

## A SYNDROME OF PREMATURE SENILITY IN TWO JORDANIAN FAMILIES

Numan M. Gharaibeh, MD

Werner's syndrome (adult progeria) has not been reported among Arabs. Very few cases of childhood progeria (Hutchinson-Gilford progeria syndrome) have been reported in Arabs.<sup>1,16,17</sup> In this paper, four cases of Werner's syndrome are presented in two unrelated Jordanian families. Peculiarities observed to be different from the classical picture include the absence of coxa valga, the absence of diabetes mellitus, the absence of dementia and the absence of neoplasms in all four cases.

The word progeria is derived from the Greek *pro*, meaning before, and *geras*, meaning old age. The term was first used by Gilford<sup>2</sup> to describe a syndrome of abnormal growth and premature senescence in children, and is currently known as Hutchinson-Gilford progeria syndrome. Adult progeria, or Werner's syndrome, is reported as a rare autosomal recessive disorder. It is generally characterized by an apparent acceleration of the processes associated with aging.<sup>3</sup> Patients with Werner's syndrome and Hutchinson-Gilford progeria syndrome serve as good examples for studying human aging and the causes of its acceleration.<sup>4</sup> The following is a presentation of four cases of Werner's syndrome in two unrelated families.

### Family 1

The pedigree of this family is shown in Figure 1. This family lives in a village in mid-Jordan and comes from a Bedouin background. The family is of Bedouin ancestry that was traced back to the northern part of Saudi Arabia.

#### Case 1

A 44-year-old male (IV in Figure 1) presented to the ophthalmology clinic with diminution of vision in his right and only eye. His left eye had been surgically eviscerated two years earlier because of endophthalmitis after cataract surgery. The patient had been married at the age of 20 to an unrelated woman. At present he had a son and three

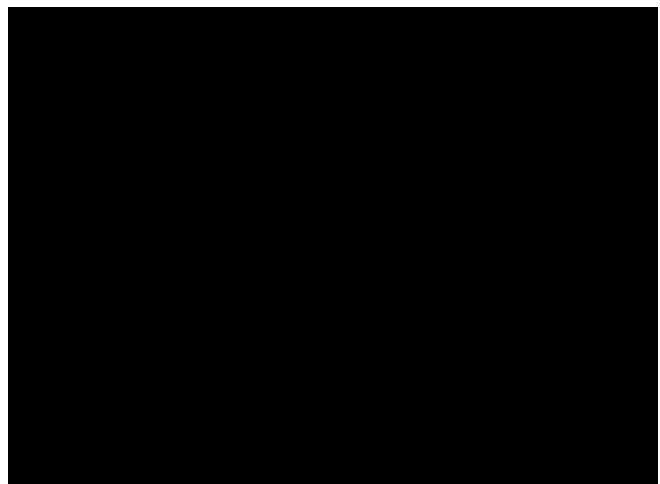


FIGURE 1. Pedigree of Family 1.

daughters who all appeared normal. The patient complained of general weakness and easy fatigability, with claudication pains of the left lower extremity. Three years after his initial presentation, he developed left foot ischemia at rest and gangrene of the left 2nd toe. He showed senile features of the face and skin. His weight was only 26 kg and his height was 129 cm. The patient had a high-pitched voice. His scalp hair was gray and very sparse, with advanced male-pattern baldness. His body hair was absent. There were sparse, gray pubic hairs. Brows and lashes had sparse, broken hairs. His beard showed gray, but growth was adequate.

His right eye was prominent and showed a dense mature cataract. The nose was sculptured and beak-shaped (Figure 2). Subcutaneous tissue loss was remarkable and the veins stood out. The skin was thickened over the extensor surfaces of the hands, feet, knees and elbows; elsewhere it was atrophic. All joints showed limitations of all movements. There were no gross deformities, and no evidence of coxa valga.

The peripheral pulses were markedly decreased with bilaterally absent dorsalis pedis and absent left posterior tibial. The laboratory work-up, including hematologic, biochemical and hormonal studies, was within normal

From New York Medical College, Valhalla.

Address reprint requests and correspondence to Dr. Gharaibeh: 12 Manor Avenue, White Plains, New York 10605.

