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SHORT REPORT

POLG-Associated Ataxia Presenting as a Fragile X Tremor/Ataxia Phenocopy Syndrome

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Abstract Hyperintensities in the middle cerebellar peduncles (MCP), known as the MCP sign, and progressive late-onset ataxia constitute major characteristics of the fragile X tremor/ataxia syndrome (FXTAS). Here, we describe a 60-year-old male affected by ataxia due to biallelic mutations in the mitochondrial polymerase gamma (POLG) gene in which hyperintensities of the middle cerebellar peduncles (MCP) were found. The initial suspicion of FXTAS was however ruled out by a normal CGG expansion size in the *FMR1* gene. We discuss the features of late-onset POLG-A as a phenocopy of FXTAS.

Keywords FXTAS · POLG · MCP sign

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Abbreviations

FXTAS	Fragile X tremor/ataxia syndrome
POLG-A	POLG-associated ataxia
MCP	Middle cerebellar peduncles
MSA	Multiple system atrophy

Background

Pathological CGG expansions in exon 1 of the *FMR1* cause three different phenotypes: fragile X syndrome, fragile X tremor/ataxia syndrome (FXTAS), and *FMR1*-related primary ovarian insufficiency (POI). Mutations in the catalytic subunit of mitochondrial DNA polymerase gamma (POLG) are the most common cause of mitochondrial disease [1]. Hyperintensities in the middle cerebellar peduncles (MCP) on T2 sequences are called the MCP sign. Late-onset ataxia and the MCP sign constitute major diagnostic criteria for definite FXTAS [2]. The MCP sign is present in up to 60 % of FXTAS patients and considered to reflect gliosis [2]. Similar abnormalities occur in other hereditary ataxia disorders and in multiple system atrophy (MSA). Here, we describe the course of disease in a man affected by POLG-associated ataxia (POLG-A) presenting as a FXTAS phenocopy syndrome. The overlapping features of POLG-A and FXTAS are highlighted.

Case description

Informed consent was obtained from the patient. A 60-year-old Swedish male born to non-consanguineous parents, was evaluated at our center due to progressive balance difficulties, impaired gait and coordination, slurred speech, diplopia, and hypoacusis. Insidious cognitive decline was also reported at

the time of motor onset. The age at onset was 48 years. His past medical history consisted of esophoria. Examination at age 55 with the Scale for the Assessment and Rating of Ataxia (SARA) yielded 10 points; 5 years later, it was 15. Upon exam, signs of both cerebellar and sensory ataxia (positive Romberg's sign) as well as chorea, myoclonus, areflexia, and complete loss of vibration sense were found. Over time, he has developed bradykinesia and marked postural instability; he requires the use of walking sticks for most of the time. His latest inventory of non-ataxia symptoms (INAS) count was 5 and his Unified Parkinson's disease rating scale (UPDRS) part III score was 19 points. Eye examination revealed broken up smooth pursuit, nystagmus, mild dysconjugation of lateral eye movements, hypometric saccades and partial restriction of vertical gaze. Psychometric evaluation revealed deficits in information processing speed, working memory, attention, and visuospatial skills. A mild sensorineuronal hearing loss was found and the subject was recommended hearing devices. Brain MRI at age 57 displayed the MCP sign, a mega cisterna magna but no evidence of cerebellar atrophy (Fig. 1). FXTAS was suspected; however, a normal CGG expansion size, 21 repeats, was found in the *FMR1* gene. Trinucleotide expansions causing Friedreich ataxia, DRPLA, SCA1, 2, 3, 6, and 7 were also ruled out. A sensory axonal polyneuropathy was found on electroneurography (ENeG). A muscle biopsy revealed variation of fiber size and lack of COX activity in some muscle fibers. In addition, reduced activity was found in complex I of the respiratory chain raising then the suspicion of a mitochondrial disorder. The homozygous mutation c.2243G>C (p.W748S) in the *POLG* gene was identified, MLPA analysis of this gene was normal.

A younger sibling was affected by an ataxia syndrome, her age at onset was 19 years and the total disease duration was 30 years. In contrast to our patient, she had epilepsy, her imaging studies were not possible to retrieve for review. In the course of her disease, she suffered from polyneuropathy, nystagmus, vertical ophthalmoparesis, involuntary movements, and cognitive decline. The exact character of her hyperkinesias was not stated in available chart notes. She became wheelchair bound and died of pneumonia at age 49.

