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Initial Cutaneous Manifestations of Hutchinson-Gilford Progeria Syndrome

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Abstract

Hutchinson-Gilford progeria syndrome (HGPS) is a rare, uniformly fatal premature aging disease with distinct dermatologic features. We sought to identify and describe the initial skin and hair findings as potential diagnostic signs of the disease. We performed a chart review of the structured initial intake histories of 39 individuals with HGPS enrolled in clinical trials from 2007 to 2010 at Boston Children's Hospital, limited to cutaneous history from birth to 24 months. Medical photographs were provided through the clinical trials and The Progeria Research Foundation Medical and Research Database at Brown University Center for Gerontology and Healthcare Research. All 39 patients reported skin and hair abnormalities within the first 24 months of life. Pathologies included sclerodermoid change, prominent superficial veins, dyspigmentation, and alopecia. The mean age of presentation for each finding was less than 12 months. The most frequently reported skin feature was sclerodermoid change, which commonly involved the abdomen and bilateral lower extremities. Prominent superficial vasculature manifested as circumoral cyanosis and pronounced veins on the scalp and body. Hypo- and hyperpigmentation were observed over areas of sclerodermoid change. Scalp alopecia progressed in a distinct pattern, with preservation of the hair over the midscalp and vertex areas for the longest period of time. HGPS has distinct cutaneous manifestations during the first 2 years of life that may be the first signs of disease. Awareness of these findings could expedite diagnosis.

Hutchinson-Gilford progeria syndrome (HGPS) is a rare, uniformly fatal autosomal-dominant premature aging disease.^{1,2} Cause of death is most commonly myocardial

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infarction or stroke, with a mean life expectancy of 13 years.³ In 2003, the genetic mutation for HGPS was identified as a single base mutation in the lamin A gene.^{4,5} This discovery has led to the availability of genetic testing and development of targeted drug therapy such as farnesyltransferase inhibitors.⁶ These recent advances emphasize the feasibility and importance of timely diagnosis.

Dermatologic abnormalities can be among the initial findings of HGPS and include sclerotic and dimpled skin over the abdomen and extremities, prominent cutaneous vasculature, dyspigmentation, and alopecia.³ These features have been documented in case reports, case series, and review articles. In this comparatively large chart review, we analyzed the skin and hair pathologies from the first 24 months of life in 39 individuals with HGPS enrolled in clinical trials at Boston Children's Hospital. Access to consistently collected histories of the largest known HGPS study cohort provides an unprecedented opportunity. The aim of our study was to describe and quantify the initial cutaneous pathologies as potential diagnostic signs of the disease. We were particularly interested in the prevalence of individual findings and the ages at which they presented.

PATIENTS AND METHODS

Patients and Data

A post-trial chart review was performed on the initial intake histories of 39 individuals with HGPS enrolled in prospective phase II clinical trials at Boston Children's Hospital from May 2007 through January 2010. The intake histories compiled data from three sources: outside medical records available through The Progeria Research Foundation Medical and Research Database at the Brown University Center for Gerontology and Healthcare Research, standardized written surveys completed by patients and outside clinicians before trial enrollment, and standardized interviews conducted during the baseline trial visit for all patients. Diagnosis of HGPS was confirmed using phenotypic expression of the disease and LMNA G608G mutational analysis. Patient sex, country of birth, age at trial enrollment, and age of HGPS clinical diagnosis were recorded. The institutional review boards of Rhode Island Hospital, Brown University, and Boston Children's Hospital approved this study.

Dermatologic Assessment

Initial intake histories were reviewed for descriptions of skin and hair abnormalities presenting from birth to 24 months. The surveys and interviews specifically asked participants to provide a description of initial skin abnormalities; the age of presentation for each skin abnormality; a description of scalp hair at birth, including presence or absence, color, and texture; the age of initial scalp hair loss; and the presence or absence of eyebrows and eyelashes at birth.

Skin abnormalities were grouped into five categories: sclerodermoid change, prominent scalp veins, prominent body veins, circumoral cyanosis, and dyspigmentation. Sclerodermoid change was defined as taut, indurated skin with soft outpouchings. Prominent scalp and body veins were defined as easily visible veins and circumoral cyanosis as perioral bluish discoloration. Dyspigmentation was defined as areas of hypo- and hyperpigmented

skin. Mean age of initial presentation for each feature was calculated. Anatomic distribution was documented.

Scalp hair color was grouped into three categories: blonde, brown, and black or dark. Hair texture was described as normal, coarse, or fine or thin. Age of initial scalp hair loss was recorded. The presence or absence of eyebrows and eyelashes at birth was documented.

Photographs corresponding to skin and hair findings were obtained from The Progeria Research Foundation Medical and Research Database or Boston Children's Hospital.

RESULTS

Initial clinical trial intake histories of 39 patients with classic HGPS from 23 countries were reviewed. Patient characteristics are described in Table 1.

