CASE REPORT

Isolated Hypogonadotropic Hypogonadism on the Rise. A Case Report

Aditi Shah[1], Samatha Polisetti[2], Padma Vishnu[3], Kameshwari S[4]

Received on: 03 November 2022; *Accepted on:* 02 December 2022; *Published on:* 19 April 2023

Abstract

Objective: The objective of this study was to study the presentation of isolated hypogonadotropic hypogonadism (IHH) in the youngest reported case till date.

Introduction: Isolated hypogonadotropic hypogonadism is a clinical syndrome associated with gonadal dysfunction and altered pituitary gonadotropin levels, while the other pituitary hormones remain within normal limits. No olfactory symptoms were present hence differentiating it from congenital hypogonadotropic hypogonadism (CHH).

Case presentation: A 16-year-old girl presented with primary amenorrhea, delayed breast and pubic hair development, and low gonadotropins, but other anterior pituitary hormones were within normal limits. Imaging of the hypothalamic–pituitary region was normal. Hormonal therapy was started to induce secondary sexual characters and increased later to induce puberty.

Discussion: Early diagnosis and treatment play a crucial role in physical and psychological development. We need to continuously monitor the patient as possibility of gonadal axis reversal can occur.

Conclusion: This is the youngest case of IHH reported in literature till date. Early identification and treatment of IHH have improved outcomes according to various studies, but compliance to treatment and constant surveillance are of utmost importance.

Keywords: Hormone replacement therapy, Hypogonadism, Infertility, Kallmann syndrome, Puberty disorders.

Journal of South Asian Federation of Obstetrics and Gynaecology (2023): 10.5005/jp-journals-10006-2177

Introduction

Hypogonadotropic hypogonadism (HH) is a clinical syndrome, which is either due to absent or inadequate secretion of gonadotropin-releasing hormone (GnRH) and gonadal dysfunction. The cause for GnRH inadequacy can be either pituitary or hypothalamic. It presents as delayed puberty. Low or low normal follicle stimulating hormone (FSH) and luteinizing hormone (LH) hormones can be presented, which is a direct effect of GnRH deficiency. Patients with HH are commonly diagnosed in late adolescence or early adulthood. Delayed puberty is defined in women as primary amenorrhea and the absence of breast development (Tanner stage I) by age of 13 years or menses by 15 years of age.[1]

Hypogonadotropic hypogonadism can be acquired or congenital. It can be presented as congenital GnRH deficiency or be associated with other developmental anomalies. Depending on the defective sense of smell, chh can be categorized into anosmic HH (Kallmann syndrome: two-thirds) and normosmic IHH (one-third). Its incidence being about 1–10:100,000 live births. It is more common in male patients affected with Kallmann syndrome and sometimes have additional abnormalities, but normosmic IHH does not. The anosmia is attributed to the hypoplasia/aplasia of the olfactory bulbs, while hypogonadism is due to GnRH deficiency, secondary to defective migration of GnRH neurons. Acquired causes are due to structural and functional abnormalities of the hypothalamic–pituitary axis. Idiopathic HH is when secondary causes of HH are excluded. Early diagnosis of HH enables timely treatment, thus preventing the negative effects on physical/psychological maturation.

[1]Department of Fetal Medicine, Fernandez Hospital, Hyderabad, Telangana, India

[2–4]Department of Obstetrics and Gynaecology, Fernandez Hospital, Hyderabad, Telangana, India

Corresponding Author: Samatha Polisetti, Department of Obstetrics and Gynaecology, Fernandez Hospital, Hyderabad, Telangana, India, Phone: +91 09052639073, e-mail: samathapolisetti@gmail.com

How to cite this article: Shah A, Polisetti S, Vishnu P, *et al*. Isolated Hypogonadotropic Hypogonadism on the Rise. A Case Report. J South Asian Feder Obst Gynae 2023;15(1):125–127.

Source of support: Nil

Conflict of interest: None

Ethical approval: No ethical approval was needed since no intervention was done. The participant has given informed consent.

