Diagnostic and Management of Idiopathic Panhypopituitarism Patient: A Case Report

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ABSTRACT

Hypopituitarism is marked by decreased secretion of one, several, or all anterior or posterior pituitary hormones. A rare disorder, panhypopituitarism indicates the loss of all the pituitary hormones but often is used in clinical practice to describe a patient's deficiency in growth hormone, gonadotropins, corticotropin, and thyrotropin in whom the posterior pituitary function remains intact. Hypopituitarism may occur because of diverse etiologies and lead to substantial morbidity and mortality. Despite advances in the diagnosis and management of pituitary disorders, hypopituitarism is still associated with increased long-term cardiovascular mortality. We report a rare case of a 22-year-old boy with idiopathic panhypopituitarism. The patient has deficiency of growth hormone, gonadotropin, corticotropin, and thyrotropin, yet the underlying etiology remains unknown in this patient because of lack of imaging data. This is very challenging to do prompt diagnosis and management of panhypopituitarism. The management is needing multiple hormone replacement therapy, based on the result of pituitary hormone laboratory examination. Prompt treatment is needed to prevent further morbidity and mortality in this patient.

Keywords: *Panhypopituitarism, hypoadrenalism, hypogonadism, hypothyroidism, growth hormon*

INTRODUCTION

Hypopituitarism is a deficiency of one or more hormones secreted by the anterior or posterior pituitary gland. [1,2] Panhypopituitarism indicates loss of all pituitary hormones but is often defined in clinical practice as a deficiency of growth hormone (GH), gonadotropins, corticotropins, thyrotrophins with intact posterior pituitary hormone function. [2,3] Hypopituitarism is a rare condition with a prevalence of 46 cases per 100,000 population.[4] In Spain, the prevalence is 45.5 cases per 100,000 population. The incidence is 4.2 cases per 100,000 population per year and increases with age.[4] According to the National Institutes of Health, a rarer condition, panhypopituitarism, affects only 200,000 patients in the United States. [3] Causes of hypopituitarism include pituitary tumors (61%), non-pituitary lesions (9%), and non-cancerous causes (30%), including 11% of idiopathic causes. Other causes that are classically rare are perinatal insults, genetics, or trauma.[5]

Given the complexity of hypopituitarism, it is very important for clinicians to be able to correctly diagnose this condition. Therefore, this case report will discuss the diagnosis and management of a case of panhypopituitarism suffered by a 22-year-old man. Hopefully this case report can increase clinician knowledge in terms of diagnosing and managing panhypopituitarism, so that mortality can be reduced.

