual delay, libido and fertility. We have reported a 22-year-old man with a diagnosis of hypogonadotropic hypogonadism

suspected of KS who experienced clinical and laboratory improvement with testosterone therapy.

Keywords: Kallmann Syndrome, hypogonadotropic hypogonadism, anosmia

037-Case Report

Journey to Identity: Case Series of 46, XY Disorder of Sex Development (DSD) Patients Undergoing Gender Transition

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Abstract

46, XY Disorders of Sex Development (DSD) involve conditions where individuals with a male karyotype show atypical sexual development. These conditions present at birth or puberty and challenge diagnosis, management, and gender identity. This case series highlights the journeys of two patients with 46, XY DSD, showcasing the complexities of their medical and psychological management. Patient A, a 22-year-old raised as female, presented with a right groin lump, later identified as intra-abdominal testes. Despite her chromosomal and gonadal configuration, she expressed no internal conflict regarding her gender identity and desired to live as a female. Her management included planned gonadectomy and possible feminizing hormone therapy. Patient NL, a 20-year-old raised as female, showed masculinization during puberty, including voice deepening and body hair growth. He identified as male and sought masculinization procedures, including testosterone therapy and potential genital reconstruction. Both non-endocrine mutations and endocrine disorders contribute to 46 XY DSD. Gender identity in DSD individuals is complex and deeply individual. A holistic approach is crucial, encompassing gender determination, gonadectomy, hormone therapy, and counseling. For those opting to live as female, gonadectomy and feminizing hormone therapy are vital. For those choosing male identity, psychological support, testosterone therapy, and surgical reconstruction are key. These cases emphasize individualized, multidisciplinary care for 46, XY DSD. The decision to pursue male or female identity is personal, shaped by physical development, psychosocial factors, and well-being. Comprehensive care addressing medical and psychological needs is essential in the gender identity journey.

Keywords: DSD 46 XY, AIS, Hypogonadism, Swyer syndrome

038-Case Report

A Rare Case: Young Female Patient with Mayer Rokitansky Kuster Hauser Syndrome Type 1 and Myelodysplastic Syndrome

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Abstract

Mayer-Rokitansky-Küster-Hauser (MRKH) syndrome is a congenital anomaly characterized by agenesis/aplasia of the uterus and upper part of the vagina in females with normal external genitalia and a normal female karyotype (46, XX). Co-occurrence of this condition with hematological malignancies such as Myelodisplastic Syndrome (MDS) is very rare. A 22-year-old female, who didn't menstruation until now. The patient had a history of blood transfusion since childhood. This condition is repeated, and the patient is hospitalized and also in Turner Stage M1P2. The Patient had a lower level of estradiol 21,63 pg/mL and an increase of Gonadotropin Hormone (Hypergonadotropic Hypogonadism), with primary amenorrhea and the concurrence the diagnosis of MDS. The patient got the supplementation of estrogen and progesterone. MRKH type 1 syndrome is a rare case and co-incidence with hematological disorders is also reported rarely. A diagnostic search was carried out using chromosome examination and found 46 XX according to the female phenotype. Giving synthetic hormones estrogen and progesterone can improve the quality of life in patients due to the growth of secondary sex signs. Deletion on chromosome q.21.1 is also thought to be the cause of MRKH type 1 syndrome with manifestations of hematological disorders such as

MDS in patients. Supportive treatment is still carried out. MRKH type 1 and MDS are rare diseases that may present together. Awareness of diagnosis should be bought in mind. We emphasize educating the patient and follow up routinely.

Keywords: MRKH type 1, MDS, deletion, chromosome q21.1

039-Case Report

Autoimmune Diabetes in Type 3 Multiple Autoimmune Syndrome in 27-years-old Woman Patient

