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.

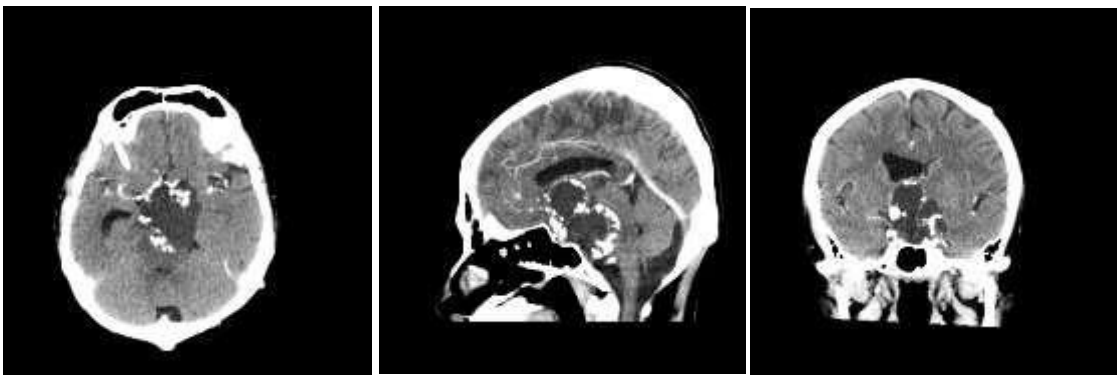

Figure 1. Coronal (A), axial (B) and sagittal (C) views of the contrast-enhanced CT scan (after craniotomy procedure) showing a heterogeneously enhancing mass with calcifications and fluid collection occupying intrasellar-suprasella. The mass pressing on the pons and mesencephalon tothe left side. The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

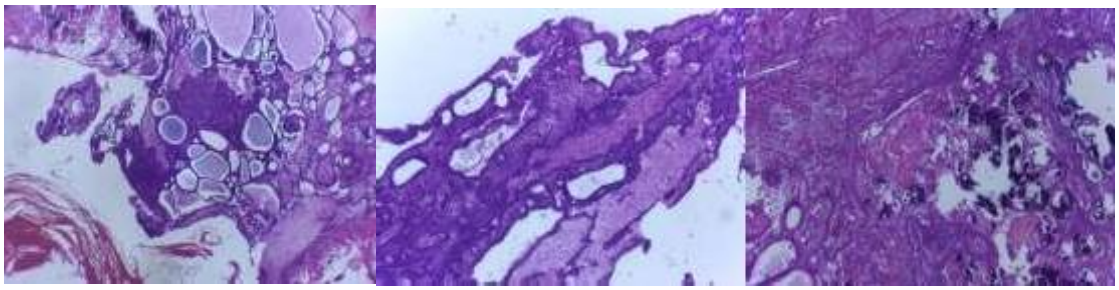

Figure 2. H&E-stained sections at 40x magnification showing tumor cells trabecular arranged(A). H&E-stained sections at 100x magnification showing tumor cells are palisaded on the peripher and stellate reticulum is visible (B). H&E-stained sections at 100x magnificationshowing tumor cells with wet keratin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

REFERENCES

1. Muller HL, Merchant TE, Warmuth-Metz M, Martinez-Baebera J, Puget S. Craniopharyngioma. Nat Rev Disease Primer. 2019, 5: 75
2. Garnett MR, Puget S, Grill J, Sainte-Rose C. Craniopharyngioma. Orphan J of Rare

Diseas. 2007, 2:18.
3. Dohle GR, Arver S, Bettocchi C, Jones TH, Kliech S. EAU Guidelines on Male Hypogonadism. Eur Assoc of Urolog. 2019.
4. Bhasin S, Brito JP, Cunningham GR, Hayes FJ, Hodis HN, Matsumoto AM, Snyder PJ, Swerdloff RS, Wu FC, Yialamas MA. Testosterone Therapy in Men with Hypogonadism: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2018;103(5):1715-44
5. Zhou Z, Zhang S, Hu F. Endocrine Disorder in Patients with Craniopharyngioma. Front. Neurol. 12:737743.
6. Isidori AM, Aversa A, Calogero A, Ferlin A, Francavilla S, Lanfranco F, Pivonello R, Rochira V, Corona G, Maggi M. Adult-and late-onset male hypogonadism: the clinical practice guidelines of the Italian Society of Andrology and Sexual Medicine (SIAMS) and the Italian Society of Endocrinology (SIE). J of Endocrinol Investig. 2022;45:2385-03.
7. Esteves SC, Acbermann AP, Simoni M, Santi D, Casarini L. Male infertility and gonadotropin treatment: What can we learn from real-world data? Best Pract Res Clin Obstet Gynaecol. 2023;86:102310.
8. Prior M, Stewart J, McEleny K, Dwyer AA, Quinton R. Fertility induction in hypogonadotropic hypogonadal men. Clin Endocrinol (Oxf). 2018;89(6):712-18.
9. Melmed S, Polonsky KS, Larsen PR, Kronenberg HM, editors. Will Textb of Endocrinol. Ed ke12. Philadelphia: Elsevier; 2011.
10. Esteves SC, Acbermann AP, Simoni M, Santi D, Casarini L. Male infertility and gonadotropin treatment: What can we learn from real-world data? Best Pract Res Clin Obstet Gynaecol. 2023 Feb;86:102310. doi: 10.1016/j.bpobgyn.2022.102310. Epub 2022 Dec 29.
11. Prior M, Stewart J, McEleny K, Dwyer AA, Quinton R. Fertility induction in hypogonadotropic hypogonadal men. Clin Endocrinol (Oxf). 2018 Dec;89(6):712-718. doi: 10.1111/cen.13850. Epub 2018 Oct 9.
12. Melmed S, Polonsky KS, Larsen PR, Kronenberg HM, editors. Will Textb of Endocrinol. Ed ke12. Philadelphia: Elsevier; 2011.