Isolated Hypogonadotropic Hypogonadism in a Young Woman with Primary Amenorrhoea: A Case Report

Zalkha Al Kharusi[1*], Nadia Al Mabaihsi[1], Amani Al Rawahi[2], Abeer Al Hadhrami[1], Maisa Al Kiyumi[3*], Almundher Al-Maawali[4] and Abdulaziz Al Mahrezi[3]

[1]Directorate-General of Primary Health Care, Ministry of Health, Muscat, Oman

[2]Armed Forces Medical Services, Muscat, Oman

[3]Department of Family Medicine and Public Health, Sultan Qaboos University Hospital, Sultan Qaboos University, Muscat, Oman

[4]Department of Genetics, College of Medicine and Health Sciences, Sultan Qaboos University Hospital, Sultan Qaboos University, Muscat, Oman

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*Corresponding authors: zalkh.krs@gmail.com; maysa8172@gmail.com

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Abstract

The diagnostic approach to primary amenorrhoea includes a thorough history taking, clinical examination, laboratory testing and imaging technology. This case report describes a young woman who was diagnosed with isolated hypogonadotropic hypogonadism that resulted in delayed secondary sexual development and primary amenorrhoea. The patient had a normal female karyotype and an atrophied uterus. Based on the results of the laboratory tests, which indicated low oestradiol, FSH and LH levels, along with normal levels of other pituitary hormones, the patient was diagnosed with isolated hypogonadotropic hypogonadism. Genetic testing revealed a rare diagnosis of autosomal recessive hypogonadotropic hypogonadism 8 (*KISS1R*, NM_032551.4:c.443T>C; p.Leu148Ser). The *KISS1R* gene encodes the kisspeptin receptor, which regulates the secretion of the gonadotropin-releasing hormone (GnRH). Treatment typically requires hormone therapy, which involves the administration of oestrogen to promote the growth of the uterus and secondary sexual characteristics. Combined contraceptive pills were initiated and repeated pelvis ultrasound after six months revealed a growing uterus.

Keywords: Hypogonadotropic Hypogonadism, KISS1R gene, primary amenorrhoea

Introduction

Primary amenorrhoea is defined as the absence of menstruation by the age of 15 years in females with normal secondary sexual development or by the age of 13 years in those who are lacking signs of pubertal development (1). The diagnosis of primary amenorrhoea involves a thorough physical examination and a series of laboratory tests, including hormone assays, genetic testing and imaging studies. A large list of causes has been postulated which is further subcategorised into: i) hypogonadotropic hypogonadism, ii) hypergonadotropic hypogonadism and iii) normogonadotropic hypogonadism (2). The constitutional delay of growth and puberty, congenital hypogonadotropic hypogonadism, functional hypothalamic amenorrhoea and pituitary tumours are among the causes of hypogonadotropic hypogonadism. Isolated hypogonadotrophic hypogonadism (IHH) is uncommon and typically classified as normosmic or anosmic (Kallman syndrome) based on the presence or absence of a smell defect, respectively (2). In this case report, we describe a young woman with primary amenorrhoea, underdeveloped secondary sexual characteristics, an atrophied uterus, a hypoplastic pituitary gland, a normal female karyotype and isolated hypogonadotropic hypogonadism due to a rare mutation in the *KISS1R* gene.

Case Report

A 22-year-old woman presented with a history of primary amenorrhoea. She had never experienced menstrual bleeding or cyclical pain but had noticed changes in her breast and pubic & axillary hair growth along with a sudden abrupt increase in height at the age of 17 years old. She denied any headache, blurring of vision, anosmia, galactorrhoea, constipation or weight loss. Also, she had no history of proximal muscle weakness, easy bruising or purplish striae. She denied any history of performing excessive exercise or a strict diet to lose weight. She was known to have allergic rhinitis, but her medical history apart from that was unremarkable and she was not taking any medications. Her antenatal and birth history was uneventful. Her parents are consanguineous and there was no family history of similar illnesses reported by the patient.

On examination, the patient appeared to be well-nourished and her weight was recorded as 59.5 kg with a height of 165 cm (BMI=22 kg/m^2). Her breast, axillary and pubic hair development was at Tanner stage 2. There were no abnormalities noted on her abdominal, pelvic or neurological examination. Her baseline blood tests, which included a full blood count, thyroid function tests and prolactin levels, were within the normal range. Hormone profiles were suggestive of hypogonadotropic hypogonadism (oestradiol level of <0.02 nmol (reference range: 0.63-1.15 nmol/L) , FSH=0.6 IU/L (reference range: 3.5-12.5 IU/L) and LH=0.1 IU/L (reference range: 2.4-12.6 IU/L)). Other pituitary hormone profiles were within the normal range.

