Proteus Syndrome with Neurological Manifestations: A Rare Presentation

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Proteus syndrome (PS) is an extremely rare and complex disorder. Approximately 200 cases have been reported, and it seems to affect people of all ethnic and racial groups. PS is characterized by segmental overgrowth of multiple tissues and organs including vascular malformations, lipomatous overgrowth, hyperpigmentation, and various types of nevi. We hereby present a 7-year-old boy who presented with seizures and overgrowth of one-half of the body. Although classical physical features have been described, epilepsy and other neurological manifestations are rarely reported features of PS. Early detection of association of epilepsy and hemimegalencephaly with PS can prevent/minimize the neurological complications, disability, morbidity, and mortality.

Keywords: Epilepsy, hemimegalencephaly, overgrowth, Proteus syndrome

INTRODUCTION

Proteus syndrome (PS) (OMIM #176920) is a rare overgrowth syndrome characterized by segmental overgrowth of multiple tissues and organs including vascular malformations, lipomas, hyperpigmentation, and various types of nevi. Limb or digital overgrowth with partial gigantism is pathognomonic of PS. PS was originally described by Cohen and Hayden (1979) as a newly recognized disorder characterized by overgrowth of multiple tissues, connective tissue nevi, epidermal nevi, and hyperostoses. The disorder was designated PS by Wiedemann et al. in 1983. About 200 cases of PS have been reported in literature with the incidence of <1 in 1 million people worldwide. The exact cause, pathogenesis and embryologic origin of PS still remains a subject of discussion.

CASE REPORT

A 7 year old boy presented to us with complaints of seizures and overgrowth of the right half of the body. He was a third child born to the couple, out of nonconsanguineous marriage. Antenatal and perinatal period was uneventful. Parents noticed progressive overgrowth of right foot from 3 to 4 months of age along with overgrowth of plantar surfaces. Few months later, overgrowth of the right half of face and gluteal region was also appreciated. The patient developed unprovoked seizures at 1½ month of age, initially left-sided hemiseizures, later on, became generalized and was started on antiepileptic drugs at the onset. Drug compliance was poor along with a history of recurrent seizures. Development milestones were appropriate for age.

On clinical examination, anthropometric measurements were within normal limits with normal intelligence. Examination of head and face revealed dolichocephaly, frontal bossing, hypertrophy of right half of face including cheek and tongue, hyperpigmented lesions over the right cheek, and right side of neck suggestive of nevus. On examination of feet, there was macrodactyly of great, second, and third toe with splaying; and hypertrophy of plantar surfaces with increased rugosity.

Investigations showed blood counts, renal and liver function tests within normal limits.

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Magnetic resonance imaging brain showed right hemimegalencephaly with dysplasia with white matter abnormalities [Figure 4a and b]. Electroencephalogram was abnormal showing generalized epileptiform discharges.

**DISCUSSION**

Our case was suspected to have PS based on characteristic facial features, skin abnormalities, dysmorphic growth, and overgrowth pattern.

PS can have varied manifestations. The characteristic features of PS include hemihypertrophy; generalized, unilateral, or localized disproportionate overgrowth of any tissue; distinctive facial features (macrocephaly, dolichocephaly, long face, downslanting palpebral fissures, and low nasal bridge); various capillary, venous and lymphatic malformations; and deep vein thrombosis.

Less common findings include CNS malformations such as hemimegalencephaly, cerebral arteriovenous malformations, abnormal gray-white matter differentiation, neuronal migration disorders, callosal dysgenesis, and hydrocephalus in brain radiology.[8-10] Intellectual disability and seizures may be the presenting features in these individuals and such individuals may have associated distinct facial features.[11] In our case, epilepsy and hemimegalencephaly were noted. The exact incidence of this association with PS is not exactly known as there are very few cases where this association has been reported.

The diagnosis of PS is primarily clinical based on the diagnosis criteria.[11] Diagnosis can be confirmed by molecular genetic studies which includes exome sequencing for activating missense mutation in the AKT1 gene.[12] As mutations occur during early development, the disorder is not inherited and does not run in families. Mutation in PTEN gene has also been reported in some case reports, but the association is not well established.[13] In our case, genetic analysis was offered to the family but could not be performed as genetic testing is not currently available at our center and parents could not afford the investigation due to its high cost.

No specific treatment is available for PS. Management includes multidisciplinary treatment approach involving geneticist, neurologist, orthopedician, and dermatologist along with family support. The child was referred to orthopedic surgeon for the management of overgrown tissues. Antiepileptic drugs were revised, and family

![Figure 1: Facial hypertrophy on right side](image1)

![Figure 2: Epidermal nevus over right side of neck](image2)

![Figure 3: (a) Macroductyly of both feet. (b) Increased plantar rugosities](image3)

![Figure 4: (a and b) Magnetic resonance imaging brain: Megalencephaly right side](image4)
was counseled for drug compliance. The child is under regular follow-up for ensuring drug compliance and for monitoring of growth and secondary complications.

**Conclusion**

PS has various systemic abnormalities, a detailed and thorough clinical examination is essential in every child suspicious of PS.

In view of our case study, we value the importance of adopting multidisciplinary approach for early detection of functional disorders with special emphasis on neurological manifestations associated with this disorder and to minimize disabilities, reduce morbidity, and mortality associated with PS. We hope our case findings increase treating physician’s/pediatrician’s attention toward the possibility of diagnosing this association in PS patients.

**Declaration of patient consent**

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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**Conflicts of interest**

There are no conflicts of interest.

**REFERENCES**