

Kallmann Syndrome with Brain Changes and Unilateral Renal Agenesis: A Rare Case Report

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ABSTRACT

Kallmann syndrome (KS) is a rare inherited disorder. It is characterized by hypogonadotropic hypogonadism in association with anosmia or hyposmia, results from defective migration of gonadotropin-releasing hormone producing neurons and olfactory axons. Because KS is a disease due to mutation of genes, patients with KS often display midline head and brain abnormalities such as cleft lip and/or palate and corpus callosum dysgenesis, septo-optic dysplasia, renal agenesis and other phenotypic abnormalities. Here we report a case of 19 years old boy presented with non-development of secondary sex characters, small penis, anosmia and clubfoot. Karyotype was 46XY and hormonal measurement revealed hypogonadotropic hypogonadism. MRI of the brain revealed bilateral agenesis of the olfactory bulb and sulcus, corpus callosal dysgenesis, septo-optic dysplasia and smaller pituitary gland. USG of abdomen revealed right renal agenesis.

Keywords

Kallmann syndrome, Hypogonadism, Anosmia, Olfactory bulb, MR imaging.

Introduction

Kallmann syndrome (KS) describes the association of hypogonadotropic hypogonadism with hypo/anosmia. The association of hypogonadism and anosmia was first described in 1856 by Maestre de San Juan in an autopsy report of a man with small penis, infantile testes, no pubic hair, and absence of olfactory bulbs, which was known to lack the sense of smell [1]. In 1944, Kallmann recognized the genetic basis of this condition in three families, and thereafter this association has been known as Kallmann syndrome [2]. KS can be sporadic or familial and affects males more than females [3]. Familial cases display different modes of inheritance: X-linked, autosomal dominant and, more rarely, autosomal recessive inheritance [4]. It has a prevalence of one in 10,000 males and one in 50,000 females [5]. KS is a genetic condition with multiple implicated genes. The most common of these is the *ANOS1* (formerly *KALI*) gene and is inherited in an X-linked recessive pattern; however, there are other genes that may

be inherited in autosomal patterns. It is thought that mutation of this gene, and other similar genes, results in failure of appropriate migration of gonadotropin-releasing hormone-secreting cells and olfactory neurons during embryogenesis [6].

Case report

A 19 years old boy of non-consanguineous parents presented with non-development of facial, axillary and pubic hair, gynecomastia, small penis and absence of smell. He also gave history of surgical correction of clubfoot. He gave no family history of same type of illness. Hormonal assay revealed hypogonadotropic hypogonadism having LH- 0.27 IU/L and testosterone- 66.98 ng/dL. Other hormonal measurements showed no evidence of pituitary hypersecretion and normal adrenal and thyroid hormone levels. His karyotype was 46XY. MRI of the brain revealed bilateral agenesis of the olfactory bulb and olfactory sulcus with contiguous gyrus rectus and medial orbital gyrus, absent rostrum and partial agenesis of body and splenium of corpus callosum, agenesis of septum pellucidum and smaller optic chiasm. Sella showed normal in size with smaller anterior pituitary gland and normal posterior pituitary bright spot. Sonographic examination of

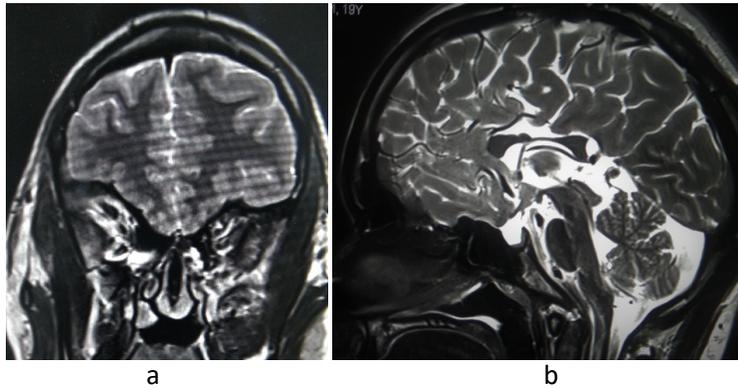


Figure 1: T2W coronal MR image through anterior cranial fossa showing absent olfactory bulb and sulcus (a) and T2W sagittal MR image showing absent rostrum and splenium and hypoplastic body of corpus callosum and smaller pituitary gland (b).

