Neurology Asia 2008; 13 : 121 – 124

Familial transthyretin-related amyloid polyneuropathy in a Malaysian patient of ethnic Chinese descent

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Abstract

Familial amyloid polyneuropathy is commonly the result of deposition of variant transthyretin in nerves and other organs. Apart from the Val30Met variant commonly seen in endemic areas of familial amyloid polyneuropathy, many transthyretin mutations have been described in various populations worldwide. We report a Malaysian patient of ethnic Chinese descent with familial amyloid polyneuropathy and a transthyretin mutation, Ala117Ser. This mutation has not been previously reported in Chinese patients. He presented in middle-age with carpal tunnel syndrome followed progressive sensorimotor polyneuropathy. There was evidence of autonomic dysfunction clinically and cardiomyopathy on 2D-echocardiography. Familial amyloid polyneuropathy is uncommon in Asian patients outside Japan, but the diagnosis should be considered in a progressive late onset sensorimotor axonal polyneuropathy.

INTRODUCTION

Amyloid neuropathies are a group of peripheral nerve disorders in which the peripheral nerve lesion is the result of amyloid deposits in the endoneurium.[1] Familial amyloid polyneuropathy (FAP), the hereditary form, is an autosomal dominant disorder, and is commonly the result of deposition of a mutated variant of transthyretin (TTR).[1,2] Other less common types of FAP-related amyloidogenic proteins include gelsolin and apolipoprotien A1.[1]

Transthyretin-related FAP was initially described in Portugal in 1952 but large foci of patients have been reported from Japan and Sweden and several other populations.[3-8] The disease is now believed to occur worldwide. TTR-related FAP has been shown to be due to point mutations or deletion of the TTR gene located in chromosome 18. Of these the commonest mutation of the TTR gene results in a substitution of methionine for valine at position 30 (Val30Met) of the TTR protein, and this variant is present in large kindreds in the major disease foci viz. Portugal, Japan and Sweden but also in other populations albeit in lesser numbers.[5-8] Many non-Val30Met mutations have been described but have involved smaller kindreds or sporadic cases.[9-10] Phenotypically some of these patients have differed from those with the Val30Met variant in the age of onset, the mode of presentation and the organs involved.[2,6-8]

Outside Japan, there have been few reports of Asian FAP patients. There have been several previous reports of single patients and small case series of ethnic Chinese patients with FAP, some with molecular genetic confirmation of mutation in the TTR gene and detection of the variant protein.[11-18] These patients have had mutations other than the common Val30Met. A recent report of 5 FAP patients with Ala97Ser TTR variant suggested that this mutation may be more common among the Chinese.[17]

We report a Malaysian patient of Chinese ethnicity with transthyretin-type FAP who presented with progressive sensorimotor polyneuropathy. He was found to have a TTR mutation, Ala 117Ser, not previously reported in Chinese patients.

CASE REPORT

Our patient first presented to the University of Malaya Medical Centre, Kuala Lumpur, Malaysia, at the age of 52 years. Three years prior to consultation, at the age of 49 years, he developed numbness of both hands, diagnosed to have carpal tunnel syndrome, underwent surgical release at another hospital with temporary improvement of numbness. However, the numbness recurred involving the lower limbs as well. He also noted wasting of the small muscles of the hands and feet, difficulty in walking, and was unable to play tennis like he used to.

