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Hutchinson–Gilford Progeria Syndrome: Review of the Phenotype

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Hutchinson–Gilford progeria syndrome (HGPS) is a rare but well known entity characterized by extreme short stature, low body weight, early loss of hair, lipodystrophy, scleroderma, decreased joint mobility, osteolysis, and facial features that resemble aged persons. Cardiovascular compromise leads to early demise. Cognitive development is normal. Data on 10 of our own cases and 132 cases from literature are presented. The incidence in the last century in the Netherlands was 1:4,000,000. Sex ratio was 1.2:1. Main first symptoms were failure to thrive (55%), hair loss (40%), skin problems (28%), and lipodystrophy (20%). Mean age at diagnosis was 2.9 years. Growth in weight was more disturbed than growth in height, and growth delay started already prenatally. Mean height > 13 years was 109.0 cm, mean weight was 14.5 kg. Osteolysis was wide-spread but not expressed, except in the viscerocranium, and remained limited to membranous formed bone. Lipodystrophy is generalized, only intra-abdominal fat depositions remain present. Cardiovascular problems are extremely variable, both in age of onset and nature. Stroke and coronary dysfunctioning are most frequent. Pathologic findings in coronaries and aorta resemble sometimes the findings in elderly persons, but can also be much more limited. Loss of smooth muscle cells seems the most important finding. Mean age of demise was 12.6 years. Patients can be subdivided in patients with classical HGPS, which follows an autosomal dominant pattern of inheritance, (almost) all cases representing spontaneous mutations, and in non-classical progeria, in whom growth can be less retarded, scalp hair remains present for a longer time, lipodystrophy is more slowly progressive, osteolysis is more expressed except in the face, and survival well into adulthood is not uncommon. Pattern of inheritance of non-classical progeria is most probably autosomal recessive. The cause of HGPS is an abnormally formed Lamin A, either directly by a mutated *LMNA* gene, or through abnormal posttranslational processing (*ZMPSTE24* gene mutations). Of 34 *LMNA* mutations found in progeria patients, there were 26 classical p.G608G mutations (76%). Pathogenesis is most likely to follow several different pathways. Potential therapeutic strategies are developed along these lines and include RNA interference techniques and inhibition of the dominant-negative influence of abnormally formed Lamin A on polymerization with normally formed Lamin A. © 2006 Wiley-Liss, Inc.

Key words: laminopathy; natural history; management; Lamin A/C; nuclear envelope

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HISTORY

In 1886, the general practitioner Jonathan Hutchinson described a 3 ½-year-old boy with 'congenital absence of hair and mammary glands with atrophic condition of the skin and its appendages' [Hutchinson, 1886]. He thought it was a form of ectodermal dysplasia. A second patient was mentioned briefly by Hutchinson in 1895 but described in much more detail by Hastings Gilford [1897] who had followed the patient for several years until his death at 17 years. Gilford provided follow-up data on the original patient described by Hutchinson, and recognized that at least some of the symptoms resembled early aging. In a subsequent publication, he suggested naming the entity 'progeria,' 'pro' meaning early and 'geras' meaning old age in ancient Greek [Gilford, 1904]. It has been suggested that an earlier case was reported in a newspaper ('Hopkin Hopkin' from

Dedicated to Bob Gorlin, my mentor and friend.

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Wales), but evidence is too scarce to accept this as a genuine patient.

After a French 15-year-old girl [Variot and Pironneau, 1910] and a 27 ½-year-old man from the Netherlands [Schippers, 1916; Manschot, 1940] (Fig. 1) were reported, there were gradually more patients reported from all continents. In 1972, in a remarkable review article, DeBusk summarized the findings in 60 patients, including four unpublished cases, from all over the world [DeBusk, 1972].

Interest in progeria increased further when both a French and an American group discovered that the disorder was caused by mutations in the gene encoding *Lamin A/C* [De Sandre-Giovannoli et al., 2003; Eriksson et al., 2003]. A host of studies followed, dealing with progeria and other laminopathies and the cellular processes they illuminated.

Here, we review the clinical findings in 132 patients from literature, and 10 of our own patients (Table I). Only the major aspects of cause, pathogenesis, and management are reviewed. The reader is referred elsewhere for more detailed discussions [Burke and Stewart, 2002; Goldman et al., 2002; Unger and Orci, 2002; Mounkes et al., 2003; Zastrow et al., 2004; Cadinanos et al., 2005]; especially the metabolic and endocrine aspects of HGPS, and data from mutant mice are not reviewed here.

DEMOGRAPHY

DeBusk calculated that 18 patients with progeria were reported from the US between 1915 and 1967, during which time 145,000,000 children were born [DeBusk, 1972] giving an incidence of 1 per 8,000,000 newborns. In Europe, 23 patients are presently known to the Europrogeria consortium [Brune et al., 2004], but ascertainment in some countries is probably low preventing calculation of an incidence. In the Netherlands, five definitively affected children born between 1900 and 2005 are known. In that period, a total of 19,981,000 children were live-born [Dutch Central Office of Statistics, personal communication 2006], giving a minimum incidence of 1 per 3,996,000 newborns. This is in agreement with the figure of 1 in 4 million suggested earlier [Brown et al., 1985]. Patients have been reported from all continents and all ethnic backgrounds, although the number of reported patients of Caucasian descent is by far the largest, probably through publication bias.

A distorted sex ratio was reported in 60 patients: 36 males:24 females (1.5:1) [DeBusk, 1972]. A literature search of 132 patients gave a ratio of 69 males to 57 females (1.2:1; in 6 patients the gender was not mentioned). In the 23 living European patients, the sex ratio is equal (11:12).

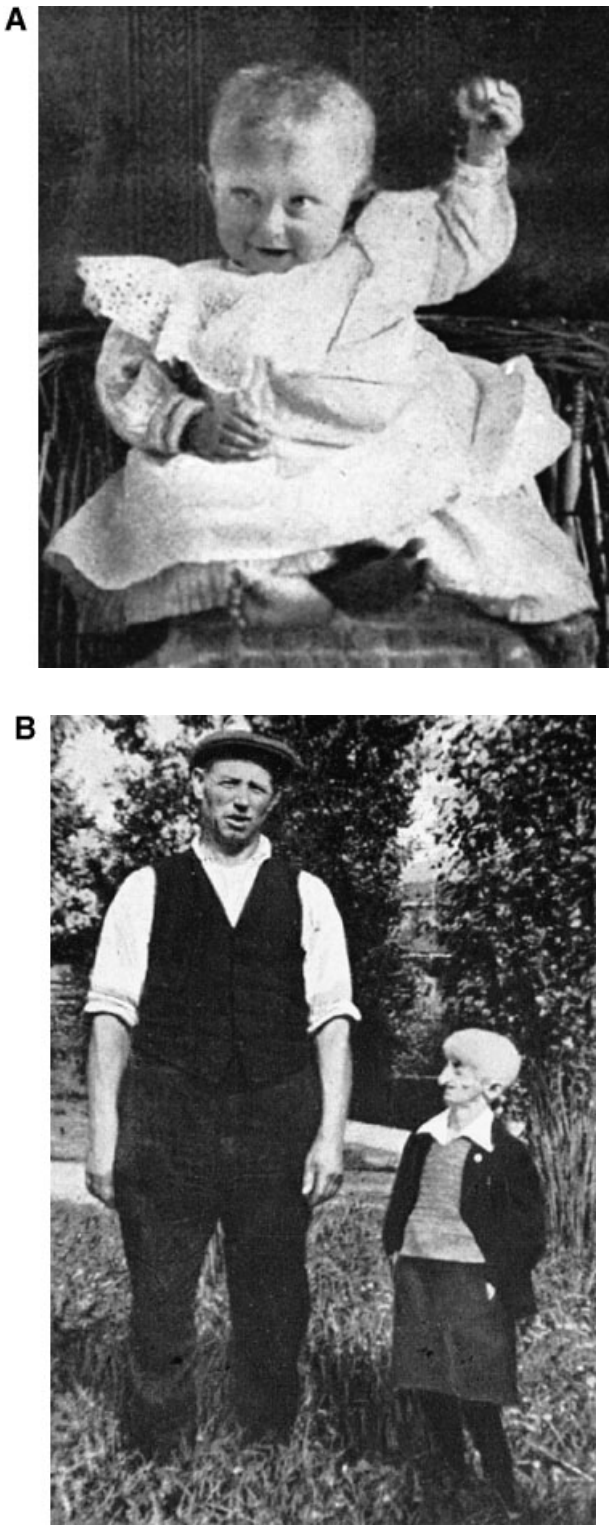

Fig. 1. First Dutch Patient 1 at the age of 11 months (**A**) and shortly before he died at the age of 26 years (**B**) [Schippers, 1916; Manschot, 1940].

TABLE I. Major Findings in 142 Patients With Hutchinson–Gilford Progeria Syndrome[a]

Feature	Frequency
Prenatal growth delay	+
Postnatal growth delay	++++
Normal skull growth	+++
Cognitive development	++++
Hair sparse/alopecia	++++
Increased visibility vessels	
Cranium	++++
Nasal bridge	++++
Prominent forehead	++
Absent eyebrows/eyelashes	+++
Small face	++++
Thin nasal skin	++++
Convex nasal profile	++
Crowded teeth	+++
Increased dental decay	+++
Absent ear lobule	++
High voice	++++
Lipodystrophy	++++
Narrow upper thorax	++++
Prominent abdomen	++++
Broadened finger tips	+++
Nail dystrophy	+++
Horse riding stance	+++
Decreased mobility	
Elbows	++++
Wrists	++
Fingers	++++
Hips	++++
Knees	++++
Ankles	++
Stroke	
Angina pectoris	

[a]+: 0–25%; ++: 25–50%; +++: 50–75%; ++++: 75–100%.

CLASSICAL VERSUS NON-CLASSICAL HGPS

The diagnosis of HGPS is usually straightforward, and the classically affected patients strongly resemble one another (Fig. 2). However, there is a group of patients with progeria that show a definite overlap with patients with mandibulo-acral dysostosis (MAD). Their clinical findings differ from classical HGPS in several respects:

a. Growth is less retarded, adult heights varying from 130 to 145 cm, while in classical HGPS height rarely exceeds 115cm;
b. In many, scalp hair persists much longer, and may not disappear completely even in old age;
c. The lipodystrophy progresses more slowly with fat pads remaining in the cheeks, submandibular region, and pubis into adulthood;
d. Osteolysis is more severe in all affected bones (vault, mandible, clavicles, ribs, distal phalanges) except for the viscerocranium where it is mild in childhood and only gradually progresses later on. The more severe osteolysis increases the risk of fractures, especially of the humerus, often at a young age (in 10 of the families, affected children had fractures, usually from the age of 2–3 years);
e. The incidence of consanguinity is increased (4/14 families);
f. The chance of survival into adulthood is somewhat increased (four cases having reached an age of 20 years or above).

