Clinical Case Reports

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CASE REPORT

Ataxia and focal dystonia in Kallmann syndrome

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Key Clinical Message

A case of Kallmann syndrome (KS) associated with rare neurological manifestations is presented. Cerebellar ataxia probably caused by a small posterior fossa and a focal dystonia affecting the left lower limb expand the spectrum of neurological manifestations occurring in KS. Further studies are needed to better understand these manifestations.

Keywords

Introduction

Kallmann syndrome (KS) is a type of isolated hypogonadotropic hypogonadism associated with anosmia, and which can also present with bone and visceral malformations and nervous disorders. Hypogonadotropic hypogonadism features low plasma concentrations of LH, FSH, and sex steroids due to low luteinizing hormone–releasing hormone (LHRH) production by the hypothalamus [1]. We present a case of KS with rare neurological manifestations, namely ataxia and dystonia. Our purpose is to determine the pathogenesis of these manifestations.

Case Report

Our patient was a 21-year-old man whose parents were not consanguineous. His mother reported little fetal movement during gestation. Cryptorchidism and micropenis were noticed in the neonatal period. The patient started walking after the age of 2 and displayed instability, difficulty walking, and lack of sense of smell. At the age of 4, he was diagnosed with bilateral conductive hearing loss, a finding attributed to middle ear malformations.

An LHRH stimulation test showed low testosterone (0.10 ng/mL, normal range values in men: 2.8–9.9 ng/mL), LH (0.83 mUI/mL, normal range values in men: 1.26–10.05 mUI/mL), and FSH (0.86 mUI/mL, normal range values in men: 1.27–19.26 mUI/mL) plasma levels. All other findings in the hypothalamic-pituitary axis were normal. The patient had received replacement therapy with testosterone enanthate. At the age of 9, cryptorchidism and vesicoureteral reflux had been treated surgically. Right ureteroneocystostomy was performed using Cohen technique with resolution of reflux nephropathy present in this patient. Bilateral orchiopexy by Schoemaker technique was performed with good results.

At the age of 20, our patient displayed asthenic habitus with oxycephaly, facial asymmetry, antimongoloid slant of the palpebral fissures, high-arched palate, retrognathia, pectus excavatum, no chest or underarm hair, and short fourth toes.

The neurological examination showed preserved tendon reflexes, flexor plantar response, a base of support of 20 cm for static balance, ataxic gait, and dystonic posture of the left lower limb, which was turned inwards (Fig. 1). The patient was unable to tandem walk. Dysmetria was
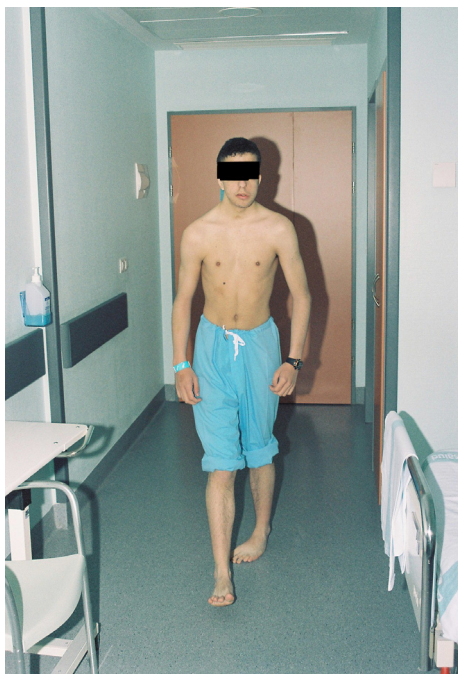
Figure 1. Ataxic gait with left lower limb dystonia.

noted in the finger-to-nose and heel-to-knee tests. Left-sided facial and lateral rectus weakness, and dysarthria were also observed.

A brain MRI scan displayed absent olfactory bulbs and tracts, a small anterior fossa (Fig. 2), and a posterior fossa with short and horizontal squama occipitalis, short and vertical clivus, cerebellar tonsils protruding below the foramen magnum, and normal bulbo–medullary junction (Fig. 3). The patient's facial skeleton was asymmetrical and orbital roofs were elevated compared to the ethmoid
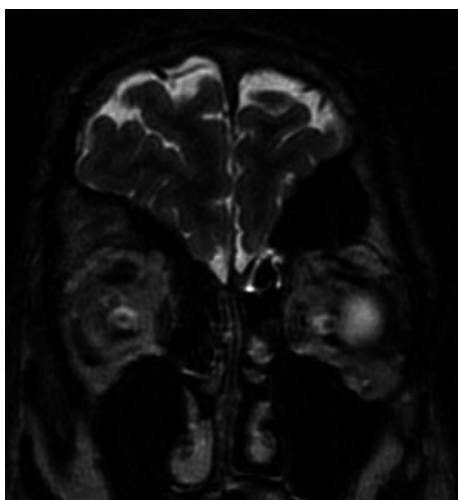

Figure 2. Brain MRI: coronal T2-weighted sequence showing absence of olfactory bulbs and tracts.

