Congenital nasal piriform aperture stenosis as a rare manifestation of monosomy 1p36

Jeroen Breckpot^a, Robert Hermans^b, Vincent Vander Poorten^c,
Joris R. Vermeesch^a and Koenraad Devriendt^a

Clinical Dysmorphology 2010, 00:000–000

Keywords: array CGH, congenital nasal piriform aperture stenosis, monosomy 1p36

^aCenter for Human Genetics, ^bDepartment of Radiology and ^cDepartment of Otorhinolaryngology, Head and Neck Surgery, University Hospitals Leuven, Belgium

Correspondence to Professor Koenraad Devriendt, Center for Human Genetics, University Hospitals Leuven, Herestraat 49 bus 602, B-3000 Leuven, Belgium
Tel: +32 16 34 59 03; fax: +32 16 34 60 60;
e-mail: Koenraad.Devriendt@uz.kuleuven.be

Received 26 November 2009 Accepted 22 December 2009

Key features

Congenital nasal piriform aperture stenosis
Ebstein malformation
Bilateral hearing loss
Anal stenosis
Epilepsy
Developmental delay

Introduction

Congenital nasal piriform aperture stenosis (CNPAS) is a rare cause of neonatal upper airway obstruction, first described radiographically by Ey *et al.* (1988) and clinically by Brown *et al.* (1989). The narrowing of the anterior part of the nasal cavity is thought to result from bony overgrowth of the nasal process of the maxilla.

Piriform aperture width is measured using computerized tomography (CT) with contiguous thin axial sections through the midface from the palate to orbital roof. In a term infant, a width of less than 11 mm at the level of the inferior meatus is considered diagnostic of CNPAS (Belden *et al.*, 1999). Moreover, CT is essential to differentiate bony inlet stenosis from choanal atresia, which may present similarly with respiratory distress, cyclical cyanosis, or feeding difficulties. Surgical intervention should be considered if respiratory distress arises or conservative treatment is insufficient or not well tolerated (Shikowitz, 2003; De Mot *et al.*, 2004).

Both isolated CNPAS and syndromic forms have been described. Guilmin-Crépon *et al.* report on additional congenital malformations in 78% of patients with CNPAS. Hypothalamo–pituitary axis abnormalities and solitary median maxillary central incisor (SMMCI) are very common observations (40 and 55%, respectively), next to cardiac, vertebral and other brain anomalies (17.5, 12.5 and 30%) (Guilmin-Crepon *et al.*, 2006). We here describe the first case with CNPAS as a feature of monosomy 1p36.

Clinical report

This girl is the second child of healthy non-consanguineous Caucasian parents. She was already briefly described by De Mot *et al.* (2004) with regard to imaging and treatment of CNPAS. Family history is negative with regard to mental handicap or congenital malformations. Growth retardation was noted on prenatal ultrasound. She was born at term with birth weight 2,400 g (third percentile is 2600 g), length 49 cm (25th percentile) and head circumference 32.8 cm (fifth percentile). At birth, she presented with bilateral clubfeet, limited hip abduction, anal stenosis, a sacral dimple and facial dysmorphic features: short palpebral fissures, hypertelorism, dysplastic low-set ears and a large anterior fontanel. The primary palate seemed to contain an extra bony plate, which was located dorsally of a prominent upper alveolar ridge and comprised a neonatal tooth (Fig. 1a). Physical examination revealed cyanosis because of nasal obstruction.

A CT study obtained at the age of 2 days, showed a narrow piriform aperture (width: 4 mm). The choanae were also slightly stenotic (width: 10 mm) (Fig. 1b). In addition, on CT, a triangular-shaped palatum and abnormal maxillary dentition (with a single medial incisor bud) were seen. The lateral ventricles were enlarged on brain ultrasound. Dextroposition of the aorta and a mild Ebstein malformation of the tricuspid valve with mild ventricular hypertrophy were detected by echocardiography. Radiographs of the spine revealed platyspondylia and small iliac wings. No anomalies were detected by ophthalmologic evaluation and abdominal ultrasound. Metabolic screening and standard karyotyping with G-banding were normal. No hypothalamo–pituitary axis anomalies were detected.

