Neurology Asia 2014; 19(1) : 99 – 103

The first case report of fragile X-associated tremor ataxia syndrome in the Republic of Korea

Gwanhee Ehm *MD*, Hui-Jun Yang *MD*, Han-Joon Kim *MD PhD*, Beom Seok Jeon *MD PhD*

Department of Neurology and Movement Disorder Center, Parkinson study group, and Neuroscience Research Institute, College of Medicine, Seoul National University, Seoul, Korea.

Abstract

We present the first case report of fragile X-associated tremor ataxia syndrome (FXTAS) in the Republic of Korea. A 75-year-old male developed progressive gait ataxia, parkinsonism, and a mood disorder. Magnetic resonance imaging revealed T2 high signal intensity within the middle cerebellar peduncles. Analysis of the fragile X mental retardation 1 gene revealed a CGG trinucleotide repeat number of 136. FXTAS should be considered when a patient has atypical parkinsonism, cerebellar ataxia, and specific MRI abnormalities.

INTRODUCTION

Fragile X-associated tremor ataxia syndrome (FXTAS) is a progressive degenerative disorder which manifests in the form of cognitive decline, emotional lability, and movement disorders. FXTAS was first reported in 2001 by Hagerman *et al* who reported on five patients with fragile X premutation who had progressive intention tremor, executive dysfunction, and generalized brain atrophy.[1] Following this initial report of this relatively new disease entity, many reports of patients with FXTAS have ensued worldwide. Until now, though, no cases of FXTAS have been reported in the Republic of Korea.

CASE REPORT

A 75-year-old male presented with rest tremor in his right hand, which he reported experiencing since the age of 69; the tremor gradually progressed to involve the left hand as well. At age 73, he was diagnosed with a major depressive disorder, which a psychiatrist managed using mirtazapine, lorazepam, and bupropion. His medical record revealed no dopamine blocking agents. His highest level of education was middle school and his min-mental state examination (MMSE) score was 27/30. He had masked facies, a monotonous and high-pitched squeaky voice, bilateral 3-5 Hz rest tremor with greater amplitude in the right hand, and a subtle postural upper extremity tremor. Upon examination, subtle slowness and a diminished amplitude of finger-tapping were observed in both hands. Rigidity in all limbs was negligible. The finger-to-nose test showed that he had a mild terminal tremor in his left hand with subtle dysmetria. Rapid alternating movement of the hands showed mild dysdiadochokinesia. He had a wide-based gait when walking and staggered when turning. The patellar tendon reflex in both knees was decreased. He complained of urinary frequency and nocturia since age 70; however, urinary incontinence was absent. He also complained of orthostatic dizziness, although he tested within the normal range for orthostatic hypotension. He has a single unmarried daughter who, as reported by the patient, underwent normal developmental milestones and has normal intellectual function. She was diagnosed with bipolar disorder at another hospital and was not available for interview or examination. Video-oculography revealed cogwheeling in smooth pursuit and hypometric horizontal saccades. A 18F-FP-CIT positron emission tomography (PET) scan showed preserved dopamine transporter density, and a magnetic resonance image (MRI) was marked with diffuse cerebral atrophy, cerebellar atrophy, and T2 high signal intensity within both of the middle cerebellar peduncles (Figure 1). Gene tests for SCA1, 2, 3, 6, 7, and 17 were negative and the patient's fragile X mental retardation 1 (FMR1) gene CGG repeat number was 136, which corresponded to a premutation range (55-200 repeats) using polymerase chain reaction and Southern blot.

DISCUSSION

We report the first case of FXTAS in the Republic of Korea. FXTAS is an adult-onset

Address correspondence to: Beom Seok Jeon, Department of Neurology, College of Medicine, Seoul National University, 28 Yongon-dong, Chongno-gu, Seoul, 110-744, Korea. Tel: +82-2-2072-2876, Fax: +82-2-3672-7553, e-mail: brain@snu.ac.kr

