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Case Report

A female with isolated hypogonadotropic hypogonadism: A case report and review article

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ABSTRACT

Background: Isolated Hypogonadotropic Hypogonadism (IHH) is a clinical syndrome that results from gonadal failure due to abnormal pituitary gonadotropin levels, in the presence of normal baseline and reserve testing of the remaining pituitary hormones.
Case presentation: An 18 years old female came with primary amenorrhea, accompanied by poor breast and pubic development, with low levels of estradiol and gonadotropins but normal levels of other anterior pituitary hormones. Imaging of the hypothalamic-pituitary region revealed hypophyseal hypoplasia due to ischemia. Sex steroids therapy was given to induce pubertal development. IHH represents a rare condition but with a good prognosis.
Discussion: Early diagnosis and treatment can prevent negative physical and psychological sequelae, and restore fertility in affected patients. Constant surveillance is required due to the possibility of gonadal axis reversal and/or relapse of gonadal axis failure and to identify any adverse effects related to therapy.
Conclusion: Early identification of IHH can help in treatment efficiency.

1. Introduction

Hypogonadotropic hypogonadism (HH) or secondary hypogonadism is defined as a clinical syndrome that results from gonadal failure due to abnormal pituitary gonadotropin levels. HH may result from either absent or inadequate hypothalamic Gonadotropin-Releasing Hormone (GnRH) secretion or failure of pituitary gonadotropin secretion. It is typically characterized by a lack or delay of pubertal sexual maturation and inappropriately low circulating sexual steroids associated with low serum concentrations of Luteinizing Hormone (LH) and Follicle Stimulating Hormone (FSH), which is an effect of GnRH deficiency. HH is most frequently acquired and caused by several pathological processes, but it can also occur as part of various congenital syndromes with genetic causes of central hypogonadism have been identified. Idiopathic or isolated HH (IHH) was then used to indicate cases in which secondary causes of HH had been excluded [1–3].

Congenital HH is divided into anosmic HH (Kallmann syndrome) and congenital normosmic IHH. The incidence of congenital hypogonadotropic hypogonadism is approximately 1–10:100,000 live births, and approximately 2/3 and 1/3 of cases are caused by Kallmann syndrome (KS) and idiopathic HH, respectively [2,4]. HH is one of the rare conditions in which specific medical treatment can reverse infertility. The precise and early diagnosis of HH can prevent negative physical and psychological sequelae, preserve normal peak bone mass, and restore fertility in affected patients. Thus, clinicians should understand the characteristics of the condition and be able to recognize and treat the condition to guarantee patients' quality of life [3,5]. Based on the description above, we are interested in reporting an 18-year-old female patient with IHH. We report based on surgical case report (SCARE) 2020 guideline [6].

2. Case presentation

An 18-year-old female came with primary amenorrhea, accompanied with poor breast and pubic hair development. The patient did not report eating disorders, vigorous physical activity, or psychological stress. She had no olfactory complaints. She had 1 older brother with a history of normal pubertal development. There was no history of opiates, glucocorticoid, or psychotropic drugs administration. On a physical examination, she had no apparent congenital anatomical defects with normal