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Abstract

Multiple autoimmune syndrome (MAS) is the combination at least three autoimmune diseases in the same patient. MAS has 3 classifications. Type 1 MAS consists of myasthenia gravis, thymoma, polymyositis, and giant cell myocarditis. Type 2 MAS consists of Sjogren's syndrome, rheumatoid arthritis, primary biliary cirrhosis, scleroderma, and autoimmune thyroid disease. Type 3 MAS consist of autoimmune thyroid disease, myasthenia gravis and or thymoma, Sjogren's syndrome, pernicious anemia, idiopathic thrombocytopenic purpura, Addison's disease, autoimmune diabetes, vitiligo, autoimmune hemolytic anemia, systemic lupus erythematosus, and dermatitis herpetiformis. In this case, the patient was diagnosed as type 3 MAS namely AIHA, autoimmune thyroid disease, SLE, and suspicious autoimmune diabetes. In endocrinology, this type 3 MAS consists of autoimmune thyroid disease and suspicious autoimmune diabetes. Autoimmune diabetes must be investigated, if we find autoimmune disease related type 3 MAS. A 27-years-old woman came to the hospital with weakness increased for 5 days before. Rush of both cheeks, enlargement of neck, arthralgia, cold intolerance for 6 months ago. History of spontaneous miscarriage in 9 weeks gestation 4 years ago. Physical examination found BMI 26.05 cm/kg^2, sclera icteric, conjunctiva anemia, diffuse enlargement of bilateral thyroid gland, splenomegaly Schaffner 2. Laboratory result hemoglobin 5.9 g/dl, hematocrit 21%, platelets 476,000mm^3, smear of peripheral blood revealed polychromasia, reticulocyte 18.49%, direct bilirubin 1.5 mg/dL, indirect bilirubin 4.9 mg/dL, coomb test +, antibody screening revealed warm type, fT4 4.5 mmol/L, TSH >60.00 u IU/mL, TPOAb 7,108.78 IU/mL, ANA profile found SS-A native +++, Acl-70 ++, random blood glucose 263 mg/dl, fasting blood glucose 209 mg/dL, postprandial blood glucose 198 mg/dL, C-peptide 2.41 ng/ml, basal insulin 6.8 u IU/mL, HOMA B 28%, HOMA-IR 2.5%, FSH 4.94 mIU/mL, estradiol 208.0 pg/mL. Thyroid ultrasound revealed bilateral diffuse struma. This patient was diagnosed as AIHA, autoimmune thyroiditis, SLE, suspected autoimmune diabetes (in investigation) with obesity, and secondary infertility. The patient was given blood transfusion, methylprednisolone, levothyroxine, disease modifying antirheumatic drugs, and short acting insulin. The patient went home in good condition. We plan to follow up blood glucose and TSH level. Early diagnosis of individual components of MAS must be done if we find an autoimmune disease. In this case, we tried to investigate autoimmune diabetes in a type 3 MAS patient.

Keywords: autoimmune hemolytic anemia, systemic lupus erythematosus, Hashimoto thyroiditis, diabetes mellitus, multiple autoimmune syndrome type 3.

040-Case Report

Gynecomastia and Galactorrhoea in Male Older Patient: Distinguish Between Drug Induced or Prolactinomas?

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Abstract

Finding the cause of gynecomastia and galactorrhoea can be challenging, hence one of the most important cornerstones is detailed case history. Gynecomastia is an enlargement of the breast in males due to hyperplasia of the glandular tissue. Causes: Physiological (20%) Pathological (30%) Drugs (10-20%) Idiopathic (25%). We report a case of gynecomastia with prolactin disorder and previous

use of antihypertensive medication. A 68 year old man, with hypertensive heart disease, controlled on medication (low dose spironolactone 25mg/day, digoxin 0.25mg/day and diltiazem 30mg three times a day), for the last 12 months; presented with painful swelling and discharge of bilateral breasts for the last 14 days; on examination of both breasts a firm, mobile lump was palpated under the right nipple; blood tests: BUN 12mg/dL; Creatinine 1.1 mg/dL; TSH 0.57 µlU/ml; Prolactin 87.5 ng/mL. Head MRI was performed; multiple chronic lacunar infarcts, intrasellar and suprasellar were normal and no mass or infection was visible. The probable cause was attributed to spironolactone and digoxin, the medications were stopped; the patient's pain and swelling improved and returned to normal after 2 months of discontinuation, prolactin was assessed at 0.193 ng/mL. Gynecomastia due to spironolactone has many mechanisms: blockade of androgen receptors, prevent binding of testosterone & dihydrotestosterone; decrease testosterone production from testes, increase estrogens by enhancing peripheral conversion of testosterone to estradiol. It has been suggested that digoxin binds to the estrogens receptor and may directly stimulate breast tissue proliferation, inducing gynecomastia.

