Case Report
Central Eur J Paed 2021;17(2):114-119
DOI: 10.5457/p2005-114.298

An Uncommon Association of Kallmann Syndrome and Arachnoid Cysts: A Case Report

Arnela Hairlahović[1], Mirzet Kovačević[2], Tina Krokter Kogoj[3], Jernej Avsenik[4]

[1]Department of Family Medicine, Community Health Center Cazin, Bosnia and Herzegovina, [2]Department of Paediatrics, Community Health Center Cazin, Bosnia and Herzegovina, [3]Department of Endocrinology, Diabetes and Metabolic Diseases, University Medical Center Ljubljana, Slovenia, [4] Clinical Institute of Radiology, University Medical Center Ljubljana, Slovenia

Correspondence: *arnela_hair@outlook.com*; Tel.: + 387 61 436 678; Fax.: + 387 37 539 027

Received: May14, 2021; **Accepted:** September 30, 2021

Abstract

Objective – To present a rare case of Kallmann syndrome associated with arachnoid cysts, and to emphasize the importance of correlation of radiological analysis with anamnestic data and clinical findings. **Case Report** – Kallmann syndrome (KS) is a form of hypogonadotropic hypogonadism in combination with a defect in the sense of smell. We report the case of KS in a 17-year old male. The patient presented with an absence of secondary sexual characteristics and anosmia. On the basis of anamnestic data, clinical findings and hormonal assay diagnosis of KS was likely but additional diagnostic workup, such as laboratory tests, karyotyping, scrotal and abdominal ultrasound, bone mineral density and X-ray of the wrist, were made to ensure the correct diagnosis. Brain MRI showed a morphologically normal pituitary gland, an arachnoid cyst on the right temporal lobe, a right frontal arachnoid cyst and hypoplastic olfactory bulbs. Androgen replacement with testosterone was started to induce virilisation. Our patient is now on regular follow-up to monitor his response to treatment. **Conclusion** – Kallmann syndrome is a condition characterized by delayed or absent puberty and an impaired sense of smell. This is the sixth reported case of KS associated with arachnoid cysts. Due to the rarity of both KS and arachnoid cysts, it is difficult to establish a relationship between these two conditions. Early diagnosis of this syndrome is important to ensure a better quality of life.

Key Words: Hypogonadotropic Hypogonadism ▪ Anosmia ▪ Kallmann Syndrome.

Introduction

Kallmann Syndrome (KS) is a congenital form of hypogonadotropic hypogonadism (HH) that manifests with hypo- or anosmia. This decrease in gonadal function is due to a failure in the differentiation or migration of gonadotropin-releasing hormone (GnRH) neurons. These neurons originate from within the embryonic olfactory epithelium and migrate to their central nervous system destinations – the hypothalamus (1). Failed neuronal migration results in aplasia or hypoplasia of the olfactory bulbs and tracts (2). It is a rare genetic disorder, with an estimated prevalence of 1/ 8000-10 000 males and 1/40 000 – 50 000 females. A higher prevalence rate of KS was found among men as it is an inherited disorder with a specific gene location on the X chromosome (3, 4). The characteristics or clinical descriptions of KS are not only reproductive, such as failure to start or reach complete puberty, but also non-reproductive, such as anosmia or hyposmia, agenesis of the corpus callosum, cleft lip or palate, abnormal eye movements, defects in hearing nerves, synkinesis and unilateral renal agenesis (4, 5). Although not a constant finding, other anomalies have sometimes been reported with KS, such as craniopharyngioma and arachnoid cysts (AC) (6). Clinical diagnosis of KS in adults should be confirmed with hormone evaluation and

magnetic resonance imaging (MRI) of the brain (7). Lifelong treatment with hormone replacement therapy is normally required (8).

We undertook a literature review and concluded that the association of KS with arachnoid cysts has so far been described in only five cases. We believe that the presentation of our patient may be important in further research of KS.

Case Report

A 17-year-old Bosnian male presented at the Department of Pediatrics, Cazin Community Health Centre, with a history of being unable to experience a sense of smell since birth, and who suffered non-development of secondary sexual characteristics. He did not have any other relevant medical or surgical history. He was born full-term via a normal spontaneous delivery, with healthy parents and a healthy older brother.

