A Japanese Case of Fragile-X-Associated Tremor/ataxia Syndrome (FXTAS)

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Abstract

A 71-year-old man developed postural tremor and was treated as an essential tremor patient. Nine years after the tremor onset, he developed symptoms resembling Fragile-X-associated tremor/ataxia syndrome (FXTAS), including exacerbated (increased coarseness and amplitude) tremor in the right arm, ataxic gait, and brain MRI showed lesions in the bilateral middle cerebellar peduncles (MCP). Evidence of premutation in the form of 83 CGG repeats of the Fragile-X-mental retardation 1 (FMR1) gene confirmed the diagnosis of FXTAS. FXTAS causes various neurological symptoms including in some cases tremor resembling essential tremor in the early stages. FMR1 gene premutation should be checked when the patient develops intention tremor, cerebral dysfunction and/or a brain MRI shows MCP lesions.

Key words: fragile-X-associated tremor/ataxia syndrome (FXTAS), tremor, ataxia, fragile X mental retardation 1 (FMR1), premutation, middle cerebellar peduncles (MCP)

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Introduction

Fragile-X-associated tremor/ataxia syndrome (FXTAS) is a newly recognized disorder, and like Fragile X syndrome and premature ovarian failure (POF), it is an FMR1-associated disorder which causes various neurological symptoms such as intention tremor, ataxia, cognitive impairment, parkinsonism, peripheral neuropathy and autonomic dysfunction in adults with premutation (55-200 CGG repeats) of the Fragile-X-mental retardation 1 gene (FMR1) (1). It mostly affects middle-aged and elderly men of 50-70 years old; however, it also affects women (2, 3) and it is difficult to differentiate from neurological disorders such as Parkinson’s disease, essential tremor or multiple system atrophy (MSA) in some cases (4, 5). We have encountered a patient who had been receiving follow-up treatment as an essential tremor patient for nine years, but then developed the characteristic tremor. With the subsequent brain MRI indicating symptoms resembling FXTAS, we checked the FMR1 gene and found a CGG repeat increase, leading us to diagnose FXTAS. This is the first FXTAS diagnosis of a living patient in Japan; here we discuss this important case.

Case Report

A 71-year-old Japanese man was admitted to our hospital in February 2009, the major complaint being postural and action tremor. The postural tremor had started 8 years prior to the hospitalization, at the age of 63. The patient had been diagnosed with essential tremor at a clinic, which had improved with the administration of arotinolol hydrochloride. However, the tremor slowly progressed, and postural tremor started to develop in the left arm 3 years previously, at the age 68. Last year, at the age 70, the postural tremor in the right arm became more severe, with increased coarseness and amplitude, and brain MRI was taken to check for cerebrovascular disease in the cerebellum and the brainstem region. Since the T2-weighted and diffusion-weighted MRI showed high intensity lesions in the bilateral middle cerebellar peduncles (MCP), he was admitted to our hospital for further examination.

He had been diagnosed with high blood pressure at the age 65, and had been taking Ca-blockers ever since. Also,
Figure 1. The axial section of the T2-weighted brain MRI showed: A) high intensity signal lesions in the bilateral MCP and atrophy of the bilateral cerebellar hemisphere; B) T2 high-intensity signal lesions in the white matter around the periventricular area and diffused atrophy of the cortical hemispheres; and C) although the sagittal section of the T1-weighted image showed atrophy of the vermis, it was not clear whether the brain stem was atrophied.

his brother had Parkinson’s disease and a grandchild was suspected of mental retardation (MR).

There were no abnormalities in the general physical findings. Neurologically, he had a clear sensorium and mild dementia, with an HDS-R score of 18 points and an MMSE of 22 points. We observed action and slow (approximately 3 Hz) postural tremor in the right side of the body, at times resembling “signe de bretteur” and “hyperkinésie volontionnelle”. We also observed truncal dominant ataxia, ataxic gait, and ataxic speech. Muscle tonus and tendon reflexes in the extremities were normal with no pathological reflexes. There was no muscle weakness, sensory disturbance or autonomic dysfunction.

Blood cell counts, liver function, kidney function and thyroid function were within the normal range. We found neither an increase in very long chain fatty acids, nor abnormalities in the cerebrospinal fluid. Nerve conduction study values were within the normal range.

The T2-weighted and fluid-attenuated inversion recovery (FLAIR) brain MRI indicated high intensity lesions in the bilateral middle cerebellar peduncles (MCP) as well as multiple sporadic high intensity lesions in the cerebral white matter. In addition, atrophy was identified in the cerebral cortex, vermis and cerebellar hemisphere (Fig. 1). Cerebral blood flow SPECT showed no reduction of blood flow to the bilateral cerebellar hemispheres. PCR and hybridization showed expansion of the premutated FMR1 gene, and the number of repeats was determined with a genetic analyzer (6). The number of CGG repeats was 83 (normal and intermediate <55 repeats), showing abnormal expansion (Fig. 2), and thus the patient was diagnosed with FXTAS.

Upon the patient’s visit to the hospital, he was informed of the results and family history was checked again. He was found to have a grandchild with Fragile X syndrome and a grandson with attention deficit/hyperactivity disorder (ADHD) (Fig. 3).