Conclusion: Spironolactone is known to cause gynecomastia; there are very few case reports of digoxin-induced gynecomastia. No other evidence of prolactinoma in this case. It is important for the clinician to keep this in mind, although low doses combination between spironolactone and digoxin may cause gynecomastia.

Keywords: Gynecomastia; Galactorrhoea, Spironolactone; Prolactin: Digoxin

041-Case Report

The Use of Teriparatide in Patient with Osteogenesis Imperfecta: A Case Report

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Abstract

Osteogenesis imperfecta is an inherited connective tissue disorder with wide phenotypic and molecular heterogeneity. Also known as brittle bone disease with very rare incidence. Diagnosis of osteogenesis imperfecta is still challenging and the treatment needs multidisciplinary approach. A 28-year-old male with frequent fractures of his right femur in the last 15 years. His first fracture happened when he was 10 months old after he tried to kick a ball. After that, frequent fractures happened with minimal or no trauma. Patients have already consumed vitamin D and calcium supplementation routinely for 5 years old. From physical examinations, patients have normal sclerae, short neck, barrel chest, and bowing bilateral legs. From radiological findings, it is showed fractures at right femur with broken plate. Even though, patient had already taken bisphosphonates routinely, the BMD showed reduction in bone mass and the patient was told to consume teriparatide 20 mcg daily subcutaneously for 24 months. Bone mineral densitometry and bone marker evaluation have not been done to evaluate the efficacy of teriparatide for the patient. Teriparatide therapy has been reported to improve bone mineral density and vertebral bone strength in adults with OI. Bisphosphonates remains the first-line treatment before teriparatide-use. The duration of therapy of teriparatide is 18 to 24 months since its risk in developing bone malignancy in rats. Other than medical treatments, the use of multidisciplinary approaches are the important things to maintain the health and quality of life OI patients. Osteogenesis imperfecta is a broad condition with varying clinical presentations. Even though it is a rare disorder, it is one of the most common congenital bone disorders in children. Many drugs are still underdeveloped but the use of teriparatide can be promising.

Keyword: osteogenesis imperfecta, recombinant human parathyroid hormone, multiple fractures

042-Case Report

A 65-Year-Old Male with Acute Upper Limb Ischemia Accompanied Insulinoma by Improvement of With Anticoagulant

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Abstract

An Insulinoma is a functioning neuroendocrine tumour of pancreas that causes hypoglicemia through inappropriate secretion of insulin, more than 90% of insulinomas are benign. Acute upper limb ischemia (AULI) is less common than acute lower limb ischemia. incidence of AULI has been reported as 1.3 cases per 100 000 patients. Nonsurgical therapies including endovascular techniques, thrombolytics, and anticoagulation. Male, 65 years old, with pain in the right little finger radiating to the palm of the hand, turning blue and cold. There is a history of hypertension and smoking. History of insulinoma diagnosis in 2018. Physical examination revealed weak palpable radial artery and capillary refill delayed. Fasting insulin level was 38 ul/ml, and Computed Tomography (CT) scan showed a pancreatic head mass. Multislice Computerized Tomography (MSCT) of the upper extremity revealed total distal occlusion of the right radial artery. The patient was initially given heparin 5000 IU/bolus IV followed by 1000 IU/hour IV and showed improvement. Oral warfarin therapy was prescribed upon discharge. Insulinoma is one of the most common causes of hypoglycemia associated with endogenous hyperinsulinism. Investigations such as C-peptide, serum insulin, CT scan, and Magnetic Resonance Imaging (MRI) can help establish the diagnosis. Hypoglycemia will cause blood coagulation disorders, which increase the risk of thrombosis and acute ischemic. AULI is often caused by thromboembolic disease, trauma, or iatrogenic factors. Incidence of AULI is rare case. Urgent anticoagulation with unfractionated heparin (UFH) is to reduce further embolism or clot propagation. Successful therapy depends on time of diagnosis and localization of the arterial occlusion. A 65-year-old male with Insulinoma accompanied by AULI that has been successfully treated by anticoagulant therapy. Keywords: Insulinoma, acute upper limb ischemia, heparin.