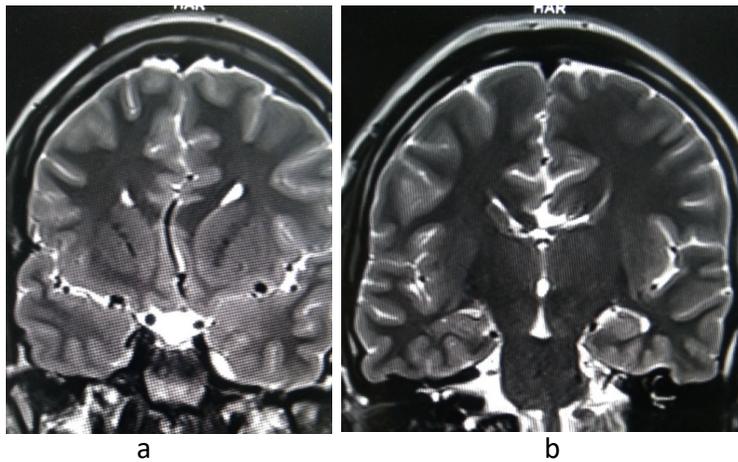


Figure 2: T2W coronal MR image showing smaller optic chiasm (a) and absent septum pellucidum with fornix below the hypoplastic corpus callosum.



Figure 3: USG showing absent right kidney (a) and normal sized left kidney (b).

Lab No:	1666-0464	Date received:	15-Aug-21	Report issued:	16-Aug-21
Patient's name:	Hasan	Age:	12 Yrs	Sex:	Male
Ward/OPD:	OPD	Bed/Cabin:		Reg No:	
Referred By:	USMU				

CYTOGENETIC REPORT (KARYOTYPING)
 Chromosomal analysis performed by peripheral blood lymphocyte culture.
 G-Banded preparations were analyzed under microscope.

Chromosome No:	46
Sex Chromosome:	XY (Structurally normal, male complement)
Autosomes:	No numerical or structural abnormality detected.
Karyotype:	46, XY

Note: Apparently normal male karyotype. No translocation, inversion or deletion detected.

a

Patient Name:	HASAN	Request No.:	00013/2250
Lab No.:	3011-21375-1502	Age:	16 Yrs 0 Mon 0 Day
Req. Date:	15/09/2021	Location:	OPD
Req. Doctor:		Gender:	MALE
Receive Date:	15/02/2021 10:55	Report Delivery Date:	15/02/2021

PATIENT LABORATORY RESULT

Test	Result	Reference Value
FT4	1.38 ng/dL	0.80 - 1.56 ng/dL
Testosterone	66.98 ng/dL	Male: 270.00 - 1754.00 ng/dL >50 years: 212.00 - 755.00 ng/dL Female: 0.00 - 0.00 ng/dL
TSH	4.73 µIU/mL	Neonates: 1.00 - 39.00 µIU/mL Adults: 0.35 - 4.50 µIU/mL Infants: 0.50 - 6.00 µIU/mL Children: 0.70 - 5.70 µIU/mL

b

Patient Name:	HASAN	Request No.:	00117/2250
Lab No.:	3011-21375-1502	Age:	16 Yrs 0 Mon 0 Day
Req. Date:	15/02/2021	Location:	OPD
Req. Doctor:		Gender:	MALE
Receive Date:	15/02/2021 10:55	Report Delivery Date:	15/02/2021

