Case Report



Cerebellar syndrome and cognitive dysfunction with characteristic MRI findings in fragile X-associated tremor ataxia syndrome: A Case Report

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Abstract

An adult male patient came to our observation for a brain magnetic resonance imaging (MRI) study because of progressive symptoms characterized by ataxia, tremor, rigidity and cognitive dysfunction. The neuropsychological tests confirmed an IQ reduction and cognitive impairment. The MRI study showed symmetric T1 decreased and T2 increased signal intensity in cerebellar white matter (wm) lateral, superior, and inferior to the cerebellar dentate nuclei. Moreover, hyperintense T2 focal areas of both deep wm cerebral hemisphere and T2 hyperintensity of the splenium of the corpus callosum were documented. The progressive neurological symptoms of our adult male patient and the MRI study features suggested a degenerative disease, due to fragile X premutation. Genetic tests confirmed the diagnostic hypothesis of fragile X-associated tremor ataxia syndrome (FXTAS).

Introduction

Fragile X syndrome is the most common inherited form of mental retardation, with the carrier frequency in the general population being approximately one in 250 female and one in 760 male persons [1,2]. The disorder is caused by an expansion in excess of 200 repeats (full mutation expansion) of a trinucleotide element, (CGG), located in the 5' untranslated region of the fragile X mental retardation 1 (FMR1) gene [3]. Full mutation expansions are generally accompanied by silencing of the FMR1 gene, with attendant lack of FMR1 protein (FMRP) synthesis; it is the lack of FMRP that leads to fragile X syndrome. Trinucleotide expansions that are in the 55 to 200 repeat range are termed permutations. Healthy subjects may have a range of approximately five to 54 repeats. Carriers of the FMR1premutation allele (55-199 repeats as defined by the American College of Medical Genetics [4] are at significant risk for a late-onset neurodegenerative disorder, fragile X-associated tremor ataxia syndrome (FXTAS) [5]. This disorder is distinct from that manifested in carriers of the full mutation (> 200 repeats), or fragile X syndrome (FXS), with respect to the molecular etiology and clinical phenotype. The primary features of FXTAS are action tremor and gait ataxia. Associated features include parkinsonism, autonomic dysfunction, peripheral neuropathy, and cognitive dysfunction. Cognitive changes are highly variable and include global impairments as well as specific executive cognitive dysfunction [6-7]. Preliminary reports suggest that psychiatric symptoms include anxiety, agitation, disinhibition, and depression. This characteristic pattern of cognitive and behavioral deficits resembles that observed in other forms of frontal-subcortical dementia [8]. Neuro-imaging features of FXTAS on T2 weighted brain MRI include middle cerebellar peduncles (MCP) and periventricular, subcortical white matter (wm) changes [9]. The MCP hyperintensity has been incorporated in the diagnostic criteria for "definite" FXTAS [10]. Though distinctive, it is found in only about 64% of individuals with FXTAS [11]. Other important radiological findings are cerebral and cerebellar cortical atrophy, thinned corpus callosum, reduction of both middle cerebellar peduncles sagittal diameter and pontine transverse/rostral-caudal dimension [12]. These radiological findings in an elderly patient with ataxia, tremor, rigidity and cognitive dysfunction, in addition to mandatory genetic specific tests, may improve the FXTAS diagnosis.

Case Report

A 63 years old Caucasian male affected by progressive and worsening intention tremor, gait ataxia, autonomic dysfunction, rigidity and cognitive decline came to our observation. Neuropsychological tests confirmed the reduction of IQ and impaired

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Key words: movement disorder, fragile X tremor Ataxia Syndrome, MRI middle cerebellar peduncle signs

Received: June 28, 2019; Accepted: July 10, 2019; Published: July 15, 2019

executive functions. The MRI brain study (Figures 1 and 2) showed pathologic symmetric signal of wm of the middle cerebellar peduncles (MCPs), specifically localized medially, superiorly and laterally to the dentate nuclei, showing restricted Diffusion on specific sequences. The MCPs transverse diameter was reduced. The infra-tentorial subarachnoid spaces were enlarged due to cerebellar cortical atrophy. The pons and the midbrain also appeared atrophic, both in axial and sagittal planes, with enlargement of the interpeduncular cistern and concave appearance of the midbrain, but Parkinsonism Index was not diagnostic for Progressive Supranuclear Palsy (PSP) or Multiple System Atrophy (MSA). The MRI documented cortico-subcortical brain atrophy, especially in frontoparietal regions and hyperintense T2 focal areas of both deep wm cerebral hemisphere and T2 hyperintensity



Figure 1. Axial (a, b, c and d) and Coronal MRI study shows pathologic signal of middle cerebellar peduncles; note hypointense onT1 (a) and hyperintense signal on T2 (b, c and e) and Diffusion sequences (d) (see red head arrows). Small and confluent deep white matter T2 hyperintense area respectively in frontal region (f) and hyperintense focal T2 hyperintense area of the splenium of corpus callosum on FLAIR weighted sequence (g) (see yellow head arrows).



