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CASE-BASED UPDATE

Arachnoid cyst: a further anomaly associated with Kallmann syndrome?

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Abstract
Background Kallmann syndrome (KS) is defined by the association of hypogonadotropic hypogonadism and anosmia. It is characterized by a significant clinical and genetic heterogeneity; actually, it may present several non-reproductive non-olfactory anomalies, and all the ways of genetic transmission can be involved in the inheritance of the disease. Although six pathogenesis-related genes have been identified so far, KS remains sporadic in 70 % of the cases, and the genetic diagnosis is not available for all of them. The purpose of this paper is to present a further disease that can enrich the wide spectrum of KS variability, that is cerebral arachnoid cyst.
Case description This 11-year-old boy presented with the typical characteristics of KS together with those related to a sylvian arachnoid cyst. He was admitted because of worsening headache. At the admission, the physical examination revealed eunuchoid aspect, micropenis, previous cryptorchidism, and anosmia. MRI pointed out a large, left sylvian arachnoid cyst, agenesia of the olfactory bulbs/tracts complex, and hypoplasia of the left olfactory sulcus. The child was operated on by endoscopic fenestration of the cyst, followed by transient external drainage for subdural hygroma and microscopic fenestration for recurrence of the cyst. His statural growth is normal but the sexual development still delayed in spite of hormone replacement therapy.
Conclusion According to the present and the other four cases in the literature, arachnoid cyst should be included among the anomalies possibly accompanying KS date although this association seems to be occasional as far as embryogenesis and physiopathology are concerned.

Keywords Hypogonadotropic hypogonadism · Anosmia · Olfactory bulbs · Sylvian fissure

Introduction

Kallmann syndrome (KS) is defined as the association of hypogonadotropic hypogonadism (HH) with anosmia. The first report on this association was given in 1856 by Maestre de San Juan who described the absence of olfactory structures and the presence of small testes in a male patient [1]. First recognized as a specific, possibly hereditary condition in 1944 by Kallmann [2], who carried out a study in three affected families, KS is a genetically heterogeneous disease with different forms of transmission, including X-linked recessive, autosomal recessive, and autosomal dominant with incomplete penetrance. It is occasionally associated with several different non-reproductive, non-olfactory anomalies. Although HH with anosmia or hyposmia was previously thought to identify a distinct subgroup of HH, recent findings put in doubt this classification and suggest that anosmia and HH form a phenotypic continuum that can result from mutations in the same gene [3].

The degree of hypogonadism and smell deficiency can vary according to the patients, even among affected members of the same families [4]. The diagnosis can be confirmed clinically and genetically other than through brain magnetic resonance imaging (MRI).

KS has been found to be associated with arachnoid cyst only in rare instances. Five cases have been described so far,

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indeed, including four patients from the literature [5–8] and the here-presented one (which is, to date, the only pediatric case). The goal of this paper is to review the main aspects of the syndrome and to find out if the association with arachnoid cyst is occasional.

Background

Definition and epidemiology

KS is a combination of HH and anosmia, which traditionally presents with lack of sexual maturation and low gonadotropins. The diagnosis of hypogonadism is established by clinic and laboratory examination, and by ultrasonography. Usually diagnosed during the puberal age, KS may be suspected in boys as early as in infancy in the presence of cryptorchidism or micropenis and, subsequently, because of subnormal concentrations of gonadotropins.

KS has been variously described. Actually, it has to be taken into account that a variety of non-reproductive non-olfactory anomalies may be associated in a fraction of KS patients, such as agenesis of the corpus callosum, ptosis, cleft lip or palate, dental agenesis, coloboma of the optical nerve, coartation of the aorta, renal agenesis, femur-fibula-ulna dysostosis, and chondroplasia punctata [9, 10].

KS mainly affects the male sex, males being involved 3–5 times more frequently than females [11]. The prevalence of KS in the male population ranges from 1/8000 to 1/29,000, while it decreases up to 1/40,000 to 1/130,000 among females, even though it is probably underestimated because of the wide spectrum of phenotypic presentations [4, 12]. No precise information about the incidence in the population is available. Idiopathic HH shows an incidence of 1–10/100,000 births. It is estimated that up to 50–60 % of patients with idiopathic HH present with associated anosmia [13].

