Letter to the Editor

Upper limb neuropathy such as carpal tunnel syndrome as an initial manifestation of ATTR Val30Met familial amyloid polyneuropathy

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Abbreviations: FAP = familial amyloid polyneuropathy; CTS = carpal tunnel syndrome; TTR = transthyretin, Val30Met = methionine is substituted for valine at position 30

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Abstract

We report here two patients with ATTR Val30Met FAP who developed numbness in both hands and were diagnosed as having bilateral carpal tunnel syndrome (CTS). In both patients systemic TTR amyoloidosis consisting of polyneuropathy affecting both upper and lower limbs and/or autonomic dysfunction gradually appeared after surgery for CTS. Although CTS associated with TTR amyloidosis has been known as an initial symptom in some patients with ATTR non-Val30Met FAP and those with senile systemic amyloidosis, this is the first report of ATTR Val30Met FAP patients starting with upper limb neuropathy including CTS-like symptoms. It is also notable that both patients had no genealogical relationship with two Japanese endemic foci of this disease.

Introduction

The carpal tunnel syndrome (CTS) is caused by entrapment of the distal part of the median nerve. Bilateral CTS usually accompanies various systemic diseases including amyloidosis, producing heavy deposition of amyloid on the tenosynovium of the wrist. CTS is well known to be an initial symptom in long term hemodialysis-related amylodosis [1], primary systemic AL amyloidosis [2], senile systemic amyloidosis [3, 4], and some forms of familial amyloid polyneuropathy (FAP) with amyloidogenic transthyretin (ATTR) non-Val30Met (other mutations except for Val30Met) [5, 6]. However, in the most common form of FAP with ATTR Val30Met CTS has not been noted [7]. Here, we describe two FAP patients with ATTR Val30Met whose diseases started as CTS-like manifestations in both hands and who showed subsequent development of systemic amyloid polyneuropathy.

Case Report

Case 1

This Japanese woman who originated from Fukaya City, Saitama Prefecture, developed numbness and dysesthesia of the first, second, and third fingers of the bilateral hands at the age of 48. She was diagnosed as having bilateral CTS and underwent bilateral surgical carpal tunnel ligament release, but the symptoms remained in both hands. Then she gradually developed abnormal sensations and weakness in the lower legs. There was family history of the same symptoms in her aunt. At the age of 50, she was diagnosed as having FAP with ATTR Val30Met by histopathological examination of biopsed sural nerve, matrix-assisted laser desorption ionization/time-of-flight mass spectrometry (MALDI/TOF MS) analysis of her serum and DNA sequencing of the TTR gene, as described previously [8, 9] (Figure 1A, 1B). DNA sequencing of four PCR-amplified exons of the TTR gene showed no additional mutations except for Val30Met.

When she was 50 years old, she was hospitalized to receive a liver transplant. Neurological examination showed severe muscle atrophy of the bilateral thenar and dorsal interossei muscles (Figure 1C), dysesthesia in the first, second and third fingers of both hands, mild wasting and weakness of the lower leg muscles, diminished tendon reflexes in the four limbs, decreased pinpick and light touch sensations in both hands and the distal parts of both legs. Autonomic symptoms were not seen. Nerve conduction studies showed that motor conduction velocity (MCV) of the left median nerve was not evoked. MCV, distal motor latency (DML), and compound muscle action potential (CMAP) amplitude of the left ulnar nerve were 52.0 m/s (elbow to wrist, normal value >55 m/s), 4.41 ms (normal value <3.2ms), and 2.60 mV (normal value >4.9 mV). MCV and CMAP amplitude of the left tibial nerve were 33.5 m/s (knee to ankle, normal value >45 m/s) and 0.031mV (normal value >6.2 mV). Sensory nerve conduction velocity (SCV) of the left median nerve and of the left ulnar nerve were not evoked. SCV of the left sural nerve was 51.9 m/s (normal value >40 m/s). Electrocardiogram and echocardiogram were normal. TTR-immunoreactive amyloid deposits were observed on biopsied gastric mucosa. She underwent liver transplantation using a graft harvested from a live donor and recovered without any complications.

