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Kallmann Syndrome: Review of Two Cases in Brothers

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Abstract

Background: Kallmann syndrome is a rare genetic disorder characterized by congenital hypogonadotropic hypogonadism associated with anosmia. We report two cases of Kallmann syndrome in two brothers followed at the University Mother and Child Hospital of N'Djamena. **Case Presentation:** An 18-year-old young man presented with micropenis (40 mm), bilateral cryptorchidism, anosmia, and severe growth retardation (height 146 cm, −4 SD). Biological investigations revealed hypogonadotropic hypogonadism (FSH: 0.42 IU/ml, LH < 0.10 mIU/ml, testosterone < 0.2 ng/ml), with a bone age delayed by 7 years. His 16-year-old brother presented similar signs: micropenis (38 mm), cryptorchidism, and anosmia. Hormonal evaluation confirmed hypogonadotropic hypogonadism. A positive family history of a paternal uncle with growth delay and infertility suggested a familial form. Both patients received intramuscular testosterone treatment (100 mg/m^2). After 5 injections, significant clinical improvement was observed: increase in penile length to 70 mm and 65 mm respectively, with regular erections, ejaculation, and testicular descent. **Conclusion:** Kallmann syndrome, although rare, warrants systematic consideration in adolescents presenting with delayed puberty, anosmia, and micropenis.

Keywords

Kallmann Syndrome, N'Djamena, Chad

1. Introduction

Kallmann syndrome is a rare genetic disorder of embryonic development charac-

terized by congenital hypogonadotropic hypogonadism associated with anosmia or hyposmia. The syndrome results from a defect in the development of the olfactory system and embryonic migration of GnRH-synthesizing neurons. Anosmia is secondary to atrophy of the olfactory bulbs and/or lobes [1].

Two forms are described: familial and sporadic, with the latter being the most common [2]. Its prevalence is estimated at 1 in 10,000 in boys and is 4 times lower in girls [1].

The diagnosis is generally made in adolescents presenting with delayed puberty, anosmia, and hypoplasia or even aplasia of the olfactory bulb.

In Chad, diagnostic resources are very limited due to the inaccessibility of MRI and the absence of genetic testing capabilities. We report two cases of brothers seen in pediatric endocrinology consultation at the University Mother and Child Hospital of N'Djamena.

2. Case Descriptions

2.1. Case 1

An 18-year-old male patient was referred for micropenis with suspected anosmia. The patient's history revealed a paternal uncle with growth delay and infertility, and a younger brother presenting with the same clinical picture (**Figure 1-5**).

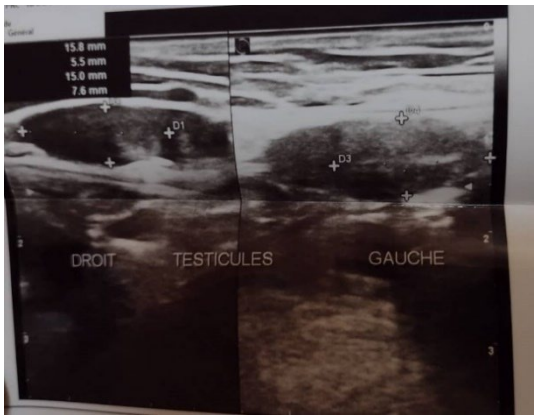

Figure 1. Pelvic ultrasound.

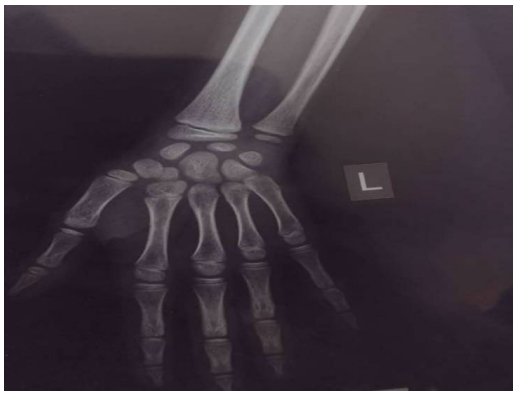

Figure 2. Bone age corresponding to 11 years.

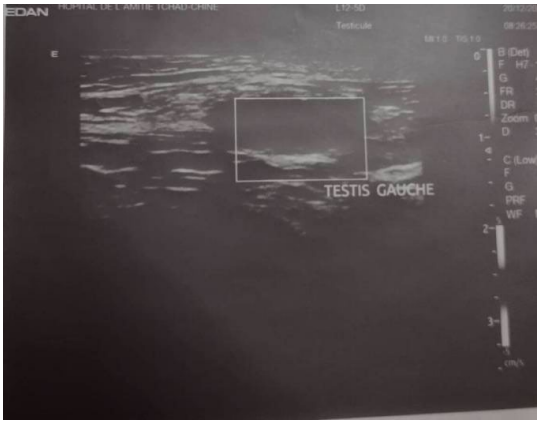

Figure 3. Pelvic ultrasound of the 2nd case revealing unilateral cryptorchidism.

