

# Clinical and psychosocial challenges in the treatment of a patient with Proteus syndrome

## *Desafios clínicos e psicossociais no tratamento de um paciente com síndrome de Proteus*

Matheus Bertanha<sup>1</sup>, Regina Moura<sup>1</sup>, Marcone Lima Sobreira<sup>1</sup>, Lied Martins Santiago Pereira<sup>2</sup>, Rodrigo Gibin Jaldin<sup>1</sup>, Manuella Pacífico de Freitas Segredo<sup>2</sup>, Hamilton Almeida Rollo<sup>1</sup>, Winston Bonetti Yoshida<sup>1</sup>

### Abstract

Proteus syndrome is a rare combination of malformations that can affect several tissues and organs. It is characterized by bilateral macrodactyly, cranial hypertrophy, bone anomalies, scoliosis, soft-tissue hamartomas, verrucous pigmented nevus, visceral abnormalities and other forms of hypertrophy. Just over 200 cases have been reported worldwide. This article reports on the clinical course of a pediatric patient with this syndrome. The child had severe malnutrition associated with extreme gigantism of the lower limbs and also psychosocial problems related to social exclusion. As the disease progressed it exacerbated and evolved into a wasting syndrome. After several years, the parents agreed to amputation of the hypertrophic lower limbs. One year after the amputations the child had been rehabilitated and had adapted to prostheses, with nutritional improvement and notable psychological recovery and social reintegration, which represented a significant improvement in his quality of life.

**Keywords:** amputation; congenital abnormalities; musculoskeletal abnormalities.

### Resumo

A Síndrome de Proteus é uma rara associação de malformações que podem afetar vários tecidos e órgãos. É caracterizada por macrodactilia bilateral, hipertrofia craniana, anomalias ósseas, escoliose, hamartomas de tecidos moles, nevo verrucoso pigmentar, anormalidades viscerais e outras hipertrofias. Há pouco mais de 200 casos notificados em todo o mundo. O presente artigo relata a evolução clínica de um paciente pediátrico com essa síndrome. A criança apresentou desnutrição grave associada ao extremo gigantismo de membros inferiores. Além disso, apresentou repercussões psicossociais relacionadas à exclusão social. A doença tornou-se mais grave e progrediu como síndrome consumptiva. Finalmente, os pais concordaram com a amputação dos membros inferiores hipertróficos. Um ano após as amputações, a criança estava totalmente reabilitada, protetizada dos membros amputados, com melhora nutricional, além de apresentar notória recuperação psicológica e reinserção social, o que representou melhora significativa da qualidade de vida para o paciente.

**Palavras-chave:** amputação; anormalidades congênitas; anormalidades musculoesqueléticas.

<sup>1</sup> Universidade Estadual Paulista – UNESP, Faculdade de Medicina de Botucatu, Department of Surgery and Orthopedics, Botucatu, SP, Brazil.

<sup>2</sup> Universidade Estadual Paulista – UNESP, Faculdade de Medicina de Botucatu, Department of Pediatrics, Botucatu, SP, Brazil.

Financial support: None.

Conflicts of interest: No conflicts of interest declared concerning the publication of this article.

Submitted: August 04, 2015. Accepted: September 14, 2015.

The study was carried out at Hospital das Clínicas da Faculdade de Medicina de Botucatu, Universidade Estadual Paulista (UNESP), Botucatu, SP, Brazil.

## INTRODUCTION

Proteus syndrome was first described by Cohen and Hayden in 1979<sup>1</sup> as a new disorder characterized by uncontrolled growth of tissues and organs. The disease was labeled Proteus syndrome (PS) in 1983 by Wiedemann et al.<sup>2</sup> as a way of describing the great variation in clinical expression, which include gigantism of hands, feet or both extremities, craniofacial hypertrophy,<sup>3</sup> bone abnormalities,<sup>4</sup> scoliosis,<sup>5</sup> soft tissue hamartomas, pigmented verrucous nevus, visceral anomalies and accelerated growth during the patient's first years of life.<sup>6-8</sup> Only approximately 200 cases have been described worldwide.<sup>9</sup>