CASE ILLUSTRATION

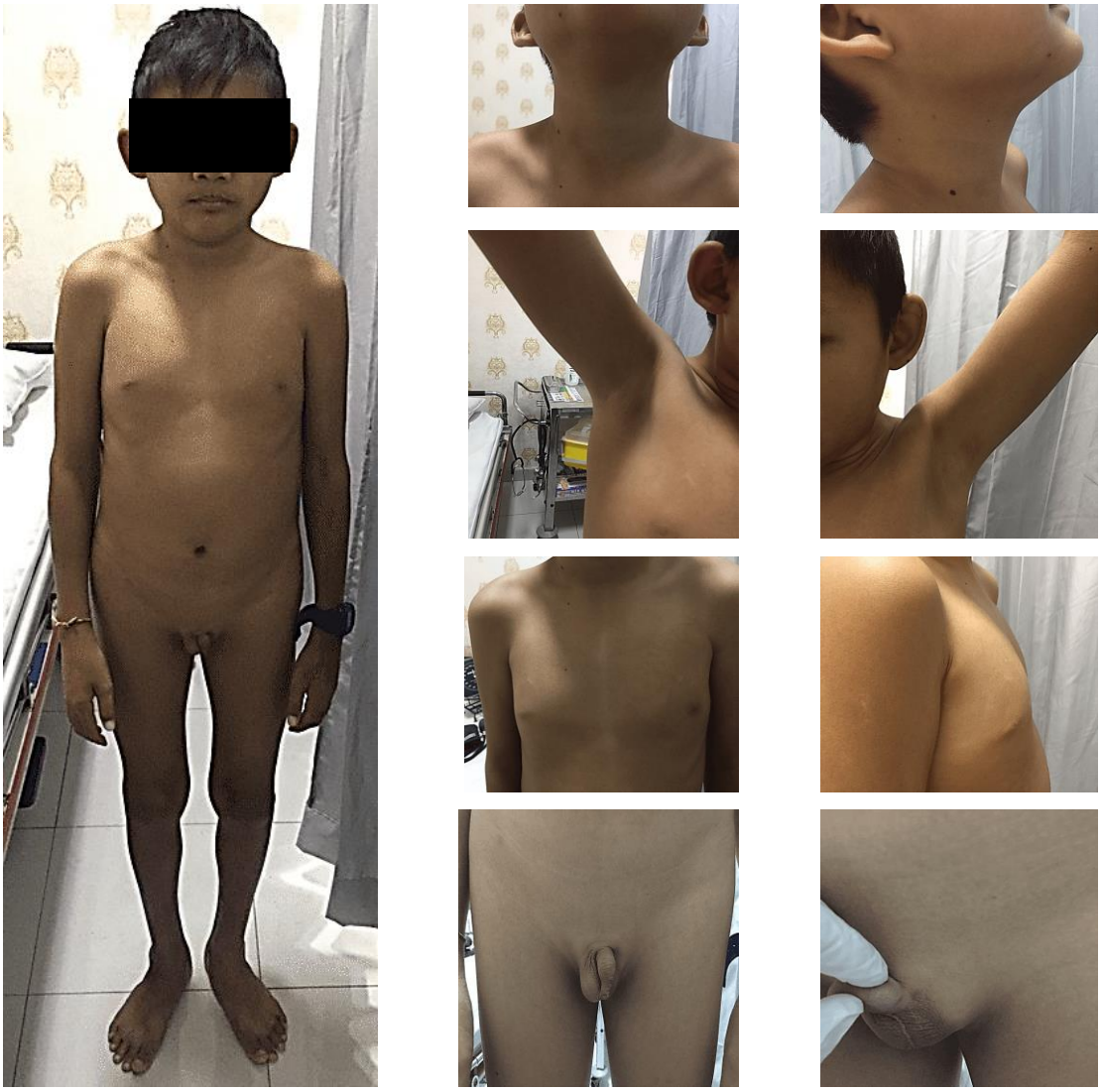
A male patient aged 22 years, Lombok ethnicity, came with the chief complaint of a delay in height growth that has been felt since the patient he was 9 years old. It is said that his height increases more slowly than his peers. The patient also complained that the small penis and the left testicles smaller than the right testicles. The testicles of the patient on the left are also smaller than the testicles on the right.

The patient's voice sounded like a child for the last 7 years or so. The patient also said that he had not experienced secondary sexual growth such as pubic and armpit hair and had no libido. It was said that his intellectual abilities also did not develop well, so the patient missed several grades at the elementary and junior high school levels. Patients also complained of weakness all the time, even when he was not active. The patient did not complain of visual or olfactory disturbances, and no appetite disturbances. The patient did not experience appetite disturbances and activities can be carried out as usual. Complaints of headaches, dizziness, nausea, and vomiting were denied.

The patient was in first grade of high school and the patient was the fourth child of four siblings. Both of his parents are normal and do not experience any hormonal disturbances, so do the patient's three siblings. The patient was said to have been born via vaginal delivery (breech presentation) and during delivery there were no notable complications. The patient was born healthy. He had a history of seizures accompanied by fever when he was 6 months old, but the family did not know the cause of the febrile seizures. The history of drug use and accidents as well as head trauma were denied by the patient and the patient's family. History of other diseases such as diabetes mellitus, congenital heart disease or kidney disease were denied by the patient and his family. At 9-year-old the patient went to a hospital in Surabaya and received hormone therapy, but the treatment was stopped voluntarily.

