Case Report

Neuropathology of a case of fragile X-associated tremor ataxia syndrome without tremor

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Fragile X-associated tremor ataxia syndrome (FXTAS) is a neurodegenerative disorder caused by a CGG trinucleotide expansion from 55 to 200 repeats in the non-coding region of the fragile X mental retardation 1 (FMR1) gene (FMR1). Clinical features include cognitive decline, progressive tremor, and gait ataxia. Neuropathologically, FXTAS shows white matter changes, hippocampal and cerebellar involvement, and p62-positive eosinophilic intranuclear inclusions in astrocytes and neurons. Here, we document the neuropathological findings from a subject who developed cognitive impairment but not tremor and was proved to have genetically confirmed FMR1 premutation. Microscopically, typical p62-positive intranuclear inclusions were present in all the regions examined. Neocortical regions demonstrated gliosis of layer I and mild degree of neuronal loss and atrophy across the other layers. The molecular, Purkinje’s cell, and granule cell layers of the cerebellar folia demonstrated mild gliosis, and cerebellar white matter was mildly affected. Aside from p62-positive inclusions, the hippocampus was spared. Arteries in the deep white matter often showed changes consistent with moderate small vessel disease (SVD). Reactive gliosis and severe SVD were features of basal ganglia. Florid reactive astrogliosis was found in the white matter of all regions. Axonal loss and features of axonal damage were found in the white matter of the centrum semiovale. Microglial activation was widespread and evenly seen in both the white matter and grey matter, although the grey matter appeared more severely affected. Pathology associated with Alzheimer’s disease was limited. Similarly, no abnormal accumulations of α-synuclein were present. We postulate that age at death and disease duration may play a role in the extent of the pathological features associated with FXTAS. The present results suggest that immunohistochemical staining for p62 can help with the diagnosis of cases with atypical phenotype. In addition, it is likely that the cognitive impairment observed was a result of white matter changes.

Key words: cognitive impairment, fragile X-associated tremor ataxia syndrome, neuropathology, p62, tremor.

INTRODUCTION

Fragile X-associated tremor ataxia syndrome (FXTAS) is a neurodegenerative disorder, first described in 2001.1 Patients with FXTAS carry a CGG trinucleotide expansion in the non-coding region of the fragile X mental retardation 1 (FMR1) gene (FMR1). Expansions from 55 to 200 repeats are defined as premutation. The full mutation consists of over 200 CGG repeats and causes fragile X syndrome (FXS).1

A recent systematic review and meta-analysis estimated the frequency of individuals with the full mutation to be around 1:7000 for males and 1:11 000 for females. The prevalence of FMR1 premutation has been reported as approximately 1:850 for males and 1:300 for females.2 Penetration rates for FXTAS are known to be higher in males (40%) than in females (16%).3 The clinical hallmarks include cognitive decline, progressive intentional tremor, and gait ataxia. Essential tremor has also been documented in patients with premutation.4 Statistically relevant differences in all subdomains of the Clinical Rating Scale for Tremor indicate that postural and kinetic tremor appears at onset while resting tremor occurs as the disease progresses.5 The age of onset of tremor and ataxia correlate

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with CGG repeat length. Other signs and symptoms, which characterize the disease, include cognitive decline, disinhibition, apathy, and peripheral neuropathy. Magnetic resonance imaging (MRI) reveals brain atrophy and white matter changes in the centrum semiovale and cerebellum.

Neuropathologically, FXTAS is defined as a degenerative white matter disease. The white matter changes seen in FXTAS are distinct from those found in ischemia, multiple sclerosis, and cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL). p62-positive eosinophilic intranuclear inclusions in astrocytes and neurons in both the cerebrum and cerebellum are typical features of FXTAS. Involvement of the hippocampus, including thickening of the cornu ammonis sector 1 (CA1) and irregularities in the dentate gyrus, and dropout of Purkinje’s cells in the cerebellum has been described.

We document the neuropathological findings from a subject who developed cognitive impairment without tremor and was proved to have genetically confirmed FMRI premutation. The clinical features of this subject have previously been documented in a study describing a series of FXTAS patients (patient 1 in the publication). This is one of the few extensive neuropathological assessments of a brain with FMRI premutation and the first describing an FXTAS patient without tremor and assessing misfolded protein pathology by immunohistochemical observations.

**CLINICAL SUMMARY**

A 57-year-old man presented to neurological services with a 4-year history of progressive incoordination, dysarthria, falls, and cognitive impairment. In 2005, at the age of 53 years, he first noticed problems with the ability to stand on each leg in turn. This began to interfere with the patient’s ability to run. He then developed more prominent gait ataxia, which progressed very slowly. The development of dysarthria and arm incoordination, as well as some cognitive difficulties, resulted in the referral to neurology. There was no suggestion of previous neurological deficits. The patient had enjoyed a very active life, with regular activities such as rock climbing, swimming, and running. He had no history of hypertension, never drank alcohol excessively, and had stopped smoking at the age of 40 years. There was a family history of ataxia, affecting his brother, and of early menopause (range 28–37 years), affecting his mother, sister, and aunt from the mother’s side.

