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Werner's Syndrome*

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This syndrome was first described in 1904 by Otto Werner in his doctoral thesis entitled "Cataract in combination with scleroderma" in a family of four siblings.[1] These patients had similar clinical findings: shortness of stature, senile appearance, graying of the hair beginning at about the age of 20, cataracts appearing at about the age of 30, various skin changes (atrophy and ulceration) and joint deformities. In 1945, Thannhauser differentiated this syndrome from scleroderma.[2] He suggested that adult progeria would be more appropriate as a name for this syndrome and he listed the following twelve principal characteristics observed in these patients:

1- Shortness of stature with characteristic habitus
2- Premature graying of the hair
3- Premature baldness
4- Hypogonadism
5- Tendency to diabetes
6- Metastatic calcifications
7- Juvenile cataracts
8- Scleropoikiloderma
9- Trophic ulcers of the legs
10- Osteoporosis
11- Calcification of the blood vessels
12- Tendency to occur in brothers and sisters

Since the time of Werner's original report, over a hundred cases have been described in various countries. We could find only one case reported from this country.[3] In this communication we will describe two new cases of Werner's syndrome.

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Case I

A.B. 68/46080, a 13-year old male. His chief complaint was that movement of the ankles, hips, and elbow joints were severely restricted and painful.

History

Except for growth retardation he was in good health until 6 months prior to his admission, when he noted a weight loss of 7 Kgs. and he began to have some pain at the ankle, hip and elbow joints. Father and mother were first cousins.

Physical Examination

Weight was 21.300 Kg.; height 130 cm.; head circumference 49 cm. (all under 3rd percentile), and blood pressure was 90/50 mm Hg. His general appearance was a small but alert child. His facial appearance resembled an aged person (Figures 1-2). His chin was small, the teeth were in poor condition and there was redness and denudation of the mucosa. The extremities were quite thin (Figure 3). The skin on the feet, legs and face was thin and shiny, the subcutaneous adipose tissue was decreased and, in addition, there was atrophy of the musculature (Figure 4). Multiple scars of healed ulcers were seen over the heels and malleoli bilaterally. The penis and testes were small and there was no axillary or pubic hair.