Figure 3. Brain MRI: sagittal T1-weighted sequence showing abnormal posterior fossa with a short squama occipitalis and a short and vertical clivus. Cerebellar tonsils protrude below the foramen magnum.

bone. He also displayed high-arched palate, mandibular hypoplasia, and a narrowed nasopharyngeal passageway due to displacement of the anterior arch of the atlas and adenoid hypertrophy. Cervical MRI showed incomplete fusion at C6 and C7, and radiograph of the feet displayed short fourth metatarsal bones.

The ophthalmological examination ruled out retinitis pigmentosa and cataracts. An abdominal ultrasound study displayed a small right kidney with poor corticomedullary differentiation and compensatory left kidney hypertrophy. Results from the echocardiogram were normal, and the molecular study revealed a 46,XY karyotype with no Xp22.3 deletions.

Discussion and Conclusions

Diagnosis of KS is based on the co-presence of hypogonadotropic hypogonadism and anosmia [1]. Both disorders are caused by abnormal cell migration from the olfactory placode during the sixth week of embryonic development [1].

Abnormal or absent olfactory bulbs and tracts in KS can be detected with neuroimaging studies [2], as in our case; other anomalies of the CNS that may also be present in KS are agenesis of the corpus callosum [1] and Dandy–Walker malformation [3].

Plasma levels of testosterone, FSH, and LH were low, and did not improve with LHRH stimulation due to lack of pituitary response that was secondary to chronic absent secretion of LHRH [2], which in turn indicates hypogonadotropic hypogonadism. This finding, in conjunction with absence of olfactory bulbs and tracts, pointed to KS.

Clinical manifestations of KS include azoospermia, cryptorchidism, micropenis, and impaired sexual development in men [1], and amenorrhoea and poor breast development in women [4]. Olfactory anomalies include partial to complete absence of the sense of smell [1].

Patients with KS can present several bone and visceral malformations [1, 5]. Unilateral renal agenesis, cryptorchidism, and brachydactyly of the fourth metacarpals have been found in the congenital and sporadic forms [5, 6], whereas midline skeletal abnormalities are suggestive of mutations in the *FGFR1* and *FGF8* genes [6].

The most frequent neurological manifestations of KS are synkinetic movements of the upper limbs. These are present in up to 85% of KS patients with *KAL1* mutations, but were absent in our patient. Some studies have also described congenital paresis of the facial and oculomotor nerves, ocular motor abnormalities, abnormal saccadic eye movements [7, 8], and palpebral ptosis [9]. Cerebellar dysfunction (associated with dysmetria, dysarthria, and ataxic gait) and neurosensory hearing loss have also been reported [7, 8].

Researchers have identified several genes associated with this syndrome, including: (1) *KAL1*, in Xp22.31, responsible for X-linked recessive KS; (2) *FGFR1* (fibroblast growth factor receptor 1, in 8p11.23) and *FGF8* (fibroblast growth factor 8, in 10q24.32), involved in the organogenesis of several structures, including the anterior telencephalon, kidneys, and limb skeleton [1, 5], and responsible for dominant inheritance and incomplete penetrance of KS; and 3) *PROKR2* and *PROK2*, which transmit KS with a recessive autosomal inheritance pattern [5]. These mutations account for 30% of all cases, meaning that KS is mainly sporadic.

In our case, midline skeletal abnormalities were pectus excavatum, Klippel–Feil syndrome, high-arched palate, retrognathia, and anomalies in the facial skeleton, and anterior and posterior cranial fossae. While these findings indicate genetically transmitted KS, brachydactyly of the fourth metatarsals can be present in both hereditary and sporadic forms. The visceral malformations seen in our patient included renal agenesis and cryptorchidism. Although hearing loss in KS is usually neurosensory, our patient presented conductive hearing loss; this finding has also been reported in a previous study [10].

Neurological manifestations in our patient include facial weakness and ocular abduction deficit, focal dystonia in the left lower limb, and nonprogressive cerebellar ataxia. An MRI scan displayed a flattened squama occipitalis with a vertical clivus, straight sinus, and cerebellar tentorium, resulting in reduced volume of the posterior fossa and subsequent herniation of the cerebellar tonsils. This finding is characteristic of type 1 Arnold–Chiari

malformation [11] and may be responsible for ataxia in our patient.

Differential diagnosis for this case must consider a wide range of disorders, including Moebius syndrome, diseases caused by *TRPV4* mutations (bone dysplasias associated with hearing loss and cranial neuropathies) [12], familial cerebellar ataxia with hypogonadism [13, 14], and ataxia-telangiectasia [15]. Despite the options mentioned above, absence of olfactory tracts and presence of hypogonadotropic hypogonadism indicated KS. Bone and visceral malformations, and neurological disorders observed in our patient were also consistent with this diagnosis.

In conclusion, presence of multiple midline skeletal malformations in our case points to genetically transmitted KS rather than sporadic KS, despite absence of deletions of *KAL1*. An undersized and abnormally shaped posterior fossa may be the cause of cerebellar ataxia in our patient; however, findings from clinical and paraclinical examinations have failed to identify any other causes of focal dystonia not previously described in the literature. Further studies are necessary to gain a better knowledge of the neurological manifestations in KS, and of their pathogenesis.

Acknowledgments

Conflict of Interests

None declared.

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