CASE REPORT

A rare case of Kallmann syndrome in a female with pulmonary valve stenosis: Coincidence or genetic link?

Un cas rare de syndrome de Kallmann chez une fille associé à une sténose de la valve pulmonaire: Coïncidence ou lien génétique?

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Abstract

Introduction: Kallmann De Morsier syndrome (KS) is a rare genetic disorder characterized by congenital gonadotropic deficiency alongside anosmia or hyposmia, with a lower prevalence in females. Diagnosis relies on clinical and biological assessment, confirmed through pituitary magnetic resonance imaging (MRI). Cardiac involvement in this syndrome is uncommon, with only a few cases documented in the literature.

Observation: We reported the case of a 22-year-old female with a history of pulmonary valve stenosis for which she underwent balloon dilatation at the age of five years. She presented with primary amenorrhoea and a history of anosmia was noted. Hormonal investigations revealed hypogonadotropic hypogonadism and a hypothalamic-pituitary MRI identified complete agenesis of the olfactory bulbs. A diagnosis of KS was made. Genetic testing for the KAL1 gene was negative. The patient was put on hormone replacement therapy in order to achieve her puberty and promote general well-being

Conclusion: This case represents the first reported association between KS and pulmonary valve stenosis, highlighting the need for further molecular biological research to explore other genes that may explain this connection.

Key words: Genetic testing, heart defects, hypogonadotropic hypogonadism, olfactory bulb agenesis.

Résumé

Introduction: Le syndrome de Kallmann De Morsier (SK) est une maladie génétique rare caractérisée par un déficit gonadotrope congénital accompagné d'une anosmie ou d'une hyposmie, avec une prévalence plus faible chez les femmes. Le diagnostic repose sur une évaluation clinique et biologique, confirmée par l'imagerie par résonance magnétique de l'hypophyse (IRM). L'association à une atteinte cardiaque est rare et seulement quelques cas ont été décrits dans la littérature.

Observation: Nous avons rapporté le cas d'une jeune femme âgée de 22 ans avec un antécédent d'une sténose de la valve pulmonaire, pour laquelle elle a subi une dilatation par ballonnet à l'âge de cinq ans. La patiente a consulté pour une aménorrhée primaire. L'interrogatoire a révélé une notion d'anosmie. Le bilan hormonal a objectivé un hypogonadisme hypogonadotrope et l'IRM hypothalamo-hypophysaire était en faveur d'une agénésie complète des bulbes olfactifs. Le diagnostic d'un SK a été retenu. L'étude génétique du gène KAL1 a été négative. La patiente a été mise sous traitement hormonal substitutif pour déclencher sa puberté et améliorer sa qualité de vie.

Conclusion: Ce cas représente la première association signalée entre le SK et la sténose de la valve pulmonaire, soulignant la nécessité de poursuivre les recherches en biologie moléculaire afin d'explorer d'autres gènes susceptibles d'expliquer ce lien.

Mots clés: Test génétique, malformations cardiaques, hypogonadisme hypogonadotrope, agénésie des bulbes olfactifs.

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Introduction

Kallmann De Morsier syndrome (KS) is a rare genetic disorder marked by congenital gonadotropic deficiency and anosmia or hyposmia [1]. The gonadotropic deficiency arises from abnormal migration of gonadotropin-releasing hormone (GnRH) neurons, while the anosmia is caused by atrophy of the olfactory bulbs [1]. KS primarily affects males, with a prevalence estimated to be four to five times lower in females [2]. The diagnosis is typically established during puberty, primarily due to an absence of spontaneous pubertal development, which is a most common reason for consultation, combined with an altered sense of smell [3]. KS is confirmed with hypothalamic-pituitary magnetic resonance imaging (MRI), revealing hypoplasia or aplasia of the olfactory bulbs [4]. The objective of treatment is to maintain secondary sexual characteristics, with a secondary aim to induce fertility [5]. Several genes are involved in the development and migration of GnRH neurons and their mutations are the common cause of KS [3].
This case report presented a rare association between KS and congenital pulmonary valve stenosis. The hypothesis that this association is not coincidental suggests the existence of a previously unrecognised genetic link witch include both hypothalamic-pituitary disorders and congenital heart defects.