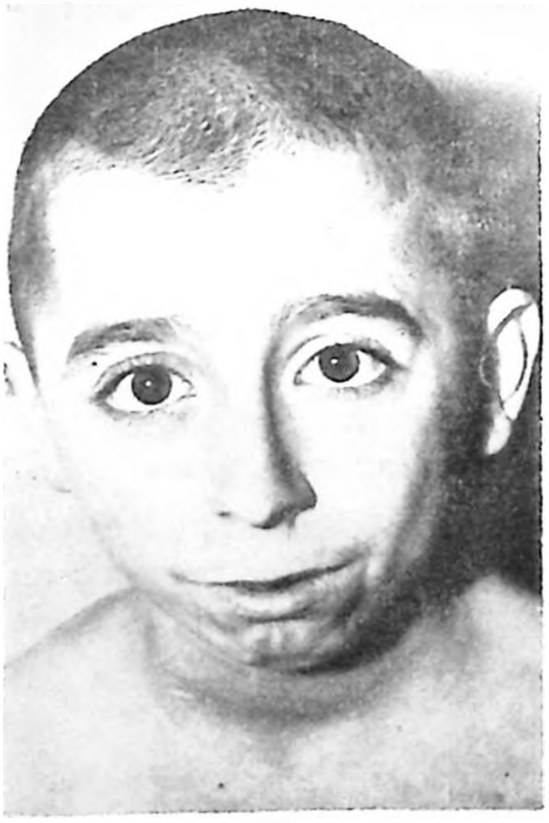


Figure 1

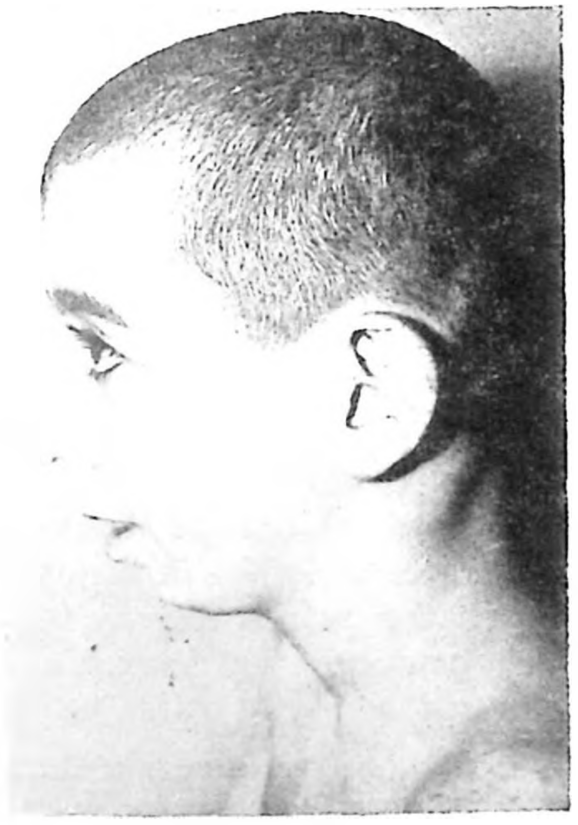


Figure 2

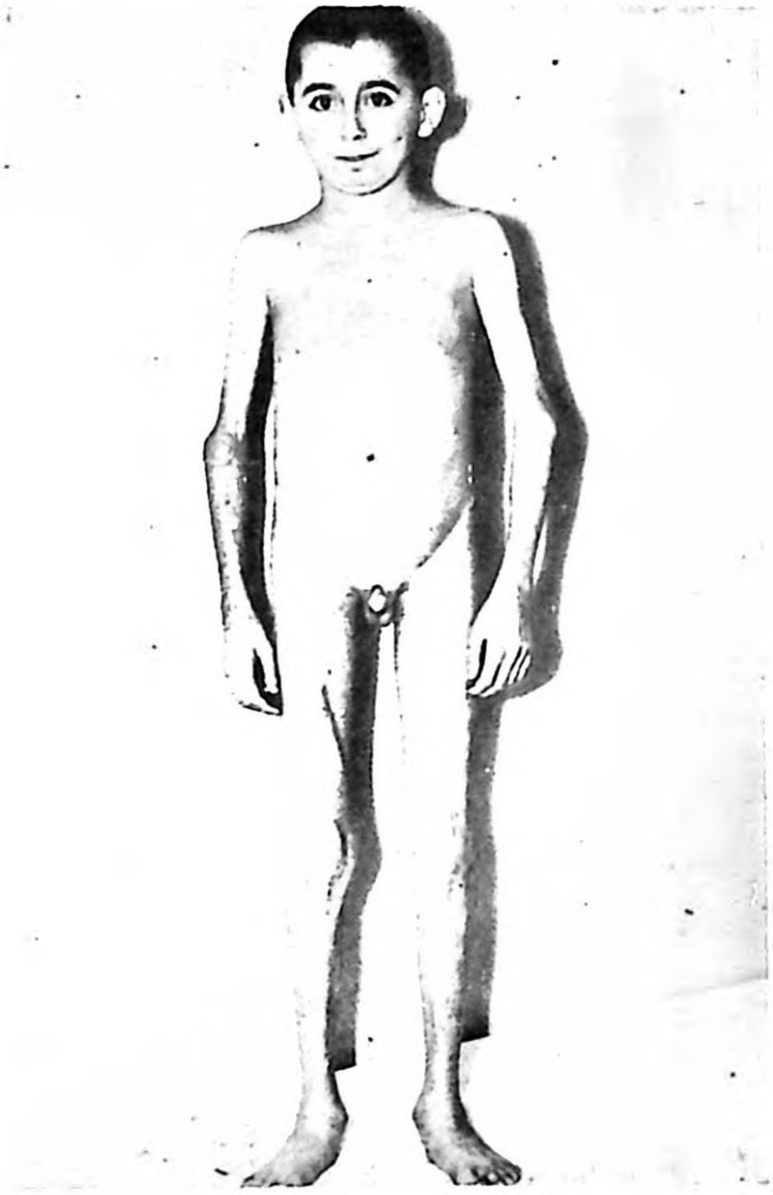


Figure 3

Laboratory Findings

Results of the following laboratory studies were normal: complete blood counts, urine analyses; BUN, BEI, serum Ca, P, alkaline phosphatase, bilirubin, cholesterol, SGOT, thymol turbidity and CCF tests, total blood proteins, protein electrophoresis and total lipids. Latex as well as L.E. cell tests were repeatedly negative. 