Accepted for publication 8 May 1996. Received 9 September 1995.

limits, except for mildly elevated cholesterol of 279 mg/dL (Lab. Ref. 140-270 mg/dL).

#### Case 2

This patient was the sister of the previously described patient. She was a 28-year-old who looked to be in her fifties. Her scalp hair was gray and coarse, but no balding was noted. She had an early cataract of the left eye. Her nose was beaked and sculptured.

The patient was 30 kg with a height of 130 cm. Her voice was abnormally high-pitched. She showed marked loss of subcutaneous tissues with hypermelanosis and prominent veins. The patient's joints showed limitation of all movements, but no deformities. All pulses were diminished; however, the patient denied claudication pains or vascular symptoms.

She showed marked callosities on both feet. Unfortunately, she refused to cooperate with photography or further investigations.

#### Family 2

This family is from the north of Jordan, and there is no relationship with the previously described family. The two cases presented are two sisters. Their parents are first-degree cousins. The full family was not available for evaluation.

#### Case 3

A 28-year-old female who presented to the ophthalmology clinic because of progressive diminution of vision in her left eye. Her right eye was operated upon for cataract four years earlier. Ophthalmic exam showed a cataract in the left eye. The patient's weight was 27 kg and her height was 133 cm.

The patient had a high-pitched voice, beaked nose, loss of subcutaneous tissues, foot callosities and corns, and limitation of all movements at the joints. There were no deformities. She showed graying of hair with advanced male pattern balding (Figure 3).

The peripheral pulses were diminished, but there were no complaints regarding poor perfusion of the extremities. The hematological, biochemical and hormonal studies were within the normal range. Total cholesterol level was 189 mg/dL (Lab Ref 140-270 mg/dL).

#### Case 4

A 30-year-old female presented with claudication pain of the right lower extremity. The patient's weight was 37 kg and her height was 138 cm. Her voice was unremarkable. Her nose was beak-shaped. Her skin was atrophic, but very thick over the palms and soles. There were multiple callosities and corns on both feet, with bilateral hallux valgus deformities. Graying of hair was

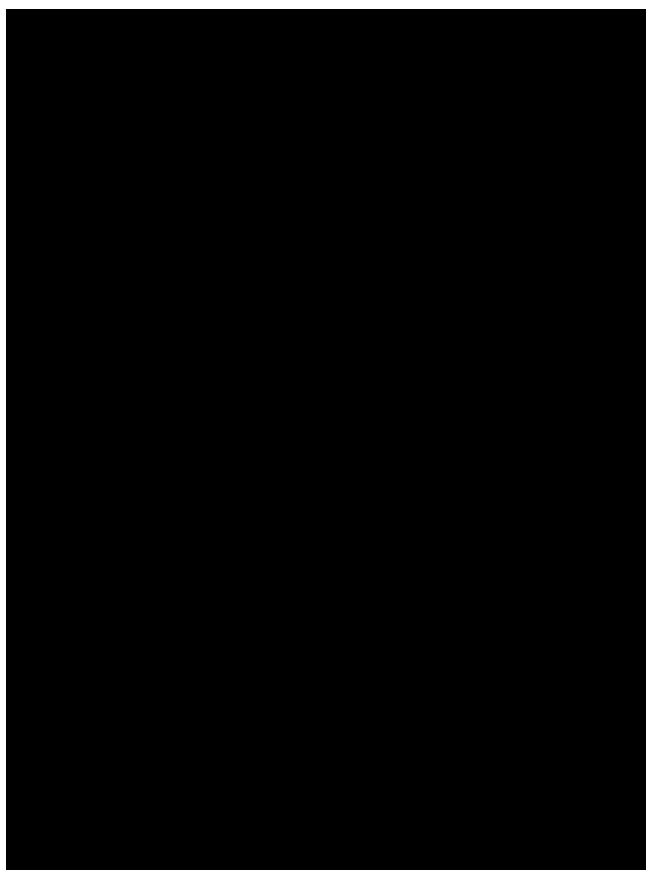


FIGURE 2. The patient presented as Case 1. Photograph taken after cataract surgery on the right eye. The left eye had been eviscerated.

noticed, but no balding. The patient exhibited limited joint mobility in all directions without evidence of muscle weakness or joint tenderness. The lower extremity pulses were reduced and the right posterior tibial and dorsalis pedis were absent. Hematologic, biochemical and hormonal levels were within normal limits. Total cholesterol level was 163 mg/dL (Lab Ref 140-270 mg/dL).