Patient information

The patient was a 22-year-old single female from a non-consanguineous background. She was born at full term via natural delivery with indications of neonatal asphyxia. She was the inborn of five siblings (four girls and one boy). While her walking was delayed until the age of three, she exhibited no language or intellectual delays. At the age of five, she underwent balloon dilation for a tight valve stenosis on a dysplastic pulmonary valve. She was subsequently referred to our endocrinology department for further investigation into the underlying cause of her primary amenorrhea. The patient's background revealed a history of anosmia since childhood. The family history showed no evidence of anosmia, and the parents and siblings reached puberty at the expected ages.

Clinical findings

Clinical examination identified a eunuchoid appearance, with a weight of 57 kg, height of 155 cm, and a body mass index of 23.7 kg/m². According to Tanner's classification [6], breast development was at stage S2, axillary hair was discreet, and pubic hair was classified as stage P4.

Timeline

Timeline from the patient's initial clinical presentation to follow-up appointments is shown in table 1.

Table 1. Timeline table summarizing the patient's information

2002	Neonatal asphyxia
2007	Balloon dilation for a tight valve stenosis on a dysplastic pulmonary valve at the age of 5, anosmia since childhood
2023, December	Presented with primary amenorrhea
2024, January	Biological assessment revealed a hypogonadotropic hypogonadism
2024, February	Pituitary magnetic resonance imaging: Complete agenesis of the olfactory bulbs
2024, February	Hormone replacement therapy
2024, July	Karyotype and genetic analysis. The patient was progressing well

Diagnostic assessment

A biological assessment indicated the presence of hypogonadotropic hypogonadism, with levels of 17β-estradiol at 26 pg/mL [normal range: 18-147], Luteinizing hormone (LH) below 0.12 IU/l [normal range: 2-11], and follicle stimulating hormone (FSH) at 0.14 IU/l [3.9-12]. Further exploration of other pituitary axes yielded unremarkable results. The pituitary MRI revealed complete agenesis of the olfactory bulbs (Figure 1). A renal ultrasound showed no malformations, and both the karyotype and genetic analysis showed normal results. Given the patient's economic circumstances, only the KAL1 gene was tested.

Therapeutic intervention

The patient was put on hormone replacement therapy, initially with low doses of 17β-estradiol, to initiate breast development, with gradual increases every six months until reaching the dose of 2 mg/day. From the second year onwards, progestin would be added to induce artificial menstrual cycles.

Follow-up and outcomes

The patient was progressing well. Breast development become at stage S4 of Tanner classification after three months of treatment and no complications of hormone therapy was noticed.

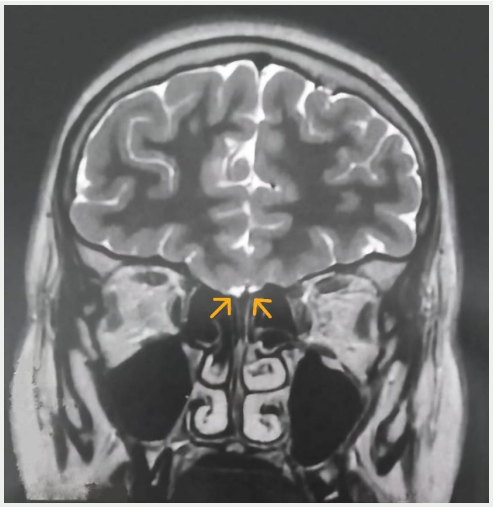

Figure 1. Coronal section of brain MRI showing total agenesis of the olfactory bulbs. The 2 arrows show the absent of olfactory bulbs.

Discussion

We reported a rare association between KS and pulmonary valve stenosis, which has never been described in the literature. A genetic link, which includes both hypothalamic-pituitary disorders and congenital heart defects, should be established through further molecular biological research.

KS is a rare genetic disorder with two distinct sets of symptoms: the absence of spontaneous puberty due to deficiency in the GnRH production and anosmia or hyposmia, linked to impaired olfactory bulb development [1]. This condition occurs at a rate of approximately 1 in 8,000 in males and 1 in 40,000 in females, with a male-to-female ratio of 5:1 [2]. The mode of transmission is heterogeneous, involving X-linked, autosomal recessive, or autosomal dominant inheritance. Several genes associated with KS have been identified, including KAL1, KAL2, PROK2, PROKR2, FGF8, FGF17, FGFR1, IL17RD, DUSP6, SPRY4, FLRT3, SEMA3A, GNRHR, CHD7, SOX10, and IL17RD [1]. However, only 40% of cases have been found to carry genetic mutations [3].

