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WERNER'S SYNDROME

BY

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In 1904 Otto Werner, whilst a medical student working in the Ophthalmological Clinic at Kiel, studied four brothers and sisters suffering from the syndrome which now bears his name, and which he described as "cataract in connexion with scleroderma." It was not until 1934 that Oppenheimer and Kugel first drew attention to the condition in America. In 1941 they reported the first post-mortem examination on a case. Thannhauser (1945) reviewed all the reported cases and literature up to that date. Subsequently, cases have been recognized with increasing frequency, although only one brief report has appeared in the English literature (Williams, 1949).

Werner's syndrome is characterized by a habitus the features of which are short stature, thin tapering limbs, a protuberant abdomen, and stocky trunk. The hair is fine and prematurely grey, whilst it is sparse or absent in the axillae and over the pubes. The disease usually appears about the third or fourth decade with presenile cataracts. Other important features are osteoporosis and diabetes mellitus, together with evidence of hypogonadism (small genitalia, sterility, and menstrual disturbances). The limbs are wasted, thin, and tapering, the legs being affected more than the arms. The skin is tense and shiny, and has a hide-like quality. Ulceration is frequent, and particles of calcium are deposited in the skin, giving rise to a condition known as calcinosis circumscripta.

The following case histories are of two sisters. A brother appears to have had a similar condition, and died in 1937; no clinical or pathological evidence is available. The other seven members of this generation of ten children in the family do not appear to be affected.

Case 1

A woman aged 51 was admitted to hospital on November 27, 1952. A right-sided cataract had been removed in 1942. Her vision in that eye remained satisfactory for nine years, but in the past year it had again become blurred. During the past seven years she had been developing a cataract of the left eye. As long as she could remember her legs had been thin, and over the past 20 years she had been unable to stand or walk for any time because of an aching pain in her feet, which was relieved by sitting. The skin had always been dry with a sallow brown pigmentation. There was no history of thirst, polyuria, loss of weight, spontaneous fractures, or cramp-like pain in the legs. Menstruation began at 17, was often irregular and scanty, and ceased at 46. She has never been pregnant.

Her father's grandmother died after a lifetime of bad feet and sight. The patient was one of 10 children, 3 of whom had "matchstick legs" and large bellies, and developed cataract early in life. No further data can be found about one (a brother), but the other sibling was investigated four years ago at the same hospital as the patient, and from her records the second case is compiled.

Examination showed a placid thin-faced woman, looking much older than her age, with sparse grey hair, advanced cataract in left eye and a ground-glass appearance of cornea on right; diffuse golden brown pigmentation; spider naevus below left eyebrow and another above right nipple; well-covered trunk, protuberant abdomen (Fig. 1), limbs very thin, with practically no subcutaneous or muscle tissue; skin dry everywhere on limbs and face, but normal on trunk. Feet had trophic claw-like appearance with ulcer over right heel (Fig. 2). Nails normal. Cardiovascular and respiratory systems normal. B.P. 160/80. Alimentary system.—Tongue and teeth healthy. Abdomen very well covered; doughy and resistant on palpation; liver, spleen, and kidneys not felt; no free fluid. Umbilicus normal. Central nervous system.—Right

Fig. 1.—Photograph of Case 1.

Fig. 2.—Case 1. Showing trophic claw-like appearance of foot.

pupil fixed; left pupil reacts to light and accommodation; neither fundus visible. Right corneal reflex diminished. Otherwise no abnormality in cranial nerves. Sterno-mastoids normal. Upper limbs.—Very thin; wasting slightly less marked at upper third of upper arm; tone, power, co-ordination, and all modalities of sensation preserved intact; tendon reflexes present, but very sluggish. Lower limbs.—Distribution of loss of tissue as in arms; both ankle-joints and small joints of the feet ankylosed, and the skin appeared to be adherent to the periosteum; no other neurological abnormality.