043-Case Report

Detection of Small Lesion Insulinoma with ^{68}Ga-DOTATATE PET/CT scan

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Abstract

Endogenous hyperinsulinism is an abnormal clinical condition that involves excessive insulin secretion and 55% related to insulinoma. In most cases after completing biochemical evaluation, CT or MRI imaging can provide lesion detection localization. In difficult cases, a nuclear medicine approach should be considered. A 36-year-old female having recurrent episode of low blood sugar for 4,5 years. The first symptoms recognized when patients are hardly waking up from bed at morning accompanied by heavy sweating. After being given a glass of sweet tea and patient regained consciousness. A laboratory examination revealed FBG was 45 mg/dL. Patient then go to endocrinologist and a prolonged fasting test conclude that patient having an endogenous hyperinsulinemia, where are at BG 44 mg/dL, the C-Peptide 2,27 ng/mL, Insulin level at 15 µIU/mL, Proinsulin level at 53,1 pmol/L and beta-hydroxybutyrate 0,1 mmol/L. Patient undergo several imaging investigations but shows no satisfying result. EUS was performed but shows no specific finding. Patient feels disappointed and stop looking for another opinion. After 1 year patient decided to restart the investigation again and nuclear medicine examination was planned. At first a ^{99m}Tc Hycnic TOC examination performs but shows no typical neuroendocrine tumour in pancreas or other organ, and then after waiting for several months a ^{68}Ga-DOTATATE PET/CT was performed in Hasan Sadikin Hospital and result shows a nodule at head of

pancreas surrounding pancreaticoduodenal junction that expressing somatostatin receptor, suggestive a insulinoma. A meeting was done, and the definitive treatment option are between whipple's procedure or radiofrequency ablation. CT or MRI imaging can provide lesion detection 70% and 86% respectively. A combination of CT and EUS can help 100% detection of location. About 80% insulinoma are less than 2cm and 40% of it less than 1 cm. In small lesion where common imaging is difficult to determine the location, a nuclear medicine such as ^{68}Ga-DOTATATE can be a choice compared to invasive procedures. Localization for small lesion can be challenging and the needs of advanced nuclear medicine strategies in those case are high. A ^{68}Ga-DOTATATE PET/CT can detect a NET as small as 6mm in size and maybe considered as a adjunct imaging study when all imaging studies are negative.

044-Case Report

Recurrent Severe Hypoglycemia in a 43-Year-Old Extreme Obese Woman with Insulinoma

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Abstract

Insulinomas are very rare neuroendocrine tumors (4 cases per million individuals per year) leading to insulin hypersecretion and occurring more often in women at any age. A 43-year-old extreme obese woman was referred to Dr Kariadi General Hospital with complaints history of repeated unconsciousness due to recurrent episodes of symptomatic severe hypoglycaemia (previously been hospitalized several times in regional hospitals in last six years). Physical examination: Body Mass Index (BMI) Class II obesity (Asia-Pacific). Laboratory: recurrent hypoglycaemia (random blood glucose range 30-50 mg/dL), Fasting Blood Glucose 105 mg/dL (n: 80-109), 2 hours Postprandial Blood Glucose 44 mg/dL (n: 80-140), C-peptide levels (taken during hypoglycaemia) 13.59 ng/ml (n:1.1-4.4). Abdominal USG: grade 2 fatty liver, Fibroscan: no fibrosis or steatosis, Plain Head MSCT: no visible abnormalities, Contrast Abdominal MRI: solid lesion in the body of pancreas (AP 1.2 x LL 1.2 x CC 1.3 cm) tends to be a picture of insulinoma. Patient underwent distal pancreatectomy with immunohistochemical results of an insulinoma. Post surgery the patient never had hypoglycaemia. We described a 43-year-old extreme obese woman with recurrent episodes of symptomatic severe hypoglycaemia. Laboratory (low random blood glucose, high C-peptide) and imaging examinations (solid lesion in the body of the pancreas on Contrast Abdominal MRI) support the diagnosis of insulinoma. Surgery is the treatment of choice for insulinomas. Patients with recurrent severe hypoglycemia, increase in c-peptide levels and solid lesion in pancreas are clinical manifestations of Insulinoma.