The diagnosis is clinically suspected based on absent spontaneous puberty associated with an olfactory dysfunction [3]. In females, KS is revealed in 90% of cases by primary amenorrhea [4], as observed in our patient. Additional clinical signs to look for include a hollow palate, cleft lip and/or palate, dental agenesis, synkinesia, visual attention abnormalities, ocular motor deficits, ptosis, deafness, renal agenesis, and cardiovascular abnormalities [1].

Hormonal assessment indicates hypogonadotropic hypogonadism [5]. In females, low estradiol levels are linked to reduced or abnormal serum concentrations of gonadotropins (LH and FSH). Diagnosis of KS can be confirmed through pituitary MRI focusing on the olfactory bulbs, often demonstrating hypoplasia or even aplasia of these structures [5].

Cardiac malformations are rarely associated with KS [7]. However, certain notable cases have been documented, detailing a variety of cardiac anomalies associated with this condition. In 1960, Gautier [8] first reported Ebstein's disease in a 24-year-old female with KS. Later, in 1976, Rosenberg and Riddick [7] documented a case involving an anomalous right aortic in a KS patient. Furthermore, Kemmann et al. [9] described an atrioventricular block in a 38-year-old patient with primary amenorrhea and anosmia, a condition that remained undetected until adulthood. In 2020, Gore [10] identified an association between Wolff-Parkinson-White syndrome and KS. In 2024, Bennani et al. [11] published a case of restrictive cardiomyopathy in a 19-year-old female with KS, presenting with global cardiac decompensation.

The pulmonary valve stenosis observed in our patient is a congenital heart defect, with an estimated incidence of 1 in 2,000 births annually, accounting for 10% of all cardiac malformations [12]. It may be present in isolation or be linked to genetic syndromes, generally within the framework of a RASopathy [13], such as Noonan syndrome, LEOPARD syndrome, or Costello syndrome, where mutations in the PTPN11 (Protein Tyrosine Phosphatase Non-Receptor Type 11) gene are observed. Notably, no association between pulmonary valve stenosis and KS has been described in the literature. Given the genetic basis of both conditions, a possible genetic pathway may explain their rare co-occurrence.

An association between KS and CHARGE syndrome was reported by Wen et al. [14] in a patient with olfactory abnormalities, cardiac malformations and external genital malformations. Molecular genetic analysis revealed a mutation in the CHD7 (Chromodomain helicase DNA binding protein 7) gene [14]. Furthermore, a mutation in the FGFR1(Fibroblast Growth Factor Receptor) gene associated with KS was described in a 4-month-old girl with a continuous 2.7 mm interruption in the middle of the atrial septum [15]. Waardenburg syndrome due to a mutation of SOX1 gene could also associate congenital heart defect with KS [16,17]. Further research is needed to define the underlying molecular mechanisms that are common to KS and congenital heart defects, which could improve the accuracy of diagnosis, refine the management of patients, and potentially lead to ground-breaking discoveries in medical genetics.

The treatment for KS involves lifelong hormonal therapy to trigger puberty and maintain secondary sexual characteristics [18]. It is also crucial to maintain bone health, increase feminine appearance, improve emotional and sexual life, and promote general well-being [18]. Infertility in females with KS is caused by GnRH deficiency which leads to an impairment in follicular terminal growth and maturation, resulting in chronic anovulation [19]. However, there is no evidence of a decreased follicular reserve [19]. Ovulation induction therapy in patients with KS can be achieved by either pulsatile GnRH therapy or gonadotropin stimulation, including extractive or rFSH treatment followed by hCG (human chorionic gonadotropin) or rLH [20]. In vitro fertilisation (IVF) may be an alternative if conception fails after repeated successful ovulation induction in females with KS [20]. The choice of therapy depends on the expertise of each centre and the local availability of the various medical therapies.

Conclusion

KS is a rare genetic disorder characterized by a distinct set of clinical, biological, and pituitary MRI findings centred on the olfactory bulbs. Although genetic studies are not always conclusive, prompting further research to identify additional genes involved in the pathophysiology of the disease. Its association with cardiac pathologies is an even rarer, underscoring the importance of cardiac evaluation in these patients to facilitate early treatment and prevent complications. The investigation of a possible genetic link between KS and pulmonary valve stenosis may help to identify new genetic mutations and may open the door to new therapeutic approaches that address the underlying molecular mechanisms common to both conditions.