Skin manifestations

Skin abnormalities were reported in all patients by age 24 months, and specific descriptions were provided in 37 patients. The most frequently reported skin finding was sclerodermoid change (78%), with a mean age of initial presentation of 1.9 months (Table 2, Figs. 1 and 2). These changes were present at birth in 24% (9/37).

Sclerodermoid change was described as taut, tight, thickened, fibrotic, rigid, indurated, outpouchings, rippled, or dimpling of the skin. Anatomic distribution most commonly involved the abdomen and bilateral lower extremities (Table 3). Combined abdominal and lower extremity involvement was reported in 10 patients (34%). We note extroverted nipples in several photographs, but this finding was present in a minority of patients. Prominent scalp veins were reported in 22 patients (59%) at a mean age of 5.4 months (Table 2, Fig. 3). Thirteen of these patients (59%) were noted to have prominent scalp veins before initial hair loss. At least two patients presented first with prominent forehead veins (Fig. 4). Prominent body veins were reported in eight patients (22%) at a mean age of 3.1 months (Table 2). The distribution of the prominent veins involved full body ($n = 6$), chest ($n = 1$), and lower extremities ($n = 1$). Circumoral cyanosis was reported in eight patients (22%) at a mean age of 2.4 months (Table 2).

Dyspigmentation was reported in six patients (16%) at a mean age of 2 months (Table 2, Figs. 1 and 2). Dyspigmentation was described as light or dark patches or spots of skin or mottling. Four patients had dyspigmentation overlying areas of sclerodermoid change. The other two patients did not report sclerodermoid change and noted dyspigmentation on the upper extremities, lower extremities, and abdomen.

Hair manifestations

All patients reported scalp hair at the time of birth. Hair colors ranged from blonde ($n=9$), brown ($n=18$), to black or dark ($n=12$). Textures were most commonly fine to normal, with two patients describing coarse hair. The age of initial scalp hair loss was provided for 37 patients, at a mean age of 10.2 months (Table 2). The pattern of hair loss was described in six patients; all reported initial loss in the temporal and occipital areas, with preservation of

hair on the midscalp and vertex for the longest period of time (Fig. 3). Descriptions of eyebrows at birth were provided for 37 patients, of whom 30 (81%) reported presence at birth (Fig. 5). Descriptions of eyelashes were provided for 36 patients, 35 of whom (97%) reported presence at birth.

DISCUSSION

During the first years of life, cutaneous findings are among the initial signs of HGPS, along with profound failure to thrive and characteristic facies.^{3,7} Dermatologic manifestations include sclerodermoid change, prominent cutaneous vasculature, dyspigmentation, and alopecia. Although the mean age of presentation for each cutaneous feature was younger than 12 months, only 54% of patients reported a clinical diagnosis of HGPS by the first year of life. Recognition of these unique findings could expedite diagnosis.

The most frequently reported finding was sclerodermoid change over the abdomen and bilateral lower extremities (78%), and patients typically present to a dermatologist with the chief complaint of discrete areas of nontender hard, bumpy skin, often with varying pigmentation. The nomenclature “sclerodermoid” captures the skin’s fibrotic qualities, but these areas often have a dimpled appearance secondary to small, soft outpouchings of subcutaneous tissue (Fig. 2). Because HGPS involves abnormalities in the extracellular matrix, these outpouchings could be secondary to collagen and elastin deposition^{9,10} and disorganized dermal collagen.¹¹ The age range of initial presentation (birth to 8 months) was comparable with published ranges of 1.5 to 6 months.³ Twenty-four percent reported sclerodermoid change at birth. Because weight and facial features are typically normal at birth,^{2,3,8} this finding may be the presenting sign of HGPS.

Sclerodermoid change in neonates carries a limited differential diagnosis. Restrictive dermopathy is an autosomal-recessive disorder characterized by diffuse skin rigidity.¹² Unlike with HGPS, the prenatal course is complicated by polyhydramnios and reduced fetal movements, and death typically occurs shortly after birth. Sclerema neonatorum and subcutaneous fat necrosis occur in the context of neonatal distress.^{13–15} Other childhood sclerodermoid conditions such as stiff skin syndrome, morphea, melorheostosis, juvenile onset systemic sclerosis, and H syndrome can present during infancy,^{16–20} although age of onset is often later. Although biopsy may be a useful diagnostic tool for the aforementioned conditions, histology of HGPS sclerodermoid change is nondiagnostic.^{3,21} If HGPS is suspected, molecular genetic analysis is the test of choice. Mottled hypo- or hyperpigmentation can occur over the areas of sclerodermoid change,^{1–3} and these features resemble the “salt and pepper” sign of other sclerotic conditions. Although not mentioned in the reviewed documentation, we have noticed that children younger than 24 months also have mottled dyspigmentation on the posterior neck, which may or may not be related to sun exposure.

