

The Manifold Faces of Proteus Syndrome

IN THIS ISSUE OF THE ARCHIVES, NGUYEN AND COLLEAGUES present a clinically oriented study of 24 consecutive patients with Proteus syndrome who were evaluated at the National Institutes of Health in Bethesda, Md.¹ The diagnostic criteria of Proteus syndrome proposed by an international working group some years ago were met in all cases.² Because this multisystem birth defect occurs rarely, an analysis of such a large cohort is most welcome.

ADDITIONAL EVIDENCE OF MOSAICISM

Nguyen and colleagues provide further support to the idea that the disorder is caused by a mutation that is lethal except in mosaicism. All cases were sporadic. A hierarchical cluster analysis showed that none of the cutaneous protean abnormalities was tightly linked to one extracutaneous defect or the other. This randomness of findings is best explained by mosaicism. On the other

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hand, the authors document a positive correlation between the number of different types of cutaneous lesions and the number of various extracutaneous abnormalities. They argue that an early postzygotic mutation would give rise to more cutaneous and extracutaneous abnormalities, whereas a late somatic mutation would result in a smaller number of different abnormal cell lineages.

THE IMPORTANCE OF SKIN SIGNS

All of the patients had at least 2 different skin abnormalities and most of them had more, including lipomas (92%), telangiectatic nevi or other vascular lesions (88%), plantar cerebriform connective tissue nevi (83%), or linear lesions of an epidermal nevus (67%). Remarkably, connective tissue nevi were likewise found on the palms, forearms, trunk, and face. Epidermal nevi were examined histopathologically in only 2 patients.

The vascular lesions documented included “capillary malformations,” “venous malformations,” and “lymphatic malformations.” The authors follow the presently fashionable Mulliken classification of vascular abnormalities.^{3,4} As a consequence, they avoid the terms *vascular nevus*, *nevus flammeus*, or *telangiectatic nevus* and use instead the ambiguous *capillary malformation*. We may guess whether they mean a *nevus flammeus*, a *nevus anemicus*, or something else. Surprisingly, they still speak

of connective tissue nevi or epidermal nevi, although, according to the Mulliken terminology, they should use *connective tissue malformations* or *epidermal malformations*. Why do they categorize lymphangioma as a “malformation,” whereas lipoma is still a “tumor”? Such inconsistencies show that the question of an appropriate classification of vascular abnormalities is as yet unsolved.

Be that as it may, the large number of associated skin lesions clearly shows that dermatologists should be familiar with the clinical spectrum of Proteus syndrome if they are to recognize both typical and oligosymptomatic cases.

NEW ELATTOPROTEUS LESIONS

Nguyen and colleagues found lesions of partial lipohypoplasia in 38% of the patients studied and patchy dermal hypoplasia in 21%. Moreover, muscular hypoplasia was noted in 3 patients (13%). Some years ago I suggested that Proteus syndrome may show, in addition to the lesions of overgrowth (the “Pleio-proteus component”), various lesions of deficient growth (the “Elattopro-teus component”).⁵⁻⁷ To explain this paradoxical association, the concept of didymosis (twin spotting) was proposed.⁵ The study of Nguyen and colleagues supports the idea of such dichotomous involvement.

Remarkably, the authors mention additional dichotomous abnormalities, such as areas of decreased or increased hairiness and hyperpigmented or hypopigmented macules. These findings can be taken as additional circumstantial evidence in favor of the concept that “Elattopro-teus” lesions represent a counterpart to “Pleio-proteus” lesions.

THE PTEN STORY NOW COMES TO AN END

In recent years some authors have suggested that Proteus syndrome may be caused by germline mutations within the *PTEN* gene.⁸⁻¹² I never believed in this etiological concept that would imply that Proteus syndrome can be inherited as an autosomal dominant trait. Other dermatologists, however, were so enthusiastic of the *PTEN* story that they included this nebulous news, against my express will, in some of my own chapters reviewing the epidermal nevus syndromes.^{13,14}

In the present study, DNA from 19 patients was examined for a *PTEN* mutation but none was found. Hence, the absence of a *PTEN* mutation in Proteus syndrome can now be taken as well established.^{15,16} Nguyen and col-

leagues emphasize that cases of "Proteuslike syndrome" showing *PTEN* mutations do not fulfill the clinical criteria of Proteus syndrome and should rather be categorized as "PTEN hamartoma-tumor syndrome."¹⁷ This disillusioning outcome should stimulate dermatologists to help geneticists elucidate the real cause of Proteus syndrome.

PRACTICAL ASPECTS

For the practical management of Proteus syndrome, the authors give us some important hints.¹ They confirm that mental retardation is not a typical sign of this disorder; that past the age of 8 years new types of abnormalities are not likely to occur; and that overgrowth of present lesions is progressive but usually appears to plateau after adolescence.² Most importantly, Nguyen and colleagues discourage us to envisage any surgical treatment of plantar cerebriiform connective tissue nevi, because the resulting scarring tends to be more painful to walk on than the lesions themselves.

Patients with Proteus syndrome need a multidisciplinary management that may be coordinated by a pediatrician or internist, but the authors rightly emphasize the dermatologist's role in this cooperative approach.

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The author has no relevant financial interest in this article.

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News and Notes

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For more information e-mail jennifer_byrnes@urmc.rochester.edu. (This project has been funded in whole or in part with federal funds from the National Institute of Arthritis and Musculoskeletal and Skin Diseases, National Institutes of Health, and Department of Health and Human Services and with funds from The Carl J. Herzog Foundation, Inc, under contract No. NO1-AR-1-2255.)