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Case Report

Proteus Syndrome in the minimal form: atypical case report

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Abstract

This is the case report involving a 14-year-old male patient with Proteus syndrome. In an outpatient consultation, the patient complained of pain in the right foot on exertion. On physical examination, the findings were gigantism observed through lateral growth of the right foot, hemangioma on the back, and lipomas on the forearm. Clinical follow-up and orthotic measures were introduced after clinical and baropodometric analyses, achieving total relief of complaints. The minimal form of Proteus syndrome is rare and its diagnosis is hard. Its diverse manifestations constitute an obstacle to a systematic approach, hence its treatment must be individualized for each particular patient.

Level of Evidence V; Therapeutic Study; Expert Opinion.

Keywords: Hamartoma syndrome, multiple; Hamartoma; Gigantism.

Introduction

Proteus syndrome is a congenital hamartomatous disease, originally described in two patients by Cohen and Hayden in 1979[1], characterized by progressive and disproportionate growth of certain parts of the body[2].Due to the considerable clinical variability in affected patients, the name of the syndrome, given by Wiedemann in 1983, is a reference to Proteus, a god in Greek mythology with the ability to change shape at will[3].

Records currently show that there are less than 500 people affected worldwide; hence the syndrome is considered a rare disease[4,5]. Its abnormalities affect tissues of any germinative lineage, but especially the skeleton, skin, adipose tissue, and central nervous system. In most individuals symptoms are absent or subtle at birth, but develop substantially in childhood, causing localized overgrowth[2] besides other typical tumors[4]. Pulmonary complications and predisposition to thromboembolic events are also associated with the syndrome[2].

We explore here the case of a patient with a localized form of Proteus syndrome, known as minimal, which reflects the broad spectrum of variability in the presentation of this syndrome and represents an even rarer set of signs and symptoms.

Case report

This study was approved by the Institutional Review Board and registered on the Plataforma Brazil database under CAAE (Ethics Evaluation Submission Certificate) number: 19811619.9.0000.0096, and through the application of an Informed Consent Form (ICF).

Patient R.C.P., male, born on September 17, 2001. The patient was admitted to the orthopedic unit of our hospital at the age of 14, complaining of disproportionate feet, with the right foot appearing significantly larger in its lateral portion (Figure 1). It was ascertained that, even during childhood growth, the patient wore the same shoe size on both feet, despite the fact that the side of the right foot was markedly enlarged.

Study performed at the Hospital de Clínicas da Universidade Federal do Paraná, Curitiba, PR, Brazil.

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Family members report that such an increase was noted after birth, with the deformity growing in proportion to the patient's growth during childhood. The patient complained of mild pain present only on exertion, especially in the region of the lateral edge of the right foot when running, without any symptoms at rest. There were no other complaints related to other body segments, although an extensive hemangioma on the back (Figure 2) and lipomas on the forearm were found during physical examination (Figure 3).

No abnormalities were noted during neuropsychomotor development in childhood, with weight gain, gait, and other developmental milestones observed at appropriate times. The patient denied other comorbidities or previous hospitalization, allergies, use of continuous medications and drug addiction. During family history taking, it was ascertained that the parents were not consanguineous and there was no other family member with signs or symptoms resembling those of the patient.

On physical examination the patient's size was considered normal for his age. Gigantism was observed through lateral growth of the right foot, accompanied by a slight increase in the ipsilateral leg. In addition, there was an extensive hemangioma on the right side of his back (Figure 2), for which the patient had received no prior treatment and that, according to his mother's reports, had grown gradually during early childhood with slight regression from the age of five. Two circumscribed nodules were also observed in the ulnar region of the right forearm, of consistencies compatible with lipomas (Figure 3), in addition to asymmetric distribution of adipose tissue on the trunk (Figure 4). The patient walked without requiring support and there was no evidence of abnormalities in ankle and toe mobility or functional limitations in active and passive mobilization. No facial abnormalities were noted.

To supplement the diagnosis a baropodometry test was performed to study weight distribution and forces applied to the feet, revealing an important weight-bearing deviation in the right foot when static (Figure 5). In the dynamic state, the test revealed a deviation of the center of gravity of the left foot from the calcaneus to the head of the second and third metatarsals and to the hallux. On the right side we also observed displacement of the center of gravity for the second toe and not for the hallux (Figure 6). A pronation force vector was observed on both sides.