Genetic considerations

Most of the KS cases are sporadic (70 %), their genetic origin being still unknown, while in 30 % of cases, a familial inheritance with different genetic transmission can be demonstrated (X chromosome-linked, autosomal dominant, and autosomal recessive inheritance) [4, 14]. To date, six pathogenesis-related genes have been identified, including Kallmann syndrome 1 (KALl), fibroblast growth factor receptor-1 (FGFRl, also known as KAL2), prokineticin receptor-2 (PROKR2), prokineticin-2 (PROK2), chromodomain helicase DNA binding protein 7 (CHD7), and fibroblast growth factor 8 (FGF8) [3, 14–17]. KAL1, the gene responsible for X-linked transmission (Xp22.3), is found in about 10 % of all KS. KAL1 encodes for anosmin-1, an extracellular glycoprotein that plays a role in promoting migration of GnRH secreting neurons from the olfactory bulbs to the hypothalamus [11, 18]. FGFR1 (8p11.2-12), CHD7 (8q12.1), and FGF8 (10q24) are the three genes responsible for the autosomal dominant form, which account for about 10 % of the cases [17, 19]. Finally, PROKR2 (20p12.3) and PROK2 (13p21.1) are found to be associated to both autosomal dominant and recessive form in 10 % of the cases [4, 15].

The clinical heterogeneity characterizing each genetic variant suggests that the phenotypes of KS may depend on other factors probably including not yet identified epigenetic factors and modifier genes [14]. Moreover, an incomplete penetrance of the disease due to digenic or oligogenic inheritance could account for such a variability. The heterogeneity can be summarized by some examples [4, 20]: (1) the degree of hypogonadism of patients with mutations in FGFR1, FGF8, PROKR2, and PROK2 shows a higher variability than in KAL1; (2) unilateral renal agenesis has been found in about 30 % of KAL1 patients whereas no cases with FGFR1, FGF8, PROKR2, and PROK2 have been reported; (3) the loss of nasal cartilage, external ear hypoplasia, and skeletal anomalies of the hands or feet seem to be exclusive of the KAL2 patients, which are also burdened by cleft lip or palate in 25–30 % of the cases.

The pathophysiology of KS is not completely understood yet. First, it was based on hypotheses formulated in the past, as failed terminal elongation or targeting of olfactory axons, primary morphogenetic defect of the olfactory bulbs, or late olfactory bulb axons defect. Currently, it is thought that KS would result from a failed embryonic migration of GnRH-1 neurons from the nasal placode to the hypothalamus because of abnormal development of olfactory nerves and bulbs and absence of adhesion proteins needed for cellular, neuronal, and axonal guidance [13]. The mechanisms leading to the failure of GnRH-1 cell migration may involve both an early degeneration of olfactory nerve and a defect of the GnRH-1 cells [21, 22]. The CCDC141 mutation, recently discovered in KS humans and mice, would suggest a primary impairment of GnRH neurons that makes them unable to migrate and form the hypothalamic neuronal network which is necessary for the pulsatile secretion of GnRH [23].

Clinical presentation

KS is characterized by incomplete sexual maturation and lack of secondary sexual features (facial and body hair growth, deepening of the voice) coupled with a compromised sense of smell. The smell deficiency varies significantly, not only among sporadic patients but also within members of affected families. Anosmia (or, in particular, hyposmia) must often be solicited, because patients may not realize they are deficient in this capacity so that this deficit is underreported [20]. Therefore, it

should be ascertained with detailed questioning and olfactory screening tests.

Males may present micropenis (defined as a stretched penile length of >2.5 standard deviations below the mean for age) and cryptorchidism during infancy [24]. Afterwards, adolescents and adults present hypogonadism, incomplete sexual maturation, and infertility. Adult males characteristically present with pre-pubertal testicular volume, absence of secondary sexual features, decreased muscle mass, decreased bone densities, diminished libido, erectile dysfunction, and infertility. Females may present with delayed puberty, primary amenorrhea, and lack of secondary sex characteristics. Late-onset KS in women can result in secondary amenorrhea [25]. Usually, KS subjects without hypothalamic-pituitary involvement show a normal statue growth (normal adrenal function).