24 hour urinary excretion of 17 ketosteroids was 8.4 mg. and creatinine 413 mg. per 100 ml. ACTH and glucose tolerance tests were normal. Total urinary amino acids were 16 taurin units (24 hours). A skin biopsy revealed chronic dermatitis.

X-ray Findings

All extremities showed marked osteoporosis and the head of the right femur had aseptic necrosis. There was also spondylitis defor-

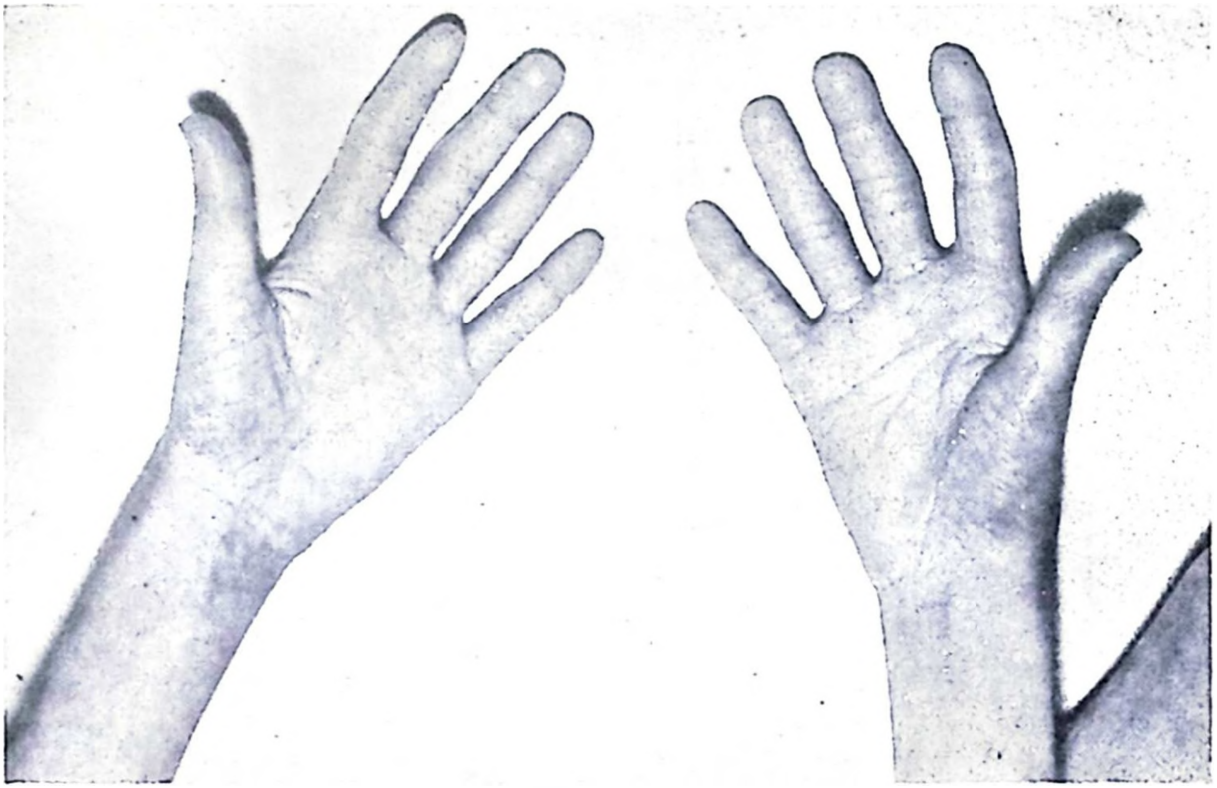


Figure 4

mans. Bone age was normal. Intravenous pyelogram revealed no abnormalities. X-ray of the hands showed spindling of the phalanges (Figure 5). Buccal smear was negative. Chromosome studies from

