Concomitancy of mutation in FRDA gene and FMR1 premutation in 58 year-old woman

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Abstract

DNA testing broadens diagnostic tools available for hereditary ataxias. However, together with current knowledge of genes and their mutations crop up new phenotype figures of diseases already well known. Diagnostic problems in practice can consist in part due to the very similar symptoms of hereditary ataxias and acquaintance in or availability of new techniques such as DNA testing and result in misdiagnosis. We present a case study of a 57 year-old woman with both expansion of the triplet repetitive sequence of FRDA gene and a premutation in FMR1 gene. At present we diagnose her with Very Late Onset Friedreich´s ataxia, but we advise of possible combinations or aggravations of her symptoms due to manifestation of Fragile X premutation tremor/ataxia syndrome. In nontypical phenotypes of DNA verifying hereditary ataxias we recommend searching of comorbidity, specifically from a range of hereditary ataxias with very similar spectra of symptoms.

Abbreviation and units:

DNA	– Deoxyribonucleid acid	MEP	– Motor evoked potentials
FMR1	– Fragile site mental retardation 1 gene	CMCT	– Central motor conduction times
FRDA	– Friedreich's ataxia	SSEP	– Somatosensory evoked potentials
LOFA	– Late Onset Friedreich's Ataxia	PCR	– Polymerase Chain Reaction
VLOFA	– Very Late Onset Friedreich's Ataxia	m	– metre
CAG	– Cytosine Adenine Guanine	m.	– musculus
GAA	– Cytosine Adenine Adenine	s	– second
FXTAS	– Fragile X Premutation Tremor/Ataxia Syndrome	ms	– millisecond
ECG	– Electrocardiograph	uV	– microvolt

CASE REPORT

Introduction

Differential diagnosis of hereditary ataxias is very complex and includes a many diseases with identified genetic and/or biochemical defects [1,9,15,19,21]. Friedreich's ataxia (FRDA) is an autosomal recessive ataxia resulting from a mutation of FRDA gene on chromosome 9 [4]. FRDA is the most common inherited ataxia with a prevalence of between 1 and 2 per 100,000 and deduced carrier frequency of 1 in 120 in European populations [5]. FRDA is characterized by a progressive gait and limb ataxia, a lack of tendon reflexes in the legs, distal loss of proprioception and vibration, pyramidal weakness, extensor plantar responses, and dysarthria. Variable features include cardiomyopathy, scoliosis, pes cavus, optic atrophy, diabetes, and sensorineural deafness, all of which may be present [2,10,11]. Identification of the mutation responsible for Friedreich's ataxia has allowed the study of genotype-phenotype correlation. The initial classification, which discounted patients with onset after 25 years, has since been broadened. Patients with late onset Friedreich's ataxia (LOFA) [14], and very late onset Friedreich's ataxia (VLOFA) [17,18] have been identified. Both LOFA and VLOFA account for up to 25% of patients with FRDA. Since the identification of the first CAG repeat-expansion underlying spinocerebellar ataxia type 1 (SCA1) in 1993 [16], more than 25 additional gene loci have been found to be responsible for autosomal dominant inherited forms of SCA. At present, this recent knowledge enlarges differential diagnosis of a group of ataxia, or tremor with unexplained etiology. Fragile X premutation tremor/ataxia syndrome (FXTAS) is a new neurodegenerative disease, for the main, characterized by intention tremor and balance problems (gait ataxia) with/or peripheral neuropathy, mild parkinsonism, lower limb proximal muscle weakness, short-term memory loss, executive function deficits, cognitive decline, and autonomic dysfunction [6,7,13]. It has very similar clinical symptoms like other spinocerebellar ataxias. The frequency of the premutation is about 1 in 259 females and 1 in 810 males in the general population [20], identification of FXTAS frequency (in males) is not finished, and only case reports in female are mentioned in the literature [3,8]. We present a case study of a 57 year-old woman with both expansion of the triplet repetitive sequence of X25 gene and a premutation in the FMR1 gene.

Case Report

A 57 year-old woman, a younger daughter of non consanguineous parents.