For the above reasons, these patients [El-Sibaie and Mokhtar, 1954; Mostafa and Gabr, 1954; Gabr

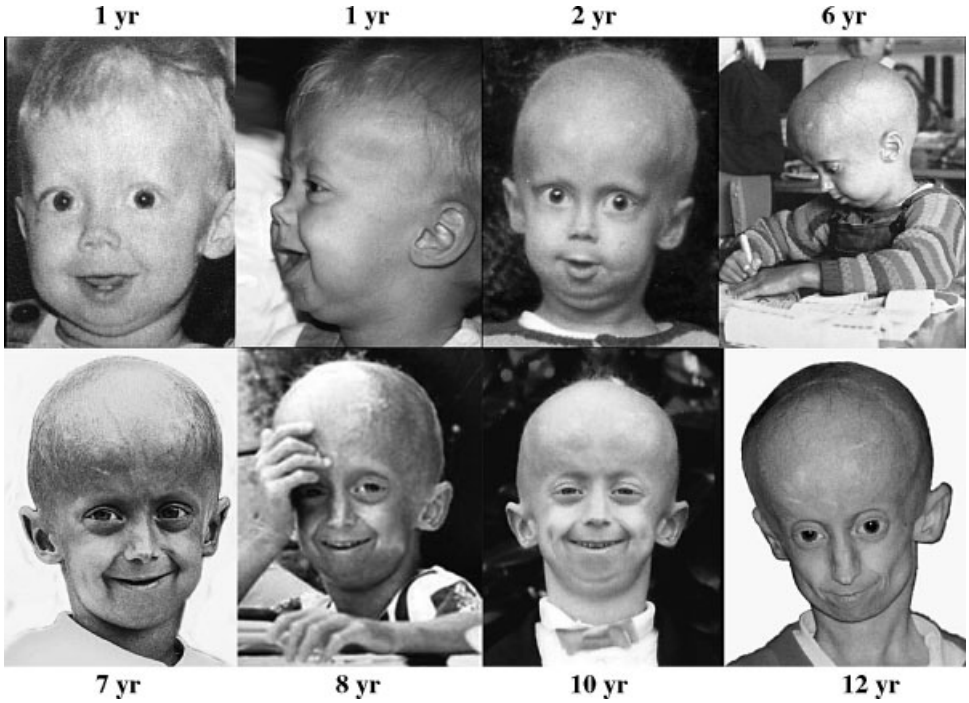

FIG. 2. Dutch Patient 2 at the age of 1 year, 1 year, 2 years, 6 years, 7 years, 8 years, 10 years, and 12 years.

et al., 1960; Zanola, 1961; Rava, 1967; Ozonoff and Clemett, 1967; Randaccio et al., 1972; Valdiserri and Stricchiola, 1974; Franklyn, 1976; Ishii, 1976; Soares et al., 1984; Ogihara et al., 1986; Ramesh and Jain, 1987; Maciel, 1988; Khalifa, 1989; De Waard-Van der Spek et al., 1993; Biswas and Reddy, 1997; Plasilova et al., 2004] are separated here from the classical HGPS patients using the criteria summarized in Table II. Their features involve the same body systems as classical HGPS, only the course and severity of the symptoms vary. This phenotype could be called non-classical progeria as the diagnosis progeria remains justified. The value of the separation is for the counseling of families. In some cases reported in literature, classification remains difficult [Corcoy et al., 1989; Fatunde et al., 1990; Monu et al., 1990], usually because of lack of sufficient data. A similar, but not identical, division into classical and 'atypical' progeria has been suggested before [Shackleton et al., 2005].

There remains another group of patients reported as having HGPS that already have clear findings at birth [De Martinville et al., 1980; Labeille et al., 1987; Faivre et al., 1999; Rodriguez et al., 1999]. These patients may show an overlap with restrictive dermopathy (RD). They are designated congenital HGPS.

DIAGNOSIS

In classical HGPS, the main reason for presentation was failure to thrive (55%), hair loss (40%), skin problems (28%), lipodystrophy (20%), and rarely other symptoms (unusual face; small clavicles; affected sib) (the total is more than 100% as several patients presented with more than one symptom). Amongst the cohort of European patients the presenting complaints were similar, although scleroderma was somewhat commoner (38%). The mean age at diagnosis in literature cases was 2.9 years (data available on 72 patients). In the European patients, it was 2.6 years (1.1–4.8 years). Almost all parents could remember the exact date the diagnosis was made.

GROWTH

The mean birth weight in term infants with HGPS is reduced (2,980 g; n = 42). Only seven children were small for gestational age (birth weight below the 3rd centile, irrespective of gestational age). Mean birth weight in European patients was 2,995 g. Of 86 children for whom data were available, 12 were born prematurely. Postnatal growth becomes severely disturbed: in the first year growth velocity is mildly decreased; thereafter, it falls off rapidly (Fig. 3). Weight is even more affected, the weight curve running almost horizontally from the age of 2 years. There is no pre-pubertal or pubertal growth spurt. Stature in boys is less impaired than in girls, and the range is greater in boys than girls. The range in 17 patients with classical HGPS of 13 years or older in whom height is known was 96 cm to 128 cm (mean 109.0 cm). Weight in patients with classical HGPS >12 years varied from 9.3 kg to 20.7 kg (mean 14.54 kg; n = 17). Bone age was reported to be slightly advanced (6–12 months) in three patients, and delayed in eight patients, the difference being greater (1–2 years) in patients above 10 years. In all other patients, bone age was reported to be within normal limits.

OSTEOLYSIS

Some form of osteolysis is invariably present in any patient with HGPS (Fig. 4). It can be found at the distal phalanges, clavicles, mandible, neurocranium, and viscerocranium. There are also reports of osteolysis involving the first ribs [Luna Ceballos et al., 1999; Sivaraman et al., 1999]. All these bones are formed by membranous ossification including

TABLE II. Differences Between Classical Hutchinson–Gilford Progeria Syndrome and Non-Classical Progeria

Feature	HGPS	Non-classical progeria
Growth deficiency		
Prenatal	Mild	Mild
Postnatal	Severe	Mild
Lipodystrophy	Expressed	Slower but in the end expressed everywhere except cheeks, submandibular, and suprapubic region
Hair loss	Expressed	Variable: minimal to severe[a]
Scleroderma	Moderate	Moderate
Osteolysis		
Acra	Moderate	Expressed
Clavicles	Mild	Expressed
Mandible	Moderate	Expressed
Viscerocranium	Moderate/severe	Mild, slowly progressive
Neurocranium	Mild	Expressed
Fractures	Late; head	Early; humeri, ribs
Vascular problems	Early; expressed	Often late, but sometimes early

[a]Some scalp hair usually remains present.

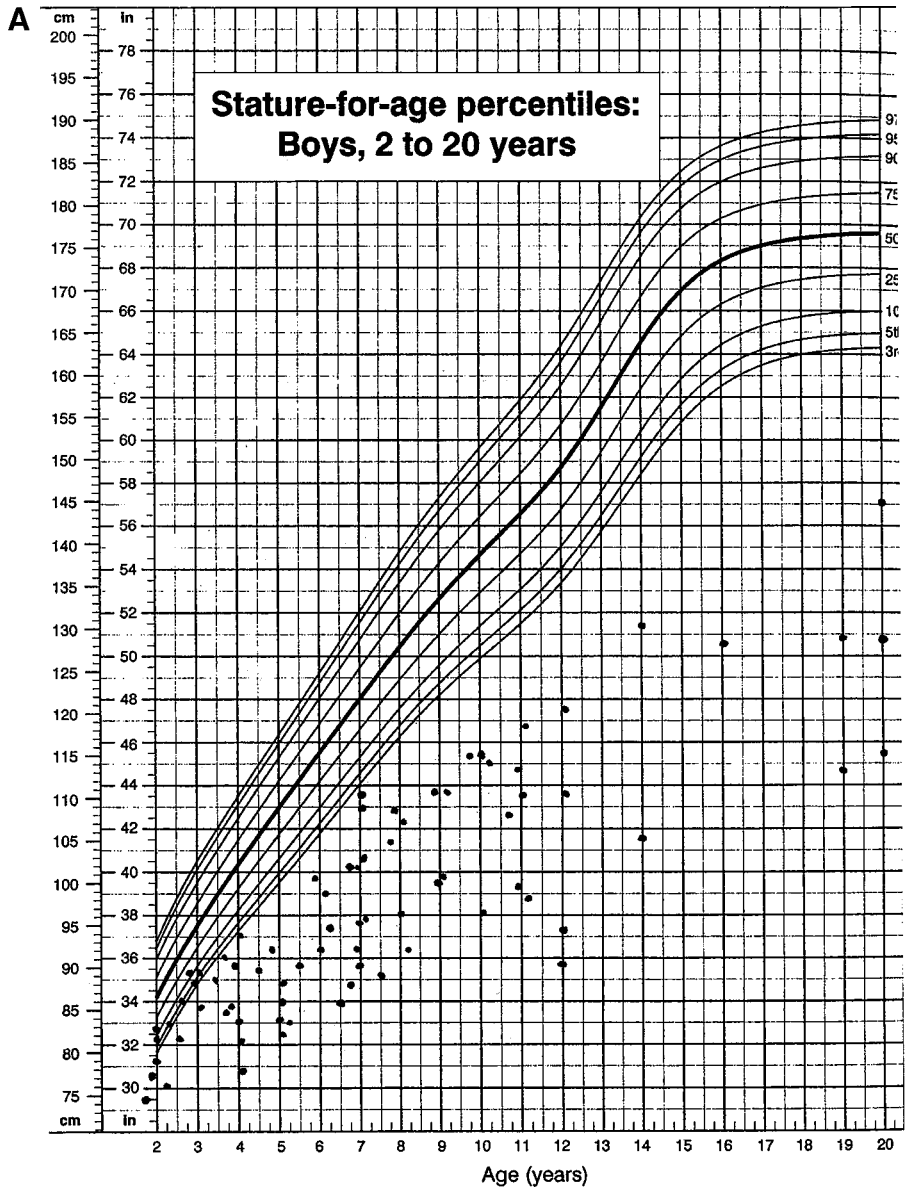

FIG. 3. Growth curves summarizing growth data of 98 patients from various ethnic backgrounds born between 1877 and 2003. **A**: Height in boys; **B**: height in girls; **C**: weight in boys; **D**: weight in girls. The curves are the CDC Growth Curves for the United States [Developed by the National Center for Health statistics in collaboration with the National Center for Chronic Disease Prevention and Health Promotion, 2000].

the middle part of the distal phalanges. In classical HGPS, osteolysis seems to be restricted to these bones. In non-classical progeria, the osteolysis is much more severe and also involves bones formed by enchondral bone formation, such as the proximal parts of the distal phalanges, the middle part of the clavicles, and long bones of the upper limb. Two patients with non-classical progeria were described with extremely marked osteolysis, including the proximal radius and distal ulna [Rava, 1967; Monu et al., 1990]. Another non-classical case showed resorption of cervical vertebrae at 3 years of age [Franklyn, 1976]. The proximal fibula is often remarkably thin. In several older patients with either form of progeria, dislocation of the hips has been described. It is uncertain whether local osteolysis plays a role here too. Fractures occur in classical HGPS [Noltenius and Wiedemann, 1960; Gamble, 1984; Mandera et al., 2003], mostly of the skull in the end stage of the disorder. Fractures in non-classical progeria usually begin in the 2nd or 3rd year, involve the humerus and also the ribs, and are often recurrent.

