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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Supported by Sulzberger Laboratory for Dermatologic Research, and the Intramural Research Program of the National Institutes of Health, National Human Genome Research Institute.

Conflicts of interest: None declared.

Accepted for publication December 13, 2009.

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Published online August 16, 2010.

0190-9622/$36.00

doi:10.1016/j.jaad.2009.12.012

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

Table I. Diagnostic criteria for Proteus syndrome

General criteria: mosaic distribution of lesions, sporadic occurrence, and progressive course
Specific criteria (either A, 2 from B, or 3 from C):
A. Cerebriform connective tissue nevus
B. 1. Linear epidermal nevus
2. Asymmetric, disproportionate overgrowth (≥ 1)
a. Limbs
b. Hyperostosis of skull or external auditory canal
c. Megaspondylodysplasia
d. Viscera: spleen or thymus
3. Specific tumors before second decade: bilateral ovarian cystadenoma or parotid monomorphic adenoma
C. 1. Dysregulated adipose tissue (1 or both)
a. Lipomas
b. Regional lipohypoplasia
2. Vascular malformation (≥ 1)
a. Capillary
b. Venous
c. Lymphatic
3. Lung cysts
4. Facial phenotype: dolichocephaly, long face, downslanting palpebral fissures and/or mild ptosis, low nasal bridge, wide or anteverted nares, and open mouth at rest

Table II. Cerebriform connective tissue nevus scoring system

Palms and/or soles:	
None	0
<50% Surface area	+1
50%-75% Surface area	+2
>75% Surface area	+3
Additional involvement of:	
Digits	+1 (per extremity)
Lateral sole or palm	+1 (per extremity)
Other cutaneous surface	+1
Progression (assessed on return visits)	
Spread	
Digits	+1 (per extremity)
Lateral sole or palm	+1 (per extremity)
Thickness	+1 (per extremity)

Points were tallied for each extremity. Progression was measured by changes in area of involvement on palms and soles plus points for spread and increased thickness of cerebriform connective tissue nevus.

Table III. Skin findings in 36 patients with Proteus syndrome

Skin lesion	Subtype or location	No.	Percentage
Connective tissue nevus	Feet	34	94
	Hands	10	28
	Other	4	11
	Total	35	97
Epidermal nevus		25	69
Cutaneous vascular malformations	Capillary	17	47
	Venous	21	58
	Lymphatic	2	6
	Capillary/venous	6	17
	Total	32	89
Dysregulated adipose tissue	Lipoma	28	78
	Lipohypoplasia	9	25
Dermal hypoplasia		8	22
Localized hypertrichosis		14	39
Patchy light scalp hair		4	11
Phylloid or linear hyperpigmented macules		16	44
Gingival overgrowth		7	19

about 2 years of age, although lesions may also appear in other areas of the body.[6] These slowly spread to previously uninvolved skin and grow thicker, becoming rubbery masses that tightly abut each other forming deep folds. It is these deep folds, resembling sulci, which led to the designation of the nevus as cerebriform. New lesions may develop elsewhere on the foot, eventually expanding to coalesce with other lesions. Once it reaches the sides of the foot, the CCTN may extend proximally around the foot, creating a progressively deeper fold between normal-appearing skin and the CCTN. When lesions occur on the toes, they appear as pale firm nodules that grow and may distort the nail. This type of postnatal disproportionate growth is distinct from that observed in other overgrowth syndromes. In patients with hemihyperplasia-multiple lipomatosis syndrome[9] or congenital lipomatous overgrowth, vascular malformations, and epidermal nevi (CLOVE syndrome),[10] the plantar surfaces may be overgrown at birth, but they are softer and compressible, have wrinkles rather than deep folds, and tend to grow with the child rather than disproportionately as in Proteus syndrome.