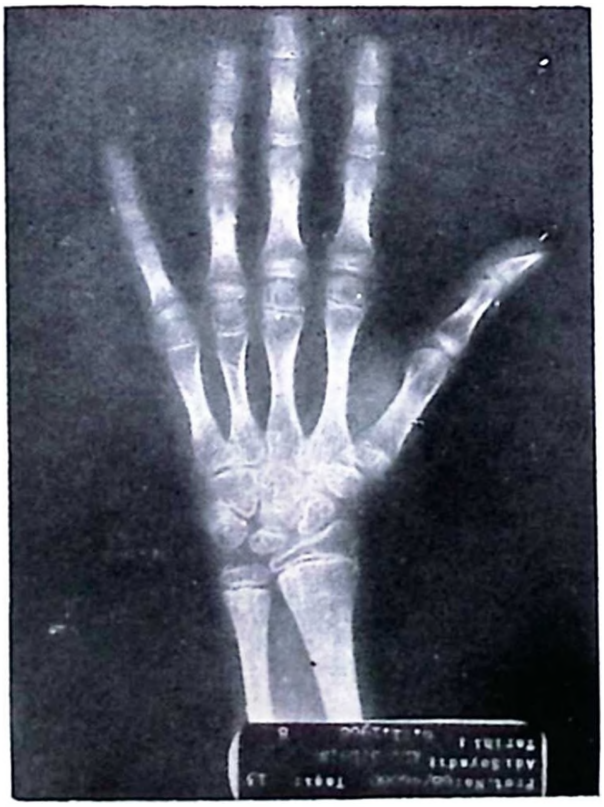


Figure 5

leucocyte cultures showed normal male karyotype. Electro-myography had greatly reduced action potentials in the legs and arms.

Case II

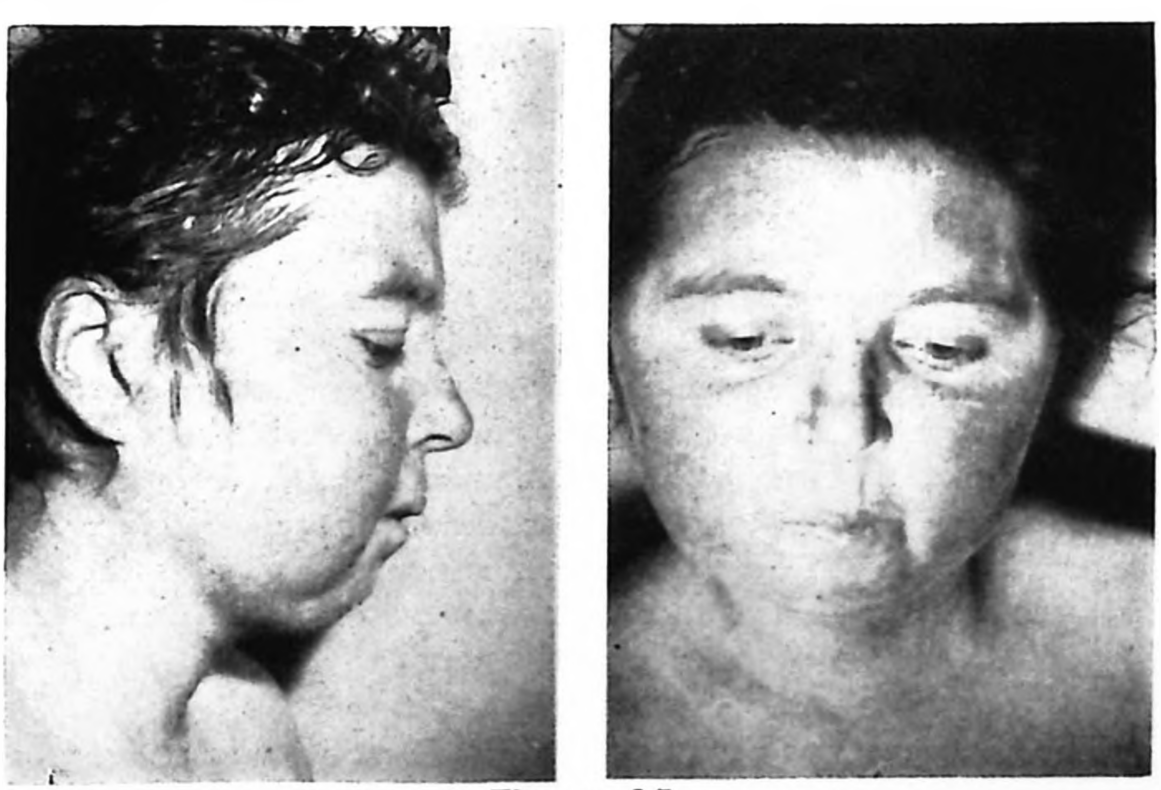
R.K. 104141, a 19-year old female, whose chief complaints were amenorrhoea, failure to grow, with loss of weight, for the past 10 years.