Acra

Osteolysis of the distal phalanges usually starts between 1 and 2 years of age, but can be as early as the first months of life or later than 5 years. The process starts in the index and little fingers, and gradually extends. The ring finger is usually the least

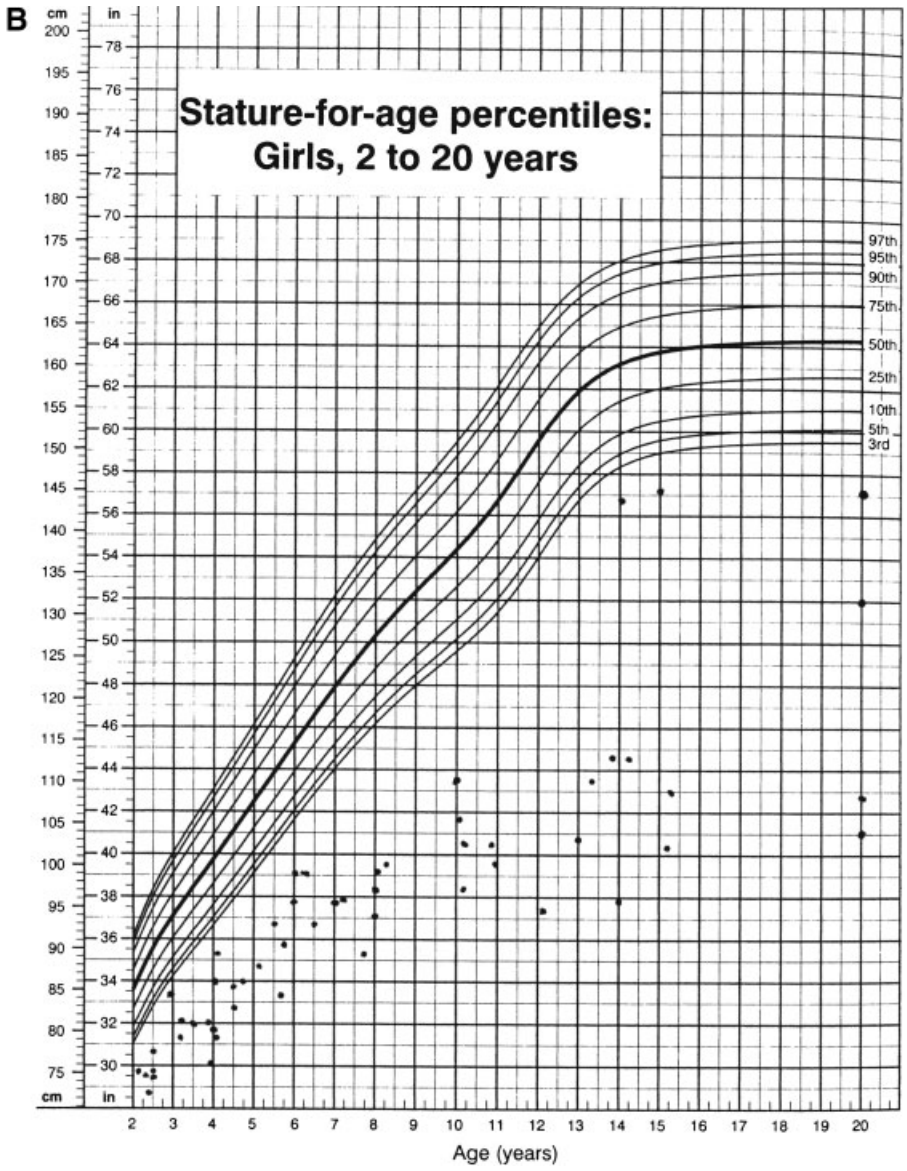

FIG. 3. (*Continued*)

affected. The skin over the phalanges usually becomes red and swollen, while the nails become dystrophic: they are small, short, and irregularly formed, first thin, later on thickened and difficult to cut. Both fingers and toes are affected, but the osteolysis of toes is less visible, and also the skin and nail changes are usually milder. However, there are children in whom nail changes do not follow the acrosteolysis, and is more expressed, which may indicate that nail dystrophy may also occur as a separate symptoms.

Clavicles

The osteolysis starts at the acromial ends of the clavicles, and is only slowly progressive. Early on it may cause just mild tapering of the distal clavicle, which may be difficult to appreciate. The clavicles are usually only mildly affected. Complete radiolucency of the clavicles has been reported in non-classical progeria. The upper part of the thorax gradually narrows with increasing osteolysis of the clavicles and upper ribs, which causes the characteristic narrow shoulders.

Mandible

The chin has a normal shape and size at birth, but becomes smaller after 1–2 years. There is osteolysis of the viscerocranium, but the osteolysis of the mandible is more marked which causes retrognathia. Both the horizontal and ascending rami become smaller with age, and the mandibular angle increases (often to about 150 degrees).

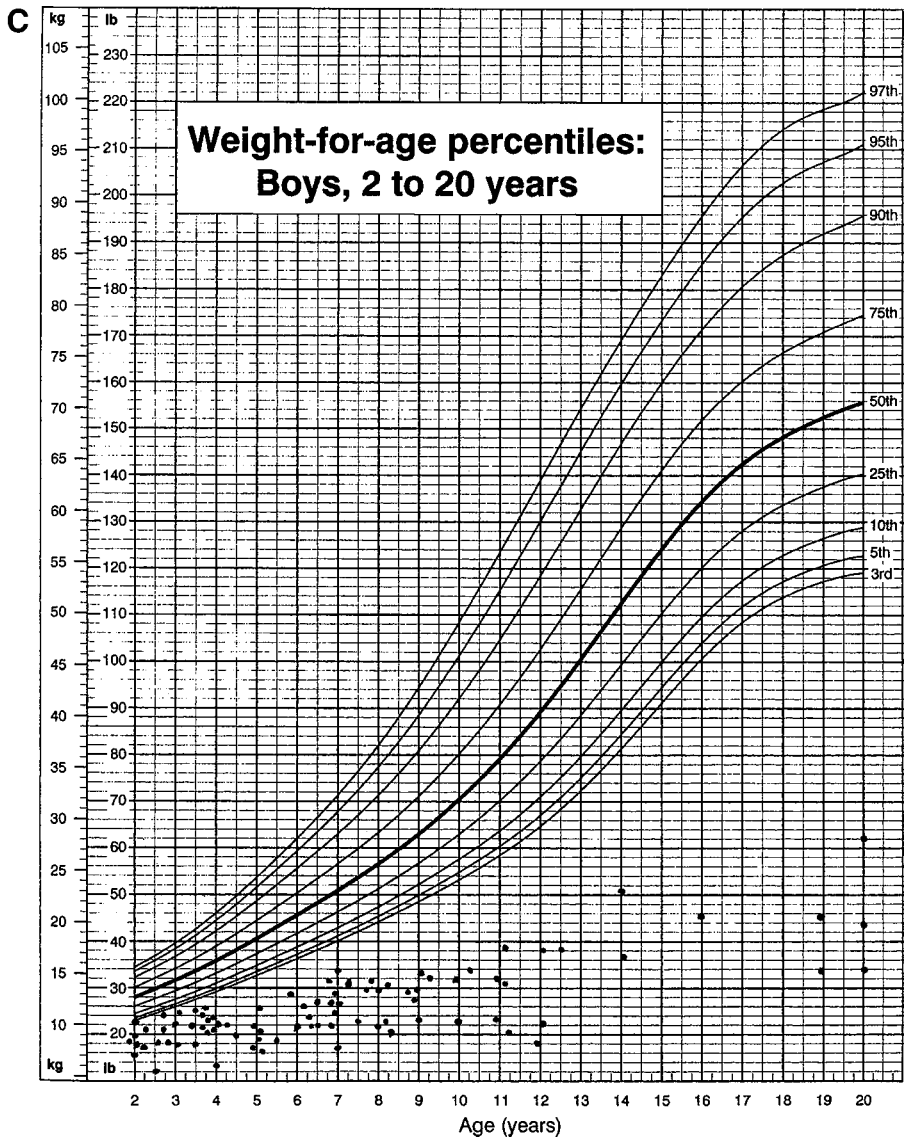

FIG. 3. (*Continued*)

Viscerocranium

The facial bones become smaller and thinner with age. Radiologically, osteolysis of the viscerocranium is difficult to prove but the decrease in size of facial bones with age and the widespread osteolysis elsewhere in these patients make it very likely. The decrease in size of the maxilla and mandible causes crowded teeth. In non-classical progeria, the size of the facial bones is preserved for longer.

Neurocranium

The deficient ossification is manifested by the widely patent anterior fontanel that may remain open well into childhood and even into puberty [Gilford, 1897; DeBusk, 1972; Bhakoo et al., 1964; Xuezhe and Xitang, 1979]. The cranial vault is thin, and wormian bones are visible in the occiput, the changes being most marked in non-classical progeria. The size of the neurocranium is in part dependent on the growth of the brain and remains near normal. Together with the decrease in the size of the facial bones, this causes the vault to appear relatively large compared to the face. The skull circumference falls often between the 25th centile and −3SD; only very rarely the skull circumference reaches above the 50th centile.

LIPODYSTROPHY

Lipodystrophy can start as early as 6 months, but may not become visible until 3–4 years of age. In classical HGPS, it becomes evident first in the limbs, followed by the thorax and neurocranium, and finally in the face, the buccal and pubic fat

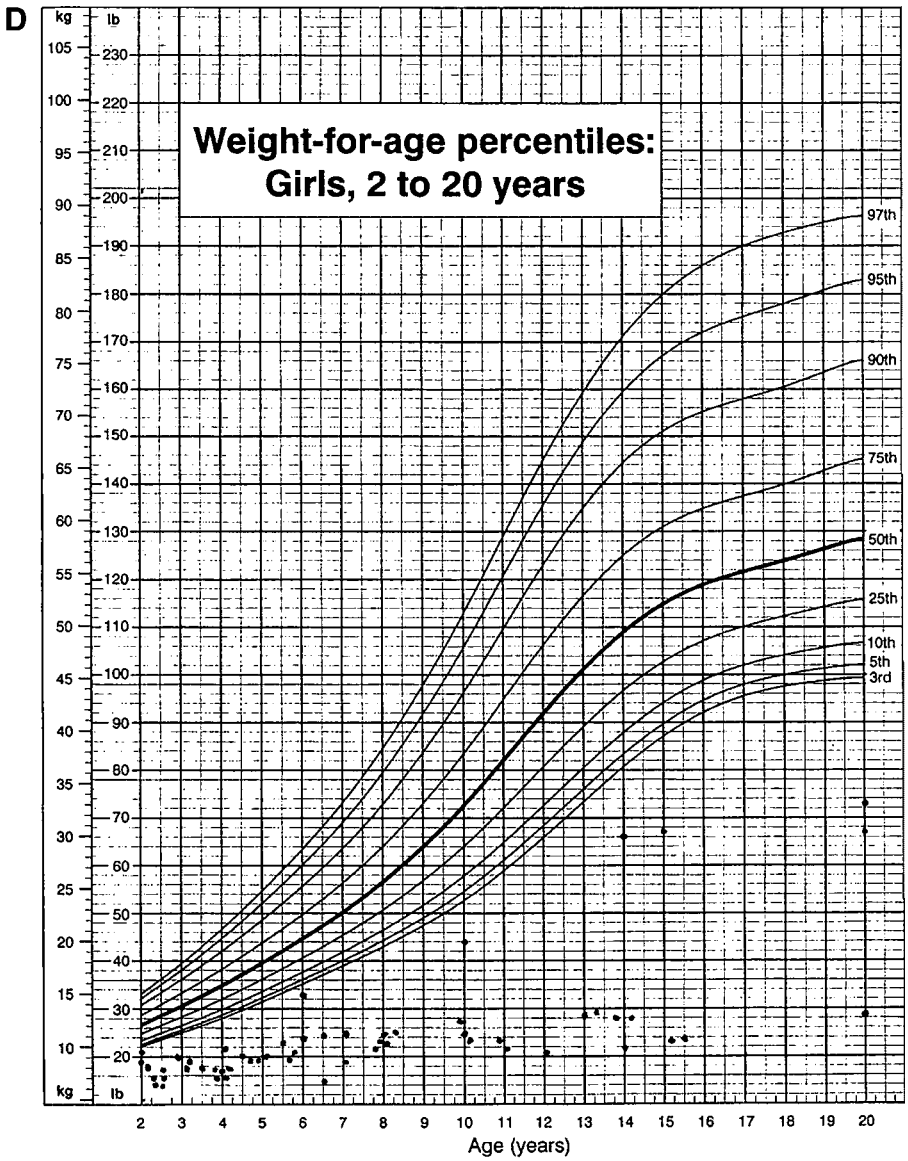

Fig. 3. (*Continued*)