Case 2

This Japanese man who was born in Nomi City, Ishikawa Prefecture, developed numbness and dysesthesia of the first, second, and third fingers of the right hand at the age of 61. The following year similar symptoms appeared in his left hand. He was diagnosed as having CTS and underwent right surgical carpal tunnel ligament release at the age of 63. However, he gradually noticed numbness and dysesthesia in the forearms and the legs, and autonomic dysfunction such as constipation and orthostatic hypotension. There was a family history of the same symptoms in his two siblings. At the age of 65 he was diagnosed with ATTR Val30Met FAP by histopathological

examination of biopsied sural nerve and TTR gene analysis in another institution. At the age of 68 he was referred to our hospital in the hope of receiving useful therapies.

Neurological examination showed severe muscle atrophy of the bilateral thenar muscles, wasting and weakness, decreased pinpick and light touch sensations in the lower extremities, paresthesia in both hands, diminished or absent tendon reflexes in all limbs, and autonomic dysfunction. Nerve conduction studies showed that MCV, DML, and CMAP amplitude of the left median nerve were 55.3 m/s (elbow to wrist, normal value >55 m/s), 4.14 ms (normal value <4.0 ms) and 3.54 mV (normal value >4.5 mV). MCV, DML, and CMAP amplitude of the left ulnar nerve were 60.7 m/s (elbow to wrist), 3.27ms, and 1.83 mV. MCV and CMAP amplitude of the left tibial nerve were 46.7 m/s (knee to ankle) and 3.30mV. SCV of the left median nerve was not evoked. SCV of the left ulnar nerve was 53.3m/s (finger to wrist, normal value >50 m/s) and 57.6 m/s (wrist to elbow, normal value >55 m/s). SCV of the left sural nerve was not evoked. Electrocardiogram showed low voltage in standard limb leads and poor r wave progression in left precordial leads. Echocardiogram showed mild symmetrical thickening of the ventricular walls and ventricular septum. Myocardial scintigraphy using technetium-99m pyrophosphate revealed high uptake of radioactive tracer. Heavy deposition of amyloid was seen in aspirated abdominal fat tissues, and the presence of ATTR Val30Met was confirmed by MALDI/TOF MS analysis of his serum [8]. He is now participating in our clinical trial of diflunisal [10].

Discussion

The clinical phenotypes of FAP are known to vary in different kindreds or individuals with diverse mutations of TTR genes [7]. Even in patients with the same gene mutation of ATTR Val30Met the clinical feature is not uniform: ATTR Val30Met FAP patients originating from endemic foci show an autosomal dominant trait with high penetration, an early age of onset, equal sex distribution, and the presence of dissociated sensory loss and severe autonomic dysfunction. However, this classic feature of FAP is not seen in patients from sporadic kindreds, whose clinical manifestations are characterized by a late age of onset, male predominance and an obscure family history [11, 12]. Concerning CTS in FAP, a family of Swiss origin living in Indiana was originally reported to start with this disorder [13] and in some patients with this form of FAP the clinical manifestations were confined to CTS even 20 or more years after onset [14]. Also, immediate relief of symptoms after surgical release of the involved median nerve was obtained in the majority of the operated patients who underwent surgery. Sensory loss later appeared more diffusely in the distal part of the upper limbs and subsequently the legs were affected. This cardinal feature of FAP was first described as type II (Indiana or Rukavina type) [14], and CTS is now seen in many FAP patients with ATTR non-Val30Met mutations [5, 6]. However, little attention has been given to CTS either in large series of ATTR Val30Met FAP patients originating from four endemic foci [15-19] or in patients unrelated to endemic areas [11, 12], even though the number of the latter has been increasing worldwide.

During the past 2 years we have had two ATTR Val30Met FAP patients originating from non-endemic areas in Japan and showing bilateral CTS-like symptoms as an initial sign of the disease: although amyloid deposition on the flexor retinaculum was not examined histologically, hand symptoms in both patients could not be ameliorated by decompression surgery, indicating that compression of the median nerve was not a major cause of their symptoms. Moreover, neuropathic symptoms extended into the proximal part of the arms, and peripheral nerve conduction study of the ulnar nerves disclosed axonal damage, suggesting the presence of amyloid-laden neuropathy in the arms at an early stage of this disease. The CTS-like symptoms in these two patients were, therefore, considered to be a neuropathic manifestation of FAP patients with ATTR Val30Met originating from non-endemic areas. This seems to be supported by recent electrophysiological analysis of peripheral nerve functions in the arms of many FAP patients with ATTR Val30Met [20]. Our report provides evidence that it is impossible to distinguish FAP patients with ATTR Val30Met from those with ATTR non-Val30Met on the basis of clinical features including serious cardiac involvement and neuropathic manifestations [21].

