Case reports

Transmission of Proteus syndrome from father to son?

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Abstract

We present a male infant with cranial hemihypertrophy, a lymphangioma, a lipoma, and epidermal naevi. A diagnosis of Proteus syndrome was made. His father had had a large lymphangioma resected from the right side of the face as a child. We propose that Proteus syndrome has been transmitted from father to son.

The features of Proteus syndrome are partial gigantism of the fingers and toes, hemihypertrophy, macrocephaly, plantar hyperplasia, haemangiomas, lipomas, lymphangiomas, and epidermal naevi. The syndrome was named by Wiedemann et al. in 1983 after the Greek god, Proteus, who was able to change his shape at will to avoid capture. The phenotype evolves over time. Joseph Merrick, the Elephant Man, now accepted to be the first documented case of Proteus syndrome, had no obvious abnormalities at birth.2 The evolution of the facial dysmorphism can be seen in the figures of case 2 described by Cohen.2 In Cohen's three carefully documented cases the pathognomonic features of digital gigantism and plantar hyperplasia were not present before 1 year of age. The naevi and plantar hyperplasia usually become apparent after the neonatal period. The sex ratio is equal. The parents of all reported cases have been normal and there have been no affected sibs. We have found only one published report of an affected subject having offspring.3 The child in this case was normal.

We describe a child with severe Proteus syndrome whose father had a lymphangioma of the right side of the face.

Case report

The proband was the first child of unrelated parents. The mother had four children by a previous consort and the father had one daughter by a previous consort. The father was 30 and the mother 38 when the proband was born. Routine ultrasound scans at 11 and 18 weeks' gestation had not detected any abnormalities. A further ultrasound scan was performed at 38 weeks' gestation because of suspected polyhydramnios. It confirmed polyhydramnios and also indicated a large, loculated, cystic swelling arising from the thoracic region on the right posteriorly and a dilated right kidney. A placental biopsy showed a normal karyotype. The mother went into spontaneous labour at term resulting in breech delivery of a male weighing 3400 g. The Apgar score was 4 at one minute and 7 at five minutes.

At birth the baby had obvious enlargement of the left side of the face and cranium, a large fluctuant mass over the right lumbar area, and wide big toe clefts (figs 1 and 2). The OFC was 40·0 cm (above the 90th centile). All structures on the left side of the face were larger, including the palpebral fissure, ear, and nostril. A difference of facial skin texture was evident with midline demarcation. Similar asymmetry was apparent in the alveolar ridge and tongue (fig 3). The mandibular central incisor on the left erupted at 10 weeks and the maxillary central incisor on the left at 26 weeks, both much earlier than their counterparts on the right.

The asymmetry of the face has increased with time (fig 4). At 7 months of age the head circumference was 51·7 cm (still above the 90th centile). The right ear was 4·2 cm long and the left 5·5 cm. The hair on the right side of the head was dark and curly

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The proband in the neonatal period. The left cheek was enlarged and there was a large fluctuant swelling over the right posterior thorax.

but the hair on the left was pale and fine. The right eyebrow had a clearly defined shape and was dark, but the left eyebrow was poorly delineated with fine hair extending up the forehead. Ophthalmological examination showed a choroidal coloboma on the left.

His leg length of 30 cm and total length of 70 cm at 7 months were on the 50th centile. His weight of 9.4 kg was on the 75th centile.

A deep transverse plantar crease originating from a wide big toe cleft.

Hypertrophy of the alveolar ridge and tongue with midline demarcation and premature tooth eruption on the hypertrophied side.

The proband at 7 months showing enlargement of the soft tissues and sparse eyebrow and scalp hair on the left.
The large swelling over the right lumbar region was partially resected and was shown to be a lymphangioma. There was a separate, smaller, firm mass, thought clinically to be a lipoma, over the lateral rib cage on the right. On abdominal examination the left lobe of the liver was palpable. The genitalia were normal.

The feet were noted to be abnormal in the neonatal period with widely spaced toes and a deep crease between the hallux and second toe (fig 2). There was a dimple on the lateral border of both feet which was more pronounced when he flexed his toes (fig 6). The fingers and toes were symmetrical with no gigantism at 7 months of age.

The skin lesions, not apparent at birth, were first noted at 4 months. At 7 months there was a raised velvety naevus on the left side anterior to the left ear extending down the neck and under the chin. A separate swirl from the lesion narrowed to a thin pigmented line terminating at the angle of the mouth (fig 5). There was a pigmented macule 1 cm in diameter lateral to the left eye, a 1.5 x 1 cm café au lait patch on the lateral border of the right foot (fig 6), and a smaller pigmented macule on the medial aspect of the right thigh. The right side of the thorax and abdomen had irregular areas of slightly hyperpigmented skin juxtaposed with hypopigmented areas.

