Cutaneous Manifestations of Proteus Syndrome

Correlations With General Clinical Severity

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Background: Proteus syndrome is a rare congenital disorder with progressive asymmetric overgrowth of multiple tissues.

Objectives: To determine the range of cutaneous findings in Proteus syndrome and to correlate cutaneous findings with overall disease severity.

Design: A prospective cohort study was performed at the National Institutes of Health, a tertiary referral center.

Patients: Twenty-four consecutive children and adults with Proteus syndrome meeting recent diagnostic criteria.

Interventions: Physical examination, including complete skin examination, and review of medical records.

Main Outcome Measures: Frequency of skin findings; correlation of skin findings with extracutaneous findings; cluster analysis of findings.

Results: The 24 patients had skin abnormalities: 22 (92%) had lipomas, 21 (88%) had vascular malformations, 20 (83%) had cerebriform connective tissue nevi on the soles of the feet, 16 (67%) had epidermal nevi, 9 (38%) had partial lipohypoplasia, and 5 (21%) had patchy dermal hypoplasia. Some patients had localized alterations in skin pigmentation and hair or nail growth. Patients with a greater number of skin abnormalities tended to have a greater number of extracutaneous abnormalities. The number of abnormalities tended to increase with age up to 8 years.

Conclusions: Patients with Proteus syndrome exhibit a variable but defined assortment of cutaneous findings. The correlation between numbers of cutaneous and extracutaneous abnormalities is consistent with the postulated mosaic basis for this syndrome.

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Proteus syndrome is hypothesized to result from mosaicism for a mutation that is lethal in the nonmosaic state. Based on this hypothesis, an early postzygotic mutation would be expected to present with more abnormalities than a late postzygotic mutation. We speculated that individuals with more skin abnormalities would have more severe internal abnormalities. To test this, we documented skin and internal findings in patients meeting diagnostic criteria for Proteus syndrome. Our results indicate that patients with a greater number of skin abnormalities tend to have a greater number of internal abnormalities.

METHODS

Twenty-four consecutive patients with Proteus syndrome were evaluated at the National Institutes of Health between November 1996 and February 2001 following approval by an institutional review board. Patients were recruited by direct contacts with colleagues, announcements in medical journals, and the Proteus Syndrome Foundations of the United States and United Kingdom. All patients underwent a standardized evaluation consisting of history taking and physical examination, total body skin examination, clinical photography, and complete review of medical records including radiological and histopathological reports. Cutaneous lesions were diagnosed based on clinical appearance, and confirmed in some cases by histologic evaluation.
RESULTS

There were 14 male and 10 female patients ranging in age from 10 months to 40 years (median, 12 years). Most were from North America but others came from Europe, the Middle East, and South America. Some were ambulatory while others required a wheelchair because of severe leg deformity. Most manifested normal intellect, but a few had mental retardation. All showed progressive disproportionate overgrowth as assessed by patient history, previous medical records, and photographs.

CUTANEOUS FINDINGS

All patients had skin abnormalities associated with Proteus syndrome. There were cerebriform connective tissue nevi in 22 patients (on the soles of the feet in 20), epidermal nevi in 16, cutaneous vascular malformations in 21 (including capillary, venous, lymphatic, and combined malformations), lipomas in 22, partial lipohypoplasia in 9, and patchy dermal hypoplasia in 5. The skin abnormalities varied from 3-mm macules and papules to massive lesions distributed over the trunk and extremities. Skin findings for the 24 patients are summarized in Table 2.

