

A Case of Concurrent Proteus Syndrome and Hemophilia A

Mozhgan Hashemieh¹, MD; Bahar Mansoori², MD; Reza Tavakoli³, MD, and Koroush Sheibani^{*2}, MD

1. Department of Pediatrics, Shahid Beheshti University of Medical Sciences, Tehran, Iran
2. Clinical Research and Development Center, Imam Hossein Medical Center, Tehran, Iran
3. Department of Orthopedics, Shahid Beheshti University of Medical Sciences, Tehran, Iran

Received: Jan 09, 2011; Final Revision: May 13, 2011; Accepted: Jul 26, 2011

Abstract

Background: Proteus syndrome is a very rare condition with less than 100 confirmed cases reported worldwide. We report a case of Proteus syndrome in a two-year-old male who has hemophilia A comorbidity.

Case Presentation: A two-year-old male patient was admitted with the chief complaint of severe bleeding in mouth cavity after trauma for two weeks. At admission he was found to have petechiae on buccal mucosa and fecal discoloration due to GI bleeding. We noted multiple abnormalities in his musculoskeletal system and skin. He had lymph edema in left leg, hemihypertrophy, macrodactyly in both feet and macrocephaly. With the history of severe bleeding and recurrent blood product transfusion, we suspected a hemorrhagic disorder. The reduced level of Factor VIII activity confirmed the diagnosis of hemophilia A. Considering patient's various musculoskeletal abnormalities according to the diagnostic criteria and after ruling out similar disorders the diagnosis of Proteus syndrome was established.

Conclusion: Because of the variability of clinical features, Proteus syndrome can be confused with other disorders of multiple tissue overgrowth. Our case of Proteus syndrome, who had hemophilia A comorbidity outlines the challenges in diagnosis of such rare combination of diseases.

Iranian Journal of Pediatrics, Volume 22 (Number 2), June 2012, Pages: 255-259

Key Words: Proteus syndrome; Musculoskeletal; Hemophilia A

Introduction

Although recognizing Proteus syndrome dates back to 1979 [1], it was first described in 1983 [2], and since then many aspects of this disorder have been observed. The cause of the Proteus syndrome is not clear, but postzygotic mutation with resulting mosaicism has been reported in many studies [3-5].

Proteus syndrome is a very rare condition with less than 100 confirmed cases reported

worldwide[6,7]. This suggests that prevalence of this disorder is less than 1 case per 1,000,000 live births[8]. The present case is unique because of the coincidence of the Proteus syndrome with another genetic disease, namely hemophilia A. Hemophilia A is an X-linked recessive bleeding disorder caused by decreased blood levels of functional procoagulant factor VIII. In hemophilia B, the defect is a decreased level of functional procoagulant factor IX. The incidence of hemophilia is 1 per 5000 live male births. Factor

* Corresponding Author;

Address: Clinical Research and Development Center, Imam Hossein Medical Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran

E-mail: sh_kouros@hotmail.com

VIII deficiency accounts for 80–85% of cases of hemophilia, with factor IX deficiency accounting for the remainder.

Case Presentation

A two-year-old male child was admitted to our hospital with the chief complaint of severe bleeding in mouth cavity due to trauma since two weeks before admission. Parents gave written informed consent to report this case and accompanying images. The patient was born to unrelated parents with an uneventful pregnancy and normal vaginal delivery. There was no history of bleeding disorder in the family.

His past medical history was remarkable for severe anemia, and packed red blood cell transfusion secondary to epistaxis, when he was five months old. He had not undergone any further evaluation for the cause of his bleeding at the time. Furthermore, he had experienced an episode of severe lower GI bleeding due to food allergy when he was one year old.

At admission he was found to have petechiae on buccal mucosa and fecal discoloration due to GI bleeding. He received packed red blood cells and fresh frozen plasma to manage his bleeding. On physical examination, we noted multiple abnormalities in his musculoskeletal system and skin. He had lymph edema in left leg, hemihypertrophy, and macrodactyly in both feet. Hemihypertrophy was prominent in left upper and

lower limbs, with maximum swelling in left forearm and left foot, and visible fusion between the 2nd and 3rd foot digits (Fig. 1, 2).