disappearing last. In non-classical progeria, this occurs much more slowly. Intra-abdominal fat remains remarkably spared, which causes the characteristic prominent abdomen in almost all children. In this respect, there is a remarkable resemblance with patients with HIV treated with protease inhibitors [Saint-Marc et al., 2000]. The umbilicus usually does not show the physiological depression, and can be hypoplastic.

The disappearance of subcutaneous fat and thinning of the skin cause the blood vessels to be more visible. A characteristic visible vein across the nasal bridge is often the earliest symptom of classical HGPS (Fig. 5A). Later on, the scalp veins become clearer, and in the later stages veins are prominent everywhere (Fig. 5B). The disappearance of intra-orbital fat makes the eyes look prominent, although usually no true exophthalmus is found. Wrinkling of the thin facial skin can be remarkable (Fig. 5C).

SKIN

Scleroderma is a transient feature in HGPS. It has been found as early as on the first day of life [DeBusk, 1972; Fleischmajer and Nedwich, 1973], is usually found between 1.5 and 6 months, but can start later at around 2 years. The skin is thick, swollen, and shows a pitting edema (Fig. 6A). Sometimes, it is slightly erythematous [Feingold and Kidd, 1971]. With time, the skin becomes more firm and sclerodermatous. Involvement of the skin of the lower abdomen, upper gluteal regions, genitalia, and thighs is particularly common, but it may be more widespread [Erdem et al., 1994]. Sometimes, there is a discolored

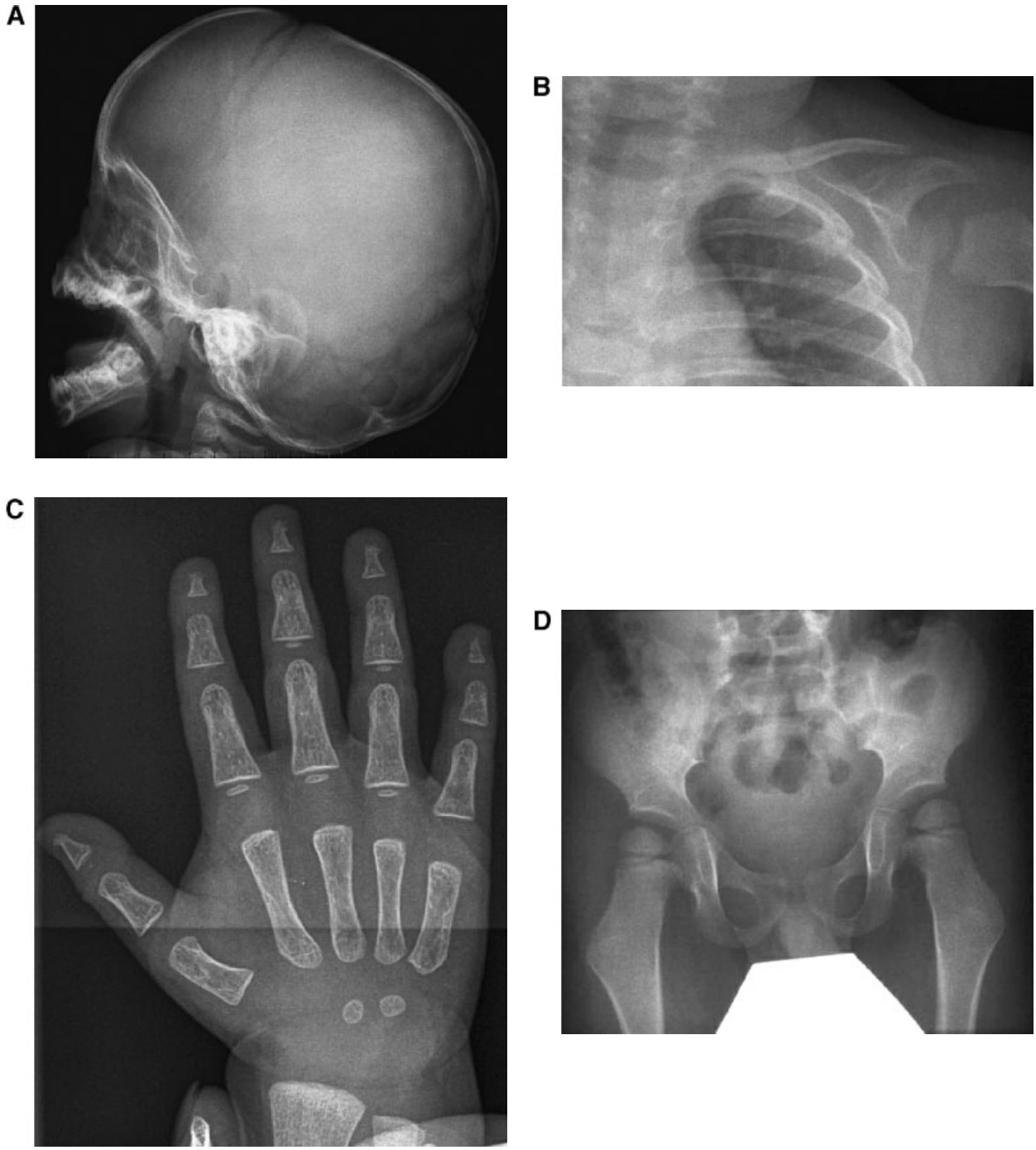

FIG. 4. Radiographs of Dutch Patient 3 at the age of 2 years. **A**: Skull. Note relatively large neurocranium compared to the viscerocranium (especially the mandible), open anterior fontanel, thin cranial vault, and mild wormian bone formation at the occiput. **B**: Clavicle. Note mild tapering of the distal part. The ribs are normal. **C**: Hand. Note limited osteolysis of the distal phalanx of the 2nd and 5th finger. **D**: Pelvis. Note expressed coxa valga.

skin zone indicating the transition between normal and sclerodermatous skin [Strunz, 1929]. The scleroderma disappears after 6 months–2 years, irrespective of whether steroids are applied or not. The skin then becomes thin, dry, and atrophic, with reduced turgor, and sometimes with fine scaling or hyperkeratosis (Fig. 6B). Small, fine, light-brown spots frequently develop on the neck and upper thorax in both classical HGPS and non-classical HGPS. Later on, similar hyperpigmentations can be seen on the scalp and limbs. A single patient showed numerous hyperplastic scars or keloid-like lesions on the dorsum of hands and feet and elsewhere on the upper limbs [Jimbow et al., 1988].

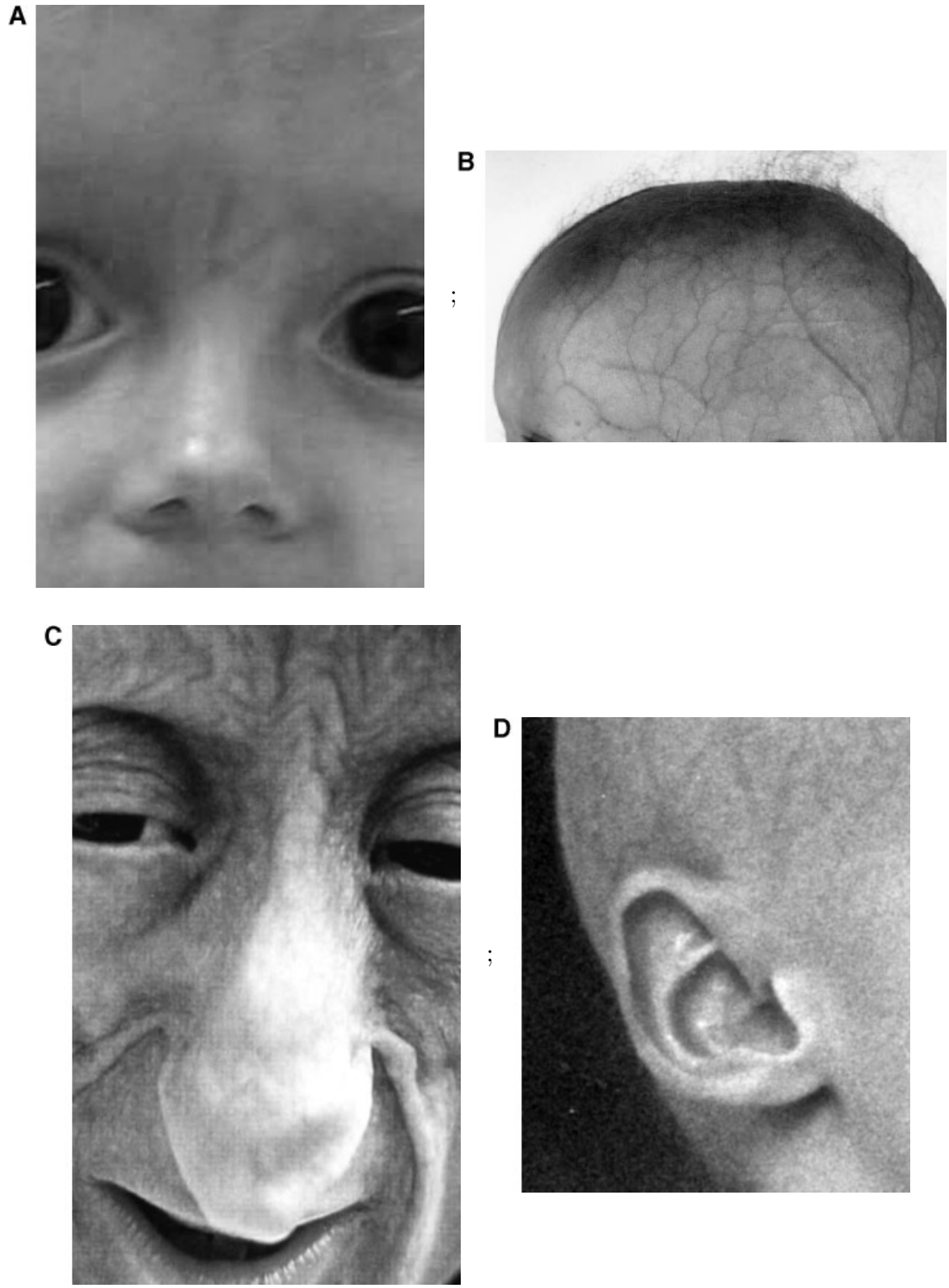

FIG. 5. Individual facial symptoms. **A**: Prominent vein across the nasal bridge, often the first symptom in patients. **B**: Thin scalp skin, well visible and often distended veins, and alopecia except for some fine, downy and curly hair. **C**: Detail of face showing thin facial skin with excessive folding on forehead and cheeks, pseudo-protrusion of the eyes, thin nasal bridge, and collapsed, flattened and broad nasal tip. **D**: Absence of ear lobule.