Cerebriform connective tissue nevi appeared as well-demarcated plaques consisting of confluent skin-colored papules and nodules. On the soles of the feet, they were pink with a rugated, cerebriform appearance (Figure 1). Larger lesions were very firm and had tight folds. The cerebriform connective tissue nevi were distributed as follows among the 20 patients who had them on the soles: 12 were bilateral with asymmetric extent of involvement, 5 were on the right foot only, and 3 on the left foot only. The average age of onset for patients with connective tissue nevi on the soles was 2 years. Growth usually began on the balls of the feet near the arch, with subsequent extension to cover the entire sole and sides of the feet. Five patients had cerebriform connective tissue nevi on the palms in addition to the soles. Connective tissue nevi were also found on the forearm in 1 patient, extensively on the chest, abdomen, and back in another, and just inferior to the nasal ala in 2. The perinasal lesions were single, firm, skin-colored nodules. Cerebriform connective tissue nevi on the soles were a common cause of morbidity as they caused difficulty in walking and pain. Patients complained of foot odor and some reported ulcerations and infections of their feet.

Epidermal nevi appeared as tan to brown, flat-topped, well-demarcated, hyperkeratotic papules in linear streaks along the lines of Blaschko. Patients had multiple patches scattered over the body in an asymmetric distribution. Biopsy specimens of truncal lesions from 2 patients revealed acanthosis and hyperkeratosis consistent with epidermal nevi.

Most patients had vascular malformations. Capillary malformations were pink to red blanchable macules. Venous malformations ranged from localized net-works of ectatic veins to violaceous compressible masses. Two patients had macrocystic lymphatic malformations appearing on imaging studies as large skin-colored chest wall masses that contained vascular channels. Some lesions were combined capillary-venous malformations (Figure 2). In 1 patient, histologic examination revealed densely aggregated dilated capillaries and thin-walled vessels lined by a single layer of endothelial cells. One patient had a combined capillary-microcystic lymphatic malformation consisting of clusters of clear and hemorrhagic vesicles on a red macule. Vascular malformations most often involved the trunk or legs.

Lipomas appeared as soft skin-colored nodules and tumors with poorly demarcated borders. They varied in size from small nodules to extensive masses invading deeper tissues and were most commonly found on the head, abdomen, groin, and legs. Partial lipohypoplasia appeared as regions of skin with minimal fat showing accentuated bony contours. Patients with Proteus syndrome had either lipohypoplasia of one half of the trunk or lipohypoplasia predominantly involving the extremities. Dermal hypoplasia ap-

Table 1. Diagnostic Criteria for Proteus Syndrome

<table>
<thead>
<tr>
<th>Mandatory general criteria</th>
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<tr>
<td>Mosaic distribution of lesions</td>
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<td>Progressive course</td>
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<td>Sporadic occurrence</td>
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Specific criteria (A, or 2 from group B, or 3 from group C)

Group A
- Connective tissue nevus

Group B
- Epidermal nevus
- Disproportionate overgrowth (1 or more)
- Limbs
- Skull (hyperostoses)
- External auditory meatus (hyperostosis)
- Vertebra (megalospondylodysplasia)
- Viscera (spleen and/or thymus)

- Specific findings before the end of the 2nd decade (either one)
  - Bilateral ovarian cystadenomas
  - Parotid monomorphomorphic adenoma

Group C
- Dysregulated adipose tissue (either one)
- Lipomas
- Regional absence of fat
- Vascular malformations (1 or more)
- Dysregulated adipose tissue (either one)
- Regional absence of fat
- Vascular malformations (1 or more)

Facial phenotype
- Dolichocephaly
- Long face
- Minor downslanting of palpebral fissures and/or minor ptosis
- Low nasal bridge
- Wide or anteverted nares
- Open mouth at rest

The diagnosis of Proteus syndrome was based on published criteria14 (Table 1) and abnormalities were tabulated as present or absent. Pearson correlations (bivariate and partial) were used to relate skin findings, extracutaneous findings, total (skin plus extracutaneous) findings, and age. The Fisher exact test was used to compare mortality rates between groups of patients characterized by total number of abnormalities. Clusters of patients and findings were identified by means of a hierarchical clustering algorithm using squared Euclidean distance and between-groups linkage. Principal components analysis was used to calculate the percentage of variance among patients explained by combinations of symptoms. All analyses were performed using SPSS(R) for Windows, version 11.0 (SPSS Inc, Chicago, Ill).
peared as reddish depressed plaques of thinned skin with prominent veins (Figure 3). It was seen mostly on the thighs and lower legs, and was typically accompanied by decreased subcutaneous fat and an absence of hair.