Cranial CT scan showed left hemimegalencephaly displacing the falx to the right of the midline (fig 7). There was ipsilateral enlargement of the lateral ventricle. The left cerebral hemisphere was grossly abnormal with enlarged hyperdense frontal and occipital lobes and relative loss of volume, probably owing to schizencephaly, in the parietal lobe. The right cerebral hemisphere had numerous small areas of low density and smaller focal areas of high density.

He developed seizures on day 3. Partial control has been achieved with a combination of carbamazepine, vigabatrin, and clobazam. EEGs have repeatedly shown a focus in the left centrotemporal region and hemispherectomy is being considered.

At 7 months he moves all four limbs but reaches for objects with his left hand. Tone is slightly increased on the right. He reacts to noise and follows objects through a short distance.

The father of the index case was noted to have facial asymmetry (fig 8). He had had a similar facial

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Figure 5. Epidermal naevus on the left side of the face and neck.

Figure 6. Deep dimple on the lateral border of the right foot exaggerated by toe flexion. A café au lait patch is visible on the dorsum of the foot.
enlargement as an infant and had undergone numerous operative procedures through childhood to reduce this swelling (fig 9). Histology of the resected tissue was of a lymphangioma. The skin overlying the lymphangioma appeared normal. His hands and feet were normal, he had no pigmented naevi or hamartomata, and did not have hemimegalencephaly on CT scan.

**Discussion**

The differential diagnosis considered in this child included Klippel-Trenaunay syndrome, Bannayan-Zonana syndrome, Maffucci syndrome, epidermal naevus syndrome, encephalocraniocutaneous lipomatosis, and Proteus syndrome. The overlapping manifestations of these disorders, which complicate diagnosis, have been the subject of a recent review.4 Hotamisligil4 suggested a diagnostic rating scale for Proteus syndrome with different features being awarded a number of points. The highest possible score for a patient with all the features was 19.5. He felt that 13 points were required to diagnose Proteus syndrome with 100% certainty. The child presented in this paper scores 15.5 on Hotamisligil’s scale.

The asymmetry in our case and the skin lesions exclude the diagnosis of Bannayan-Zonana syndrome. Maffucci syndrome is characterised by enchondromatosis with classical radiographic changes which were not present in our case. The presence of a lymphangioma and a lipoma in our case excludes Klippel-Trenaunay syndrome and epidermal naevus syndrome. Encephalocraniocutaneous lipomatosis (ECCL) is a syndrome with unilateral cutaneous and ophthalmological lesions with...
ipsilateral cerebral atrophy, seizures, and mental deficiency. Superficial lipomas and connective tissue naevi have been observed in this syndrome and Wiedemann and Burgio have suggested that ECCL may be part of the Proteus spectrum. Hemimegalencephaly has not been reported in ECCL.

The association of hemihypertrophy, a lymphangioma, a lipoma, and pigmented skin lesions in our patient makes Proteus syndrome the most likely diagnosis. Widely splayed, abnormal toes and optic coloboma have also been reported in Proteus syndrome. Our case does not yet have the characteristic enlargement of digits or plantar hyperplasia. Proteus syndrome is an evolving phenotype and not all features are apparent in the neonatal period. It may also be argued that it is a contradiction in terms to consider involvement of a particular part of the body as prerequisite for the diagnosis of Proteus syndrome.

A child has been reported who was mosaic for a duplication of 1q11–q25 and had clinical features consistent with a diagnosis of Proteus syndrome. She had right hemihypertrophy, macrocephaly, multiple cavernous haemangiomas, scoliosis, and a coloboma of the optic nerve. No cytogenetic abnormality was seen in lymphocytes or fibroblasts in our patient.

The parents of all previous cases of Proteus syndrome have been normal and there have been no affected sibs. The lack of any affected sibs, now that many cases have been described, is against autosomal recessive inheritance. The reports are compatible with all cases representing somatic or germ line new mutations.

The most intriguing feature of our case is the presence of facial asymmetry in the father. He does not fulfil the diagnostic criteria of Proteus syndrome but the occurrence of an extensive facial lymphangioma in the parent of a child with Proteus syndrome is unlikely to be a coincidental finding.

A plausible explanation for this observation is that Proteus syndrome is an autosomal dominant disorder with variable expression. This would be analogous to the variable expression seen in neurofibromatosis which can cause hemihypertrophy even when the mutant gene is inherited in the germline. An alternative explanation is that a mutant gene present in the father has undergone a further mutation leading to more severe disease in the son. A third explanation is that the father is a mosaic with the mutation causing overgrowth in a proportion of his cells. Transmission of this mutation in the germline could account for the greater severity in the proband. This interpretation is at odds with the hypothesis put forward by Happle that Proteus syndrome is a manifestation of mosaicism for a mutation that would be lethal in the non-mosaic state. However, precedents for this have been described and characterised at a molecular level. Subjects with mild osteogenesis imperfecta have had severely affected offspring and have been shown to be mosaic for mutations causing collagen abnormalities.