

## CASE REPORT

**Kallmann Syndrome with Short Stature and Pituitary Hypoplasia****Salwa Baki, Raja El Latifi, Ghizlane El Mghari, Nawal El Ansari**

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**Abstract**

Kallmann syndrome (KS) is a rare disease in which hypogonadotropic hypogonadism and anosmia co-exist. In KS, the gonadotropic deficiency is isolated, the other pituitary hormones, especially the growth hormone, are preserved. We report the case of a 17 year old male having a sporadic case of KS associated with growth retardation. The diagnosis was based on hormonal workup and specific features on the MRI. The pituitary gland was hypoplastic. The patient was diagnosed to have Kallmann's syndrome with short stature associated to pituitary hypoplasia. To the best of our knowledge, this is the first case to be described in the literature combining KS, short stature and hypoplastic pituitary gland.

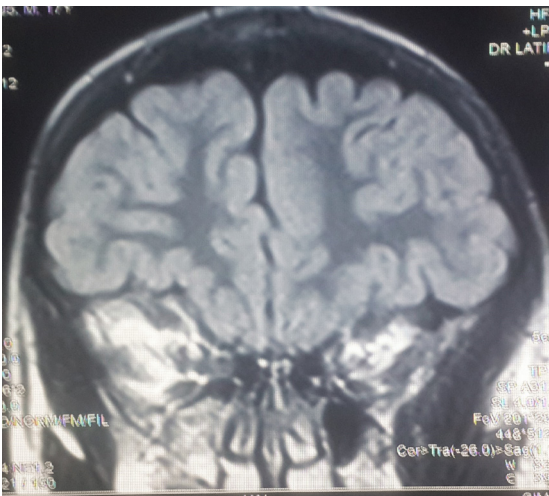
**Key words:** Anosmia. Short stature. Hypogonadism. Kallmann syndrome.

**Introduction**

The anosmic hypogonadotropic hypogonadism, also known as Kallmann syndrome (KS), is a frequent cause of congenital hypogonadism. It was first described by Maestre de San Juan in 1856 and characterized later by Franz Josef Kallmann (1). It is characterized by the combination of anosmia and hypogonadism. Anosmia is the clinical expression of olfactory bulb aplasia or hypoplasia, whereas hypogonadotropic hypogonadism is the result of gonadotrophin releasing hormone (GnRH) deficiency (2). In the classical KS, gonadotropic deficiency is isolated, the other pituitary hormones, especially the growth hormone (GH), are preserved. This phenotype has been challenged recently by some workers who showed a genetic overlapping between KS and other syndromic situation (combined pituitary hormone deficiency, pituitary stalk interruption, septic optic dysplasia, and CHARGE syndrome) (3-5). Here, we report a sporadic case of KS associated with growth retardation. To the best of our



**Figure 1.** Absence of pubic hair with undervirilized testicles and microphallus

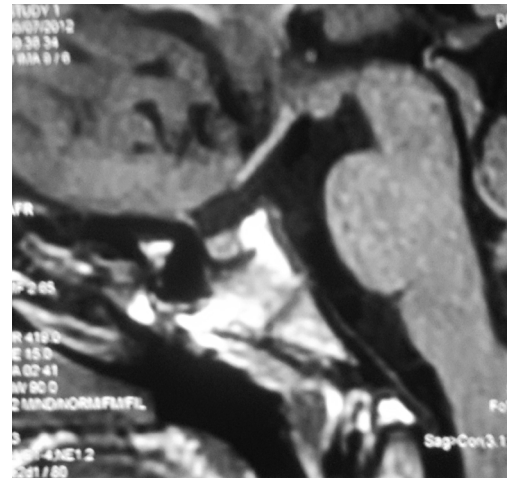


**Figure 2.** MRI showing hypoplastic olfactory bulbs

knowledge, this is the first case described in the literature combining KS, short stature and hypoplastic pituitary gland. This case lends support to the new hypothesis (3-5).