Discussion

This patient we describe met the major clinical and radiological diagnostic criteria for definite FXTAS. However, he was found to be affected by POLG-A. Varying degrees of cerebelllar hyperintensities occur in 38 % of POLG-A patients [3]. As in our case, absence of cerebellar atrophy has been reported in up to 31 % of POLG-A subjects [3]. Ataxia, cognitive decline and varying degrees of polyneuropathy occur in both POLG-A and FXTAS. Sensory axonal polyneuropathy is very common in subjects with POLG mutations [1, 3]

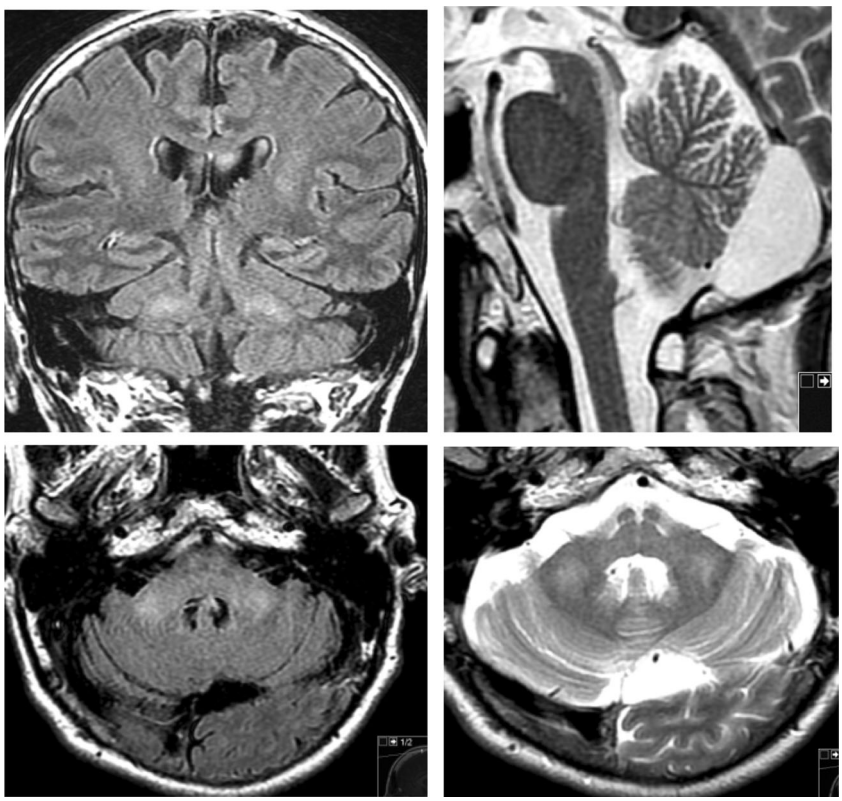

Fig. 1 *Upper* and *lower left panel*: coronary and axial FLAIR image sequences displaying symmetric MCP hyperintensities. *Upper* and *lower right panels*: T2-weighted sagittal and axial sequences displaying a mega cisterna magna but normal size cerebellum. *MCP* middle cerebellar peduncles

whereas large-fiber sensory polyneuropathy occurs in FXTAS [4]. Evidence of sensory neuronopathy also exist in FXTAS [5]. An unusual feature in our case is the presence of parkinsonism, which is rather rare among subjects with POLG mutations in the absence of progressive external opthalmoplegia (PEO) [6] but is more common in FXTAS with prevalence ranging between 24 and 67 % [5, 7, 8]. Hearing loss is common in mitochondrial disorders and in FXTAS; it has been reported in 50 % of FXTAS patients [8] and in 31 % of POLG-A patients [3]. Interestingly, premature ovarian failure, commonly seen in *FMR1* premutation carriers, has also been described in POLG-associated ataxia [9, 10]. Thus, the overlap between POLG mutations and *FMR1*-associated syndromes is striking. There are however differences, for instance the manifestations of POLG mutations are protean and include features unseen in FXTAS (epilepsy, myopathy, liver failure, PEO, and /or encephalopathy), with onsets ranging from early infancy to late adulthood and the presence of hyperkinetic features like chorea and/or myoclonus [1, 3]. Dystonia occurs also in POLG mutations [3] but seems to be very rare in FXTAS [8].

There are no specific radiological abnormalities for POLG-associated ataxia; however, white matter abnormalities (WMA) in the cerebellum are common [3]. In the present case, the abnormal muscle biopsy contributed to raise the suspicion of a mitochondrial disorder. However, muscle biopsies in subjects with POLG mutations are normal in most cases [11]. There are no specific biochemical analyses for POLG-ataxia and analysis of respiratory chain enzymes can also be normal [11, 12]. In summary, the diagnosis of POLG-ataxia requires a high index of suspicion.

The pattern of inheritance of POLG mutations is complex; in most cases, it is autosomal recessive and less often autosomal dominant [1, 9]. W748S is one the most common autosomal recessive POLG mutations [1]. Of note, there is increasing evidence of mitochondrial dysfunction in FXTAS [13].

E. Apartis et al. proposed a revision of the diagnostic criteria for FXTAS [5] based on the fact that hyperintensities of the corpus callosum were more common than the MCP sign (68 %, respectively, 64 %) and for the fairly common presence of polyneuropathy (81 %). Other conditions with MCP hyperintensities include MSA [14], adult-onset leukoencephalopathies [15], cerebrotendinous xanthomatosis (CTX), and mitochondrial disorders like PEO and infantile onset spinocerebellar ataxia (IOSCA) [16]. Taking both radiological and clinical features into consideration, late-onset POLG-A is the disease that resembles FXTAS in many features, yet external ophthalmoplegia might be a characteristic feature that—if present—clearly distinguishes POLG-A from FXTAS [17].

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Compliance with Ethical Standards

Consent Oral and written consent was obtained for this report.

Conflict of Interest The authors declare that they have no conflicts of interest.

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