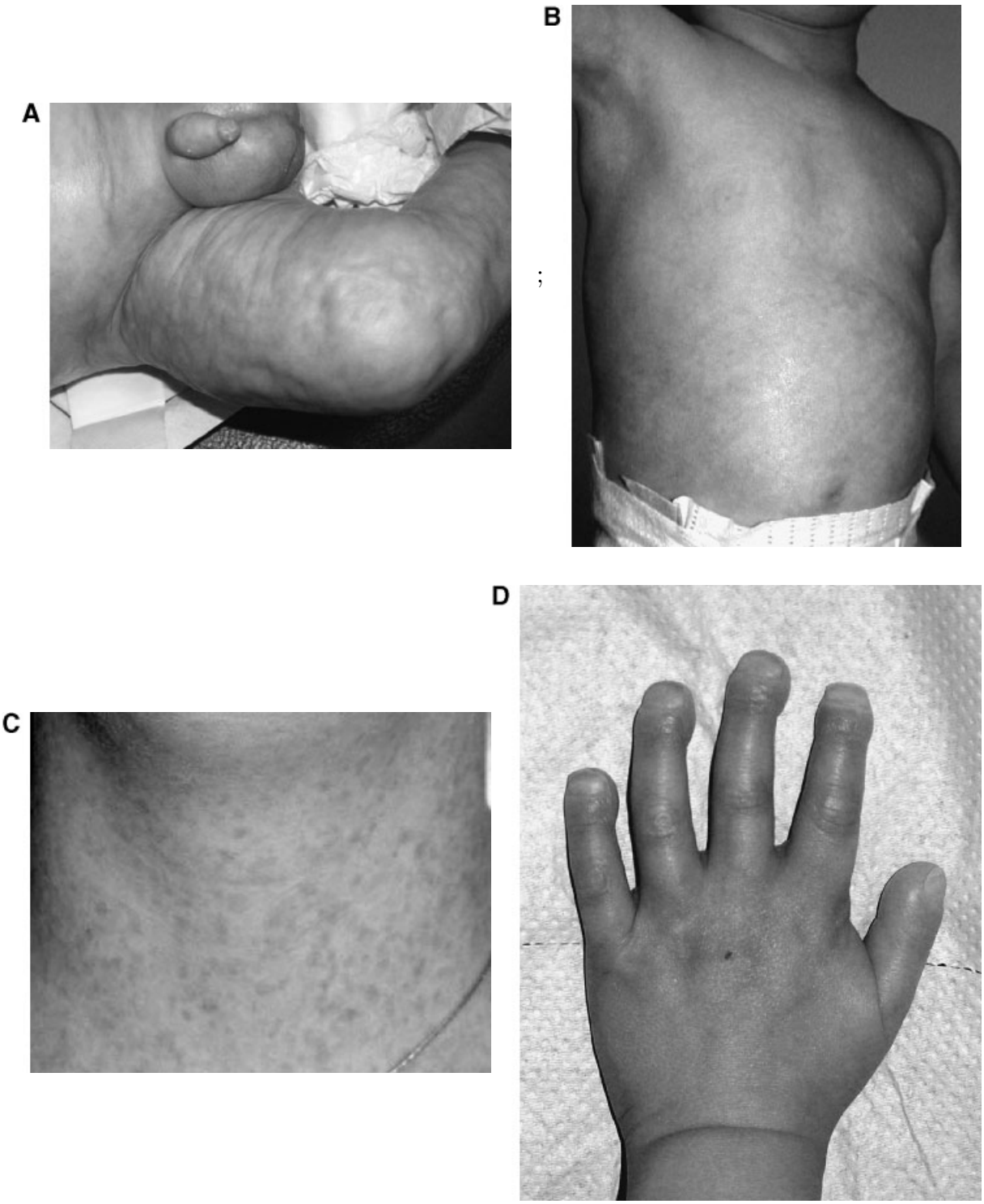

FIG. 6. Skin. **A**: Patient at 6 weeks of age showing early phase scleroderma. Note swollen skin, pitting, and predilection localization (lower abdomen, genitalia, upper legs). **B**: Same patient at 2 years of age. Note slight discolored skin of lowed thorax and abdomen, which ward thick and firm on palpation. **C**: Hyperpigmentations. Small, spotty pigmentations with a café-au-lait color or somewhat darker. Note predilection localization (neck, upper thorax); later on hyperpigmentations can also be seen on the scalp. **D**: Hands of 3-year-old Dutch Patient 4. Note swollen and discolored distal phalanges and flexion of the fingers (the fingers could still be extended completely passively). The nails are still normal.

Biopsies of the sclerodermatous skin in the acute phase have shown a normal epidermis, thickened corium, hypertrophic collagen accompanied by scattered lymphocytes that may invade the subcutis in bundles, superficially telangiectatic vessels, and a decreased number of fibroblasts and other subcutaneous tissue [Strunz, 1929; Feingold and Kidd, 1971; DeBusk, 1972; Erdem et al., 1994]. Biopsies taken at a later stage show a thickened dermis, with thick mature collagen bundles in the upper part, homogenized collagen in the lower half, and decreased cellularity [Zeder, 1940; Fleischmajer and Nedwich, 1973]. Blood vessels throughout the dermis show moderate thickening of the muscle wall and narrowing of the lumen. Skin biopsies in older patients show a thin epidermis, replacement of the corium by fibrotic hyaline tissue, reduced number of sweat glands and sebaceous glands, and atrophic subcutaneous adipose tissue [Ishii, 1976; Ackerman and Gilbert-Barness, 2002].

Hutchinson [1886] mentioned in the title of his publication '. . . atrophic condition of the skin and its appendages . . .' and stressed the hypoplasia of the nipples and breasts. Marked hypoplasia of the nipples has been described several times [Gilford, 1897; Schwartz and Cooke, 1945; Mitchell and Goltman, 1946; Thomson and Forfar, 1950; De Martinville et al., 1980; Dyck et al., 1987; Ackerman and Gilbert-Barness, 2002], but true athelia has not been found. Breast development is usually completely absent. In the non-classical progeria patient described by Corcoy et al. [1989], a 32-year-old woman was described with Tanner stage IV pubertal development, but with complete absence of mammary fat tissue.

The skin over the distal phalanges of fingers and toes undergoing acro-osteolysis becomes swollen and reddened (Fig. 6D). It is not tense or painful. The nails are first thin but eventually thick, have an irregular surface, and grow slowly. As stated above, it seems likely that nail dysplasia can also occur as separate symptom.

HAIR

With rare exceptions [Exchaquet, 1935], patients are born with normal hair texture and coloring. At the age of 6 months–2 years, the hair usually falls out. Between 2 and 3 years, most children are found to be bald, apart from fine, downy hair, which has the tendency to curl (Fig. 5B) [Schippers, 1916; Cooke, 1953]. Rarely, the hair is still present at the age of 12–15 years [Ishii, 1976]. The eyebrows and eyelashes also disappear, although some of the lateral eyelashes may remain [Gilford, 1897]. The hair usually becomes light in color, with rare exceptions [Ishii, 1976; Labeille et al., 1987]. Body hair (chest, axilla, pubis, limbs) is sparse or completely absent. Hair as part of secondary sexual characteristics is very unusual [Ishii, 1976]. Histological or electron-microscopic hair investigations have occasionally been reported, and show no abnormalities on polarizing light, but abnormal superficial cuticular scales, and a longitudinal depression of the hair surface on histology [Fleischmajer and Nedwich, 1973; Labeille et al., 1987; Gillar et al., 1991].

MOBILITY

Joint mobility is normal at birth but decreases from the 2nd to 3rd year, initially in the knees followed by the elbows and fingers. The children develop a wide-based, shuffling gait, caused by the combination of coxa valga and joint stiffness. At rest, they stand with their knees flexed and have an increased distance between the thighs ('horse riding stance') (Fig. 7). At first, the muscles appear prominent due to the decrease in subcutaneous fat. However, with time the muscle bulk decreases, first proximally, then distally in the limbs. Many patients have a virtual absence of their buttocks, and their joints, especially the knees protrude. Winging of the scapulae is present in most patients. The joint mobility worsens and in late phases the ankles, wrists, shoulders, and hips are involved. Joints may then become painful, and the loss of plantar fat may cause painful feet with callosities [Gamble, 1984]. Some patients present in infancy with a torticollis [Franklyn, 1976], and a cervicothoracic kyphosis is not uncommon [Variot and Pironneau, 1910; Strunz, 1929; Chawla et al., 1986; Monu et al., 1990]. Other reported orthopedic problems include acute arthritis of a hip in the neonatal period [Makous et al., 1962], dislocated shoulders [Liesmann, 2001], scoliosis [Rodriguez et al., 1999; De Paula Rodrigues et al., 2002], and avascular sclerosis of the femoral head [Curtin and Kotzen, 1929; Moen, 1982; Fernandez-Palazzi et al., 1992].

Radiologically, with time osteopenia of the long bones develops. The long bones are slender and sometimes somewhat bowed [Schwarz, 1962; Kozlowski, 1965; Monu et al., 1990]. In the elbows, the capitulum is large and the head of the radius is wide with flattening and broadening of the epiphysis. The shoulders show the small and tapered distal ends of the clavicles, the pelvis the extreme coxa valga, and the vertebral bodies become ovoid with a 'fish-mouth' appearance. Arthritic changes are only visible in the end stages of the disorder and seem secondary. Recently, a patient with classical HGPS and symptoms consistent with a myopathy has been published [Kirschner et al., 2005]. The patient harbored a non-classical *LMNA* mutation (p.S143F).