Five patients exhibited relative hypertrichosis of 1 extremity or as a localized patch. Others had focal decreased hair growth: one had thin and sparse scalp hair, another had sparse eyebrows, and a third had a loss of lateral eyebrows. One had a low anterior hairline, another had a low posterior hairline, and 2 had scalp hair with patches of lighter color. Nine patients had nail abnormalities that, in most cases, were localized to a few nails. These abnormalities included thick nails, thin nails, brachyonychia, koilonychia, and bluish nails.

Several patients exhibited nonpalpable pigmentary alterations. Four patients had 1 or a few faintly hyperpigmented macules. These were linear and followed the lines of Blaschko, or were truncal macules that did not cross the midline. Two patients had solitary café au lait macules, and 3 had sharply circumscribed hypopigmented oval macules. They measured up to 2.5 cm in their greatest dimension and were located on the upper lip and lower back in one patient or on the lower back (2 lesions) in another, and they were scattered on the upper back in a third.

Craniofacial structures were asymmetric in most patients and facial asymmetry was present in 15, 6 of whom also had cranial asymmetry (Figure 4). Ear asymmetry was present in 5 patients, downslanting palpebral fissures were observed in 8, dolichocephaly in 7, wide or anteverted nares in 5, and low nasal bridge in 4. Oral findings included crowded dentition in 11 patients, a high-arched palate in 10, gingival overgrowth in 9, and prominent tongue papillae in 3. Three patients had heterochromic irides.

### EXTRACUTANEOUS FINDINGS

Extracutaneous manifestations were divided into the following categories: skeletal overgrowth, visceral overgrowth, other overgrowth, tumors, cysts, vascular abnormalities, deformity, and hypoplasia/maldevelopment (Figure 5). Overgrowth of the hands or feet was present in all of the patients and usually involved the fingers and toes. Overgrowth of the arms or legs was the second most common form of skeletal overgrowth. It affected 23 (96%) of the 24 patients, and usually involved the knees and restricted joint mobility. Hyperostotic overgrowth of the skull and external auditory canal were observed in 14 and 6 patients (38% and 25%), respectively. The spleen was enlarged in 8 (33%) and the kidneys in 4 (17%) of the patients. Fat infiltration (involving the spinal cord/paraspinal region, heart, pancreas, or other organs) and pharyngeal or vocal cord overgrowth affected 11 (46%) and 9 (38%) of the patients.

### Table 2. Skin Findings in Proteus Syndrome

<table>
<thead>
<tr>
<th>Patient No./†</th>
<th>Sex/Ethnicity</th>
<th>Connective Tissue Nevus</th>
<th>Epidermal Nevus</th>
<th>Cutaneous Vascular Malformations</th>
<th>Dysregulated Fat Distribution</th>
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<td>Feet/Hands/Other</td>
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Total Positive: 20/24, 5/24, 4/24, 16/24, 14/24, 14/24, 2/24, 4/24, 1/24, 22/24, 9/24, 5/24

Percentage: 83, 21, 17, 67, 58, 58, 8, 17, 4, 92, 38, 21

Abbreviations: Cap, capillary; H, Hispanic; Lym, lymphatic; Ven, venous; W, white.

* Skin findings are tabulated as present (+) or absent (−).