Clonazepam (1 mg/day) was administered to treat the tremor, which by this time was disturbing daily activities; however, due to severe shakiness and difficulty walking, the medication was switched to primidone 500 mg/day (7) and arotinolol hydrochloride 20 mg/day, which reduced the tremor without disturbing daily activities. Since the continuous pharmacological treatment improved the tremor, the patient was treated as an outpatient.

Discussion

We referred to the diagnostic criteria proposed by Jacquemont et al in diagnosing the patient with definite FXTAS. Intention tremor and gait ataxia fulfilled the two major clinical criteria, while MCP lesions on the brain MRI fulfilled the one major radiological criterion, as well as the abnormal expansion of CGG repeats of the FMR1 gene meeting the molecular criteria (8). The presence of the minor signs of memory disorder, cerebral white matter lesions and diffused brain atrophy also confirmed our diagnosis.

Since FXTAS has various clinical phenotypes, it has been often diagnosed as essential tremor, Parkinson’s disease or multiple system atrophy. There are a few reports of cases where FXTAS has been diagnosed as essential tremor in the early stages, as in the current case (4, 9). In these cases, a brain MRI showing T2WI high intensity lesions in the bilateral MCP provided useful diagnostic evidence in differentiating from essential tremor. In addition, Peters et al reported that FXTAS might have different phenotypes within a family, citing a case where the elder brother had tremor resembling essential tremor while the younger brother had typical FXTAS symptoms like postural tremor, cerebellar disorder and bipolar disorder (10). Since the family history in our case indicated that the elder brother had Parkinson’s disease, this may also be an example of a variable phenotype of FXTAS within a family. Though the existence of MR in the grandsons is important as in the cases of ataxic symptoms and neurological signs of elderly patients, physicians should note that in some cases, the family purposely tries to hide the family history of the existence of MR.
Figure 2. Genetic diagnosis of FXTAS. A) Genomic DNA of the present patient was purified from peripheral blood samples. A polymerase chain reaction was performed using the genomic DNA sample and the sample was electrophoresed on 2% agarose gels and transferred to a nylon membrane. The membrane was hybridized with the biotin-labeled CGG oligomer. The membrane was exposed to X-ray film. Lane 1: fragile X syndrome, Lane 2: normal, Lane 3: FXTAS (present case). B) PCR products from the present case were detected around 470 base pairs, which is equivalent to 83 CGG using an ABI3130xl Genetic Analyzer.

Figure 3. Pedigree of the present case.

- There is a report on the occurrence of FMR1 premutation in patients with cerebellar ataxia, but not genetic cerebellar ataxia such as SCAs, Friedreich ataxia, or DRPLA. According to the report, the frequency of FMR1 premutation was 17/1,320 (1.3%) for men and 1/414 (0.24%) for women. In addition, FMR1 premutations are unlikely to be common in the essential tremor population (0/152). FMR1 premutation occurrence in patients with essential tremor, parkinsonism, or tremors such as MSA was 5/1,351 (0.37%) (11).

- The characteristic MRI symptoms were reported by Brunberg et al in their evaluation of the brain MRIs of 17 FXTAS cases with abnormal expansion of CGG repeats. They found T2WI high intensity signals in the bilateral MCP and cerebellar white matter (14/17, 15/17 respectively) and atrophy in pons, midbrain, cerebellar cortex, cerebrum and corpus callosum (12).

- This T2 high intensity lesion of the MCP is believed to be spongiosis of the deep cerebellar white matter and Bergmann gliosis. In addition, eosinophilic ubiquitin-positive intranuclear inclusion bodies were found in a large number of neurons and astrocytes in the cerebellum, corpus callosum and hippocampal girus, providing important information about histological changes involved in the pathogenesis of this syndrome (13, 14).

- Fragile X syndrome occurs when the number of CGG repeats at 5'UTR of the FMR1 gene exceed 200 (full mutation), which triggers methylation in the promoter region (15) and the subsequent silencing of the FMR1 gene, resulting in failure to produce the translational product FMR protein (16). Since FMR protein affects synaptic plasticity
through RNA transport and translation in the dendrite region (17), a deficit causes MR (18). On the other hand, when CGG repeats are between 55 and 200, this is generally called a premutation (PM), leading to CGG expansion in the next generation causing Fragile X syndrome especially via maternal CGG expansion. FXTAS mostly affects adult men possessing PM after middle age, indicating that PM causes an increase in FMR1 mRNA production, which with aging is toxic to neural and glial cells, and reaches "gain of function" (19, 20).

This is the first case in Japan where FXTAS was diagnosed in a living patient. In Europe and North America, there have been many reports about FXTAS following the report of Hagerman et al in 2001 (1); however, there have been no reports in Asia, or at least in Japan, to date. There are reports of prevalence levels of FXS -- FMR1 full mutation -- within the population of men with MR being from 0.8 (6) to 2.4% (21), which is lower than for the Caucasian man population with MR, with prevalence levels of 2.6-8.7% (22, 23). This suggests a lower prevalence of premutation alleles--one step prior to full mutation--, and thus a lower FXTAS prevalence rate. However, since there is a great difference in the number of reports about FXTAS published in western countries and Japan, it is highly possible that FXTAS may develop but may not be correctly diagnosed in Japan. We need to increase awareness of the existence of FXTAS, and stress the importance of checking for FMR1 premutation in patients above the age of 50 who present with tremor and cerebellar disorder when a T2-weighted MRI shows bilateral MCP lesions.

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