Proteus syndrome*

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Abstract: Proteus syndrome is a rare syndrome characterized by disproportionate overgrowth of limbs, multiple hamartomas, and vascular malformations. The cerebriform connective tissue nevi, also called cerebriform plantar hyperplasia, are present in most patients, and is the main characteristic of the syndrome. If present, even alone, they can be considered as a pathognomonic sign. This article reports a classic case of Proteus syndrome in a 2-year-old male patient who began to show a discrete asymmetry of the right hemibody in relation to the left one after birth, which increased over the months. He also showed cerebriform plantar hyperplasia and Port-wine stains, among other alterations.
Keywords: Congenital abnormalities; Genetics; Hyperplasia; Mosaicism; Neoplasms; Proteus; Syndrome

INTRODUCTION

Proteus syndrome is a rare, congenital hamartomatous syndrome that causes asymmetric and disproportionate overgrowth of limbs, connective tissue nevi, epidermal nevi, dysregulated adipose tissue, and vascular malformations.[1,2]

It was described by Cohen and Hayden as a distinct clinical entity in 1979, but it was only in 1983 that Wiedeman would give its name.[3-6] The earliest case of Proteus syndrome was reported by Joseph Merrick and described by Treves, in the 19th century.[3,5,7]

It might be associated with mosaicism with a somatic activating mutation in the AKT1 gene, located at chromosome 14q32.3.[8] Several allelic mutations occur at the *locus* of the gene responsible for the Proteus syndrome, which triggers the somatic tissue overgrowth.[6]

This syndrome is poorly described, and has an estimated prevalence ranging from 1:1,000,000-1:10,000,000 population. Less than 100 cases have been reported in the literature.[9] Its rare occurrence justifies this report.

CASE REPORT

A 2-year-old brown male patient showed discrete asymmetry of the right hemibody in relation to the left one at birth, which increased over the months. Physical examination revealed macromelia of the upper and lower right limbs, syndactyly involving the 2nd and 3rd toes, and wide space between the 1st and2nd toes, bilaterally (Figures 1-3).

He also showed skin folds mimicking the cerebral whorls in the plantar surfaces, exhibiting an increase of adipose tissue in irregular manner, especially in the right side of the body. He also had slightly erythematous-violaceous macules (Port-wine stains) scattered throughout the body, which, according to his mother, were red and are disappearing (Figures 4 and 5). No facial phenotypic alteration was detected.

Karyotype test, abdomen ultrasound, and Doppler ultrasound of the upper and lower limbs and nuclear magnetic resonance of the skull showed no alterations. Doppler echocardiography revealed patent foramen ovale and atrial septal defect, without hemodynamic repercussion.

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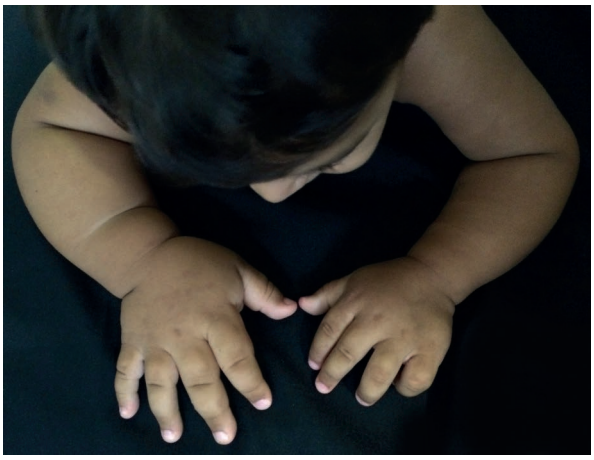

