Progressive overgrowth of the cerebriform connective tissue nevus in patients with Proteus syndrome

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Background: Proteus syndrome is a rare overgrowth disorder that almost always affects the skin.

Objective: Our purpose was to evaluate progression of skin lesions in patients with Proteus syndrome.

Methods: Skin findings were documented in 36 patients with Proteus syndrome. Progression of skin lesions in 16 of these patients was assessed by comparing photographs obtained on repeated visits for an average total duration of 53 months.

Results: The skin lesion most characteristic of Proteus syndrome, the cerebriform connective tissue nevus, showed progression in 13 children but not in 3 adults. The cerebriform connective tissue nevus progressed by expansion into previously uninvolved skin, increased thickness, and development of new lesions. Lipomas increased in size, number, or both in 8 of 10 children with lipomas. In contrast, epidermal nevi and vascular malformations generally did not spread or increase in number.

Limitations: Only 3 adults with Proteus syndrome were evaluated longitudinally.

Conclusion: The cerebriform connective tissue nevus in Proteus syndrome grows throughout childhood but tends to remain stable in adulthood. (J Am Acad Dermatol 2010;63:799-804.)

Key words: cerebriform connective tissue nevus; overgrowth; progression; Proteus syndrome.

Proteus syndrome is a rare overgrowth disorder affecting multiple tissues including bone, soft tissue, and skin. The syndrome was described by Cohen and Hayden[1] in 1979 and given its current name by Wiedemann et al[2] in 1983. As of October 2004, there were fewer than 100 published cases fulfilling current diagnostic criteria worldwide.[3] Diagnosis is made by evidence of 3 mandatory general criteria, including sporadic occurrence, mosaic distribution of lesions, and progressive course. These must be accompanied by specific criteria, several of which comprise skin lesions.[4] The cerebriform connective tissue nevus (CCTN) is one of the most characteristic skin findings. It commonly occurs on the soles of the feet, and is frequently a cause of pain, pruritus, infection, bleeding, exudation, odor, and walking impairment.[5] Patients without a CCTN may be given a diagnosis based on the presence of other specific features, but it is typical to have a CCTN and one or more additional skin findings, such as linear verrucous epidermal nevus, dysregulated adipose tissue (lipomas and/or lipohypoplasia), and vascular malformations (capillary, venous, lymphatic, and mixed). Other skin abnormalities, not in the diagnostic criteria but nonetheless associated with Proteus syndrome, include hyperpigmented or hypopigmented macules, patches of dermal hypoplasia, localized hypertrichosis, thick or thin nails, and areas of lighter-colored scalp hair.[6]

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Progression is a mandatory feature for the diagnosis of Proteus syndrome but little is known about the natural history of the skin lesions, whether different lesions progress at different rates, and if the rate of progression is affected by age. In an earlier study, we assessed the progression of skin lesions using a questionnaire. Most patients or their caregivers reported progressive growth in the CCTN and subcutaneous lipomas, whereas the linear verrucous epidermal nevus and vascular malformations tended not to spread to new areas.[5] In the current study we used serial photographs to study changes in the extent of the skin lesions.

CAPSULE SUMMARY

- Proteus syndrome is a rare disorder characterized by postnatal disproportionate overgrowth of the skeletal system, tumor predisposition, and dermatologic abnormalities.
- The cerebriform connective tissue nevus is frequently observed in patients with Proteus syndrome and it is an important specific criterion for diagnosis.
- The cerebriform connective tissue nevus may not be present at birth but grows throughout childhood. Periodic follow-up is needed to manage complications of pain, skin breakdown, and walking impairment.

METHODS

In all, 36 patients were evaluated at the National Institutes of Health after enrolling in protocol 94-HG-0132. They met diagnostic criteria for Proteus syndrome as listed in Table I. Each patient had a complete skin examination and documentation of lesions by photography. Skin manifestations of some patients were reported previously.[5,6] Sixteen patients were included in the longitudinal study as they had two or more visits at least 6 months apart with repeated photographs. Photographs were evaluated retrospectively for interval changes, using a semiquantitative scale for the connective tissue nevus (Table II). Change in the CCTN score over time was estimated using a mixed linear regression model with patient-specific random intercepts. The age and status (adult or child) and their interaction were included in the model as fixed effects. The mixed model analysis module in a software program (SPSS, Version 14, SPSS Inc, Chicago, IL) was used to estimate the model.

RESULTS

There were 14 female and 22 male patients with age at first visit ranging from 1 to 56 years (mean age 14 ± 13 years). Skin lesions associated with Proteus syndrome were observed in all patients (Table III). The frequencies of these lesions were similar to those previously reported.[6]

Sixteen patients were studied longitudinally for an average of 53 months. At presentation, the CCTN in 9 patients was a solitary plaque on one or both soles (4 with ≥ 1 separate papules or plaques on the toes) and 7 patients had multifocal plaques (4 with toe lesions). The CCTN grew by expansion and development of new lesions. Expansion was evident when a CCTN gradually overtook previously uninvolved skin of the sole, with the convoluted ridges of the CCTN increasing in size and number (Figs 1 and 2). Nearly all CCTNs in children showed expansion, and 3 children also developed apparently distinct lesions during the study period. New lesions appeared in areas that were previously uninvolved (Fig 1, *E* to *H*) or had barely detectable involvement (Fig 2, *C*, *arrow*). Discrete lesions also grew until they coalesced (Fig 2, *A* to *C*). All patients younger than 20 years showed progression of the CCTN. One child, in whom the CCTN was unusual in that it involved the chest and abdomen, did not show an increase in the CCTN score during the study period, but progression was clearly evident in the first 4 years of his life.[7] Little or no progression was observed in the 3 adults (Fig 3). Mixed model analysis indicated that the CCTN score increased on average by 1.24 points per year in those younger than 20 years ($P < .001$). This rate of increase was significantly greater than in adult patients ($P < .001$), in whom lesions increased by 0.05 points per year ($P = .78$).

Lipomas increased in size, number, or both in 8 of 10 children with lipomas. Linear verrucous epidermal nevi were stable in size but became darker over time in 4 of 10 children, and one child developed small new epidermal nevus papules between ages 3 and 6 years. Capillary vascular malformations remained stable in extent. Venous varicosities on the legs gradually became more prominent.

DISCUSSION

A mandatory criterion for the diagnosis of Proteus syndrome is a progressive course. This clinical criterion refers primarily to the skeletal system, in which patients experience distorting and disproportionate overgrowth of bones.[8] Here we show that progression throughout childhood is a consistent feature of the CCTN.

The typical course for the Proteus CCTN is for one or a few lesions to appear on the sole or soles at