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Paediatric phenotype of Kallmann syndrome due to mutations of fibroblast growth factor receptor 1 (FGFR1)

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Abstract

Kallmann syndrome characterised by hypogonadotropic hypogonadism (HH) and anosmia is genetically heterogeneous with X-linked, autosomal dominant and autosomal recessive forms. The autosomal dominant form due to loss of function mutation in the fibroblast growth factor receptor 1 (FGFR1) accounts for about 10% of cases. We report here three paediatric cases of Kallmann syndrome with unusual phenotype in two unrelated patients with severe ear anomalies (hypoplasia or agenesis of external ear) associated with classical features, such as cleft palate, dental agenesis, syndactylia, micropenis and cryptorchidism. We found de novo mutation in these two patients (Cys178Ser and Arg622Gly, respectively), and one inherited Arg622Gln mutation with intrafamilial variable phenotype. These genotype–phenotype correlations indicate that paediatric phenotypic expression of FGFR1 loss of function mutations is highly variable, the severity of the oro-facial malformations at birth does not predict gonadotropic function at the puberty and that de novo mutations of FGFR1 are relatively frequent.

Keywords: Kallmann syndrome; Fibroblast growth factor receptor 1; Children

1. Introduction

Kallmann syndrome is a developmental disease that combines hypogonadotropic hypogonadism (HH) and anosmia/hyposmia. Hypogonadism is due to gonadotropin releasing hormone (GnRH) deficiency (Naftolin et al., 1971) resulting probably from a GnRH neurons migration failure during embryonic development that leads to absence of spontaneous puberty in most patients. Anosmia/hyposmia is related to the absence or hypoplasia of the olfactory bulbs and tracts.

Kallmann syndrome prevalence is estimated at 1/10,000 in males and at 1/50,000 in females. Sporadic cases of Kallmann syndrome are more frequent than familial cases and a higher prevalence of affected males is seen. Kallmann syndrome is genetically heterogeneous with three modes of inheritance: X-linked form due to mutation in the KAL1 gene (Xp22.3) (Hardelin, 2001) autosomal dominant form due to mutations in fibroblast growth factor receptor 1 (FGFR1) (KAL2) (8p12) (Dode et al., 2003), and less often autosomal recessive form for which no causal mutation has been so far identified. KAL1 and KAL2 mutations account for only 20% of Kallmann syndrome (Dode et al., 2003; Sato et al., 2004, 2005; Albuisson et al., 2005; Pitteloud et al., 2005).

In Kallmann syndrome due to KAL1 mutation, a homogeneous phenotype (almost constant hypogonadism and variable degree of anosmia) is often seen with variable associated malformations, such as unilateral renal agenesis and bimanual synkinesis. In contrast, the phenotype expressivity is highly variable in Kallmann syndrome due to FGFR1 (KAL2) mutations with several degrees of hypogonadism and/or anosmia. Several malformations have been described in patients with FGFR1 mutation (Dode et al., 2003; Albuisson et al., 2005), such as cleft palate or lip, dental agenesis, bimanual synkinesis, corpus callosum agenesis, unilateral hearing loss, fusion of the fourth and fifth metacarpal bones (or syndactylia), unilateral nasal cartilage agenesis and iris coloboma. Other mutations in FGFR1 gene have been recently reported in Kallmann syndrome without any associated malformation (Sato et al., 2004; Albuisson et al., 2005; Pitteloud et al., 2005).

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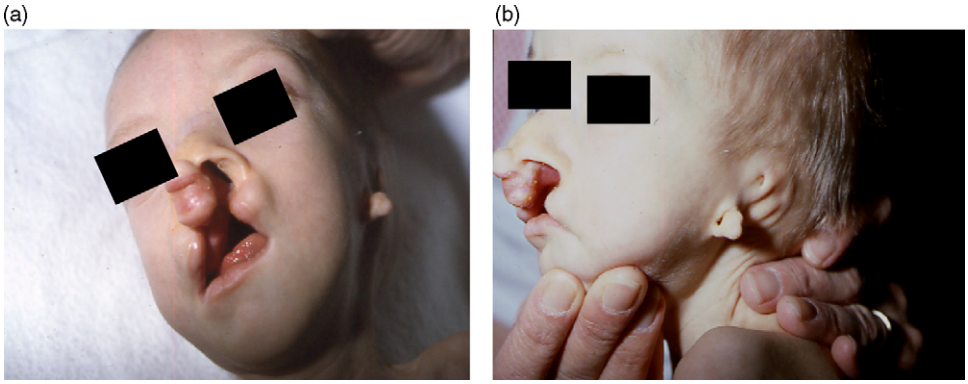