History

After the age of 7 or 8 years, various changes were noticed in the hands, face and ankles. The ankles had ulcers which were very difficult to cure. Her hair had been turning grey since the year before admission. The parents were first cousins.

Physical Examination

Height was 135 cm.; weight 31.5 Kg. and head circumference 50 cm. (all below the 3rd percentile). The patient had a bird-like face, including a beaked nose, puffy cheeks and a generally senile appearance. The hair and eyebrows were very thin and grey (Figures 6-7). The hands, forearms and feet were of a reddish-brown colour, and the skin was tightly attached to the subcutaneous tissue (Figure 8). There were ulcers in the right and left tibial areas. The left lobe of the thyroid had a



Figures 6-7

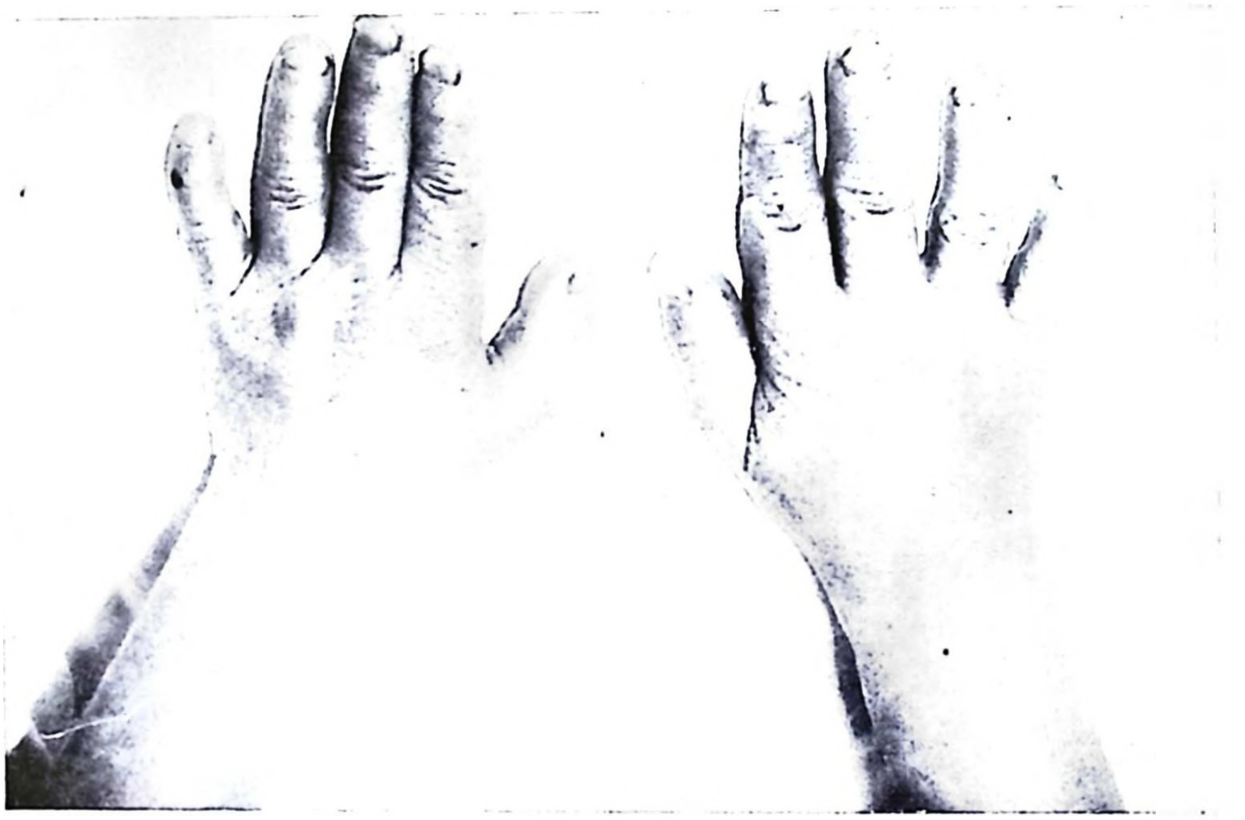


Figure 8

nodule, of 2.5 cm. in size. The pubic and axillary hair was sparse and the breasts were underdeveloped. The patient had bilateral posterior cortical cataracts and both temporal papillae were pale.

Laboratory Findings

Complete blood counts, urine analyses and routine blood chemistry revealed no abnormalities. PBI was 3.35 gamma per 100 ml. However, radioactive iodine uptake for 4 hours was 47 %, and for 24 hours 77 %. Radioactive scanning showed normal activity in the thyroid nodule. The urinary 17 ketosteroid excretions was 5.11 mg., 17 hydroxy corticosteroids 1.28 mg. and creatinin 734.02 mg /24 hours. Barr bodies were 28 % positive. Chromosome analysis revealed no abnormalities, electromyography was normal and a glucose tolerance test showed a diabetic curve. Electroencephalogram was normal. A skin biopsy revealed atrophy and increased pigmentation in the basal layer. The collagen fibres showed basophilic degeneration and sclerosis, the capillary tissue was broadened and there was loss of elastic tissue.

X-ray Findings

The bone age was slightly retarded. There was generalised osteoporosis and Schmar nodules were noticeable in the vertebrae.

Discussion