Case Description

A 16-year-old girl presented with primary amenorrhea, along with delayed breast and pubic hair development. The patient did not have eating disorders, strenuous physical activity, or psychological stress. There were no olfactory complaints thus ruling out Kallmann syndrome. She had a younger sister who had normal pubertal development. There was no history of drug usage. Previous reports showed hypoplastic uterus in ultrasound. She was advised karyotyping, which revealed a normal female pattern 46, (Fig. 1).

Diagnosis

We relied on a multidimensional approach to reach a diagnosis of IHH.

Physical Examination

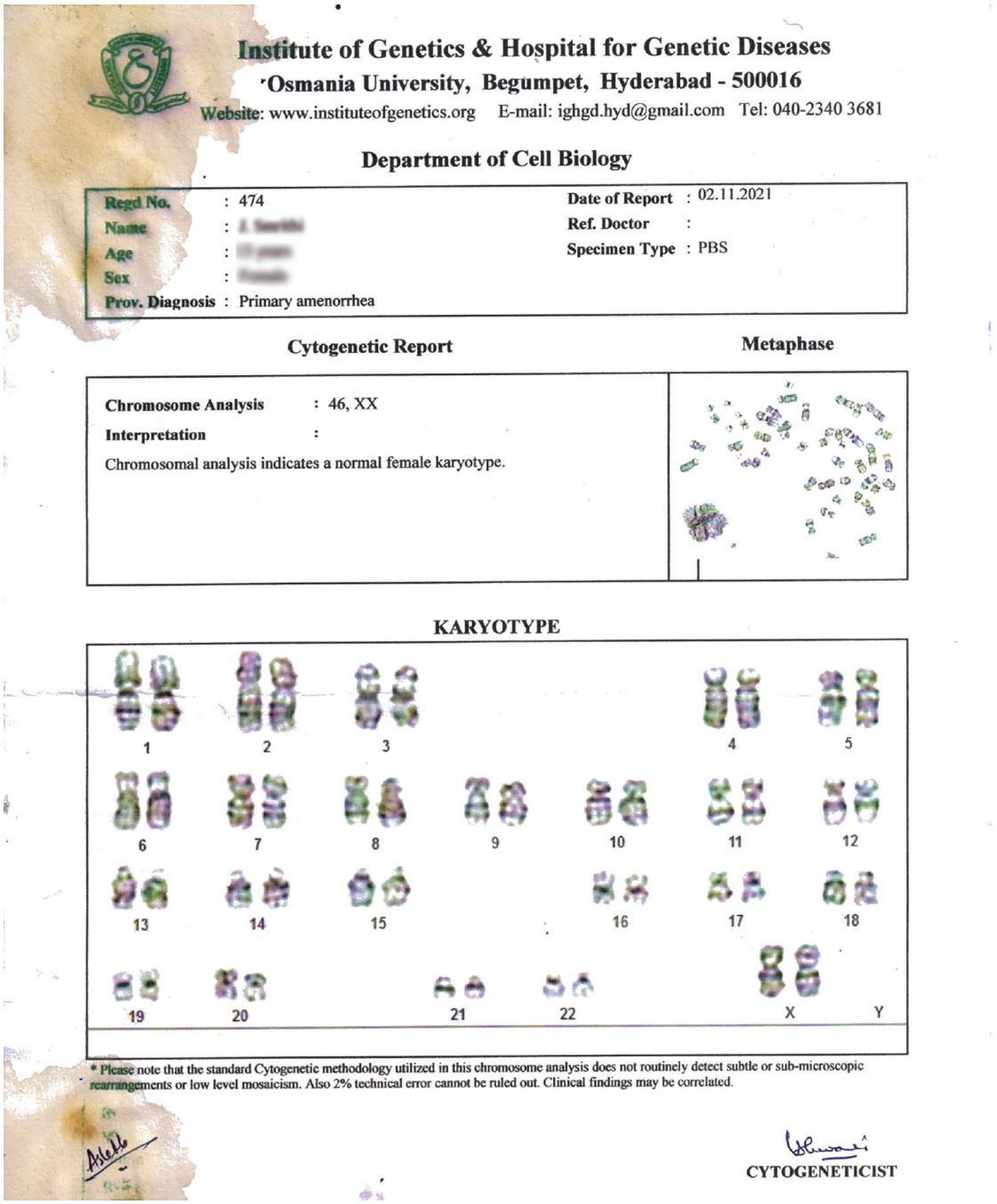
The patient had no apparent congenital anatomical defects. Her height: 144 cm (3rd centile), weight: 34 kg (<3rd centile), and body mass index of 16 (underweight). Pubic and axillary hair growth corresponded to Tanner stage II with no pubertal growth spurt. Lab parameters showed low estrogen, testosterone, and low normal LH. Follicle stimulating hormone and thyroid stimulation hormone (TSH) were normal (Table 1).

