A case of Wolfram syndrome: neurological features

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The case of a 24-year-old man with diabetes mellitus, diabetes insipidus, multisensory deficits and peripheral neuropathy is discussed.

Key-Words: Wolfram syndrome — polyneuropathy

Introduction

Wolfram syndrome is the name given to the association of diabetes mellitus, bilateral optic nerve atrophy and less frequently perceptive hearing loss, diabetes insipidus and diffuse dystrophic symptoms affecting mainly the nervous system. The first attempt at nosological classification of the syndrome, which occurs in early infancy, was made by Pilley and Thompson [8], who referred to the familial combination of diabetes insipidus, diabetes mellitus, optic atrophy and deafness as the D.I.D.M.O.A.D. syndrome. In 1977 Cremers [3] collected 88 cases, adding 3 of his own, and gave the association the name of Wolfram syndrome. Inheritance is autosomal recessive according to most authors: Rose et al 1966 [9], Laffay and Lestradet 1974 [6].

Case report

The patient was a 24-year-old man, whose parents were unrelated and whose maternal grandmother suffered from an ill-defined polyuria-polydipsia syndrome. Speech development was slow because of a hearing deficit that arose at 3-5 years and gradually worsened with time. At the age of 22 months he was admitted to a pediatric department as an emergency in ketoacidotic diabetic coma, which was treated with insulin. At the age of 9 he began to complain of progressive bilateral loss of vision. At the age of 20, with the aggravation of his visual and hearing disturbances, the patient was admitted for the first time to the Neurological Clinic and was discharged with the diagnosis of “polyneuropathy, bilateral perceptive deafness and progressive loss of vision in a subject with diabetes mellitus”. In 1978 he was hospitalised again for hypoglycemic coma preceded by generalized seizures. In 1979 he was again admitted to the Pavia Neurological Clinic, this time for paresthesias and dysesthesias of the lower limbs, nocturnal cramp, walking difficulties and subcontinuous headache. Neurological examination showed: prognathism, slanting palpebral fissures, no direct or consensual light reflexes, accommodation reflex not evaluable due to the hearing loss, bilateral nystagmus on lateral gaze, complete amaurosis in the left eye, hypokinesia of the lower division of the right facial nerve, bilateral deafness, ageusia and hyposmia, sluggish pharyngeal reflex. The nutrition and segmental strength of the lower limbs were normal. Tone was reduced bilaterally, more markedly in the upper limbs. The triceps, radial and knee reflexes could not be elicited, the biceps reflexes were weak and the ankle reflexes very weak. Coordination was intact. On examination of the sensory modalities only malleolar hypalgesia on the right was noted. In the standing position the patient tended to sway slightly when his eyes were closed and to fall to the right. His walking was correct. The patient’s intelligence seemed to be within normal limits. There was some evidence of hypochondria for the patient kept analysing his disturbances and sensations.

The blood and blood chemistry tests showed, in addition to the diabetic syndrome, a dyslipi-
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Lumbar puncture showed an above-normal CSF albumin and a normal IgG index: the CSF Alb/serum Alb ratio pointed to an alteration of the blood/CSF barrier. Computed tomography of the brain ruled out pathological findings but showed two very small optic nerves. Visual acuity was 1/50 on the right with almost complete amaurosis on the left: there was absolute central scotoma in the left eye and a marked concentric contraction in the right eye. The optic disk was pale bilaterally with signs of optic atrophy due to vascular disease with dilated, tortuous and hard-walled arteries. The electroretinogram was normal. Visual evoked potentials on stimulation with white light showed waves of markedly below normal amplitude and increased latency; with red light, elective for the macular fasiculus, the response was rudimentary. The somatosensory evoked potential was much reduced in amplitude and with pathologically increased latency on stimulation of the vestibular nerve at the ankle.

The electromyographic recordings from the anterior tibial and from the abductor digitum minimi showed a slightly neurogenic pattern. Motor conduction studies were done on the median, ulnar and lateral popliteal nerves of both sides. The conduction velocities and distal latencies were normal but the amplitude of the M responses of the extensor digitorum brevis muscle was reduced.

The sensory conduction velocity, studied at median, ulnar and sural level on the right side, was decreased.

The ischemia resistance test according to Horowitz and Ginsberg-Fellner [5] yielded the pathological pattern described by these workers in diabetic neuropathy (Horowitz et al 1978) [5]. It was not possible to elicit the H reflex on stimulation of the posterior tibial nerve. Histological examination of the right sural nerve indicated both demyelination and wallerian degeneration.

The baseline levels of FSH and LH were within normal limits and the testosterone levels were reduced. The LSH and LH levels after stimulation were below-normal. Exploration of the neurohypophyseal antidiuretic function confirmed the presence of true diabetes insipidis (Decontet test, Carter Robbins test and water restriction test).

Urography showed that the concentrating power of both kidneys was reduced, especially the right, with dilatation of the cavities; the ureters were canalised and hypotonic with bilateral reflex.

The Wechsler intelligence scale (verbal) yielded an IQ of 88; the olfactory test according to Amoretti 1980 [2] confirmed the suspicion of a specific sensory deficit.

**Discussion**

The association of early-onset insulin-dependent diabetes mellitus, late-onset diabetes insipidus and multisensory deficits (perceptive hearing loss bilateral optic atrophy, hyposmia and anosmia) is typical of Wolfram syndrome, as described by Cremer et al 1977 [3].

Our patient also presented a polyneuropathy marked by mainly subjective symptoms and by a slight slowing of sensory conduction velocity in the median and ulnar nerves.

Refsum disease can be excluded, even without the serum phytanic acid assay, because there was no retinitis pigmentosa or disabling peripheral neuropathy, outright deafness, cardiomyopathy or bone deformities.

In Friedreich disease there is reduced carbohydrate tolerance but not frank diabetes mellitus as in Wolfram syndrome. Alstrom syndrome (1959) [1] in its turn is characterised by degenerative retinopathy, obesity, diabetes mellitus and perceptive hearing loss and Laurence-Moon-Biedl syndrome by retinitis pigmentosa, obesity, hypogeusia and anosmia) have a different origin: the optic atrophy not associated with retinopathy is hereditary; the perceptive hearing loss, in view of its early onset (3-4 years after diabetes) and anosmia are undoubtedly quite unconnected with the diabetes.

Our patient also presented a polyneuropathy typical of Wolfram syndrome is missing.

In our patient the central nervous system is not affected and the peripheral nervous involvement is secondary, probably to the diabetes. This interpretation is supported by the ischemia resistance test according to Horowitz 1978 [5]. The sensory deficits (optic atrophy, perceptive hearing loss, hyposmia and anosmia) have a different origin: the optic atrophy not associated with retinopathy is hereditary; the perceptive hearing loss, in view of its early onset (3-4 years after diabetes) and anosmia are undoubtedly quite unconnected with the diabetes.

Lassel and Rosman 1977[7] argue that the cause of the multisensory deficits, specifically of the optic atrophy and anosmia, may be a disease of the central myelin. The endocrine symptoms may be attributed to a lesion of the diencephalo-hypophyseal axis (Ferrari et al 1980) [4].

Wolfram syndrome thus appears to be an elective multisensory and diencephalo-hypophyseal axis disease attributable perhaps to a lesion partly of the neurosensory epithelia and partly of the nerve trunks. Its etiology is unknown but the possibility of autosomal recessivetransmission is documented.