A Mayo canule was placed temporarily and oxymetazoline hydrochloride 0.01% nose drops were administered. At the age of 2 months, the piriform aperture was surgically widened by a sublabial incision. The postoperative CT

Fig. 1

Patient at the age of 2 months: prominent upper alveolar ridge with a palatal neonatal tooth (a). Axial CT image at the level of the inferior meatus showing narrowing of the piriform aperture (between arrowheads; width 4 mm) at the age of 2 days (b).

at 5 months of age, showed the piriform aperture to be 10 mm in width. The palatal neonatal tooth was surgically removed at the age of 14 months. Clubfeet were corrected by serial casting. Nissen fundoplication was performed to treat severe gastroesophageal reflux disease at the age of 1 year.

At the age of 4 months she developed generalized seizures, with bifrontotemporal polyspikes and spike-waves on the electroencephalogram, requiring multiple antiepileptic drugs. Brain imaging by MRI at age of 2 years, revealed mild periventricular leucomalacia and a mildly enlarged ventricular system. A moderate-to-severe bilateral hearing loss was detected by Brainstem Evoked Response Audiometry test (60 decibel normal hearing level right and 70 decibel normal hearing level left at 2000 Hz) at age-7 months.

At the age of 22 months, head circumference (46.3 cm) and length (83 cm) were between the 10th and 25th percentile (46.3 cm), weight (9.4 kg) was below the third percentile. She presented with a round face with deep-set blue eyes, short palpebral fissures, straight eyebrows with medial flare, a prominent nasal root, anteverted nares, simple ears with thickened ear helices and a small mouth with a smooth philtrum. The hands and feet appeared normal. With age the face became more triangular with a pointed chin and full cheeks, suggestive

of 1p36 monosomy. At the age of 7 years, both length and weight were below the third percentile. Her development was severely delayed; she did not acquire speech nor the ability to walk.

A terminal 7.8 Mb deletion of chromosome 1p36 was detected by means of a bacterial artificial chromosome/P1-derived artificial chromosome array with 1 Mb resolution performed as described (Menten *et al.*, 2006), and was confirmed by fluorescence in situ hybridization using subtelomeric probe RP11-465B22. The deletion-flanking clone is RP11-338N10. A normal standard karyotype was found in both parents.

Discussion

Monosomy 1p36 is currently recognized as one of the most common terminal deletion syndromes. Main features of this contiguous gene syndrome include severe developmental delay, hypotonia, seizures, growth impairment, microcephaly, cardiac malformations (Ebstein anomaly) and hearing impairment (Gajecka *et al.*, 2007; Battaglia *et al.*, 2008), and were seen in the present case. The distinct craniofacial characteristics became evident with age, as the face appeared more triangular with a pointed chin, deep-set eyes, straight eyebrows, midface hypoplasia and simple ears with thickened ear helices (Gajecka *et al.*, 2007; Battaglia *et al.*, 2008).

CNPAS was not described in 1p36 thus far. CNPAS is suggested to be a minor form of holoprosencephaly (HPE), based on the common cooccurrence of SMMCI or HPE in about half of the patients with CNPAS and the familial occurrence of midline malformations (Tavin *et al.*, 1994; Guilmin-Crepon *et al.*, 2006). Of interest is the presence of HPE in one member of monozygotic twins and CNPAS in the other (Krol *et al.*, 1998). Holoprosencephaly nor SMMCI are a common feature of monosomy 1p36 (Campeau *et al.*, 2008), with the exception of a fetus with intrauterine growth retardation, lobar HPE and a 46,XY,der(1),t(1;6)(p36.3;q25.2) karyotype owing to a familial cryptic translocation (Cavani *et al.*, 2003). As cerebral malformations are frequently observed in trisomy 6q as well, the genetic etiology of HPE in the latter case remains unclear.

The pathogenesis of CNPAS is still unknown. The variable expressivity of this disorder could be because of polygenic influences. However, parental consanguinity is a common finding, suggesting an underlying autosomal recessive mechanism (Guilmin-Crepon *et al.*, 2006). Hence, the reported deletion might unmask an autosomal recessive locus for CNPAS (or HPE) on 1p36.

This case report shows a chromosomal cause of syndromic CNPAS and supports the value of molecular karyotyping in the diagnostic workflow of this rare disorder.

Acknowledgement

J.B. is funded by a PhD grant obtained from the FWO (Fonds voor Wetenschappelijk Onderzoek) – Flanders.

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