IJMS
Vol 41, No 3, May 2016

Case Report

Familial Amyloid Polyneuropathy Type IV (FINNISH) with Rapid Clinical Progression in an Iranian Woman: A Case Report

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Received: 12 August 2014
Revised: 08 October 2014
Accepted: 19 October 2014

Abstract

Familial amyloid polyneuropathy (FAP) type IV (FINNISH) is a rare clinical entity with challenging neuropathy and cosmetic deficits. Amyloidosis can affect peripheral sensory, motor, or autonomic nerves. Nerve lesions are induced by deposits of amyloid fibrils and treatment approaches for neuropathy are challenging. Involvement of cranial nerves and atrophy in facial muscles is a real concern in daily life of such patients. Currently, diagnosis of neuropathy can be made by electrodiagnostic studies and diagnosis of amyloidosis can be made by genetic testing or by detection of amyloid deposition in abdominal fat pad, rectal, or nerve biopsies. It is preferable to consider FAP as one of the differential diagnosis of a case presented with multiple cranial nerves symptoms. The authors present a case of familial amyloid polyneuropathy (FAP) type IV with severe involvement of multiple cranial nerves, peripheral limb neuropathy, and orthostatic hypotension.

Please cite this article as: Babaei-Ghazani A, Eftekharsadat B. Familial Amyloid Polyneuropathy Type IV (FINNISH) with Rapid Clinical Progression in an Iranian Woman: A Case Report. Iran J Med Sci. 2016;41(3):241-244.

Keywords ● Amyloid neuropathies ● Familial ● Cranial nerve diseases ● Hypotension ● Orthostatic

What's Known

- Familial amyloid polyneuropathy (FAP) type IV (FINNISH) is a very rare life-threatening disorder transmitted as an autosomal dominant.
- This neurodegenerative disorder is associated with extracellular deposition of amyloid fibrils, particularly in the peripheral nervous system.

What's New

- This case highlights one of the rare conditions that causes neuropathy, presenting mainly with facial muscle wasting.
- In case of symptomatic progressive multiple cranial nerve involvement and peripheral polyneuropathy, FAP should be considered in the differential diagnosis.

Introduction

Familial amyloid polyneuropathy (FAP) type IV (FINNISH) is a very rare life-threatening disorder and reported only in a few countries.[1] FAPs transmitted as an autosomal dominant trait neurodegenerative disorder associated with extracellular deposition of amyloid fibrils, particularly in the peripheral nervous system.

There are several forms of hereditary amyloidosis associated with peripheral neuropathy.[2] FAP is a progressive sensorimotor and autonomic neuropathy of adulthood onset. There is phenotypic and genetic heterogeneity among the different forms of FAPs. Mutations in the genes for transthyretin (prealbumin), apolipoprotein A1 or gelsolin are responsible for the various forms of FAP.[2] FAP type IV is caused by mutations in the gelsolin gene.[3] Diagnosis of amyloidosis can be made by genetic testing or by detection of amyloid deposition in abdominal fat pad, rectal, or nerve biopsies. We present the first case of familial amyloid polyneuropathy (FAP) type IV in an Iranian woman with severe involvement of multiple cranial nerves, peripheral limb neuropathy, and orthostatic hypotension.

Case Presentation

A 27-year-old Iranian woman referred to the authors' electrodiagnostic department with severe facial muscles atrophy causing cosmetic problems and avoidance of social activities. Her medical history was positive for familial amyloidosis diagnosed based on abdominal and rectal biopsies when she was in second grade. She had biopsies because of positive familial history of amyloidosis in her mother and older sister. She was symptom-free until 22 years of age. Her symptoms developed during 5 years. Symptoms developed with mild weakness during chewing food and progressed to severe facial muscle atrophy with cosmetic problems and mild tingling in feet. Soon after, she presented with dizziness during standing up from sitting position and blurred vision.

At examination, she showed bilateral severe facial muscle and tongue atrophy and fasciculation of the tongue and left side ptosis. Her appearance was sad, with drooping eyelids, and hanging skin of the face (figure 1). She also showed generalized hyporeflexia without muscular weakness or atrophy in the limbs. Corneal sensation was decreased and sensation was impaired on face with mild sensory disturbances in feet accompanied by mild sensory ataxia. Slit lamp examination revealed multiple streaks on the cornea (corneal lattice), which was compatible with a characteristic feature of FAP type IV. The jaw reflex was absent and speech was incomprehensible. We observed orthostatic hypotension of 45 mmHg. No abnormal findings were observed on MRI of the brain and spinal cord.

In electrodiagnostic study, severe bilateral facial neuropathy with reduction in facial nerve compound muscle action potentials (CMAP) amplitude and severe denervation in needle electromyography (EMG) was present. Also in lower limbs, low amplitude sural sensory nerve action potential (SNAP) and low amplitude with mild reduction in conduction velocity of deep peroneal and tibial nerves CMAP were evident. There was not any evidence of conduction block except for mild carpal tunnel syndrome (CTS) in the right side.

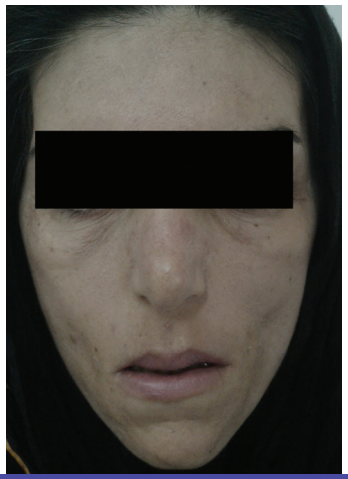

Figure 1: Shows familial amyloid polyneuropathy (FAP) type IV (FINNISH) in a 27-year-old Iranian woman presented with severe bilateral facial muscles atrophy.