On physical examination, the general condition was good, and the patient was alert. Blood pressure was 110/70 mmHg, pulse rate was 88 times per minute, respiratory rate was 18 times per minute, axillary temperature was 36.7^{o}C. The head and neck examination were within normal limits, no lymph nodes enlargement. Examination of the chest impression was within normal limits. Abdominal examination was also within normal limits, no enlargement of the liver or spleen. Extremities felt warm. There were no signs of secondary sex growth including axillary hair. Examination of the genitalia region showed the absence of pubic hair, the penis was small, and the left testicle was smaller (left testicles was barely palpable) than the right one (right testicles still palpable).

Anthropometric measurements taken on March 2020 found as such: height 147 cm, body weight 39 kg, head circumference 56 cm, upper arm circumference 22 cm, abdominal circumference 72 cm. The height of the patient's biological father was 170 cm while the patient's biological mother was 165 cm. The calculation of the genetic potential height of a boy was [(Mother's Height (cm) + 13 cm) + Father's Height (cm)] / 2 ± 8.5 cm. So, the patient's genetic potential height calculation is [(165 + 13 cm) + 170] / 2 ± 8.5 cm resulting in 165.5-174 cm. Currently, the patient's height can be categorized as having not reached the genetic potential height.



The first laboratory examination was carried out at the Endocrine clinic on August 25, 2019. The result of hormone examination were as follow: Thyroid-Stimulating Hormone (TSH) 2.311 µIU/mL (N = 0.35-4.94 µIU/mL), free T4 (FT4) 0.61 ng/dL (N= 0.79-1.34 ng/dL), testosterone ≤ 2.5 ng/ mL (normal levels depending on Tanner stage), prolactin 6.07 ng/ml (N= 4.3 -23.04 ng/ml), morning serum cortisol <0.8 µg/dL (N=3.7-19.4 µg/dL), IGF-1 <15 ng/mL (57-426 ng/ mL). The HbA1c level was 4.6% (N ≤ 6.5%). Follicle stimulating hormone (FSH) levels were found to be 0.1 mIU/ml (N= 0.49-9.98 mIU /ml), luteinizing hormone (LH) <0.5 mIU/mL (N= 0.78-4.93 mIU/mL).

Complete blood results showed the following values: leukocyte levels 5.91 x 10^3/µL (4.10 -11.0 x 10^3/µL), lymphocytes 3.00 x 10^3 /µL (1.00-4.00 x 10^3/ µL), monocytes 0.32 x 10

^{3}/µL (0.10-1.2 x 10 ^{3}/µL), eosinophils 0.53 x 10 ^{3}/µL (0.00-0.5 x 10 ^{3}/µL), basophils 0.07 x 10 ^{3}/µL (0.00-0.1 x 10 ^{3}/µL), neutrophils 1.99 x 10 ^{3}/µL (2.50-7.50 x 10 ^{3}/µL), hemoglobin 10.38 g/dL (13.5-17.5 gr/dL), hematocrit 30.6 % (41-53%), MCV 76.32 fL (80-100 fL), MCH 25.89 pg (26-34 pg), platelets 216.2 x 10 ^{3}/µL (150-440 x 10 ^{3}/µL), Serum Glutamic Oxaloacetic Transaminase (SGOT) 77.0 U/L (11-33 U/L), Serum Glutamic Pyruvic Transaminase (SGPT)) 53.2 U/L (11-50 U/L), Blood Urea Nitrogen (BUN) 8.4 mg/dL (8-23 mg/dL), serum creatinine 0.71 mg/dL (0.7- 1.2 mg/dL), sodium 137 mmol/L (136-145 mmol/L) and potassium 4.14 mmol/L (3.5-5.1 mmol/L). Considering that the Hb level is less than the normal range, the peripheral blood smear, Serum Iron (SI), TIBC, and ferritin were examined. Examination of the peripheral blood smear found normochromic normocytic erythrocytes, normal leukocyte count, no immature cells, and toxic granulosa, negative vacuolization, normal platelet count, and no giant platelets. Conclusion of peripheral blood with normochromic normocytic anemia. Meanwhile SI levels were 97.38 ng/dL (65-175 ng/dL), TIBC 289 ng/dL (261-478 ng/dL), ferritin 84.64 (30-400 ng/dL). Hepatitis virus marker examination was also carried out due to an increase in liver enzymes but was found to be negative for both HbsAg and anti HCV. This liver enzyme examination was repeated, and other liver function tests were also carried out. On repeat examination, levels of SGOT 28.1 U/L (11-33 U/L), SGPT 20.3 U/L (11-50 U/L), total bilirubin 0.34 mg/dL (0.30- 1.30 mg/dL), direct bilirubin 0.15 mg/dL (0.00-0.3 mg/dL), indirect bilirubin 0.19 mg/dL, alkaline phosphatase 105 U/L (53-128 U/ L), total protein 7.6 g/dL (6.4-8.3 g/dL), albumin 4.8 g/dL (3.2-4.5 g/dL), gamma GT 25 U/L (11-49 U/L).