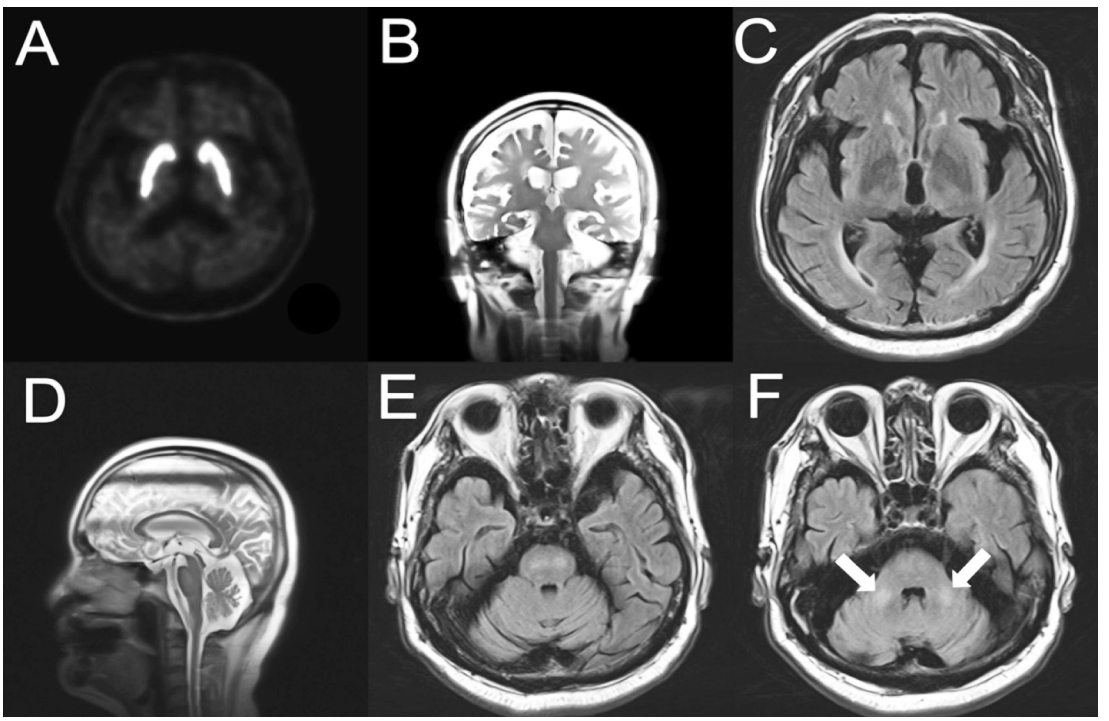

Figure 1. FP-CIT PET shows normal presynaptic uptake (A). Brain MRI reveals diffuse cerebral atrophy and subsequent prominent subarachnoid space (B, C). Cerebellar atrophy and pontine T2 high signal intensity are remarkable (D, E). T2 high signal intensity is observed in the bilateral middle cerebellar peduncles (F).

neurodegenerative disorder that affects carriers of the CGG trinucleotide repeat expansion of the FMR1 gene in the premutation range (55-200).[2] A CGG repeat size between 55 and 200 triplets is considered premutation because it can expand to full mutation (>200). The full mutation of FMR1 leads to hypermethylation and transcriptional silencing of the FMR1 gene and the absence of the corresponding mRNA and protein products, fragile X mental retardation protein (FMRP), which is an important modulator of neural development and synaptic plasticity. However, premutation carriers have elevated FMR1 mRNA levels. The excess mRNA causes a neurotoxic gain-of-function effect which is very different mechanistically relative to what occurs in full mutation carriers.[3]

The principle clinical features of FXTAS include intention tremor and cerebellar gait ataxia. The diagnostic criteria for FXTAS were proposed by Jacquemont *et al*. based on clinical and radiological findings.[4] The onset usually occurs in the sixth decade with tremor as an initial symptom; the penetrance is age-dependent, affecting 30%-40% of male carriers over 50 years of age.[4-6] Individuals with small premutation alleles (<70 CGG repeats) are much less likely to develop FXTAS.[7] Several studies have identified a broad spectrum of neurological involvement and psychotic symptoms that do not meet the criteria for FXTAS, such as peripheral neuropathy, prominent paraparesis, hyperreflexia, autism, hyperactivity, perseverative behaviors, tactile defensiveness, and an increased prevalence of seizures.[8-13] Cognitive decline can be seen across the lifespan of premutation carriers without FXTAS. Specific executive dysfunction and memory deficits have been reported as well, including poor inhibitory control, working memory deficit, and poor planning skills. It has been suggested that these early cognitive deficits may herald later onset of FXTAS.[11]