Investigations

Blood.—Group A, rhesus-positive; Hb 76%, 76% (11 g.), and 81% (12 g.); red cells, 4,630,000 per c.mm.; C.I. 0.8; white cells, 5,900 per c.mm. (72% neutrophils); E.S.R., 79 mm. in 1 hour (Westergren). Bleeding-time, 3 minutes; clotting-time, 13 minutes (capillary method); prothrombin concentration, 50%. After treatment with vitamin K parenterally the latter values became 1½ minutes, 10½ minutes, and 100% respectively. Blood urea, 30 and 40 mg. per 100 ml. Serum calcium, 10.6 and 9.8 mg. per 100 ml. Serum inorganic phosphate, 3.6, 4, and 3.5 mg. per 100 ml. Alkaline phosphatase, 8, 6, and 9 units (King-Armstrong). Acid phosphatase, 1 unit. Plasma proteins, total 8 mg.% (albumin 5.6 g., globulin and fibrinogen 2.4 g.). CO₂ combining power, 61.3 vols.%.
Glucose Tolerance Test.—Fasting level of 290 mg. per 100 ml., rising to 600 mg. after 30 minutes, and remaining at 540 mg. two hours after the administration of glucose.

Urine.—Albumin, 0.09 g. per litre; glucose, ++++; no acetone (Rothera's test). Total excretion of inorganic phosphates in 24 hours, 4,715 and 3,675 mg.; 24-hour excretion of calcium, 92 mg. per 100 ml.

Renal function tests: urea clearance, 42.4%, 64.35%, and 26% of normal at 1, 2, and 3 hours (Van Slyke); phenol-sulphonphthalein, 18%, 24%, and 6% at 1, 2, and 3 hours respectively; 24-hour excretion of amino-acids (paper chromatography) showed that the excretion of only one amino-acid was significantly raised—*aspartic acid*. Urinary keto-acids (24-hour excretion): L-ketoglutaric acid, 24.2 and 19.9 mg.; pyruvic acid, 8.4 and 18.2 mg. Aceto-acetic acid was absent. 24-hour urinary excretion of 17-ketosteroids, 4,725 mg.

Faeces.—Examination of single specimen: total fat, 13%; split fat, 7%; Unsplit fat, 6%. Of the fat, 50% was split and 47% unsplit.

Liver.—Aspiration biopsy: Very firm liver tissue encountered; aspiration failed to produce liver tissue.

Case 2

A woman aged 42, a sister of Case 1, was admitted to hospital under Dr. C. R. Gibson on January 12, 1948, with an ulcerating condition of her feet, from which spicules of "bone" had been discharged six months previously. A cataract had been removed from the right eye nine years earlier, and one subsequently developed in the left eye. One month previously severe thirst, polyuria, pruritus, and loss of weight had led to a diagnosis of diabetes. The menopause occurred at the age of 32; there were no children. Her weight was 5 st. 3 lb. (33.1 kg.).

Examination showed severe wasting of the limbs, below mid-thigh and middle of arms, simulating peroneal muscular atrophy. Over the distal part of the limbs the skin was atrophic and shiny, with patches of brown pigmentation; there were five ulcers on the right foot and one on the left; she had bilateral pes cavus and cataract in the left eye. Secondary sex characteristics: breasts normally developed; axillary and pubic hair normal. Cardiovascular and respiratory systems normal. B.P. 170/80. Alimentary system.—Tongue clean, teeth false; abdomen full, no free fluid; liver edge felt two fingerbreadths below right costal margin, firm and smooth. Central nervous system.—Apart from

muscle-wasting in limbs, nothing abnormal found; tendon reflexes sluggish but equal; sensations normal.

Investigations

Urine.—Albumin, cloud; sugar present; no amino-acids in crystal form; scanty pus cells; Bence Jones proteose, negative. Renal function.—Urea clearance moderately diminished to 54% of normal. 17-ketosteroids, 1.7 g. per litre (assuming total 24-hour urine dispatched, which is doubtful, as specimen totalled only 735 ml.).

Blood.—Hb 70%; red cells, 3,930,000; C.I., 0.89; white cells, 6,000 per c.mm. (polymorphs 46.5%, lymphocytes 50%, monocytes 2.5%, eosinophils 1%); platelets plentiful. Serum calcium, 14.8 mg. per 100 ml. (not repeated); serum phosphate, 2.75 mg. per 100 ml.; alkaline phosphatase, 4.3 units; acid phosphatase, 1.7 units; thymol turbidity, 2 units; colloidal gold, 0.

