

Reassessment of the Proteus Syndrome Literature: Application of Diagnostic Criteria to Published Cases

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The medical care of patients affected by rare disorders depends heavily on experiences garnered from prior cases, including those patients evaluated by the treating physician and those published in the medical literature. The utility of published cases is wholly dependent upon accurate diagnosis of those patients. In our experience, the rate of misdiagnosis in Proteus syndrome (PS) is high. Diagnostic criteria have been published, but these criteria have not been applied consistently and were published after many case reports appeared in the literature. We reviewed 205 cases of individuals reported to have PS in the literature and three of us independently applied the diagnostic criteria to these case reports. Our initial diagnostic congruence was 97.1% (199/205); the discrepancies in six cases were easily resolved. Only 97 (47.3%) of reported cases met the diagnostic criteria for PS; 80 cases (39%) clearly did not meet the criteria; and although 28 cases (13.7%) had features suggestive of PS, there were insufficient clinical data to make a diagnosis. Reported cases that met the PS criteria had a higher incidence of premature death, and other complications (scoliosis, megaspondyly, central nervous system abnormalities, tumors, otolaryngologic complications, pulmonary cystic malformations, dental and ophthalmologic complications) compared to those in the non-Proteus group. The cases that met the criteria were more often male, which has implications for hypotheses regarding the etiology and pathophysiology of PS. We also studied the attributes that led authors to conclude the reported patients had PS when we concluded they did not. We found that two of the diagnostic criteria (disproportionate overgrowth and connective tissue nevi) were often misinterpreted. In PS, the abnormal growth is asymmetric, distorting, relentless, and occurred at a faster rate compared to the rest of the body. Furthermore, PS was associated with irregular and disorganized bone, including hyperostoses, hyperproliferation of osteoid with variable calcification, calcified connective tissue, and elongation of long bones with abnormal thinning. In contrast, non-Proteus cases displayed overgrowth that was asymmetric but grew at a rate similar to the

growth found in unaffected areas of the body. Also, the overgrowth in non-Proteus cases was associated with normal or enlarged bones together with ballooning of the overlying soft tissues. Taken together, these data show that (1) PS diagnostic criteria sort individuals with asymmetric overgrowth into distinct groups; (2) individuals with PS were more likely to have serious complications; (3) PS affects more males than females; and (4) the published diagnostic criteria are useful for clinical care and research. This article contains supplementary material, which may be viewed at the American Journal of Medical Genetics website at <http://www.interscience.wiley.com/jpages/0148-7299/suppmat/index.html>.

Published 2004 Wiley-Liss, Inc.[†]

KEY WORDS: hemihyperplasia; lipomas; asymmetry; disproportionate overgrowth; hyperostoses; disorganized bone; cerebriform connective tissue nevus

INTRODUCTION

Proteus syndrome (PS) is a generally severe but highly variable disorder with asymmetric and disproportionate overgrowth of body parts, connective tissue nevi, epidermal nevi, dysregulated adipose tissue, and vascular malformations [Cohen and Hayden, 1979; Wiedemann et al., 1983]. Although the cause of PS is, as yet, unknown [Barker et al., 2001; Biesecker et al., 2001], it is thought to arise from a postzygotic mutation based on (1) mosaic distribution of lesions, (2) sporadic occurrence, (3) exclusively unaffected offspring born to affected individuals, and (4) discordant identical twins [Happle, 1987; Cohen, 1993; Cohen et al., 2002].

Like all syndromes, some features of PS overlap with other disorders. The overlapping features of overgrowth syndromes have caused many patients to be misdiagnosed [Biesecker et al., 1998]. Interestingly, this misdiagnosis is directional in that we have found many patients with the diagnosis of PS who we concluded do not have the disorder, but we have not identified patients who carry another diagnosis when we believe that they have PS. About two-thirds of the individuals with a diagnosis of PS who have been referred to us for consultation or for inclusion in the National Institutes of Health (NIH), PS research study failed to meet diagnostic criteria (*vide infra*). Additionally, PS case reports published prior to, and after, the development of the diagnostic criteria have included individuals who were affected with other overgrowth conditions [Cohen et al., 2002]. Those misdiagnoses have further confused clinical diagnosis, management, and research efforts. The issue of misdiagnosis of PS and the erroneous association of *PTEN* mutations have been addressed elsewhere [Cohen et al., 2003] and are not further discussed here.

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Received 18 February 2004; Accepted 29 March 2004

DOI 10.1002/ajmg.a.30327

To address the general problem of misdiagnosis in the literature, we undertook a study to apply the published diagnostic criteria [Biesecker et al., 1999] to case reports in the literature to (1) distinguish cases of PS from other conditions, (2) delineate the PS phenotype, and (3) re-emphasize the PS diagnostic criteria.

METHODS

Review of Case Reports

A literature search was performed using PubMed to identify published cases. Search terms included "Proteus syndrome," "exostoses," "hyperostoses," "asymmetric overgrowth," "disproportionate overgrowth," and "encephalocraniocutaneous lipomatosis." Non-English language case reports suggestive of PS were translated into English. Duplicate descriptions of single patients were common (37 cases were reported a total of 97 times), and these were consolidated when recognized.

Diagnostic Criteria, Coding, Data Analysis, and Statistics

Diagnostic criteria were applied to published reports [Biesecker et al., 1999]. If an individual met these criteria, they were coded as "PS" for Proteus syndrome. Individuals for whom there was insufficient information available but who had features suggestive of PS were coded as "NSF" for non-sufficient. Those who did not meet the PS diagnostic criteria and who had another condition were coded as "NP" for not PS. Each case was independently reviewed and coded by each author. Discrepancies were resolved by discussion among the authors. Diagnostic criteria and additional complications were coded as "Y" for yes or present, "N" for not having the feature, "NSF" for non-sufficient or no information. Data were collected and entered into Excel (Microsoft). Statistical methods were Fisher's exact test for 2 × 2 contingency tables unless otherwise specified (InStat, GraphPad, Inc., San Diego, CA).