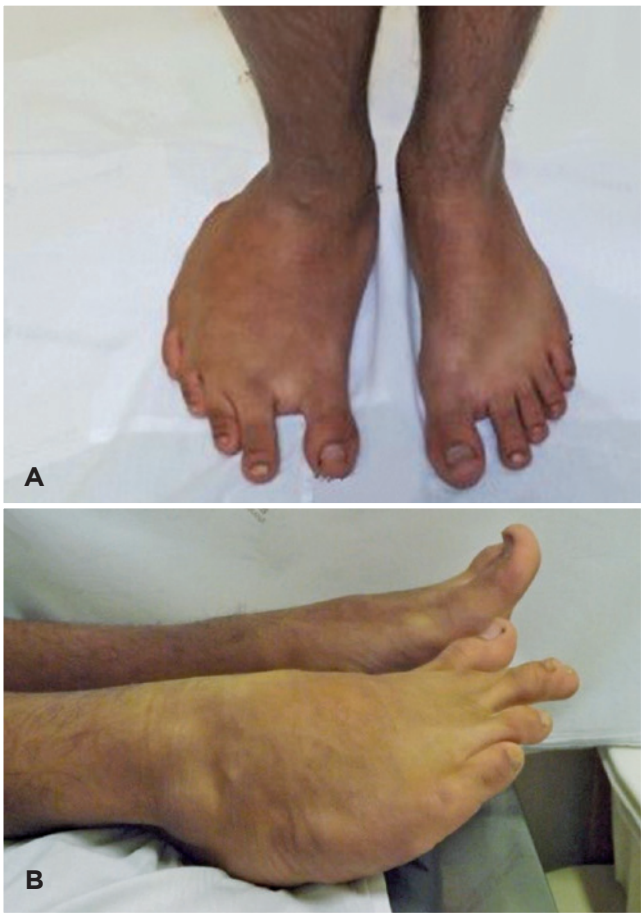

Figure 1. The patient's feet, showing gigantism observed through growth of the lateral edge of the right foot (A) and the abnormal growth of the edge of the right foot in the lateral view, with slight enlargement of the right ankle (B). There are no signs of growth abnormalities in other parts of the body.

Discussion

Patients with Proteus syndrome represent a clinical and diagnostic challenge, not only due to the broad spectrum of the disease, but also because of the lack of clear diagnostic criteria, leading to underdiagnosis[6]. For this reason, the First Conference on Proteus Syndrome was held in Bethesda, Maryland, in 1998. As a result, recommendations for confirmation, differential diagnoses, evaluation and management of patients were gathered[7] and used for the diagnostic approach of our patient. These recommendations are presented in this report.

Diagnosis of the syndrome is based on mandatory clinical criteria and specific characteristics that may or may not be

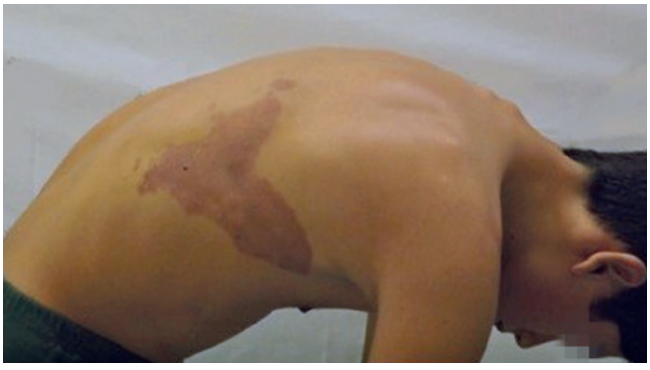

Figure 2. Extensive hemangioma present on the patient's back, in right posterolateral view. The presence of hemangiomatous alterations is part of the minor clinical criteria for the clinical diagnostic characterization of Proteus syndrome.