References

1. Cho HJ, Shan Y, Whittington NC, Wray S. Nasal placode development, GnRH neuronal migration and Kallmann syndrome. Front Cell Dev Biol. 2019;11(7):121.
2. Chamseddin BH, Berg EE, Shah G, Mitchell RB. Anosmia in an adolescent. Ear Nose Throat J. 2019;98(3):129-130.
3. Stamou MI, Georgopoulos NA. Kallmann syndrome: phenotype and genotype of hypogonadotropic hypogonadism. Metabolism. 2018;86:124-134.
4. Sonne J, Leslie SW, Lopez-Ojeda W. Kallmann Syndrome. 2024 Dec 11. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan–.
5. Marhari H, Chahdi Ouazzani FZ, Ouahabi HE, Bouguenouch L. Kallmann-de Morsier syndrome: about 3 cases. Pan Afr Med J. 2019;18;33:221.
6. Marshall WA, Tanner JM. Variations in pattern of pubertal changes in girls. Arch Dis Child. 1969;44(235):291-303.
7. Rosenberg SM, Riddick DH. Dynamic pituitary testing in a female with Kallman's syndrome and associated cardiac anomaly. Obstet Gynecol. 1976 Aug; 48(2):230-3.
8. Gauthier, G. La dysplasie olfacto-génitale. Acta Neurovegetativa.1960;21: 345–394.
9. Kemmann E, Conrad P, Jones JR. Cardiac abnormalities in female hypogonadotropic hypogonadism with anosmia. Am J Obstet Gynecol. 1980;136(7):964-6.
10. Gore MR. Association of olfactory neuropathy spectrum disorder and Wolff-Parkinson-White syndrome: A Report of a case. Clin Case Rep. 2020;8(9):1638-1641.
11. Bennani G, Zahri S, Khaldi M, Benouna G, Drighil A, Habbal R. Unusual coexistence of restrictive heart disease and Kallmann syndrome: a case report. Egypt Heart J. 2024;76(1):50.
12. Bouhlel I, Ajmi H, Slim M, Gribaa R, Naffati E. Immediate results of balloon valvuloplasty in congenital pulmonary valve stenosis. Tunis Med. 2021;99(2):291-297.
13. Weaver KN, Chen J, Shikany A, White PS, Prada CE, Gelb BD, et al; Pediatric cardiac genomics consortium investigators. Prevalence of genetic diagnoses in a cohort with valvar pulmonary stenosis. Circ Genom Precis Med. 2022;15(4):e003635.
14. Wen J, Pan L, Xu X, Wang J, Hu C. Clinical data and genetic mutation in Kallmann syndrome with CHARGE syndrome: Case report and pedigree analysis. Medicine (Baltimore). 2018;97(27):e11284.
15. Dai J, Zeng J, Tan H, Cai X, Wu B. Novel 12 Mb interstitial deletion of chromosome 8p11.22-p21.2: a case report. BMC Med Genomics. 2022 Jun 6;15(1):126.
16. Maione L, Brailly-Tabard S, Nevoux J, Bouligand J, Young J. Reversal of congenital hypogonadotropic hypogonadism in a man with Kallmann syndrome due to SOX10 mutation. Clin Endocrinol (Oxf). 2016;85(6):988–989.
17. Zhang W, Xiao L, Chen B, Xu Y, Yan N. 22q12.3-q13.1 microdeletion including SOX10 causes atypical Waardenburg syndrome. Eur J Ophthalmol. 2021;31(4):2127-2134.
18. Jacques Y, Cheng X, Georgios EP, et al. Clinical Management of Congenital Hypogonadotropic Hypogonadism, Endocr Rev. 2019;40(2):669–710.
19. Youssef MA, Abou-Setta AM, Lam WS. Recombinant versus urinary human chorionic gonadotrophin for final oocyte maturation triggering in IVF and ICSI cycles. Cochrane Database Syst Rev. 2016;4:CD003719.
20. Bry-Gauillard H, Larrat-Ledoux F, Levaillant JM, et al. Anti-Müllerian hormone and ovarian morphology in women with isolated hypogonadotropic hypogonadism/Kallmann syndrome: effects of recombinant human FSH. J Clin Endocrinol Metab. 2017;102(4):1102–1111.