Fig. 1. Orofacial phenotype of Proband I with bilateral cleft palate (Fig. 1a), bilateral external ear agenesis (Fig. 1b) at 6 months.

We report here in three different families, three paediatric cases of Kallmann syndrome due to FGFR1 heterozygous loss of function mutations (two sporadic cases with de novo mutations and one familial case inherited from the father). Interestingly in the first family, the propositus was the only affected member with an extremely severe and unusual phenotype of Kallmann syndrome. In the second family, the mutation was found in the boy born with severe facial malformations and delayed puberty. In the third family, the mutation was found in the propositus and his father with a variable intrafamilial phenotype.

2. Material and methods

2.1. Case reports

Proband I was born at term, eutrophic, with a severe polymalformative syndrome associating a bilateral cleft palate, bilateral external ear agenesis (Fig. 1), right mandibular hypoplasia, thoracic dystrophia, severe micropenis with hypoplasic scrotum and small palpable testis (that became ectopic upon further evolution) associated with bilateral inguinal hernia (Table 1). Respiratory problems and glossoptosis needed tracheotomy until 19 months of age. Parenteral and then enteral nutrition was needed during the first 2 years because of an extremely severe hypotrophy. A solitary median maxillary central incisive was subsequently found. Pubertal induction with daily oral testosterone was started at the age of 14 years 9 months because of a lack of pubertal development. Family history was negative with normal phenotype in the relatives. The biological findings are shown in Table 2. The low postnatal peak (0.48 nmol/l) and the low testosterone levels after hCG and the results of the GnRH test are in favour of hypogonadotropic hypogonadism at the age of 5 months. Other anterior pituitary hormones were normal. The caryotype was normal 46 XY. Hypoplasic olfactory bulbs were found on cerebral MRI. Nevertheless, no anosmia was found when tested at the age of seventeen.

Proband II was born prematurely at 34 week, eutrophic, with a polymalformative syndrome with bilateral cryptorchidism without micropenis, multiple fusions of metacarpal bones on both hands and feet, right ear hypoplasia associated later on with multiple dental agenesis (Table 1). A Bartter syndrome tubulopathy was diagnosed in the neonatal period because of hyponatremic con-

Table 1
Clinical phenotype and cerebral MRI findings in affected patients

	Family I Proband I	Family II Proband II	Family III Proband III
CA first clinical examination	Birth	6 years	3 months
Sex	M	M	M
Micropenis	Yes	No	Yes
Cryptorchidism	Yes	Yes	Yes (unilat)
Puberty: absent/delayed	Absent	Sligtly delayed	*
Anosmia	No	Yes	*
Olfactory bulbs on MRI	Hypoplasia	Agenesis	ND
Associated symptoms			
Cleft palate	Yes	No	Yes
Dental agenesis	Yes	Yes	*
Syndactylia	No	Yes	No
Bimanual synkinesia	No	No	*
Ultrasonographic renal anomaly	No	No	ND
Deafness	Yes	No	*
Other unexpected symptoms	Bilateral external ear agenesis, right mandibular hypoplasia thoracic dystrophia, hyperthelorism multiple naevis, vermis hypoplasia	Unilateral external ear hypoplasia, member length asymmetry, thoracic dystrophia, Bartter syndrome	

ND: undone.
In family II, dental agenesis and slightly delayed puberty were observed in the mother.
In family III, the father had been treated during infancy for bilateral cryptorchidism. Dental agenesis was reported in the father, the paternal grand mother and the paternal great grand father.
One aunt on maternal side had a cleft palate with Down syndrome.
* Unknown (incomplete phenotype as Proband III is only 1 year old at the time of this publication).