† Patients 1 through 13 were younger than 10 years and patients 14 through 24 were 10 years or older.
The most common tumors were epibulbar dermoid of the eye, which was found in 7 (29%) of the patients, and a benign ovarian tumor (ovarian cystadenoma), which was found in 3 (33%) of the 10 female patients. Cysts were found in the lungs in 5 (21%) and brain in 4 (17%) of the patients. Internal vascular abnormalities were observed in 7 patients and were multiple in 3. Scoliosis and chest asymmetry were seen in 17 (71%) and 13 (54%) of the patients. Hernias, hydrocele, and undescended or absent testes were each observed in 4 (29%) of the 14 male patients, some of whom had more than 1 of these abnormalities. Tracheomalacia and muscle hypoplasia each affected 3 (13%) of the patients.

The 4 patients who died during the course of this study were 1 year 9 months, 9 years, 15 years, and 17 years of age; 2 died of pulmonary emboli,1 1 of pulmonary emboli and internal bleeding, and 1 of unknown causes. They all had reduced mobility and 3 had leg varicosities, including the patient who died from unknown causes. The most severely affected of them had deep venous thrombosis in the leg as well as internal vascular malformations.

RELEVANCE OF FINDINGS

Patients with a greater number of skin abnormalities tended to have a greater number of extracutaneous abnormalities (Figure 6). The partial correlation of the number of skin findings and the number of extracutaneous findings, after adjusting for age, was 0.575 (P = .004).

The correlation between age and total number of findings was positive up to age 8 years (r = 0.51; P = .11) but negative for patients older than 8 years (r = −0.34; P = .26) (Figure 7). This trend may reflect the progression of Proteus syndrome with age as well as the survival of only the less severely affected individuals. Consistent with this hypothesis, there were no deaths among 13 patients with a total of 17 or fewer findings, but 4 deaths among 11 patients with a total of more than 17 findings (P = .03, Fisher exact test).

Hierarchical cluster analysis was used to test the hypothesis that there may be nonrandom clinical subtypes of Proteus syndrome. Clusters of findings would suggest that some abnormalities were linked to the occurrence of other abnormalities. None of the abnormalities, however, were tightly linked to other abnormalities (data not shown). Furthermore, principal components analysis indicated that no combination of findings explained more than 14% of the variance among patients. These results suggest that findings do not tend to occur in well-defined patterns.

Clusters of patients would suggest that there are subgroups of patients, which would raise concerns about the diagnostic criteria used in assembling the patient population. However, no clear subgroups of patients were identified (data not shown).
While patients with Proteus syndrome have a variable clinical appearance, they exhibit a defined constellation of skin abnormalities. The variability in appearance is partly due to the presence or absence of specific skin lesions as well as differences in their extent and location. All 24 patients in this series had at least 2 skin abnormalities and most had several.

Cerebriform connective tissue nevi on the soles of the feet are particularly characteristic of Proteus syndrome. Before the age of 2 years these lesions may be inapparent. Initially there may be a slight thickening of the skin at the ball of the foot, with minimal folds. This early manifestation is not sufficient to be considered a diagnostic criterion since it resembles the sole overgrowth seen in other conditions. In the latter, the ballooned sole may present some exaggeration of the normal wrinkling pattern, but this should not be confused with the cerebriform connective tissue nevus characteristic of Proteus syndrome, in which the folds deepen and come into apposition as the nevus thickens. Called cerebriform because of their resemblance to the surface of the brain, they may involve the entire sole and extend onto the dorsum of the foot. In 12 of the patients, cerebriform connective tissue nevi involved both feet, one foot more severely than the other. Patients with the most extensive involvement of the feet also had cerebriform connective tissue nevi on the hands.

Cerebriform connective tissue nevi are a major problem for patients. They hinder walking by changing the contour of the sole, can be painful, and are prone to ulceration and infection. The tight and deep folds make cleaning difficult, and malodor can be a source of embarrassment. After surgical excision of cerebriform connective tissue nevi, patients had scarring that was more painful to walk on than the original lesions. Therefore, we recommend conservative medical management whenever possible. Management includes (1) keeping the feet clean by soaking them and cleaning between the folds with a cotton-tipped swab; (2) keeping the feet dry by carefully drying between the folds (eg, with a hair drier set on low heat), wearing shoes that breathe, and using cotton socks; (3) applying an antibacterial lotion as needed to reduce odor; (4) applying topical antiperspirants as needed to reduce moisture; (5) closely monitoring for ulcerations and infections; and (6) using orthotic devices that conform to the lesion and spread pressure across the sole of the foot.