045-Case Report

Unresectable Malignancy Insulinoma in a 43 Year old woman

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Abstract

Insulinoma is a type of functional neuroendocrine tumor characterized by hypersecretion of insulin, causing Hypoglicemia characterized profuse sweating, palpitations, tremors, decreased consciousness, seizures and coma. Supporting examinations include 72-hour fasting blood sugar, C-Peptide, serum insulin, sulfonyl urea screening, CT scan and MRI can help with diagnosis, intraoperative palpation by a surgeon can confirm the presence of a mass in the pancreas. A woman 43 years old with the main complaint is often unconscious at night and was diagnosed with suspicion of insulinoma. For 7 months before admitted has complained of sudden weakness, the complaints decrease after drinks sugar water. Laboratory examination BSS 23 mg/dL, Fasting C-Peptide 8,59 ng/mL, Fasting insulin 192,2 uIU/mL. MRI with Contrast Pancreatic Head Mass, Hepatomegaly accompanied by multiple hepatic nodules in the right lobe. Anatomical Pathology results pancreatic neuroendocrine tumour grade 2 in the head of the pancreas, with metastases in the liver. From the history, whiple triad was found, with no history of Diabetes Mellitus in the patient and his family, examination to support low blood sugar,normal HbA1c,to ensurethatthe cause of hypogycemia in this patient was a type of endogenous Hyperinsulinemic Hypoglycemia, C-Peptide and low fasting insulin were examined, then an MRI examination with contrast was carried out and continued with Pathology examination to support an insulinoma. Patient got better after sandostatin LAR 30 mg injection blood sugar levels 75 → 82 → 92 → 119. A 43 years old woman with the main complaint often being unconscious at night and palpitations, tremor was diagnosed with I nsulinoma, the patient experienced improvement with administration of sandostatin LAR.

046-Case Report

Overcoming Obesity Through Multidisciplinary Approach: Case Series from Cipto Mangunkusumo Hospital

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Abstract

Obesity is a complex, multifactorial disease that can lead to catastrophic complications. Obesity management requires a comprehensive and multidisciplinary approach that addresses the patient's individual conditions and needs. Cipto Mangunkusumo as a national referral hospital forms an integrated obesity clinic that focus on multidisciplinary approach on managing obese patients. Integrated Obesity Clinic in Cipto Mangunkusumo Hospital has 17 patients in the span of 6 months. All the patients underwent internal medicine, clinical nutrition, and physical medicine and rehabilitation assessment. Nine patients received medical therapy, two patients received intragastric balloon, and four patients underwent bariatric surgery. Overall, the highest weight reduction was achieved by bariatric surgery. This

case series emphasizes the importance of multidisciplinary approach to form a personalized treatment plan that acknowledge the individuals' specific needs. This multidisciplinary approach began when patient admitted to the clinic in accordance with the pathway. Case manager will schedule multi-doctor appointments with endocrinologist, clinical nutritionist, and physical medicine and rehabilitation. After the first appointment, consultation to another specialist can be conducted as needed. Case meeting will be conducted to facilitate discussion to reach the treatment plan. The adherence to the program as well as the cost of therapies are the most common obstacles on these patients. The multidisciplinary approach at Cipto Mangunkusumo has demonstrated a considerable success in managing obesity. We hope that this concept can also be applied using National Health Insurances to further improve the quality of life and reduce mortality and morbidity of patients with obesity.