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habitus, height: 157 cm, arm span: 156 cm, weight: 61 kg, and normal body mass index (24.7 kg/m^2). Pubic hair and breast development were tanner stage II-III. Her bone age was 13 years old. At the time, the patient had already received hormonal therapy from the gynecology department for 2 months (Primolut 1 × 5mg and Esthero 1 × 0.625mg), with cyclical bleeding occurring regularly following therapy. Before therapy, there was poor development of breasts and pubic hair until the age of 18, so the possibility of Constitutional Delay of Puberty can be ruled out. Both anamnesis and physical examination showed clinical characteristics suggestive of HH, with functional (drugs, eating disorder, physical activity, stress) and autoimmune causes being ruled out. Serum karyotype examination such us 46, XX (N), ruling out gonadal dysgenesis. Basal hormonal evaluation revealed low serum estradiol 7.245 pg/mL (N 11–133 pg/mL) and serum progesterone 0.08 pg/mL (N 0.21–60 pg/mL). Laboratory result on June 2019 showed suppressed LH 0.03 mIu/mL (N 0.7–5.6 mIu/mL) and FSH 0.23 mIu/mL (N 1.5–10.2 mIu/mL). Anterior pituitary function were otherwise normal, prolactin 3.52 ng/mL (N 2.8–29.2 ng/mL), insulin 8.80 mU/L (N 0.5–300 mU/L), Growth Hormone 1.96 ng/mL (N 0.05–40.0), TSH 3.586 uIu/mL (N 0.55–4.78 uIu/mL), FT4 1.15 ng/dL (N 0.89–1.76 ng/dL), cortisol 10.55 μg/dL (N 4.3–22.4 μg/dL), ACTH 12.0 pg/mL (N <46 pg/mL), FBG 86 mg/dL, 2 hour post prandial BG 89 mg/dL. Ferritin test 112 ng/mL (N 20–278 ng/mL). All laboratory studies are suggestive of IHH with serum ferritin and other antepituitary hormones concentrations within normal limit, ruling out the possibility of hemochromatosis and other pituitary cause.

Abdominal ultrasound examination revealed uterus hypoplasia (1.4 × 2.4 × 3.4 cm). Pelvic MRI confirmed uterus hypoplasia and revealed no apparent normal ovaries (Fig. 1). MRI of the hypothalamic-pituitary region revealed hypophyseal hypoplasia (Fig. 2) with small vessel ischemic in right and left corona radiata and right temporal subcortical with MR Angiography showed right segment A1, ACA hypoplasia (embryonal variant). There were no radiological signs suggestive of Kallman syndrome.

The patient was assessed with isolated HH with no additional therapy from the endocrinology polyclinic and was recommended to continue her outpatient care in both endocrinology and gynaecology polyclinic regularly.

3. Discussion

In both males and females, secretion of LH and FSH is episodic, with secretory bursts that occur each hour and are mediated by a concordant episodic release of GnRH. Pulsatile secretion of GnRH by hypothalamic neurons is a crucial element of the reproductive cascade, initiating the release of pituitary gonadotropins, gonadal secretion of sex steroids, pubertal development, and gametogenesis. LH and FSH bind to receptors in the ovary and testis and regulate gonadal function by promoting sex steroid production and gametogenesis. In women, LH stimulates estrogen and progesterone production from the ovary. A surge of LH in the mid-menstrual cycle is responsible for ovulation, and continued LH secretion subsequently stimulates the corpus luteum to produce progesterone by enhancing the conversion of cholesterol to pregnenolone. Development of the ovarian follicle is largely under FSH control, and the secretion of estrogen from this follicle is dependent on both FSH and LH [3,7].

The diagnosis of IHH is confirmed by the findings of low levels of sex steroids (total testosterone (T) <100 ng/dL in males and estradiol (E2) <50 pg/mL in females) in the presence of low or inappropriately normal LH and FSH serum levels with typically normal levels of other anterior pituitary hormones. Acute stimulation with GnRH (GnRH test) is of little value in differentiating between a hypothalamic and pituitary defect. Most patients with GnRH deficiency show little or no response to an initial dose of GnRH, but normal responses may be elicited after repeated injections, in the presence of a hypothalamic defect. This initial slow response is attributed to the down-regulation of GnRH receptors after prolonged GnRH deficiency. Although widely used, the practical