On physical examination, his body weight was 60 kg, height was 172 cm, and body mass index was 20 kg/m². He showed the absence of pubic hair as well as hair over the face, axillae, and legs, bilateral descended prepubertal testis measuring 1-2 ml, microphallus. There were no other abnormalities on systemic examination. Neurological examination was otherwise unremarkable except for a decreased sense of smell. The patient was referred to an endocrinologist and otorhinolaryngologist. The otorhinolaryngologist made the diagnosis of anosmia and vasomotor rhinitis. He requested X-ray of the paranasal sinuses (PNS). The X-ray revealed soft tissue shadows of the mucocele or polyp type in the maxillary sinus, so a computed tomography scan (CT) of the PNS was also performed. The CT of the PNS showed mucosal hyperplasia and a retention cyst on the right maxillary sinus with an approximate size of 15 mm, as well as a small retention cyst 10 mm in diameter in the left maxillary sinus on the upper wall.

The endocrinologist ordered laboratory tests. Hormonal assay showed: low total testosterone, high sex-hormone binding protein (SHBP), low LH, low FSH and normal prolactin level (Table 1).

Table 1. The Results of Hormone Tests

Hormone	Results	Reference ranges
Testosterone (ng/ml)	0.25	>2.25
SHBP (mmol/l)	96.4	13-71
LH (mIU/ml)	0.4	2-12
FSH (mIU/ml)	0.91	1-8
Prolactin (ng/ml)	7	3.3-19.7

SHBP=Sex hormone binding globulin; LH=Luteinizing hormone; FSH=Follicle-stimulating hormone.

Table 2. The Results of the GnRH Test Showing Increased Levels of LH and FSH

Hormone	Time (minutes)			
	0	20	30	60
LH (mIU/ml)	0.5	8.7	9.7	9.5
FSH (mIU/ml)	1.0	3.1	4.2	5.6

GnRH=Gonadotropin-releasing hormone; LH=Luteinizing hormone; FSH=Follicle-stimulating hormone.

LH and FSH increased promptly within 20, 30, and 60 min in response to intravenous GnRH (Table 2). These values revealed hypogonadotropic hypogonadism. In addition, further diagnostics were undertaken. Karyotyping was normal male (46 XY), a scrotal ultrasound revealed empty scrotal sac, testicles were visualized in the distal part of the inguinal canals, the right testis measured 1.64×0.81 cm and the left testis measured 1.98×0.76 cm. Abdominal ultrasonography revealed normal liver, gallbladder, pancreas, spleen, kidneys, and urinary bladder.

MRI of the pituitary gland revealed normal radiology findings of the pituitary gland (Fig. 1), an arachnoid cyst on the right temporal lobe up to 17 mm in diameter that behaved compressively to the temporal lobe, and also a right frontal arachnoid cyst 35×19 mm in diameter (Fig. 2).

New laboratory tests were ordered to assess hormonal status. Hormonal examination results showed normal ACTH, TSH, prolactin, IGF-1, IGFBP3, T4, cortisol, progesterone, inhibin B. In addition, total Immunoglobulin A (IgA) and tissue transglutaminase IgA were normal, while vitamin

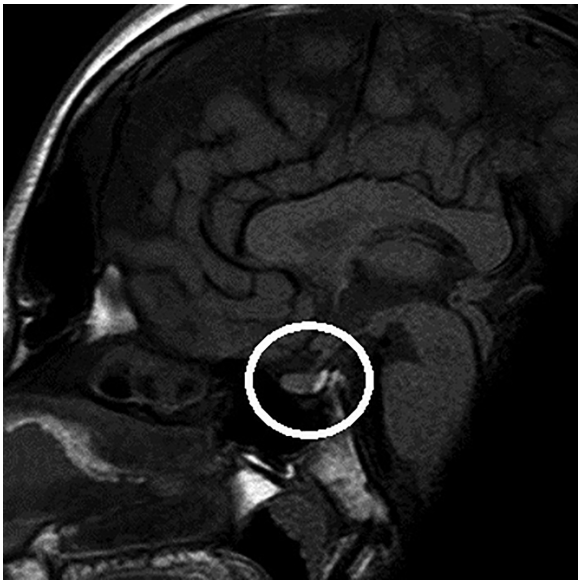

Fig. 1. *MRI of the pituitary gland, sagittal plane, revealed normal radiology findings of the pituitary gland (white circle).*

D value was low. His bone age at seventeen years and four months of age was fourteen years and one month (Tanner-Whitehouse 3 method). Bone mineral density (BMD) showed osteoporosis. Taking all the above data into consideration, it was concluded that the patient was suffering from a hypogonadal hypogonadotropic deficiency with anosmia, namely Kallmann syndrome. Consequently, to confirm the clinical diagnosis, morphological evaluation of the olfactory system was also done by performing a new MRI, this time MRI of the brain. This showed hypoplasia of the olfactory bulbs (Fig. 3), which is consistent with MRI findings in KS.