A variety of non-reproductive non-olfactory additional anomalies is present in only a fraction of KS patients. These disorders include mental retardation, involuntary upper limb mirror movements (described as insuppressible involuntary movements that mirror voluntary contralateral hand movements), hearing impairment, abnormal eye movements, congenital ptosis, abnormal visual spatial attention, color blindness, agenesis of the corpus callosum, unilateral (occasionally bilateral) renal agenesis, cleft lip or palate, dental agenesis (hypodontia), increased arm span and decreased upper/lower ratio, brachydactyly, syndactyly, shortened fourth metacarpals (as in Turner's syndrome), osteopenia, obesity [4, 18].

Diagnosis

The clinical diagnosis is based on the evidence of hypogonadism and incomplete sexual maturation; therefore, it is commonly diagnosed during the adolescence or the early adulthood. However, in familial cases, KS can be suspected even in the fetal life, thanks to the family context and the fetal ultrasounds findings (e.g., renal agenesis, syndactyly) [26]. Delayed puberty is classically defined as the absence of virilization and testicular enlargement (testicular volume <4 ml) in conjunction with the lack of or low sperm production by the age of 14 years in males and as primary amenorrhea and the absence of breast development according to Tanner's staging (Tanner stage I) by the age of 13 years in females [27]. Eunuchoid habitus along with either anosmia or hyposmia strongly suggest the diagnosis of KS. Micropenis and/or cryptorchidism are present in infant males in 5–10 and 30 % of cases, respectively. Occasionally, males can present with a partial pubertal phenotype, termed as the "fertile eunuch syndrome" after the first description by Pasqualini and Bur [28]. These patients are hypogonodal with eunuchoid body proportions but their testicular measurements and spermatogenesis are nearly normal. Similarly, in females, partial phenotypes with variable degree of breast development and menses may occur. These partial phenotypes may be seen across all genetic forms of the disease and indicate some attenuated activity of their GnRH neuronal secretory activity.

Sense of smell is evaluated by assessing the clinical history and by olfactory screening tests. According to the widely used University of Pennsylvania Smell Identification Test (UPSIT), the identification of anosmia, hyposmia, or normosmia is based on the individual's score, age at testing, and gender, and it is interpreted using a standard normogram provided by the UPSIT manual [29].

As far as laboratory tests are concerned, serum concentration of the gonadotropins LH and FSH and sex steroids are considered for diagnosis since GnRH is not measurable. These examinations usually point out low levels of sex steroids and pituitary gonadotropins with subnormal response to GnRH stimulation, with normal anterior pituitary function [30]. However, patients with KS not rarely show normal or slightly decreased LH and FSH as well as steroids serum levels.

Neuroimaging is used to find out possible associated anatomical abnormalities and to rule out other hypothalamic or pituitary lesions as the cause of HH. MRI demonstrates a defect in the rhino-encephalon development, including bilateral aplasia or hypoplasia of olfactory bulbs and tracts and/or olfactory sulci [31, 32]. In spite of the rhino-encephalon modifications, which consist of symmetric clusters of gray matter volume increase and decrease and white matter volume decrease close to the olfactory sulci, and increased cortical thickness within the olfactory sulcus, the total amount of the remaining white and gray matter volume is normal [33]. The best assessment of olfactory bulbs, tracts, and sulci is done by MRI coronal view (Fig. 1). A well-detailed neuroimaging may reveal that also the anterior portions of the olfactory sulci may be uniformly hypoplasic in patients with hypoplasic or aplasic bulbs and tracts [34]. Some patients present hypoplasic anterior pituitary gland, probably because of the lacking stimulation resulting from the absence of hypothalamic GnRH neurons [35]. In the series of 14 patients recently published by Zhang and coworkers, MRI showed bilateral absence of olfactory bulbs and tracts in 8 cases (57 %), unilateral absence in 2, and bilateral hypoplasia in the remaining 4; the olfactory sulci were absent in 5 cases and hypoplasic in 9 (64 %); finally, the anterior pituitary gland was hypoplasic in 6 cases (43 %) while the posterior part was normal in all the subjects [36].

