Turkish Journal of Endocrinology and Metabolism, (1999) 2 : 95-98 **CASE REPORT**

Werner's Syndrome

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Werner's syndrome is a rare disorder resembling premature a ging. This autosomal recessive disorder is frequently associated with endocrinological problems, particularly diabetes mellitus and hypogonadism. Although the diagnosis is not difficult when it is kept in mind it may be so because of its rarity. In this report we present a case of Werner's syndrome who was hospitalized in our clinic because of diabetic foot. Detailed physical and laboratory examinations revealed that this 53-year-old male patient also had hypergonadotropic hypogonadism, gynecomastia and mental deficiency. Details of the syndrome with regard to clinical characteristics, diagnosis and therapeutic modalities are discussed.

KEY WORDS Werner's syndrome, early aging

Introduction

Werner's syndrome is a rare autosomal recessive disorder. Several characteristics of this syndrome resemble early aging (1,2). Patients frequently develop cataracts, atherosclerosis, malignancies and osteoporosis (3). Several endocrinological abnormalities including hypogonadism and impaired glucose tolerance have been reported in these patients (4). In this report we present a case of Werner's syndrome who was hospitalized in our clinic because of diabetic foot infection.

Case Report

The 53-year-old male patient had had a history of diabetes mellitus for 9 years and in this period he had used several oral antidiabetic drugs irregularly. An abscess developed on the plantar surface of the right foot 2 weeks and another one on the neck 3 days before hospitalization.

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He had been married for 33 years and had no children. He had been suffering from low libido and impotence for 10 years.

Physical examination revealed that the skin and subcutaneous tissue was atrophic; his lips were thin and stretched and had circumoral radial furrows. His nose was beaked and his chin was relatively recessed. He had a 4x4 cm infected ulcer on the plantar surface of the right foot and a 2,5x2 cm abscess on the neck. He had bilateral symmetric sensory polyneuropathy. Detailed examination by an ophthalmologist revealed the presence of bilateral posterior subcapsular cataracts. He had eunochoid appearance and pubic and axillary hair was sparse. His testicles were soft and 2x2 cm in size. Penile length was 5 cm on passive extension. He also had bilateral gynecomastia.

His body measurements were as follows: height 162 cm, vertex-pubis length 78 cm, pubis-foot length 84 cm, arm span 168 cm, and body weight 62 kg.

Psychiatric examination and appropriate tests revealed an IQ level of 70 in our patient.

On laboratory examination we found that his fasting and postprandial plasma glucose and Lp(a) values were high. Apart from these his blood biochemistry, urinalysis and complete blood count were all within the normal range. Scleroderma-70

antibodies were negative. His chromosome analysis was found to be 46 XY.

His 12-lead electrocardiogram and telecardiogram was normal. Ultrasonographic examination of the pelvic region showed that the prostate was of normal size and had a homogenous echo pattern. We found osteoporotic appearance but no periarticular or soft tissue calcification on anteroposterior and lateral lumbar vertebra, knee, wrist and foot X-rays.

Bone mineral densiometry is summarized as follows:

Region	bone mineral density (g/cm^2)	t value	z value
Upper extremity	0,698	-3,58	-3,16
Lower extremity	0,704	-3,36	-2,15
Spine	0,718	-3,16	-1,86

Physical and laboratory examination revealed that our patient had hypergonadotropic hypogonadism. A hormonal profile is shown in Table 1, and dynamic testing of the hypothalamic-pituitary-adrenal axis is presented in Tables 2 and 3.

Table 1. Hormone profile of the patient.

	Patient's value	Normal range
FSH (mIU/mL)	68	1-8
LH(mIU/mL)	22	2-10
Prolactin (ng/mL)	9.5	3.5-15
Testosteron (ng/mL)	0.5	3.5-10
Free testosteron (pg/mL)	2.5	10-30
Plasma cortisol (µg/dL)	8.7	7-29
Growth hormone (IU/mL)	3.4	0-10
17-hydroxy-progesteron (ng/mL)	0.5	0.2-2
TSH (mIU/mL)	1.3	0.2-4
Free T3 (pg/mL)	3.7	1.8-5.5
Free T4 (ng/dL)	1	0.7-2
ACTH (pg/mL)	80	0-100
Androstenedion (ng/mL)	1.1	0.4-4.5
11-deoxycortisol (ng/mL)	1	<8
C-peptide (fasting) (pmol/mL)	0.52	0.15-1.3
C-peptide (postprandial) (pmol/mL)	1.3	-

Table 2. Results of ACTH stimulation test.

Time	Plasma cortisol (µg/dL)
Basal level	7
1st day	28
2nd day	39
3rd day	53

Table 3. Results of Insulin-hypoglycemia test.

Time	Plasma Glucose (mg/dL)	Cortisol (µg/dL)	Growth Hormone (mIU/mL)
0'	138	7	3.4
15'	55	14	6.3
30'	33	29	13.8
45'	51	34	11.2
60'	78	31	9.4
90'	98	23	6.5
120'	125	18	7.9

Discussion

Werner's syndrome is a rare autosomal recessive disorder first described by doctor Otto Werner in 1904 in his doctoral thesis (5). From 1904 up to today about 400 cases have been reported (4). Although there is no accepted diagnostic criteria, Goto et al proposed a list of diagnostic criteria in 1981 (6): a) Characteristic habitus and stature; b) Scleroderma-like skin changes; c) Signs and symptoms of premature senescence; d) Endocrinological abnormalities; e) Miscellaneous manifestations (e.g. mental disorders, malignant tumors); and f) Parental consanguinity.