The patient was treated with testosterone undecanoate, 300 mg by intramuscular injection every three months, which was gradually increased to 500 mg. Additional vitamin D replacement therapy and Ca carbonate were also prescribed. He is now on regular follow-up to monitor his response to treatment. During his latest evaluation, improvements were observed, such as a deeper voice, increased weight and height, as well as the appearance of coarse pubic hair.

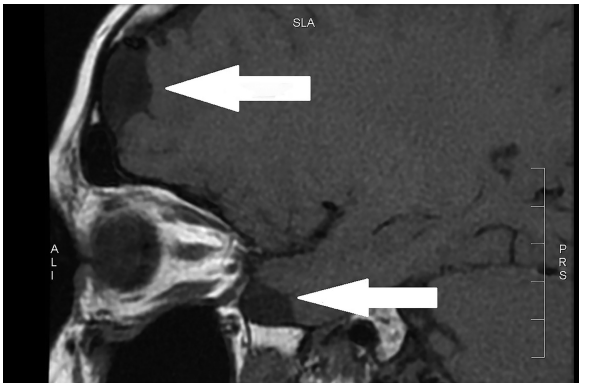

Fig. 2. *Sagittal T1 weighted image showing the arachnoid cyst on the right temporal lobe and the frontal arachnoid cyst (white arrow).*

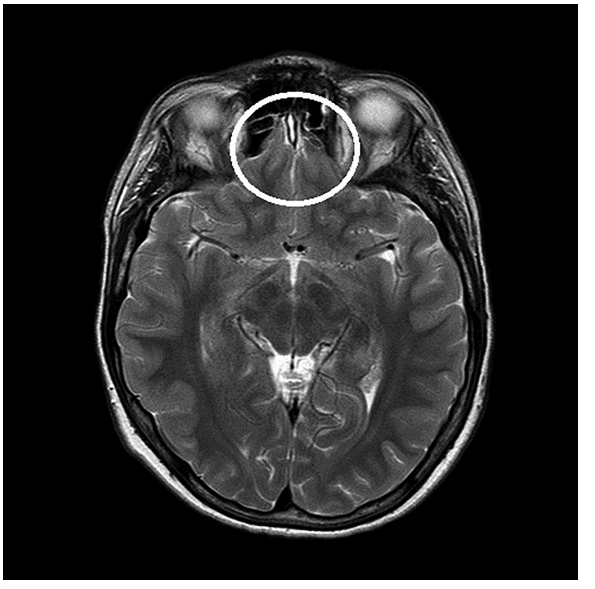

Fig. 3. *MRI of the brain, axial plane, showing hypoplasia of the olfactory bulbs, more on the left side (white circle).*

Disscussion

KS is a relatively rare disorder, but it is the most common form of gonadotrophin deficiency (9). The diagnosis of KS could be difficult to make until adolescence, when the absence of spontaneous puberty is obvious. Our patient presented at the age of 17 with an absence of secondary sex characteristics and anosmia. Complete hormonal status showed HH with no other hormonal abnormalities. After the GnRH challenge test, there was a prompt

increase in serum FSH and serum LH, consistent with normal pituitary function. These discoveries strongly suggested KS. Karyotyping was performed to rule out chromosomal abnormality as a possible cause of his condition. To exclude functional HH caused by celiac disease, total Immunoglobulin A (IgA) and tissue transglutaminase IgA were checked, and were in the normal range.