Molecular genetic testing can be used to investigate the genes involved in each affected subject responsible as well as to reinforce the diagnosis in familial cases [27]. A possible diagnostic flow chart for KS is summarized in Fig. 2.

Management

When dealing with KS subjects, the possibility of a wide spectrum of associated anomalies has to be considered.

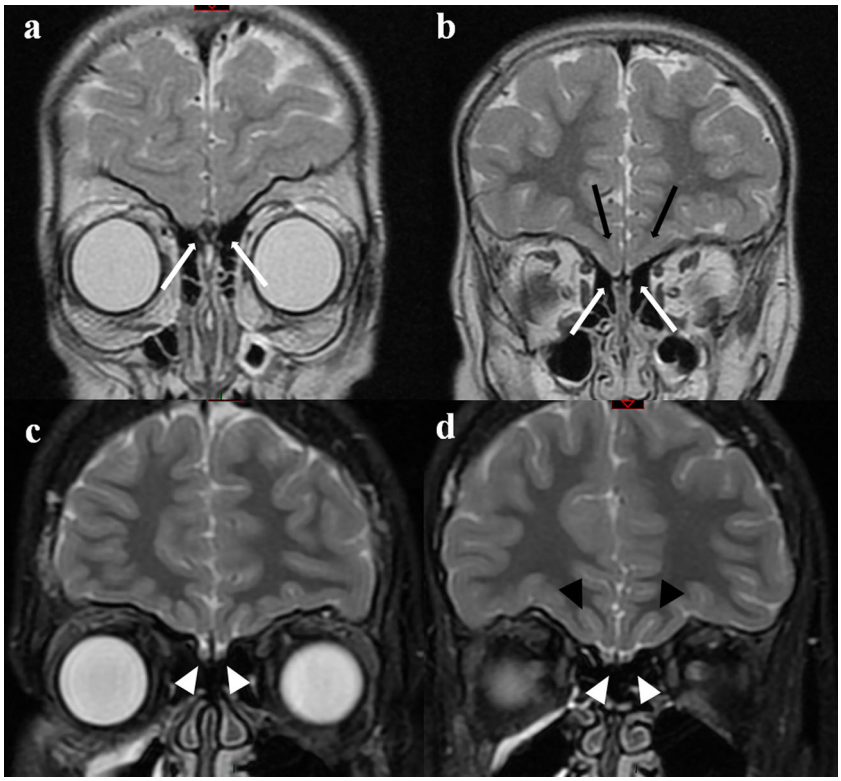

Fig. 1 **a**, **b** MRI, coronal view, of an 8-year-old girl with KS. The olfactory bulbs are absent (**a**, *white arrows*) as well as the olfactory tracts (**b**, *white arrows*). The olfactory sulcus is bilaterally missing, and there is no clear differentiation between the right and the orbital gyrus (**b**, *black arrows*); **c**, **d** MRI, coronal view, of a control subject (10-year-old boy). Note the normal olfactory bulbs (**c**, *white arrowheads*) and tracts (**d**, *white arrowheads*) and the bilateral, normal representation of the orbital sulcus (**d**, *black arrowheads*) with clearly visible right and orbital gyrus

Their management is carried out according to the different characteristics of each anomaly. On the other hand, the main managing problem specifically concerning KS is the life-long treatment of the hypogonadism, which is tailored according to the age and the characteristics of each patient. Hormone replacement therapy (HRT) is used to stimulate the development of secondary sexual characters at the time of puberty (induction of puberty) and to maintain normal hormone levels, usually by administering testosterone in males (various formulations are currently available for this purpose) and a combination of estrogens and progesterone in females [13]. The induction of male sexual characteristics (virilization) is a primary goal in young boys, and it is obtained by injectable testosterone ester or transdermal testosterone [37]. The male fertility (spermatogenesis) is induced by pulsatile GnRH administration or, more commonly, by subcutaneous gonadotropin administration [38]. Typically, spermatogenesis is rarely seen in the semen analysis until testicular volume reaches at least 8 ml. In most KS individuals without a history of cryptorchidism, however, sperm function is usually normal, and conception can occur even with relatively low sperm counts [39]. Early hormone treatment has been found to prevent the occurrence of eunuchoid behavior and appearance [40]. In young girls, the sexual maturation is achieved by oral or, more preferably, transdermal estradiol administration, adding cyclic progesterone during adulthood [13]. Either gonadotropins or pulsatile GnRH can be used to induce the fertility by stimulating the ovulation and folliculogenesis [20]. A further goal of sexual hormone replacement is to prevent late osteoporosis.

