Proteus syndrome: More vigilance needed to diagnose it

Sir,

We read with interest the article 'Proteus syndrome: Clinical diagnosis of a series of cases' by Alves *et al.*,[1] and would like to make some important comments.

Proteus syndrome (PS) is a rare hamartomatous syndrome characterized by asymmetric overgrowth of multiple organs, hyperplasia of connective tissue, vascular malformations, epidermal nevus, and hyperostosis, which are mosaic in distribution, sporadic in occurrence, and follow progressive course.[2,3] The characteristic features may not be present at birth or infancy, but there may be subtle facial asymmetry, or mild hemihyperplasia. Clinical features typically worsen with the age. Therefore, diagnosis is usually delayed until lesions are fully expressed in later childhood or adolescence.[4]

Till recently, over 200 cases of PS have been reported in literature and only a few cases are reported from the Indian subcontinent. This may be due to non-familiarity with clinical signs of this condition and unavailability of diagnostic tests. Alves *et al.*,[1] reported 13 patients with diagnosis of PS from Brazil. Recently, we also reported six cases of PS from north India.[5] In both these series, the diagnosis of PS was established by clinical criteria proposed by Biesecker *et al.*[2] The number and percentages of patients showing different clinical features in these two series are shown in Table 1 and the salient differences are discussed below.

We reported six cases of PS seen over a period of 3 years[5] where as Alves *et al.*,[1] reported 13 cases seen over a period of 13 years. This may be due to the large population catered by the hospital in which the study was performed and increased awareness among pediatricians about this condition. The age at presentation was 6.92 ± 5.1 years in the study by Alves *et al.,* and among them 76.9% (10 of 13) were females.[1] Whereas in our study, the patients were presented almost 2.73 years earlier with mean age of 4.19 ± 3.77 years (range: two months to ten years) and out of these four were females and two were males.[5] This is in contrast to male to female ratio of 1.9:1 reported in literature.[2,3]

Asymmetrical overgrowth was the presenting feature in all the cases in both case series followed by macrodactyly. A higher percentage of our cases[5] had café-au-lait spots, and abnormal facial phenotype; lower percentages had scoliosis, hemangioma, and lipoma; and none had linear epidermal nevus, respiratory problem, ocular lesions, lymphangioma, and dental abnormalities than among cases reported by Alves *et al.*[1] The cerebriform connective tissue nevus (CCTN) in 2 cases; and megalencephaly, and lissencephaly in 1 each were noted in our cases.[5] but not by Alves *et al.*[5] The CCTN is hallmark of the disease and presence of single CCTN along with general criteria confirms the clinical diagnosis of PS. CCTN usually develops later in the childhood with a tendency to maintain stability in adult hood. It commonly involves soles and palms, but rarely back, lateral and dorsal aspects of fingers, and nose.[1,2,5] The risk of development of tumors is higher in cases with PS. None of the cases had any tumor during the study period. The differences in clinical features may be due to presentation at different ages or different disease causing mutations in different populations.

PS needs to be differentiated from other hamartomatous conditions such as Klippel-Trenaunay-Weber syndrome, Maffucci disease, Ollier's disease, neurofibromatosis type I, Bannayan-Zonana syndrome, hemihyperplasia and multiple lipomatosis syndrome (HHML) and other disorders that present with hemihyperplasia.[1]

Although the molecular diagnosis of PS (mutations in *AKT1* gene) is just recently reported.[6] but it is not yet commercially available at all places. Therefore, the diagnosis of PS relies mainly on strict clinical criteria.[2] Therefore, clinicians should be aware of the diverse clinical features of PS so that the

Table 1: Proportion of patients showing different clinical features of Proteus syndrome in two recently reported case series

Clinical features, (*n* (%))	Alves *et al.*, 2013 *n*=13	Angurana *et al.*, 2013 *n*=6
Asymmetrical overgrowth	13 (100)	6 (100)
Macrodactyly	11 (84.6)	5 (83.3)
Linear epidermal nevus	6 (46.1)	0
Scoliosis	6 (46.1)	1 (16.7)
Macrocephaly, cranial asymmetry and/or exostosis	5 (38.4)	Macrocephaly: 1 (16.7) Facial/cranial asymmetry: 2 (33.3) Exostosis: 1 (16.7)
Hemangioma	4 (30.7)	1 (16.7)
Respiratory findings	4 (30.7)	0
Ocular disorder	4 (30.7)	0
Lipoma	3 (23)	1 (16.7)
Café-au-lait spots	2 (15.3)	4 (66.7)
Lymphangiomas	2 (15.3)	0
Dental anomalies	2 (15.3)	0
Facial phenotype	2 (15.3)	3 (50)
Bullous pulmonary disease	1 (7.6)	0
Cerebriform connective tissue nevi	0	2 (33.3)
Megalencephaly and lissencephaly	0	1 each (16.7)

diagnosis can be established earlier and multidisciplinary preventive and therapeutic strategies could be started promptly.

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