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Dystonia in a female fragile X premutation carrier: a case report

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Fragile X-associated tremor ataxia syndrome (FXTAS) is the most common neurological manifestation described in carriers of a premutation expansion (55–200 CGG repeats) of the fragile X mental retardation 1 (FMR1) gene[1]. FXTAS affects mainly men, partially because of a protective effect of the second X chromosome in females[1]. Female carriers often develop FMR1-related primary ovarian insufficiency but movement disorder phenotypes other than FXTAS have rarely been described[1]. Here, we report a female carrying the FMR1 premutation who presented in our clinic with cervical dystonia as the main symptom.

CASE REPORT

This 59-year-old woman was referred to our movement disorders clinic because of progressive head tremor since age 58. She had a son aged 29 years old with fragile-X syndrome and she had been found to be a carrier of the premutation expansion of the FMR1 gene in the family screening. She was not on any medication. The neurological examination showed mild saccadic intrusions in slow pursuit movements and a “no-no” head tremor with right torticollis. Gait was normal and there were no other cerebellar signs including intention tremor (Video 1). She did not report any sensory trick for her dystonia. Laboratory tests, including ceruloplasmin, copper, ferritin and thyroid function, were normal. Genetic testing revealed 90 CGG repeats in the FMR1 gene. Brain MRI showed no abnormalities in cerebellum, middle cerebellar peduncles (MCP) or corpus callosum in FLAIR, diffusion tensor imaging or fractional anisotropy (Figure 1). No specific treatment was started, as she did not report a significant impact of her symptoms in her daily life.

DISCUSSION

We herein report a female FMR1 premutation carrier who presented with cervical dystonia as the main clinical phenotype in whom other secondary causes of dystonia were excluded.

Since the initial description, an increasing number of women with FXTAS have been identified, but there are very few reports of female FMR1 premutation carriers presenting with dystonia. A small case series has suggested that dystonia and bruxism present more commonly in female FMR1 premutation carriers than in the general population and a prevalence of 35% (8 out of 23 female carriers) for dystonia compared to 0.73% ($p < 0.01$) has also been reported[2]. Of those with dystonia, only four presented with cervical involvement[2]. A case of oromandibular dystonia in a patient carrying the FMR1 premutation has also been reported[3] and only one female patient with FXTAS diagnosis who presented with cervical and laryngeal dystonia has been published to date[4].

Our patient did not meet criteria for FXTAS[1]. Therefore, our report contributes to the previous literature emphasizing that dystonia should be included in the spectrum of clinical manifestations in FMR1 premutation carriers. That is of interest as dystonia is not included in the diagnostic criteria of FXTAS and could potentially be another etiology of the tremor seen in FXTAS[5].

Premutation carriers have slightly reduced FMR1 protein levels with significant elevation of FMR1 messenger RNA (mRNA) and a potential toxic effect in brain white matter and motor fiber tracts has been proposed[6,7]. Pathophysiologic findings in patients with FXTAS include marked dropout of Purkinje cells and white matter disease throughout the cerebellum, including the MCP[8]. Typical neuroimaging findings in patients with FXTAS include brain and cerebellar atrophy and white matter tracts changes with involvement of the MCP known as the MCP sign[6]. Radiological abnormalities in thalamus, basal ganglia and the splenium of the corpus callosum have also been reported[9]. However, radiologic findings are milder in female premutation carriers as compared with males and white matter hyperintensities in the splenium and genu of corpus callosum are more frequent than the MCP sign[5].

Recent studies have suggested that alterations in activity, connectivity and structure of the cerebellum may play a role in the development of dystonia. There is evidence supporting that cerebellar atrophy, cerebellar degenerative disease, cerebellar lesions and histopathological alterations such as Purkinje cell loss or dentate nucleus cell loss may be associated with dystonia[10]. One could argue that abnormalities in the cerebellum and its connections with the basal ganglia and motor cortex may be involved in the development

of dystonia in patients with the FMR1 premutation. Our patient did not display abnormalities in the neuroimaging studies, which is in concordance with the previous mentioned low rate of brain MRI abnormalities in females. However, it could be suggested that dystonia is a manifestation secondary to a cerebellar dysfunction occurring without neuroimaging evidence of the disease or even before neuroimaging abnormalities occur. Further follow-up is warranted to assess clinical and neuroimaging disease progression in those patients.

In conclusion, our case supports the previous suggestion that dystonia can be part of the clinical spectrum of females carrying a premutation expansion in the FMR1 gene and that FMR1 premutation-sized repeat expansions should be added to the differential diagnosis of craniocervical dystonia in females. However, larger studies are needed to confirm this clinical observation.

Author Roles:

(1) Research Project: A. Conception, B. Organization, C. Execution; (2) Statistical Analysis: A. Design, B. Execution,C. Review and Critique; (3) Manuscript: A. Writing of the First Draft, B. Review and Critique.

1. VRC: 1A, 1B, 1C, 3A
2. AL: 1C, 3A, 3B
3. JAL: 1C, 3B
4. JCMC: 3B
5. KB: 1A, 3B
6. IP: 1A, 1B, 3A, 3B

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Ethical Compliance Statement

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines. The authors confirm that the approval of an institutional review board was not required for this work. Oral informed consent was obtained from the patient.

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Legend

Figure 1. Brain MRI showing no abnormalities in cerebellum and middle cerebellar peduncules in FLAIR (A), corpus callosum in sagittal FLAIR (B)

and diffusion tensor imaging with tractography (C) or fractional anisotropy (D).

Video

Video 1. Segment 1: “No-no” head tremor with right torticollis. Segment 2. Finger to nose test with no cerebellar signs. Segment 3. Normal tandem walking test. Segment 4. Null point: tremor is alleviated when head is turned completely to the right.