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Case Series – General Neurology

Fragile-X-Associated Tremor/Ataxia Syndrome or Alcohol-Induced Cerebellar Degeneration? A Case Report

Giulia Grigioni^a Christian Saleh^b Phillip Jaszczuk^a Dorothea Wand^c
Stefanie Wilmes^a Margret Hund-Georgiadis^a

^aREHAB Basel, Clinic for Neurorehabilitation and Paraplegiology, Basel, Switzerland;

^bDepartment of Neurophysiology and Neurology, University Hospital Basel, Basel, Switzerland; ^cDepartment of Medical Genetic and Pathology, University Hospital of Basel, Basel, Switzerland

Keywords

Fragile-X-associated tremor · Tremor · Ataxia · Cerebellar atrophy

Abstract

Fragile-X-associated tremor/ataxia syndrome (FXTAS) is a neurodegenerative disorder that manifests with intention tremor, progressive gait ataxia, and cognitive impairment. The disease is genetically characterized by a premutation of the *FMR1* gene on the X-chromosome manifesting with a CGG triplet expansion between 55 and 200. Given the phenotypical variety of this disease, diagnosis is frequently delayed. We present and discuss a male patient whose diagnosis of FXTAS was delayed due to his concomitant alcohol abuse.

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G.G. and C.S. contributed equally to the manuscript.

Introduction

Fragile-X-associated tremor/ataxia syndrome (FXTAS; OMIM #300623) is a neurodegenerative disorder characterized by late-onset progressive gait ataxia, intention tremor, parkinsonism, and cognitive impairment [1]. The penetrance is estimated between 17% (in male patients aged between 50 and 60 years) and 75% in patients over 80 years old. The genetic hallmark consists of a premutation of the *FMR1* (OMIM #309550) gene on the X-chromosome manifesting with a CGG triplet expansion between 55 and 200 repeats [1]. As the *FMR1* gene is located on the long arm of the X-chromosome, only females can be affected by the disease; male children of affected subjects will not obtain the X-chromosome with the premutation. Therefore, male offspring will not develop FXTAS or fragile-X syndrome (FXS) [2]. The transmission of the X-chromosome with the premutation occurs only to a female offspring, who would be carrier of the affected gene [3]. The risk of a full mutation would present only in the following generation, namely when the female carrier transmits the gene with the premutation to a male offspring; female carriers have an increased risk of premature menopause [2].

A triplet repeat greater than 200 results in FXS (OMIM #300624) [4]. FXS presents with a range of clinical manifestations, such as autism and mental retardation. The diagnosis of FXTAS requires the presence of the premutation and a combination of clinical, radiological and genetic findings. Therapy is supportive [4]. We present and discuss a male patient whose diagnosis of FXTAS was delayed due to his concomitant alcohol abuse.

Case Report

A 48-year-old male patient with a history of alcohol abuse started to show progressive difficulties walking and a tremor of both hands starting 6 years earlier. Additionally, the patient presented with dysarthria and peripheral neuropathy. Repeated neurological examinations showed a wide-based gait, dysmetria in both upper and lower extremities, intention tremor, and dysidiadochokinesia. The increasing gait difficulties ultimately led to the use of a walking aid. Brain imaging (MRI) showed a mild degree of frontoparietal atrophy as well as diffuse, cerebellar atrophy without signs of Wernicke's encephalopathy (Fig. 1–3). His clinical presentation was repeatedly considered to be alcohol related. In 2010, genetic testing showed a premutation in the *FMR1* gene (87 CGG triplets). The testing was carried out because two cousins of maternal origin were diagnosed with FXS. The patient is the only child of two healthy parents. The mother has three siblings, two sisters and one brother, who are all healthy. At age 46, the diagnosis of FXTAS was made and genetic counseling for the patient and his family initiated. The patient has a son who is healthy.