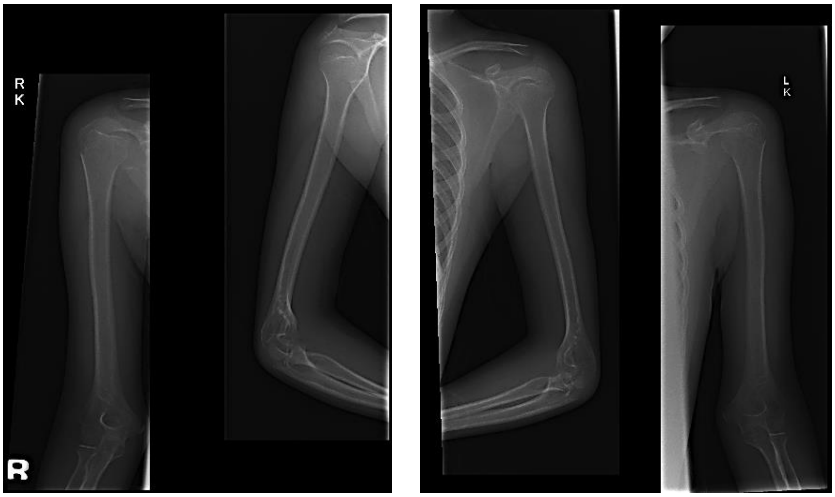


Figure 1. Left: X-ray photo of the right elbow; Right: X-ray photo of left elbow.

Due to sub optimal height compared to the genetic potential, a radiological examination was carried out to determine bone age and epiphyseal plate closure. Plain AP/lateral x-ray of the right and left elbows showed that the epiphyseal plate of both proximal radius bone, no fractures or dislocations were seen at the location of both elbows (Figure 2). Plain AP/lateral x-ray of the right and left femurs showed growth plates on both femur bones, and no bone fractures or joint dislocations were seen (Figure 3). Meanwhile, on the AP/lateral manus x-ray, a bone age picture of a 13-year-old boy was obtained (according to the Atlas of Hand Bone Age) (Figure 4). From the history, physical examination, results of hormonal and radiological examinations performed on this patient, it can be concluded that the patient suffered from panhypopituitarism.

