Pai Syndrome:
First reported case in Qatar and review of literature

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Background:

Pai Syndrome was first described in 1987 as a constellation of three developmental anomalies: i) complete median cleft palate, ii) cutaneous polyps and iii) midline lipomas of the central nervous system. (1) Since then, eighteen cases have been reported by Pai et al, (1) Preece et al, (2) Morgan and Evans, (3) Rudnikschoneborn and Zerres, (4) Mishima et al, (5) Al Mazrou et al, (6) Coban et al, (7) Szeto et al, (8) Guion-Almeida et al, (9) and Castori et al, (10) Vaccarella et al, (11) Chousta et al, (12) and Ochoa et al. (13) To our knowledge, this is the first case of Pai Syndrome to be reported in Qatar and the second case in a patient of Arabian descent.

The aim of this paper is to describe the clinical presentation of a variant of Pai Syndrome including a novel ocular finding.

Case Presentation:

A full term Qatari male baby, was born by normal vaginal delivery to a 27-year-old primigravida mother of a nonconsanguineous Qatari couple on 25 November 2010. His birth weight was 2750 grams, and head circumference was 32 cm.

Delivery was uncomplicated and no resuscitation was needed (Apgar score was 9 and 10 at 1 and 5 minutes respectively). The baby was admitted to the Intermediate Care Unit due to severe cleft lip and palate. Antenatal history was significant for cleft of the upper lip and palate seen on ultrasound at 25 weeks plus 3 days of gestational age, and later confirmed in the Fetomaternal Unit (FMU). No other gross anomalies were detected and there was no family history of any congenital anomalies.

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.

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Figure 1A: Clinical view of the patient at third month of age showing facial cutaneous polyps on the right ear.

Figure 1B: Clinical view of the patient at third month of age showing facial cutaneous polyps on the left ear.
Figure 2A: Clinical view of the patient at third month of age showing severe complete median cleft lip with facial cutaneous polyp on the right angle of the mouth.

Figure 2B: Clinical view of the patient at third month of age showing severe complete median cleft lip and palate with facial cutaneous polyp on the right angle of the mouth.

Figure 3A: CT brain of the patient showing midline calcification.

Figure 3B: CT brain showing fat density in the frontal region.

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

Figure 5: Sagittal section in brain MRI showing hypogenesis of corpus callosum.
Investigation:

- **Routine laboratory investigations**: Complete blood count and serum electrolytes were normal.
- **Chromosomal study**: Normal male karyotyping (46 XY).
- **Microarray**: Normal.
- **DNA banking**: Done.
- **TORCH screening**: Negative.
- **Echocardiography**: Normal.
- **Abdominal ultrasound**: Normal.
- **CT of the head**: Midline calcification and query fat density in the frontal region, right lateral ventricle is distended; features are suggestive of midline brain anomaly for MRI.
- **MRI of the head**: Hypogenesis of corpus callosum. Midline paracallosal calcifications and lipomas; for follow up after 6 months.
- **Ultrasound brain**: Mineralizing vasculopathy suggestive of TORCH infection excluded by laboratory investigations.

Differential Diagnosis:

Midline cleft of the upper lip is rare as an isolated finding, and is more commonly found in association with other anomalies or as part of a recognized 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, Clefting-premaxilla agenesis and others.

Treatment:

The baby was assessed by the following subspecialties:

1. The Otolaryngology Team removed the skin polyp related to the right nostril and sent for histopathology. The histopathology result revealed it to be a fibroepithelial polyp.
2. Cardiology team assessed the baby and they reported normal cardiovascular system.
3. Genetic team assessed the baby and suggested Pai Syndrome as the main differential.
4. The maxillofacial surgery team assessed the baby and planned to give an appointment to their outpatient clinic to follow-up.
5. Occupational therapist assessed the baby during his stay in Neonatal Intensive Care Unit (NICU) and reported no difficulties in feeding with Hypermann nipple.

Outcome and follow-up:

The first appointment at 3 months of age in our outpatient clinic: No problems encountered with feeding, motor and mental development was normal for his age. Follow up with maxillofacial surgery, ophthalmology and genetic team.

Discussion:

In 1987, G.S. Pai(1) described an unusual combination of three rare congenital anomalies including complete median cleft lip, cutaneous polyps, and calcification and lipomas of the corpus callosum. The newborn's mother was found to have antimongoloid slant to her palperbral fissures and CT evidence of asymptomatic hydrocephaly (1). Since then, many variants of the syndrome have been described. In 1988, Preece et al. 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.(2)

In 1994, Rudnik-Schoneborn and Zerres described a case with skin tag on the forehead, downward slanting palperbral fissure, bifid vulvula, and high plate with main elements of Pai Syndrome.(4) Other variants included tongue-like alopecia of the anterior frontal hairline and bifid nose as reported by Coban et al. and Guion-Almeida et al.(7,9) Up to date, there has been only one reported case of ocular abnormality as a variation of the expression of Pai syndrome. Mishima et al. described the presence of a conjunctive lipoma in the right eye, which was on the same side as the nasal polypoid skin mass.(5) However, in our patient, hypopigmentation of the fundi and maculae was seen in both eyes. To our knowledge, this variant of ocular anomalies has not been reported previously.

Currently, only two cases regarding antenatal diagnosis of Pai Syndrome 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 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 lead 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. 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.(16) As a result, the fibroepithelial polyps develop due to excessive mesodermal tissue in the oral cavity.(18)

The etiology of Pai Syndrome continues to be debatable. Autosomal dominant inheritance was first suggested by Rudnik-Schoneborn and Zerres 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. 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. However, it was argued that the incidence of Pai Syndrome is much higher in males than in females, X-linked recessive inheritance cannot be excluded. Furthermore, the karyotype of the proband 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; however, it's excluded. Furthermore, the karotype of the proband which is one of the main characteristics of Pai's. How-ever, our patient's chromosomal studies showed normal male, XY karyotype, and normal microarray. This supports the theory that the underlying aetiology is multifactorial, as suggested by many case reports, which also found normal karotype. Furthermore, a reported case in Saudi Arabia showed that only one of identical twins demonstrated the features of facial polym and lipoma in the corpus callosum, suggesting a multifactorial or intrauterine aetiology. However, one of the defining features as described by Pai i.e. median cleft lip was not seen in that patient. Therefore, it can be argued that the patient may have not had Pai syndrome.

Learning points:
- Pai Syndrome is a rare combination of development-al anomalies, mainly median cleft lip, cutaneous facial polyps and midline lipomas in the central nervous system.
- Many variations of the expression of Pai Syndrome exist. These include 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.

References: