Case Reports in Neurology

Case Rep Neurol 2011;3:118–123
DOI: 10.1159/000328838

Published online:
May 24, 2011

ISSN 1662–680X
www.karger.com/crn

A Patient with Fragile X-Associated Tremor/Ataxia Syndrome Presenting with Executive Cognitive Deficits and Cerebral White Matter Lesions

Kensaku Kasuga Takeshi Ikeuchi Keiko Arakawa
Ryuji Yajima Takayoshi Tokutake Masatoyo Nishizawa

Department of Neurology, Brain Research Institute, Niigata University, Niigata, Japan

Key Words
CGG repeat expansion · Executive dysfunction · Fragile X-associated tremor/ataxia syndrome · Premutation · White matter lesion

Abstract
Fragile X-associated tremor/ataxia syndrome (FXTAS) is a late-onset neurodegenerative disorder that primarily affects males who are carriers of a premutation of a CGG expansion in the *FMR1* gene. In Asian populations, FXTAS has rarely been reported. Here, we report the case of a Japanese FXTAS patient who showed predominant executive cognitive deficits as the main feature of his disease. In contrast, the patient exhibited only very mild symptoms of intention tremor and ataxia, which did not interfere with daily activities. A gene analysis revealed that the patient carried a premutation of a CGG expansion (111 CGG repeats) in the *FMR1* gene. The mRNA expression level of *FMR1* in the patient was 1.5-fold higher than in controls. On brain MRI scans, fluid-attenuated inversion recovery images showed high-intensity lesions in the middle cerebellar peduncles and the cerebral white matter, with a frontal predominance. The present case extends previous notions regarding the cognitive impairment in FXTAS patients. Recognizing FXTAS patients with predominant cognitive impairment from various ethnic backgrounds would contribute to our understanding of the phenotypic variation of this disease.

Takeshi Ikeuchi, MD, PhD

Department of Neurology, Brain Research Institute, Niigata University
1 Asahimachi, Chuo-ku, Niigata 951-8585 (Japan)
Tel. +81 252 270 747, E-Mail ikeuchi@bri.niigata-u.ac.jp

Case Reports in Neurology
Case Rep Neurol 2011;3:118–123
DOI: 10.1159/000328838
Published online: May 24, 2011

ISSN 1662–680X
www.karger.com/crn

Introduction

Fragile X-associated tremor/ataxia syndrome (FXTAS) is a late-onset neurodegenerative disorder that primarily affects male carriers of a premutation expansion, ranging from 55 to 200 CGG repeats, in the *FMR1* gene [1, 2]. The main features of FXTAS are intention tremor and gait ataxia. Less distinctive symptoms include parkinsonism, peripheral neuropathy, and cognitive decline [3]. Here, we report the case of a Japanese patient with a CGG premutation expansion in the *FMR1* gene, who presented with predominant executive dysfunction and cerebral white matter lesions on MRI.

Case Report

A 59-year-old Japanese male patient first noticed occasional gait unsteadiness at the age of 44 years. The symptoms remained stable for a decade. There is no family history of mental retardation or neurological disease. His birth and early development were unremarkable. The patient gradually exhibited various cognitive symptoms including slowness in initiation and completion of simple tasks, excessive sleepiness during daytime, and poor concentration. He was referred to our hospital at the age of 59 years. On admission, detailed neuropsychological examinations were performed, the results of which are shown in **table 1**. General intellectual function, determined by the Wechsler Adult Intelligence Scale-III and Mini-Mental State Examination, was moderately impaired. The patient demonstrated poor performance in executive cognitive function tasks, examined by the Trail Making Test, Wisconsin Card Sorting Test, and Stroop test. His Frontal Assessment Battery score was also very low. Visual-spatial perception and language skills were preserved, and there were no signs of mood disorder or anxiety. On neurological examination, the patient showed mild intention tremor with terminal kinetic movement. His handwriting was well preserved. He showed mild truncal ataxia but was fully ambulant. There was no ataxia in his limbs, and muscle tendon reflexes in the extremities were attenuated. In addition, there was no sign of autonomic failure.

On brain MRI, fluid-attenuated inversion recovery images showed high-intensity lesions in the middle cerebellar peduncles (MCPs) (**fig. 1**a). Prominent cerebral white matter hyperintensities with a frontal predominance were also noted (fig. 1b, c). In addition, atrophy was observed in the cerebral cortex and cerebellar hemispheres. ^{99m}Tc-ethyl cysteinate dimer single-photon emission computed tomography revealed hypoperfusion in the cerebellum and the medial temporal lobe.

On the basis of these findings, we suspected that the patient suffered from FXTAS, although he exhibited minor motor symptoms and predominant cognitive symptoms. We determined the CGG repeat in the *FMR1* gene using genomic DNA extracted from peripheral blood leukocytes as previously reported [4]. PCR analysis showed that the patient carried a premutation of a CGG expansion (**fig. 2**a). The size of the premutation determined by a fluorescent-sequencer method was 111 CGG repeats (fig. 2b). We next examined the *FMR1* mRNA expression level in peripheral blood. SYBR green real-time PCR assay was performed as previously reported [5]. In our patient, the mRNA expression level of the *FMR1* gene, normalized to that of β-glucoronidase, was 1.5-fold higher than in 4 male healthy controls.

Discussion

According to diagnostic criteria [2, 3], the present case is defined as definite FXTAS, because the patient showed 2 clinical features (intention tremor and gait ataxia) as well as 1 major radiological finding (MCPs). However, motor dysfunction due to ataxia and tremor was very mild and did not interfere with activities of daily life. In contrast, the patient showed prominent executive cognitive deficits as the predominant feature of his disease.

Case Rep Neurol 2011;3:118–123
DOI: 10.1159/000328838
Published online: May 24, 2011

ISSN 1662–680X
www.karger.com/crn

In recent years, cognitive impairments in FXTAS patients have increasingly been investigated [6–8]. The cognitive phenotype of FXTAS is characterized by fronto-subcortical dementia with impairment of executive functioning [9, 10]. It is as yet unknown when cognitive impairment begins in relation to the neurological signs of FXTAS. Gonçalves et al. [11] reported the case of a 70-year-old patient with atypical FXTAS, who presented rapidly progressive dementia as the major symptom. We here showed that our Japanese FXTAS patient exhibited frontal and executive dysfunctions characterized by psychomotor slowness, bradyphrenia, distractibility as well as attention and concentration difficulties. Prominent hyperintensities in the cerebral white matter with a frontal dominance might be attributable to the development of these manifestations in the patient. These findings extend the previous notions regarding the cognitive impairment associated with FXTAS.

Asian patients with FXTAS have rarely been reported in the literature. The exact reason for this is currently unknown. Recently, Ishii et al. [12] reported the first Japanese FXTAS patient who was initially diagnosed with essential tremor. Recognizing FXTAS patients with predominant cognitive impairment would contribute to our understanding of the disease's phenotypic variation. Genetic testing should be considered in patients with unidentified causes of cognitive impairment, particularly when an MRI shows hyperintensities in the cerebral white matter and/or MCPs.

Acknowledgment

This study was supported in part by the Research Committee for Ataxic Diseases, the Ministry of Health, Labor and Welfare, Japan.

Disclosure Statement

The authors have no conflicts of interest to declare.

Case Rep Neurol 2011;3:118–123
DOI: 10.1159/000328838

Published online:
May 24, 2011

ISSN 1662–680X
www.karger.com/crn

Table 1. Neuropsychological test results of the patient

Test	Result
MMSE	23/30
WAIS-III	
Verbal IQ	81
Performance IQ	70
Total IQ	73
FAB	5/18
Trail Making Test	
Part A	210
Part B	744
Stroop test	
Word	41
Color	65
Interference	24
WCST	
Category achieved	0

MMSE = Mini-Mental State Examination; WAIS-III = Wechsler Adult Intelligence Scale, third edition; FAB = Frontal Assessment Battery; WCST = Wisconsin Card Sorting Test.

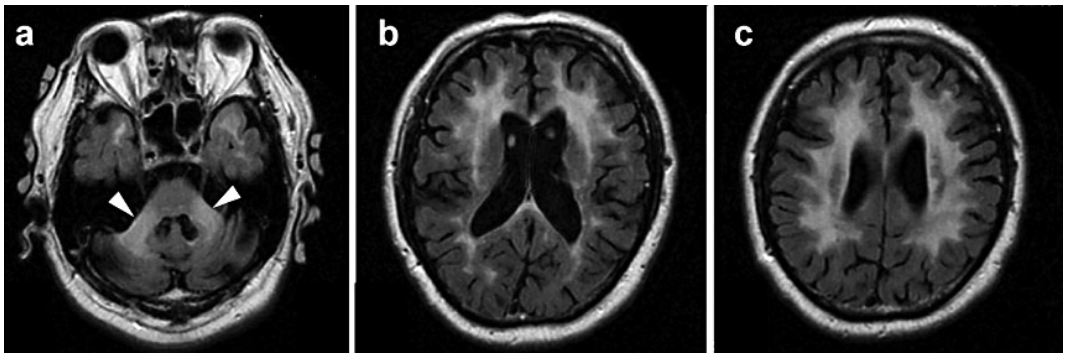

Fig. 1. MR images of the patient's brain. **a** An axial fluid-attenuated inversion recovery image shows high intensities in the bilateral MCPs, as indicated by arrowheads. In addition, atrophy in the pons, MCPs, and cerebellum can be identified. **b**, **c** Prominently increased signal intensities in the cerebral white matter as well as diffuse cortical atrophy can be observed.

Case Rep Neurol 2011;3:118–123
DOI: 10.1159/000328838

Published online:
May 24, 2011

ISSN 1662–680X
www.karger.com/crn

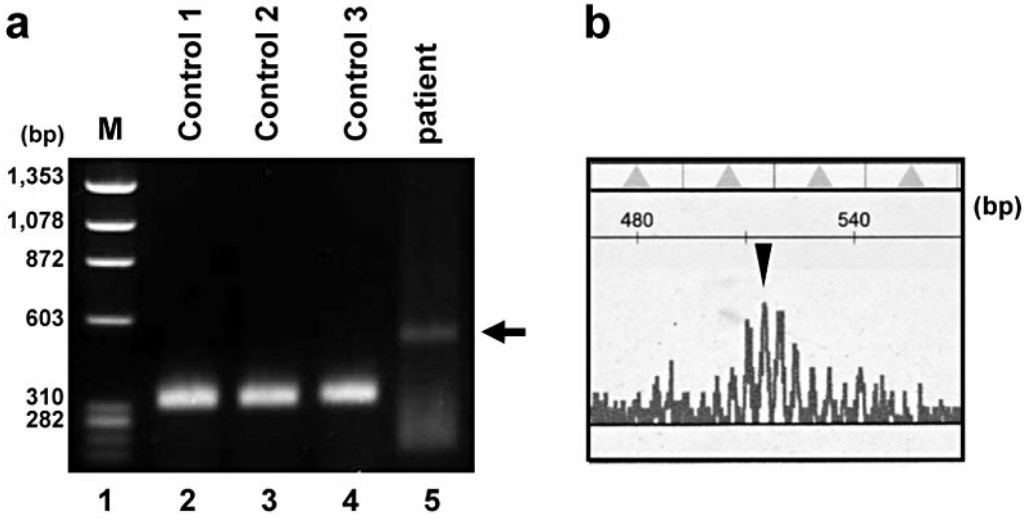

Fig. 2. Genetic molecular analysis of the *FMR1* gene. **a** PCR-amplified genomic DNA samples from male control subjects (lanes 2–4) and the patient (lane 5) were run on a 2% agarose gel and stained with ethidium bromide. In the patient's sample (lane 5), the PCR product containing the premutation of CGG repeats is shown (arrow). The DNA size marker (M, lane 1) is a mixture of λ-*Hin*dIII and ΦX174-*Hae*III digests. **b** The PCR product from the patient was further analyzed using an ABI3130x sequencer. The size of the premutation determined using GeneMapper software (version 4.0, Applied Biosystems) was 514 bp (arrowhead), which corresponds to approximately 111 CGG repeats.

References

1 Hagerman RJ, Leehey M, Heinrichs W, Tassone F, Wilson R, Hills J, Grigsby J, Gage B, Hagerman PJ: Intention tremor, parkinsonism, and generalized brain atrophy in male carriers of fragile X. Neurology 2001;57:127–130.

2 Berry-Kravis E, Abrams L, Coffey SM, Hall DA, Greco C, Gane LW, Grigsby J, Bourgeois DA, Finucane B, Jacquemont S, Brunberg JA, Zhang L, Lin J, Tassone F, Hagerman PJ, Hagerman RJ, Leehey MA: Fragile X-associated tremor/ataxia syndrome: clinical features, genetics, and testing guidelines. Mov Disord 2007;22:2018–2030.

3 Jacquemout S, Hagerman RJ, Leehey M, Grigsby J, Zhang L, Brunberg JA, Greco C, des Portes V, Jardini T, Levine R, Berry-Kravis E, Brown WT, Schaeffer S, Kissel J, Tassone F, Hagerman PJ: Fragile X permutation tremor/ataxia syndrome: molecular, clinical, and neuroimaging correlates. Am J Hum Genet 2003;72:869–878.

4 Saluto A, Brussino A, Tassone F, Arduino C, Cagnoli C, Pappi P, Hagerman P, Migone N, Brusco A: An enhanced polymerase chain reaction assay to detect pre- and full mutation alleles of the *fragile X mental retardation 1* gene. J Mol Diagn 2005;7:605–612.

5 Tassone F, Hagerman RJ, Taylor AK, Gane LW, Godfrey TE, Hagerman PJ: Elevated levels of *FMR1* mRNA in carrier males: a new mechanism of involvement in the fragile-X syndrome. Am J Hum Genet 2000;66:6–15.

6 Bourgeois J, Coffey S, Rivera SM, Hessl D, Gane LW, Tassone F, Greco C, Finucane B, Lelson L, Berry-Kravis E, Grigsby J, Hagerman PJ, Hagerman RJ: Fragile X premutation disorders – expanding the psychiatric perspective. J Clin Psychiatr 2009;70:852–862.

7 Grigsby J, Brega AG, Jacquemont S, Loesch D, Leehey MA, Goodrich GK, Hagerman RJ, Epstein J, Wilson R, Cogswell JB, Jardini T, Tassone F, Hagerman P: Impairment in the cognitive functioning of men with fragile X-associated tremor/ataxia syndrome (FXTAS). J Neurol Sci 2006;248:227–233.

Case Rep Neurol 2011;3:118–123
DOI: 10.1159/000328838

Published online:
May 24, 2011

ISSN 1662–680X
www.karger.com/crn

8 Bourgeois JA, Cogswell JB, Hessl D, Zhang L, Ono MY, Tassone F, Farzin F, Brunberg JA, Grigsby J, Hagerman RJ: Cognitive, anxiety and mood disorders in the fragile X-associated tremor/ataxia syndrome. Gen Hosp Psychiatry 2007;29:349–356.

9 Bacalman S, Farzin F, Bourgeois JA, Cogswell J, Goodlin-Jones BL, Gane LW, Grigsby J, Leehey MA, Tassone F, Hagerman RJ: Psychiatric phenotype of the fragile-X-associated tremor/ataxia syndrome (FXTAS) in males: newly described fronto-subcortical dementia. J Clin Psychiatry 2006;67:87–94.

10 Grigsby J, Brega AG, Leehey MA, Goodrich GK, Jacquemont S, Loesch DZ, Cogswell JB, Epstein J, Wilson R, Jardini T, Gould E, Bennett RE, Hessl D, Cohen S, Cook K, Tassone F, Hagerman PJ, Hagerman RJ: Impairment of executive cognitive functioning in males with fragile X-associated tremor/ataxia syndrome. Mov Disord 2007;22:645–650.

11 Gonçalves MR, Capelli LP, Nitrini R, Barbosa ER, Porto CS, Lucato LT, Vianna-Morgante AM: Atypical clinical course of FXTAS: rapidly progressive dementia as the major symptoms. Neurology 2007;68:1864–1866.

12 Ishii K, Hosaka A, Adachi K, Tamaoka A: A Japanese case of fragile-X-associated tremor/ataxia syndrome (FXTAS). Intern Med 2010;49:1205–1208.