Imaging

Abdominal ultrasound examination revealed uterine hypoplasia with thin endometrium. Ovaries were normal. Magnetic resonance imaging (MRI) of the hypothalamic–pituitary region done outside revealed normal study (Fig. 2). She was advised X-ray [left-hand Antero-posterior (AP) view] for bone age, which revealed skeletal maturation corresponding to 12.5 years.

MRI Brain

Therapeutic intervention was initiated by prescribing 0.3125 µg Premarin for 3 months followed by 0.625 µg for 2 years


Institute of Genetics & Hospital for Genetic Diseases
Osmania University, Begumpet, Hyderabad - 500016
Website: www.instituteofgenetics.org E-mail: ighgd.hyd@gmail.com Tel: 040-2340 3681

Department of Cell Biology

Regd No. : 474
Name : [redacted]
Age : [redacted]
Sex : [redacted]
Prov. Diagnosis : Primary amenorrhea

Date of Report : 02.11.2021
Ref. Doctor :
Specimen Type : PBS

Cytogenetic Report

Chromosome Analysis : 46, XX
Interpretation :
Chromosomal analysis indicates a normal female karyotype.

Metaphase

KARYOTYPE

1 2 3 4 5
6 7 8 9 10 11 12
13 14 15 16 17 18
19 20 21 22 X Y

* Please note that the standard Cytogenetic methodology utilized in this chromosome analysis does not routinely detect subtle or sub-microscopic rearrangements or low level mosaicism. Also 2% technical error cannot be ruled out. Clinical findings may be correlated.

CYTOGENETICIST

Fig. 1: Karyotyping report showing normal female phenotype

Table 1: Laboratory parameters of reference versus case

Parameter	*Reference*	*Case*	*Comment*
FSH	1.5–10.2 mIu/mL	0.35 mIu/mL	Normal
LH	0.7–5.6 mIu/mL	0.06 mIu/mL	Low limit of normal
Prolactin	2.8–29.2 ng/mL	0.85 ng/mL	Normal
Testosterone	8–60 ng/dL	<0.07 ng/dL	Low
TSH	0.55–4.78 uIu/mL	3.35 uIu/mL	Normal
Estrogen	17–400 pg/mL	26 pg/mL	Low

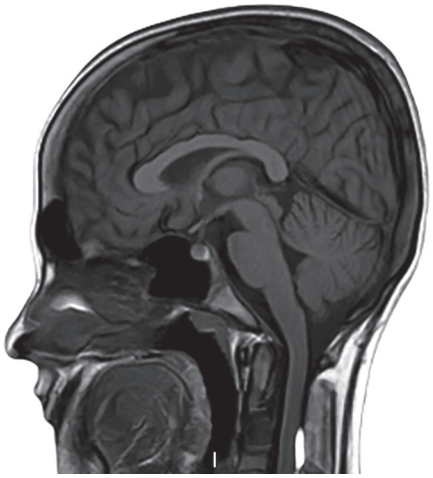


Fig. 2: MRI brain showing normal study of pituitary

followed by the addition of progesterone after 2 years or earlier if breakthrough bleeding as per current guidelines.[2]

Discussion

Congenital HH

Hypogonadotropic hypogonadism is categorized into anosmic HH (Kallmann syndrome) and normosmic IHH.

Isolated hypogonadotropic hypogonadism is seen less commonly in women by about 5 times. It could be attributed to varied presentations, incomplete penetrance, biased referral patterns, and under reporting in women.