Neurological examination revealed broken pursuit but no nystagmus. The patient had mild dysarthria. He had minimal limb ataxia, affecting legs more than arms, but more prominent gait ataxia. No tremor was observed. He did not use a walking aid but had a mild difficulty in tandem walking. He exhibited normal reflexes and normal peripheral sensation.

Brain MRI revealed signal changes in the centrum semiovale and middle cerebellar peduncles (Fig. 1). The dopamine active transporter scan revealed normal results. A hexamethylpropyleneamine oxime single photon emission computed tomography scan revealed reduced perfusion in the medial temporal lobe.

Analysis of FMRI was considered based on the patient’s presentation, the family history of early menopause, and the history of ataxia affecting the patient’s brother, as well as the MRI signal change in the middle cerebellar peduncles. The clinical ataxia and radiological white matter lesions involving the middle cerebellar peduncles features were sufficient to make a diagnosis of definite FXTAS. Unmethylated CGG expansion was detected using fluorescent methylation-specific quadruple polymerase chain reaction (PCR) as described by Zhou and colleagues. This test documented 100 repeats. Formal cognitive screening revealed some memory impairment that was thought to have been secondary to FXTAS. The patient also exhibited low mood. A more detailed clinical work-up of this case can be found in a previous publication.

The patient died at the age of 65 years, 12 years after the onset of ataxia. His death was attributed to severe decline in his mobility and cognition. At the time of death, the patient was no longer under neurological review. The cause of death recorded on the death certificate was fragile X syndrome rather than FXTAS. Such nomenclature is inaccurate as the former refers to the range of conditions named under the fragile X disorder spectrum rather than the late-onset manifestation often occurring in patients.

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**Fig. 1** MRI findings of the brain. (A) A sagittal T1-weighted image (T1WI) shows atrophy of the superior vermis of the cerebellum. (B) An axial T2-weighted fluid-attenuated inversion recovery (FLAIR) image shows hyperintense areas in both sides of the cerebral white matter. (C) An axial T2 FLAIR image shows hyperintense areas in both sides of the middle cerebellar peduncles.
older than 50 years. The personal consultee (wife) of the brain donor gave written, informed consent for the use of brain tissue in research.

**PATHOLOGICAL FINDINGS**

The fresh brain weight was 1412 g. The postmortem interval was 66 h. The left hemisphere was fixed in 10% neutral-buffered formalin, and the right hemisphere was frozen and stored at −80°C. After fixation, the left hemisphere was examined. Macroscopically, the leptomeninges over the convexity and at the base of the brain were translucent. Gyration was normal. The vessels at the circle of Willis were of medium caliber. No atheromatous plaques were present. There was no indentation of the uncal cortices or cerebellar tonsils. The substantia nigra demonstrated normal pigmentation for the age of this individual.

Coronal slices of the cerebral hemisphere showed only mild discoloration and softening of the white matter of centrum semiovale, and no obvious changes in the periventricular white matter. The grey-white matter junction was sharp. The lateral ventricle was of normal size. Sagittal slices of the left cerebellar hemisphere and the coronal slices of the midbrain, pons, and rostral medulla oblongata did not show any pathological changes of note. The regions sampled are listed in Table 1, including the corresponding Brodmann’s areas. Large slice blocks were taken from the frontal and occipital poles and cerebellar hemisphere.

Six-micrometer-thick sections were cut from formalin-fixed, paraffin-embedded conventional and macro blocks, and processed for staining with hematoxylin and eosin (HE) and Luxol fast blue (LFB) and periodic acid-Schiff (PAS) as well as immunohistochemical staining. Microscopically, all neocortical regions demonstrated gliosis of layer I and a mild degree of neuronal loss and atrophy across the other layers. The hippocampus was spared. Reactive gliosis, axonal loss, and features of axonal damage, such as wavy and swollen axons and spheroids, were present. Such changes varied from region to region, while the temporal lobe, primary motor cortex, and primary visual cortex were only mildly affected. The molecular, Purkinje’s cell, and granule cell layers of the cerebellar folia demonstrated mild gliosis. There was only focal loss of Purkinje’s cells, apart from in two folia, which showed more severe cell loss and gliosis. The cerebellar white matter was only focally affected. The dentate nucleus showed mild gliosis and mild neuronal loss. The typical intranuclear inclusions associated with FXTAS were observed in all of the regions examined.