Since there is no effective treatment for olfactory deficit yet, some practical precautions, e. g., fitting gas detectors within the home, are recommended to prevent serious consequence. Due to the congenital deficit, KS patients do not complain of flavor perception impairment, especially if compared with patients with acquired anosmia [41]. However, psychotherapy should be considered, especially in the crucial teenage years, for an adequate management of the discomfort caused by the delayed/lacking sexual maturation and anosmia [20].

Exemplary case description

This 11-year-old boy, affected by anosmia, came into our attention after a 2-year history of progressing headache. On physical examination, he exhibited eunuchoid aspect, micropenis, surgical scar of orchidopexy performed for right cryptorchidism when he was 2-year-old, and normal neurocognitive development. Laboratory investigations revealed pre-pubertal level of testosterone and normal anterior pituitary function, except for slight increase of prolactine levels (20.9 ng/ml, with normal range: 02.0–10.0 ng/ml). An ophthalmology evaluation excluded visual deficits or visual field defects. Brain MRI showed a left, large, sylvian fissure,

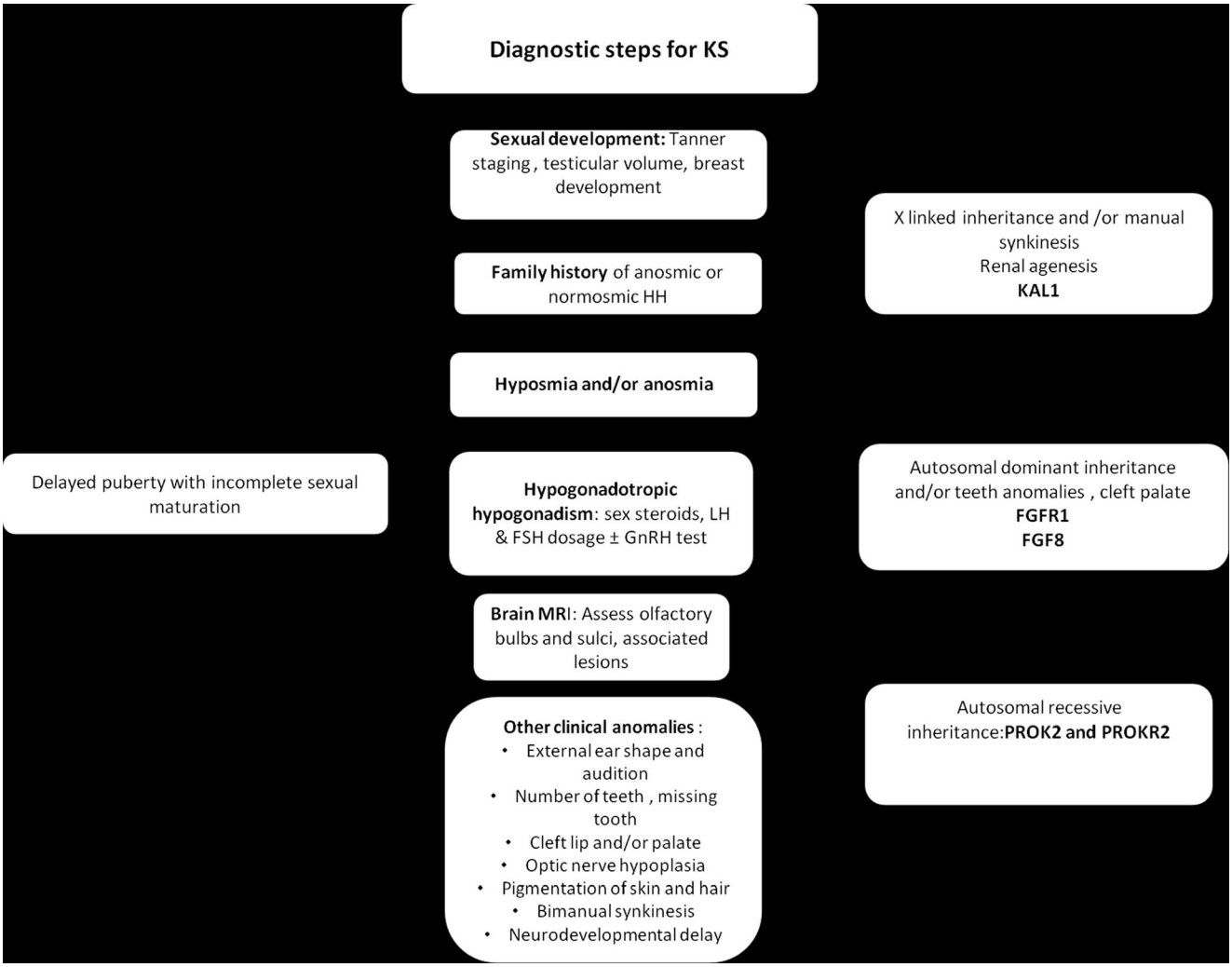

Fig. 2 Main steps for the diagnosis of KS

grade III arachnoid cyst, with midline shift and left temporal bone remodeling, extending to the suprasellar cistern, absence of olfactory bulbs, and hypoplasic left olfactory sulcus (Fig. 3). Since the parents refused the genetic tests, a clinical diagnosis of Kallmann syndrome was done based on anosmia, olfactory bulbs aplasia, micropenis, and cryptorchidism.