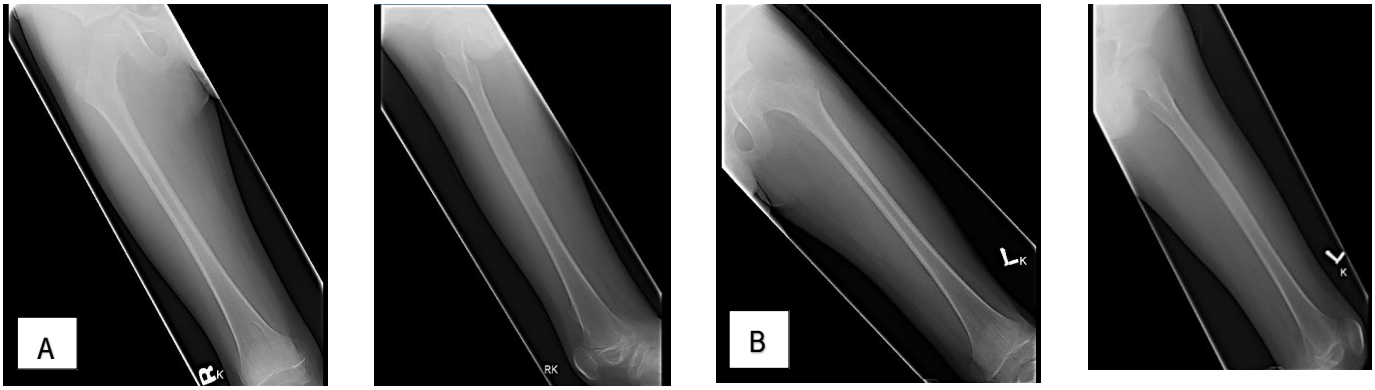


Figure 2. A, AP/lateral plain radiograph of the right femur; B, AP/lateral plain radiograph of the left femur.

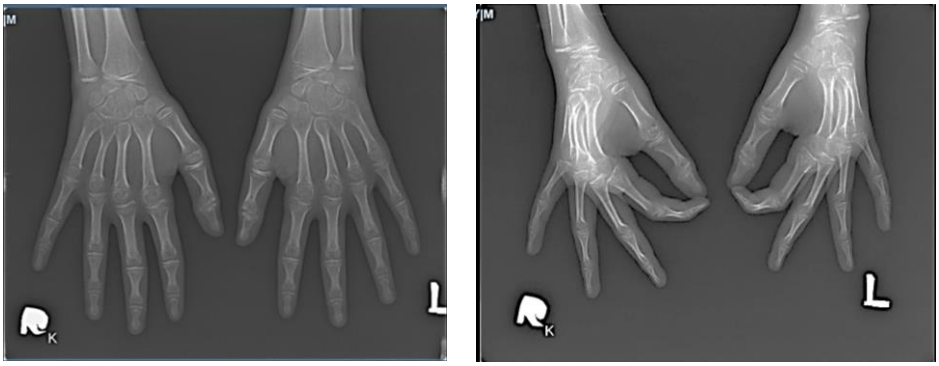


Figure 3. AP/lateral manus plain radiograph X-ray.

The patient also underwent several imaging tests. Figure 4 shows the results of an ultrasound imaging of the testicles with a picture of the right scrotum, testicles measuring 1.15x0.67x1.03 cm (volume 0.56 cc), normal echoparenchime with no visible nodules or masses or calcifications, normal epididymis, no intrascrotal abnormal free fluid was seen. In the left scrotum, testis measuring 1.24x0.7x0.8 cm (0.49 cc volume), normal echoparenchime, no visible nodules/ mass/ calcifications, normal epididymis, no intrascrotal abnormal free fluid. From the results of testicular ultrasound, it can be concluded that the size and volume of the right and left testicles matched the testicles in children aged 9 months to prepuberty.