RESULTS

Subjects and Demographics

We reviewed 155 articles that included 205 cases. Reports that lacked a clinical summary or description of physical features were excluded (e.g., cases were not included if the article indicated only that the patient had PS or met the diagnostic criteria, but no specific information was provided). Application of the diagnostic criteria led to the designation of 97 cases of PS (47.3%). Eighty cases (39%) were designated as not Proteus and 28 cases (13.7%) were designated as non-sufficient to make a diagnosis (see the online Appendix A at <http://www.interscience.wiley.com/jpages/0148-7299/suppmat/index.html>). The three of us initially disagreed on six of 205 cases for a congruence rate of 97.1%. Discrepancies were resolved by further discussion among the authors. In all six cases, one or two of us had missed a feature described in the

report, and when this was pointed out, agreement was readily made.

Among those with confirmed PS (Table I), there were more males than females (63 males and 33 females; 1 unknown), and this difference was statistically significant ($P < 0.0028$, two-tailed binomial calculation). In contrast, the sex ratio for those coded as NP or NSF was not significantly different from 1:1 (38 males and 33 females for NP; 17 males and 9 females for NSF). The parental ages at the time of birth were within the normal reproductive age range and did not differ among the three groups. Reporting of overgrowth and asymmetry in the non-Proteus group (30/80 or 37.5%) at the time of birth was twice that found in those with PS (17/97 or 17.5%; $P = 0.0037$). The presence of any manifestation at birth was also more frequent in the non-Proteus group (50/80 or 62.5% for NP; 42/97 or 43.3% for PS; $P = 0.0154$).

Specific Criteria Evaluated

The most common overlapping features of PS with other overgrowth conditions were dysregulated fat and vascular malformations (Fig. 1). A greater percentage of individuals in the non-Proteus group compared to the Proteus group had an abnormal fat distribution (62.5%, $n = 50$ NP and 58.8%, $n = 57$ PS) and vascular malformations (77.5%, $n = 62$ NP and 66%, $n = 64$ PS). Cerebriform connective tissue nevi (CCTN) were present in 72.2% ($n = 70$) of the PS group but were absent in individuals labeled as non-Proteus. Four individuals (14.3%) [Samlaska et al., 1989; Botella-Estrada et al., 1991; Winik et al., 2000] with CCTN in the NSF group either did not meet the general criteria or had insufficient information to assess the general criteria. Epidermal nevi were observed in all three groups, although 73% ($n = 71$) of individuals with PS had epidermal nevi, compared to 28.8% ($n = 23$) of those in the non-Proteus group, and 32.1% ($n = 9$) in the NSF group. Ovarian cystadenomas and monomorphic adenomas of the parotid gland (4.1%, $n = 4$ PS) were not clearly present in the non-Proteus and NSF groups, and the PS facial phenotype (27.8%, $n = 27$ PS) was rarely observed in the non-Proteus (1.3%, $n = 1$) and NSF (3.6%, $n = 1$) groups. Many authors of the case reports cited asymmetric or disproportionate overgrowth. This was the most common specific criterion in the PS group (92.8%, $n = 90$) but less common in the non-Proteus (28.8%, $n = 23$) and NSF (50%, $n = 14$) groups. Many non-Proteus cases were said to have disproportionate overgrowth, but very often we could not confirm this (vide infra). Hyperostoses and hyperproliferation of osteoid with variable calcification were reported in 74.2% ($n = 72$) of cases of PS, while 7.5% ($n = 6$) of those designated as non-Proteus and 42.9% ($n = 14$) classified as NSF were said to have this manifestation, but sufficient information was not presented to confirm this. Note that no statistical comparisons are made in this section as these features were used to sort the patients and were not independent of the diagnosis that was assigned. The frequencies are provided to assist the reader in generating a picture of PS. In this regard, nearly half (46.4%, 45/97) of PS patients met specific criteria "A" and "B" (i.e., they

TABLE I. Number of Males and Females, Average Parental Age, and Birth Findings

	Proteus	Not Proteus	Non-sufficient
Number	97	80	28
Males	63	38	17
Females	33	33	9
Unknown	1	9	2
Paternal age	31.2 ($n = 32$)	30.4 ($n = 16$)	30.8 ($n = 4$)
Maternal age	27.9 ($n = 36$)	27.9 ($n = 20$)	25.0 ($n = 3$)
Overgrowth at birth	17.5% ($n = 17$)	37.5% ($n = 30$)	32.1% ($n = 9$)
Any signs at birth	43.3% ($n = 42$)	62.5% ($n = 50$)	32.1% ($n = 9$)

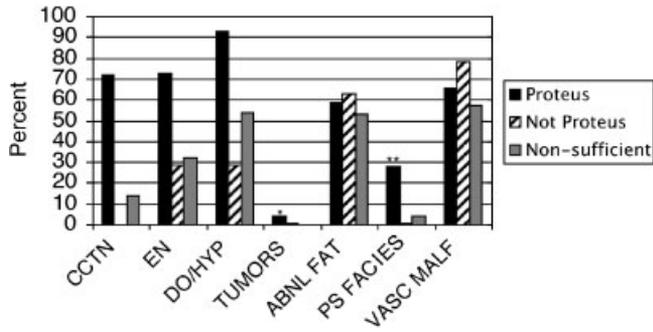


Fig. 1. Specific diagnostic criteria analyzed. Cerebriform connective tissue nevus (CCTN), epidermal nevus (EN), disproportionate overgrowth/hyperostoses (DO/HYP), abnormal fat distribution (ABNL FAT), Proteus facial features (PS FACES), and vascular malformation (VASC MALF). Bars indicate individuals displaying specific features; (they do not take into account the development of specific features that may have developed since the publication of the case reports). *Indicates one individual in the NP group with “voluminous serous ovarian cysts” [Lacombe et al., 1991]. No pathology was available. **The PS facies (see text for description) has only been observed, to date, in cases with seizures, mental retardation and CNS anomalies.

had a CCTN and at least two of the category B signs). About one-fifth (18.6%, 18/97) of PS cases satisfied specific criteria “A” and “B,” as well as two of the three criteria from category “C.” Eight individuals (8.3%) with PS satisfied all three specific criteria “A,” “B,” and “C.”