Her diabetes was insulin-resistant. She died in September, 1952, of metastases from a melanotic sarcoma which had appeared over the right hip a year previously. Her doctor reports that by this time she was blind with cataract, and the skin was dry and parchment-like, with no appreciable subcutaneous tissue. As soon as one ulcer on the feet healed another appeared, and occasionally "sequestra" were extracted therefrom.

Skeletal Survey

Case 1

Skull.—There is well-marked hyperostosis frontalis interna. The remainder of the vault appears slightly osteoporotic.

Lower Limbs.—The lower ends of both femora show slight osteoporosis with a few small cystic areas. There is calcification in the quadriceps tendon on the right side at its insertion into the patella. Both tibiae and fibulae show very marked decalcification with cystic-looking areas present. In places the cortex is so thin as to be scarcely visible. There are similar, even more marked, changes in both feet and ankles. On both sides there is calcification at the site of insertion of the tendo Achillis. On both sides there is linear calcification adjacent to the dorso-medial margin of scaphoid in the soft tissues, and on the left side there is further calcification at the base of the fifth metatarsal in the soft tissues. There is marked flexion deformity of the toes. The bases of the third and fourth metatarsals on both sides appear to be partially fused.

Dorso-Lumbar Spine and Pelvis.—The vertebral bodies appear rather osteoporotic, as does also the lower part of the sternum. The pelvis appears normal.

Upper Limbs.—There are small irregular areas of translucency in the radius and ulna, more marked in the ulna on both sides. The cortex is of normal or almost normal thickness. The carpal bones are not noticeably decalcified. The metacarpals and phalanges all appear more translucent than normal, with multiple cystic areas, particularly noticeable in the phalanges. The periphery of all the subungual expansions is very dense. A few small areas of calcification lie scattered in the soft tissues of the hands.

Nothing abnormal was found in the chest and the renal tracts (plain film and I.V.P.).

Key to the family tree. I. Paternal grandmother died after a lifetime of "bad feet and bad sight." IV.—1 (female): Died in infancy. 2 (Male): Died aged 50+; cataract and matchstick limbs; had three children. 3 and 4: Two sisters in Canada; both healthy, with big families; one weighs 20 st., the other 15 st. 5: Healthy man; died of dysentery in 1914-18 war. 6: Male, of normal build and health. 7: Case 1. 8: Healthy man of normal build. 9: Female, always pale; swollen knuckles. 10: Case 2, died 1952.

Case 2

The appearance of the bones is strikingly similar to that of Case 1, though rather more pronounced in all areas. Case 2 also shows some calcification at the insertion of the tendo Achillis, and there is well-marked calcification in arterial walls in the feet and legs, and to a less extent in the pelvis and thighs. Some tiny areas of calcification lie scattered in the soft tissues of the feet and hands, and there is one linear area lying under the head of the first metatarsal of the right foot.

Discussion

These two cases fulfil the diagnostic criteria of Werner's syndrome: the characteristic habitus—striking wasting of the limbs contrasting with a well-covered trunk and protuberant abdomen, osteoporosis, metastatic calcification, diabetes, cataracts, hypogonadism, and skin changes—was present in both sisters. An unusual feature was the striking resistance to insulin, both patients receiving at one time over 100 units of insulin with little effect on their glycosuria and no hypoglycaemic episodes. In previous descriptions of Werner's syndrome the diabetes has appeared to be mild and insulin-sensitive.

The ulceration of the feet and legs in Case 2 has been seen in many of the cases previously reported. It is usually ascribed to metastatic calcification rather than simple ulceration over pressure points. The calcareous discharge from these sores is more likely to be of this origin than sequestra.

The fatal termination of Case 2 with a melanotic sarcoma is probably significant. Cases have been described in which death has occurred from primary hepatomata (Oppenheimer and Kugel, 1941; Case 2) and sarcoma of the left radius (Oppenheimer and Kugel, 1941; Case 3).

None of the aetiological theories so far advanced explains this syndrome adequately.