It is currently unclear who should undergo genetic analysis for the FMR1 premutation. The prevalence of the FMR1 premutation in the general Caucasian population is approximately 1 in 800 men and 1 in 250 women.[14] If the penetrance rate – 30%-40% for males over age 50 – is universally applicable, FXTAS may affect as many as 1 in 3,000 men over age 50, although ethnic genetic variability exists. Studies on FMR1 premutation screening with Japanese and Singaporean cohorts revealed no premutation among 824 and 200 unrelated individuals within the normal population, respectively.[15,16] A

Table 1: Results of screening of movement disorder patients for FMR1 expansion

Cohort	Ethnicity	Prevalence of premutation range expansion		Investigators
Sporadic ataxia				
142 male patients	Caucasian (Italian)	3/142	2.1%	Cellini, 2006[9]
143 male patients, age >50	Caucasian (Italian)	6/143	4.2%	Brussino, 2005[21]
122 male patients, age >50	Caucasian (Belgian)	5/122	4.1%	Esch, 2005[22]
55 patients (30 male, 25 female)	Asian	0/55	0	Tan, 2004[16]
59 male patients	Caucasian (UK)	3/59	5.1%	Macpherson, 2003[23]
Multiple system atrophy				
77 patients (36 male, 41 female)	Asian (Japanese)	0/77	0	Yabe, 2004[24]
507 patients (253 male, 254 female)	Caucasian (European)	4/507 (2 men, 2 women)	0.94%	Kamm, 2005[25]
65 patients (40 male, 25 female)	Caucasian (US)	0/65	0	Garland, 2004[26]
15 patients (12 male, 3 female)	Asian	0/15	0	Tan, 2004[16]
Parkinsonism				
903 male Parkinson's disease patients	Caucasian (Italian)	3/903	0.33%	Kraff, 2007[27]
137 male Parkinson's disease patients	Caucasian (European)	0/137	0	Kurz, 2007[28]
389 male Parkinson's disease patients	Caucasian (European)	0/389	0	Toft, 2004[29]
203 male Parkinson's disease patients	Caucasian (Italian)	0/203	0	Annesi, 2004[30]
595 female Parkinson's disease patients	Caucasian (Italian)	2/595	0.34%	Cilia, 2009[31]
228 male Parkinsonian syndrome patients	Caucasian (Australian)	4/228	1.75%	Loesch, 2009[32]
66 males with ataxia, tremor, parkinsonism, age > 45	Brazilian	0/66	0	Reis, 2008[33]
121 Parkinson's disease patients (65.2% male)	Asian	0/121	0	Tan, 2004[16]
216 male Parkinson's disease patients	Caucasian (US)	0/216	0	Deng, 2004[34]
Essential tremor				
71 patients (34 male, 37 female)	Asian	0/71	0	Tan, 2004[16]
81 patients (40 male, 41 female)	Caucasian (US)	0/81	0	Garcia Arocena, 2004[35]
196 male patients	Caucasian (US)	0/196	0	Deng, 2004[34]

number of studies have screened patient cohorts experiencing sporadic ataxia, multiple system atrophy, essential tremor, and parkinsonism whose clinical features may be similar to the FXTAS phenotype (Table 1). According to the results of the studies, the cohort experiencing sporadic ataxia showed approximately a 5% prevalence of FMR1 premutation carriers. However, instances of FMR1 premutation in the multiple system atrophy, parkinsonism, and essential tremor cohorts were very rare. Along with these results, Hall *et al*. proposed phenotypic groups recommended for the FMR1 gene.[17] Another diagnostic consideration is scans without evidence of dopaminergic deficit (SWEDD) in parkinsonian patients, as is the case with our patient. Hall *et al*. reported a premutation carrier with normal beta-CIT SPECT, suggesting that, unlike in Parkinson's disease, FXTAS-related parkinsonism may not be related to a presynaptic dopamine deficit[18], although another study reported reduced presynaptic uptake using beta-CIT SPECT.[19]

FXTAS is a relatively newly identified and recognized neurodegenerative disorder having a broad clinical presentation. Accordingly, its clinical diagnostic criteria and recommendation guidelines for genetic testing continue to be revised.[20] Our patient has unilateral rest tremor rather than intention tremor as the initial motor symptom, and does not show cognitive decline. Awareness of the variable clinical features of FXTAS is paramount for clinicians when choosing candidates for a FMR1 test.

DISCLOSURE

Conflict of interest: None

REFERENCES

1. Hagerman RJ, Leehey M, Heinrichs W, *et al.* Intention tremor, parkinsonism, and generalized brain atrophy in male carriers of fragile X. *Neurology* 2001; 57(1):127-30.
2. Leehey MA, Berry-Kravis E, Min SJ, *et al.* Progression of tremor and ataxia in male carriers of the FMR1 premutation. *Mov Disord* 2007; 22(2):203-6.
3. Hall DA, O'Keefe J A. Fragile x-associated tremor ataxia syndrome: the expanding clinical picture, pathophysiology, epidemiology, and update on treatment. *Tremor Other Hyperkinet Mov (N Y)* 2012;2.
4. Jacquemont S, Hagerman RJ, Leehey M, *et al.* Fragile X premutation tremor/ataxia syndrome: molecular, clinical, and neuroimaging correlates. *Am J Hum Genet* 2003; 72(4):869-78.
5. Jacquemont S, Leehey MA, Hagerman RJ, Beckett LA, Hagerman PJ. Size bias of fragile X premutation alleles in late-onset movement disorders. *J Med Genet* 2006; 43(10):804-9.
6. Milunsky JM, Maher TA. Fragile X carrier screening and spinocerebellar ataxia in older males. *Am J Med Genet A* 2004; 125A(3):320.
7. Leehey MA, Berry-Kravis E, Goetz CG, *et al.* FMR1 CGG repeat length predicts motor dysfunction in premutation carriers. *Neurology* 2008; 70(16 Pt 2):1397-402.
8. Bailey DB, Jr., Raspa M, Olmsted M, Holiday DB. Co-occurring conditions associated with FMR1 gene variations: findings from a national parent survey. *Am J Med Genet A* 2008; 146A(16):2060-9.
9. Cellini E, Forleo P, Ginestroni A, *et al.* Fragile X premutation with atypical symptoms at onset. *Arch Neurol* 2006; 63(8):1135-8.
10. Chonchaiya W, Utari A, Pereira GM, Tassone F, Hessl D, Hagerman RJ. Broad clinical involvement in a family affected by the fragile X premutation. *J Dev Behav Pediatr* 2009; 30(6):544-51.
11. Cornish KM, Kogan CS, Li L, Turk J, Jacquemont S, Hagerman RJ. Lifespan changes in working memory in fragile X premutation males. *Brain Cogn* 2009; 69(3):551-8.
12. Hagerman RJ, Coffey SM, Maselli R, *et al.* Neuropathy as a presenting feature in fragile X-associated tremor/ataxia syndrome. *Am J Med Genet A* 2007; 143A(19):2256-60.
13. Moore CJ, Daly EM, Schmitz N, *et al.* A neuropsychological investigation of male premutation carriers of fragile X syndrome. *Neuropsychologia* 2004; 42(14):1934-47.
14. Dombrowski C, Levesque S, Morel ML, Rouillard P, Morgan K, Rousseau F. Premutation and intermediate-size FMR1 alleles in 10572 males from the general population: loss of an AGG interruption is a late event in the generation of fragile X syndrome alleles. *Hum Mol Genet* 2002; 11(4):371-8.
15. Arinami T, Asano M, Kobayashi K, Yanagi H, Hamaguchi H. Data on the CGG repeat at the fragile X site in the non-retarded Japanese population and family suggest the presence of a subgroup of normal alleles predisposing to mutate. *Hum Genet* 1993; 92(5):431-6.
16. Tan EK, Zhao Y, Puong KY, *et al.* Fragile X premutation alleles in SCA, ET, and parkinsonism in an Asian cohort. *Neurology* 2004; 63(2):362-3.
17. Hall DA, Berry-Kravis E, Jacquemont S, *et al.* Initial diagnoses given to persons with the fragile X associated tremor/ataxia syndrome (FXTAS). *Neurology* 2005; 65(2):299-301.
18. Hall DA, Jennings D, Seibyl J, Tassone F, Marek K. FMR1 gene expansion and scans without evidence of dopaminergic deficits in parkinsonism patients. *Parkinsonism Relat Disord* 2010; 16(9):608-11.
19. Zuhlke C, Budnik A, Gehlken U, *et al.* FMR1 premutation as a rare cause of late onset ataxia--evidence for FXTAS in female carriers. *J Neurol* 2004; 251(11):1418-9.
20. Apartis E, Blancher A, Meissner WG, *et al.* FXTAS: new insights and the need for revised diagnostic criteria. *Neurology* 2012; 79(18):1898-907.
21. Brussino A, Gellera C, Saluto A, *et al.* FMR1 gene

premutation is a frequent genetic cause of late-onset sporadic cerebellar ataxia. *Neurology* 2005; 64(1):145-7.
22. Van Esch H, Dom R, Bex D, *et al*. Screening for FMR-1 premutations in 122 older Flemish males presenting with ataxia. *Eur J Hum Genet* 2005; 13(1):121-3.
23. Macpherson J, Waghorn A, Hammans S, Jacobs P. Observation of an excess of fragile-X premutations in a population of males referred with spinocerebellar ataxia. *Hum Genet* 2003; 112(5-6):619-20.
24. Yabe I, Soma H, Takei A, Fujik N, Sasaki H. No association between FMR1 premutations and multiple system atrophy. *J Neurol* 2004; 251(11):1411-2.
25. Kamm C, Healy DG, Quinn NP, *et al*. The fragile X tremor ataxia syndrome in the differential diagnosis of multiple system atrophy: data from the EMSA Study Group. *Brain* 2005; 128(Pt 8):1855-60.
26. Garland EM, Vnencak-Jones CL, Biaggioni I, Davis TL, Montine TJ, Robertson D. Fragile X gene premutation in multiple system atrophy. *J Neurol Sci* 2004; 227(1):115-8.
27. Kraff J, Tang HT, Cilia R, *et al*. Screen for excess FMR1 premutation alleles among males with parkinsonism. *Arch Neurol* 2007; 64(7):1002-6.
28. Kurz MW, Schlitter AM, Klenk Y, *et al*. FMR1 alleles in Parkinson‘s disease: relation to cognitive decline and hallucinations, a longitudinal study. *J Geriatr Psychiatry Neurol* 2007; 20(2):89-92.
29. Toft M, Aasly J. The genetics of Parkinson disease. *Tidsskr Nor Laegeforen* 2004; 124(7):922-4.
30. Annesi G, Nicoletti G, Tarantino P*, et al*. FRAXE intermediate alleles are associated with Parkinson’s disease. *Neurosci Lett* 2004; 368(1):21-4.
31. Cilia R, Kraff J, Canesi M, *et al*. Screening for the presence of FMR1 premutation alleles in women with parkinsonism. *Arch Neurol* 2009; 66(2):244-9.
32. Loesch DZ, Khaniani MS, Slater HR, *et al*. Small CGG repeat expansion alleles of FMR1 gene are associated with parkinsonism. *Clin Genet* 2009; 76(5):471-6.
33. Reis AH, Ferreira AC, Gomes KB, *et al*. Frequency of FMR1 premutation in individuals with ataxia and/or tremor and/or parkinsonism. *Genet Mol Res* 2008; 7(1):74-84.
34. Deng H, Le W, Jankovic J. Premutation alleles associated with Parkinson disease and essential tremor. *JAMA* 2004; 292(14):1685-6.
35. Garcia Arocena D, Louis ED, Tassone F, *et al*. Screen for expanded FMR1 alleles in patients with essential tremor. *Mov Disord* 2004; 19(8):930-3.