The basis of the joint and muscle problems in progeria has rarely been studied [Moen 1982; Fernandez-Palazzi et al., 1992]. The diminished joint mobility does not appear to be due to tightening of the skin. Biopsies have shown normal-appearing

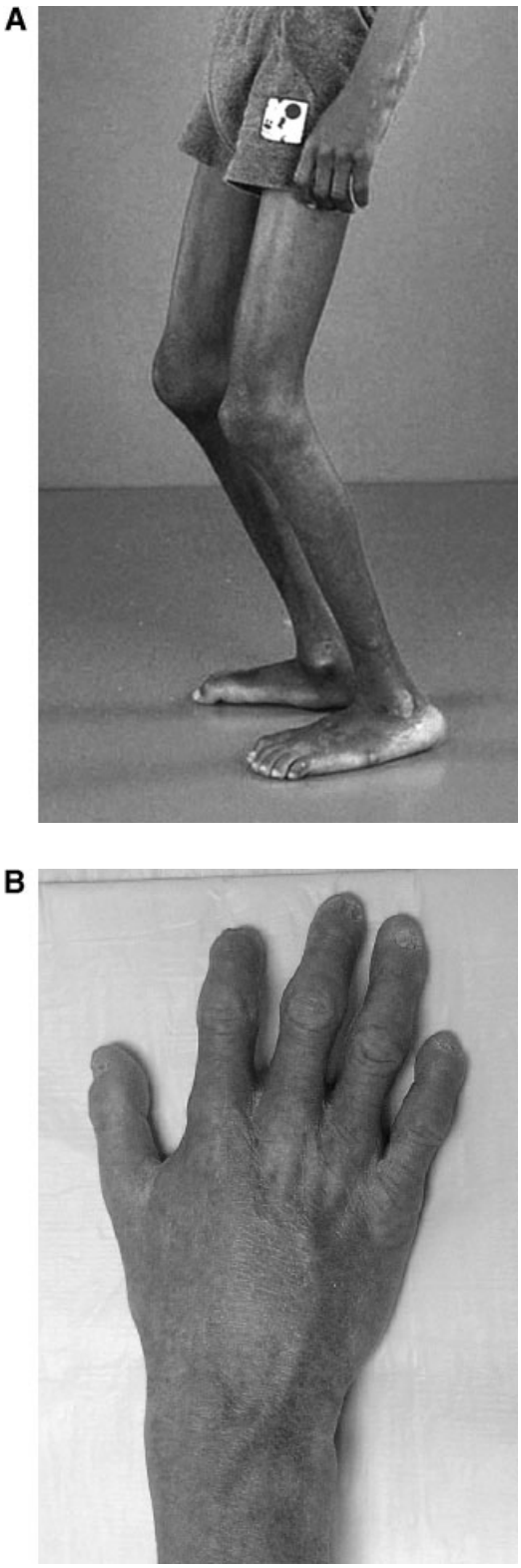

FIG. 7. Joints. **A**: Legs of 8-year-old Dutch Patient 3. Note flexed knees, prominent joints, and decreased subcutaneous fat tissue. The mobility in the ankles was already severely limited. **B**: Camptodactyly in a 7-year-old patient. Also note dystrophic nails.

muscle but thickening of some of the axons of intramuscular nerves [MacNamara et al., 1970]. Follow-up studies of neurophysiologic investigations have not been published.

CARDIOVASCULAR SYSTEM

Initially, patients do not have any cardiovascular problems, clinically nor at sonography or Electrocardiography (ECG) [Makous et al., 1962; Baker et al., 1981]. Blood pressure is also normal. Murmurs can be heard from 4 years of age on, usually are found between 6 and 8 years, but sometimes are only present shortly before demise. The children gradually develop shortness of breath with exertion and easy fatigability from 6 to 8 years, and pulse rates and blood pressure rise. On X-rays or at sonography, the heart appears enlarged. ECG shows signs of impaired coronary functioning and enlargement of the left ventricle, either at rest or on treadmill exercise testing [Matsuo et al., 1994; Shiraishi et al., 2001]. Sometimes, evidence of earlier, silent infarctions is found. Angina pectoris occurs frequently usually within a year of death but sometimes up to 5 years beforehand. In the end phase, dyspnoea can be extreme [Manschot, 1940; Doub, 1953; Dyck et al., 1987]. In some patients, the coronary dysfunction occurs acutely, with rapid demise over weeks or even hours [Cooke, 1953; Doub, 1953; Atkins, 1954]. Coronary artery bypass surgery has been tried [Dyck et al., 1987].

At autopsy, the major finding is the relatively small diameter of the intima and media, and extensive loss of smooth muscle cells [Stehbens et al., 1999]. Thickening of the coronary arteries has been found, with or without calcification. There are also patients in whom no plaque formation in the coronaries is found [Reichel and Garcia-Bunuel, 1970; Ishii, 1976; Shiraishi et al., 2001], or in whom the plaque formation and obstruction were very focal [Atkins, 1954; DeBusk, 1972; Baker et al., 1981]. A hypertrophy of myocardial cells occurs, often accompanied by interstitial fibrosis [Orrico and Strada, 1927; King et al., 1978; Baker et al., 1981; Shiraishi et al., 2001]. The aortic valve leaflets are thickened, especially at the base, and can be calcified [Gilford, 1897; Manschot, 1940; Makous et al., 1962; Reichel and Garcia-Bunuel, 1970; DeBusk, 1972; Baker et al., 1981; Gamble, 1984; Stehbens et al., 1999]. Mitral valve abnormalities occur in about half of the cases including calcification. The findings in the aorta vary from an almost normal appearance [Shiraishi et al., 2001] to severe atheromatosis [Orrico and Strada, 1927; Rosenthal et al., 1956; Makous et al., 1962; Reichel and Garcia-Bunuel, 1970; King et al., 1978; Stehbens et al., 1999]. Marked medial hypertrophy of the pulmonary muscular arteries with fibrous intimal thickening as result of fatal pulmonary hypertension has been reported [Shiraishi et al., 2001].

Vascular problems occur also in the brain and elsewhere. Strokes have been reported at a median age of 9 years (4–19 years). Cerebral infarctions can result in (focal) seizures, hemiplegia, and dysarthria [Curtin and Kotzen, 1929; Dyck et al., 1987; Naganuma et al., 1990; Smith et al., 1993; Alghamdi, 1995], but also in a more protracted course with episodes of headaches, vertigo, and limb weakness [Atkins, 1954; Dyck et al., 1987; Wagle et al., 1992; Smith et al., 1993], and can even be completely symptomless [Matsuo et al., 1994]. Neuroimaging findings are available [Matsuo et al., 1994; Alghamdi, 1995; Rosman et al., 2001; Shiraishi et al., 2001], including Magnetic Resonance Angiography [Smith et al., 1993]. Some patients recover completely, while others have persisting sequel like dysarthria, facial palsy, or hemiplegia. Reichel and Garcia-Bunuel [1970] found renal infarctions. Gilford [1897] reported his patient to have tortuous temporal arteries, and thickened and tortuous peripheral arteries have also been reported [Curtin and Kotzen, 1929]. Sivaraman et al. [1999] reported on a 4-year-old girl with a gangrenous ulcer of the foot and amputation of a great toe. An adult Japanese patient had also toes amputated because of spontaneous gangrene [Ogihara et al., 1986]. Post-traumatic epidural or subdural hematoma, frequently after only limited trauma, have been reported [Rosenthal et al., 1956; DeBusk, 1972; Stehbens et al., 1999; Mandera et al., 2003].

OTHER ABNORMALITIES

Almost all patients have a high-pitched voice. Dental crowding is another very frequent finding, due to the limited size of both the maxilla and mandible [Gorlin and Sedano, 1968]. Eruption of teeth is delayed. The median eruption of the primary teeth was 14 months (8–24 months), both for literature patients and European patients. Data on eruption of secondary teeth are scarce, but seem to indicate a similar, significant delay (varying from 8 to 14 years). Dental care is hampered by the small oral aperture [Batstone and MacLeod, 2002]; however, this does not explain the near universal increase in dental decay, since it also occurs in patients with an excellent oral hygiene. Detailed histological dental studies are not available, although localized areas of enamel hypoplasia on the permanent central incisors and periodontitis have been reported in a single patient [Hasty and Vann, 1988]. Pulp chambers have been reported to be thin and small [Wesley et al., 1979].

With one exception [Dyck et al., 1987], cataracts have not been found in patients with HGPS. Strabismus and mild myopia is not uncommon. Unusual eye findings have been irregular nystagmoid movements [DeBusk, 1972], ptosis and Marcus–Gunn phenomenon [Gupte, 1983], retinal arteriolar narrowing and tortuosity [Atkins, 1954], and photophobia [Doub, 1953]. A 14-year-old girl was found to have bands of skin running from the upper lids to the cornea bilaterally, her corneae showing full thickness opacities [Bhakoo et al., 1964]. Usually, hearing is normal in HGPS. Conductive hearing loss [Baker et al., 1981] and moderate bilateral sensorineural loss [Nelson, 1962] are occasionally mentioned in the literature, but mild conductive hearing loss was found in most European patients. Most children have relatively few intercurrent disorders and are not specifically prone to infections. Some do have recurrent airway infections however, and this also occurs in the terminal phase of the disorder when cardiac failure may play a role. Immunological studies gave either normal results [Jimbow et al., 1988] or showed a hypogammaglobulinaemia and disturbances in cell proliferation upon stimulation with various mitogens [Harjacek et al., 1990]. Male genitalia may be normal or the penis may be somewhat small. Testes are usually descended. Complete absence of spermatogenesis [Orrico and Strada, 1927; Talbot et al., 1945], maturation arrest of spermatogenesis [Reichel and Garcia-Bunuel, 1970], normal spermatogenesis [Manschot, 1940], and nocturnal emissions [Gilford, 1897; Plunkett et al., 1954] have been reported. No male patient is known to have fathered a child. Female external and internal genitalia have been reported to be normal, except for hypoplastic labia in an adult [Corcoy et al., 1989], a single large ovarian cystadenoma [Rosenbloom et al., 1983], and multiple follicular ovarian cysts of various size [Gabr et al., 1960]. Development of secondary sexual characteristics is very unusual; breast development is virtually absent, as is axillary and pubic hair growth. Menarche has been reported at 14 years, with subsequent irregular cycle (every 2–3 months) [Ishii, 1976]. A 32-year-old woman with non-classical progeria has been described who had her menarche at 12 years and gave birth to a healthy child at 23 years [Corcoy et al., 1989].

A 13-year-old girl with an osteosarcoma of the chest wall has been the only patient with a malignancy reported to date [King et al., 1978]. Other infrequent findings have included a duodenal ulcer [Reichel and Garcia-Bunuel, 1970], wide external auditory canal [Viegas et al., 1974; Ogihara et al., 1986], preauricular pits [Gillar et al., 1991], and a Meckel diverticulum [Talbot et al., 1945].

In 62 reports, the cognitive development of the patient was mentioned specifically. Four patients had a mildly delayed development; all others were estimated to be normal. The development of HGPS patients can, therefore, be considered to have a normal distribution. All European patients have had normal cognitive development. Specific behavioral problems are not frequently mentioned. Children are often remarkably alert, active, and cheerful.