The skin abnormalities included thickening of skin and epidermal nevi over the trunk and lower extremities, with the largest one being 5×5 cm in diameter. Another prominent feature in this case was macrocephaly (head circumference=52 cm).

With the history of severe bleeding and recurrent blood product transfusion, we suspected a hemorrhagic disorder. Blood coagulation findings including prolonged activated PTT (66 seconds with APTT Control 31 sec) and reduced level of Factor VIII activity (5% conducted after transfusion of fresh frozen plasma) were consistent with the diagnosis of hemophilia A.

Patient's other significant test results were as follow: normal activated PTT mixing test, normal factor XIII screen test, normal PT activity, normal fibrinogen level, and normal PT INR. We also found factor IX activity to be 88%.

Radiographic images confirmed disproportionate overgrowth in the left leg (Fig. 3). Color Doppler sonography of arteries and veins revealed normal flows and there were no signs of deep vein thrombosis. In popliteal area of both legs there were some enlarged lymph nodes with the largest one being 11×8 mm in diameter. The patient also underwent abdominal and brain MRI, which were reported as normal. According to the diagnostic criteria and after ruling out similar disorders, the diagnosis of Proteus syndrome was established.

According to the rating scale in Tachdjian's Pediatric Orthopaedics, our patient had macrodactyly, hemihypertrophy of left leg,



Fig. 1: Enlarged left foot showing fusion between 2nd and 3rd digits and hyperpigmented lesions



Fig. 2: Lymph edema and hemihypertrophy in the left leg



Fig. 3: Radiograph images of disproportionate overgrowth of left leg seen in patients with Proteus syndrome

thickening of skin, epidermal nevi, and macrocephaly with total score of 14.5. A score of 13 or more is required to establish a diagnosis [9]. In our case, genetic study was not done and according to his mother, asymmetric disproportionate limb overgrowth has a progressive course. Also there was not a positive family history in this case.

Discussion

The diagnosis of Proteus syndrome is entirely clinical. The genetic implications of Proteus syndrome are not well understood. Possible transmission from father to son has been reported. Spontaneous mutation as a lethal autosomal dominant condition, with survival attributed to mosaicism, has been postulated by others [9].

The diagnosis is based on a demonstration of the characteristic features of this disorder and on a failure to fulfill the criteria of similar congenital hamartomatous conditions. Table 1 represents the rating scale based on the presence of six clinical features to assist in the diagnosis of Proteus

syndrome[9]. This diagnostic set of criteria for diagnosis of Proteus syndrome was first introduced by Biesecker et al in 1999[10]. A score of 13 or more was required to establish a diagnosis based on this set of criteria[10]. Biesecker modified the first diagnostic criteria to have two categories of attributes, general and specific[11]. The general attributes delineate the non specific features of Proteus syndrome by requiring that all patients have a mosaic distribution of the phenotype, are sporadic and the manifestations are progressive in nature. If a patient does not have all three of these criteria, the diagnosis of Proteus syndrome is rejected. If a patient has all three of the general attributes, the specific criteria should be assessed. Specific criteria include; cerebriform connective tissue nevus, linear epidermal nevus, asymmetric and disproportionate overgrowth, specific tumors before 2nd decade, dysregulated adipose tissue, vascular malformations, lung cysts and facial phenotype[11]. In our patient general findings (mosaic distribution of lesions, progressive course, and sporadic occurrence) and also specific findings (asymmetric disproportionate limb overgrowth and epidermal nevi) met the aforementioned criteria.

There is another method for diagnosis of

Table 1: Rating scale based on the presence of six clinical features to assist in the diagnosis [9]

Clinical feature	Points
Macroductyly, Hemihypertrophy, or both	5.0
Thickening of skin	4.0
Lipomas and subcutaneous tumors	4.0
Verrucous epidermal nevus	3.0
Macrocephaly, buckelshadel, or both	2.5
Other minor abnormalities	1.0

Proteus syndrome called Turner criteria which includes five finding categories: 1) Partial gigantism of the hands, feet, or both, 2) pigmented nevi, 3) hemihypertrophy, 4) subcutaneous hamartomatous tumors, 5) macrocephaly or other skull anomalies^[12].