Arteries in the deep white matter often showed wall thickening, perivascular gliosis, and widening of the perivascular space, consistent with moderate small vessel disease (SVD). Reactive gliosis and severe SVD were features of the basal ganglia, including calcification of the walls of several perforating arteries in the globus pallidus. No infarcts were observed, and only scattered white matter arteries showed minimal perivascular deposits of hemosiderin to suggest minimal microbleeding; no perivascular hemosiderin-laden macrophages were seen. The basal nucleus of Meynert showed neuronal atrophy and mild gliosis. Mild white matter changes similar to those of the frontal lobe were seen in the deep white matter of the cerebellum; the folia were spared. The midbrain, pons and medulla oblongata showed no pathological features of note.

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The subcortical and deep white matter of the frontal and parietal lobes and the cingulate and paracingulate gyri displayed discoloration on sections stained with LFB-PAS. Although it was difficult to assess in postmortem tissues, the spared myelin sheaths in the frontal lobe were often swollen. No myelin-laden macrophages to indicate active myelin breakdown were observed. PAS staining only highlighted a few subpial corpora amylacea.

Nuclear inclusions containing p62 were present in all neocortical regions, allocortex, basal ganglia, cerebellum, midbrain, pons, and medulla oblongata. Notably, inclusions were considerably more common in glial cells of the cerebellar white matter compared to the cortex and dentate nucleus. Despite appearing unremarkable at light microscopic examination, over 50% of the pyramidal neurons in the CA4–CA2 regions of Ammon’s horn and approximately 30% of those in the CA1 region and subiculum showed inclusions. Immunohistochemical staining for glial fibrillary acidic protein (GFAP) revealed florid reactive astrogliosis of the white matter in all regions and less prominent astrogliosis of the cortical and subcortical grey matter, with cortical layers I and VI being more affected. Immunohistochemical staining with an antibody against neurofilament protein (NFP) of 80 and 200 kDa revealed axonal loss and features of axonal damage in the white matter of the centrum semiovale. Microglial activation identified by immunohistochemistry for ionized calcium-binding adaptor molecule 1 (Iba1) was widespread and evenly observed in both the white and grey matter across all regions examined, although the grey matter appeared more severely affected. Microglial cells displayed both ramified and amoeboid morphology.

Immunohistochemical staining for phosphorylated tau and amyloid-β (Aβ) revealed occasional tau deposits in the frontal, temporal and parietal lobes. No tau deposits were detectable in the hippocampus, entorhinal cortex, occipital cortex, or cerebellum (Braak & Braak tau stage I). No Aβ deposits were detectable in any of the brain regions examined (CERAD score 0; Thal phase 0). No abnormal accumulations of α-synuclein were detectable (Braak Lewy body stage 0). Fibrinogen immunohistochemistry revealed no extravascular deposits to suggest disruption of the blood brain barrier. The special histochemical and immunohistochemical observations are summarized in Table S1.

The relevant pathological changes are presented in Figures 2–6 and Figures S1 and S2. A summary of pathological findings is presented in Table 2.

**DISCUSSION**

We have described postmortem features of a genetically confirmed carrier of FMR1 premutation. The patient exhibited ataxia and progressive cognitive impairment but never developed tremor. The clinical phenotype met the criteria for definite FXTAS (one major clinical criterion of gait ataxia and one major radiological criterion of MCP signal change), but the absence of tremor was unusual.
Absence of tremor occurs in approximately 20% of the FXTAS cases, but no neuropathological descriptions corresponding to this subgroup are known to have been published.7

Cognitive decline is a feature of FXTAS.18 Alzheimer’s type pathology including senile plaques and neurofibrillary tangles is mostly seen in women that clinically present with dementia.19 In the present case, we demonstrated that cognitive impairment associated with FXTAS was not due to Alzheimer’s type or α-synuclein pathology, suggesting that white matter damage was the most relevant cause of cognitive impairment. It is of note that brains of male subjects in their sixth decade are expected to show some level of Aβ accumulation, even if cognitively intact.20 Further to the recent evidence that a decrease in FMRP expression levels leads to accumulation of misfolded α-synuclein in dopaminergic neurons,21 we investigated α-synuclein pathology in the neocortex, allocortex, midbrain and medulla oblongata, and found no abnormal accumulation of the protein. In addition, the substantia nigra was well-preserved, further supporting the evidence that anatomical substrates of resting tremor were not affected.

White matter changes and appearance of p62-positive inclusions in neurons and astrocytes are the pathological hallmark of FXTAS. Unlike previous descriptions,13,19,22 white matter changes were not prominent at macroscopic examination, and no obvious cortical atrophy or ventricular widening was observed. In addition, the cerebellum appeared unremarkable at gross inspection. Limited neuronal loss in the neocortex, only a mild and focal reduction in number of Purkinje’s cells, mild change of the basal ganglia, and preservation of the substantia nigra were observed; these observations may explain why tremor did not manifest in this subject. Similar to other descriptions,23 we observed appearance of florid reactive astrocytes and widespread microglial activation in the white matter but much less prominent reactive changes in the neocortex.

