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Case Report

Isolated growth hormone deficiency and amenorrhea – Case report

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ABSTRACT

Introduction and importance: Growth hormone (GH) deficiency is the most common hypopituitarism disorder. We highlight the challenges to its diagnosis and management in the setting of a developing country.

Case description: A 14-year-old came with a chief complaint of inability to menstruate. Menarche was at 12-years old, lasted 7 days, soaking 2 pads/day which discontinued shortly after. Thelarche was at 12-years-old and her breast is at Tanner stage 3. Her axillary and pubic hair are at Tanner stage 1. Height was 120 cm, weight 34.8 kg, height for age z-score < -3. Her lab results were normal for estradiol, luteinizing hormone (LH), follicle-stimulating hormone (FSH) and prolactin. Bone age was suitable for age. Magnetic resonance imaging revealed pituitary gland hypoplasia (5.3 mm). A hormonal panel 3 years prior showed abnormally low GH level but normal cortisol and thyroid hormone levels. She was diagnosed with isolated growth hormone deficiency (IGHD) with delayed puberty. She was treated with medroxyprogesterone tablets once daily, after which her menstruation restarted. However, due to her economic background, she declined genetic tests, discontinued her medication and amenorrhea recurred.

Clinical discussion: Amenorrhea present after a brief menarche should alert gynaecologists of a possible multi-hormone disorder with an underlying structural abnormality. IGHD may be due to a structural abnormality, such as pituitary gland hypoplasia. Unfortunately, economic reasons prevented the patient from receiving optimal treatment.

Conclusion: IGHD rarely presents with a gynaecological complaint. Hormonal and genetic tests along with imaging should be undertaken. Growth hormone supplementation is the treatment of choice.

1. Introduction

The pituitary gland is the central endocrine system regulator [1]. Composed of 2 lobes, the anterior lobe through various cell lineages produce 6 hormones: growth hormone (GH), thyroid-stimulating hormone (TSH), prolactin, luteinizing hormone (LH), follicle-stimulating hormone (FSH) and adrenocorticotropic hormone (ACTH) [1]. The posterior lobe secretes arginine vasopressin (AVP) and oxytocin [1].

Hypopituitarism refers to the partial or complete loss of a single or multiple pituitary hormones from the anterior or posterior pituitary, whereas panhypopituitarism refers to the loss of all pituitary hormones [1]. Data regarding anterior pituitary homone deficiency, including growth hormone deficiency (GH) are scarce, with only a Spanish study showing an increase in prevalence from 29 to 45.5 per 100,000 people between 1992 and 1999 with an annual incidence of 4.21 per 100,000 population [2]. Its clinical manifestation differs depending on the number and severity of hormone deficiencies [1]. Growth hormone deficiency (GHD) is the most common presentation [1]. There are congenital and acquired causes of hypopituitarism [3]. Isolated growth hormone deficiency (IGHD) is an example of a congenital hypopituitarism with various possible mutations in transcription factors and similar variety of transmission patterns [4]. Being a congenital disorder, IGHD may have various phenotypes associated with varying levels of severity [4]. The classical symptom is short stature but there may be other complaints. In this case report, we aim to describe an extremely rare case of IGHD presenting with amenorrhea. Due to its rarity, we wish to discuss the challenges to its diagnosis and management in the setting of a developing country.

2. Case description

The reporting of this case is according to the SCARE 2020 guideline [5]. This case report is registered at clinicaltrials.gov under the following registration: NCT05448924 (URL: https://clinicaltrials.gov/c

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t2/show/NCT05448924). The patient has consented to the publication of her anonymized data for this case report.

A 14-year-old girl presented to Adolescent Gynaecology clinic with a primary complaint of lack of menstruation for 2 years. Her menarche was 2 years ago, lasted 7 days, wetting 2 pads/day. Her thelarche was at 12 years old. There is no history of menstrual pain, cyclic abdominal pain, lumps in the abdomen, or vaginal discharge. The patient is shorter than her peers.