047-Case Report

Pickwickian Syndrome in a Schizophrenic Patient on Antipsychotic Medication: A Case Report

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Abstract

Weight gain and obesity are significant concerns for patients with schizophrenia. The prevalence of obesity and diabetes in individuals with schizophrenia is estimated to be 3-5 times higher than in the general population. Approximately 50% of patients with schizophrenia are reported to be obese, up to 40% have metabolic syndrome, up to 25% experience glucose intolerance, and up to 15% have diabetes. The increased prevalence of these conditions is attributed to multiple factors. Schizophrenia itself can contribute to an increased BMI and a higher risk of obesity. Additionally, patients with schizophrenia often have unhealthy diets and insufficient physical activity, which can be linked to lower socioeconomic status, lower educational levels, and suboptimal living conditions. This a case of Pickwickian syndrome (PS) in a patient with schizophrenia on antipsychotic medication. A 27-year-old male presented to the emergency room with complaints of shortness of breath that had persisted for the past six months and worsened over the last week. He was diagnosed with mixed-type respiratory failure, Pickwickean syndrome with morbid obesity (BMI = 58.8 kg/m2), and recurrent episodic paranoid schizophrenia. The patient was successfully extubated on the ninth day of admission and was transferred to a high care unit and received oxygen at 6 LPM via a simple mask, a low-calorie high-protein diet of 1700 kcal/day, salbutamol nebulization every 8 hours, and chest physiotherapy. Patients with obesity hypoventilation syndrome (OHS) are at an increased risk for conditions such as congestive heart failure, angina pectoris, and cor pulmonale, and they experience higher rates of hospitalization. Patients, their families, and caregivers should be informed that treatment with some SGAs may be associated with significant weight gain, which can contribute to the development of PS. Continuous positive airway pressure (CPAP) and weight loss programs are critical components in managing PS to reduce morbidity and mortality.

048-Case Report

Relapse Of Pheochromocytoma with Hipertensive Heart Disease Mildly Reduced Left Ventricle Ejection Fraction

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Abstract

Pheochromocytoma is a tumor originating from the medulla of the adrenal gland. Elevated metanephrines and normetanephrine in plasma or urine confirm the diagnosis. radiological examination helps in the tumor's location. A case study of a 19-year-old woman. This patient was previously

diagnosed at the age of 13 with pheochromocytoma. The patient experienced symptoms of headache, sweating, especially in the forehead area, trembling hands, and hypertension. Examination found a right adrenal tumor, so an adrenalectomy was performed on the patient and an increase in plasma metanephrine and normetanephrine levels was found. A CT scan of the abdomen revealed a right adrenal tumor, so this patient underwent another adrenalectomy. Pheochromocytoma is a rare form of endocrine tumor, the tumor may return or relapse after removal. Relapse rates vary depending on tumor size, location, and cell type.

049-Case Report

Improvement Of Menstrual Cycle in an 18-Year-Old Female With Congenital Adrenal Hyperplasia Following Hydrocortisone Therapy

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Abstract

Congenital Adrenal Hyperplasia (CAH) is an autosomal recessive disorder resulting from mutations in genes encoding enzymes involved in adrenal steroidogenesis. The most common form, 21-hydroxylase deficiency, accounts for 90-95% of cases and impairs cortisol and aldosterone synthesis, leading to androgen excess. This case report presents an 18-year-old female with classic 21-hydroxylase deficiency, exhibiting signs of virilization from childhood, including ambiguous genitalia, early pubarche, and rapid linear growth. She was treated with hydrocortisone therapy, which regulated her menstrual cycle. Despite the virilization effects, continuous monitoring and hormone replacement therapy significantly improved her quality of life. This case highlights the importance of early diagnosis and lifelong management for patients with CAH to prevent complications such as adrenal crises, growth abnormalities, and fertility issues.

050-Case Report

A 24-year-Old Female with Post Adrenalectomy Recurrent Adrenocortical Carcinoma

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Abstract

Adrenocortical carcinoma (ACC) is a malignancy involving the adrenal cortex. The incidence of ACC is 0.5-2 cases/million population per year with poor prognosis. The clinical features of ACC include hypercorticolism, hyperaldosteronism and androgen hypersecretion. Management of ACC include surgical resection, mitotane and adjuvant chemotherapy. A 24-year-old female consulted from Urology with post adrenalectomy recurrent ACC. The Chief Complaints were abdominal pain, swelling face, and weight gain. Physical examination revealed moon face, a palpable mass in the left upper quadrant abdomen, purple striae on the abdomen, armpits and thigh. Laboratory examination with high serum cortisol 28.7 ug/dl and suppressed ACTH level 6 pg/mL. Histopathological examination revealed a suprarenal cortical carcinoma. The result of abdominal CT was a recurrent mass of left suprarenal with tumor metastatic to the liver. The patient was planned to undergo surgery again and receive mitotane with adjuvant chemotherapy. We report a case of post adrenalectomy recurrent ACC with symptoms of hypercorticolism, further examination is needed to assess the incidence of hyperaldosteronism and androgen hypersecretion. ACC recurrence and metastatic rates are very high, even > 80%. A 24-year-old female was reported with a diagnosis of post adrenalectomy recurrent ACC.