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Figure Legends

Figure 1.

(A) MALDI/TOF mass spectrometry of immunoprecipitated serum TTR of case 1. The spectrum had ion peaks originating from wild-type TTR (m/z 13762.2) and ATTR Val30Met (m/z 13794.8), and these peaks were accompanied by additional doublet ion peaks of wild-type (m/z 13883.3) and ATTR Val30Met TTR (m/z 13916.2) combined with cysteine. (B) Analysis of patterns of PCR-amplified exon 2 of the *TTR* gene digested with *Bal* I. Lane M, DNA molecular weight marker; lane 1, normal control ; lane 2, heterozygote for ATTR Val30Met; lane 3, case 1. (C) Severe atrophy of thenar and dorsal interossei muscles in both hands of case 1.

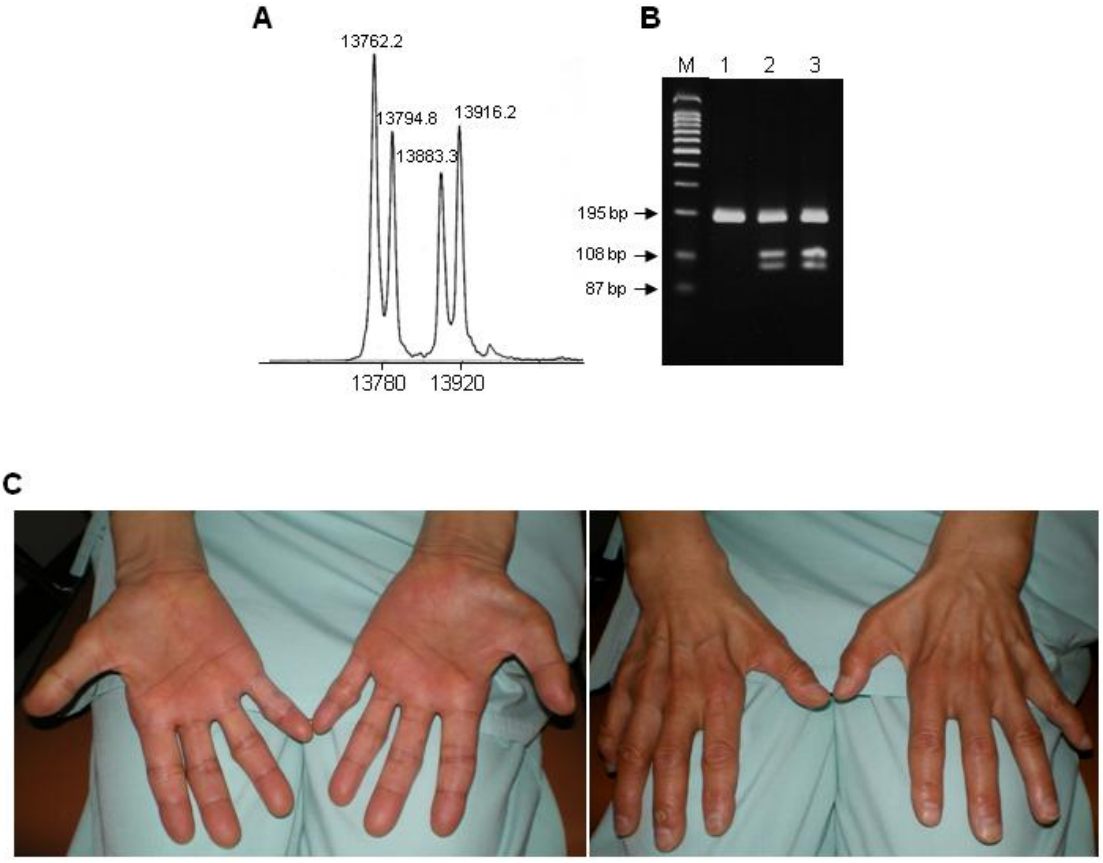
A
13762.2
13794.8
13916.2
13883.3
13780
13920
B
M
1
2
3
195 bp
108 bp
87 bp
C

Figure 1.