### Case report

A 17 year old male was referred to our endocrine clinic for investigation of growth retardation. He was born of non-consanguineous marriage and his birth was unremarkable. As a child, he had delayed milestones; the parents reported that his walking age was at 20 months. He had no history of seizures, blurring of vision, color blindness, hearing loss or movement disorders. His sister is reportedly short but was not examined by us. On questioning he admitted that he does not appreciate the smells well. On physical examination, his height was 143 cm and weight was 35 kg, both were below the fifth percentile. There were no dysmorphic features. His Tanner staging was P1 G1 A1 (Figure 1). His penis was small for his age with penile length



**Figure 3.** MRI showing the hypoplastic pituitary gland.

of 3.5cm (microphallus), his scrotum was undervirilized and he had an oscillating testis. Cardiovascular, respiratory and neurological examinations were all within the normal limits. The hormonal workup confirmed hypogonadotropic hypogonadism; total serum testosterone was markedly low at 0.04 ng/ml. Both gonadotrophins were markedly lower than normal values; serum luteinizing hormone (LH) was 0.66 mIU/ml and follicle stimulating hormone (FSH) was 0.86 mIU/ml. Serum prolactin level, thyroid profile and cortisol level were normal. Serum insulin-like growth factor-1 (IGF-1) level was 95 ng/ml which is below the normal range for his age and sex (127-483 ng/ml). Bone age assessment based on left carpal and wrist X ray, was delayed (12 years), compared to his chronological age (17 years) according to the Greulich and Pyle bone age atlas. Two dynamic tests of GH status demonstrated GH deficiency (insulin stimulation test: GH peak was 5.3 ng/ml, glucagon betaxolol test: GH peak was 3.2 ng/ml). MRI of the hypothalamic-pituitary found hypoplastic and small olfactory sulci (Figures 2) associated with pituitary gland hypoplasia (Figure 3). The pituitary dimensions were: 3.1mm for height and 6.3 mm for width. No stalk interruption was evident. Hearing test and ophthalmological examination were both normal. The abdominal and heart ultrasound did not detect any abnormalities. No choanal atresia was present. Smell testing was performed in clinic using common aromas such as freshly cut apple and strawberries found a reduced sense of smell, however the patient was able to recognize mint and ginger. The testicular ultrasound revealed a testicular volume around 15ml bilaterally. Accordingly, the patient was diagnosed to have Kallmann's syndrome with short stature secondary to GH deficiency. The diagnosis of CHARGE syndrome

**Table1.** Summary of the different genetic mutations described in Kallman syndrome

Genetic defect (references)	Peculiarities
KAL1 (10)	<ul style="list-style-type: none"> <li>- Encodes an extracellular glycoprotein called anosmin, which associates with the cellular membrane via heparin sulfate proteoglycans</li> <li>- 10-20% of KS mutation</li> <li>- X linked recessive</li> <li>- Clinical features: mirror movements or synkinesia, unilateral renal agnesis</li> </ul>
FGFR1, FGF8 and related genes (FGF 17, IL 17PD, DUSP6, SPRY4, FLRT3) (11-13)	<ul style="list-style-type: none"> <li>- 10 % of patients with KS were found to have loss of function in FGFR1</li> <li>- These patients exhibits varied degrees of olfactory function and GnRH deficiency</li> <li>- Clinical features: cleft palate, ear cartilage abnormalities, digital abnormalities</li> </ul>
PROK2, PROKR2 (11, 14,15)	<ul style="list-style-type: none"> <li>- Found in 9% of KS patients, most of which heterozygous</li> <li>- Considerable phenotype variation</li> <li>- May be accompanied by fibrous dysplasia, synkinesia, epilepsy</li> </ul>
CHD7(16)	<ul style="list-style-type: none"> <li>- Defective in CHARGE syndrome which include: coloboma, heart abnormalities, Choanal atresia, retardation, genital and ear abnormalities</li> </ul>
WDR11 (11)	<ul style="list-style-type: none"> <li>- WDR11 gene product interacts with EMX1, a transcription factor involved in the development of olfactory neurons</li> </ul>
SEMA3 (17)	<ul style="list-style-type: none"> <li>- Encodes for a protein that interacts with neuropilins</li> </ul>
SOX 10 (11)	<ul style="list-style-type: none"> <li>- Implicated in Waardenburg syndrome</li> <li>- Causes variable features that include olfactory bulb agenesis</li> <li>- Should be screened if KS associated to deafness</li> </ul>
HS6ST1 (18)	<ul style="list-style-type: none"> <li>- Encodes for a sulfation enzyme required for optimal cell-cell communication such as during olfactory neuronal migration and ligand-receptor interactions</li> </ul>
NELF(11)	<ul style="list-style-type: none"> <li>- Encodes the nasal embryonic LH-RH factor</li> <li>- Have been reported in KS but it is not clear whether NELF mutation cause hypogonadotropic hypogonadism</li> </ul>
FEZF1 (11,19)	<ul style="list-style-type: none"> <li>- FEZF1 is required for the establishment of the central component of the gonadotrope axis</li> </ul>

is possible but seems unlikely. The patient has 2 minor criteria if the Blake's diagnostic criteria used and only 1 minor criteria according to Verloe's diagnostic criteria. The genetic testing was not performed. He was started on replacement therapy with testosterone and GH.