Werner's syndrome seems to be a hereditary condition. In an analysis of 125 cases the clinical picture followed a definite pattern.[4] Graying of the hair occurred at a mean age of 20 years and seems to be one of the earliest signs. Mean ages for various dermatological changes is 25.3 years; for loss of hair 25.8 years; for alterations of the voice 26.6 years; for visual symptoms or detection of cataracts 30 years; for skin ulcers 33 years; and lastly for diabetes 34.2 years. Several ocular abnormalities other than cataract have also been found. Retinitis pigmentosa, blue sclera, telangiectasia of the iris and vitreous opacities, diabetic retinopathy and healed chorioretinitis have been occasionally noted.[4]

Dermatological findings are of great diagnostic importance. Atrophy of the skin due to a depletion of the subcutaneous adipose tissue results in shiny, smooth skin which cannot be lifted up from the underlying tissue. Atrophy of the face produces a thinning and sharpening of the nose giving it a beaked appearance. Loss of circumorbital tissue results in pseudoexophthalmos. All these facial changes produce a bird-like or 'mask-like' appearance. An early feature of the skin involvement is the development of hyperkeratosis on the soles of the feet.

Pathological findings observed in the reported cases are summarised in Table I.

Incidence of tumours is increased in patients with Werner's syndrome. The tumours observed were predominantly mesenchymal in nature (10 %); fibroliposarcoma, osteogenic sarcoma, melanotic sarcoma and meningioma were most common.

Although osteoporosis has been observed radiologically in half of the cases, the skull is not usually affected. Osteoarthritis of the peripheral joints, spondylitis deformans and vertebral collapse are also noted. Soft tissue and vascular calcification are observed in about one-third of the patients.[5]

Endocrine features of Werner's syndrome were similar to those seen in adrenal hyperactivity; Bauer and Conn suggest that this entity might be due to a defect in the inactivation of glucocorticoids.[6]

Electromyography shows greatly reduced action potentials. LDH and SGOT, aldolase levels are normal but there is a high urinary creatine /creatinine ratio which reflects the loss of muscle mass.

Thyroid functions are generally within normal limits.