During the diagnostic workup, an X-ray of the hand and wrist revealed delayed bone maturation, and the BMD showed osteoporosis. These findings may be the result of insufficient testosterone production, as well as low serum vitamin D levels. Abdominal ultrasonography was also performed, but nothing was showing anatomical abnormalities, which occur frequently in patients with KS. In the case presented here, retention cysts in the maxillary sinuses were incidentally detected during the diagnostic workup. It is difficult to establish a relationship between KS and retention cysts on sinuses. Furthermore, MR of the brain revealed hypoplasia of the olfactory bulbs and arachnoid cysts. As is well known, an arachnoid cyst (AC) is a mass-effect lesion in the central nervous system. According to Starmark et al., the likely cause for an AC is the splitting of the arachnoid membrane in an early, intrauterine developmental period. Intracranial ACs may be primary (congenital) or secondary (acquired). The most common occurrence of primary Acs during the childhood years supports their congenital origin (10). Small cysts are usually asymptomatic, requiring observation and follow up. However, larger cysts can have a mass effect on neurovascular structures, leading to neurological symptoms (11).

According to Massimi et al., the association between KS and AC has been previously reported in only five cases (Table 3) (12). It is interesting that all cases were males, 11-33 years old. Furthermore, all arachnoid cysts presented in the left middle cranial fossa (12). Our case also follows these features. We do not have sufficient data to explain this, but this emphasizes the need for further investigation. Massimi et al. suggest that this association should be considered as occasional, as far as embryogenesis and physiopathology are concerned. However, arachnoid cysts should be included among the several non-reproductive non-olfactory anomalies possibly accompanying KS, in order to achieve a complete diagnosis and correct clinical management (12).

MRI is highly valuable in evaluating suspected KS. It is suggested that MRI should be the first ra-

Table 3. Synopsis of the Cases of KS Associated with Arachnoid Cyst (12)

Author	Sex, age	Genetics	Arachnoid cyst	Clinical findings	Kallmann syndrome	Treatment
Fernandes et al. 1995	M, 18 years	Not available	Left middle fossa	Growth retardation, eunuchoid aspect, micropenis, manual and oral apraxia, mild retardation, right convergent strabismus	Anosmia, hypogonadotrophic hypogonadism, aplasia of olfactory bulbs	Cysto-peritoneal shunt
Takorashi et al. 1997	M, 28 years	Not available	Left middle fossa empty sella	Acute slipped capital epiphysis, femoral head necrosis	Hyposmia, hypogonadotrophic hypogonadism	Not available
Scontto et al. 2002	M,33 yeares	X-linked inheritance	Left middle fossa empty sella	Erectile dysfunction, reduced hair growth, oligoasthenospermia	Left hyposmia, hypoplastic left olfactory tract-bulb	Not reported
Tesar et al. 2005	M, 19 yeares	No anomalies found	Left middle fossa extending to the suprasellar cystern	Delayed puberty, small testis and penis, low school performance, anosmia	Anosmia, hypogonadotrophic hypogonadism, aplasia of olfactory bulbs	Refused by the patient
Massimi et al. 2016	M, 11 yeares	Not available	Left middle fossa	Eunuchoid aspect, micropenis, cryptorchidism	Anosmia, hypogonadotrophic hypogonadism, plasia of olfactory bulbs	Endoscopic + microscopic cyst fenestration

diological step for investigating the pituitary gland, as well as abnormalities of the ethmoid, olfactory bulb and tracts in all cases of HH. In patients with suggestive clinical findings, MRI can contribute to the diagnosis, especially high resolution coronal fast spin echo T1-weighted (T1W) and T1-weighted (T2W) images with large matrix size and decreased intersection gap, which are the best modality for showing aplasia/hypoplasia of the bilateral olfactory bulbus and grooves, and sagittal T1W and T2W to observe the status of the pituitary gland (3, 5). As reported in the literature, in KS the hypothalamus and pituitary gland are most often morphologically normal in appearance. However, the anterior pituitary can also be assessed as hypoplastic (5). Normal olfactory bulbs can also be present in up to 20% of KS patients, which means that normal MRI does not rule out the disease (13).

The treatment options for KS depend on whether the goal is to develop secondary sexual characteristics (virilization or estrogenization), or to induce fertility as well (8). Testosterone is used to induce and maintain secondary sexual characteristics and sexual function in men with HH, but it does not return fertility. The administration of exogenous pulsatile GnRH is used to induce the phasic release of LH and FSH, and can restore puberty and fertility (7). Patients typically require lifelong treatment to maintain normal sexual function, yet some patients may reverse hypogonadism after testosterone withdrawal, a variant known as "reversible" KS. The estimated lifetime incidence of the spontaneous recovery of reproductive function might be as high as 22% (8).