Delineation of Several Specific Criteria

We interpreted several PS criteria differently than did the authors of a number of the cases. These differences most commonly involved disproportionate overgrowth and CCTN. Figure 2A–D shows a boy with disproportionate bony overgrowth and typical PS. In contrast, Figure 2E–G shows a boy with hemihyperplasia multiple lipomatosis (HHML, Fig. 2E–G) at 9 and 30 months of age; his bones are large but grew proportionately. No disproportionate bony overgrowth or bony invasion of the joints was present. He displayed progressive splaying of his fingers, but there was little change in overgrowth over 21 months. Soft tissue overgrowth gave a “ballooning effect” not observed in this or other cases of PS. Overgrowth of the soles and palms were often confused with CCTN. In PS, the CCTN has deep grooves and gyrations, a consistency that is firmer than the normal tissue [Cohen and Hayden, 1979], and cerebriform appearance (Fig. 3A–D), whereas in non-Proteus patients, such overgrowth has only mildly exaggerated creases and is either softer or not different from the consistency of normal sole tissue (Fig. 3E–G).

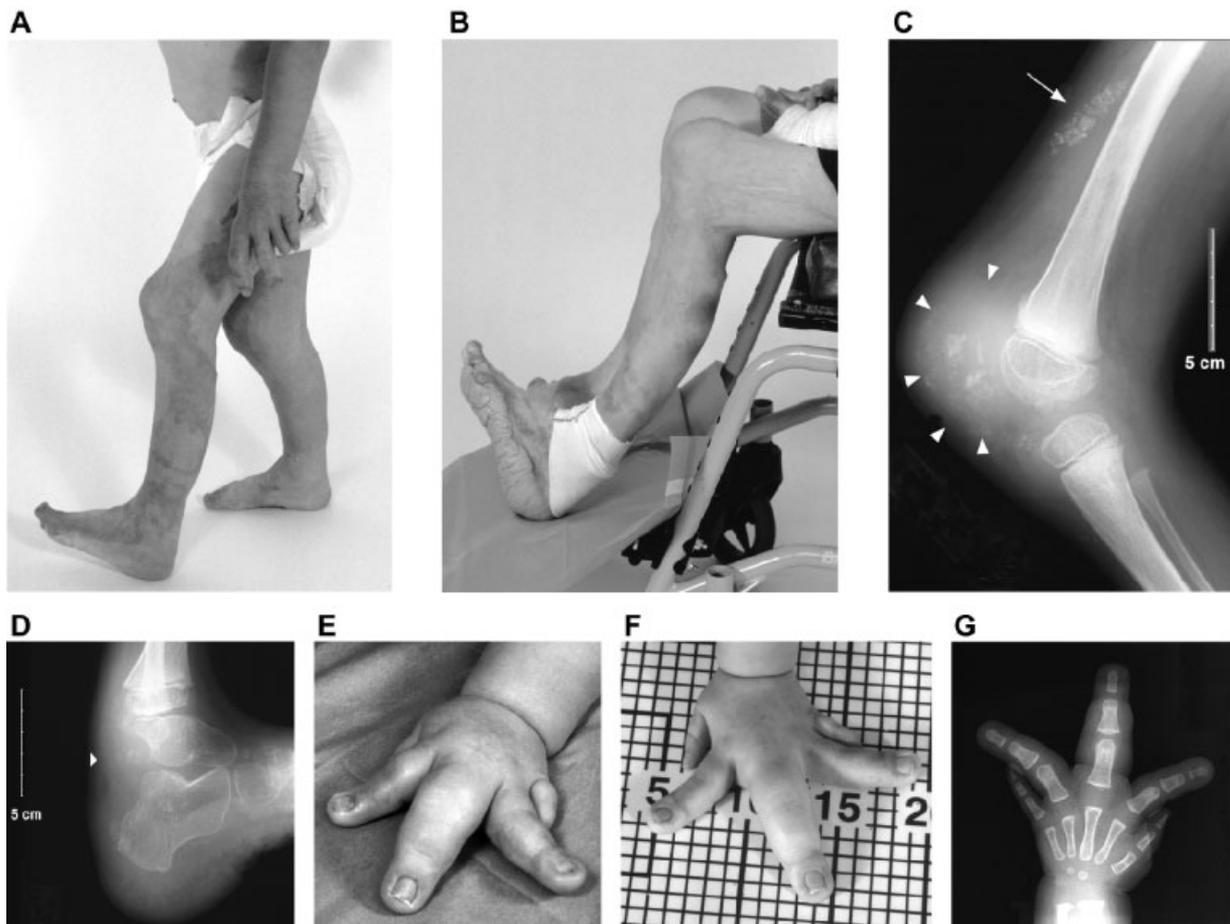


Fig. 2. **Panels (A)–(D)** demonstrate disproportionate overgrowth seen in patients with Proteus syndrome. **Panels (E)–(G)** demonstrate the proportionate overgrowth seen in patients not classified as Proteus syndrome. Images A–D reproduced from JAMA [Biesecker, 2001].