Keywords: Adrenocortical carcinoma, ACTH, Cortisol

051-Case Report

Spontaneous Resolution of Hypoglycemia with Elevated Insulin in Non-Diabetic Patients: Diagnostic Challenges

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Abstract

Non-diabetic hypoglycemia is rare but can lead to significant morbidity, making early recognition crucial for effective treatment. We report a challenging case of recurrent severe hypoglycemia caused by elevated insulin levels that resolved spontaneously. A 27-year-old woman was admitted multiple times over two months for recurrent severe hypoglycemia, consistently accompanied by abdominal pain, diarrhea, nausea, and vomiting. Despite extreme weakness and diaphoresis during hypoglycemia, she remained conscious. There was no history of diabetes and no intake of sulfonylureas. The lowest recorded blood glucose (BG) level was 34 mg/dL, and hypoglycemic episodes occurred mostly during fasting, requiring dextrose 10% infusions at night while sleeping at home, along with occasional boluses of dextrose 40%. During each hospital admission, leukocytosis was observed, and antibiotic treatment improved both blood glucose levels and gastrointestinal symptoms. During a prolonged fasting test, hypoglycemia occurred within three hours (BG 25 mg/dL), with significantly elevated fasting insulin and C-peptide levels. No focal lesions were observed on the abdominal CT scan or functional imaging using 99mTc-HYNIC-TOC SPECT/CT. Surprisingly, the hypoglycemia symptoms resolved spontaneously after several months, with fasting blood glucose levels in the low normal range. **Discussion** Whipple's triad confirms hypoglycemia. In non-diabetic patients, insulin-secreting neuroendocrine tumors (insulinomas) are often the cause of hypoglycemia. Although our patient had elevated insulin and C-peptide levels, the negative findings on imaging modalities, particularly the highly specific Tc-99m HYNIC-TOC (specificity 90-95%), and the spontaneous resolution of hypoglycemia argue against an insulinoma diagnosis, suggesting the need for further investigation. Diagnosing non-diabetic hypoglycemia is challenging and requires multi-modal approaches to identify the underlying cause.

052-Research

The Associations between Inflammatory Parameters, Adipokines and HOMA-IR with Antibody Seroconversion Failure in COVID-19 Patients with Central Obesity

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Abstract

Central obesity is related to the pro-inflammatory state, adipokines dysfunction and insulin resistance. Besides, central obesity showed antibody dysfunction during antigen exposure, such as COVID-19 infections. However, the relationship between inflammatory parameters, adipokines and HOMA-IR with antibody response in COVID-19 patients with central obesity is unclear. This is a cohort study among COVID-19 patients with central obesity in Dr. Cipto Mangunkusumo National General Hospital Jakarta, Indonesia, during the early phase of the COVID-19 pandemic. Our study is a part of the COVID-19, Aging, and Cardiometabolic Risk Factors (CARAMEL) study. From the CARAMEL study, we selected adult non-ICU/HCU inpatient subjects with central obesity that met inclusion/exclusion criteria and collected clinical and anthropometric data. We measured inflammatory cytokines, adipokines, HOMA-IR, and IgG S-RBD SARS-CoV-2 antibody titers from a stored sample taken at day 2 of hospitalization. We used the Mann-Whitney test to analyse non-normally distributed data, and T-test for normally distributed data. The higher pro- and anti-inflammatory cytokines (IL-6, IFN-γ, MCP-1, IL-1Ra, IL-4 and IL-10), leptin, and leptin-to-adiponectin ratio were associated with antibody seroconversion failure. However, no significant result from HOMA-IR. In COVID-19 patients with central obesity, we confirmed the association between the chronic inflammatory state and hyperleptinemia with antibody seroconversion failure.

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