Other conditions were also linked to this syndrome later, such as: partial or complete hemi-hypertrophy, macrodactylia, exocytosis, palmar or plantar gyriform mass, linear epidermal nevus and subcutaneous tumors with a blood and lymph vascular component.<sup>7,10,11</sup> Some of these abnormalities are also seen in other syndromes, such as Klippel-Trenaunay, Maffucci and neurofibromatosis, but PS can be differentiated from other syndromes because it characteristically includes mesodermal and asymmetrical malformations.<sup>9,12</sup>

The objective of this report is to describe the clinical case of a patient with PS who had severe malnutrition

and psychosocial problems, which were reversed after amputation of the heavily involved lower limbs.

## PART I - CLINICAL SITUATION

A 3-year-old male child who was being managed by a vascular surgery team exhibited gigantism of both feet, gigantism of the left leg and thigh, verrucous and hyperpigmented nevus on the thigh, varicose veins in the left lower limb and flat hemangioma on the left side, including left arm and leg, initially thought to be Klippel-Trenaunay syndrome (Figure 1). However, this patient also had scoliosis of the cervical and thoracic spine and hamartoma of the right hemithorax, leading to a re-designation of the case as PS (Figure 1).

For 4 years management was limited to clinical monitoring of the child, whose family did not authorize any type of intervention during this period. A large number of supplementary examinations were conducted during this period of clinical observation. Of these, vascular duplex ultrasound (USD) demonstrated that the deep vein system in the lower limbs was normal, but there was a dilated posterior sciatic vein in the left lower limb and superficial arteriovenous malformations including communicating fistulas in the same limb. Angiotomography and magnetic resonance



Figure 1. Hypertrophy of both lower limbs, worse on the left (A, B); Hemangioma (C).

angiography did not add to the USD findings. X-rays, computed tomography, magnetic resonance imaging, electrocardiogram and hematological and urinary tests all showed no significant abnormalities beyond the orthopedic conditions already described.

During the period of observation, the child exhibited progressive worsening of the hypertrophy of the feet and began to become extremely underweight. In addition to malnutrition, ambulation worsened, primarily because of the hypertrophy of the feet (Figure 2) and because of his deformities the child developed an introverted psychological profile, making few friends and with weak social relationships.

Faced with this situation, after 4 years, the patient's family finally agreed to the proposal to perform a bilateral amputation of the lower limbs.

The treatment options for PS are as follows:

- 1) Clinical observation (watchful waiting);
- 2) Embolization of vascular malformations with microspheres;
- 3) Reconstructive plastic surgery;
- 4) Amputation of limbs.

(Figure 3). He also exhibited psychosocial improvement, recovered his self-confidence and had resocialized, with increased enthusiasm for the games that are normal for his age. He achieved good intellectual performance at school, with no difficulty keeping up with the activities appropriate for his age.



Figure 2. Patient with hypertrophy of both lower limbs, hamartomas, hemangiomas and malnutrition.

## ■ PART II - WHAT WAS DONE

A multidisciplinary team comprising orthopedists, physiotherapists, vascular surgeons, plastic surgeons, pediatricians and psychiatrists arrived at a consensus that the best option would be to perform a transfemoral amputation of the left lower limb and a transtibial amputation of the right lower limb. This option was presented to the child's parents and they accepted the suggestion.

The procedures were conducted during a single operation: left transfemoral amputation and right transtibial amputation. The intraoperative appearance of the skin and deeper tissues of the right lower limb were normal, but the left lower limb exhibited vascular malformations, with tangles of vessels with fibrosis and thrombosis, with no active bleeding, and superficial arteriovenous fistulas. The procedures were accomplished with no intercurrent conditions. During the postoperative period, healing of the right side was satisfactory and fast. However, on the left side, which was the side with vascular malformations, dehiscence set in and healing was slow and by secondary intention. Infection of the dehiscence operating wound was treated with antibiotics and complete healing took 2 months.