### Discussion

KS is a developmental disorder characterized phenotypically by congenital hypogonadotropic hypogonadism (CHH) with anosmia or hyposmia (6). KS results when the embryonic gonadotropin releasing hormone neuron migration from the nasal placode to the hypothalamus is disrupted. The

disease affects 1 boy in 8000 and is five times more common in men than women. Several patterns of inheritance have been described including X linked recessive, autosomal dominant and autosomal recessive. However, KS is often sporadic. Important variations in clinical expression of the same genetic mutation has been described from complete anosmia and hypogonadotropic hypogonadism to a simple delayed puberty with normosmia (7-9). During the past 30 years, remarkable advances have been made regarding the molecular basis of KS, which partially explain the variation in the phenotypical abnormalities. KAL1 mutations are responsible for X-linked KS and fibroblast growth factor

receptor type 1 (FGFR1) mutations underlie one form of autosomal dominant KS, but mutations in these two genes account for only 20-25% of KS cases (2). The different genes that have been described in the literature with their corresponding phenotypic features are summarized in table 1. Our patient does not fit the classic features of the CHARGE syndrome and any of those described for the listed mutations. He did not fulfil the Blake and Verloë's criteria for CHARGE syndrome (20). However, the association of hypogonadotropic hypogonadism with anosmia and the hypoplasia of the olfactory bulbs demonstrated by MRI scan do confirm the diagnosis of KS.

The usual presentation of KS includes micropenis, loss of voice change, absence of definite hair distribution and infertility. Anosmia is usually noted on clinical examination. Kidney agenesis is present in 30%, mirror movements in 75% of cases with KAL1 mutation, an arched palate characterize this mutation (6). Short stature is unusual feature of KS. Subramanian et al. were the first to report Kallmann syndrome as one of the causes of short stature (21). Few cases of KS with short stature have since been reported but in almost all the cases the olfactory bulbs were normal (22-24). Our case report is the first to describe hypoplastic olfactory bulbs associated with abnormalities of the pituitary gland associated with the GH deficiency. Associated abnormalities of sellar and parasellar regions are less frequent.

MRI, employed in our case, is the modality of choice for assessing the olfactory bulbs. The coronal scanning with large matrix size and decreased intersection gap is recommended to visualize the olfactory bulbs optimally (25). Koenigkam-Santos et al found that the olfactory bulb and sulcus aplasia were the most common findings in KS patients (26). The pituitary hypoplasia may be related to the lack of stimulation of the anterior pituitary lobe by the GnRH.

The initial treatment goal for adolescent and young men with KS is to increase the penile size, voice masculinization, development of muscle mass and body hair growth. The treatment contributes to also enhancing libido and modifying sexual behaviors (27). Another important result of treatment is the correction of the delay in bone maturity and the prevention of osteoporosis. Testosterone therapy is preferred over pulsatile GnRH or combined gonadotropins therapy. Patients who wish to obtain an increase in testicle volume or fertility will need gonadotropin combination

therapy or pulsatile GnRH (27). Counselling of patient and family regarding the clinical condition and its long term management is crucial aspect of care.

In conclusion, advances in molecular genetics have recently demonstrated a genetic overlap between different KS phenotypes and other clinical entities. Our case perhaps exemplifies such an overlap. The association of gonadotropic deficiency to other pituitary hormones deficiencies is possible depending on the genes involved. Guidelines are needed regarding the genetic testing which is primordial to determine the clinical features to look for and to propose adapted genetic counselling for the patients and their families. However the MRI combined with full hormonal workup remain the cornerstone of the diagnosis. The evaluation of other pituitary axis is fundamental to eliminate other hormonal deficiencies especially in cases of short stature that can sometimes be attributed to constitutional delay of growth.

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