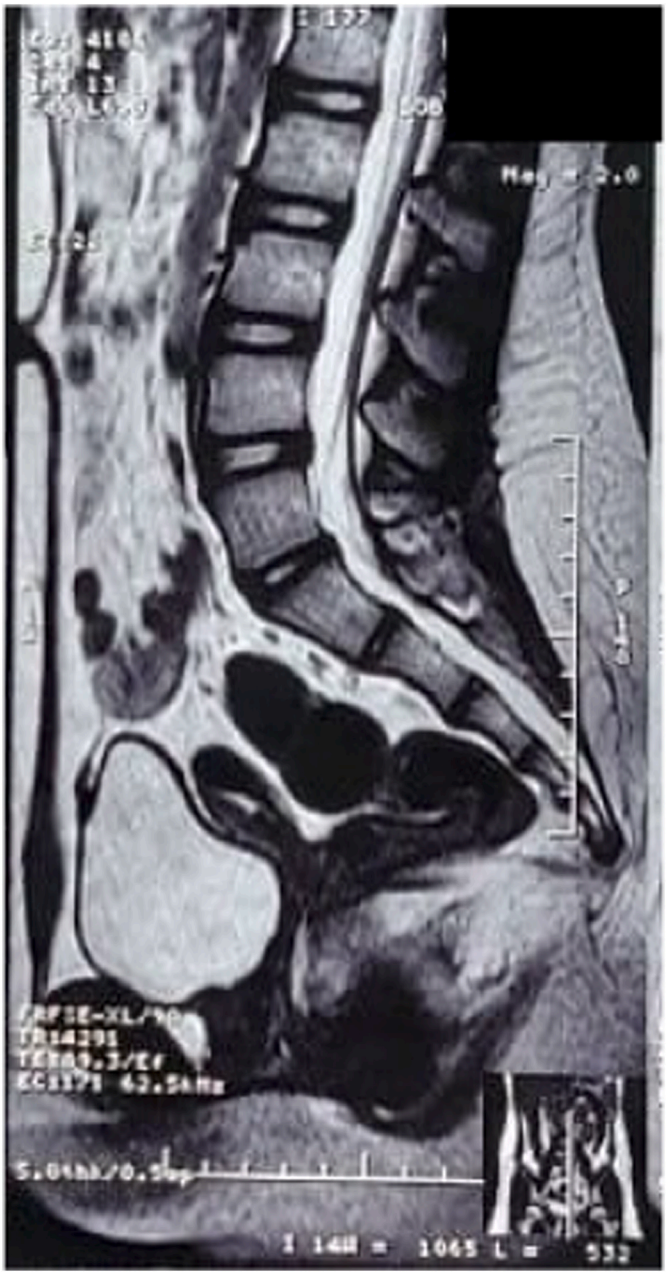

Fig. 1. MRI of hypoplasia uterus 1.

value of the GnRH test has been questioned because of its low cost-effectiveness. Indeed, the GnRH test provides no extra diagnostic information relative to baseline gonadotropin levels. The anterior pituitary function must be investigated by basal hormonal levels to rule out a more complex endocrine disorder with multiple hormone deficiencies. Thyroid function should be assessed by TSH combined with free T4. Secondary adrenal deficiency can be assessed by measuring morning cortisol and ACTH. Because sex steroids are necessary for growth, performing a bone age measurement should be considered in all hypogonadal patients, who may have delayed bone age compared with chronologic age [3,8,9].

Hormonal replacement therapy is required to induce pubertal development, to maintain normal sexual function and avoid osteoporosis. In women, replacement therapy can be started initially with low-dose estrogen (ethinyl estradiol 5 μg or conjugated estrogen 0.3 mg daily). After 6 months or sooner, if breakthrough bleeding occurs, cyclical therapy is initiated by adding a progestin for endometrial

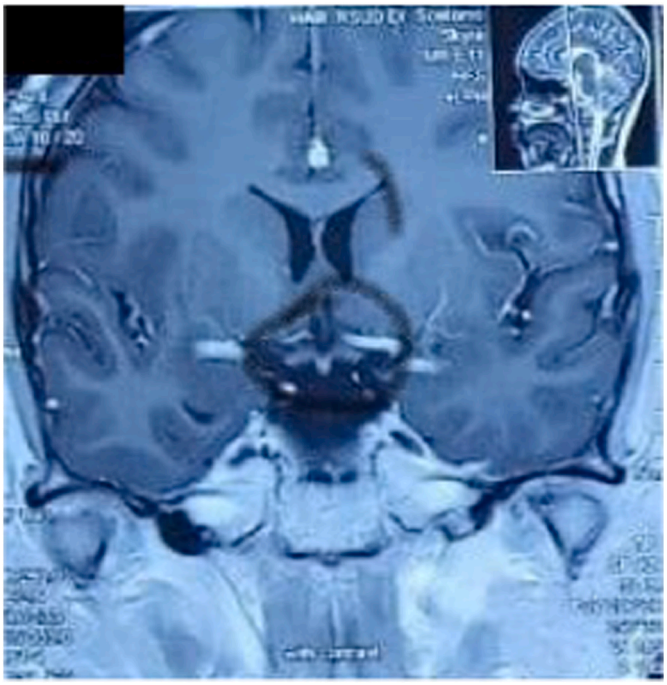

Fig. 2. Hypophyseal hypoplasia with small vessel ischemic.