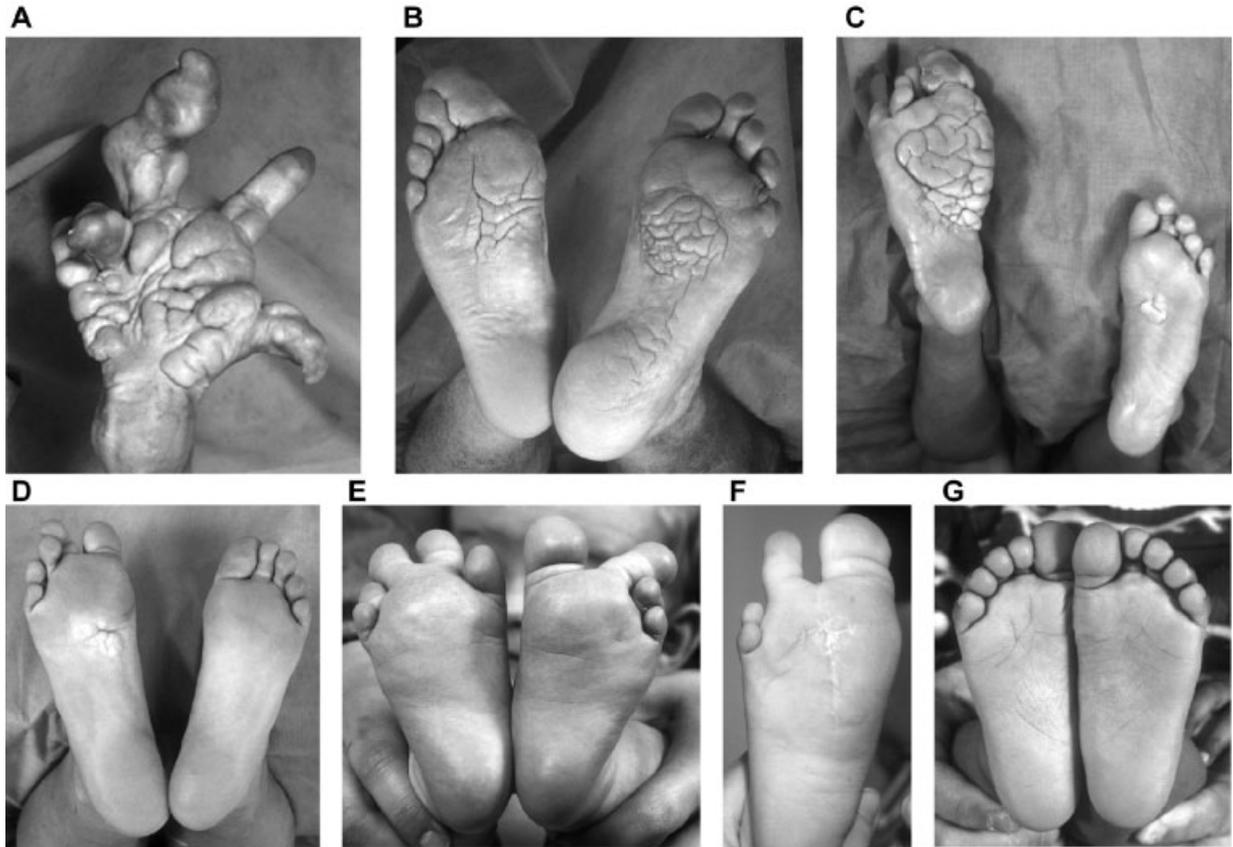


Fig. 3. **Panels (A)–(D)** are cerebriform connective tissue nevi (CCTN) of the palm of the hand or the sole of the foot. Note that in **panel (D)**, the CCTN is small, but it is distinct from the overgrowth seen in the feet of patients not classified as Proteus syndrome. **Panels (E)–(G)** include images of the feet of patients classified as not Proteus, with thickening of the soles of the foot and increased wrinkling not consistent with a CCTN.

We also observed differences in the interpretation of the epidermal nevus. Patients with these lesions have been incorrectly described as having café-au-lait spots. In addition, patients with severe, thickly scaled skin lesions have been incorrectly described as having epidermal nevus (Fig. 4). The epidermal nevus has a slightly raised and rough texture. It is brown or brown black in color and often has faint lines coursing throughout; it is not waxy, yellow, or scaly.

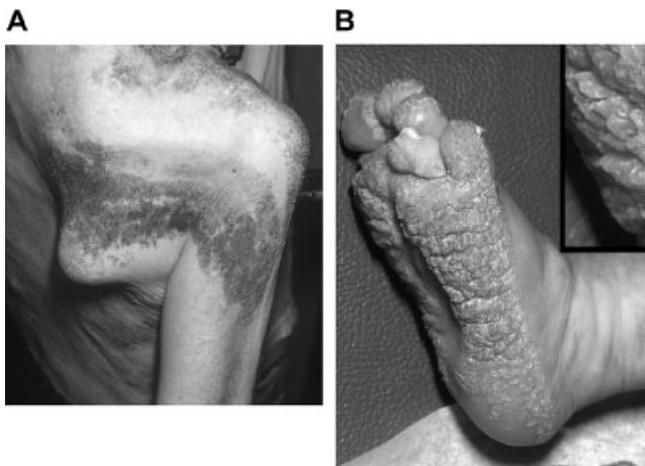


Fig. 4. **Panel (A)** is an epidermal nevus observed in Proteus syndrome. **Panel (B)** is a non-Proteus epidermal nevus.

Complications

Complications were more common in PS than in the non-Proteus patients (Fig. 5, Table II), with the exception of renal/urologic complications. Premature death was reported more frequently in PS than in the non-Proteus cases. Nineteen individuals (almost 20%) in the PS group were reported to have died prematurely compared to 3/80 (less than 4%) of the

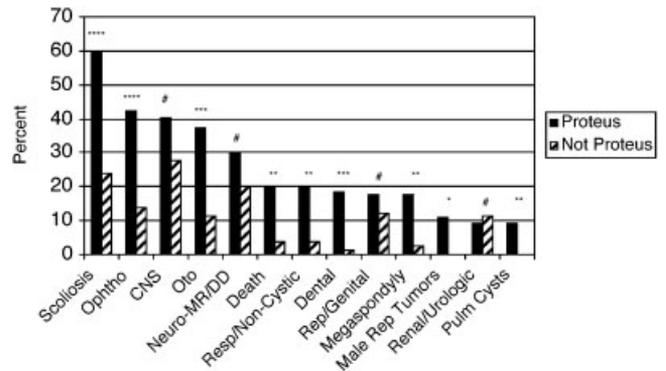


Fig. 5. Complications observed in Proteus syndrome versus non-Proteus. Ophthalmologic (Ophtho), central nervous system (CNS), otolaryngologic (Oto), neurologic (mental retardation/developmental delay) (MR/DD), reproductive/genital non-tumor abnormalities (Rep Genital), male reproductive tumors (Male Rep Tumors), pulmonary (Pulm Cysts), respiratory problems excluding cystic pulmonary disease (Resp/Non-Cystic). **** $P < 0.0001$; *** $P = 0.0001$, ** $P < 0.005$; * $P < 0.05$; #not significant.