Lipomas, vascular malformations, and epidermal nevi were observed in most patients (22 [92%], 21 [88%], and 16 [67%], respectively). These lesions ranged from solitary and small to multiple, widespread, and disfiguring.

It has been recently recognized that Proteus syndrome can result in deficient growth as well as over-
growth. In the skin, this can appear as partial lipohypoplasia or patchy dermal hypoplasia. Some of our patients showed patches of increased or decreased hair growth (both in length and thickness of hair), nails that were thicker, thinner, or broader than normal nails, and changes in skin pigmentation that included hyperpigmented and hypopigmented macules. Further studies will be needed to determine whether these findings fit the pattern of overgrowth and deficient growth seen in Proteus syndrome.

A greater number of skin abnormalities correlated with a greater number of extracutaneous abnormalities. This suggests that patients with more skin abnormalities need to be evaluated more thoroughly for internal ones. This observation may also have implications for etiology. Recently, germline mutations in PTEN have been identified in some patients with features of Proteus syndrome. The diagnosis has been questioned in these patients and these findings have not been replicated. Most authors suggest that Proteus syndrome results not from a germline mutation, but from mosaicism for a mutation that is lethal in a nonmosaic state. The positive correlation between the number of different types of skin lesions (with different cellular lineages) and the number of internal abnormalities is consistent with mosaicism. An early postzygotic mutation would be expected to present with more skin and internal abnormalities than a late postzygotic mutation because an early somatic cell carrying a mutation would give rise to more abnormal cell lineages.

Children with Proteus syndrome are often born with few visible anomalies and subsequently show progressive overgrowth of multiple tissues. One might expect, there-
fore, an increasing number of abnormalities with age. In our cross-sectional study there did appear to be a greater number of abnormalities as children became older, but only up to the age of about 8 years. The lower number of abnormalities in older patients may reflect improved survival of individuals with reduced disease severity. Consistent with this, 4 of the more severely affected patients died at a young age. These findings are useful for understanding the nature of this disease, but should not be used to predict mortality in individual patients because of the small group size and resulting wide confidence limits.

The patients in this series could not be clearly separated into subgroups with similar findings, which suggests that the diagnostic criteria, tentatively proposed based on recommendations of experienced clinicians,13 are useful in delineating a single syndrome. This does not, however, confirm that these patients share a single etiology, nor does it eliminate the possibility that some patients who do not meet the proposed diagnostic criteria actually have Proteus syndrome. It signifies that these diagnostic criteria define a patient population on which to base further clinical and molecular studies. The fact that no PTEN mutations have been identified in 19 patients confirmed by us to have Proteus syndrome shows that the diagnostic criteria define a cohort of patients who are clinically distinct from the PTEN hamartoma-tumor syndrome.23

In conclusion, patients with Proteus syndrome have a variety of cutaneous and extracutaneous abnormalities appearing as overgrowth, deficient growth, tumors, and malformations. Dermatologists may play an important role in diagnosing and treating the many skin lesions of Proteus syndrome. Because of the wide array of abnormalities, patients diagnosed with Proteus syndrome benefit from a multidisciplinary approach. A pediatrician or internist may coordinate care between multiple specialists including a general surgeon, an orthopedic surgeon, a dermatologist, an ophthalmologist, an otolaryngologist, an oral and maxillofacial surgeon, an urologist or gynecologist, a radiologist, a geneticist and a genetic counselor. In addition, families should be referred to a patient support group, the US Proteus Syndrome Foundation (http://www.proteus-syndrome.org/) or the affiliated UK organization (http://www.proteus-syndrome.org.uk/).

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