Figure 1: Macromielia of the upper left limb

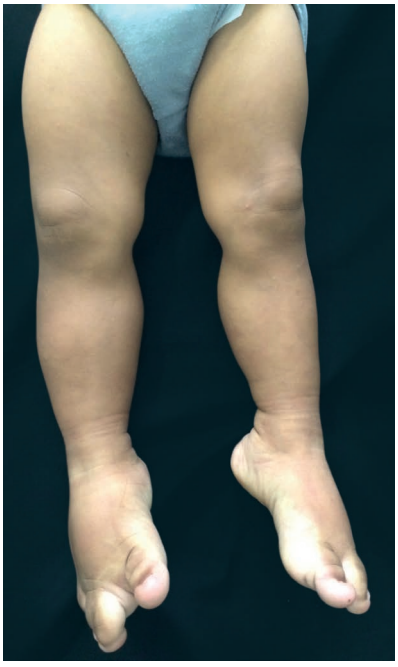

Figure 2: Macromielia of the lower left limb

The Proteus syndrome diagnosis was established by the clinical findings described above, more specifically, plantar cerebriform hyperplasia associated with the patterns of the lesion: mosaic distribution, progressive course, and sporadic occurrence.[10]

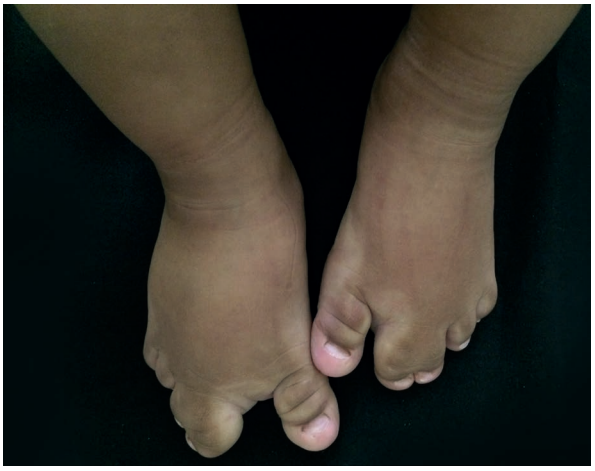

Figure 3: Second and third toes syndactyly of both feet

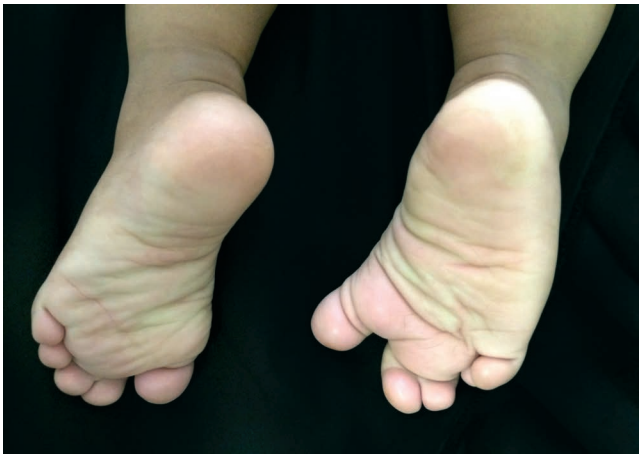

Figure 4: Plantar cerebriform hyperplasia

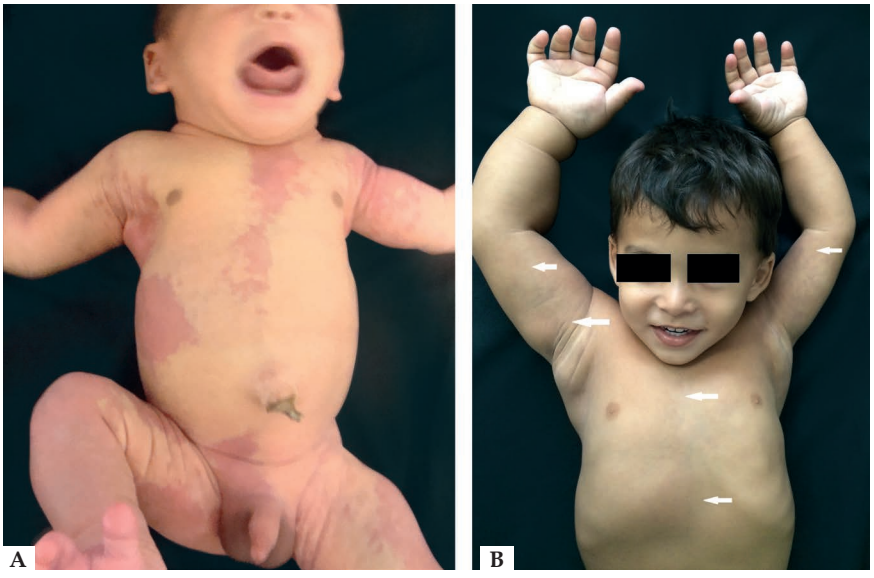

Figure 5:
(A) Port-wine stains at birth **(B)** Clearing of stains at 2 years of age

Chart 1: Diagnostic criteria of Proteus syndrome
General criteria (diagnosis includes all listed)
Mosaic distribution of lesions
Sporadic occurrence
Progressive course
Specific criteria (1 in category A, 2 in category B, or 3 in category C)
• Category A:
o Cerebriform connective tissue nevi (skin lesions characterized by deep grooves and whorls, similar to the brain surface)
• Category B:
o Linear epidermal nevus
o Asymmetry, disproportionate growth of one or more
Limbs: arms, legs, hands, feet, digits
Skull (hyperostosis)
External auditory meatus (hyperostosis)
Vertebrae (megaespondylodysplasia)
Viscera: spleen or thymus
o Specific tumors before 20 years of age:
Ovarian cystadenoma
Monomorphic adenoma of the parotid glands
• Category C:
o Adipose tissue dysregulation:
Lipomas
lack of adipose tissue in the area
o Vascular malformations:
Capillary Malformation
Venous malformation
Lymphatic malformation
o Pulmonary cysts
o Facial phenotype (shown in patients with Proteus syndrome who have intellectual disability and, in some cases, cerebral convulsions and/or malformations):
Dolichocephaly
Elongated face
Oblique palpebral fissures and/or ptosis
Depressed nasal bridge
Narrow or wide nostrils