Conclusion

We highlighted the clinical, hormonal, and radiological aspects of KS, which is a rare disorder characterized by the association of HH and anosmia/hyposmia. It is important to be aware of KS symptoms so that appropriate diagnostics can be made. Anamnestic data, hormonal assays, and MRI are crucial for the diagnosis. MRI should include not only MRI of the pituitary gland but also the MRI of the forebrain. Arachnoid cysts accompanying KS are occasional and the author's opinion is that this anomaly must be further investigated. KS is treatable, with the development of secondary sexual characteristic and improved quality of life.

Authors' Contributions: Conception and design: AH, MK; Acquisition, analysis and interpretation of data: AH, MK and JA; Drafting the article: AH, MK; Revising it critically for important intellectual content: AH, TKK; Approved final version of the manuscript: AH, MK, TKK and JA.

Conflict of Interest: The authors declare that they have no conflict of interest.

References

1. Laitinen EM, Vaaralahti K, Tommiska J, Eklund E, Tervaniemi M, Valanne L, et al. Incidence, phenotypic features and molecular genetics of Kallmann syndrome in Finland. Orphanet J Rare Dis. 2011;6:41. doi: 10.1186/1750-1172-6-41.
2. Zaghouani H, Slim I, Zina NB, Mallat N, Tajouri H, Kraiem C. Kallmann syndrome: MRI findings. Indian J Endocrinol Metab. 2013;(Suppl 1):S142-5. doi: 10.4103/2230-8210.119536.
3. Dash PK, Raj DH. Biochemical and MRI findings of Kallmann's syndrome. BMJ Case Rep. 2014;bcr2014207386. doi: 10.1136/bcr-2014-207386.
4. Nuring P, Khairun N, Shofwal W. Kallmann Syndrome: A Case Report. KnE life sci. 2019;4(11);56-66.
5. Dodé C, Hardelin JP. Kallmann syndrome. Eur J Hum Genet. 2009;139-46. doi: 10.1038/ejhg.2008.206.
6. Ach T, Marmouch H, Elguiche D, Achour A, Marzouk H, Sayadi H, et al. A case of Kallmann syndrome associated with a non-functional pituitary microadenoma. Endocrinol Diabetes Metab Case Rep. 2018;18-0027. doi: 10.1530/EDM-18-0027.
7. Arkoncel ML, Arkoncel FR, Lantion-Ang FL. A case of Kallmann syndrome. BMJ Case Rep. 2011;bcr0120113727. doi: 10.1136/bcr.01.2011.3727.
8. Boehm U, Bouloux PM, Dattani MT, de Roux N, Dodé C, Dunkel L, et al. Expert consensus document: European Consensus Statement on congenital hypogonadotropic hypogonadism--pathogenesis, diagnosis and treatment. Nat Rev Endocrinol. 2015;11(9):547-64. doi: 10.1038/nrendo.2015.112.
9. Kim SH. Congenital Hypogonadotropic Hypogonadism and Kallmann Syndrome: Past, Present, and Future. Endo-

crinol Metab (Seoul). 2015;30(4):456-66. doi: 10.3803/EnM.2015.30.4.456.

10. Tasar M, Bozlar U, Yetiser S, Bolu E, Tasar A, Gonul E. Idiopathic hypogonadotrophic hypogonadism associated with arachnoid cyst of the middle fossa and forebrain anomalies: presentation of an unusual case. J Endocrinol Invest. 2005;28(10):935-9. doi: 10.1007/BF03345326.
11. Mustansir F, Bashir S, Darbar A. Management of Arachnoid Cysts: A Comprehensive Review. Cureus. 2018;10(4):e2458. doi: 10.7759/cureus.2458.
12. Massimi L, Izzo A, Paternoster G, Frassanito P, Di Rocco C. Arachnoid cyst: a further anomaly associated with Kallmann syndrome? Childs Nerv Syst. 2016;32(9):1607-14. doi: 10.1007/s00381-016-3154-7.
13. Silveira LF, Latronico AC. Approach to the patient with hypogonadotropic hypogonadism. J Clin Endocrinol Metab. 2013;98(5):1781-8. doi: 10.1210/jc.2012-3550.