Family history: Her father died at the age of 75 (a neoplasm of the brain), her mother at the age of 87 years, cachexy, profound visual impairment. Her sister, a 66 year-old, started to have problems with her gait from 48 years of age, has refused diagnostic investigations. Our patient has a son and a daughter, they are healthy.

Personal history: Delivery and post partum development were normal. No increased morbidity. At the age of 30 years cholecystectomy, in 1978 Caesarean section, 1982 appendectomy. From 2002 therapy for high blood pressure and thyreotoxicosis. Menses from 11 years of age, climacterical from 48 years of age. She was employed in a bank, now is an old-age pensioner.

Current illness: Patient noticed mild instability at age 49, however she had no limitations in daily life. She didn't seek medical advice. Her problems markedly increased in connection with the death of her husband in 2002 (55 years of age). Her gait was wide-based, and she fell sometimes. Her vision, hearing, and swallowing were intact, bladder and bowel functions were normal. Neurological examinations started in January 2003. At the time she was alert and oriented. Her speech was intelligible, only minimal dysarthria. Cranial nerves were intact, no nystagmus. Muscle strength and tone were normal, deep tendon reflexes C5–8 were quick, L2–4 high, L5–S2 present. She had an inconstant right Babinski sign. Ataxia with mild intention tremor of her right upper limb and lower limbs. No impairment of vibration sense and joint position sense, positive Romberg sign. Her gait was slightly wide based, aggravated by closing her eyes. She was able to walk on her toes, slightly worse on heels, without assistance.

Complete blood cell counts and routine chemistry test results were normal. The level of vitamin B12, and vitamin E were in the low normal range. Thyroid functions were stabilized by therapy.

Brain magnetic resonance imaging scans revealed two nonspecific supratentorial focuses of gliosis. Spinal cord magnetic resonance imaging showed bulging of disks L5–S1, spondylosis of cervical and lumbar vertebral column, degeneration of disks Th8–9, and L4–S1 with normal spinal cord size and signal.

No optic atrophy has been seen, visual evoked potentials were normal.

ECG findings were normal.

Psychological examinations revealed no cognitive impairment.

Conduction studies on motor and sensory nerves (2003) were normal on lower limbs (peroneal motor conduction velocity 50m/s, compound motor action potential amplitude 8,7 mV; sural motor conduction velocity 52 m/s, sensory nerve action potential amplitude 22uV). By contrast, motor evoked potentials (MEP) confirmed abnormality of central motor pathway for upper and more for lower limbs. Central motor conduction times (CMCT) for m. abductor digiti quinti were (dx/sin) 4,0/5,0 ms, for m. biceps brachii 5,4/5,6 ms, m. tibialis anterior 10,6/20,0 ms, and m. vastus medialis 8,6/8,4 ms.

Somatosensory evoked potentials (SSEP) revealed no pathology in 2003.

Examinations of cerebrospinal fluid (protein, glucose, cytology, isofocusing, virology, and antibody tests for CNS Lyme disease) were normal.

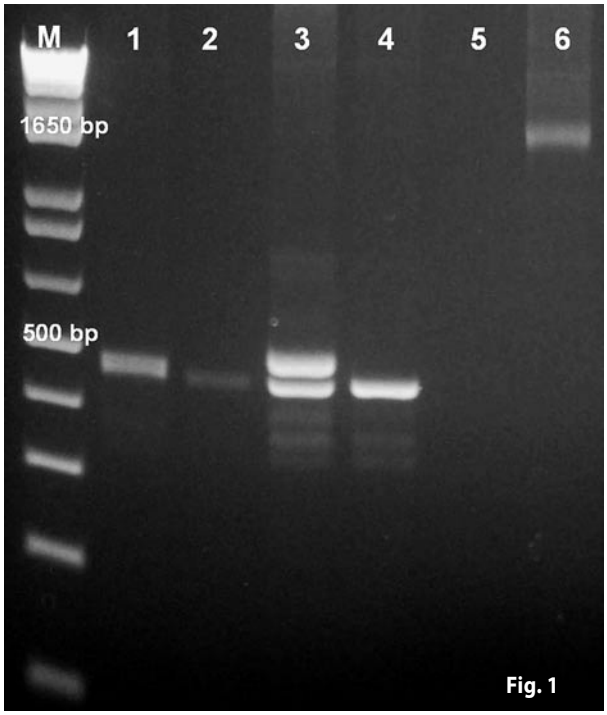

Figure 1: PCR analysis of GAA repeat in FRDA gene
M – marker, 1, 2, 3, 4 – normal, 5 – blank, 6 – our patient (homozygous GAA triplet expansion – approximately length of 400 repeats)