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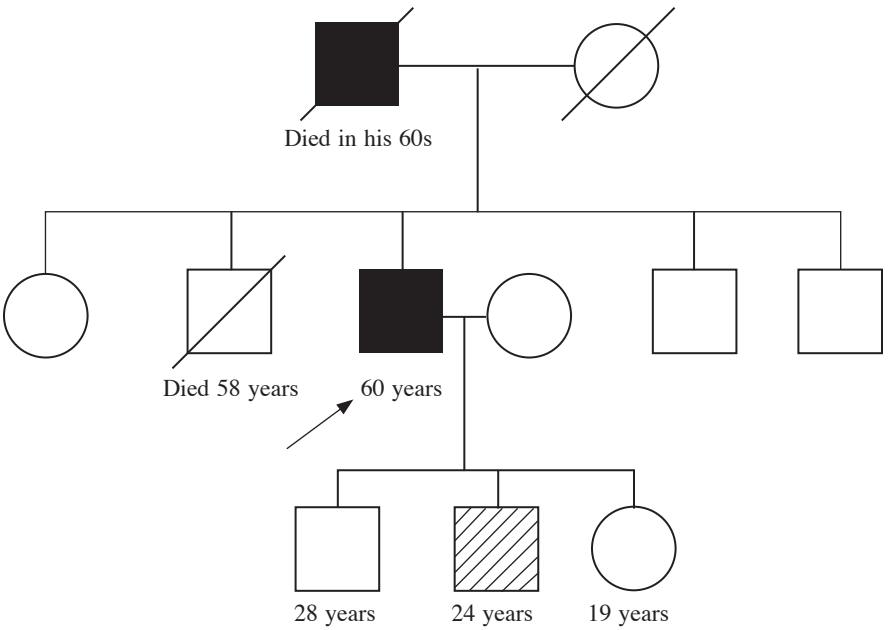

Figure 1: Pedigree of family, the arrow indicates the proband. Solid symbols indicate affected individuals while diagonally-lined symbols indicate asymptomatic individuals

There was significant family history (Figure 1). His father, an immigrant from Guangdong province, China, developed progressive difficulty in walking from about 50 years and died in his sixties. He was not seen medically at the time and no diagnosis was made. The patient was the third of 5 siblings (4 brothers and one sister) and an older brother had died from a sudden cardiac arrest. None of the other siblings had symptoms of neuropathy or weakness. He has 3 children, 2 sons and a daughter, aged 28, 24 and 19 years respectively, all of whom were asymptomatic.

He did not complain of any orthostatic giddiness, bowel disturbances but did admit to some degree of impotence.

Clinically, he had wasting of the small muscles of the hands and feet, generalised areflexia and glove and stocking pattern of loss to pain. Propioception was normal. Cranial nerve examination was normal. There was no postural hypotension on initial examination. Nerve conduction studies and electromyography showed a diffuse axonal sensorimotor peripheral neuropathy. ESR was normal and serum protein electrophoresis was normal. He continued to progress over the next few years and developed difficulty in climbing stairs and getting up from sitting.

At the age of 56 years he was investigated at the Samsung Medical Centre, Seoul, Korea. Sural nerve biopsy showed evidence of chronic axonal neuropathy and positive congo red stain of the epineurial and endoneurial blood vessels suggestive of amyloid neuropathy.

Autonomic function tests showed abnormal findings suggestive of both sympathetic and parasympathetic dysfunction. 2D echocardiography showed concentric ventricular wall hypertrophy and granular appearance of the myocardium suggestive of myocardial amyloidosis. Renal function test was normal and urinalysis showed no proteinuria. Renal ultrasound was showed small kidneys bilaterally but was otherwise normal. Repeat serum protein electrophoresis was normal and bone marrow examination showed no evidence for haematological malignancy.

TTR gene analysis by direct sequencing of all 4 exons showed G>T mutation at position 349 of exon 4 resulting in Ala117Ser TTR variant. (Figure 2) This is likely to a pathogenic mutation. Screening of the patient's younger son revealed the same mutation but not his daughter. His elder son has not been tested.

The patient has continued follow up in Malaysia and at last review he has shown progression in his muscle weakness, being only able to ambulate with a walking stick. He has developed significant postural hypotension. However, he has remained well cardiac wise with no symptoms of heart