The scoring system we used provides strong evidence for progression of the CCTN in children with Proteus syndrome. It is only semiquantitative, however, and should not be used to conclude that the rate of growth of the CCTNs was linear or that it was similar in all children. Also, it is not inevitable that all CCTNs progress to involve the entire sole, because the 3 adults in this study had stable areas of

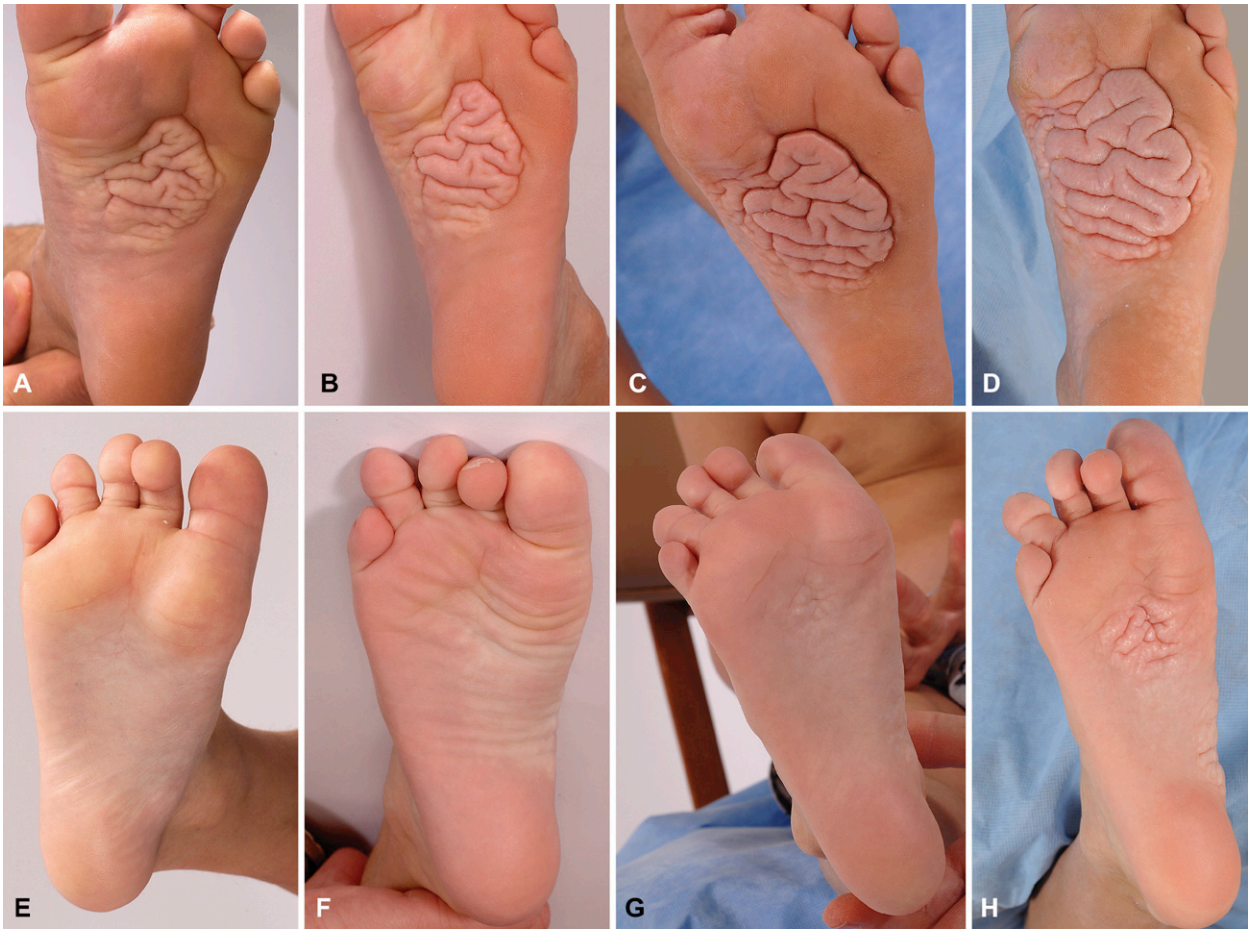

Fig 1. Progression of cerebriform connective tissue nevus early in childhood. Left (**A** to **D**) and right (**E** to **H**) soles of patient with Proteus syndrome at ages 3.7 (**A** and **E**), 4.5 (**B** and **F**), 5.5 (**C** and **G**), and 7.5 (**D** and **H**) years. Plaque on left sole expanded and new plaques appeared near ball of foot and instep of right sole.