#### Discussion

Werner's syndrome (WS), or adult progeria, is a rare autosomal recessive disease that presents with symptoms and signs of premature aging.<sup>3</sup> Of the four cases presented, two presented with cataract, one presented with claudication, and one was asymptomatic. WS is diagnosed if three of the following are present:<sup>3,5</sup> 1) characteristic habitus, 2) premature senility, 3) scleroderma-like skin, and 4) endocrine abnormalities. The four cases presented met the first three criteria and, therefore, have WS with slight variation.

The typical manifestations of Werner's syndrome are: growth arrest at puberty, cataracts by age 30 or 40, premature graying of hair, balding, scleroderma-like skin,

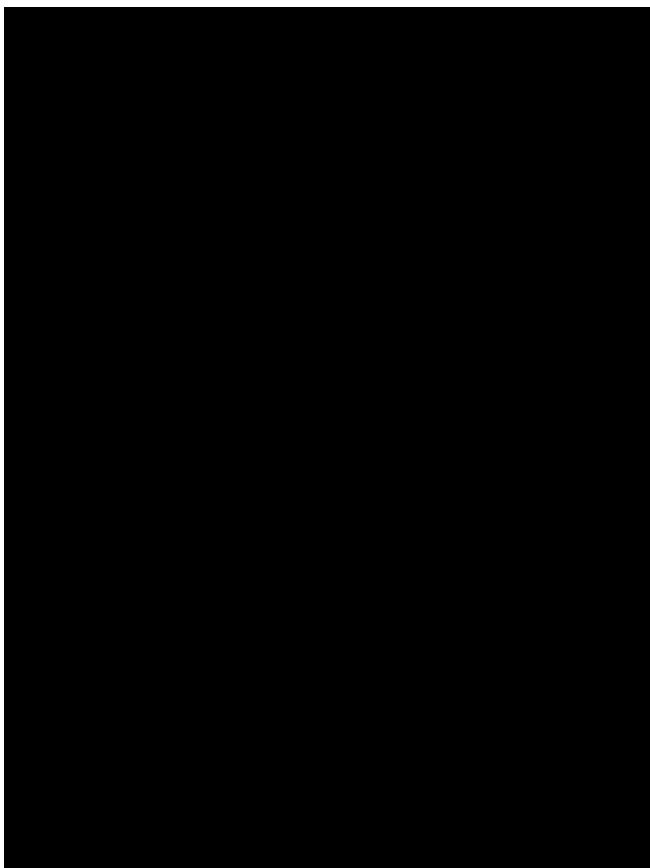


FIGURE 3. The patient presented as Case 3, showing beaked nose and advanced male pattern baldness.

chronic ulcers over the extremities, decreased muscle and subcutaneous tissues, beak-shaped nose, premature atherosclerosis and death in middle life.<sup>6</sup>

Other reported features include hypermelanosis of the skin, skin calcifications, hyperkeratosis, osteoporosis, coxa valga, small mandible, high-pitched voice, thymic atrophy and hypogonadism.<sup>7</sup>

Variably present are diabetes,<sup>8</sup> dementia and increased incidence of neoplasms.<sup>9</sup> The diagnosis of Werner's syndrome is not usually made until the patients are in their thirties. The usual cause of death in Werner's syndrome is cardiac or cerebrovascular disease.<sup>6</sup>

Although WS is a clinically complex entity, genetic linkage studies are in agreement with the idea of a mutation at a single locus as the cause of this disease. This locus lies close to, or within, the region 8p12 on chromosome 8.<sup>10</sup> Mapping studies support the idea that the location of WRN (the locus for WS mutation) is telomeric (away from the centromere) to the locus D8S87.<sup>11</sup> This syndrome serves as a genetic disease model of human aging. Other entities with accelerated aging include the childhood onset progeria, identified as

TABLE 1. Summary of the clinical features of the four cases presented.

