Portuguese-type amyloid neuropathy in an English family

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Summary

A 31-year-old woman thought to be suffering from a psychiatric illness was found to have peripheral and autonomic neuropathy, keratoconjunctivitis sicca and vitreous opacities. Her mother had died 10 years previously, aged 42 years from an undiagnosed illness with similar features. Histological proof of amyloidosis was obtained in both cases. This is the second report of familial amyloid neuropathy in an English family.

Introduction

Of the familial amyloidoses there are 4 types with predominant nervous system involvement. The first to be described was the Portuguese variety (Andrade, 1952) and is characterized by (1) a progressive decline in the general state of health; (2) autonomic disturbances; (3) progressive peripheral neuropathy; (4) gastrointestinal dysfunction. Around 200 families have now been studied, mostly in the Oporto region of Portugal. Several kindreds with the same features have been reported from Japan (Araki *et al.*, 1968) and Sweden (Andersson, 1970). There have also been case reports from Brazil, U.S.A., France, Germany and Poland (Stanbury, Wyngaarden and Fredrickson, 1978) and one of an English family (Zalin *et al.*, 1974). The disease is transmitted by an autosomal dominant gene and proceeds a relentless course from its onset in early adult life to death from cachexia, intercurrent infection and heart failure within 5-10 years of the onset of symptoms. Renal involvement is rare in contrast to the Iowa type of familial amyloid neuropathy (Van Allen, Frohlich and Davis, 1969). The Indiana type (Rukavina *et al.*, 1956) predominantly involves the upper limbs with a more benign course lasting 15-20 years. The Finnish type (Meretoja 1969) comprises progressive cranial nerve palsies in association with lattice dystrophy of the cornea. No treatment has been shown to be effective in any of these disorders.

Patients

Case 1

A 31-year-old woman was referred to the skin

clinic after having spent nearly one year in a psychiatric hospital. She had recently developed blistering and ulceration of the sole of her left foot (Fig. 1). This was considered to have been self-inflicted and indeed seemed to improve after occlusion and appropriate local therapy. Some weeks later, however, she developed further ulceration of both feet and buttocks and she was admitted for further investigation. For 3 years she had been suffering from weight loss, nausea, vomiting and abdominal pain. Extensive investigations on 3 occasions following admission with these complaints were negative. It was concluded that she was suffering from a depressive illness and little was made of additional complaints such as deteriorating eyesight and difficulty in assessing the temperature of her bath water.

On examination she was wasted and unwell with pale smooth skin. She had puffy eyes with a 'waxy' appearance of the periorbital tissues. Her lips were rather prominent, the tongue being normal. She had absent pin-prick sensation in a stocking distribution up to mid-calf bilaterally and also in the sacral area. There was wasting of the quadriceps bilaterally and absent ankle jerks. There was absent thermal sensation up to the waist. Her pupils were equal but showed no response to light and in conjunction with the absent ankle jerks this was at first thought consistent with Holmes-Adie syndrome, the sensory findings being considered as hysterical in origin. However, the pupils showed no reaction on accommodation, and electrical nerve studies indicated a profound peripheral sensorimotor neuropathy. Further examination of her eyes revealed absent tear secretion bilaterally with superficial punctate corneal ulceration. The discs were normal and vitreous opacities were seen in the left eye.

The presence of a co-existent autonomic neuropathy was considered, to explain the pupillary signs and predominant gastro-intestinal symptomatology. This was confirmed by the following tests: ECG showed complete lack of beat-to-beat variation and no response on changing posture, performing the Valsalva manoeuvre or after i.v.

FIG. 1. Blistering and ulceration of the left foot on presentation.

0.4 mg atropine; a postural BP change from 130/75 mmHg lying to 80/50 mmHg standing; much diminished sweating over most of the body on starch/iodine testing; a positive finger-wrinkling test (Bull and Henry, 1977) was obtained.

A biopsy was taken from the lip to exclude Sjögren's disease and also to look for amyloid. There was considerable deposition of amyloid around vessels and in association with mucous glands. Amyloid was also found in biopsy material from skin and from sural nerve. Screening for other causes of peripheral neuropathy was negative. Other positive findings were: Hb 10.5 g/l, serum iron 8 $\mu\text{mol/l}$, TIBC 49.5 $\mu\text{mol/l}$, bone marrow: absent iron stores, normal erythropoiesis, no increase in plasma cells. Creatinine clearance 65 ml/min. Protein electrophoresis: slight increase in α_2 -globulin, otherwise normal. CSF protein 100 mg/100 ml. There was no evidence of any underlying disease capable of causing secondary amyloidosis, nor was there any evidence of plasma cell dyscrasia.