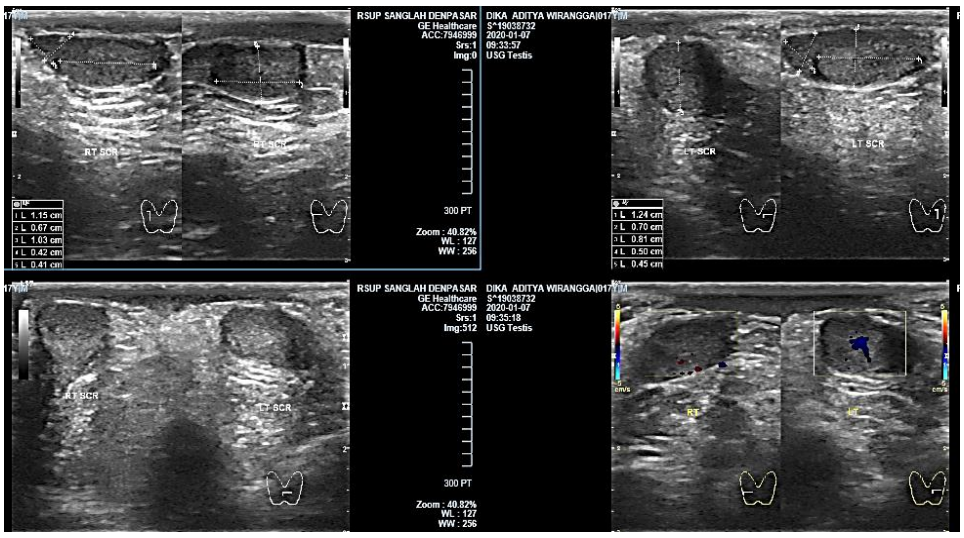


Figure 4. Ultrasonography result of patient's testicles

After the first pituitary hormone examination, the patient was then given hydrocortisone treatment (10 mg in the morning and 5 mg in the afternoon) and planned to receive GH. However, due to the patient's busy school activities, GH administration could only be given from March 2020 at a dose of 0.2 mg subcutaneous injection per day. GH therapy which had been done for 30 days, later was discontinued due to insurance issues. The patient also received levothyroxine therapy 100 mcg per day and testosterone hormone replacement 250 mg intramuscularly per month. Figure 5 is a summary of the patient's disease history and treatment.

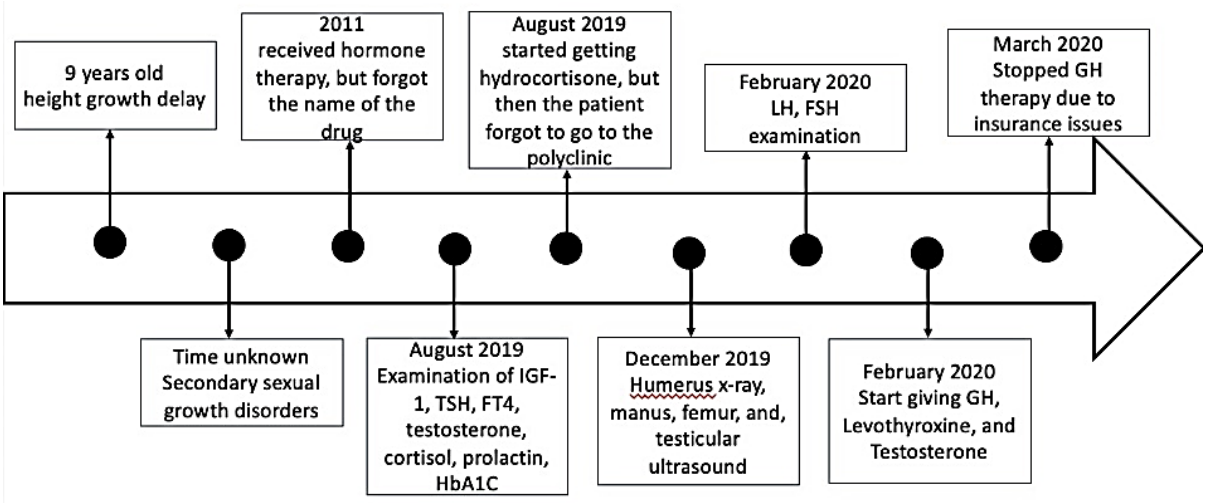


Figure 5. Timeline and course of the disease.

DISCUSION

The pituitary gland itself is supplied by blood that comes from branches of the internal carotid artery. These branch vessels form a plexus in the region of the median eminence of the hypothalamus. Blood from this branching area then reaches the anterior pituitary via the pituitary stalk. The middle and inferior pituitary arteries supply the pituitary stalk and neurohypophysis. However, the anterior lobe is not included in the blood supply of this artery; it receives oxygenated blood via the internal plexus and external median eminence. Through the regulation of hypothalamic releasing factor, hypothalamic inhibiting factor, and peripheral hormonal negative feedback inhibition, the anterior pituitary produces adrenocorticotropic hormone (ACTH), thyrotropic hormone (TSH), luteinizing hormone (LH), follicle- stimulating hormone (FSH), prolactin (PRL), and GH. The posterior pituitary is a storage organ for the hypothalamic antidiuretic hormone (ADH) and oxytocin hormones.