TABLE II. PS Versus NP Complications¹

1. CNS: PS
 Individuals: 39 (40.2%)
 Manifestations: 30
 Hemimegalencephaly
 Seizures
 Abnormal cerebral cortex
 Hydrocephalus
 Meningiomas
 Astrocytoma
 Thickened leptomeninges
 Dural ectasia
 Polymicrogyria
 Periventricular heterotopias
 Porencephalic cysts
 Subarachnoid cysts
 Periventricular cysts
 Cystic brain lesions
 Dandy–Walker malformation
 Cortical atrophy
 Cortical thickening
 Hypoplastic white matter
 Calcifications
 Spinal cord stenosis
 Spinal canal lipomas
 Hypotonia
 Abnormal gait
 Thromboses
 Fatty matter infiltration
 Subependymal nodules
 Parenchyma distortion
 Abnormal vasculature
 Increase in subarachnoid space
 Subarachnoid space deformation

2. CNS: NP
 Individuals: 22 (27.5%)
 Manifestations: 18
 Hemimegalencephaly
 Seizures
 Cortical atrophy
 Cortical dysplasia
 Dysplastic white matter
 Hypoplastic or absent corpus callosum
 Hydrocephalus
 Fatty deposits
 Meningeal lesion
 Dilated ventricles
 Lissencephaly
 Cysts
 Polymicrogyria
 Calcification of basal ganglia
 Cerebral calcifications
 Stroke
 Hypotonia
 Sella turcica hypertrophy
 Dilated insulae cysternae

3. Ophthalmologic: PS
 Individuals: 41 (42.3%)
 Manifestations: 42
 Epibulbar dermoids
 Epibulbar cysts
 Strabismus
 Nystagmus
 Esotropia
 Heterochromia
 Coloboma
 Optic nerve atrophy
 Optic nerve tumor
 Optic nerve hyperplasia
 Chorioretinal atrophy

TABLE II. (Continued)

Chorioretinal tumor
 Decreased movement
 Retinitis pigmentosa
 Retinal detachment
 Thin retina
 Retinal pigmentary changes
 Pale optic discs
 Retinal coloboma
 Macular coloboma
 Glaucoma
 Cataracts
 Exophthalmos
 Fat infiltration
 Amblyopia
 Epiblepharon
 Asymmetry
 Scotomas
 Anisocoria
 Proptosis
 Ptosis
 Elevated IOP
 Vascular malformation of iris
 Hemorrhage
 Keratopathy
 Papillary drusen
 High myopia
 Hamartomatous lesion
 Scleral tumor
 Yellow drusen
 Photopsia
 Vitreous detachment
 Pterygium invasion of cornea
 Grey optic disc

4. Ophthalmologic: NP
 Individuals: 11 (13.8%)
 Manifestations: 16
 Choroid coloboma
 Colobomas
 Choroid tumor
 Retinal tumor
 Strabismus
 Cloudy corneas
 Megalopapilla
 Absent retinal pigment
 Scleral tumor
 Poor foveal reflex
 PHPV
 Lipodermoid
 Epiblepharon
 Abnormal movement
 Asymmetry
 Myopia

5. Otolaryngologic: PS
 Individuals: 36 (37.1%)
 Manifestations: 25
 Dyspnea
 Apnea
 Obstructive Airway disease
 Tracheomalacia
 Uvula hyperplasia
 Distorted pharynx
 Hypertrophy of external auditory canal
 Hyperostosis external auditory canal
 Conductive hearing loss
 Sensory neural hearing loss
 Ear asymmetry
 Tonsil hypertrophy
 Occlusion of nasal passages
 Tongue overgrowth

TABLE II. (Continued)

Cheek hypertrophy
Hypertrophy of the smooth muscle in the airway
Nose asymmetry
Tonsil cysts
Nodule on vocal cords
Gingival hyperplasia
Mandible asymmetry
Condylar hyperplasia
Osteoma of the mandibular alveolus
Palate asymmetry
Tongue with verrucous projections
6. Otolaryngologic: NP
Individuals: 9 (11.3%)
Manifestations: 8
Tonsil hypertrophy
Ear hypertrophy
Ear dysplasia
Narrowing of the external auditory canal
Tongue hypertrophy
Alveolar overgrowth
Ear asymmetry
Lip and cheek hypertrophy
7. Pulmonary (cysts): PS
Individuals: 9 (9.3%)
8. Pulmonary (Cysts): NP
Individuals: 0 (0%)
9. Dental: PS
Individuals: 18 (18.6%)
Manifestations: 5
Malocclusion
Enamel hypoplasia
Dental hypoplasia
Early eruption
Dental dysplasia
10. Dental: NP
Individuals: 1 (1.3%)
Manifestations: 1
Early eruption
11. Renal/urologic: PS
Individuals: 9 (9.3%)
Manifestations: 9
Renal asymmetry
Renal failure
Ureter asymmetry
Renal cysts
Nephrogenic diabetes
Hematuria
Hydronephrosis
Proteinuria
Hydroureter
12. Renal/urologic: NP
Individuals: 9 (11.3%)
Manifestations: 11
Pyelocalyceal junction syndrome
Hydronephrosis
Hydroureter
Ureterectasis
Ureterovesical stenosis
Hypoplastic kidneys
Renal asymmetry
Renal cysts
Hematuria
Renal cavernous hemolymphangioma
Reflux

TABLE II. (Continued)

13. Male reproductive (tumors): PS
Individuals: 7 (11.1%)
Manifestations: 5
Testicular neoplasms
Cystadenomas of the tunica albuginea
Epididymal papillary cystic adenomas
Mesotheliomas of the tunica vaginalis
Undefined scrotal masses
14. Reproductive (tumors): NP
Individuals: 0 (0%)
Manifestations: 0
None
15. Reproductive/genital issues (non-tumor): PS
Individuals: 17 (17.5%)
Manifestations: 11
Hernias
Undescended testes
Epididymal cysts
Labial hypertrophy
Clitoral hypertrophy
Ovarian cysts
Premature adrenarache
Cervical cysts
Endometrial polyps
Uterine polyps
Uterine capsular fibrosis
16. Reproductive/genital issues (non-tumor): NP
Individuals: 10 (12.5%)
Manifestations: 10
Undescended testes
Atrophic testicle
Hemorrhagic testicle
Hemorrhagic testicular cyst
Hernia
Hydrocele
Micropenis
Advanced development
Ovarian cysts
Clitoromegaly
17. Low frequency tumors: PS
Individuals: 5 (5.2%)
Manifestations: 7
Breast cancer
Bladder angioma
Brain meningioma(s)
Breast intraductal papilloma
Breast epithelial hyperplasia
Papillary neoplasm of the diaphragm, musculature, omentum, lymph nodes
Papillary cystic adenoma of the kidney
18. Low frequency tumors: NP
Individuals: 2 (2.5%)
Manifestations: 2
Polypoid lesion of the jejunum and colon
Sacrococcygeal teratoma

¹Does not include diagnostic criteria features.

non-Proteus patients ($P = 0.0012$). The known causes of death in PS patients included pulmonary embolism, post-operative complications, and pneumonia.