She had presented to a separate pediatric clinic three years earlier with a different complaint of being shorter than her peers. There were no complaints of lethargy, excessive weight gain or preference for warm environments. At that time, she was in her final year of elementary school and progressing well. Her birth history revealed a spontaneous term breech delivery from a P2A0 mother. Her birthweight and birth length were appropriate for her gestational age at 2750 g and 51 cm respectively. However, she developed hyperbilirubinemia <24 hours postpartum and received phototherapy for the subsequent 3 weeks. There was no further history of allergies or adverse reactions to medicine. Her physical examination had revealed no abnormalities except for a short stature. At that time, her height was 116 cm, weight 26 kg a height-for-age −5.10 SD and BMI for age 0.54 SD. Her lab results revealed decreased IGF-1 level (<15 ng/mL) but normal cortisol level (5,51 μg/dl) and thyroid function (T3 1.0 ng/ml, fT4 1 ng/mL, and TSH 2,1 μIU/ml).

On physical examination, the body weight was 34.8 kg and body height 120 cm, height for age z-score < -3. Her paternal height is 170 cm, maternal height is 155 cm, her sibling's height is 160 cm and her midparental height is 156 ± 8.5 cm. Her abdomen was flat, smooth with no palpable mass. Gynaecological examination showed breast development at Tanner stage 3, axillary hair and pubic hair at Tanner stage 1. Genital examination revealed presence of labia majora, labia minora and hymen.

Laboratory examination demonstrated normal levels for estradiol (70.22 pg/mL), luteinizing hormone (4.48 mIU/mL), FSH (6.38 mIU/mL) and prolactin (10.13 ng/mL). Additional hormonal panel indicated the following: Homa 1-IR 1.8, Homa 1-1%B 763.2, HOMA 2-IR 1.26, HOMA 2-%β 207%, HOMA 2-%S 79.1%, insulin 10.6 μIU/ml, and fasting blood glucose 68 mg/dL. Her bone age (wrist joint) was appropriate for her age. Gynaecological ultrasound showed no abnormalities (Figs. 1 and 2). MRI without contrast suggested pituitary gland hypoplasia (5.3 mm). Her karyotype is 46, XX. Unfortunately, due to economic reasons, she declined to have further genetic tests.

The patient was diagnosed with isolated growth hormone deficiency with delayed puberty. The patient is given a progestin challenge test with medroxypregosterone tablet 1 × 10 mg for seven days. There was withdrawal bleeding, suggesting a positive progestin challenge test. She had also been reviewed by a pediatric endocrinologist who prescribed her recombinant human GH. Unfortunately, due to similar economic reasons, she declined the treatment. Currently, hormonal treatments (recombinant human GH and medroxyprogesterone among others) are not covered by the Indonesian health insurance.

3. Discussion

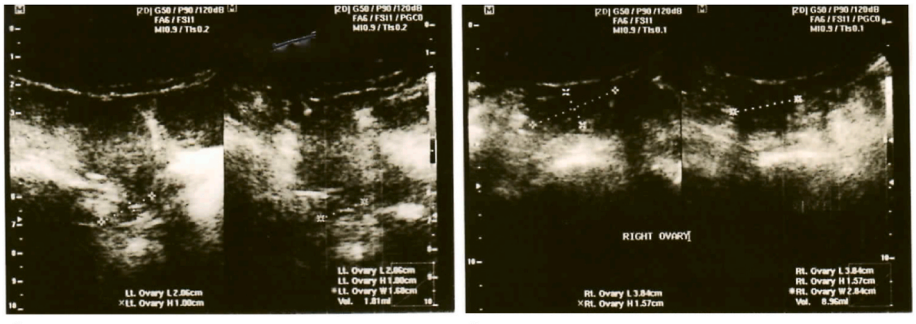
Amenorrhea may be primary or secondary [6]. Secondary amenorrhea is the absence of menstruation for at least 3 consecutive cycles after previously menstruating [6]. Secondary amenorrhea may be due to an array of causes: physiological, iatrogenic, and pathophysiological [7]. Pathophysiological causes include an array of differential diagnosis such as hyperprolactinemia, sellar mass/lesion, infectious/infiltrative processes, traumatic brain injury and genetic causes [7].

Amenorrhea is rarely encountered simultaneously with complaints of short stature/dwarfism. Dwarfism is defined as height-vertex below 2 standard deviations (-2SD) or in the 3rd percentile for a given age and sex [8]. Dwarfism may be caused by a variety of etiologies [8]. When all other diagnoses, such as genetic short stature, constitutional delay of growth and puberty, hypothyroidism, Turner syndrome, and chronic disease such as celiac disease, are ruled out, the question of growth hormone deficiency (GHD) arises [8]. Pituitary dwarfism or GHD is characterized by short stature, delayed dentition, and delayed skeletal maturation. GHD may exist singly or as part of a broader hypopituitarism. Combined pituitary hormone deficiencies (growth hormone deficiency plus at least one other adenohypophyseal hormonal deficiency) are less common than IGHD.