Karyotyping revealed a normal female karyotype (46, XX). A pelvic ultrasound showed an atrophied uterus with normal ovaries (Figure 1). Brain MRI revealed a hypoplastic pituitary gland, but an otherwise normal brain structure (Figure 2).

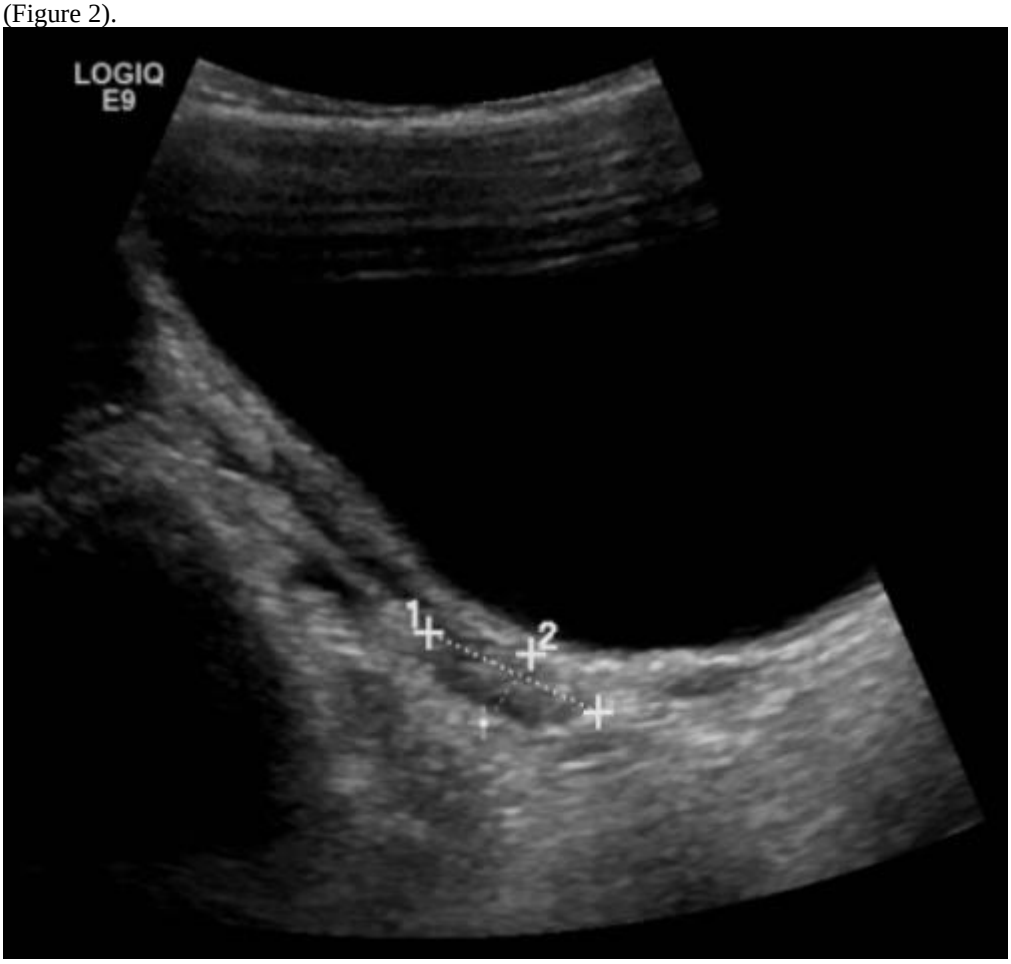

Figure 1: Atrophied uterus at diagnosis.