Therapeutic interventions were more common among PS patients than non-PS patients. Although the frequency of any type of surgical procedures (61/97 or 62.9% PS, 39/80 or 48.8% NP, $P = 0.0684$) was not significantly different in the two groups, orthopedic surgery was more common (34/97 or 35.1% PS, 15/80 or 18.8% NP, $P = 0.0184$) in PS. Significantly, more

individuals with PS than with non-Proteus overgrowth had scoliosis (58/97 or 59.8% PS, 19/80 or 23.8% NP, $P < 0.0001$) and megaspondyly (primarily cervical) (17/97 or 17.5% PS, 2/80 or 2.5% NP, $P = 0.0011$). Complications in the following systems were significantly more frequent in the PS than the non-Proteus group: ophthalmologic (41/97 or 42.3% PS, 11/80 or 13.8% NP, $P < 0.0001$), otolaryngologic (36/97 or 37.1% PS, 9/80 or 11.3% NP, $P = 0.0001$), cystic lung disease (9/97 or 9.3% PS, 0/80 or 0% NP, $P = 0.0043$), respiratory/non-cystic (19/97 or 19.6% PS, 3/80 or 3.8% NP, $P = 0.0012$), dental anomalies (18/97 or 18.6% PS, 1/80 or 1.3% NP, $P = 0.0001$), and male reproductive system tumors (7/63 or 11.1% PS, 0/80 or 0% NP, $P = 0.043$) (note that ovarian cystadenomas were not included as they are part of the diagnostic criteria). Several groups of complications were not significantly different in the two groups including CNS anomalies (39/97 or 40.2% PS, 22/80 or 27.5% NP, $P = 0.083$). The majority of individuals with PS had normal intelligence. The frequency of mental retardation was not significantly different (29/97 or 29.9% PS, 16/80 or 20% NP, $P = 0.1656$). Eleven of 14 individuals with PS and 5 of 9 non-Proteus individuals with asymmetric cranial overgrowth (hemimegalencephaly) had developmental delay. Non-tumor genital/reproductive anomalies (17/97 or 17.5% PS, 10/80 or 12.5% NP, $P = 0.4055$) and renal/urologic anomalies (9/97 or 9.3% PS, 9/80 or 11.3% NP, $P = 0.8037$) were also not significantly different between the two groups. Table II shows the specific complications and tumor types.

DISCUSSION

Utility of the Diagnostic Criteria

We have previously shown that a cohort of 18 NIH patients referred to us with the label of PS could be segregated into distinct disorders with implications for prognosis and management [Biesecker et al., 1998]. These two groups appeared to differ in their overall severity and whether they were static or progressive. Furthermore, we suggested that PS was the proper diagnostic label for the more severe, progressive patients as their features clearly matched the seminal descriptions of PS in the literature [Cohen and Hayden, 1979; Wiedemann et al., 1983]. Our impressions from the initial NIH cohort were merged with the clinical experience of a number of clinicians experienced in the diagnosis of overgrowth syndromes to develop simple diagnostic criteria [Biesecker et al., 1999]. We have taken the next step by applying these results to literature cases of patients with a diagnosis of PS. Not surprisingly, some patients who were reported prior to the publication had the diagnosis of PS removed when the 1999 criteria are applied. Surprisingly, our results show differences in interpretation of the diagnostic criteria among those cases published *after* the diagnostic criteria appeared in the literature. Another example of this problem is our experience in performing eligibility evaluations on individuals referred to the NIH study (LGB and JTT, unpublished data) and consultations to one of us (MMC, unpublished data). A substantial majority of patients referred to us with a diagnosis of PS have had the diagnosis removed when we examined their clinical data and applied the diagnostic criteria. Among the 205 cases identified here, the areas that generated the most confusion included disproportionate overgrowth and the CCTN, and less commonly epidermal nevi. In most case reports, overgrowth was identified as a feature.

We define overgrowth as a body part that has grown excessively and is, therefore, larger than normal.¹ Overgrowth

can be symmetric or asymmetric, progressive or non-progressive, and distorting or non-distorting. The assessment of symmetry and asymmetry was not an apparent source of confusion or controversy. In contrast, distinguishing proportionate from disproportionate overgrowth was confusing because it actually incorporated two concepts: progression and distortion. Proportionate overgrowth is usually non-progressive and non-distorting. It refers to an enlarged body part that is growing at the same, or similar, rate as the rest of the body and is normal in structure. By normal structure and non-distorting, we mean that individual bones are normally shaped, just larger than normal. There are no bony growths invading joint spaces or jagged bone edges. Rather, bones are bigger than normal and bone surfaces are smooth. The disproportionate overgrowth of PS is progressive, distorting, and relentless. It refers to a bone or portion of a bone that is growing at a faster rate than the rest of that particular bone and/or the rest of the body. It also refers to bony growths that are invading joint spaces and are associated with jagged bone edges. The rate of growth within the overgrown body part is quite uneven, leading to disfiguring, irregular overgrowth that is very different in character from that seen in proportionate overgrowth. The disproportionate overgrowth seen in PS is commonly associated with irregular and disorganized bone, including hyperostosis of the skull, other bony overgrowths (hyperproliferation of osteoid with variable calcification resulting in abnormal bone edges as opposed to smooth bone surfaces), and abnormally calcified connective tissue. The bones are sometimes so abnormal that, in isolation, they may be difficult to recognize in radiographs. Also, the long bones in PS can be elongated, but they commonly have abnormally thin cortices whereas in non-Proteus cases, they are normal or thickened. Furthermore, asymmetric, proportionate bony overgrowth in individuals with non-Proteus overgrowth is associated with overgrowth of overlying soft and fatty tissues, making the overgrown body part appear as if air has been pumped into it creating a "ballooning effect" (compare Figs. 3E and 4A). The soft tissue overgrowth of patients with non-Proteus overgrowth may cause somewhat decreased mobility but is distinct from the bony overgrowth in PS that may eventually eliminate all mobility from affected joints, large and small. The ballooning effect is usually absent in PS, and there is often a deficiency of overlying soft tissues in the areas of bony overgrowth.