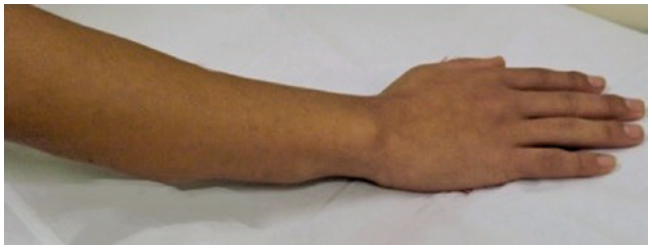

Figure 3. Image of the patient's right forearm, showing two lipomas in the ulnar region of the forearm. The presence of lipomatous disease is part of the minor clinical criteria for the clinical diagnosis of Proteus syndrome.

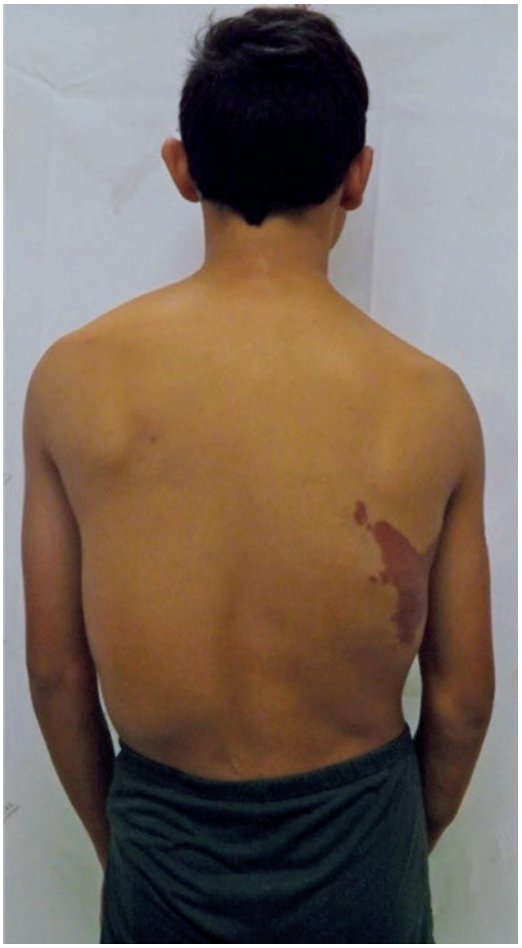

Figure 4. Patient's dorsal region with clear asymmetric distribution of adipose tissue on the trunk and part of the hemangioma in the right posterolateral region.

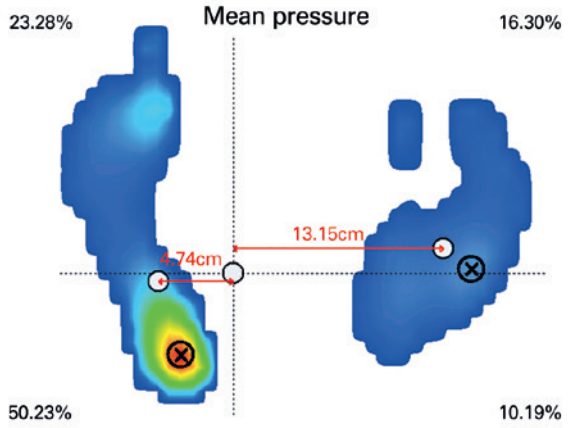

Figure 5. Image of the static baropodometric analysis with lateral deviation of the base of the right foot.

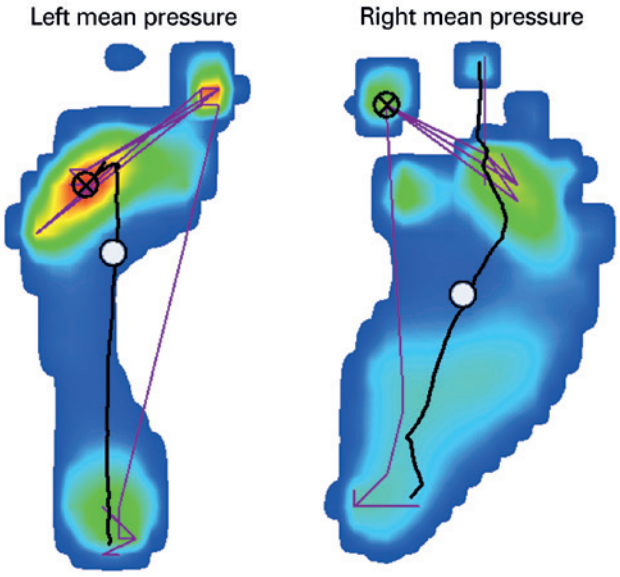

Figure 6. Dynamic baropodometry showing a normal line of displacement of the center of gravity to the left and right. A pronation force vector can be seen on both sides.