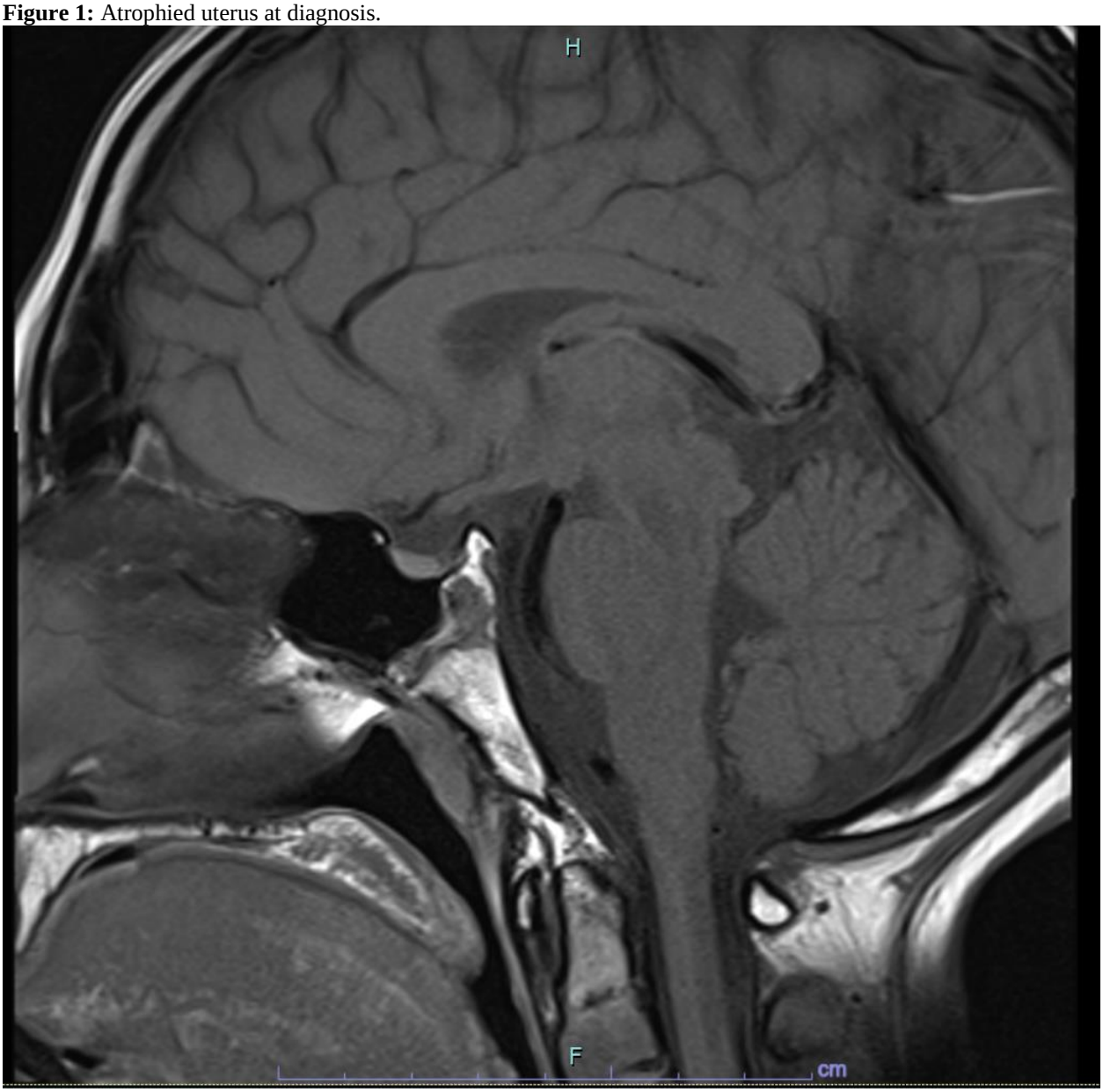

Figure 2: Hypoplastic pituitary gland.

While the presence of an atrophied uterus and normal karyotyping had narrowed our differential diagnoses and directed our approach towards Mullerian agenesis syndrome as a likely diagnosis in this case, but the unexpected hypogonadotropic hypogonadism diverted our search for other causes. With further evaluation (detailed history, blood and radiological work-up), two primary differential diagnoses were identified: congenital hypogonadotropic hypogonadism (CHH) and constitutional delay of growth and puberty (CDGP). Both CHH and CDGP are diagnosed by excluding other differential diagnoses and differentiating between the two is often difficult. In our case, there were some clues that favoured CHH as the most likely diagnosis, such as the normal bone age and genetic testing results. Genetic testing revealed a diagnosis of autosomal recessive hypogonadotropic hypogonadism 8 with or without insomnia (*KISS1R*, NM_032551.4:c.443T>C; p.Leu148Ser). Olfactory sensations were normal. The patient was started on combined contraceptive pills (each containing 3 mg of drospirenone and 0.03 mg of ethinyl oestradiol) for six cycles for withdrawal bleeding with a follow-up uterine pelvis ultrasound to look for changes in uterine size. She

started to have regular cycles after the combined contraceptive pills were started. The follow-up pelvis ultrasound after six months showed an interval increase in the size of the uterus compared to the first ultrasound (size: 5 X1.5 cm, compared to 2.5 X 1.1 cm at baseline) (Figure 3). Therefore, she was advised to continue taking the combined contraceptive pills with regular follow-up pelvic imaging every six months. In addition, bone density was below the expected range for age and gender (Z score in the lumbar spine -3.6 and -1.8 in the hip) and vitamin D and calcium supplements were prescribed in addition to combined contraceptive pills.