The distinction of proportionate from disproportionate overgrowth is generally obvious by the time an individual is two to three years of age but can be difficult to assess in infancy. If the rate of overgrowth is subtle, mild, or needs measurement to be appreciated, the disproportionate overgrowth criterion is negative. The typical patient with non-Proteus asymmetric overgrowth has asymmetric growth that is apparent at the time of birth (*vide infra*). In typical non-Proteus cases, the degree of asymmetry (the proportion or ratio of size of the overgrowth to the normal contralateral body part) does not substantially change over time. The rate of growth in non-PS patients is typically comparable to the normal tissue. However, we and others have observed that growth may occasionally exceed that of the normal body parts, but even so, it does not have the relentless character of PS. In contrast, the typical patient with PS essentially has a normal limb at birth with severe, relentless disfiguring overgrowth developing postnatally. Thus, the relative sizes of the paired structure changes dramatically over time. Figure 6 summarizes types of overgrowth and provides some diagnostic guidance.

Because of the rarity of PS, confusion in terminology, and the overlapping phenotypic features seen in PS and other overgrowth conditions, making the diagnosis of PS can be challenging. We have found it useful to review plain radiographs for the presence of hyperostoses, abnormal epiphyses, and

¹Growth and overgrowth occur by hyperplasia, not hypertrophy. However, the term overgrowth is a proper description of enlargement from a physical examination.

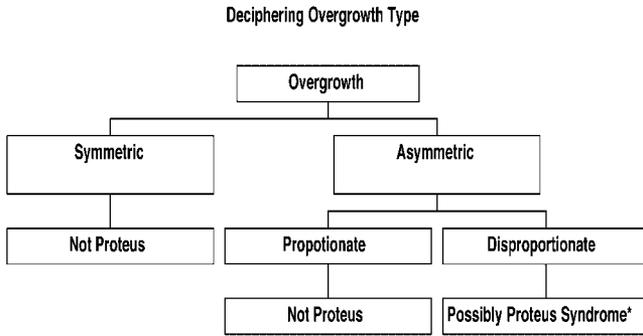


Fig. 6. Determining types of overgrowth. Proteus syndrome is associated with asymmetric, disproportionate overgrowth. *When asymmetric, disproportionate overgrowth is present and other Proteus diagnostic criteria are satisfactorily met, a diagnosis of Proteus syndrome can be made.

bony growth into joint spaces [Jamis-Dow et al., 2004]. Distinguishing symmetric from asymmetric, and proportionate from disproportionate overgrowth is often helpful in determining whether an individual has PS or some other condition with overgrowth.

We had previously believed that a reliable distinguishing factor for PS from other overgrowth conditions was the presence or absence of overgrowth at birth. The results of the present study show that although congenital overgrowth is more common in those in the non-Proteus group, overgrowth was present at birth in some individuals with PS. We suspect that our impression was a reflection of the rapid, progressive, and relentless postnatal overgrowth that is so dramatic in PS that findings at birth are often ignored, forgotten, or only apparent in hindsight. In contrast, typical individuals affected by other overgrowth disorders grow in such a proportionate manner that it is readily recognized and recalled that the findings have been present since birth.

The CCTN is another criterion for PS that has been a source of confusion. The terms plantar hyperplasia, “moccasin foot” lesion, cerebriform hyperplasia, and collagenoma are used interchangeably with CCTN [Cohen and Hayden, 1979; Tibbles and Cohen, 1986; Cohen, 1993; Biesecker et al., 1999; Cohen et al., 2002]. The CCTN is composed of highly collagenized fibrous connective tissue [Cohen and Hayden, 1979; Cohen, 1995] and a collagenoma has been defined as an abnormality of the extracellular dermal matrix, in which collagen is found in excess [Martinez et al., 1994]. The components of the extracellular matrix include collagen, elastic fibers, and glycosaminoglycans [Atherton, 1998], and they may be inherited or acquired [Uitto et al., 1980]. Although CCTN are collagenomas, not all collagenomas are CCTN. When collagenomas are acquired as an isolated abnormality, they should not be considered pathognomonic for PS, but patients with these lesions should be followed to determine if other manifestations of PS develop [Botella-Estrada et al., 1991; Martinez et al., 1994; Gautman et al., 1996]. Plantar overgrowth and thickened soles are non-specific and when misdiagnosed as a CCTN, this leads to confusion in distinguishing patients with PS from those who have other overgrowth conditions. The CCTN can be found on the sole of the foot [Cohen and Hayden, 1979], palm of the hand [Biesecker et al., 1998; Cohen et al., 2002] and more rarely on the chest and abdomen [Cohen, 1993], dorsal aspect of the fingers, eyelid, and nasal tissues [Tibbles and Cohen, 1986; Cohen, 1995; Cohen et al., 2002]. The CCTN is progressive, firm and nodular or cobblestone-like in structure, and develops deep grooves and gyrations (hence the term cerebriform) [Cohen, 1995]. Physical examination of a CCTN should be sufficient for diagnosis; biopsies are not recommended, particularly when the lesion

is present on the sole of the foot. To minimize confusion, we propose the use of the descriptor *cerebriform connective tissue nevus* (CCTN) for this lesion to replace the less specific terms, connective tissue nevus (CTN), collagenoma, plantar hyperplasia and moccasin lesion.

We found that many individuals we classified as non-Proteus were reported in the literature as having PS if they had: (1) overgrowth, (2) thickened soles, (3) lipomas, (4) vascular malformations, and (5) epidermal nevus. Lipomas and vascular malformations were more frequent in the non-Proteus group, and from our experience, they are often much more extensive than those observed in individuals with PS. An epidermal nevus is commonly present in individuals with PS; however, it is common in other overgrowth conditions as well. In our experience in evaluating cases for the NIH study, consultations from colleagues, and reviewing the literature, many patients diagnosed by others as having PS actually have another condition known as HHML [Biesecker et al., 1998]. This diagnosis should be considered in the differential when an individual presents with the above features. It is important to emphasize that we do not consider the term “non-Proteus overgrowth” to be a diagnosis. We use it here only to denote that the patient does not meet the diagnostic criteria for PS and that designation does not imply phenotypic similarity or etiologic homogeneity for patients so designated. The diagnostic refinement of that group of patients is an important task that we encourage others to undertake, as we believe it will be clinically useful and scientifically interesting.