Acquired HH

Acquired causes of HH are due to structural and functional abnormalities of the hypothalamic–pituitary–ovarian axis (HPO) axis. In our case, the patient neither had visual/spatial complaints nor loss of sense of smell. After finding no evidence of any structural cause, we proceeded to rule out the functional causes like hyperprolactinemia, drugs, nutritional disorders, or chronic diseases. We should exclude hypothyroidism (if growth velocity is below expected and bone age is delayed). Our case had low normal LH, low testosterone, and normal FSH with no other pituitary hormonal deficiencies. The patient was evaluated by a nutritionist to rule out eating disorders.

We were steered toward the diagnosis of IHH as our case had Tanner stage II pubic and axillary hair growth (normal adrenal androgens) with absence of pubertal growth spurt. Bone age was delayed but there was no family history of delayed puberty, allowing for the exclusion of constitutional delay. Anterior pituitary function was investigated by basal hormone levels to rule out a more complex multiple hormone deficiency. Sugiarto et al.[3] conducted a large case series in women with GnRH deficiency and found that clinical presentation in women varied from absence of any secondary sexual characters to isolated breast development (51%) and to isolated menses (10%).

Management

Early diagnosis and appropriate management in these women help in symptom resolution, thus promoting adherence to treatment. There should be robust interdepartmental communication when transitioning from pediatric care to gynecological care. Our major challenge will be adherence and appropriate follow up. The primary goal is to determine the aim of our treatment depending on whether the patient requirement is secondary sexual characters or fertility as well. They would require lifelong treatment to maintain sexual function.[3,4] The secondary goal would be replacement therapy. In prepubertal cases, we start with low doses of estrogen to help in breast development (5 µg ethinyl estradiol, 0.3 mg conjugated equine estrogen, or 0.5 mg micronized estradiol daily). We started our case on 0.3125 Premarin low dose (combination of estradiol and estrone) for 3 months followed by 0.625 µg for 6 months, and the dose is increased over an 18- to 24-month period. After 18–24 months of estrogen, cyclical therapy is started. We need to add a progestin for endometrial protection. We can then proceed to increase the estrogen dose to 20–30 µg over a 24-month period.[2] If breakthrough bleeding occurs before 6 months, we can start combined therapy. Ideal dosage of estrogen and progesterone can be achieved with 0.625–1.25 mg conjugated estrogen with cyclical dose of 5–10 mg medroxyprogesterone acetate or 200 mg oral micronized progesterone. We should perform a bone age measurement before starting hormone replacement. The tertiary goal would be overall wellbeing.

Conclusion

A 16-year-old patient with IHH is the youngest reported case till date in literature. IHH is a clinical syndrome of gonadal failure and gonadotropin deficiency in the presence of other normal pituitary hormones. Clinical presentation may be varied, but our case came with primary amenorrhea, delayed breast, and pubic hair development. The diagnosis of IHH was confirmed by low levels of estradiol while LH and FSH serum levels may be either low or low normal. Magnetic resonance imaging of the hypothalamic–pituitary region was normal and no loss in smell was demonstrated thereby ruling out CH. She was started on hormone therapy to induce puberty. IHH is a rare condition in women with a good prognosis both physically and psychologically with early diagnosis and treatment. Gonadal axis reversal/relapse must be kept in mind while on long term therapy.

References

1. Pediatric Endocrinology Referral Guidelines CHOC children's specialists, pp. 19. https://www.choc.org/wp/wp-content/uploads/referrals/Endocrinology-Referral-Guidelines.pdf
2. Howard SR, Dunkel L. Management of hypogonadism from birth to adolescence. Best Pract Res Clin Endocrinol Metab 2018;32(4):355–372. DOI: 10.1016/j.beem.2018.05.011.
3. Sugiarto AM, Soelistijo SA. A female with isolated hypogonadotropic hypogonadism: A case report and review article. Ann Med Surg 2022;74:103289. DOI: 10.1016/j.amsu.2022.103289.
4. Merck Manuals of Endocrinology. https://www.merckmanuals.com/professional/pediatrics/endocrine-disorders-in-children/male-hypogonadism-in-children.