



SCIENTIFIC LETTERS

Late-diagnosed Kallmann syndrome[☆]



Síndrome de Kallmann de diagnóstico tardío

Kallmann syndrome is the most common form of isolated hypogonadotropic hypogonadism with delayed puberty. The syndrome characteristically includes GnRH deficiency associated with anosmia or hyposmia due to agenesis or hypoplasia of the olfactory bulbs.¹ This is a hereditary, genetically heterogeneous disease that may be transmitted as an x chromosome-linked trait or as an autosomal dominant or recessive trait. Its incidence is approximately 1/8000 in males and 1/40,000 in females.² It is usually diagnosed at 14–16 years of age when medical advice is sought for delayed puberty.

The first case reported was a 52-year-old male who was referred for severe osteoporosis with hypogonadal phenotype. His clinical history included severe hearing loss in the left ear and a cleft lip from birth. Examination revealed an absence of body hair, cryptorchidism, micropenis, and gynecomasty. The patient had previously concealed these signs. Hypogonadism was suspected based on the clinical data, and hormone and imaging tests were performed. Hormone test results (Table 1) suggested hypogonadotropic hypogonadism. Brain MRI confirmed severe hypoplasia of both olfactory bulbs. Based on the above data, the most likely diagnosis was Kallmann syndrome.

The second case was a 44-year-old female treated with oral contraceptives since the age of 18 for primary amenorrhea, which persisted after several attempts at treatment discontinuation. In the clinical history, the patient reported anosmia. Hormone tests revealed hypogonadotropic hypogonadism, a densitometric study showed osteoporosis, and brain MRI confirmed severe hypoplasia of both olfactory bulbs.

Kallmann syndrome was first described in 1856.³ The prevalence of the syndrome is approximately four times greater in males as compared to females. From the pathophysiological viewpoint, it is explained by a defect in the

migration of GnRH-secreting fetal neurons from the olfactory placode (where they originate) to the medial basal hypothalamus, where they represent the GnRH pulse generator. This defect may be absolute or partial. Because of this, cells that contain GnRH and neurites end up in a tangle around the lamina cribrosa and in the dural layers adjacent to the meninges, below the prosencephalon.⁷

There are several genes involved in the development of the syndrome. The best known is the KAL1 gene, located in locus Xp 22.3, an X chromosome-linked gene⁴ that escapes x inactivation, which is responsible for so-called Kallmann syndrome 1 (KAL1). The KAL1 gene encodes for a 680-amino acid glycoprotein called anosmin-1, with characteristics of extracellular neural adhesion, which may function as an “explorer” to guide GnRH neurons to the medial basal hypothalamus. Anosmin-1 has been shown to be distributed in the olfactory placode and prosencephalon by weeks 5–6 of fetal life. KAL1 gene deletion and/or mutations cause a frameshift and premature stop codons that result in the changes defining Kallmann syndrome.⁵ This change rarely has an impact on females.

Other hereditary forms are less well known. The autosomal dominant form is known as Kallmann syndrome 2 (KAL2), and the autosomal recessive form is called Kallmann syndrome 3 (KAL3).

The involvement of several genes⁴ may account for phenotype variability in each case. However, intrafamilial heterogeneity is also seen.⁶

The cases reported here showed the main two clinical characteristics, hypogonadism and anosmia.¹ A detailed clinical history with a special focus on anosmia suggested the diagnosis. It should not be forgotten, however, that there may be other associated characteristics such as gynecomastia, cryptorchidism, micropenis, cleft lip, cleft palate, imperfect facial fusion, seizures, short metacarpal bones, pes cavus, sensorineural hearing loss, cerebellar ataxia, etc., some of which were found in the first patient.

In patients with hyposmia, smell tests are often difficult to interpret. Coronal and axial cranial MRI of olfactory sulci-bulbs provides greater sensitivity, showing olfactory bulb aplasia or hypoplasia in approximately 90% of cases and leading to diagnosis, especially in small and prepubertal children. With MRI, olfactory sulci may be detected from week 30 of pregnancy, and olfactory bulbs between weeks 30 and 34.⁸ Genetic study is very important, and could almost be considered as mandatory, but was not performed in the reported cases due to patient refusal.

[☆] Please cite this article as: Cabrejas Gómez MC, Vicente Vicente MÁ, Antón Miguel MÁ, Urcelay Rojo M. Síndrome de Kallmann de diagnóstico tardío. Endocrinol Nutr. 2015;62:106-108.

Table 1

	Cortisol ($\mu\text{g/dL}$)	TSH (mIU/mL)	Free T4 (ng/dL)	FSH (IU/L)	LH (IU/L)	Total testosterone (ng/mL)	Free testosterone (pg/mL)	Estradiol (pg/mL)	PRL (ng/mL)	Total cholesterol (mg/dL)	HDL (mg/dL)	Triglycerides (mg/dL)	Weight (kg)	BMI
Reference values	6-25	0.3-4.5	0.9-1.9			1.9-7.4								
Case 1	23.82	1.53	1.24	0.4	<0.1	0.148	2.6	<12	5.2	234	106	46	59	22.20
Case 2	21.86	2.19	1.21	0.7	0.1	0.11			10.8	242	151	75	52.3	20.42

According to the literature, most cases are usually diagnosed at 14–16 years of age.^{8,9} The uniqueness of our cases lies in their being diagnosed at such a late age. In the first case, late diagnosis was due to a psychosocial and cultural component which had previously prevented the patient from consulting a specialist. By contrast, our second patient consulted a doctor at 18 years of age, but the etiology of primary amenorrhea was not investigated at the time, and was simply treated as a symptom.