Patients with Werner's syndrome are generally short in stature with a stocky trunk and relatively thin extremities (Cushingoid appearance) (4,7). Cessation of physical growth between 10 and 18 years of age results in small size and thin limbs (7). Our patient showed these characteristics.

Atrophy of skin, subcutaneous tissues and muscles, relatively stretched and thin lips, circumoral radial furrows, beaked nose and relatively recessive chin were the scleroderma-like changes observed in our patient. Goto et al have reported that scleroderma-like skin changes are present in 96% of 196 Japanese cases (4). Other scleroderma-like

skin changes reported in patients with Werner's syndrome but not present in our patient are circumscribed hyperkeratosis especially on the soles of the feet, skin ulcers and gangrene in the legs, localized calcifications and telangiectasias.

We accepted grayish hair, osteoporosis and bilateral cataracts as signs of early aging in our 53-year-old patient. We learnt that his hair began to become gray in his early twenties. Because our patient was not under regular medical control we could not learn when cataracts started and whether it is a complication of diabetes or not. Cataracts are frequently observed in patients with Werner's syndrome, and they are generally posterior cortical or subcapsular in type (4,7). Goto et al have reported bilateral cataracts to be present in 95% of Japanese cases which generally began around 30 years of age and are usually unrelated to the presence of diabetes mellitus (7). Graying of hair generally begins around 20 years of age in these patients, although it may also begin in childhood (7). We did not observe any sign of atherosclerosis in our patient. Goto et al reported atherosclerosis in 21% of these patients (4).

In Japanese cases hypogonadism and abnormal glucose tolerance were observed in 77% and 46%, respectively (4). We established hypergonadotropic hypogonadism on physical and laboratory examination. The absence of children in the history of our patient, who with a low educational and cultural level never used any contraceptive method, suggested hypogonadism to have been present since an early age. In Japanese cases male hypogonadism has been reported in 49% (60% hypergonadotropic, 9% hypogonadotropic and 9% unknown type) of patients with Werner's syndrome (4). Gynecomastia observed in our patient was seen in 22% of Japanese cases with hypergonadotropic hypogonadism (4). Prostatic hypertrophy is unusual in patients with Werner's syndrome (7). Abnormalities of thyroid function were reported in only 14% of these patients (4). We did not observe any functional thyroid disorder in our patient.

Low IQ level seen in our patient was observed in 9% of Japanese cases (4). We could not find any malignancy in our patient.

Goto et al reported mild liver dysfunction in 8% and high cholesterol and triglyceride levels (frequently associated with diabetes mellitus) in 11% of patients on laboratory examination (4). Although our patient was under poor glycemic control his plasma cholesterol, triglycerides, HDL-, LDL- and VLDL-cholesterol levels were normal but Lp (a) level was elevated.

Our patient's parents were not consanguineous. This figure is reported to be 70% in Japanese cases (4). Chromosomal analysis of 20 Japanese patients with Werner's syndrome revealed mosaic-type Klinefelter syndrome in one case and abnormal pattern in another one (4). Our patient's chromosomal analysis was normal.

Werner's syndrome is equally seen in both sexes and the average lifespan is found to be 43.5 years (range 29 to 70 years) in Japanese cases (4,7). Cardiac decompensation, cerebrovascular accident and malignancy are the most frequent causes of death in these patients (7).

Goto et al reported that most of the diabetic patients with Werner's syndrome could be regulated with sulphonylureas or biguanide but 20% required over 200 units of insulin per day (4). We were able to regulate plasma glucose with 40 units of insulin per day in our patient.

Some features of the Werner syndrome may also be seen in progeria, Rothmund-Thomson syndrome, myotonic dystrophy, and scleroderma. Progeria can be differentiated by its early onset and absence of cataracts, hyperkeratoses, skin ulcers, and diabetes mellitus (3). Rothmund-Thomson syndrome begins at an earlier age and has distinguishing cutaneous features such as telangiectasias, scaling, and dyschromia. Myotonic dystrophy is characterized by autosomal dominant inheritance, prominent muscular dystrophy, and myotonic features (3). Patients with scleroderma do not seem prematurely aged and have important distinguishing gastrointestinal, pulmonary, renal and cardiac manifestations.

There is no way to treat Werner's syndrome effectively. Genetic counseling must be advised for the prevention of the disease. Treatment of the skin ulcers, diabetes mellitus, cataracts and malignancy when present is very important. Skin ulcers may be resistant to local measures and skin autografts had

a fair success rate (7). Diabetes mellitus in Werner's syndrome may be insulin resistant but proper diet and oral antidiabetic agents are mostly sufficient for the maintenance of euglycemia (4,7). Oral methyl testosterone or parenteral testosteron enanthate may be useful to achieve normal height and weight beginning at the age of fourteen (7). When necessary cataract surgery must be done with extreme caution to avoid corneal degeneration, secondary glaucoma, and consequent total loss of vision (7).

In conclusion, Werner's syndrome is a rare autosomal recessive disorder characterized by premature aging, hypogonadism (77%) and diabetes mellitus (46%) besides its several characteristics. Although the syndrome has typical stigmata, diagnosis is only possible when it is kept in mind. Our patient could not be diagnosed until he was 53 years old. Early diagnosis is important for genetic counseling and for the close follow-up and early treatment of the potential problems.

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