One year after the amputations, the child had adapted to and undergone rehabilitation with prostheses for both lower limbs and had recovered from malnutrition



Figure 3. Post-surgical follow-up with rehabilitation with lower limb prostheses and nutritional improvement.

## DISCUSSION

Diagnosing PS remains difficult today<sup>13,14</sup> and the criteria for its diagnosis are controversial.<sup>8</sup> Clinically, the disease involves hypertrophy of skin, connective tissue, brain, bones and other tissues. Genetic mapping of PS identified a somatic activation mutation of AKT1. This enzyme is called v-akt murine thymoma viral oncogene homolog 1 (AKT1), or protein kinase B-alpha (PKB-ALPHA), and belongs to the protein kinase superfamily. AKT1 is one of the most important mediators of the responses to insulin, to insulin-like growth factor (IGF1) and to glucose. Somatic activation of the AKT1 mutation provokes disproportional growth of tissues and also makes tumors more likely.<sup>15</sup>

Treatment of PS tends to be complex.<sup>16</sup> Lesions involving the ovaries and testicles should be treated aggressively because of the risk of neoplasms.<sup>17</sup> Gastrointestinal and renal lesions can be treated conservatively, with rigorous follow-up using serial imaging exams.<sup>18</sup> The lungs may exhibit emphysematous abnormalities, sometimes requiring pneumonectomies.<sup>19</sup> Involvement of the bladder is rare.<sup>20</sup> The airways and tonsils should be assessed before surgery, because malformations are common<sup>21</sup> and could make oral endotracheal intubation difficult. Craniofacial abnormalities affect around 30% of patients and reconstructive treatment should be initiated early because the condition is progressive.<sup>3,22,23</sup> Since the incidence of neoplasms is high, systematic screening is fundamental.<sup>24</sup>

The extremities tend to exhibit large scale deformities, involving soft tissues, bones and blood vessels. Treatment with reconstructive plastic surgery is challenging and often unfeasible,<sup>25</sup> because of concurrent malformations of deep vascular systems. Consequently, in some cases, the option that remains is amputation of the affected limb, but family members are often resistant to this course of action.

In the case described here, when amputation of the lower limbs was proposed, because restorative treatment was not possible, the parents were reluctant to accept the suggestion, which delayed the definitive treatment, during which time the nutritional and psychological status of the patient deteriorated. However, as the case worsened, the parents accepted surgery. This was performed with a good outcome, allowing rehabilitation with prostheses to be initiated; to which the patient adapted easily. The patient reintegrated well socially and gained weight, with consequent improvement in quality of life.

In conclusion, the deformities seen in PS have a wide variety of clinical presentations and include complex deformities that can have a severe negative impact on patients' self-esteem. Treatment should be managed by a multidisciplinary team and will very often be of a palliative nature. In some cases, in which reconstructive surgery is impossible, major amputations will be needed to save the lives of the most severely affected patients. Although amputations are an extreme solution, they can have good results because they open the way to physical rehabilitation with prostheses, allowing for reintegration into society and nutritional recovery. Proteus syndrome is a disease that is little understood and is rare, but PS patients suffer from serious limitations and so presentation of these rare cases can provide useful guidance for treatment in similar situations.

