CASE REPORT

Biochemical and MRI findings of Kallmann's syndrome

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SUMMARY

Kallmann's syndrome is a neuronal migration disorder characterised by anosmia/hyposmia and hypogonadotropic hypogonadism. We present a case of a 21-year-old man who was unable to sense smell since birth and who displayed non-development of secondary sexual characteristics for the past 10 years. Blood investigations showed low basal levels of serum follicle stimulating hormone (FSH), serum luteinising hormone (LH) and serum testosterone. After a gonadotropin releasing hormone challenge test there was a slight increase in serum FSH and serum LH, and after a human chorionic gonadotropin (HCG) challenge test the patient's serum testosterone level increased to 34 times that of his basal level. MRI of the brain showed absence of bilateral olfactory bulbs and sulcus with an apparently normal appearing pituitary gland, and bilateral loss of distinction between the gyrus rectus and medial orbital gyrus, thus confirming the diagnosis. The patient is on treatment with injection of HCG 2000 IU deep intramuscular twice a week and is on follow-up.

BACKGROUND

The term hypogonadism (HH) describes a low level of the circulating sex hormone testosterone in men and oestrogen and progesterone in women. The use of the term hypogonadotropic relates to the fact that the HH found in this case is caused by a disruption in the production of the gonadotropin hormones normally released by the anterior pituitary gland, known as luteinising hormones (LH) and follicle stimulating hormones (FSH).¹ Kallmann's syndrome (KS) describes the association of isolated hypogonadotropic HH with hyposmia/anosmia. The association of HH and anosmia was first described in 1856 by Maestre de San Juan in an autopsy report of a man with an underdeveloped penis, infantile testes, no pubic hair and absence of olfactory bulbs who, when living, had also lacked a sense of smell.² Our case is a classic case of sporadic KS, the biochemical and MRI features of which we will discuss in detail.

CASE PRESENTATION

A 21-year-old Indian man presented to the medicine department with a history of being unable to experience a sense of smell since birth, and who suffered non-development of secondary sexual characteristics resulting in an underdeveloped penis for the past 10 years. He did not have any other relevant medical or surgical history. His three brothers, parents and other relatives did not have similar symptoms. On physical examination, the

patient's anthropometry was normal. His vitals were normal and he had a normal systemic examination. On local examination of genitalia we found Tanner 1 prepubertal genitalia (pigmented pubic hair, bilateral small testis and small penis).

INVESTIGATIONS

The patient's blood investigations revealed very low serum FSH, LH and testosterone (FSH-0.76 mIU/mL, LH-0.35 mIU/mL, testosterone-12.98 ng/dL). On a gonadotropin releasing hormone (GnRH) challenge test there was a slight increase in FSH and LH (FSH-0.90 mIU/mL, LH-0.46 mIU/mL). After a HCG challenge test, to our surprise, the patient's testosterone level increased to 34 times that of his basal level (serum testosterone-445.14 ng/dL). MRI of the brain was performed on a 1.5 T GE (Signa) scanner. MRI sequences included coronal T1-weighted (T1W) (TR/TE 600/15) and T2-weighted (T2W) (TR/TE 4500/90) images from the anterior margin of the frontal sinus to the hypothalamus. Images were obtained at 3 mm thickness with 0.3 mm interslice gap. In addition, axial T1W, T2W and sagittal T1W and T2W images were obtained, which revealed absence of bilateral olfactory bulbs and grooves (figure 1) with bilateral loss of distinction between gyrus rectus and medial orbital gyrus (figure 2) and an apparently normal pituitary (figures 3 and 4). Hence, a diagnosis of KS was given.

Figure 1 Coronal T2-weighted MRI shows bilateral absence of olfactory bulbs and sulci denoted by arrows.

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Figure 2 Axial T1-weighted MRI shows bilateral loss of demarcation between the gyrus rectus and medial orbital gyrus denoted by arrows.

TREATMENT

The patient was counselled about his condition and irreversibility of his anosmia, and is now on treatment with injection of HCG 2000 IU deep intramuscular twice a week.

OUTCOME AND FOLLOW-UP

There is a significant improvement in the patient's biochemical parameters, but he has yet to show physical improvement and is on follow-up.