PATIENT LABORATORY RESULT

Test	Result	Reference Value
LH	0.27 mIU/mL	Male: 0.80 - 7.80 mIU/mL Adults: 0.00 - 0.10 mIU/mL Children: 0.00 - 0.44 mIU/mL Children: 10-11 Y: 0.00 - 2.28 mIU/mL Children: 12-14 Y: 0.31 - 3.29 mIU/mL Children: 15-17 Y: 0.15 - 3.33 mIU/mL Female: 0.00 - 0.00 mIU/mL Follicle Phase: 1.10 - 11.60 mIU/mL Luteal Phase: 0.00 - 14.70 mIU/mL Menopausal: 11.20 - 39.80 mIU/mL Children: 1-7 Y: 0.00 - 0.40 mIU/mL Children: 8-9 Y: 0.00 - 3.36 mIU/mL Children: 10-11 Y: 0.00 - 3.68 mIU/mL Children: 12-14 Y: 0.00 - 11.00 mIU/mL Children: 14-17 Y: 0.00 - 15.90 mIU/mL

c

Figure 4: Cytogenic report (a), Testosterone (b) and LH (c) level.

abdomen was also done and revealed right renal agenesis. Normal volume of both testes was revealed on USG. The clinical and MR imaging features of the boy are diagnostic for KS.

Discussion

KS typically combines hypogonadotropic hypogonadism with hypo/ anosmia. When anosmia is absent, it is idiopathic hypogonadotropic hypogonadism (IHH).

This uncommon disorder is due to abnormal intrauterine migration of olfactory axons and gonadotropin-releasing hormone (GnRH) producing neurons resulting in GnRH deficiency with different degrees of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) deficiencies and aplasia or hypoplasia of olfactory bulb and tracts [7]. This decrease level of gonadotrophin was noted in our case. According to Koenigkam-Santos et al. [8] most common findings in KS patients were olfactory bulb and sulcus aplasia with contiguous cerebral cortex (85%). However, in predicting KS higher accuracy was suggested by evaluating olfactory bulb than olfactory sulcus. Our patient has absented olfactory bulb as well as sulcus on both sides (Figure 1a).

MRI of the brain plays a vital role in the diagnosis of KS. MRI could assess accurate volumetric measurement of olfactory bulb in various pathological conditions. Optimal visualization of olfactory bulbs and tracts is with MRI through anterior cranial fossa in high resolution coronal fast spin-echo T2W and T1W images [9]. Normal anatomy of the region consists of olfactory bulb located in the olfactory groove, which runs along with cribriform plate and olfactory sulcus at inferior surface of frontal lobe, separating the gyrus rectus from medial orbital gyrus. These structures are abnormal in KS. In our case, there was absent olfactory bulb and olfactory sulcus with contiguous gyri on both sides. In some cases, there may be hypoplasia of anterior pituitary probably secondary to limited stimulation due to absence of hypothalamic GnRH neurons. Our patient has smaller anterior pituitary (Figure 1b).

Because KS is a disease due to mutation of genes that are involved in neuronal migration, patients with KS often display midline head and brain abnormalities such as cleft lip and/or palate and corpus callosum dysgenesis [10]. In a study by Manara et al. [11] MR imaging study was done on a group of male patients with KS featured significant morphologic and structural brain changes including olfactory bulb hypo/ aplasia and involvement of basal forebrain cortex. However, corpus callosum dysgenesis is rare and their study among large sample KS patients revealed corpus callosum partial agenesis in only 1/45 (2.2%).

In a study by Taneli et al. [12] suggested a significant genetic overlap between conditions affecting the development of anterior midline in human forebrain include Ks, combined pituitary hormone deficiency and septo-optic dysplasia. They also reported cases with phenotype of clubfoot with genetic mutation of *PROKR2 R85G* gene. Our reported case has corpus callosum dysgenesis, septum pellucidum agenesis, hypoplastic optic chiasm (Figure 2) and clubfoot.

Renal agenesis is the most common association with KS. Renal agenesis is considered as a signature phenotype of *KAL1* mutations and can be used as an early marker for genetic screening [13]. In the study by Quinton et al. [14] observed the percentage of renal agenesis in X-linked KS patients is 31%. Our reported patient has right renal agenesis (Figure 3).

Conclusion

The diagnosis of Kallmann syndrome in adult is made with clinical features of hypogonadism with hyposmia/ anosmia with co-existing decrease serum levels of gonadotropic hormones and steroids and characteristics imaging features. MRI of brain plays a significant role in demonstrating characteristic morphologic abnormalities in olfactory bulb and sulci and other brain changes. Imaging has important role for detecting multiple anomalies associated with Kallmann syndrome for proper management of the patient.

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