sparing. The adults tended to have lower CCTN scores than the children. This may reflect an overall lower disease severity for those who survive into adulthood.[6] Further longitudinal studies with more accurate volume measurements and more adult patients are required to better predict the growth of the Proteus CCTN.

Currently, there is no medical therapy that slows the growth of the CCTN,[11] and surgery is discouraged because of recurrence and painful scarring that may make walking impossible.[12] However, there is one report in the medical literature of a patient with bilateral plantar CCTN who underwent successful surgical removal of the CCTN with skin grafting.[13] New treatments are urgently needed, as these lesions are disfiguring and cause functional impairment. Patients encounter difficulties with foot hygiene, which can lead to odor and recurrent bacterial and fungal infections. Shoes may need to be modified and custom orthoses designed to help prevent blisters and skin breakdown.

One approach to medical therapy would be to target the abnormal cells that contribute to the growth of the CCTN. The CCTN of Proteus syndrome has decreased fibroblasts, variable thick collagen bundles in a disorganized pattern, sparse fragmented elastic fibrils, and increased fat and sweat glands in the reticular dermis.[14] It would appear that the plantar fibroblasts are defective, and investigations into fibroblasts grown from a CCTN in one patient documented decreased collagenase expression.[13]

The genetic basis for these cellular abnormalities is unknown. Proteus syndrome appears to result from mosaicism,[15] making it especially challenging to identify the causative mutation or mutations.