Mouth open at rest

Source: Thomason *et al.*, 2012.[10]

DISCUSSION

Proteus syndrome is mostly characterized by a postnatal asymmetric overgrowth that might affect many tissues, and it is barely noticeable at birth.[5,6] In most cases, it first appears at 6-18 months of age in an irregular, progressive manner, as shown in the patient described here, who, as the months went by, showed an increase in the discrepancy between the limbs. The lesion locations and intensity vary significantly among patients, and are sometimes limited, which makes the diagnosis difficult.[3,5,6]

As it is a poorly delineated syndrome, it is confused with other syndromes that also show asymmetric overgrowth. he most prevalent signs are unspecific, such, such as epidermal nevus or macrodactyly, which usually represent isolated malformations.

Vascular malformations are common - with cutaneous capillaries being the most prevalent, such as Port-wine stains- followed by venous malformations and arterial malformations, which are less common. They might disappear over time, as occurred to our patient.[9]

Dysregulation of adipose tissue is a common characteristic of this syndrome, and can be seen throughout the patient's body. One intriguing fact is that it might include both overgrowth and fatty atrophy.[9]

Cerebriform nevi of connective tissue, also called cerebriform hyperplasia, is present in most patients. They usually appear

in childhood and last through adolescence. They are most commonly found in the plantar and palmar regions and ears. They show a firm consistency with a brain-groove pattern. These grooves may be deep, making it difficult to be cleaned.[9] This cutaneous signal is the main characteristic of Proteus syndrome. If present, even isolated, it might be considered pathognomonic, such was the diagnosis of our patient, since the other alterations shown might also be seen in other syndromes.[5,6]

