

Doubtful descent, dilemma and diagnosis: a case of Kallmann syndrome

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ABSTRACT

A 16-year-old boy with a diagnosis of bilateral cryptorchidism was referred for preoperative evaluation. He had diminished hearing and difficulty in vision since birth, with inattentiveness, poor school performance and delayed milestones. He was previously operated on for cleft lip. General survey revealed bilateral short fourth metacarpals and an operative scar mark over the left nostril and upper lip. He had a micropenis, small soft testes with anosmia, and sensory-motor deafness. The hormonal assay was consistent with hypogonadotropic hypogonadism. Magnetic resonance imaging of the brain and computed tomography cisternography revealed almost hypoplastic olfactory bulb with an ill-defined olfactory tract and sulci, supporting the clinical diagnosis of Kallmann syndrome.

Keywords: anosmia, cisternography, cryptorchidism, hypogonadotropic hypogonadism, Kallmann syndrome

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INTRODUCTION

The Kallmann syndrome is a rare nosological phenomenon characterised by hypogonadotropic hypogonadism and anosmia. In 1944, Kallmann first studied the genetic aspects of this syndrome in three different families. In these patients, histological studies revealed either degeneration in the olfactory bulb/tract or a generalised hypoplasia of the olfactory system. The diagnosis can be clinically suspected and is established by confirming hormonal studies. This anatomical defect can also be demonstrated by magnetic resonance (MR) imaging. We report this teen-aged male patient who had almost all the morphological features of a classical Kallmann syndrome.

CASE REPORT

A 16-year-old boy presented to our surgical outpatient clinic for the absence of both testes since birth. For



Fig. 1 Clinical photograph shows nose asymmetry and a scar over the left nostril and upper lip.

his age, he also had a relatively small penis and a poorly-developed scrotum. Bilateral cryptorchidism was diagnosed and he was referred to us for preoperative evaluation before explorative laparotomy. On enquiry, his parents revealed that he had a below normal intelligence (student of Class V) with poor school performance. They also noticed diminished hearing, difficulty in distant vision since birth, inattentiveness and delayed milestones. He had not complained of headache, vomiting, abdominal pain, urinary difficulty, or abnormal sense of smell. There was no preceding history of trauma, radiation or prolonged drug intake. He was born of a non-consanguineous marriage, with insignificant antenatal, natal and postnatal history. He was operated on for cleft lip and palate at the age of two years.

General survey revealed a tall stature with body mass index of 20.4 kg/m², waist-hip ratio of 0.6 and a poor intelligence, compared to his chronological age. His height and arm span was equal (143 cm), with lower and upper segment being 79 cm and 64 cm, respectively. His vitals were normal. However, he had bilateral short fourth metacarpals, asymmetrical nose, and an operative scar over the left nostril and upper lip (Fig. 1). The patient had no gynaecomastia. The axillary and pubic hairs were absent. Examination of the genitalia revealed a short

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Fig. 2 Clinical photograph shows a short penis, small scrotum and absent secondary sexual characteristics.

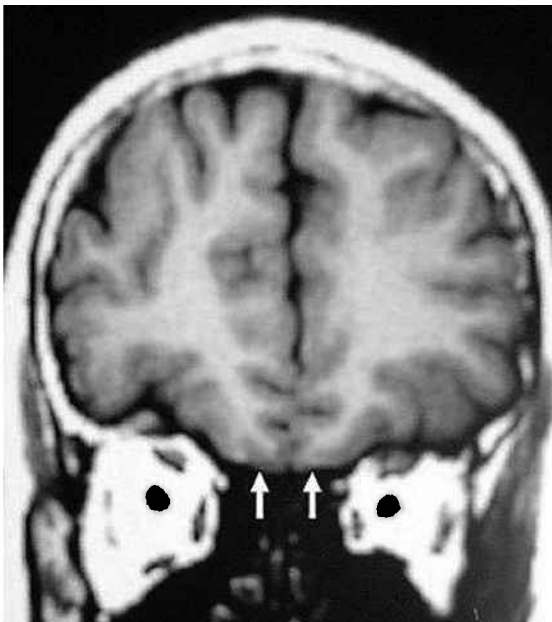


Fig. 3 Coronal T1-W MR image shows a hypoplastic olfactory bulb with ill-defined olfactory tract and sulci (arrows).

penis (stretched penile length 2.3 cm). The scrotum was small but had rugosities (Fig. 2). The testes were palpable at the root of the scrotum but were small and very soft.