DISCUSSION

KS is a rare genetic disorder with an estimated prevalence of 1 in 10 000 males and 1 in 50 000 females. Both clinically and genetically, KS is heterogeneous, and although most cases are

sporadic, all modes of inheritance (X linked, autosomal dominant and autosomal recessive) have been described. Most cases have been recorded among men as it is an inherited disorder with a specific gene location on the X chromosome.^{3 4} The X linked form of the disease is caused by the mutation of KAL gene on Xp22.3.⁵ The loss of function mutation of FGFR1, mutation in prokineticin-2 signalling and in nasal embryonic LH-releasing hormone (LHRH) factor (NELF) have been associated with the autosomal dominant form.⁶⁻⁸ HH in KS is due to deficient gonadotropin-releasing hormone (GnRH) secretion caused by defective migration of GnRH neurons that depend on the guidance of olfacto-terminal nerve axons to reach the hypothalamus.⁹⁻¹¹ Clinical diagnosis of KS in adults is dependent on the coexistence of anosmia with signs of hypogonadotrophic HH. However, the diagnosis may be difficult to establish in patients of prepubertal age and may require genetic testing and MRI. Moreover, even though anosmia is present from birth, it is not apparent to either the parents or the child. The diagnosis is only made when puberty does not occur. Occasionally, the diagnosis is performed earlier due to investigation of other associated anomalies, including cardiovascular abnormalities, renal agenesis, cryptorchidism, midline defects, sensorineural deafness, small anterior lobe of the pituitary gland, short fourth metacarpal and facial anomalies (cleft lip and palate, enlarged paranasal sinuses, septo-optic dysplasia).¹² The main biochemical parameters in men are low serum testosterone and low levels of the gonadotropins LH and FSH, and in women low serum oestrogen and low levels of LH and FSH. When the GnRH and human chorionic gonadotropin (HCG) challenge tests are performed there is an increase in serum FSH, LH values and testosterone values, respectively, which gives the biochemical diagnosis of KS.¹³ Olfactory bulbs are normally seen as well-defined structures along a cribriform plate. Olfactory sulci are seen between the gyrus rectus and medial orbital gyrus.¹⁴ MRI is the modality of choice in assessing the absence of olfactory bulbs. Coronal scanning with large matrix size and decreased intersection gap is recommended to visualise the olfactory bulbs optimally. It is the best suited plane for anatomical olfactory tract overview, detection of parenchymal lesions

Figure 3 Sagittal T1-weighted and T2-weighted MRI shows an apparently normal pituitary gland denoted by arrows.

Figure 4 Sagittal T1-weighted and T2-weighted MRI shows an apparently normal pituitary gland denoted by arrows.

and olfactory bulb volumetry.^{12 15} Axial MRI allow the visualisation of the olfactory sulci of the frontal lobes; however, in our case they did not evaluate the patient's olfactory bulbs or tracts, which were optimally visualised in coronal planes.¹⁶ The paramedian sagittal sequences in thin slices objectify the tract within the olfactory sulcus, but their lower sensitivity make them more useful to the study of the pituitary gland, the corpus callosum or the posterior fossa. Gadolinium injection is not usually necessary. High resolution coronal fast spin echo T2W and T1W images are the preferred sequences for a morphological evaluation of the olfactory system.^{16–18}

Treatment is primarily aimed at restoring normal pubertal development and in some case normal fertility. The former can be achieved by administration of exogenous sex steroids, appropriate to the gender of the patient. If fertility is desired, pulsed gonadotropin-releasing hormone can be administered with variable success.¹⁹

Learning points

- ▶ Kallmann's syndrome is the most common cause of hypogonadotrophic hypogonadism.
- ▶ Hormonal study and gonadotropin releasing hormone and human chorionic gonadotropin challenge tests are useful in both diagnosis and prognosis.
- ▶ MRI, especially coronal T1-weighted (T1W) and T2-weighted (T2W) MRI, are the best modality for showing aplasia/hypoplasia of bilateral olfactory bulbs and grooves, and sagittal T1W and T2W to observe the status of the pituitary gland.

Contributors PKD involved in the conception and design, acquisition of data, analysis and interpretation of data and final approval of the version to be published. DHJ involved in the drafting the article and critical revision of the article.

Competing interests None.

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