Previous studies have shown a correlation between the number of CGG repeats in the premutation range and the number of intranuclear inclusions.18 The number of CGG repeats in the present case (100) was enough for a clinical diagnosis of premutated FXTAS.16 As the pathological changes were not as severe as expected, other factors put forward by previous studies, such as age at death and disease duration,24 may play a greater role in determining the number of intranuclear inclusions found and, therefore, affect the severity of other associated pathologies.

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The typical intranuclear inclusions of FXTAS consist of more than one protein and contain highly enriched levels of small ubiquitin-related modifier 2 (SUMO 2) protein and p62/sequestosome-1 (p62/SQSTM1) protein. These inclusions are negatively stained with PAS, and negatively immunostained for tau and α-synuclein but positively immunostained for ubiquitin and αB-crystallin. It is worth-noting that inclusions can also be found outside the central nervous system, in other words, in the peripheral nervous system, enteric nervous system, endocrine glands, heart, and kidney. We show in the present study that these inclusions are clearly immunoreactive for p62 and can easily be identified in the brain of individuals with FXTAS.
Table 2  Summary of neuropathological findings

| Region          | Neuronal loss and atrophy | Grey matter astrogliosis† | Grey matter microgliosis‡ | White matter astrogliosis† | White matter microgliosis‡ | Myelin loss§ | Axonal damage¶ | Small vessel disease | Microbleeds | Inclusions†† |
|-----------------|---------------------------|---------------------------|---------------------------|---------------------------|---------------------------|--------------|---------------|---------------------|-------------|--------------|
| Anterior frontal lobe | Mild | Moderate | Mild | Severe | Severe | Severe | Severe | Moderate | Absent | Neurons |
| Temporal lobe    | Mild | Moderate | Moderate | Severe | Mild | Mild | Mild | Moderate | Possible | Neurons |
| Basal ganglia    | Mild | Moderate | Moderate | Not tested | Not tested | Not tested | Not tested | Not tested | Severe | Absent | Neurons and glia |
| Thalamus         | Mild | Moderate | Not tested | Not tested | Not tested | Not tested | Not tested | Not tested | Moderate | Absent | Neurons and glia |
| Hippocampus      | Absent | Mild | Mild | Moderate | Moderate | Mild | Mild | Moderate | Possible | Neurons |
| Parietal lobe    | Mild | Moderate | Mild | Severe | Moderate | Moderate | Moderate | Moderate | Absent | Neurons |
| Occipital lobe   | Mild | Moderate | Mild | Severe | Severe | Severe | Severe | Moderate | Absent | Neurons |
| Cerebellum       | Mild | Mild | Moderate | Moderate | Mild | Mild | Mild | Moderate | Absent | Glia |
| Midbrain         | Absent | Not tested | Not tested | Not tested | Not tested | Not tested | Not tested | Not tested | Absent | Absent | Neurons and glia |
| Pons             | Absent | Not tested | Not tested | Not tested | Not tested | Not tested | Not tested | Not tested | Absent | Absent | Neurons and glia |
| Medulla          | Absent | Not tested | Not tested | Not tested | Not tested | Not tested | Not tested | Not tested | Absent | Absent | Neurons and glia |

†Astrogliosis assessed with glial fibrillary acidic protein.
‡Microglial response assessed with Iba1.
§Myelin loss assessed with Luxol fast blue/periodic acid-Schiff (LFB/PAS).
¶Axonal damage assessed with neurofilament proteins.
††Inclusions assessed with p62; the table reports the cell population with predominant inclusions.
In conclusion, we described the neuropathological features in an FXTAS case without tremor and only mild involvement of the cerebellum. Age at death and disease duration may play a role in the extent of the pathological features associated with FXTAS. The present results suggest that immunohistochemical staining for p62 can help with the diagnosis of patients with atypical phenotype. In addition, we showed that the cognitive impairment found in this individual was not due to misfolded protein accumulation but was more likely to be a result of white matter changes.

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DISCLOSURE
The authors have no conflict of interest to report.

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SUPPORTING INFORMATION

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**Figure S1** This artery in the temporal white matter shows thick, hyalinized wall; minimal extracellular deposits of hemosiderin and perivascular astrocytosis are present (A – HE); perforating arteries in the globus pallidus show calcified wall (B – HE); the cerebellar cortex demonstrates focal loss of Purkinje’s cells (C – HE).

**Figure S2** Several pyramidal neurons of the CA2-CA3 sectors of Ammon’s horn contain nuclear p62-positive inclusions (A – immunoperoxidase); reactive astrocytis in the neocortex is more prominent in layers I and VI (B, superior temporal gyrus – immunoperoxidase).

**Table S1** Summary of histochemical and immunohistochemical stains