Complications and Management

Among the numerous complications associated with PS, there are several that have been previously reported, but which are now recognized to be common. The careful application of the diagnostic criteria defines a cohort of individuals that have frequent and, in many cases, severe complications. Proper use of the diagnostic criteria will allow health care providers to focus their monitoring and treatment efforts on patients who are at high risk for these complications and therefore more likely to benefit from medical attention to these risks.

Ophthalmologic complications were common (~42%) [Burke et al., 1988; Bouzas et al., 1993; De Becker et al., 2000; Cohen et al., 2002; Sheard et al., 2002]. Therefore, periodic ophthalmologic evaluations are indicated. Because of the number of CNS complications (~40%) and cognitive impairments (30%) linked to PS, baseline brain MRIs and early educational intervention should be considered when the diagnosis is made. Interestingly, asymmetric cranial growth (hemimegalencephaly) is associated with mental retardation independently of the diagnosis of PS or a non-Proteus overgrowth disorder. Taking all patients together, 16/23 patients with asymmetric cranial overgrowth had mental retardation compared to 29/154 patients who did not have asymmetric cranial overgrowth ($P < 0.0001$, relative risk of 3.69, 95% CI of 2.41–5.65). Breathing difficulties and malocclusion suggest the need for periodic evaluations by an otolaryngologist, pulmonologist, and a dentist. Although the urologic and renal complications were less frequent, physicians should be aware of them and promptly evaluate symptoms. Reproductive complications occur and can include malignancies [Gordon et al., 1995]. Therefore, periodic testicular and ovarian ultrasounds in males and females should be considered.

It is crucial for health professionals caring for PS patients to be aware of the association of deep venous thrombosis and pulmonary embolism [Slavotinek et al., 2000]. We concluded that pulmonary embolism is a major contributor to the early mortality of PS. Because thrombosis and embolism are extremely rare in children, health professionals and families of children with PS must be educated about the signs of these

TABLE III. Revised Proteus Syndrome Diagnostic Criteria

General criteria	Specific criteria
All of the following: Mosaic distribution of lesions Sporadic occurrence Progressive course	Either: Category A or, Two from category B or, Three from category C
Specific criteria categories	
A. 1. Cerebriform connective tissue nevus ^a	C. 1. Dysregulated adipose tissue Either one: a. Lipomas b. Regional absence of fat
B. 1. Linear epidermal nevus 2. Asymmetric, disproportionate overgrowth ^b One or more: a. Limbs: Arms/legs Hands/feet/digits Extremities b. Hyperostoses of the skull c. External auditory meatus d. Megaspondylodysplasia e. Viscera: Spleen/thymus	2. Vascular malformations One or more: a. Capillary malformation b. Venous malformation c. Lymphatic malformation
3. Specific tumors before 2nd decade One of the following: a. Ovarian cystadenoma b. Parotid monomorphic adenoma	3. Lung cysts 4. Facial phenotype ^c All: a. Dolichocephaly b. Long face c. Down slanting palpebral fissures and/or minor ptosis d. Low nasal bridge e. Wide or anteverted nares f. Open mouth at rest

To make a diagnosis of PS, one must have *all* the general criteria, and various specific criteria.

^aCerebriform connective tissue nevi are skin lesions characterized by deep grooves and gyrations as seen on the surface of the brain.

^bAsymmetric, disproportionate overgrowth should be carefully distinguished from asymmetric, proportionate overgrowth (see Discussion for recommended methods of distinction).

^cThe facial phenotype has been found, to date, only in PS in patients who have mental deficiency, and, in some cases, seizures and/or brain malformations.

complications and encouraged to seek immediate medical attention should they occur. Signs include calf pain, calf or leg swelling, shortness of breath, and chest pain [Biesecker, 2000; Cohen, 2001]. We have successfully treated venous thrombosis and pulmonary embolism in two patients at the NIH by standard anticoagulation therapy (L.G.B., unpublished observations). At this time, there are insufficient data to recommend prophylactic anticoagulation in PS patients.

The data shown here suggest that PS is more common in males than in females. It is worth noting that the NIH clinical cohort includes 14 more males and eight females who have not been published, which would further increase the significance of the statistics (L.G.B. and J.T., unpublished data). We conclude that this sex difference is real. It is possible that the PS disease process interacts in a distinct manner with the male and female endocrine systems. This different interaction may increase the prevalence or severity of a manifestation that is included in the diagnostic criteria, thus distorting the sex ratio. If this were true, we might expect to see an excess of females included in the non-Proteus or the group with insufficient data. However, both of those groups also have an excess (statistically insignificant) of males. Alternatively, the interaction of the PS disease process may manifest in females in a very different way and that interaction generates a phenotype that is sufficiently distinct from PS that it is, as yet, unrecognized. We think this is unlikely because many females with PS have manifestations that are indistinguishable from those in males. An alternative hypothesis is that a male cell has a higher probability of acquiring the molecular alteration that causes PS. This model would generate more affected males than females with PS without the existence of another syndrome with an excess of females. Tests of these hypotheses must await the discovery of an *in vitro* assay or molecular etiology of PS.

The numerous and highly significant differences in the rates of complications among the PS and non-Proteus groups

substantially validated the diagnostic criteria. Most of these marked differences in outcome were caused by attributes that were not directly related to the diagnostic criteria and show that application of the criteria identified a group of patients who not only were recognizably distinct, but whose natural history was also distinct. Our high rate of diagnostic congruence strongly suggests that the diagnostic criteria are robust when properly applied. Although PS is variable, it may be less than previously believed because most individuals whose diagnosis of PS was removed by proper application of the diagnostic criteria were more mildly affected. Taken together, these factors strongly suggest that the criteria, when properly applied, are useful for clinical care.

Re-Emphasizing the Diagnostic Criteria

We have re-emphasized several of the criteria to reflect our experiences in their application, further delineating the particular criteria that generated confusion. We added more detail to the criteria to more accurately describe CCTN and asymmetric disproportionate overgrowth and we have added the criterion of lung cysts. We also tried to simplify the organization of the criteria (Table III). These clarifications do not reclassify or change our opinion of the status or diagnosis of any of the patients whose case reports were included in this study, under our care, or in our prior comments on misdiagnosis [Cohen et al., 2003; Cohen et al., this issue].

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