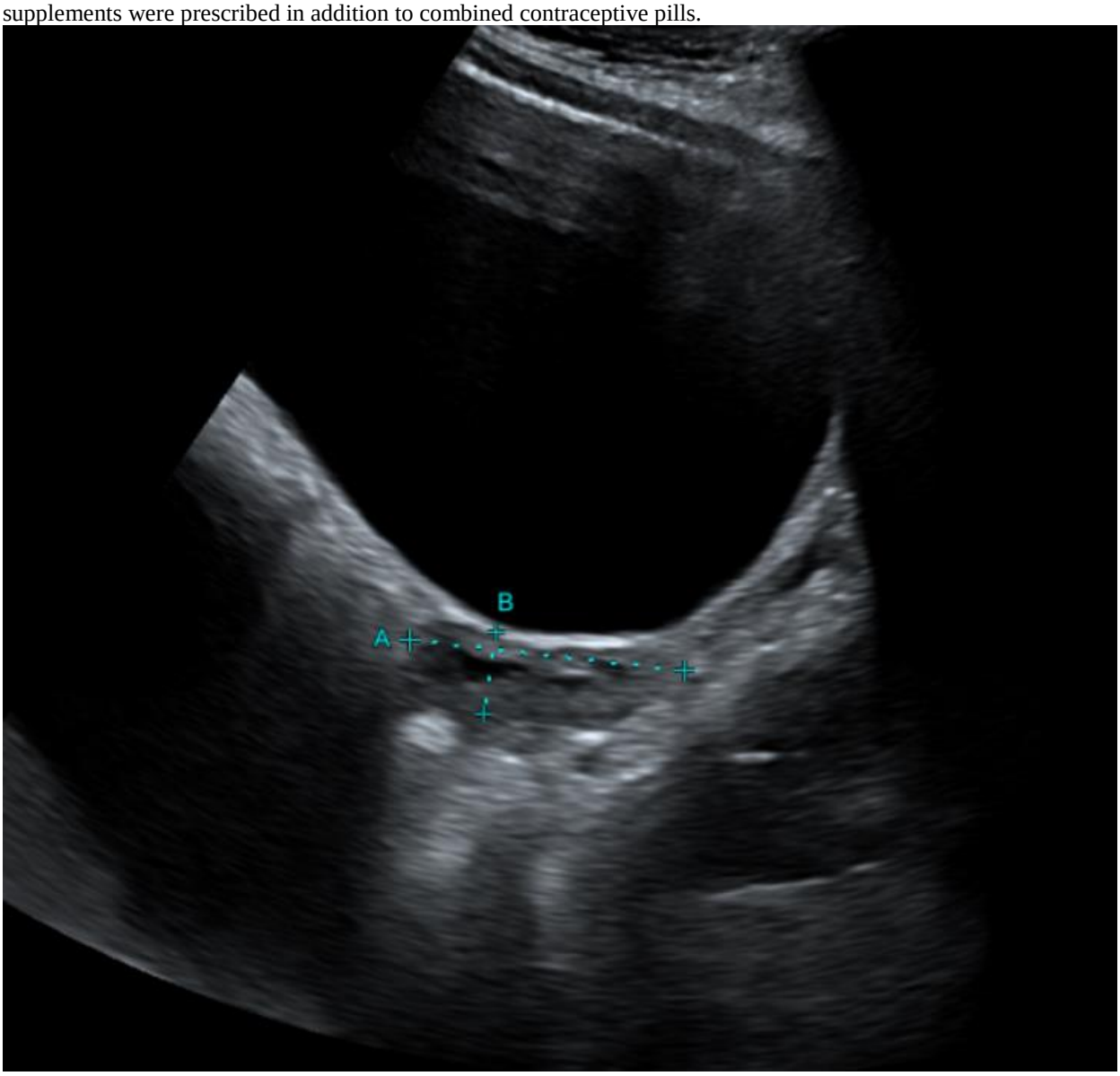

Figure 3: Growing uterus at six months follow-up.

Discussion

The diagnostic approach to primary amenorrhoea includes a thorough history taking and clinical examination, laboratory testing and imaging technology. In this case, the patient presented with primary amenorrhoea, hypogonadotropic hypogonadism, an atrophied uterus with normal ovaries and a hypoplastic pituitary gland. Genetic testing confirmed the diagnosis of autosomal recessive hypogonadotropic hypogonadism 8, with or without insomnia.