A test panel for hormones should be undertaken when an endocrine disorder is suspected. In this case, the level of IGF-1 in this patient is very low, but other pituitary hormones such as TSH, LH, FSH, and prolactin are within normal limits. Thus, the patient seems to have an isolated growth hormone deficiency (IGHD).

IGHD may be caused by a variety of mutations [9]. There are several well-characterized genetic forms of IGHD that show autosomal recessive, autosomal dominant, or X-linked patterns of inheritance and they are respectively termed type 1-A, 1-B, 2 and 3 [9]. The most severe forms of IGHD, type 1-1A, are linked to recessive deletions of genes encoding GH, characterized by a very short birth length, recurrent hypoglycemia and severe dwarfism [3]. The dwarfism may be so severe as to allow patients only achieving a mean height of less than −4.5 to −4.0 SD [3]. Among such patients, due to the total absence of growth hormone, they develop antibodies towards recombinant human GH during treatment, which worsens the prognosis [3]. Incomplete mutations of the genes encoding GH production (types 1-B, type 2 and type 3) produce less severe phenotypes and a height less than −2 SD [3].

In our case, alongside amenorrhea, the patient had developed a short stature. She was well below her midparental height, shorter than her peers and bone age examination revealed delayed skeletal maturation. Her hormonal profile showed a very low level of GH amid normal levels of other anterior pituitary hormones. This supported IGHD, further supported by the MRI revealing a hypoplastic pituitary gland. This finding would suggest somatotrophic hypoplasia [10]. Pituitary hypoplasia may be associated with septo-optic dysplasia, holoprosencephaly,



A B

Fig. 1. Abdominal ultrasound showed the left ovary (A) with a size of 2.51 cm × 1.47 cm and the right ovary (B) with a size of 2.43 cm × 1.41 cm.

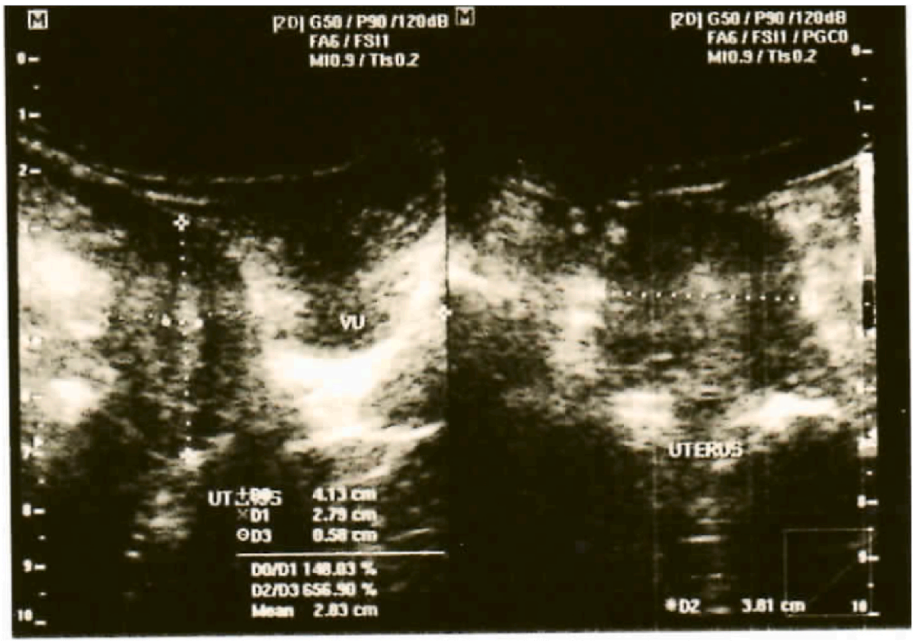


Fig. 2. Abdominal ultrasound showing uterus with homogenous density 4,02 cm x 2,61 cm x 2,60 cm. Endometrial line (+) with 8,0 mm in diameter, body to cervix ratio 2:1.