## REFERENCES

1. Cohen MM Jr, Hayden P. A newly recognized hamartomatous syndrome. *Birth Defects Orig Artic Ser.* 1979;15(5B):291-6. PMID:118782.
2. Wiedemann HR, Burgio GR, Aldenhoff P, Kunze J, Kaufmann HJ, Schirg E. The proteus syndrome: partial gigantism of the hands and/or feet, nevi, hemihypertrophy, subcutaneous tumors, macrocephaly or other skull anomalies and possible accelerated growth and visceral affections. *Eur J Pediatr.* 1983;140(1):5-12. <http://dx.doi.org/10.1007/BF00661895>. PMID:6873112.
3. Sakamoto Y, Nakajima H, Kishi K, Shimizu R, Nakajima T. Management of craniofacial hyperostosis in Proteus syndrome. *J Craniofac Surg.* 2010;21(2):414-8. <http://dx.doi.org/10.1097/SCS.0b013e3181cfa7f0>. PMID:20216456.
4. Pazzaglia UE, Beluffi G, Bonaspetti G, Ranchetti F. Bone malformations in Proteus syndrome: an analysis of bone structural changes and their evolution during growth. *Pediatr Radiol.* 2007;37(8):829-35. <http://dx.doi.org/10.1007/s00247-007-0486-1>. PMID:17569038.
5. White NJ, Cochrane DD, Beauchamp R. Paraparesis caused by an angioliomatous hamartoma in an adolescent with Proteus syndrome and scoliosis. *J Neurosurg.* 2005;103(3, Supl):282-4. PMID:16238085.
6. Samlaska CP, Levin SW, James WD, Benson PM, Walker JC, Perlik PC. Proteus syndrome. *Arch Dermatol.* 1989;125(8):1109-14. <http://dx.doi.org/10.1001/archderm.1989.01670200085015>. PMID:2667470.
7. Barmakian JT, Posner MA, Silver L, Lehman W, Vine DT. Proteus syndrome. *J Hand Surg Am.* 1992;17(1):32-4. [http://dx.doi.org/10.1016/0363-5023\(92\)90109-3](http://dx.doi.org/10.1016/0363-5023(92)90109-3). PMID:1538109.
8. Biesecker L. The challenges of Proteus syndrome: diagnosis and management. *Eur J Hum Genet.* 2006;14(11):1151-7. <http://dx.doi.org/10.1038/sj.ejhg.5201638>. PMID:16883308.
9. Turner JT, Cohen MM Jr, Biesecker LG. Reassessment of the Proteus syndrome literature: application of diagnostic criteria to published cases. *Am J Med Genet A.* 2004;130A(2):111-22. <http://dx.doi.org/10.1002/ajmg.a.30327>. PMID:15372514.
10. Stricker S. Musculoskeletal manifestations of Proteus syndrome: report of two cases with literature review. *J Pediatr Orthop.* 1992;12(5):667-74. PMID:1517432.