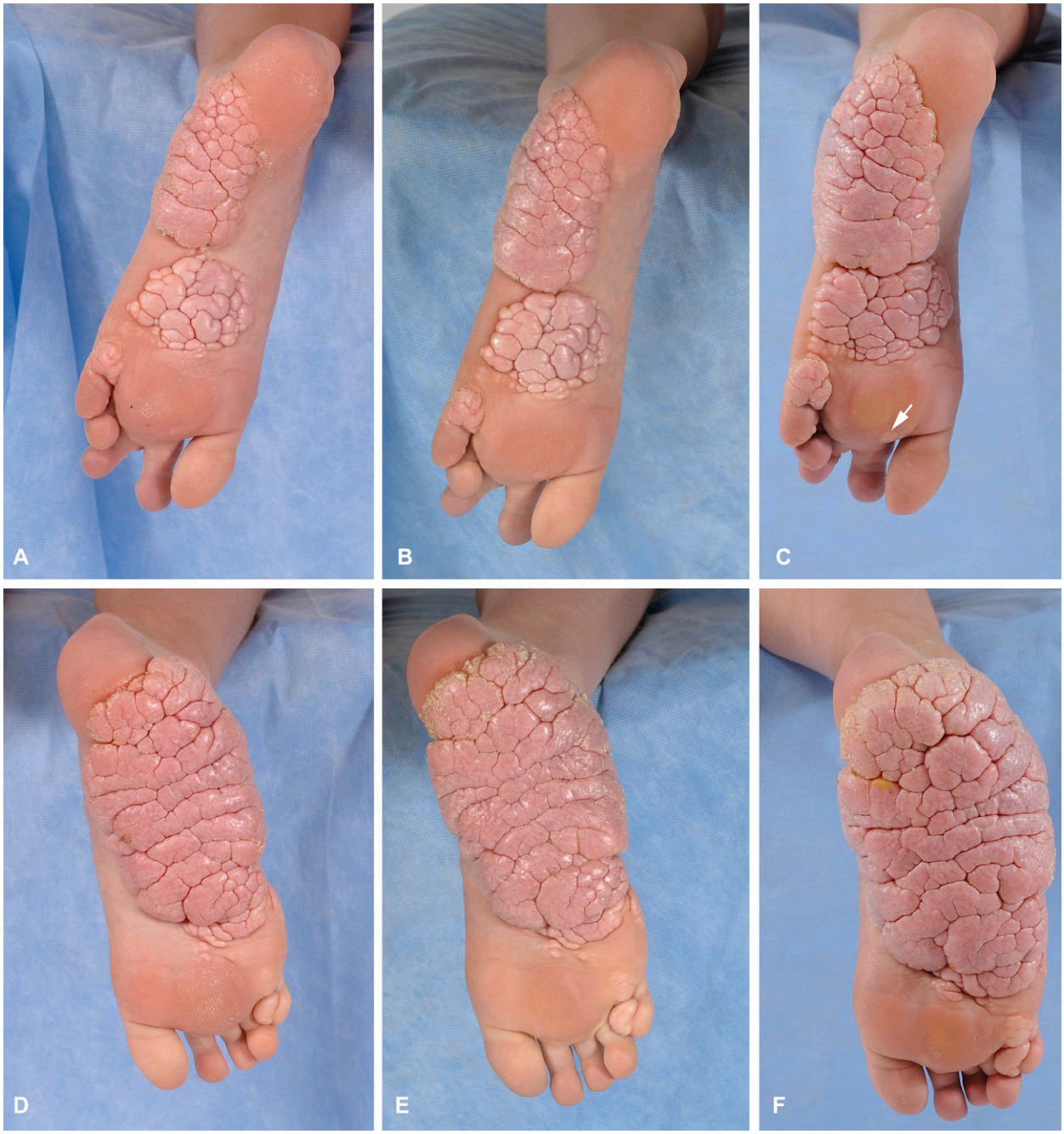

Fig 2. Progression of cerebriform connective tissue nevus later in childhood. Left (**A** to **C**) and right (**D** to **F**) soles of patient with Proteus syndrome at ages 11.4 (**A** and **D**), 12.1 (**B** and **E**), and 13.4 (**C** and **F**) years. Arrow in **C** indicates a growing papule separate from the main plaque.

Mutations in *PTEN* have been documented in several children with an overgrowth syndrome with features of Proteus syndrome,[16] but the diagnosis of Proteus syndrome has been disputed.[17,18] Genetic analysis may have therapeutic implications, as one child with life-threatening overgrowth caused by a germline *PTEN* mutation showed decreased size of soft-tissue masses in the mediastinum and pelvis during treatment with oral rapamycin.[19] This promising result needs to be confirmed for others with PTEN hamartoma tumor syndrome. It provides hope that further investigations into the genetic and molecular abnormalities in patients with Proteus syndrome will provide clues leading to a targeted therapy.

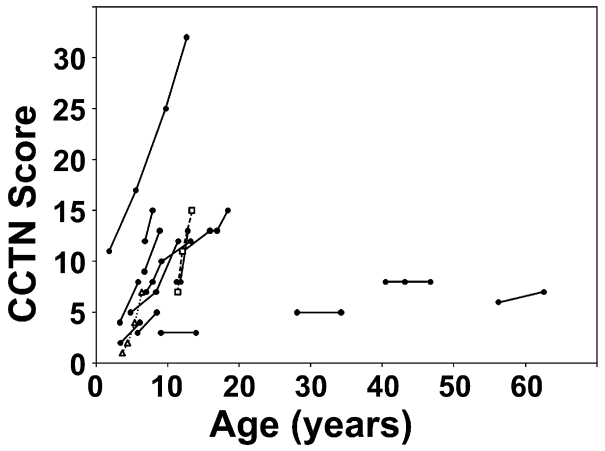

Fig 3. Graphic analysis of interval changes in cerebriform connective tissue nevus (*CCTN*). Total CCTN scores at different ages are plotted for each patient in longitudinal study. CCTN scores for patients in Figs 1 and 2 are represented by *dotted line* with *open triangles* and *dashed line* with *open squares*, respectively.

We thank Cara Olsen for statistical analysis.

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