Rare disease

Pai syndrome: first reported case in Qatar and review of literature of previously published cases

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Summary

A full-term male baby born with severe complete median cleft lip and palate and multiple facial cutaneous polyps on the right nostril, left and right ears and angle of the mouth. Eye fundus examination revealed hypopigmented fundi, pigmented rings around both discs and hypopigmented maculae. Neurological, Cardiovascular and abdominal examination was unremarkable, with normal echocardiography and abdominal ultrasound. CT and MRI of the brain revealed hypogenesis of the corpus callosum and midline paracallosal lipomas and calcifications. Chromosomal study showed normal male 46, XY karyotype. This is the first reported case in Qatar and the second case in a patient of Arabian descent.

BACKGROUND

Pai syndrome (PS) was first described in 1987 as a constellation of three developmental anomalies:

(1) Complete median cleft palate (2) cutaneous polyps and (3) midline lipomas of the central nervous system.¹ Since then, 18 cases have been reported by Pai *et al* (1987),¹ Preece *et al* (1988),² Morgan and Evans (1990),³ Rudnikschoneborn and Zerres (1994),⁴ Mishima *et al* (1999),⁵ Al-Mazrou *et al* (2001),⁶ Coban *et al* (2003),⁷ Szeto *et al* (2005),⁸ Guion-Almeida *et al* (2007),⁹ and Castori *et al* (2007),¹⁰ Vaccarella *et al* (2008),¹¹ Chousta *et al* (2008)¹² and Ochoa *et al* (2010).¹³ To our knowledge, this is the first case of PS to be reported in Qatar and the second case in a patient of Arabian descent. The aim of this report is to describe the clinical presentation of a new variant of PS with novel ocular findings of hypopigmented fundi and maculae together with pigmented discs.

CASE PRESENTATION

A full-term Qatari male was born by normal vaginal delivery to a 27-year-old primigravida of a non-consanguineous Qatari couple. There was no family history of any congenital anomalies. His birth weight and head circumference were in the 50th centile. Delivery was uncomplicated with

Apgar score 9 and 10 at 1 and 5 min, respectively. The baby was admitted to the Intermediate Care Unit, Women's Hospital, Hamad Medical Corporation, Qatar due to severe cleft lip and palate. The cleft of the upper lip and palate was detected antenatally at 25.3 weeks of gestational age, confirmed by scanning in the Fetomaternal unit. No other gross anomalies were detected.

On examination, the baby had severe complete median cleft lip and palate with multiple facial cutaneous polyps on the right nostril, left and right ears and angle of the mouth. Fundus examination revealed hypopigmented fundi, pigmented rings around both discs and hypopigmented maculae. Neurological, cardiovascular, abdominal and genitourinary examination was normal (figures 1 and 2).

INVESTIGATIONS

- ▶ Normal male karyotyping (46 XY)
- ▶ Normal Microarray and DNA banking done
- ▶ Normal Echocardiography
- ▶ Normal abdominal ultrasound

Ultrasound of the brain showed mineralising vasculopathy suggestive of TORCH infection excluded by negative laboratory investigations.

Figure 1 Clinical view of the patient at third month of age showing facial cutaneous polyps on the left and right ears.

Figure 2 Clinical view of the patient showing severe complete median cleft lip and palate with facial cutaneous polyps on the right nostril and angle of the mouth.

CT of the head showed midline calcification with abnormal fat density in the frontal region, right lateral ventricle is distended; features are suggestive of midline brain anomaly (figures 3 and 4).

MRI of the head showed hypogenesis of corpus callosum, midline paracallosal calcifications and lipomas (figures 5 and 6).

DIFFERENTIAL DIAGNOSIS

Midline cleft of the upper lip is as rare as an isolated finding, and is more commonly found in association with other anomalies or as part of a recognised syndrome. A search conducted in the London Dysmorphology Database for median cleft of the upper lip; showed 40 possible syndromes such as holoprosencephaly, oral-facial-digital syndromes I and II, Ellis-van Creveld and Clefting-premaxilla agenesis among several other clefting syndromes.

TREATMENT

Skin polyp related to the right nostril was resected surgically and sent for histopathology that revealed a fibroepithelial polyp.

The cardiology team assessed the baby and they reported normal cardiovascular system.

The genetic team assessed the baby and suggested PS as the main differential. Maxillofacial surgery team assessed the baby for future surgical intervention.

An occupational therapist assessed the baby and reported no difficulties in feeding with Hypermann nipple.

OUTCOME AND FOLLOW-UP

No problems encountered with feeding. Motor and mental developments were normal for his age. The maxillofacial surgery, ophthalmology and genetic teams are following the case.