According to the protocol of our Center, the boy underwent prolonged ICP monitoring that revealed raised intracranial pressure. Therefore, a cyst fenestration was realized through a microscopic, endoscopically assisted surgical approach. The post-operative course was complicated by a subdural collection that required the insertion of a subduro-peritoneal shunt which was removed 6 months later after the hygroma effacement. In spite of the resolution of the subdural collection, the patient presented a recurrence of headache. MRI did not show significant differences with the preoperative size and morphology of the cyst. A new microscopic fenestration of the cyst was carried out because of symptoms and cyst

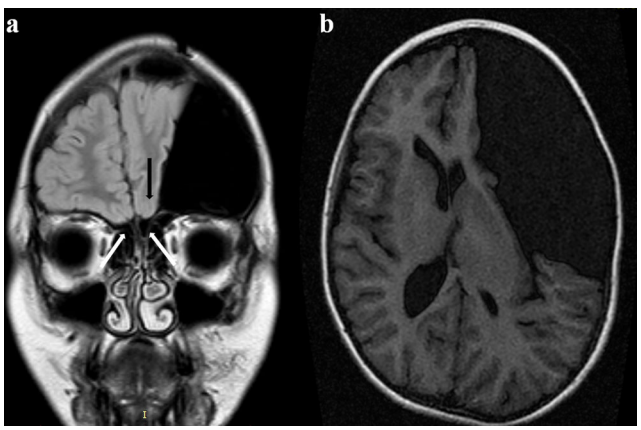

Fig. 3 **a** Preoperative MRI (coronal view) of the exemplary case showing the absence of olfactory bulbs (*white arrows*) and the hypoplasia of the left olfactory sulcus (*black arrow*). The left orbital gyrus and right gyrus are poorly differentiated and partially compressed by the arachnoid cyst; **b** Note the left, large, sylvian arachnoid cyst (preoperative MRI axial view)

persistence obtaining a reduction of the cyst volume. At the 6-year follow-up, the boy is symptom-free. The stature growth is normal. In spite of the HRT, he did not reach an acceptable sexual maturation yet.