Neoplasms of various organs may be associated. The benign ones include lipomas, ovarian cystadenomas, and monomorphic parotid adenomas. The malignant neoplasm includes testicular papillary adenocarcinoma, mesothelioma of the tunica vaginalis, and peritoneal mesothelioma.[4] Therefore, the patient must be monitored.[2]

Other findings include growth of other tissues and organs, especially spleen, liver, thymus, intestine, and lungs, in addition to facial dysmorphia, which was not shown in the present case.[9]

Diagnosis is established for individuals who show all general characteristics (mosaic distribution of lesions, sporadic occurrence, and progressive course), as well as one characteristic of category A or two of category B or three of category C according to the specific characteristics described in chart 1.

Differential diagnosis should be made with other congenital disorders, such as neurofibromatosis, Klippel-Trenaunay-Weber syndrome, Bannayan syndrome, Maffucci syndrome, and hemihyperplasia/lipomatosis syndrome.[1,4,6]

Treatment includes clinical and psychological support due to its deforming nature. Skeletal overgrowth may result in biomechanical dysfunction and functional limitation, requiring orthopedic corrections. However, recurrence of deformities is common.[3,4] Follow-up should be referred to a team of vascular surgery, plastic surgery, and pneumology.[2]

Prognosis is based on the overgrowth location and degree, and based on the presence or absence of significant complications, such as bullous lung disease and pulmonary embolism.[8] Life expectancy ranges from nine months to 29 years, according to the severity of the anomalies.[4]

The main cause of premature death is pulmonary thromboembolism and respiratory failure, which are predisposed by vascular malformations, surgical convalescence, and, in extreme cases, by restricted mobility due to deformities.[4]

Through this case report and a brief review of the literature, we emphasize the importance of early diagnosis of Proteus syndrome and the need for multidisciplinary follow-up in view of complications and early mortality rate. Treatment should always be associated with psychological support, since deformities carry great social stigma. ❑

REFERENCES

1. Sene LS, Sales PO, Chojniak R. Síndrome de Proteus: relato de caso. Rev Assoc Med Bras. 2013;59:318-20.
2. Biesecker L. The challenges of Proteus syndrome: diagnosis and management. Eur J Hum Genet. 2006;14:1151-7.
3. Almeida HL Jr, Fiss RC, Happle R. Macrodactyly with skin hypertrophy: a minimal form of the Proteus syndrome. An Bras Dermatol. 2011;86:557-9.
4. Ncbi.nlm.nih.gov [Internet]. Biesecker LG, Sapp JC. Proteus Syndrome. In: Pagon RA, Adam MP, Ardinger HH, Wallace SE, Amemiya A, Bean LJH, et al., editors. GeneReviews. Seattle (WA): University of Washington, Seattle; 1993-2014. 2012 Aug 09. [cited 2014 May 2]. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22876373.
5. Sethi SK, Yadav D, Garg P, Chawla J, Goyal D. A child with mental retardation and asymmetrical hypertrophy of limbs. Eur J Pediatr. 2011;170:813-4.
6. Schepis C, Greco D, Siragusa M, Romano C. Cerebriform plantar hyperplasia: the major cutaneous feature of Proteus syndrome. Int J Dermatol. 2008;47:374-6.
7. Brosius S. Neurognostics question metamorphosis of a man: diagnosing Joseph Merrick. J Hist Neurosci. 2010;19:171-2; 207-8
8. De Souza RA. Hotspots. Origins of the elephant man: mosaic somatic mutations cause Proteus syndrome. Clin Genet. 2012;81:123-4.
9. Omim.org [Internet]. Proteus syndrome. [cited 2014 May 2]. Available from: http://www.omim.org/entry/176920?search+proteus&highlight+proteus.
10. Thomason JL, Abramowsky CR, Rickets RR, Culbertson JH, Clifton MS, Shehata BM. Proteus syndrome: three case reports with a review of the literature. Fetal Pediatr Pathol. 2012;31:145-53.

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