DISCUSSION

In 1987, GS Pai¹ described an unusual combination of three rare congenital anomalies including complete median cleft lip, cutaneous polyps, calcification and lipomas of the corpus callosum. The baby's mother shows antimongoloid slant to her palpebral fissures and CT scan evidence of asymptomatic hydrocephalus.¹ Since then, many variants of the syndrome were described. In 1988, Preece *et al*² presented a 1-month-old infant with anomalies similar to Pai's description, in addition to dysgenesis of the anterior segment of the left eye. In 1994, Rudnik-Schoneborn and Zeres⁴ described a case with skin tag on the forehead, downward slanting palpebral fissure, bifid uvula and high plate associated with main elements of PS. Other variants included tongue like alopecia of the anterior frontal hairline and bifid nose as reported by Coban *et al*⁷ and Guion-Almeida *et al*.⁹

Up to date, there has been only one reported case of ocular abnormality as an additional finding of the expression of PS. Mishima *et al*⁵ described the presence of a conjunctive lipoma in the right eye, which was on the same side as the nasal polypoid skin mass. However, in our patient, hypopigmentation of the fundi and maculae was

Figure 3 CT brain of the patient showing (A) midline calcification and (B) fat density in the frontal region.

Figure 4 CT scan showing severe complete median cleft lip and palate.

seen in both eyes. To our knowledge, this variant of ocular anomalies has not been reported previously.

Currently, only two cases regarding prenatal diagnosis of PS have been reported.^{14 15} The features reported included cleft lip and palate, cutaneous polyps and lipoma of the corpus callosum. Although our patient did exhibit features of median cleft lip and palate on fetal ultrasound

Figure 5 Sagittal Section in Brain MRI showing hypogenesis of corpus callosum.

Figure 6 MRI of the brain showing midline paracallosal calcifications.

at 25 weeks plus 3 days of gestational age, the other anomalies were not detected until after birth.

The underlying pathophysiology remains unknown; however, several embryological theories have been proposed to explain the pathogenesis of these fibroepithelial polyps. Clusters of epithelial cells might have become sequestered during the fusion of the frontonasal processes.¹⁶ Another explanation was that the failure to obliterate an early embryological communication between an outpouching of dura and nasal tissue leads to an ectodermal residue.¹⁷ Consequently, the midline cleft may occur as a secondary event to the presence of nasal dermoid.¹⁴ On the other hand, Stark *et al*¹⁶ suggest that the midline cleft is the primary event, which occurs due to failure of mesodermal migration or inadequate consolidation of the median nasal process. As a result, the fibroepithelial polyps develop due to excessive mesodermal tissue in the oral cavity.¹⁸

The aetiology of PS continues to be debatable. Autosomal dominant inheritance was first suggested by Rudnik-Schoneborne and Zerres⁴ who described a patient with a median cleft lip, facial polyps and lipoma of the corpus callosum, whose father had similar facial dysmorphism and coloboma of the right iris. However, coloboma has never been previously reported and may not be part of the syndrome.⁵ It was concluded that a common genetic defect in mesodermal differentiation might be the underlying aetiology. This was supported by a report about a family in which five generations have been affected by these midline anomalies with variable expression.¹⁰ Knowing that the incidence of PS is much higher in men than in women, X linked recessive inheritance cannot be excluded.⁵ Furthermore, the karyotype of the proband of one patient with PS revealed a reciprocal translocation, 46, X, t(X; 16) (q28; q11.2), which was proposed as a candidate region for the gene responsible for the

anomalies.⁵ However, it is argued that this proband may not have had PS because she did not have lipomas in the corpus callosum, which is one of the main characteristics of Pai's.⁸ Our patient's chromosomal studies showed normal XY karyotype, and normal microarray. This supports the theory that the underlying aetiology can be multifactorial, as suggested by many case reports, which also found normal karyotype.^{6-9 16-19} Also many authors suggested an underlying multi-factorial aetiology; supported by the discordance between monozygous twins in one previously reported case in Saudi Arabia.⁶ However, one of the defining features as described by Pai, that is, median cleft lip was not seen in that patient. Therefore, it can be argued that the patient may have not had PS.

Learning points

- ▶ Pai syndrome (PS) is a rare combination of developmental anomalies, mainly median cleft lip, cutaneous facial polyps and midline lipomas in the central nervous system.
- ▶ Many variations of the expression of PS exist including bifid nose, ocular anomalies and tongue like alopecia of the anterior frontal hairline.
- ▶ Pathogenesis involves a defect in mesodermal differentiation and migration.
- ▶ Inheritance is still debatable. Some studies suggest autosomal-dominant inheritance, while others suggest X linked recessive or multifactorial aetiology.

Competing interests None.

Patient consent Obtained.

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