TABLE I

Skin and Subcutaneous tissue:
- a - Atrophy of subcutaneous fat
- b - Diffuse hyperkeratosis
- c - Focal lymphocytic infiltration
- d - Dermal fibrosis

Muscle:
- a - Abnormalities in the muscle fibers (swelling, loss of striations)
- b - Increase in connective tissue

Respiratory system:
- a - Squamous metaplasia in the bronchial mucosa
- b - Pulmonary emphysema

Cardiovascular:
- a - Arteriosclerosis, myocardial infarction
- b - Monckeberg's sclerosis (medical calcinosis)
- c - Hypertrophy of the myocardium and fibrosis

Genitourinary:
- a - Testicular atrophy
- b - Cystic degeneration of the ovary

Renal:
- a - Arteriolosclerosis and arteriosclerosis
- b - Hyalinization of glomeruli
- c - Chronic pyelonephritis

Endocrine glands:
- a - Adenomatous hyperplasia and atrophy of the adrenals
- b - Atrophy of thyroid
- c - Chromophobe adenoma in pituitary gland

Lymphatic:
- a - Atrophic spleen

Neurologic:
- a - Cerebral cortical atrophy

Jacobs reported in these patients a tendency to increased aneuploidy, primarily hypodiploidy in both sexes with increasing age.[7] The missing chromosomes in males were usually from the 21 - 22, Y group and in females in 6 - 12 - X group, suggesting that in both sexes the missing chromosome is one of the sex chromosomes. Most cases, however, had no chromosomal abnormalities.[7]

Table II summarises the differential diagnosis. As is seen here, Werner's syndrome may be confused with Rothmund's syndrome,

Con	Hypogona-dism	Diabetes	Genetic transmission
Werner's sy	+	+	Aut. Rec.
Rothmund'	∓	−	Aut. Rec.
Scleroderm	−	−	−
Progeria	+	−	Aut. Rec.
Myotonic d	+	∓	Aut. Dom.
Herediter e dystrophy	−	−	Aut. Dom.
Triparanol (MER-29)	−	−	−
Cockayne's	−	−	Aut. Rec.
Hallerman-S	−	−	Aut. Dom. (?)

TABLE II

Conditions	Age at onset	Short stature	Skin	Hair	Eye	Extremities	Osteoporosis	Hypogonadism	Diabetes	Genetic transmission
Werner's synd.	20-30 yrs.	+	Atrophy, skleropoikiloderma	Early graying, premature baldness	Cataract	Atrophy	+	+	+	Aut. Rec.
Rothmund's synd.	Early (<4 Yrs.)	∓	Telangiectasia, poikiloderma, desquamation pigmentation	–	Cataract	–	–	∓	–	Aut. Rec.
Scleroderma	Rare in childhood	–	Induration and pigmentary changes on feet, hands	–	–	Atrophy (upper ext.)	–	–	–	–
Progeria	2-5 months	+	Atrophy of the subcutaneous fatty tissue	Pigment deficiency, alopecia	–	Atrophy of the distal extremities contractures	+	+	–	Aut. Rec.
Myotonic dystrophy	20-30 yrs.	–	Atrophy of the skin on the eyelids and hands	Premature baldness	Cataract	–	–	+	∓	Aut. Dom.
Herediter ectodermal dystrophy	Birth	–	Hyperpigmentation, hyper keratosis	Hypotrichosis	–	–	–	–	–	Aut. Dom.
Triparanol intoxication (MER-29)	All ages	–	Dryness and rashes of skin	Loss of hair, change in hair color	Cataract	–	–	–	–	–
Cockayne's synd.	About 1 year	–	Photosensitivity, thin shin, diminished subcutaneous tissue	Hypotrichosis	Retinal degeneration	–	–	–	–	Aut. Rec.
Hallerman-Streiff synd.	Birth	–	Atrophy localised to the nose	Hypotrichosis	Microphthalmia, cataract	Spasticity	–	–	–	Aut. Dom. (?)

scleroderma and progeria. A careful clinical investigation, however, helps greatly in differentiating these conditions from Werner's syndrome.

Summary

Two cases of Werner's syndrome are presented.

Acknowledgements

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