Individual patients may not exhibit all these features, and the severity of findings varies among patients^[13]. For example, lower extremity hemihypertrophy can be a relatively minor finding, or it can be severely grotesque, affecting limb function and greatly challenging the treating physician^[14]. Macroductyly is the most common feature described. The digits are usually normal at birth but can enlarge massively over time. In the hand, the third and fourth digits are most commonly affected ^[14,15]. Hemihypertrophy is nearly as common and may be partial or complete and independent of macroductyly ^[13]. Pigmented (epidermal) nevi are present in these patients and may be located anywhere on the body^[14]. Subcutaneous soft tissue tumors may also be found anywhere in the body which are mostly lymphangiomas in biopsies^[14]. Axial skeletal anomalies include vertebral gigantism, with or without scoliosis or kyphosis, and bony protuberances of the skull in the fronto-temporal or parieto-occipital area^[3]. Other skeletal features include genu valgum, hind foot deformities, verrucous soft tissue hypertrophy of the sole of the foot, hip dysplasia, exostoses, and generalized acceleration of skeletal growth^[3]. Reported neurologic sequelae include gross motor delay, mental retardation in some patients, intracranial lesions, sinus thrombosis and peripheral nerve enlargement with entrapment syndrome^[16].

Because of the variability of its clinical features, Proteus syndrome can be confused with other disorders of multiple tissue overgrowth^[10,17]. Most important entities to be distinguished from Proteus syndrome include idiopathic

hemihypertrophy, isolated macroductyly, neurofibromatosis, Ollier's disease, Maffucci's syndrome, and Klippel-Trenaunay syndrome^[18,19]. Idiopathic hemihypertrophy and isolated macroductyly are normally distinguished by the absence of other clinical manifestations associated with Proteus syndrome^[20,21]. Neurofibromatosis patients often have a family history of the disorder, as well as cafe au lait spots, axillary freckling, Lisch nodules, and distinctly different bony abnormalities ^[21]. Ollier's disease is characterized primarily by typical osseous lesions and by the skeletal distortions that result from the enchondromas' interference with normal physical growth ^[21]. Maffucci's syndrome is similar to Ollier's disease, with the additional features of hemangiomas and a propensity for soft tissue malignancies ^[23,24].

Klippel-Trenaunay-Weber syndrome is characterized by more severe and extensive vascular anomalies rather than simple pigmented nevi, and as a rule, the skeletal abnormalities are limited to gigantism associated with soft tissue hypertrophy ^[19,22]. The diagnosis of Klippel-Trenaunay syndrome is made based on the presence of at least two of the three cardinal features of capillary malformations; venous malformations and limb hypertrophy ^[1-3,19]. The orthopedic problems encountered in the reported cases of Proteus syndrome include macroductyly, limb length inequality, genu valgum, hindfoot deformity, and spinal deformity (especially scoliosis). Association of tumors is an important feature of Proteus syndrome. The tumors commonly associated with Proteus syndrome are testicular tumors, ovarian cystadenoma, meningioma and monomorphic adenoma of parotid gland^[6]. The association between Proteus syndrome and hemophilia has not been reported in literature and the relationship between them in our case is incidental.

Conclusion

Because of the variability of its clinical features, Proteus syndrome can be confused with other disorders of multiple tissue overgrowth. Our case of Proteus syndrome with hemophilia A comorbidity outlines the challenges in diagnosis of such rare combination of diseases.

Acknowledgment

The authors would like to thank Dr. Ali Omidian for his valuable contribution to this study.