Oppenheimer and Kugel (1941), whose post-mortem report is the only one available, described the presence of multiple adenomata of the thyroid, parathyroid, and suprarenal cortex. In consequence, these writers proposed an endocrine basis for Werner's syndrome. Certainly hypogonadism, diabetes, and osteoporosis fit well within this concept, which has been accepted by Williams (1949) and Brink and Findlay (1950). Williams (1949) found a normal level of 17-ketosteroid excretion in his case, a male, but an unduly high proportion of this was of suprarenal origin, and this suggests a primary gonadal deficiency.

In neither of our cases does it appear likely that 17-ketosteroid excretion was significantly depressed, but there is little doubt regarding the presence of clinical hypogonadism. Although both women were married, neither had conceived; this is in contrast with their sisters, described as large women of normal configuration who had families of varying size.

The patterns of endocrine syndromes are now well recognized, and it is difficult to reconcile the pleomorphic features of Werner's syndrome with these. It seems probable that the endocrine features of the syndrome are secondary to the fundamental pathological process, whatever that may be. In this respect an analogy might be made with haemochromatosis, with its sequels of insulin-resistant diabetes mellitus and hypogonadism; a point in this connexion is the clinical evidence of hepatic fibrosis in our cases. Serum iron and copper studies, however, gave normal values.

Thannhauser (1945), in an exhaustive review of the literature on Werner's syndrome, and Schott and Dann (1949), reject the endocrine theory. Their explanation that the condition originates in a defect of the germ-plasm which does not manifest its effects until the third or fourth decade is impossible to dispute, although it fails to cast any further real light on the subject.

The association in Werner's syndrome of albuminuria, impaired renal function, glycosuria, skeletal decalcification,

and clinical evidence of hepatic fibrosis raises the possibility of its relationship to the group of innate defects of renal tubular reabsorption, which includes the Fanconi syndrome and cystinosis.

It is our belief that this relationship is more apparent than real, for the following reasons. Firstly, we were unable to demonstrate an increase or alteration in the urinary spectrum of excreted amino-acids, with the questionable exception of aspartic acid.

Secondly, the characteristic habitus of Werner's syndrome is not encountered in these conditions; nor are the widespread defects of ectodermal tissues. In contrast, rachitic dwarfism, with which the tubular defects may present, has not been described in Werner's syndrome.

Thirdly, glucose-tolerance tests consistently show that the glycosuria of Werner's syndrome is a true diabetes. The glycosuria of the Fanconi syndrome and related conditions, however, is renal in origin, although occasionally impairment of glucose tolerance is encountered where there has been previous restriction of carbohydrate intake (Anderson, Miller, and Kenny, 1952).

The fourth major point of distinction between Werner's syndrome and the renal tubular defects lies in the character of the bone lesions. These are due to osteomalacia in Fanconi's syndrome, nephrocalcinosis, and cystinosis. Neither of our cases of Werner's syndrome, however, nor those reported in which there has been adequate biochemical examination, have fulfilled the criteria for a diagnosis of osteomalacia as stipulated by Albright and his associates (1946). Thus the serum calcium, phosphorus, and alkaline phosphatase were normal even though gross skeletal demineralization was present.

In our two cases of Werner's syndrome the only biochemical abnormality of the blood was an isolated discovery of hypercalcaemia in Case 2. Taken in conjunction with the probable hyperphosphaturia of Case 1, this raises the question of a hyperparathyroid contribution, in addition to hypogonadism.

Finally, biochemical examination of our two patients showed no evidence of the hyperchloraemia or acidosis met with in hyperchloraemic acidosis and occasionally in Fanconi's syndrome. The reaction of the urine was variable. Ammonia production was not studied.

The parallelism of the features of this syndrome with much of the natural history of dystrophia myotonica raises the question of their relationship. The onset of dystrophia myotonica at the third or fourth decade with the features of cataract, baldness, and hypogonadism in this heredo-familial muscular disease come to mind. It is probable that these two diseases are associated in some way.

Summary

Two cases of Werner's syndrome are described, with a brief review of the literature, which contains only one reported post-mortem examination. The clinical features of the disease are discussed in relation to the nature of the condition.

It is a pleasure to acknowledge the permission of Dr. C. R. Gibson to publish the second case, and our thanks are due to Dr. H. Lovell Hoffman for his clinical collaboration, advice, and criticism.

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