Despite a trial of colchicine therapy her disease has continued to progress. She now (1979) has profound postural hypotension, her vitreous opacities have increased and 'neuropathic' skin lesions have continued to appear over the legs, back and scalp.

Case 2

The mother of patient 1 died in 1969 aged 42 years. Her problems began 6 years before her death with iron deficiency anaemia requiring parenteral iron therapy. She then developed diarrhoea, weight loss, ulceration on her feet and 'septic spots' over other areas of her body. She had a transient cerebral ischaemic episode which went unexplained and later developed ulceration of her buttocks. Severe diarrhoea continued and she was investigated extensively without any firm diagnosis being made. In particular, sigmoidoscopy and barium enema were within normal limits until just before her death. A jejunal biopsy suggested minimal coeliac disease but there was no response to a gluten-free diet. On her final admission to hospital she was noted to have unequal pupils which were unreactive to light and keratoconjunctivitis sicca. Her ECG showed lack of beat-to-beat variation. A further barium enema showed some superficial ulceration and, because of continuing clinical deterioration, a colectomy was performed. There was no improvement post-operatively and her death was attributed to ulcerative colitis. The histology of the resected colon showed some features of this but the distal colon was spared.

Recently the resected colon and material from the post-mortem were stained for amyloid, this not

having been done in 1969. Considerable amounts of amyloid were found in blood vessels of the colonic mucosa and serosa and in one area in close relationship to a nerve. Of the post-mortem tissues, amyloid was found in the thyroid, pituitary, jejunum, appendix and renal medulla but not in the adrenals. No other tissues were available for staining.

Discussion

The predominant gastro-intestinal symptoms, skin ulceration and eye signs are common to both patients and, with the histological proof of amyloid deposition, strongly suggests they were suffering from the same disease. Patient 1 does not appear to have secondary amyloidosis since investigations for any underlying disease are negative and furthermore involvement of skin and nerve is said not to occur in this type (Brownstein and Helwig, 1970; Benson *et al.*, 1975). Against primary amyloidosis is the age of onset of symptoms in patient 1 (Thomas and King, 1974), the lack of evidence for plasma cell dyscrasia and the presence of vitreous opacities which seem to be found only in the familial varieties (Kyle and Bayrd, 1975). Of the familial amyloidoses, the pattern of disease in both the present cases follows most closely the Portuguese type. The only unusual feature is keratoconjunctivitis sicca but this has been reported previously in primary amyloidosis (Kuczynski, Courtenay Evans and Mitchinson, 1971).

The author has no histological proof of amyloid in any other family member. The brother of case 1, aged 28, has symptoms suggestive of the disorder but as yet no evidence of amyloid in a skin biopsy taken recently. The family have lived in the North of England for as long as any of them can remember and there are no known Portuguese connections.

Colchicine was used because of certain theoretical considerations. Firstly, it has been shown to inhibit casein-induced amyloid production in experimental animals (Kedar, Greenwald and Ravid, 1976). Secondly, it is of well established efficacy in familial Mediterranean fever, another of the genetic amyloidoses (Zemer *et al.*, 1974). It may be that treatment aimed at prevention rather than cure is more realistic in this disorder, bearing in mind that the penetrance of the dominant gene was calculated at 30% in the Swedish families.

The early Portuguese cases were variously diagnosed as sufferers from psychiatric disorders, syringomyelia and even leprosy before the deposition of amyloid material was discovered. Regrettably the prognosis is so bad and treatment so unhelpful that many choose suicide once they develop symptoms. Recent work (Costa, Figueira and Bravo, 1978) suggests these patients may be producing an abnormal pre-albumin which is deposited as

amyloid preferentially in the neural tissues; further characterization of this protein may offer some hope therapeutically.

Acknowledgments

I am indebted to Dr I. B. Sneddon for permission to publish this case and for assistance in the preparation of the text. I am grateful to Dr A. Kennedy for his help with the pathology in Case 2 and to Mr A. C. Palmer for his ophthalmological advice in Case 1.

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