present. If a patient has the three mandatory clinical conditions and some of the sporadic characteristics, it is possible to consider a diagnosis of Proteus syndrome. The three mandatory criteria are: 1) Mosaicism, which means areas of excessive growth visible in a fragmented manner; 2) Sporadic occurrence, i.e., there are no other affected family members; 3) Progressive course, which indicates that overgrowth visibly and progressively alters the appearance or that new areas of overgrowth will appear over time[8]. The patient presented in this case report meets all the essential primary requirements for the diagnosis of this syndrome.

The characteristics of sporadic presence, in turn, are grouped into three categories: A, B and C. Connective tissue nevi are included in category A. Category B contains three criteria: linear epidermal nevi, asymmetric, disproportionate growth, and specific tumors occurring in the first decade of life. Category C also contains three criteria, namely: irregular adipose tissue, vascular malformations and facial phenotype characteristics. The diagnosis of Proteus syndrome requires, in addition to the mandatory characteristics, the presence of at least one criterion from group A, two from group B or three from group C[7]. The presence of hemangioma, irregular distribution of adipose tissue and the presence of lipomas in the patient from this particular case report is compatible with some of the minor criteria for the clinical diagnosis of the syndrome.

The minimal form of the disease, which is even rarer, may not present the major physical disfigurements that are typical of the syndrome, as in the case presented in this report, in which the patient presented with localized deformity of the right foot, which was vital for clinical suspicion, in addition to a negative family history. The treatment of localized deformities is nonspecific and individualized, and surgical indications can be limited in cases with no significant functional limitation. Because the patient has localized distortion, we instituted clinical management through baropodometric evaluation to study the distribution and concentration of force in the plantar region and the use of compensation insoles, with improvement of complaints, opting for a series of reassessments during the growth phase.

In 2011, a localized and sporadic mutation that causes the disease was identified in the AKT gene. A spontaneous mutation at the time of embryogenesis, in which only cells descended from the affected parent will express the disease. Accordingly, the individual will have a population of normal cells and another of mutated cells, thus developing a genetic mosaic[9]. The severity of disease manifestation depends on the stage of embryonic development when the mutation occurred and in which part of the body it developed. The newborn may appear normal, yet symptoms appear in the first two years and may increase susceptibility to typical tumors[5,9]. Such characteristics were observed in the patient in this report, since he presented with typical benign tumors and developed disproportionate growth of the right foot during childhood.

Due to the essentially musculoskeletal manifestations, it is important for orthopedists to become familiar with this syndrome, since they will often be the specialist approached initially, as in the case presented here. In addition, it is advisable to adapt the treatment on a case-by-case basis to decide on the best intervention, and be aware that surgical treatment will not always be indicated. As in this particular case report, despite the appearance, in the absence of major functional limitations, patients can be treated conservatively with serial monitoring, physiotherapy and orthoses to improve gait, since the surgical risk of an intervention can outweigh the real benefits in these specific cases with limited deformities. After the adoption of measures such as insoles, guidance on gait and posture, and clinical follow-up, the patient showed an improvement in the initial complaints, and no new abnormalities or progression of existing deformities were found during outpatient follow-up.

Conclusion

Therefore, we conclude that the physician must have a high degree of clinical suspicion in order to confirm this rare syndrome, especially when present in its minimal form, and must rely on clinical criteria for the diagnosis. When available and in cases of diagnostic uncertainty, genetic tests may also be carried out. In addition, surgical treatment will not always be the choice, especially in minimal cases of disease presentation, characterized by localized deformities, and clinical treatment may produce good results.

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