11. 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(3):145-53. <http://dx.doi.org/10.3109/15513815.2012.656830>. PMID:22413928.
12. Gontijo B, Pereira LB, Silva CMR. Malformações vasculares. *An Bras Dermatol.* 2004;79(1):7-25. <http://dx.doi.org/10.1590/S0365-05962004000100002>.
13. Satter E. Proteus syndrome: 2 case reports and a review of the literature. *Cutis.* 2007;80(4):297-302. PMID:18038691.
14. Cohen MM Jr. Proteus syndrome: clinical evidence for somatic mosaicism and selective review. *Am J Med Genet.* 1993;47(5):645-52. <http://dx.doi.org/10.1002/ajmg.1320470514>. PMID:8266991.
15. Lindhurst MJ, Sapp JC, Teer JK, et al. A mosaic activating mutation in AKT1 associated with the Proteus syndrome. *N Engl J Med.* 2011;365(7):611-9. <http://dx.doi.org/10.1056/NEJMoa1104017>. PMID:21793738.
16. Vieira NRN, Pereira LB, Silva CMR, Gontijo B. Síndrome de Proteus: relato de caso. *An Bras Dermatol.* 2001;76:201-208.
17. Raju RR, Hart WR, Magnuson DK, Reid JR, Rogers DG. Genital tract tumors in Proteus syndrome: report of a case of bilateral paraovarian endometrioid cystic tumors of borderline malignancy and review of the literature. *Mod Pathol.* 2002;15(2):172-80. <http://dx.doi.org/10.1038/modpathol.3880510>. PMID:11850547.
18. Kaduthodil MJ, Prasad DS, Lowe AS, Puneekar AS, Yeung S, Kay CL. Imaging manifestations in Proteus syndrome: an unusual multisystem developmental disorder. *Br J Radiol.* 2012;85(1017):e793-9. <http://dx.doi.org/10.1259/bjr/92343528>. PMID:22514103.
19. Li CY, Chang YL, Chen WC, Lee YC. Pulmonary manifestations and management of proteus syndrome. *J Formos Med Assoc.* 2010;109(5):397-400. [http://dx.doi.org/10.1016/S0929-6646\(10\)60069-1](http://dx.doi.org/10.1016/S0929-6646(10)60069-1). PMID:20497874.
20. Abbo O, Bouali O, Galinier P, Moscovici J. Proteus syndrome: case report of bladder vascular malformation causing massive hematuria. *Prog Urol.* 2012;22(2):132-5. <http://dx.doi.org/10.1016/j.purol.2011.07.011>. PMID:22284599.
21. Lublin M, Schwartzenruber DJ, Lukish J, Chester C, Biesecker LG, Newman KD. Principles for the surgical management of patients with Proteus syndrome and patients with overgrowth not meeting Proteus criteria. *J Pediatr Surg.* 2002;37(7):1013-20. <http://dx.doi.org/10.1053/jpsu.2002.33832>. PMID:12077761.
22. Adolphs N, Tinschert S, Bier J, Klein M. Craniofacial hyperostoses in Proteus syndrome: a case report. *J Craniomaxillofac Surg.* 2004;32(6):391-4. <http://dx.doi.org/10.1016/j.jcms.2004.06.007>. PMID:15555524.
23. Becktor KB, Becktor JP, Karnes PS, Keller EE. Craniofacial and dental manifestations of Proteus syndrome: a case report. *Cleft Palate Craniofac J.* 2002;39(2):233-45. [http://dx.doi.org/10.1597/1545-1569\(2002\)039<0233:CADMOP>2.0.CO;2](http://dx.doi.org/10.1597/1545-1569(2002)039<0233:CADMOP>2.0.CO;2). PMID:11879083.
24. Nazario APM, Alves MR, Ellis C, Morais FC, Panico MB, Vieira GM. Síndrome de Proteus: hamartose desde o nascimento. *J Vasc Bras.* 2011;10:124.
25. Havard S, Enjolras O, Lessana-Leibowitch M, Escande JP. Proteus syndrome. 8 cases. *Ann Dermatol Venereol.* 1994;121(4):303-8. PMID:7702248.

---

**Correspondence**

Matheus Bertanha  
 Faculdade de Medicina de Botucatu, Universidade Estadual Paulista  
 – UNESP  
 Campus de Botucatu Rubião Júnior, s/n  
 CEP 18618-970 - Botucatu (SP), Brazil  
 Tel.: +55 (14) 3815-7428  
 E-mail: matheus.fameca@ig.com.br

**Author information**

MB - Assistant professor at the Department of Surgery and Orthopedics, Faculdade de Medicina de Botucatu, Universidade Estadual Paulista (UNESP).  
 RM and MLS - PhD's assistant professors at the Department of Surgery and Orthopedics, Faculdade de Medicina de Botucatu, Universidade Estadual Paulista (UNESP).  
 LMSP and MPFS - Primary physicians at the Department of Pediatrics, Faculdade de Medicina de Botucatu, Universidade Estadual Paulista (UNESP).  
 RGJ - Primary physician at the Department of Surgery and Orthopedics, Faculdade de Medicina de Botucatu, Universidade Estadual Paulista (UNESP).  
 HAR - Adjunct professor at the Department of Surgery and Orthopedics, Faculdade de Medicina de Botucatu, Universidade Estadual Paulista (UNESP).  
 WBY - Full professor at the Department of Surgery and Orthopedics, Faculdade de Medicina de Botucatu, Universidade Estadual Paulista (UNESP).

**Author contributions**

Conception and design: MB, RM  
 Analysis and interpretation: MB, RM, MLS, RGJ  
 Data collection: LMSP, MPFS  
 Writing the article: MB, MLS, RGJ, WBY  
 Critical revision of the article: MB, HAR, MLS  
 Final approval of the article\*: MB, RM, MLS, LMSP, RGJ, MPFS, HAR, WBY  
 Statistical analysis: N/A.  
 Overall responsibility: MB, WBY

\*All authors have read and approved of the final version of the article submitted to *J Vasc Bras.*