protection, and the dose of estrogen is gradually increased to 20–30 μg over a 2- to 3-year period so as to respect the normal cadence of puberty. Full replacement dose of estrogen and progesterone is attained with 0.625–1.25 mg conjugated equine estrogen daily combined with cyclic 5–10 mg medroxyprogesterone acetate or 200 mg oral micronized progesterone [10,11].

If fertility is desired, treatment with gonadotropins or GnRH is needed to induce ovulation. In women, the gonadotropin regimen is initiated with purified human Menopausal Gonadotropin (hMG) at a starting dose of 37.5 IU/d IM, the dose being carefully titrated upward to 75–150 IU/d using cycle tracking by ultrasonography. Ideally, monofollicular growth is induced, and if the leading follicle is bigger than 18 mm, human Chorionic Gonadotropin (hCG) is administered at a dose of 5,000 to 10,000 IU IM to induce ovulation. Luteal support with one to two IM injections of hCG (2000–5000 IU) is subsequently required. Pulsatile GnRH therapy can be used as an alternative to gonadotropins, being equally or more effective. GnRH pulses (75–250 ng/kg for women) are administered, SC or intravenously, by a portable infusion pump with an interpulse frequency of 120 minutes [12,13].

Reversal of HH, defined as restoration of normal serum gonad concentrations after cessation of even brief treatment with sex steroids, gonadotropin, or GnRH, occurs in about 10% of all HH cases, including those with Kallman Syndrome. This post-treatment awakening of the hypothalamo-pituitary-gonadal (HPG) axis suggests the presence of hypothalamic GnRH neurons that do not function during adolescence and possibly require undefined stimuli (potentially environmental/sex steroid exposure) to initiate normal activity. The precise physiologic basis of the reversal phenomenon is yet to be fully understood but previous studies have shown a role of androgen exposure as a common factor for reversal. The androgen exposure can either be due to exogenous testosterone or via endogenous testosterone production stimulated by HCG/GnRH. It has been known that sex steroids can influence a neuronal generation. The increased androgen levels have been proposed to stimulate GnRH cells and regeneration of GnRH neurons by taking advantage of the plasticity of GnRH neurons. Another feature seen in previous studies is a relapse of hypogonadism in those who have achieved reversal due to the susceptibility of the gonadotropic axis to insult. Thus constant surveillance of patients with HH on therapy is important to look for adverse effects, or even the possibility of reversal of axis and/or further relapse [14–17].

4. Conclusion

An 18 years old female patient with IHH has been reported. IHH is defined as a clinical syndrome that results from gonadal failure due to abnormal pituitary gonadotropin levels, in the presence of normal baseline and reserve testing of the remaining pituitary hormones. Clinical presentations may vary according to age, however, the patient came with complaints of primary amenorrhea and poor breasts, and pubic hair development. The diagnosis of IHH is confirmed by the findings of low levels of estradiol in the presence of low or inappropriately normal LH and FSH serum levels with typically normal levels of other anterior pituitary hormones. MRI of the hypothalamic-pituitary region revealed hypophyseal hypoplasia due to ischemia. The patient received sex steroids therapy from the gynaecology department to induce pubertal development. IHH represents a rare condition with a good prognosis in which specific medical treatments can reverse infertility. Due to the possibility of gonadal axis reversal and/or relapse of gonadal axis failure and to identify any adverse effects related to long term hormonal therapy, the patient should be closely monitored during therapy and constant surveillance is required.

Ethical approval

Not applicable.

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Author contribution

All authors contributed toward data analysis, drafting and revising the paper, gave final approval of the version to be published and agree to be accountable for all aspects of the work.

Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Registration of research studies

Not applicable.

Guarantor

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Declaration of competing interest

The authors declare no conflict of interest.

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