The patient had a visual acuity of 6/36 and normal colour vision when tested with Ishihara chart. Ophthalmoscopy revealed a white sharp myopic cup with chorioretinal atrophic patches and secondary peripapillary degenerative changes. We also documented anosmia and sensorineural deafness during an extensive otorhinolaryngological examination which included odour identification, alcohol sniff test (with 70% isopropyl alcohol), butanol threshold test (with 4% n-butanol), and the Rinne and Weber Tests. The rest of the systemic

examination was normal.

An initial workup unveiled a normal complete haemogram, serum electrolytes and biochemistry including a fasting plasma glucose (FPG) of 81 mg/dL. A radiograph of the hands confirmed bilateral short fourth metacarpals. Abdominal ultrasonography (US) and other skeletal imagings were normal with normal bone age. US of the scrotum disclosed infantile testes (4 mm in anteroposterior diameter) in the vaginal sac. A pure tone audiometry and brainstem evoked response audiometry confirmed bilateral sensorineural deafness. The hormonal assay documented a low luteinising hormone (< 0.10 mIU/ml; N: 1.7–8.6), low follicle stimulating hormone (0.32 mIU/ml; N: 1.5–12.2) and low testosterone (0.061 ng/ml; N: 0.28–11.1) levels, consistent with the diagnosis of hypogonadotrophic hypogonadism. His prolactin level was 12.21 ng/ml (N: 2.7–16.9) and his thyroid profile was normal.

MR imaging of the brain revealed hypoplastic olfactory bulb with an ill-defined olfactory tract and sulci (Fig. 3). Computed tomography (CT) cisternography at the level of sella showed filling of the contrast agent in the anterior interhemispheric fissure and the posterior subarachnoid spaces. The olfactory groove on the right side showed only partial contrast filling and on the left side, the groove could not be visualised due to hypoplasia (Fig. 4). A normal CT cisternography at the same level showing both the olfactory sulci is provided for comparison. (Fig. 4).

He was diagnosed with Kallmann syndrome and was started on hormone replacement with monthly intramuscular injections of testosterone derivatives (1 ml containing testosterone propionate 30 mg, testosterone phenylpropionate 60 mg, testosterone isocaproate 60 mg, testosterone decanoate 100 mg). His secondary sexual characteristics developed satisfactorily after only five months of treatment (Fig. 5).

DISCUSSION

Kallmann syndrome results from defective hypothalamic gonadotropin releasing hormone (GnRH) synthesis, and is associated with anosmia or hyposmia due to olfactory bulb agenesis or hypoplasia.⁽¹⁾ It is most commonly due to mutations in the KAL gene (Xp22.3). This genetically-heterogeneous syndrome is the most common form of isolated hypogonadotrophic hypogonadism with delayed puberty.⁽²⁾ Inconstant defects include cleft lip, cleft palate, imperfect facial fusion, seizure disorders, short metacarpals, pes cavus, neurosensory hearing loss, cerebellar ataxia, oculomotor abnormalities and renal aplasia or dysplasia. Often, affected individuals do not notice impaired olfaction.⁽²⁾ We documented many of these features in our patient.

Patients with gonadotropin deficiency are usually

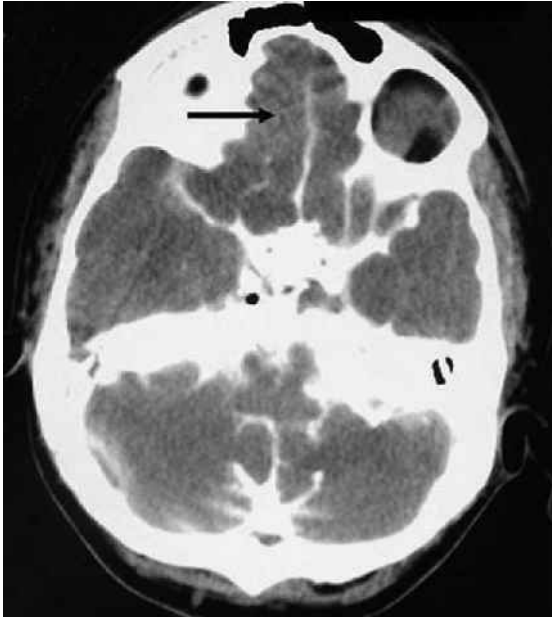


Fig. 4a Axial CT cisternogram shows partial filling of the right olfactory groove (arrow) and lack of filling of the left olfactory groove due to hypoplasia.