GENERAL PHENOTYPE AND COURSE

The general course in children with classical HGPS is very similar. There are no problems during pregnancy or delivery; the children are somewhat small for gestational age, but do well initially. The first sign is often a clearly visible vein across the nasal bridge. From 6 to 12 months or somewhat later, failure to thrive develops, often accompanied by a loss of hair and subcutaneous fat tissue. The diagnosis is often suspected between 2 and 3 years. The facial characteristics gradually develop: almost complete loss of hair except for some fine, downy hair, wide veins over the scalp, eyes that look prominent although there is no true exophthalmia, a narrow nasal bridge and ridge, thin skin that wrinkles around the mouth, irregular teeth with decay, small chin, and prominent ears that lack lobules. The face and body changes with time: the chin becomes smaller, the point of the nose becomes flattened and collapses which causes the nasal ridge to be convex, and the viscerocranium also becomes small relative to the neurocranium; the subcutaneous fat in the face disappears completely and the facial muscles decrease in size. The body shows increasing loss of subcutaneous fat and muscle bulk, the joints protrude and contractures become more severe. In the meantime, the children follow a normal psychosocial development. They speak well but with an unusual voice quality. Their behavior is normal for their age. They hardly grow, especially not in weight. Their appearance becomes increasingly that of an older person. The main health problems that follow are from the vascular system. They can develop strokes, from a young age, with sequel for mobility and speech. The cardiac problems can be slowly progressive or acute leading to sudden fatality. The decreased mobility on one hand and the coronary problems on the other hand limit activity and exercise tolerance.

DeBusk [1972] mentioned a mean age of demise of 13.4 years in 18 patients. The present literature search provided data on 51 classical HGPS patients: mean age at demise was 12.6 years (1.5–27 years). The cause of death is usually of vascular origin, of which myocardial infarctions are by far the most common. Intracranial bleeding (sometimes elicited by only minor trauma) [Rosenthal et al., 1956; DeBusk, 1972; Wesley et al., 1979; Stehbens et al., 1999], and infections [Makous et al., 1962; Franklyn, 1976; Ishii, 1976; King et al., 1978; Khalifa, 1989], convulsions [Gabr et al., 1960], and complications of cardiac surgery [Corcoy et al., 1989] are other reported causes of death.

CONENITAL HGPS

A small number of patients show features of HGPS, but they are present from birth [De Martinville et al., 1980; Labeille et al., 1987; Faivre et al., 1999; Rodriguez et al., 1999]. Major findings at birth are a low birth weight, absence of subcutaneous fat, sparse hair, and osteolysis of the distal phalanges, cranial vault (causing wide sutures and enlarged fontanels), viscerocranium (causing small facial bones, relatively prominent eyes, and small chin), and clavicles (the latter in two of the reports). Also more minor features such as hypoplasia of nipples, absence of ear lobes, dystrophic nails, prominent joints, and prominent scalp veins were found at birth. Scleroderma can be marked [De Martinville et al., 1980]. Interestingly, the patient described by Faivre et al. [1999] had iridocorneal adhesions and corneal clouding which resembles eye findings reported in one patient with HGPS [Bhakoo et al., 1964]. In one patient [Labeille et al., 1987], the typical longitudinal depression of hairs was seen by electron microscopic studies. The main difference has been the absence of clavicular abnormalities in two of the patients, but these are notoriously difficult to evaluate at a young age. The patient described by Sevenants et al. [2005] shows a clinical course consistent with classical HGPS. There are similarities with restrictive dermopathy (RD) (Table III), but the loose skin in congenital HGPS should allow differentiation from the tight skin in restrictive dermopathy. It will be interesting to learn whether patients with congenital HGPS harbor *ZMPSTE24* mutations or *Lamin A* mutations, and, if the latter, whether these act in an autosomal dominant or autosomal recessive way. Such studies are not reported as yet.

CAUSE

In 2002, *Lamin A/C* (*LMNA*) was known to be the cause of at least five different entities: AD Emery-Dreyfuss muscular dystrophy (MIM 181350), limb-girdle muscular dystrophy type IB (MIM 159001), dilated cardiomyopathy type 1A (115200), AR Charcot-Marie-Tooth type 2B1 (MIM 605588), and familial partial lipodystrophy Dunnigan type (115200) [review in Burke and Stewart, 2002]. An Italian-French group realized that lipodystrophy could also be syndromic, including as part of MAD [Novelli et al., 2002]. By autozygosity mapping, they localized MAD to chromosome 1q21, and detected

TABLE III. Comparison of Major Symptoms in the Three Laminopathies that Show Generalized Symptoms: Hutchinson–Gilford Progeria Syndrome (HGPS), Mandibulo-Acral dysostosis (MAD), and Restrictive Dermopathy (RD)

	HGPS	MAD	RD
Pinched nose	++	+	+
Prominent vessels	+++	+	+
Lipodystrophy	+++	+	−
Clavicular hypoplasia	+	+++	+
Micrognathia	+	+++	+
Acro-osteolysis	+	+++	+
Stiff skin	+	−	+++

homozygosity for the R527H mutation in *LMNA*. Subsequently, a French group noted the resemblance between MAD and HGPS, investigated two patients with HGPS, detecting the p.G608G mutation in *LMNA* in both, and demonstrating the distortion of the nuclear envelope that resulted [De Sandre-Giovannoli et al., 2003].

An American group followed a different approach: they performed a whole-genome scan using polymorphic microsatellite markers in 12 patients, looking for regions of homozygosity [Eriksson et al., 2003]. Serendipitously, they found uniparental isodisomy (UPD) of chromosome 1q (1q22-1q44) in two patients. They also had access to cell lines of a monozygotic twin with HGPS with a mosaic inverted insertion of 1q23-q44 [Brown et al., 1990]. They detected a 6 Mb microdeletion of the paternal allele in the twin, realized that *LMNA* which mapped within the region was an excellent candidate gene, detected *LMNA* mutations in 20 of 23 studied patients (18 having the G608G mutation), and showed similar disturbances of the nuclear envelope to the French group. The two patients with UPD 1q did not show a mutation. This region is not known to be imprinted. The authors postulated that this UPD is the result of a somatic rescue: initially, the two patients harbored the classical *LMNA* mutation, post-fertilization a mitotic cross-over occurred, generating a duplication of the wild-type *LMNA* allele and loss of the HGPS mutation [Eriksson et al., 2003]. They postulated that cells with this somatic rescue will have a growth advantage over cells with the HGPS mutation, and will be detected preferentially. Also, in the patient with the 6 Mb microdeletion they did not detect a *LMNA* mutation. It was postulated this was another example of a somatic rescue: initially, the patient must have harbored the HGPS mutation, and this mutation must have been deleted as a post-fertilization defect. This seems more difficult to accept, as one would expect to find such deletions more often in patients with HGPS. Indeed, in a patient reported to have an interstitial deletion of 1q23 [Delgado Luengo et al., 2002], a G608G mutation was found. However, it cannot be excluded that the patient with the 6 Mb microdeletion had an unusual *LMNA* mutation that has been more prone to be deleted mitotically. The classical p.G608G mutation has been found in 26 cases to date, and overall a *LMNA* mutation has been reported in 34 patients with Progeria [De Sandre-Giovannoli et al., 2003; Cao and Hegele, 2003; Eriksson et al., 2003; D'Apice et al., 2004; Fukuchi et al., 2004; Plasilova et al., 2004; Kirschner et al., 2005; Sevenants et al., 2005]. A database showing all known *LMNA* mutations and the accompanying phenotype is available (URL: http://www.umd.be).

As occurs with almost any protein, Lamin A is processed through a series of post-translational modifications (see below). One of the key enzymes involved is a zinc metalloproteinase, ZMPSTE24. Its only known substrate is prelamin A. Homozygous *Zmpste24* deficient mice showed a phenotype that resembles HGPS [Bergo et al., 2002]. In humans, *ZMPSTE24* mutations have been reported in patients with MAD [Agarwal et al., 2003], RD [Navarro et al., 2005], and in a patient who showed a phenotype resembling both RD, MAD, and HGPS [Shackleton et al., 2005]. It seems quite possible that many of the patients with atypical progeria will have *ZMPSTE24* mutations as well, especially those with early fractures, which is a prominent feature in the *Zmpste24*-deficient mice [Bergo et al., 2002]. The number of patients known with non-classical progeria and fractures is too small to conclude that they show a more severe course than those without fractures, and it needs further studies to investigate whether those without fractures have mainly homozygous *LMNA* mutations [Plasilova et al., 2004; Cao and Hegele, 2003; Verstraeten et al., in press].

PATHOGENESIS

The lamins belong to the multiprotein-family of intermediate filaments, and consist of an N-terminal head domain, an alpha-helical (coiled-coil) rod domain important for the dimerization, and a usually globular C-terminal tail domain (Fig. 8). Lamins are located in the nuclei of multicellular eukaryocytes. They have very many functions: they give the nuclear envelope its mechanical strength [Broers et al., 2004], determine the nuclear shape, the nuclear pore complexes, and form the structure in which many other proteins anchor. They can be regarded as the main determinants of the nuclear architecture. In addition, lamins are essential for DNA replication and mRNA transcription [Goldman et al., 2002], and have functions in gene regulation and many signal transduction pathways, both by themselves as through direct interactions with the DNA or a wide range of protein partners [reviewed in Zastrow et al., 2004].

There are two major types of lamins: the B-type lamins, indispensable for replication and transcription and expressed in all cells (cells are not viable without Lamin B) and the A-type lamins, expressed in all differentiated cells. *LMNA* encodes four A-type lamin isoforms: Lamin A, AΔ10, C, and C2, generated by alternative mRNA splicing.

Lamin A is translated from *LMNA* as a precursor, prelamin A. The C-terminal tail ends in a group of 18 amino acids, of which the last four are a CaaX group (cysteine–aliphatic–aliphatic–other). Such a tail is the hallmark of farnesylated proteins. Prelamin A undergoes a series of posttranslational processing steps (Fig. 9): first, a farnesyl group is attached to the cysteine residue at the C-terminal tail (farnesylation); second, the C-terminal three amino-acids (aaX) are cleaved off by the endoprotease ZMPSTE24; third, a

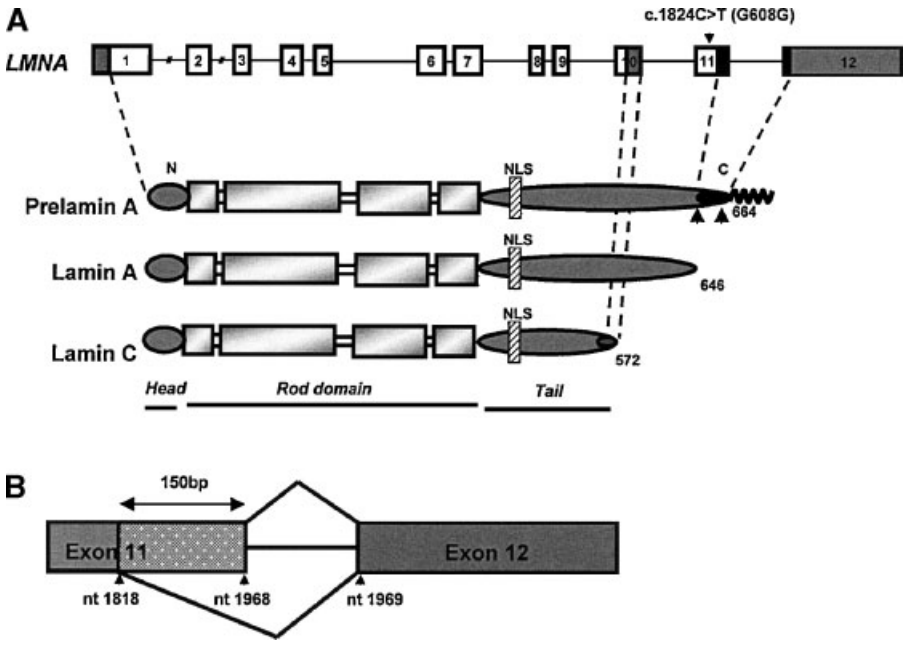

FIG. 8. Structure of the *Lamin A* gene. **A**: Schematic representation of total *LMNA* gene. 1–12: exons of *LMNA*. Exons encoding specific prelamin A tail: indicated in black. Exons encoding specific for Lamin C tail: indicated in dark gray. Alternative splicing for Lamin A and Lamin C: indicated in exon 10. Structural domains: head (N-terminal globular part); rod (coiled-coil domain); tail (C-terminal globular part). NLS: nuclear localization signal. Number of amino-acids of Prelamin A and mature Lamin A: indicated. Farnesyl moiety: shown as a zigzag at Prelamin A tail. Sites of proteolytic cleavage of ZMPSTE24: indicated by two arrowheads. Major division of mutations in various laminopathies: indicated in the upper part. Most common, classical *LMNA* mutation p.G608G: indicated in bold. **B**: Schematic representation of cryptic splice site and alternative splicing products associated with the c.1824C>T mutation. C>T transition at nt 1824 activates a cryptic splicing site, and removes 150 bases of the cDNA. The transcript encoding Progerin includes an aberrant junction between nt 1818 (exon11) and 1969 (1st base of exon12) (Figure courtesy of Nicolas Levy).