Bipolar needle EMG of bilateral facial innervated muscles (orbicularis oris, orbicularis ocoli, nasalis, and frontalis), trigeminal innervated muscles (temporalis and masseter) and hypoglossal (tongue) demonstrated florid denervation by the way of ample fibrillations (3/4), and positive sharp waves (3/4 for all).

Additionally, there was a reduction in the recruitment and interference pattern of motor units and chronic motor unit remodeling changes to these muscles. Their amplitudes, duration, and polyphasia were within chronic neurogenic range (MUAP duration 3-4 msec and MUAP amplitude 4-5 mV). The motor unit action potential (MUAP) characteristics of cervical and thoracic innervated muscles were normal, with no obvious evidence of denervation, and no changes in motor unit morphology, interference, and recruitment patterns. In lower limbs, EMG demonstrated mild denervation by the way of a few fibrillations (1/4) and positive sharp waves (1/4) in distal muscles. There was a reduction in the recruitment and interference pattern of motor units and chronic motor unit remodeling changes to these muscles. Their amplitudes, duration, and polyphasia were within chronic neurogenic range. Thus, these studies were indicative of a severe ongoing on chronic denervating process of mainly cranial nerves and length dependent mild axonal neuropathy in the limbs.

Discussion

This patient was diagnosed as having type IV (FINNISH) FAP on the basis of clinical manifestations, positive amyloid deposition on biopsied tissues and electrophysiologic findings. Clinical features of FINNISH type FAP characterized with the combination of lattice corneal dystrophy and multiple cranial neuropathies (e.g., facial palsies, and bulbar weakness).[4] Onset of symptoms is usually in the third decade of life. Over time, a mild generalized sensorimotor polyneuropathy develops.

Type IV amyloidosis is caused by mutations in the gelsolin gene. The resultant mutations and amino acid substitutions are felt to lead to a charge change on the protein, which may render

the molecule resistant to proteases.[2] We could not perform genetic testing for this patient due to technical unavailability for FAP diseases in our country.

In type IV FAP, cranial nerves are mainly affected by the disturbance of sympathetic nervous system and axonal sensorimotor peripheral polyneuropathy in advanced stages. The clinical electrophysiological patterns in our patient are similar to that of FINNISH families with cranial neuropathy and corneal lattice dystrophy.[2]

Biopsy of abdominal fat tissues has been commonly employed for the histological diagnosis of familial amyloidosis, including FAP. Amyloid deposits in a multifocal or diffuse pattern in ganglia and peripheral nerves. Nerve histopathology of the different forms of FAP is similar showing fiber-length-dependent polyneuropathy, loss of myelinated nerves, particularly small myelinated and unmyelinated nerve fibers.[5] The deposits are located in the endoneurium and within blood vessel walls. Endoneurial amyloid deposits can be noxious to nerve fibers in several ways, including mechanical and toxic effects on nerve fibers and impairment of blood supply.[5] These deposits encroach upon the nerve fibers resulting in axonal degeneration and segmental demyelination.[2]

As suspected from the clinical features and histopathology, electrophysiologic studies reveal abnormalities consistent with a generalized or multifocal axonal sensorimotor polyneuropathy.[4]

SNAPs are diminished in amplitude and are normal or only mildly prolonged in latency or slow in conduction velocity. CMAPs can show similar findings in long-standing disease. Some forms of FAP are associated with carpal tunnel syndrome. Electromyography can demonstrate fibrillation potentials and positive sharp waves in the more distal weak limb muscles along with decreased recruitment of polyphasic, long-duration, large-amplitude MUAPs.[2]

With regard to treatment of FAP, liver transplantation has reportedly halted the progression of clinical manifestations. In recent years, many new therapeutic strategies have been proposed and several ongoing therapeutic trials involving, for instance, stabilizers of transthyretin tetramers (tafamidis and diflunisal) and gene therapies to suppress transthyretin expression.[6]

We reported the first type IV FAP (FINNISH) Iranian woman with neurological deficits, including rapidly progressive cranial neuropathies, mild sensorimotor axonal peripheral polyneuropathy, unilateral CTS, corneal lattice dystrophy, and orthostatic hypotension.

In 2010 Lüttmann RJ et al., reported the first German family with FINNISH type FAP. Their youngest, clinically symptomatic family member was 26 years old. All patients suffered from an often asymmetric but not severe facial palsy. The disease took a slow chronic progressive course.[4] In comparison, our case presented with rapidly progressive and severe clinical presentation, especially in the cranial region.

In the more advanced stages of the disease, most patients showed grossly enlarged protuberant lips and the clinical finding of cutis laxa. It is characterized by loose skin, which causes the patients to look older than their age.[7] Our patient showed loose facial skin, mostly in the lower eyelid, but we did not find clinically relevant cutis laxa in other parts.

Conclusion

The authors conclude that in any case of symptomatic progressive multiple cranial nerves involvement and electrodiagnostic evidence of polyneuropathy, FAP should be considered as differential diagnosis. Based on high accuracy of abdominal fat, rectal or nerve tissue histopathology, we encourage biopsies in countries where genetic testing is not available.

This case highlights one of the rare conditions causing neuropathy, presenting mainly with facial muscle wasting.

Conflict of Interest: None declared.

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