Figure 4. The size of the penis.

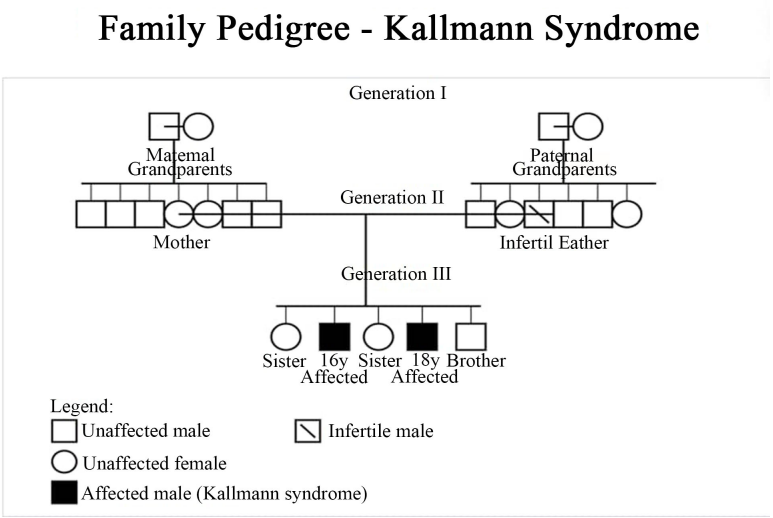

Figure 5. Pedigree.

General examination:

- Height: 146 cm (−4 SD), indicating severe growth retardation
- Weight: 45 kg

- No significant dysmorphic features noted

Genital examination:

- Micropenis measuring 40 mm
- Prepubertal presentation with bilateral cryptorchidism
- Tanner stage P2 for pubic hair development

Anosmia was established by an olfactory test during consultation using odoriferous substances (soap) that the patient was unable to identify, confirming complete loss of smell.

Biological investigations: Hormonal evaluation revealed hypogonadotropic hypogonadism:

- FSH: 0.42 IU/ml (low)
- LH: <0.10 mIU/ml (low)
- Testosterone: <0.2 ng/ml (low)
- IGF-1: 145 ng/ml (<−4 SD)

Imaging:

- Left wrist radiograph showing a bone age corresponding to 11 years (7 years delayed compared to chronological age) (**Figure 2**)
- Pelvic ultrasound revealing bilateral cryptorchidism with both testes located in the upper inguinal region with reduced volume (**Figure 1**)

Diagnosis: Kallmann syndrome

Treatment and outcome: The patient was started on intramuscular testosterone injection at a dose of 100 mg/m^2 body surface area every 15 days for 3 doses, then every 4 weeks. After 5 injections, the patient showed the following clinical improvements:

- Increase in penile length to 70 mm
- Regular occurrence of erections and ejaculation
- Testicular descent

2.2. Case 2

A 16-year-old male patient presented with micropenis and anosmia. His older brother (Case 1) had the same clinical picture, and their paternal uncle had short stature and infertility **(Figure 5)**.

General examination:

- Height: 175 cm
- Weight: 74.7 kg
- No significant dysmorphic features

Genital examination:

- Micropenis measuring 38 mm (**Figure 4**)
- Prepubertal presentation with bilateral cryptorchidism
- Tanner stage P2 for pubic hair

Anosmia was confirmed by the same simple olfactory test using common odoriferous substances that the patient was unable to identify.

Biological investigations: Hypogonadotropic hypogonadism was confirmed:

- FSH: <1 mIU/ml (low)
- LH: <0.1 mIU/ml (low)
- Testosterone: <0.2 ng/ml (low)

Imaging: Pelvic ultrasound revealed:

- Left cryptorchidism with homogeneous severely hypotrophic testis (0.33 ml)
- Right testis not visualized

Treatment and outcome: The patient was started on androgen therapy (testosterone) at 100 mg/m^2 body surface area intramuscularly every 15 days initially, then every 4 weeks. Clinical evolution after 5 injections showed:

- Increase in penile size to 65 mm
- Regular occurrence of erections and ejaculation

3. Discussion

Our study concerns Kallmann syndrome in two brothers. Kallmann syndrome can be sporadic or familial. Sporadic forms are the most common, while familial forms affect approximately 30% of cases. They are linked to several modes of genetic transmission: X-linked recessive (KAL-1), autosomal dominant, or autosomal recessive [3]-[5].

Pedigree analysis and probable mode of transmission: In our observation, the involvement of a paternal uncle and two brothers strongly suggests autosomal rather than X-linked transmission. Indeed, in X-linked transmission, an affected paternal uncle cannot transmit the pathological gene to his nephews through his brother (the patients' father), since men only transmit their X chromosome to their daughters. The presence of an affected paternal uncle rather points toward autosomal recessive transmission or, less probably, autosomal dominant with variable penetrance [6]. The absence of involvement in the patients' father favors the hypothesis of autosomal recessive transmission, where both parents would be heterozygous carriers [7].