Clinical features	Case 1	Case 2	Case 3	Case 4
Atherosclerosis	+	-	-	+
Graying of hair	+	+	+	+
Loss of hair	+	-	+	-
Skin atrophy	+	+	+	+
Hypermelanosis	+	+	-	-
Hyperkeratosis	+	+	+	+
Short stature	+	+	+	+
Osteoporosis	+	?	+	+
Coxa valga	-	-	-	-
Small mandible	+	+	+	+
High-pitched voice	+	+	+	-
Diabetes	-	-	-	-
Cataracts	+	+	+	-
Dementia	-	-	-	-
Neoplasms	-	-	-	-
Joint movement limitation	+	+	+	+

Hutchinson-Gilford progeria syndrome,<sup>12</sup> and Down syndrome.

Werner's patients express a high level of collagenase *in vitro*; however, they show no induction of collagenase activity by platelet-derived growth factor (PDGF) in comparison to normal skin fibroblasts. It seems plausible that the secreted collagenase may play a role in the cutaneous atrophy and ulcerations that are phenotypic characteristics of premature aging. This is possibly due to increased turnover of skin collagen and connective tissue remodeling.<sup>13</sup>

Skin fibroblasts from subjects with WS show a universally curtailed replicative life span.<sup>14,15</sup> The underlying genetic mutation(s) result in abnormal cellular growth and differentiation, which is important in the phenotypic expression of WS.<sup>13</sup>

#### Acknowledgment

My thanks to Dr. Mahmood Al-Salem, MD, from the Department of Ophthalmology at Jordan University of Science and Technology (JUST), Irbid, Jordan, for helping me with photography and preparation of this text.

#### References

1. Khalifa MM. Hutchinson-Gilford progeria syndrome: report of a Libyan family and evidence of autosomal recessive inheritance. *Clinic Genet* 1989;35:125-32.
2. Gilford H. Progeria: a form of senilism. *Practitioner* 1904;73:188-217.
3. Epstein CJ, Martin GM, Schultz AL, Motusky A. Werner's syndrome: a review of its symptomatology, natural history, pathological features, genetics and relationship to the natural aging process. *Medicine* 1966;45:177-221.

4. Brown WT. Human mutations affecting aging: a review. *Mechanisms Aging Develop* 1979;9:325.
5. Goto M. *Neurocutaneous Diseases*. Gomez, MR, editor. Boston: Butterworth, 1987:242-6.
6. Cohen JI, Arnett EN, Kolodny AL, et al. Cardiovascular features of the Werner's syndrome. *Am J Cardiol* 1987;59:493-5.
7. Brown WT, Kieras FJ, Houck GE Jr., Dutkowski R, Jenkins EC. A comparison of adult and childhood progerias: Werner's syndrome and Hutchinson-Gilford progeria syndrome. *Adv Exp Med Biol* 1985;190:229-44.
8. Vannini P, Ciavarella A, Forlani G, et al. Investigation of insulin associated with Werner's syndrome. *Diabetes Metab* 1987;13:81-5.
9. Usui M, Ishii S, Yamawaki S, et al. The occurrence of soft tissue sarcomas in three siblings with Werner's syndrome. *Cancer* 1984;54:2580-6.
10. Goto M, Rubenstein M, Weber J, et al. Genetic linkage of Werner's syndrome to five markers on chromosome 8 (letter). *Nature* 1992;355:735-8.
11. Nakura R, Wijsman EM, Miki T, et al. Homozygosity mapping of the Werner syndrome locus (WRN). *Genomics* 1994;23:600-8.
12. Debusk FL. The Hutchinson-Gilford progeria syndrome. *J Pediatr* 1972;80:697-724.
13. Bauer EA, Silverman N, Busiek DF, et al. Diminished response of Werner's syndrome fibroblasts to growth factors PDGF and FGF. *Science* 1986;234:1240-3.
14. Goldstein S. Human genetic disorders with features of accelerated aging. In: Schneider EL, editor. *The genetics of aging*. New York: Plenum Press, 1978.
15. Salk D. Werner's syndrome: a review of recent research with an analysis of connective tissue metabolism, growth control of cultured cells, and chromosomal aberrations. *Hum Genet* 1982;62:1-5. resistance
16. Gabr M. Progeria: review of literature with report of a case. *Arch Pediatr* 1954;71:35-46.
17. Alghamdi SA. A case of progeria in a Saudi child presenting with cerebral infarction. *Ann Saudi Med* 1995;15:631-33.