Fig. 4b Normal axial CT cisternogram is shown for comparison. Both olfactory sulci are seen (arrows).



Fig. 5 Follow-up clinical photograph taken after five months of hormone treatment. There is satisfactory development of secondary sexual characteristics.

of appropriate height for age in contrast to patients with central nervous system (CNS) tumours or constitutional growth retardation. Moreover, because levels of gonadal steroids are too low to fuse the epiphysis, these patients develop increased arm span and decreased upper/lower ratio,⁽²⁾ which were present in this case. Neuroradiological studies in patients with Kallmann syndrome documented normal MR imaging in fewer than 10% of patients.⁽³⁾ Majority of them showed bilateral agenesis of olfactory bulb and absent or abnormal olfactory sulci bilaterally. MR imaging of our patient confirmed these findings. Though the role of cisternography in diagnosing

Kallmann syndrome is well-documented in literature,⁽⁴⁾ in this patient, it was done for academic interest only.

Differential diagnoses of our patient included sellar/parasellar mass, septo-optic dysplasia (SOD) and DAX1 gene mutation which present with similar features. DAX1 gene mutation is characterised by severe glucocorticoid, mineralocorticoid and at puberty, androgen deficiency. Though majority of the affected boys die due to severe primary adrenal deficiency, those presenting in later childhood rarely have micropenis.⁽²⁾ Micropenis with normal BP, FPG and serum electrolytes made the diagnosis of DAX1 gene mutation unlikely in our patient. SOD is characterised by absence or dysgenesis of the septum pellucidum in conjunction with optic nerve hypoplasia and imaging studies typically show squared off frontal horns without a septum pellucidum.⁽⁵⁾ MR imaging findings ruled out the possibility of a CNS mass or SOD in this patient.

The selection of a therapeutic method in Kallmann syndrome should be individualised, bearing in mind the degree of hypoplasia and the presence of cryptorchidism. Treatment protocols are basically a choice between androgen replacement to virilise, gonadotropin therapy to induce fertility and LHRH analogue administration for most physiological replacement.⁽⁶⁾ In Kallmann syndrome with cryptorchidism, chorionic gonadotropin therapy results in the elimination of cryptorchidism without surgery. It is also appropriate to treat male infants and children

with micropenis with short courses of androgens to enlarge the penis into the normal childhood range.⁽²⁾ In these cases, fertility may be restored by the administration of gonadotrophins or subcutaneous pulsatile GnRH. Considering the age of the patient, our therapeutic aim was to restore normal pubertal development of the genitals and secondary sex characteristics. Our experience with testosterone replacement in this patient was overwhelming in this regard.

It has also been well documented that hypogonadotropic patients may visit paediatricians, general practitioners, endocrinologists or urologists, presenting with micropenis, cryptorchidism or puberties tarda and delayed bone maturation.⁽⁷⁾ In such a scenario, meticulous testicular examination is warranted. An attempt to search for the testes in the inguinal canal and to “milk” it downwards should be made before labelling a case of cryptorchidism.⁽⁸⁾ In our case, a lack of proper genital examination by the treating physician had led to this initial erroneous diagnosis. As has been suggested by various authors, we also feel that an early and correct diagnosis and adequate treatment may not only prevent unnecessary surgical interventions but also lead to proper sexual and social rehabilitation, decreasing the number of sterile men.^(9,10)

In conclusion, we document this case of Kallmann syndrome to highlight the importance of early recognition of the condition which would lead

to successful treatment and therefore, improved quality of life. This case serves as an example where meticulous clinical examination saved the patient from unnecessary surgical intervention.

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