References

- Cohen MM, Hayen PWA. Newly recognized hamartomatous syndrome. *Birth Defects* 1979; 15(5B):291-6.
- Widemann HR, Burgio GR, Aldenhoff P, et al. 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;140:5-12.
- Jamis Dow CA, Turner J, Biesecker LG, Choyke PL. Radiologic manifestation of proteus syndrome. *Radiographics* 2004;24(4):1051-68.
- Hamm H. Cutaneous mosaicism of lethal mutations. *Am J Med Genet* 1999;85(4):342-5.
- Cohen MM. Causes of premature death in Proteus syndrome. *Am J Med Genet* 2001;101:1-3
- Cohen MM. Proteus syndrome: an update. *Am J Med Genet C Semin Med Genet* 2005;137C(1):38-52.
- Shalimar A, NorHazla MH, Jamari S, Srijit D. A case of disproportionate macrodactyly or a mild form of proteus syndrome? An interesting case. *Acta Medica (Hradec Králové)* 2010; 53(4):243-6.
- Furquim I, Honjo R, Bae R, Andrade W, et al. Proteus syndrome: report of a case with recurrent abdominal lipomatosis. *J Pediatr Surg* 2009;44(4):E1-3.
- Birch JG, Johnston CE, Karol LA et al. "Orthopaedic related syndromes". In: Herring JA Tachdjian's Pediatric Orthopaedics. 4th ed. Philadelphia; Saunders. 2008; Pp: 1897-1899.
- Biescker LG, Happle R, Mulliken JB, et al. Proteus syndrome: diagnostic criteria, differential diagnosis, and patient evaluation. *Am J Med Genet* 1999;84(5):389-95.
- Biesecker L. The challenges of Proteus syndrome: diagnosis and management. *Eur J Hum Genet*. 2006;14(11):1151-7.
- Turner JT, Cohen MM, 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.
- Miura H, Uchida Y, Ihara K, et al. Macrodactyly in proteus syndrome. *J Hand Surg* 1993;18(3), 308-9.
- Öztürk H, Karnak B, Turgay Sakarya M, et al. Proteus syndrome: clinical and surgical aspects. *Annales de Génétique* 2000;43(3-4):137-42.
- Mayatepek E, Kurczynski TW, Ruppert ES, et al. Expanding the phenotype of the Proteus syndrome: A severely affected patient with new findings. *Am J Med Genet* 1989;32(3):402-6.
- Tercan M, Yakinci C, Kutlu O, et al. Proteus syndrome: a case report and review of the literature. *Eur J Plast Surg* 2000;23(7):379-82.
- Hotamisligil GS. Proteus syndrome and hamartoses with overgrowth. *Dysmorphol Clin Genet* 1990; 4:87-102.
- Alman BA, Goldberg MJ. "Syndromes of Orthopedic Importance". In: Lovell WW, Winter RB, Morrissy RT, et al (eds). Lovell and Winter's Pediatric Orthopaedics. 6th ed. Philadelphia; Lippincott Williams & Wilkins. 2006; Pp: 268-70.
- Abdul-Rahman NR, Mohammad KF, Ibrahim S. Gigantism of the lower limb in Klippel-Trenaunay syndrome: anatomy of the lateral marginal vein. *Singapore Med J* 2009;50(6):223-5.
- Tracy Ballock R, Wiesner GL, Myers MT, et al. Current Concepts Review - Hemihypertrophy. Concepts and controversies. *J Bone Joint Surg* 1997;79(11):1731-8.
- Barmakian JT, Posner MA, Silver L, et al. Proteus syndrome. *J Hand Surg* 1992;17(1):32-4.
- Sinha R, Shekhar C, Sodhi K, Kiran YK. Proteus syndrome. *Scand J Plast Reconstruct Surg Hand Surg* 2003;37(5):307-10.
- Wallis LA, Asch T, Maisel BW. Diffuse skeletal hemangiomas: Report of two cases and review of literature. 1964;37(4):545-63.
- Katz P, Colbert R, Drolet B. Unilateral mosaic cutaneous vascular lesions, enchondroma, multiple soft tissue chondromas and congenital fibrosarcoma - a variant of Maffucci syndrome?. *Pediatr Dermatol* 2008;25(2):205-9.