Discussion

The underlining cause of FXTAS is a genetic disorder in form of a premutation of the X-chromosome expressing itself in a CGG expansion ranging between 55 and 200. A subset of

patients will develop FXTAS, which is a clinical and radiological diagnosis. Major clinical criteria are intention tremor and gait ataxia, while lesions in the middle cerebellar peduncle (“MCP sign”), corpus callosum and splenium constitute the major radiological diagnostic criteria. An array of motor diseases needs to be considered in the differential diagnosis including Parkinson’s disease, multi-system atrophy, essential tremor, and progressive supranuclear palsy [5]. However, as Robertson et al. [5] underline in the differentiation from the aforementioned motor diseases, certain clinical and radiological findings should point the clinician to FXTAS, such as cerebral ataxia/tremor in a patient over 50, the MCP sign, cerebellar atrophy and a family history for genetic diseases [5]. In our patient, tremor, ataxia, CGG expansion as well as the aforementioned radiological findings were present meeting the diagnostic criteria for FXTAS. However, the prompt diagnosis was made difficult and even delayed by the concomitant alcohol abuse by the patient. Differentiation between alcohol-related symptomatology and FXTAS may be clinically and radiologically difficult; alcohol may even accelerate the progression of FXTAS [6, 7]. However, in particular settings, the differentiation between FXTAS and alcohol-induced cerebellar degeneration is academic and the diagnosis of FXTAS should be favored to allow prompt genetic counseling. This is in the patient’s best interest because his offspring have a high risk for FXTAS [4].

Conclusion

FXTAS is a rare disease and, in light of its clinical heterogeneity, may be underrecognized [4]. The clinical and radiological presentation can be confused with multiple other diseases such as multisystem atrophy or alcohol-induced cerebellar degeneration (Table 1). Prompt genetic counseling is paramount for the patient and his/her family. Only a high level of suspicion for FXTAS will allow for diagnosis.

Take-Home Points

- FXTAS is an important differential diagnosis particularly in patients over 60 years old, with tremor, a history of alcohol abuse, PNP, gait instability, and ataxia. Males with the premutation are at highest risk of FXTAS while their daughters will be heterozygous for the premutation [3].
- 40% of patients with the premutation develop FXTAS and 16–20% of females are heterozygous for the premutation [3].
- The initial diagnostic workup should include a neurological examination, a full family anamnesis over 3 generations (male members with mental retardation or female members with fragile X-associated primary ovarian insufficiency), and a cranial MRI [3].
- Prompt genetic counseling is paramount [3].
- Treatment is symptomatic (a rehabilitation program should be considered).

Statement of Ethics

Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

Conflict of Interest Statement

The authors declare that they have no conflict of interest.

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Author Contributions

Giulia Grigioni: Analyzed the data, wrote the draft, and critically revised the final version.
Christian Saleh: Analyzed the data, wrote the draft, and critically revised the final version.
Phillip Jaszczuk: Wrote the draft and critically revised the final version.
Dorothea Wand: Analyzed the data and critically revised the final version.
Stefanie Wilmes: Analyzed the data and critically revised the final version.
Margret Hund-Georgiadis: Analyzed the data and critically revised the final version.

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Fig. 1. Cranial FLAIR-MRI: axial view showing periventricular lesions (yellow arrows).

Fig. 2. Cranial FLAIR-MRI: coronal view with cerebellar atrophy (red arrows).

Fig. 3. Cranial FLAIR-MRI: coronal view evidencing frontotemporal atrophy (white arrows).

Table 1. Tremor and cerebellar atrophy: Some common genetic and non-genetic causes

Disease	Clinic / Comment
Alzheimer's disease	Motor symptoms are common in Alzheimer's disease, but tremor is rare
Amyotrophic lateral sclerosis	Tremor with upper and lower motor neuron signs
Frontotemporal disease	Early cognitive decline, changes in behavior
Multisystem atrophy	Tremor tends to be more bilateral with axial and autonomic symptoms
Friedreich's ataxia	Onset frequently in childhood, gait ataxia, scoliosis, cardiomegaly
Spinocerebellar ataxia	Postural tremor, gait ataxia
Multiple sclerosis	Multiple symptoms (e.g., paresthesia, paresis, ocular symptoms, tremor), transient or fluctuating course, foremost in young females
Alcohol	Anamnesis
Phenytoin	Anamnesis, only by long term use
Cerebellitis	Acute/subacute onset, headache, fever, nystagmus, altered consciousness