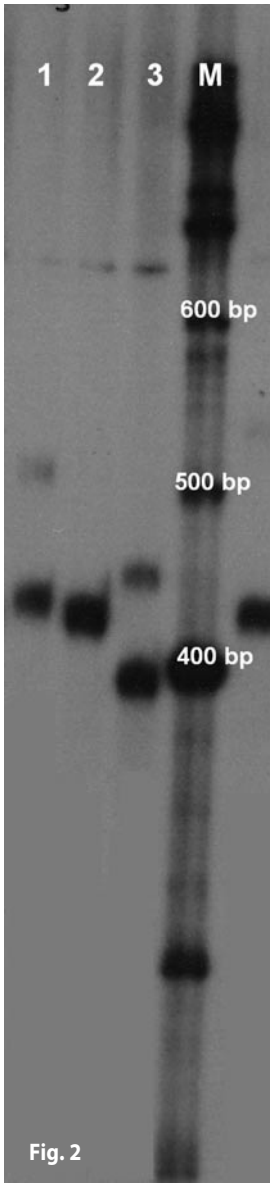

Figure 2: PCR analysis of CGG repeat in FMR1 gene
M - marker, 1 - our patient (62/35 CGG repeat), 2, 3 - normal

DNA testing for FRDA (July of 2003): DNA was isolated from blood leukocytes. $(GAA)_n$ repeat in intron 1 of the FRDA gene was amplified with GAAF and GAAR primers according to Campuzano et al, 1996 [4]. PCR products were separated in 2% agarose gel. *Homozygous GAA triplet repeat expansion was detected with approximately length of 400 repeats* (Fig. 1).

In 2004 slowly deteriorate ataxia and dysarthria of our patient. Deep tendon reflexes are retained, but vibration sense markedly decreased in lower limbs. She is uncooperative and disinterested in her treatment, including physiotherapy and further study.

DNA testing for fragile X: (December 2004; within the frame of screening of FXTAS in the set of patients with spinocerebellar ataxia): DNA was isolated from blood leukocytes. The size of CGG repeat was detected by polymerase chain reaction (PCR). PCR products were separated in 6% PAGE with urea and lengths of products were sized by Multianalyst software. *In our patient we detected heterozygous premutation in FMR1 gene in length of 62 CGG repeat.*

Discussion

We have examined a series of 490 patients from unrelated families receiving genetic testing because of idiopathic, progressive ataxia and inheritance compatible with autosomal recessive or sporadic disease. All patients were of Czech origin except 2 (of Slovak origin). 28 patients from the examined group (5,7%) were homozygous for a GAA triplet-repeat expansion in intron 1 of the FRDA gene. The age of onset has been observed to be between 4–20 years in 18 patients (64%), between 20–25 in 6 patients (21%), between 25–39 years in 3 patients (11,5%), and after 40 years in 1 patient. The last patient is the above mentioned woman with a rare Very Late Onset Friedreich´s ataxia and, at present, with unique concomitancy with premutation in the FMR1 gene. Her clinical progress as well as results of neuroimaging and electrophysiological methods accord with a diagnosis of VLOF, but in the future, we cannot exclude FXTAS signs due to her DNA test results. A combination of clinical symptoms especially radiological criterion for FXTAS will be important, that means we will look for symmetrical regions of increased T2 signal intensity in the middle cerebellar peduncles and adjacent cerebellar white matter [12]. Inherited ataxias represent one of the most heterogeneous groups of diseases in neurology. Advances in molecular genetics have led to identification of an increasing number of genes responsible for them. Their correlation of phenotype/genotype is in progress, so some of patients are denoted by atypical form. Following our observations we recommend considering and searching for comorbidity in nontypical phenotypes of DNA verifying hereditary ataxias, namely from a range of hereditary ataxias with very similar spectra of symptoms, because coexistence of them exists.

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