The prevalence is estimated at 1/10,000 and is four times less frequent in girls compared to boys [8]. The diagnosis is generally made after the age of 14 years and is related to delayed puberty [9]. In our study, we found two male cases, aged 16 and 18 years respectively. Our results are consistent with those of Halima [3] in 2019 and Aynou [10] in 2015 in Morocco, who reported an age of consultation beyond 14 years.

A careful history allows for the search for family history of infertility or delayed puberty, which supports the diagnosis of familial Kallmann syndrome [2] [7] [11]. Our two patients were from the same family and both presented similar symptoms. Family history revealed short stature and infertility in their paternal uncle. Our cases suggest a probable familial form of Kallmann syndrome.

The main clinical signs of Kallmann syndrome include anosmia or hyposmia, micropenis, and cryptorchidism. These features allow differential diagnosis from simple delayed puberty. Pubic hair development can be encountered at an advanced age due to peripheral tissue conversion of dehydroepiandrosterone (DHEA) se-

creted by the adrenal glands [12] [13].

We found similar symptomatology in our study: micropenis, anosmia, bilateral cryptorchidism in the first case and unilateral cryptorchidism in the second, pubic hair development (Tanner P2) in both patients, and severe growth delay in the first patient.

Growth discordance between the two brothers: The severe growth retardation observed in Case 1 (146 cm, −4 SD) with a very low IGF-1 level (145 ng/ml, <−4 SD) contrasts with the normal height of Case 2 (175 cm). This phenotypic discordance suggests that Case 1 might present a more extensive hormonal deficit, potentially a combined deficiency in gonadotropins and growth hormone, while Case 2 would present isolated hypogonadotropic hypogonadism [14]. This clinical heterogeneity, although both brothers probably share the same genetic mutation, can be explained by genetic, epigenetic, or environmental modifying factors [6] [15]. A complete exploration of the somatotropic axis with growth hormone stimulation would have been ideal in Case 1 to confirm a possible combined deficit, but could not be performed in our context of limited resources.

Growth delay is not a classic symptom of Kallmann syndrome; however, it is recommended to explore all pituitary axes to determine whether it is isolated hypogonadotropic hypogonadism or panhypopituitarism [16] [17].

Hormonal evaluation confirmed hypogonadotropic hypogonadism in both cases. Our results are consistent with literature data [1] [16] and confirm the diagnosis. Morphologically, pelvic ultrasound in both patients revealed bilateral cryptorchidism in one and unilateral left cryptorchidism in the other.

Left wrist radiography performed in Case 1 showed a bone age of 11 years (7 years less than chronological age) with absence of closure of epiphyseal cartilages of long bones. This is explained by delayed bone maturation and osteopenia due to sex hormone deficiency [16] [18].

In our Chadian context, MRI and genetic tests could not be performed in either patient due to their unavailability. This limitation raises important questions about the reliability of clinical diagnosis of Kallmann syndrome in resource-limited settings [17]. In the absence of imaging of the pituitary and olfactory bulbs, we relied on a rigorous clinical approach combining family history, olfactory assessment during consultation, detailed clinical examination, and hormonal assays. Although formal diagnostic criteria such as those proposed by Quinton *et al.* [19] are not universally established for diagnosis without imaging, the combination of at least three major criteria (hypogonadotropic hypogonadism, anosmia/hyposmia, compatible family history) with minor criteria (cryptorchidism, micropenis, delayed bone age) allows a reasonably reliable clinical diagnosis [9] [17] [19]. Nevertheless, we acknowledge that in the absence of MRI confirmation showing hypoplasia or aplasia of the olfactory bulbs, our diagnosis remains presumptive. This diagnostic limitation underscores the need to develop diagnostic algorithms adapted to resource-limited contexts and to facilitate access to imaging technologies for complex cases [17].

Treatment of hypogonadism in Kallmann syndrome aims to trigger pubertal development with testosterone injections in males, then to ensure maintenance of secondary sexual characteristics. Fertility development can be achieved using gonadotropins or pulsatile GnRH to obtain testicular growth and spermatogenesis, allowing restoration of fertility in a large majority of cases [17] [20] [21].

We introduced injectable testosterone at a dose of 100 mg/m^2 body surface area every 15 days for three doses, then one dose every 4 weeks. Evolution after 5 injections was marked by an increase in penile size to 70 mm and 65 mm respectively, and the regular occurrence of erections and ejaculation.

4. Conclusion

Kallmann syndrome is a rare pathology. The diagnosis is based on micropenis, cryptorchidism with anosmia, and hypogonadotropic hypogonadism on hormonal evaluation. Familial forms, although less frequent, must be systematically sought through careful patient history, given the difficulty of performing genetic tests in our context. Early diagnosis and appropriate hormone therapy can lead to significant improvement in pubertal development and quality of life.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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