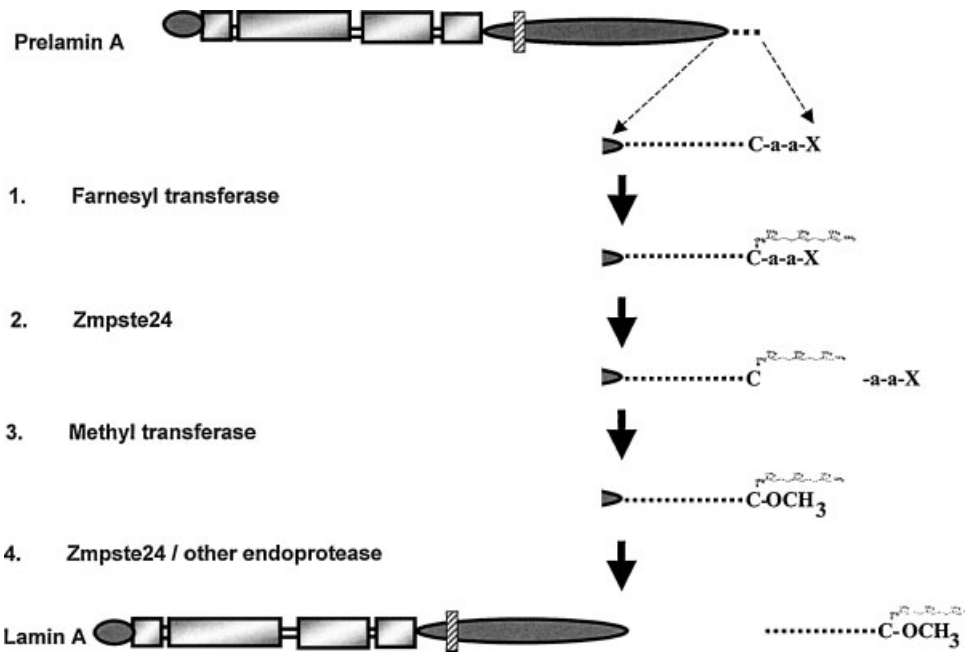

FIG. 9. Post-translational processing of Lamin A. The four steps are indicated: farnesylation of Cysteine; cleavage of –aaX group from C-terminal end; methylation of Cysteine; cleavage of terminal 15 amino acids from C-terminal end. The process is needed as farnesylation of prelamin A is needed, most likely for its attachment to the inner nuclear membrane.

methyl group is coupled to the terminal cysteine; lastly, the C-terminal 15 amino-acids are removed, again by ZMPSTE24 or another endoprotease. The farnesylation of prelamin A is required for its incorporation into the inner nuclear membrane: farnesylation increases lipophilicity and the membrane association of Lamin A.

The mutation found in classical HGPS is p.G608G (c.1824C>T) in exon 11. This change is predicted to be a silent mutation as it does not cause any change at the amino-acid level. However, the mutation activates a cryptic splice site, which causes the removal of 150 nucleotides, till the start codon of exon 12 [De Sandre-Giovannoli et al., 2003; Eriksson et al., 2003]. With the removal of these nucleotides, the last step in the posttranslational processing of prelamin A (removal of the C-terminal 15 amino-acids) cannot occur. The mutant prelamin A persists and is called Progerin.

In a remarkable study, Scaffidi and Mistelli [2005] investigated whether the phenotypic effects were caused by lack of Lamin A or toxicity of Progerin. They introduced wild-type Lamin A protein into fibroblasts of patients with classical HGPS bearing the p.G608G mutation. This did not rescue the cellular disease symptoms. Subsequently, they introduced a modified oligonucleotide (morpholino) targeted to the cryptic splice site that is been activated by the p.G608G mutation. The fibroblasts resumed their normal morphology, and the nuclear distribution of various studied proteins normalized. The study indicated on one hand that it is the presence of Progerin and not the lack of normal Lamin A that causes the phenotype, and, even more important, that the HGPS phenotype can be corrected on a cellular level. [Scaffidi and Mistelli, 2005].

Therefore, it seems likely that the persistence of the last 15 amino acids with farnesyl-group and methyl-group causes the classical HGPS phenotype. However, there are patients with HGPS (either classical or non-classical; data are not always provided to determine this) who have mutations in other parts of Lamin A. Although the clinical phenotype is non-classical, the same organs are affected and although their course and symptoms may be different, they still show a strong resemblance to classical HGPS. Therefore, other causal mechanisms will have to exist. Verstraeten et al. [in press] have made likely that abnormal polymerization of Lamin A can be critical. Furthermore, Prelamin A accumulation has been shown to activate the p53 targets and to induce DNA repair defects [Varela et al., 2005]. Further studies, particularly in different mutant mice will be needed to explain the pathogenesis in more detail [Cadinanos et al., 2005].

INHERITANCE

Consanguinity in classical HGPS has been reported twice [Broc et al., 1935; Bhakoo et al., 1964]. One couple of the parents of the current European patients is related (their child has the classical *LMNA* mutation). Data on siblings was available for 59 families from the literature: there were 220 siblings in total, of whom 3 were also affected [Erecinski et al., 1961; Gupta et al., 1976; Sood et al., 1991]. Data on each of these families was incomplete however, and full evaluation has not been possible. None of the siblings of patients born to the European parents has been affected. The number of miscarriages ($n = 31$) in the literature cases and in the European patients ($n = 6$) is not increased.

The mean paternal age at birth of the patients was 36.4 years ($n = 65$), and mean maternal age was 29.1 years ($n = 65$). While there are no reliable data regarding the mean parental ages for this period of time worldwide, the data are similar to those found in other disorders with a proven increased paternal age [Rannan-Eliya et al., 2004], which supports the suggestion first made by Jones et al. [1975] that there is an increased paternal age in HGPS. For the European patients mean paternal age was 33.3 years and mean maternal age 28.4 years.

Chromosome studies have been reported in most patients and were abnormal in only two families: Brown et al. [1990] reported a mosaic inversion insertion on chromosome 1q [46, XY, inv ins (1;1)(q32; q44q23)] in 70% of cells of a monozygotic pair of twins. Delgado Luengo et al. [2002] reported an interstitial deletion of 1q [46, XY, del(1)(q23)]. Two patients with UPD1q were found by Eriksson et al. [2003].

Classical HGPS is an autosomal dominant disorder, each patient arising through a spontaneous mutation in *LMNA*, consistent with the increased mean parental age. D'Apice et al. [2004] found a paternal origin of the mutations, but the number of patients studied was small. Germ line mosaicism is possible. In a patient with a classical p.G608G mutation, the phenotypically normal mother was found to have a somatic mosaicism, 10% of her buccal cells harboring the same mutation [Wuyts et al., 2005]. She must have had a germ line mosaicism too. Recurrence in classical HGPS has not been described.

Non-classical progeria has been reported as an autosomal recessively inherited disorder, either because of parental consanguinity or because of recurrence in siblings [Mostafa and Gabr, 1954; Gabr et al., 1960; Rava, 1967; Franklyn, 1976; Soares et al., 1984; Ramesh and Jain, 1987; Maciel, 1988; Khalifa, 1989; Plasilova et al., 2004]. *LMNA* mutations acting as an autosomal recessive trait without any heterozygote phenotype have been reported [Plasilova et al., 2004; Cao and Hegele, 2003; Verstraeten et al., in press]. It remains possible that the patient reported by Shackleton et al. [2005] with compound heterozygous *ZMPSTE24* mutation has in fact non-classical progeria.

Prenatal diagnosis through molecular analysis will be possible, although this has not yet been published.

MANAGEMENT

There is currently no definitive therapy for HGPS but several potential strategies exist. The restoration of the normal phenotype on a cellular level by the use of a morpholino [Scaffidi and Misteli, 2005] provides hope for HGPS patients with the classical mutation, although many obstacles have to be passed. Possible strategies include the use of viral vectors to deliver antisense molecules to blood vessels such as the aorta and coronary arteries, the sites where they are needed most. Selective inhibition through small molecules (or other RNA interference techniques) of the alternative splicing caused by the classical mutation may be another option [Garcia-Blanco, 2005; Huang et al., 2005; Soret et al., 2005]. Much attention has recently been paid to inhibition of farnesylation of pre-lamin A, which was shown to restore the nuclear envelope phenotype in vitro [Glynn and Glover, 2005; Toth et al., 2005]. The inhibition of farnesylation will inhibit incorporation of Progerin into the nuclear envelope, and it has been shown that only partial reduction of this incorporation still reduces the dominant-negative effect of Progerin considerably, restoring the normal phenotype [Glynn and Glover, 2005; Scaffidi and Misteli, 2005]. It remains uncertain what the effect will be of the accumulation of the non-incorporated Progerin in the nucleoplasm, and whether other functions of Lamin A, for instance on chromatin structure, will be restored in this way too. Alternatives such as the use of statins, with or without biphosphonates, can also be considered [Graaf et al., 2004].

At present only symptomatic support is possible. Quality of life for the patients is paramount. This means that minimizing invasive medical interventions, avoidance of regular pain, and adequate psychological support to patients and their parents and sibs are very important. A normal diet, accepting the severely impaired growth, non-surgical support of the limited joint mobility, sealing of the teeth, and provision of wigs are simple and achievable goals that help patients and families to cope with the disorder. Guidelines on how to deal with children with HGPS, their parents, and their sibs have been published [Livneh et al., 1995], but more work in this area is needed.

HGPS is a rare disorder, involving a large number of different organ systems, with a complex pathogenesis. Centralization is likely to be necessary for optimal care of patients with HGPS since no single clinician will be able to obtain sufficient experience otherwise. Centralized care and research occurs worldwide in two places: through the Progeria Research Foundation in NIH (Bethesda) and through the consortium Europrogeria in AMC (Amsterdam, The Netherlands).

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