Congenital hypogonadotropic hypogonadism (CHH) is a rare disorder with an estimated prevalence of about 1 in 8000 individuals. The disorder is caused by abnormal episodic gonadotropin-releasing hormone (GnRH) secretion, which disrupts normal reproductive function (2). Any dysfunction in GnRH synthesis, mechanism of action or both can lead to congenital hypogonadotropic hypogonadism. The various genetic causes of congenital hypogonadotropic hypogonadism are typically divided into two primary categories. The first group involves variations in the formation or shift of GnRH neurons during prenatal stages, which is exemplified by Kallmann syndrome. The second group comprises structural abnormalities that specifically impact GnRH formation, maturation, or signalling in the hypothalamus, without altering the typical anatomical location of GnRH neurons. Patients in the latter group do not experience any neurological disorders and possess a normal sense of smell, indicating normosmic CHH (nCHH) (3, 4). In recent years, significant advancements in our understanding of the genetic factors contributing to nCHH have occurred (3,4).

Isolated hypogonadotropic hypogonadism (IHH) is an uncommon condition that leads to the decreased or absent production of GnRH. As a result, there is reduced luteinising hormone (LH) and follicle-stimulating hormone (FSH), which ultimately causes decreased levels of sex hormones (5). IHH occurs due to various genetic mutations that affect the production or action of GnRH, LH or FSH, including mutations in genes such as *KISS1R, GNRHR, TAC3* and *TACR3*. It can also occur due to non-genetic factors such as tumours, brain injuries, or infections that affect the hypothalamus or pituitary gland (5).

Mutations in the *KISS1R* gene are rare and can disrupt the normal function of the kisspeptin receptor, leading to reduced or absent GnRH secretion and subsequent HH (6). The specific mutation c.443T>C p. (Leu148Ser) is rare, and has been reported in a few studies (7, 8, 9, 10). In a genetic analysis of 603 participants with normosmic congenital HH, only 2% (12 patients) had at least one mutation, with only one patient having the c.443T>C p.(Leu148Ser) mutation (7). Also, a family with six members who were homozygous for c.443T>C p.(Leu148Ser) and had hypogonadotrophic hypogonadism was reported from Saudi Arabia(8,9, 10).

Symptoms typically include delayed or absent puberty, infertility and low levels of sex hormones. In some cases, individuals with IHH may also experience other health problems related to low sex hormone levels, such as osteoporosis or cardiovascular disease. Treatment for IHH typically involves hormone replacement therapy (HRT) (5). Genetic testing may be recommended for individuals with a familial history of HH. Genetic counselling is also recommended for individuals and families who have been diagnosed with HH or are at risk for the condition.

In individuals with primary hypogonadism, oestrogen replacement therapy has been observed to stimulate uterine growth. A case study has been reported involving a 23-year-old woman with 46, XX gonadal dysgenesis and primary amenorrhoea. The patient was administered oral conjugated equine oestrogen daily as a hormone substitution therapy. After six months of treatment, the patient exhibited a Tanner breast stage III, which further progressed to a Tanner breast stage V within 18 months. A repeat pelvic ultrasound unexpectedly revealed rudimentary uterine buds measuring 1.3×3.8 cm, but no ovaries or upper part of the vagina were observed. At 24 months, a pelvic MRI was performed to confirm the presence of a developing uterus (11).

A retrospective study reported the effect of oestrogen replacement therapy on uterine development in women with different causes of primary hypogonadism and primary amenorrhoea. The study aimed to evaluate changes in uterine cross-sectional area and maturity, as assessed by pelvic ultrasound, after 2 years of oestrogen replacement therapy. Patients were categorized into three groups based on the cause of hypogonadism: Turner syndrome, hypogonadotropic hypogonadism following brain surgery and premature ovarian insufficiency following cancer treatment. Results showed that the mean uterine cross-sectional area significantly increased after oestrogen replacement therapy, but patients with premature ovarian insufficiency had a significantly smaller final uterine cross-sectional area compared to other aetiologies. Logistic regression analysis in the study also revealed that aetiology and cumulative oestrogen dose were associated with uterine maturation (12).

Conclusion

Primary amenorrhoea is a rare condition that requires a thorough diagnostic evaluation. Our case report highlights the importance of a systematic approach in the evaluation of primary amenorrhoea, including a thorough medical history,

clinical examination, laboratory tests and imaging technology. In this case, the diagnosis of congenital hypogonadotropic hypogonadism was made, which was confirmed by further genetic testing.

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