The mechanism by which hypopituitarism (including panhypopituitarism) develops depends on the cause of the disease and may not be fully understood in some cases. Table 1 shows the causes of hypopituitarism. In determining the cause of hypopituitarism, it is recommended to perform pituitary imaging. In this case magnetic resonance imaging (MRI) of the sella is the first choice for assessing the sella region.[1] In this case, an MRI examination has not been carried out, so the exact cause of hypopituitarism is not yet known. In making the diagnosis of panhypopituitarism, it is necessary to evaluate the clinical picture and examination of the pituitary hormone. Pituitary hormone deficiency will cause various clinical symptoms depending on the hormone deficiency that occurs (Table 2). In this case, the patient showed symptoms of deficiency of corticotropin, thyrotropin, gonadotropin, and GH hormones in the form of chronic weakness, delayed puberty, loss of libido, cognitive delay, and growth retardation. Symptoms of ADH deficiency were not found.

Table 1. Causes of hypopituitarism[3]

Cause of hypopituitarism	
Brain damage	**Infection**
- Traumatic brain injury	- Apoplexia
- Subarachnoid hemorrhage	- Sheehan's Syndrome
- Neurosurgery	- **Autoimmune Disease**
- irradiation	- Pituitary lymphocytic
- Strokes	**Haemochromatosis, granulomatous disease, histiocytosis**
Pituitary tumors	**Empty sella**
- Adenomas	**Perinatal insult**
- Etc.	**Pituitary hypoplasia or aplasia**
Non-pituitary tumor	**Genetic cause**
- Craniopharyngiomas	**Idiopathic cause**
- Meningioma	
- Glioma	
- Chordoma	
- Ependymoma	
- Metastases	

Thyrotropin deficiency can be diagnosed by testing TSH and free T4 (FT4). In panhypopituitarism, central hypothyroidism will be found, in which FT4 level is low and TSH level is low or normal (Table 3).[1] Examination of thyroid function in this case showed that the patient had central hypothyroidism, considering that the Free T4 level was 0.61 ng/dL (low) and TSH was 2.311 μIU/mL (normal).

Table 2. Clinical features and investigation findings of hypopituitarism[1,5]

	Investigative findings
Corticotropin Deficiency	
Chronic: Chronic weakness, pallor, anorexia, weight loss	Hypoglycemia, hypotension, anemia, lymphocytosis, eosinophilia, hyponatremia
Acute: Acute weakness, spinning dizziness, nausea, vomiting, circulatory collapse, fever, shock	-
Children: delayed puberty, failure to thrive	-
Thyrotropin Deficiency	
Fatigue, intolerance to cold, constipation, hair loss, dry skin, hoarseness, cognitive delay	Weight gain, bradycardia, hypotension
Children: growth and development disorders	-
Gonadotropin Deficiency	
Women: oligomenorrhea, loss of libido, dyspareunia, infertility	Osteoporosis
Men: loss of libido, loss of sexual function, absence of facial, scrotal and trunk hair	Decreased muscle mass, osteoporosis, anemia
Child: delayed puberty	-
Growth Hormon Deficiency	
Reduced muscle mass and strength, visceral obesity, fatigue, decreased quality of life, impaired attention and memory	Dyslipidemia
Child: growth retardation	-
Prolactin Deficiency	
Women: failure to lactate in post-partum conditions	-
Man: no consequence	
Anti Diuretic Hormon deficiency	
Polyuria, polydipsia	Decreased urine osmolality, hypernatremia, polyuria

Secondary hypogonadism or hypogonadotropic hypogonadism (HH) is a condition that occurs due to deficiency of gonadotropins (FSH and LH). The diagnosis of HH is established in the second or third decade (after the age of 18 years), in which the patient will experience clinical symptoms in the form of loss of libido, delay or absence of signs of secondary sex growth which include eunuchoid body proportions, infertile, unilateral and/or bilateral cryptorchidism and micropenis in man.[5] The symptoms and clinical manifestations of HH in these patients are decreased libido and tend to be absent altogether, as well as secondary sex development disorders (absence of hair on the armpits and penis, and micropenis). The diagnosis of HH is established when there is a decrease in the levels of the hormones FSH, LH, and testosterone. In our case we found very low testosterone levels of <2.5 ng/dL, FSH level of 0.1 mIU/ml (N= 0.49-9.98 mIU/ml), and LH <0.5 mIU/mL (N= 0 .78-4.93 mIU/mL).