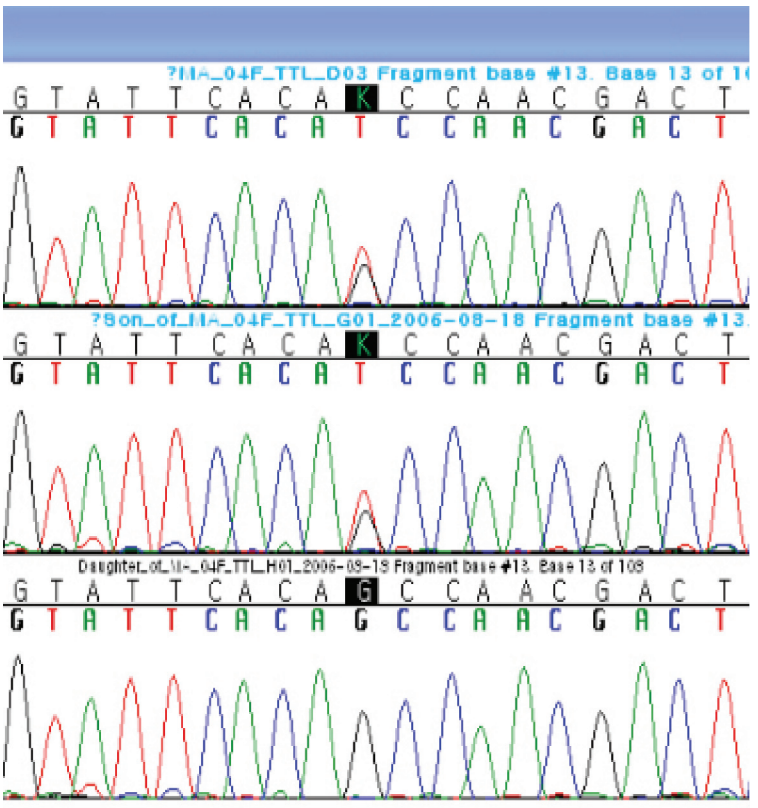

Figure 2: DNA sequence chromatogram showing mutation in exon 4 of the transthyretin gene with a nucleotide change at position 349 (G349T) resulting in Ala117Ser variant of the transthyretin protein for patient and his second son, (a) and (b), but not for his daughter, (c).

failure. A repeat 2D-echocardiogram a year later showed left ventricular hypertrophy with normal left ventricular systolic function.

DISCUSSION

We report the first Malaysian patient of ethnic Chinese descent confirmed to have FAP. Our patient like most ethnic Chinese in Malaysia are descended from immigrants from Southern China; in his case, Guangdong province. The family history is consistent with an autosomal dominant inheritance. His father, deceased, was most likely affected based on history while his younger son was genetically confirmed to have the same mutation. His elder brother died suddenly from what was described as a cardiac arrest. It is possible that the brother may have also succumbed to arrhythmias due to cardiac involvement of amyloidosis.

He demonstrates a mutation, in exon 4 of the TTR gene resulting in an Ala117Ser variant of the TTR protein. This variant has not been previously reported in Chinese patients with FAP.[10]

Similar to other reports on non-Val30Met mutations, our patient's clinical features differed from the more common Val30Met mutation.[6-8] The typical Val30Met phenotype has been well described, presenting between the late twenties to early forties with ascending sensory polyneuropathy (with dissociated sensory loss) and prominent autonomic dysfunction.[2] Our patient presented at a later age of 49 years with carpal tunnel syndrome and then developed a slower progressive sensorimotor polyneuropathy. His father developed weakness of the limbs in his fifties while his son remains asymptomatic. Autonomic symptoms were not prominent symptomatically although he had orthostatic hypotension and autonomic dysfunction on testing. Similarly, although there was cardiac involvement on echocardiographic evidence, the patient was not symptomatic. He had no evidence of renal dysfunction.

Previous reports of Asian patients with non-Val30Met mutations have suggested differences in the clinical presentation of these patients including

a later age of onset, milder autonomic involvement and presentation with carpal tunnel syndrome.[15,17] However, severe cardiac involvement with intractable heart failure was reported in non Val30Met Japanese patients but this was not the case in our patient.[6] A recent report suggested that Ala97Ser mutation may be a possible hotspot among Chinese FAP patients but more studies of Chinese patients will be needed to verify this.

Asymptomatic carriers of TTR-FAP have been reported.[15,16] Our patient's younger son was also positive for the Ala117Ser mutation and is currently asymptomatic. However, as he was still in his twenties, it is uncertain if he will develop symptoms at a later age or remain asymptomatic. The possibility of other asymptomatic carriers in our family was not determined as other family members (apart from the patient's daughter, who was negative) were not tested. If other affected family members are asymptomatic, cases may seem sporadic and may be misdiagnosed without a high index of suspicion and genetic testing.[19]

In summary, we report a case of FAP in a Chinese patient from Malaysia, with a mutation of the TTR gene not previously described in ethnic Chinese, presenting with a later age of onset and slower progression of disease. FAP should be included in the differential diagnosis of older patients with progressive sensorimotor axonal polyneuropathy.

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