Discussion and conclusion: arachnoid cyst and Kalmann syndrome

The here-presented case, whose recent clinical history was dominated by the arachnoid cyst, offers only a few points of discussion about the mere neurosurgical aspects. Sylvian arachnoid cysts are rare (about 0.5 % intracranial space-occupying lesions), usually incidental lesions, mainly affecting children and the left side [42]. Our patient actually harbored a left, grade III sylvian arachnoid cyst, according to the Galassi's classification [43]. He was symptomatic because of headache and raised intracranial pressure, which is quite a rare combination in an 11-year-old patient. Indeed, in spite they can be found in association with headache, seizures, psychomotor retardation, and post-traumatic hemorrhage, sylvan arachnoid cyst often remains asymptomatic through the life [44] For these reasons, the indication for surgical treatment of incidental arachnoid cyst has been questioned [45]. Our patient underwent surgery after invasive ICP monitoring, which is part of a protocol we discussed elsewhere and that we use, in combination with brain SPECT in selected cases, to identify patients requiring a surgical treatment [46]. The operation was realized by endoscopic-assisted surgery although now we use prevalently a pure endoscopic approach. The debate on the best treatment of sylvian arachnoid cyst is still ongoing [47–49]. Our patient experienced a well-know and frequent complication of surgery for arachnoid cyst, that is subdural collection, which complicate the postoperative course of 5.8 % of cases and may require a temporary shunt to be resolved [50].

The most interesting aspect of the present case is the association with KS. According to the literature review, only four patients with a similar association have been previously described [5–8]. All these four patients were young adults (age range: 18–33 years) where the arachnoid cyst was asymptomatic and was incidentally detected during the diagnostic work-up for HH. This is in agreement with the timing of the diagnosis of KS. Differently, in our patient, which is the first pediatric case of arachnoid cyst associated with KS reported so far, the arachnoid cyst was early detected because of the worsening headache. The MRI also showed the aplasia of the olfactory bulbs, thus leading to the diagnosis of KS that was

Table 1 Synopsis of the cases of KS associated with arachnoid cyst

Author	Sex, age	Genetics	Arachnoid cyst	Clinical findings	Kallmann syndrome	Treatment
Fernandes et al. 1995 [5]	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
Takahashi et al. 1997 [7]	M, 28 years	Not available	Middle fossa + empty sella	Acute slipped capital epiphysis Femoral head necrosis	Hyposmia Hypogonadotrophic hypogonadism	Not available
Scuotto et al. 2002 [6]	M, 33 years	X-linked inheritance	Left middle fossa + empty sella	Erectile dysfunction, reduced hair growth, oligo-asthenospermia	Left hyposmia Hypoplastic left olfactory tract-bulb	Not reported
Tasar et al. 2005 [8]	M, 19 years	No anomalies found	Left middle fossa extending to the suprasellar cistern	Delayed puberty, small testis and penis Low school performance Anosmia	Anosmia Hypogonadotrophic hypogonadism Aplasia of olfactory bulbs	Refused by the patient
Present case	M, 11 years	Not available	Left middle fossa	Eunuchoid aspect, micropenis, cryptorchidism	Anosmia Hypogonadotrophic hypogonadism Aplasia of olfactory bulbs	Endoscopic + microscopic cyst fenestration

only suspected before the admission based on the eunuchoid aspect and the anosmia. The main characteristics of these five patients are summarized in Table 1.

Clinical findings, such as anosmia and HH, remain the most important criteria for the diagnosis of KS. MRI of the forebrain may show the hypoplasia or aplasia of the olfactory bulbs and tracts, with/without hypothalamic hypoplasia. In case of a large sylvian arachnoid cyst extending to the suprasellar region, like in our case, the hypothalamic hypoplasia could also result from the chronic mass effect of the cyst. As previously reported, the genetic confirmation of the KS may be missing [12].

Because of the rarity of both KS and sylvian arachnoid cyst, it is difficult to establish a relationship between these two conditions. In our opinion, to date, this association should be considered as occasional as far as embryogenesis and physiopathology are concerned. However, arachnoid cyst should be included among the several non-reproductive non-olfactory anomalies possibly accompanying KS in order to achieve a complete diagnosis and a correct clinical management.

Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

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