When hypogonadism is diagnosed late, its manifestations include absent or poor sexual development inappropriate for the patient's age, eunuchoid proportions due to the late closure of growth cartilages in limbs with a reduced relationship between the upper and lower segment and increased arm span, osteopenia/osteoporosis due to decreased bone matrix mineralization and increased bone resorption, and body composition changes with increased fat mass (including abdominal mass) of gynoid distribution and decreased muscle mass. Late treatment of hypogonadism thus leads to an increase in fracture and cardiovascular risks, and also to earlier aging.

It may be concluded that Kallmann syndrome is an uncommon condition that should be suspected in patients with hypogonadotropic hypogonadism irrespective of age, and that special attention should be paid in the clinical history to the presence of hyposmia.¹ This will allow for an adequate diagnosis to be made and, consequently, for early replacement therapy to be started, so decreasing all potential consequences of the deficiency.

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Silent pituitary infarction of an uncommon etiology[☆]



Infarto hipofisario silente de etiología infrecuente

Pituitary apoplexy (PA) is an uncommon, life-threatening clinical syndrome that occurs after acute pituitary hemorrhage or infarction. PA may occur in a pituitary gland with no prior pathological process, but usually occurs as a complication of an adenoma.¹ Its clinical presentation varies widely, and may consist of a nonspecific clinical picture, typical signs and symptoms (headache, nausea, vomiting, visual changes) or, in most severe cases, pituitary insufficiency leading to coma and death. Subclinical presentation is most uncommon. This, combined with the low prevalence of the syndrome, makes diagnosis difficult, with the resultant increase in morbidity and mortality. We report the case of a patient with no relevant personal history who experienced PA secondary to tooth extraction, an etiology not previously reported.

A 41-year-old male was referred to our endocrinology outpatient clinic by his family physician for hypotension and chronic anemia. The patient had an unremarkable family and personal history, except for tooth extraction four years before with bleeding of approximately 2 L that required hospital admission and treatment with plasma expanders. The patient had had since then a nonspecific clinical picture consisting of anorexia and weight loss, abdominal discomfort, intolerance to cold, normocytic normochromic anemia, and decreased libido without impotence. Physical examination found low blood pressure levels (90/60 mmHg), normal weight (height 172 cm and weight 68.7 kg), no goiter on palpation, and dry and rough skin. No abnormal findings were made in cardiopulmonary, abdominal, or limb examination. Hypopituitarism was suspected, and baseline hormone tests were therefore performed with the following results: basal serum cortisol (1st and 2nd measurements): 2.3 and 3.15 g/dL (normal: 5–30), ACTH 6.7 pg/mL (10–80), prolactin 6.8 ng/mL (2.5–7.5), TSH 0.15 U/mL (0.30–5.5), FT4 3.9 pg/mL (8.5–18), LH 6.95 mU/mL (0.6–12), FSH 3 mU/mL (1.0–8.0), and total testosterone 3.92 ng/mL (1.8–18.5). Based on a diagnosis of corticosteroid and thyroid deficiency, replacement therapy was started with hydrocortisone and

levothyroxine. To diagnose a potential GH deficiency, the insulin-induced hypoglycemia test was performed: glucose 88, 39, 30, and 20 mg/dL (the test was discontinued at this blood glucose level); GH 0.19, 0.49, 2.78, and 2.84 ng/mL respectively. Basal IGF-1 was 65 ng/mL (normal: 90–360). After checking patient compliance with protocol criteria, treatment for such deficiency was started.

Magnetic resonance imaging (MRI) showed a small remain in the pituitary parenchyma in the sella turcica floor, whose signal was typical of normal adenohypophysis, as well as sella turcica enlargement. This pituitary atrophy and a large sella turcica were defined as consistent with PA. Radiographic studies performed two years later showed evolution to an empty sella turcica with no other changes. The patient is currently asymptomatic and has no complications secondary to replacement therapy. In most cases of PA, the underlying pathological process is a pituitary tumor (known either before or after PA occurrence). Although PA is an uncommon condition, various studies have shown the existence of factors precipitating its development in up to 40% of patients^{2,3}: high blood pressure, head trauma, anticoagulant therapy, radiation therapy, a history of major surgery (specially heart surgery), or procedures such as dynamic pituitary function tests, general anesthesia, or coronary perfusion scintigraphy, in a recently reported case.⁴ The pathophysiology of PA has not been fully elucidated yet. For PA occurring on an adenoma, there are several theories, including rapid tumor growth exceeding blood supply and causing necrosis, or potential vasculopathies intrinsic to pituitary tumors (because these bleed up to 5.4 times more than other central nervous system tumors).⁵

In the reported case, tooth extraction and subsequent bleeding were considered to be the most likely causes of pituitary infarction and the subsequent development of hypopituitarism. The patient's history revealed no causes of hypopituitarism such as neurosurgical procedures or radiation therapy, a history of head trauma or compression symptoms, of hormone hypo- or hyperfunction, suggesting pituitary or suprasellar tumor. There was also no history or clinical signs consistent with systemic or infectious infiltrative disease. We think that this was a particularly uncommon case because PA did not occur in the setting of a pituitary adenoma. In addition, the patient had none of the precipitating factors associated with PA. Etiology is however the most unique characteristic. After a systematic review, we found no case reported in the scientific literature where the only triggering factor of PA was bleeding after tooth extraction in a healthy patient with no concomitant diseases or treatment, or during the performance of certain procedures. The pathogenesis of PA in our patient may

[☆] Please cite this article as: López Valverde ME, Albero Gamboa R, Boj Carceller D, Melchor Laclea I, Trincado Aznar P. Infarto hipofisario silente de etiología infrecuente. *Endocrinol Nutr.* 2015;62:108–109.