Chiari malformation, and a single central maxillary incisor [11]. The discovery of a markedly hypoplastic pituitary gland should prompt a search for other midline defects [11,12].

GHD should be suspected in a child who has a reduced height velocity, low serum levels of insulin-like growth factor-1 (IGF-1), and insulin-like growth factor-binding protein-3 (IGFBP-3), key surrogate markers of growth hormone, and delayed skeletal maturation as measured by bone age X-ray imaging. Because growth hormone is released in a pulsatile manner, direct measurement of random growth hormone levels is ineffective. As a result, although controversial, the diagnosis of GHD frequently includes growth hormone stimulation testing with a variety of pharmacologic agents [1]. Insulin, glucagon, clonidine, arginine, and L-dopa are the most commonly used stimulants [8]. GHD is diagnosed when there is an inadequate rise in serum GH in response to provocative stimuli or some other measure of GH secretion [8]. The inability of GH to rise above 10 ng/mL with stimulation is accepted as a diagnostic of GH deficiency [8].

Early detection and treatment of GHD with subcutaneous daily recombinant human GH (rhGH) injections is critical for maximizing growth response [1]. rhGH is currently only available as a subcutaneous injection that must be administered daily [13]. To mimic physiologic growth hormone release, the initial recommended dose is 0.16–0.24 mg/kg/week, given in the evening [13]. Subsequent dosing should be individualized based on height velocity and IGF-1 levels, and treatment should be discontinued if growth velocity falls below 2–2.5 cm/year [14]. Growth hormone treatment is generally well tolerated, but adverse effects must be discussed prior to starting therapy [14]. Patients should be monitored for hypothyroidism and adrenal insufficiency because growth hormone treatment increases thyroid hormone and cortisol metabolism, which may mask these conditions [14]. Unfortunately for our patient, such treatment is still not yet covered under the national health insurance and due to economic reasons, she could not afford it.

As for her complaint of amenorrhea, a progestin challenge test was performed. The presence of withdrawal bleeding suggested a successful progestin challenge test and her amenorrhea was due to a normogonadotropic hypogonadism with IGHD being the most likely cause [15].

It is rare to have amenorrhea due to IGHD. There have been reports of such occurrence, but they are extremely rare. Uské et al. first presented a case of primary amenorrhea in GH-deficient woman with ectopic posterior pituitary [16]. She had a hypoplastic anterior pituitary with a small sella tursica and an ectopic posterior pituitary lobe below the median eminence [16]. LH and FSH levels were normal with low estrogen levels [16]. Upon further investigation, LH pulse frequency was increased but FSH bioactivity was low [16]. She had not been treated with recombinant human GH and this contributed to the dysfunction of her ovaries [16]. It was concluded that poor oocyte maturation could be ascribed to lack of GH and IGF-1, which further hampered any corrective attempts through exogenous gonadotropins [16].

Lee presented another case report of GHD being the only identifiable cause of primary amenorrhea among 3 patients in Korea [17]. The patients had a history of intracranial surgery due to malignancy and during adolescence, all three showed growth hormone deficiency amid normal levels of all other pituitary hormones [17]. He suggested that GH may play a complementary role to gonadotropins in the occurrence of menarche and the continuation of menses [17].

4. Conclusion

The diagnosis of IGHD remains difficult. Whilst complaints of short stature is often the presenting symptom, other complaints including amenorrhea may be present. Clinical assessment supported by hormonal panel, imaging and genetic tests should be the basis for diagnosis and evaluation of IGHD. Early treatment with subcutaneous rhGH injections is critical for maximizing growth response.

Ethical approval

This study has been exempted from an ethical review per institutional and departmental guidelines.

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This study did not receive any external funding

Author contribution

AFPS, KDT, and AR conceived the study. AFPS was the lead consultant of the patients. AFPS was responsible for collecting patient

data. AFPS and KDT drafted the manuscript. All authors reviewed the manuscript and have agreed this final form of manuscript for publication.

Research registration

Registration of research is not applicable in our case. Guarantor.

Guarantor

The guarantor of this study is Artha Falentin Putri Susilo, M.D.

Provenance and peer review

Not commissioned, externally peer-reviewed.

Consent

Written informed consent was obtained from the patients 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.

Declaration of competing interest

The authors declare that we do not have any conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.amsu.2022.104909.

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