

Case Report

Proteus syndrome and hypothyroidism

An unusual association

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ABSTRACT

نستعرض في هذا المقال حالة طفلة بعمر 1½ تم تشخيصها بمتلازمة بروتوس وهي تعاني من تشوهات شكلية شديدة: تعدد أصابع، ضخامة شقبة في الوجه والأطراف، وكبر حجم المادة الدماغية، وذمة لمفاوية في اليدين والقدمين مع تأخر روحي شديد. وهي تعاني أيضاً من صرع صعب الضبط. بالإضافة لذلك وجد أن الطفلة لديها قصور درق بدئي وهذا التشارك لم يذكر في الأدب الطبي.

We present a case of a 3½-year-old girl diagnosed as Proteus syndrome with severe cosmetic disfigurement-macroductyly, hemi-hypertrophy of the face and limbs, megalencephaly, lymph edema of both hands and feet along with severe global developmental delay. She was found to have severe recalcitrant epilepsy and also primary hypothyroidism; the association of which is not mentioned in the previous literature.

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Proteus syndrome, also known as Wiedemann syndrome is a congenital disorder.¹ It is named after the Greek sea-god Proteus, who could change his shape. The phenotype of Proteus syndrome is highly variable.² It is characterized by progressive, segmental, or patchy overgrowth of diverse tissues of all germ layers, most commonly affecting the skeleton, skin, adipose, and central nervous system, often accompanied by various tumors.³ In 1976, Temtamy and Rogers⁴ were the first to describe this condition in the American medical literature. Cohen and Hayden⁵ described it in 1979. In the majority of cases, Proteus syndrome has minimal or no manifestations at birth. It usually manifests in the toddler period and progresses rapidly through childhood resulting in severe overgrowth of various tissues and disfigurement. There is an association with a range of tumors and pulmonary complications; there is also a remarkable tendency to develop deep vein thrombosis and pulmonary embolism. The clinical criteria for diagnosis include 3 general characteristics and a specific symptom checklist.^{6,7} A mosaic somatic mutation of AKT1 has been identified in more than 90% of individuals meeting diagnostic criteria.⁸

Management includes corrective surgeries for overgrown tissues. The approaches are diverse, which include various orthopedic procedures to modify linear bone growth, correction of skeletal deformities such as scoliosis, monitoring for and treating deep vein thrombosis, pulmonary embolism, parenchymal pathology, and restrictive lung disease. Skin manifestations especially the cerebriform connective-tissue nevi also need to be managed. Developmental intervention or special education is needed for children with developmental delays. In this paper we present a unique case of Proteus syndrome associated with hypothyroidism. This association is rarely found in the literature.

Case Report. Our patient, a female child was born after a non-consanguineous marriage to a primi mother in the United Arab Emirates on September 2010 with uneventful pregnancy with Apgar score of 7 at 1 minute, and 9 at 5 minutes. Her birth weight was 2.7 kgs. On the basis of clinical features she was diagnosed to have Proteus syndrome.

On the second day of life, she developed generalized seizures, which were controlled with multiple anti-convulsants. At the age of 3 months, the parents decided to take her abroad for further investigations and management. There, the diagnosis was confirmed by genetic studies. She was transferred to our hospital from the United Kingdom in February 2013 at the age of 2 years and 3 months.

Her current problems are: 1) poor neurological status, which has been worsening over time; 2) there is no interaction with her surroundings; 3) she has arrested hydrocephalus, megalencephaly, and lymph edema of hands and feet; 4) she has epilepsy needing multiple anti-convulsants; 5) she has tracheostomy and needs oxygen from time to time through thermovent and occasionally requiring continuous positive airway pressure or pressure support especially at night; and 6) she is also being fed through gastrostomy tube. Soon after admission to our hospital, she was noted to have hypothermia, madarosis, bradycardia, and constipation. The results of thyroid function test confirmed the clinical impression of hypothyroidism.

She was started initially on L-thyroxine 50 µgms/day and later increased to 75 µgms/day. This resulted in normalization of body temperature, improvement in madarosis and heart rate. Her general condition is stable. Seizures are under control with valproate sodium, topiramate, levetiracetam, and clobazam. She is tolerating feeds via gastrostomy tube and is receiving regular physiotherapy care.

On examination, there is a left hemi hypertrophy totally involving the face and limbs (Figure 1), an asymmetric overgrowth of hands and feet including fingers and toes (Figures 2 & 3), and hypoplasia of the right optic nerve, and the right eye is smaller in size with right inferior coloboma of iris. There is non-pitting edema of both feet (Figure 3). There are minimal spontaneous movements mainly in response to tracheal suction, and there is no interaction with the surroundings. She has tracheostomy and gastrostomy tube in place. Investigations for thyroid functions reveal low T4 8.1 pmol/L (normal values: 11.5-22.7) and high TSH 21.815 mIU/l (normal values: 0.640-6.270) without any circulating anti-thyroglobulin anti-bodies

and anti-thyroid peroxidase anti-bodies suggesting primary hypothyroidism. Skeletal survey showed generalized osteopenia with developmental dysplasia of the left hip with dislocation of the left femoral head. There is gross soft tissue swelling of the dorsum of both feet with bony overgrowth of metatarsal and phalanges. Magnetic resonance imaging of the brain showed dilated ventricles with arrested hydrocephalus with lissencephaly and cerebellar hypoplasia. Chest



Figure 1 - Asymmetric overgrowth of the limbs; more on the left side. Both feet have non-pitting edema.



Figure 2 - Asymmetric overgrowth of the limbs and fingers.



Figure 3 - Asymmetrical overgrowth and non pitting edema of both feet.

and abdominal MRI showed multiple cystic lesions in the chest, possibly multiple lymphangiomas, and cystic lesions in the kidneys and liver. Abdominal ultrasound revealed bilateral nephrocalcinosis. Upper gastroenterology contrast study showed gross gastroesophageal reflux with hiatus hernia for which she underwent Nissan fundoplication and gastrostomy tube insertion. The EEG was very abnormal bilaterally, with frequent multifocal and generalized epileptiform activity. Echocardiography was normal.

A genetic study analysis carried out in Seattle, United States of America for this patient revealed that there is a somatic mutation in the gene within the AKT3 pathway suggesting Proteus syndrome. A written consent from the parents was obtained to present the baby's pictures for publication.

Discussion. Proteus syndrome is a rare condition. The number of confirmed cases of Proteus syndrome is a little more than 200. Currently, 120 cases of this syndrome are estimated to be alive.⁹ As attenuated forms of the disease may exist, there could be many people with Proteus syndrome who remain undiagnosed.

This case of Proteus syndrome, which is associated with primary hypothyroidism, was clinically suspected and confirmed by laboratory findings. There is a lack of such associations between Proteus syndrome and hypothyroidism mentioned in the literature. This may be due to the absence of clinical manifestations that indicate hypothyroidism, or this clinical manifestation was too subtle that it was overlooked among other manifestations of the disease. Another explanation

could be an occasional association of Proteus syndrome with hypothyroidism, that may not be seen in all cases.

In conclusion, careful observation for the clinical features of hypothyroidism and laboratory tests in cases of Proteus syndrome may reveal more cases associated with hypothyroidism.

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