Prominent superficial veins from loss of subcutaneous fat can also help distinguish HGPS from other pathologies. Scalp veins specifically become more prominent as alopecia progresses, although they are often visible beforehand. Perioral cyanosis is also believed to be related to a paucity of subcutaneous fat rather than being cardiac in origin. This can be a

subtle finding, which may explain the small reported number in this review. Alopecia is a universal finding of HGPS.² This feature does not appear to be evident at birth; all children were reported to have terminal scalp hair at birth, with a mean age of hair loss of 10 months. The described pattern of alopecia begins with initial loss in the temporal and occipital areas, with preservation of hair over the midscalp and vertex areas for the longest period of time. This pattern is distinct to HGPS and has been previously documented.^{2,8,22–24} The majority of our patients reported presence of eyebrows (81%) and eyelashes (97%) at birth. Hair loss ultimately progresses to near total alopecia.^{3,7} There are several limitations to this study. Nail dystrophy is a recognized feature of HGPS. Nails are reportedly normal at birth but become small, short, and irregularly formed.³ Initial description and presenting age of nail abnormalities were not part of the standardized interviews and surveys; thus, we cannot comment on temporal pattern. In addition, because the clinical trials involved children at age 2 years and older, many dermatologic descriptions were based on parent or provider recall rather than documented physical examinations. It is possible that features were overlooked or described incorrectly.

In conclusion, HGPS has early cutaneous manifestations, including distinct sclerodermoid change, prominent superficial vasculature, dyspigmentation, and alopecia. Together these features are distinguishable from those of other diseases. Many can present within the initial months of life and may be the first signs of the disease. Dermatologists should be aware of these features to minimize testing and expedite diagnosis.

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Figure 1.

Sclerodermoid changes of the chest and abdomen in HGPS. Each photograph originates from a different patient. A 6-month-old female (A) and 10-month-old female (B) demonstrate symmetrical chest and abdominal sclerodermoid changes with prominent, extroverted nipples. A 2-month-old male (C) and 2-year-old female (D) demonstrate similar sclerodermoid changes with flattened nipples. Mottled hypo- and hyperpigmentation is evident in Photograph D.

Figure 2.

Sclerodermoid changes of the extremities in HGPS. A 10-month-old female (A) with bilateral lower extremity sclerodermoid changes. Notice the small, soft outpouchings with a pseudo-cellulite appearance. An 11-month-old female (B) demonstrates similar findings with involvement of the buttocks and overlying mottled dyspigmentation. The same child had relative sparing of the upper extremities (C).

Figure 3.

Progression of scalp alopecia in HGPS. Each photograph originates from a single child: normal hair texture and distribution at 1 week (A). At 7 weeks (B) and 8 weeks (C), development of hair thinning especially in the temporal area. At 8 months (D), hair loss continues to progress involving the occipital area. By 2 years (E–F), nearly complete scalp alopecia with the exception of the midscalp and vertex areas. Superficial scalp and forehead veins are prominent. Complete scalp alopecia with thinning of eyebrows has developed by age 3 years (G–H)

Figure 4.
Prominent superficial forehead veins in a 5-month-old male (A) and 11-month-old female (B) with HGPS.

Figure 5. Progression of eyebrow and eyelash loss in HGPS. This series originates from a single patient. At 2 years (A) eyebrows and eyelashes are present. By 3 years (B), eyebrows have markedly thinned with loss of upper eyelashes

Table 1

Patient characteristics

Characteristic	Study Children, No. (%) (n = 39)
Sex	
Male	16 (41)
Female	23 (59)
Age at clinical trial enrollment, y	
2	1 (3)
> 2 to 6	20 (51)
> 6 to 10	15 (38)
> 10	3 (8)
Age of HGPS clinical diagnosis, mo	
6	10 (26)
> 6 to 12	11 (28)
> 12 to 24	11 (28)
> 24	7 (18)

Abbreviations. Mo = month; y = year

Table 2

Initial age of presentation of cutaneous manifestations

Characteristic	Reported, No. (%) (n = 37)	Mean (mo)	Median (mo)	Minimum (mo)	Maximum (mo)
Skin manifestations					
Sclerodermoid change	29 (78)	1.9	1	0	8
Prominent veins					
Scalp	22 (59)	5.4	3	0	20
Body	8 (22)	3.1	1.5	0	15
Circumoral cyanosis	8 (22)	2.4	2	0	7.5
Dyspigmentation	6 (16)	2	2	0.25	3
Hair manifestations					
Scalp hair loss	37 (100)	10.2	10	1.5	24

Abbreviations. Mo = month

Table 3

Anatomic distribution of sclerodermoid changes

Location	Reported, No. (%) (n = 29)
Abdomen	24 (83)
Lower extremities (bilateral)	14 (48)
Chest	4 (14)
Back	2 (7)
Buttocks (bilateral)	1 (3)
Upper extremities (bilateral)	1 (3)