In general, to diagnose GH deficiency, stimulation examination is required (Table 3), unless all pituitary axes are deficient and IGF-1 levels are low. According to Schneider HJ et al., An insulin tolerance test is the best choice, but it should be noted that not all GH deficiency tests are 100% reliable.[5] The probability that GH deficiency will be proven through this test will increase as the number of pituitary hormone deficiencies increases. In our case, patient showed clinical growth retardation, the patient also had low IGF-1 levels (IGF-1 <15 ng/mL). Our patient also has other pituitary axis deficiencies, thereby strengthening the diagnosis of a GH deficiency.

Table 3. Endocrine examination to evaluate pituitary function[1,5]

	Hormone deficiency criteria
Corticotropic Function	
• Morning cortisol	<100 nmol/L: hypocortisolism; >500 nmol/L: hypocortisolism excluded
• ACTH in the morning	Below normal reference range: secondary adrenal insufficiency
• Insulin tolerance test	Cortisol <500 nmol/L
• 250 µg ACTH test	Cortisol <500 nmol/L after 30 minutes
Thyrotropic Function	
• Free T4	Low (<11 pmol/L)
• TSH	Low or normal (sometimes slightly increased)
Gonadotropic Function	
• Woman	
Clinical	Oligomenorrhea, estradiol <100 pmol/L, low LH and FSH
Post menopause	Low LH and FSH
• Man	
Testosterone	Low (<10-12 nmol/L), LH and FSH
Somatotropic Function	
• IGF-1	Below normal value
• Insulin tolerance test	Adult: GH ≤3 µg/L Child: GH≤10 µg/L Transition phase: GH ≤5 µg/L
• GHRH + arginine test	Underweight or normal BMI (BMI<25): 11.5 µg/L Overweight (BMI ≥ 25 to <30): 8 µg/L Obesity (BMI ≥30): 4.2 µg/L
• GHRH+GHRP-6 test	GH≤10µg/L
Prolactin function	
• prolactin serum	Not detected
Posterior Pituitary Function	
• Basal urine, plasma samples	Urinary volume (≥40 ml/kg/day) + urine osmolality <300 mOsm/kg + hypernatremia
• Water deprivation test	Urinary osmolality <700 mOsm/kg; urine to plasma osmolality ratio <2

The principle in management of panhypopituitarism is in the form of hormone replacement therapy that mimics the normal physiological pattern of hormones as much as possible. For conditions of corticotropin deficiency (ACTH), according to the recommendations of the Endocrine Society Clinical Practice Guideline, patients can be given oral hydrocortisone 15-20 mg per day in single doses or divided doses. [7] In this case the patient was given oral hydrocortisone therapy 10 mg in the morning then 5 mg in the afternoon (total 15 mg per day). Meanwhile, for thyrotropin (TSH) deficiency, initiation of levothyroxine administration can be done when Free T4 levels begin to decrease (no need to wait until FT4 levels are below normal). In this case, the patient was the patient given 100 mg of levothyroxine per day and this dose was in accordance with the recommended dose in young patients (without evidence of heart disease), which is 75-100 mcg per day (1.6-1.8 mcg/kg/day).[7,8]

The management of HH in this patient is to replace the existing hormone deficiency and improve the patient. This patient received testosterone hormone replacement at a dose of 250 mg intramuscularly monthly. The presence of androgen hormones will improve male libido and erectile function. Another effect is to increase muscle mass and strength, increasing bone density and homeostasis which will prevent early osteoporosis in men. [9]

GH deficiency in this patient had been treated by subcutaneous injection of GH at a dose of 0.2 mg per day. Before it was decided whether this patient can be given GH or not, bone age must be checked, and the epiphyseal plate must be identified whether it had closed or not. Through radiological examination, it was found that the patient's epiphyseal plate had not closed yet, and the patient had not reached his genetic height, so GH administration was indicated. According to the Endocrine Society Clinical Practice Guideline, the recommended initial dose for patients younger than 60 years is 0.2-0.4 mg per day.[7] The dosage recommendation for GH is different from the dosage recommendation issued by the Pediatric Formulary Committee, which is 23-39 mcg/kg/day.[10] The patient was finally unable to continue GH injections due to cost issues.

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