Figure 2. Sagittal (a, c and d) and transverse (b) MRI T1 sequences. Diffuse enlargement of peri cerebellar sulci, mild atrophy of the pons, corpus callosum and mesencephalon (a) with slight enlargement of interpeduncular cistern (b) and reduction in diameter of the middle cerebellar peduncles (c and d)

of the splenium of the corpus callosum. The corpus callosum also appeared with a reduced thickness. The Evans index was normal, but the third ventricle was dilated. Both MRI findings and the worsening of neurologic symptoms suggested an adult-fragile X premutation. The genetic tests, conducted with Southern blot and PCR, showed an expansion of CGG triplets in the 5' untranslated region of the Fragile X Mental Retardation gene. At the end, a defined diagnosis of the fragile X-associated tremor ataxia syndrome (FXTAS) carrier was made.

Discussion

Fragile X syndrome is caused by absence or deficiency of the Fragile X mental retardation protein (FMRP), a protein that is crucial for early brain development, maturation and plasticity [1-2]. Although the focus of fragile X syndrome has been on its relationship to early child development, a newly recognized disorder, associated with fragile X premutation, has been noted to manifest in elderly men as the presence of tremor, ataxia, dyssynergia, cognitive decline, rigidity, and impotence. The FXTAS represents this disorder [5]. The diagnostic criteria of FXTAS comprise three domains: clinical, radiological, and pathological [13]. Whether definite, probable or possible, FXTAS diagnosis requires a degree of functional/clinical impairment. While the clinical presentation is variable, the initial presenting motor symptom is often an intention or kinetic tremor, followed by cerebellar ataxia, both of which typically progress over time [14]. Other clinical features may include executive dysfunction, ranging from mild to dementia-like in severity, which often presents later in the disease course [15]. The most prominent neuropathological features of FXTAS are: (1) cerebral and cerebellar wm disease that is pathologically distinct from that found in cerebrovascular and demyelinating disorders, (2) astrocytic pathology in wm, and (3) eosinophilic, ubiquitin-positive intranuclear inclusions in brain and spinal cord [16,17].Currently, FXTAS neuropathology can only be confirmed after death and hence cannot be used as a prognostic tool. The radiological phenotype emphasizes FXTAS as a wm neurodegenerative disease, as prior studies have highlighted the presence of wm lesions in the MCPs, known as the MCPs sign, and brainstem, as well as generalized cerebral lesions and atrophy throughout the neocortex [18-20]. Indeed, it has been suggested that hyperintensity of the splenium of the corpus callosum should be added as a minor criterion for FXTAS, given that these lesions were found to be more common than MCPs lesions in female premutation carriers with FXTAS [21]. The MCPs sign is not specific to FXTAS [22] and is occasionally seen in other rare neurodegenerative diseases. With the exception of the required premutation allele, none of the clinical features are absolutely specific for FXTAS [23].Although the MR findings of symmetrically increased T2 signal intensity within the MCPs and adjacent cerebellar wm have been shown in this study to be characteristic of symptomatic elderly men with fragile X premutation, these findings are not specific. The phenotype of FXTAS is very similar to that of other neurodegenerative disorders (ND). The movement abnormalities seen in FXTAS overlap with those of several more wellknown disorders. In 2016, Robertson, et al. published a systematic review in which they compared the phenotype of FXTAS to that of essential tremor (ET), Parkinson's disease (PD), spinocerebellar ataxias (SCAs), multiple system atrophy (MSA) and progressive supranuclear palsy (PSP) [23]. Although patients with FXTAS show complex clinical phenotypes, features such as parkinsonism can make it difficult to distinguish from persons with Parkinson's disease [24]. Symptoms early in the disease course may be mild and difficult to categorize. Individuals with minor unsteadiness and tremor may be diagnosed with essential tremor. It is important to be aware that patients with essential tremor

who develop unsteadiness and/or executive dysfunction, may have alternative diagnoses, including FXTAS. This also applies to cases with atypical development of other movement disorders. Although clinical manifestations are essential for placing a correct diagnosis, morphological MRI imaging plays a fundamental role in the diagnosis and follow-up of patients with ND. However, since different diseases of this heterogeneous group may have overlapping morphological elements, the interpretation of the image must be performed only in correlation with the clinical presentation of the patient [25]. In FXTAS, action tremor can be present alone or in association with resting tremor. Half of all patients can show cerebellar ataxia, while parkinsonism can be present in around one third of them. We can also find other symptoms like cognitive impairment with executive dysfunction, neuropathy and sleep disturbances [26]. In ET symptoms like cerebellar ataxia and parkinsonism have not been reported (only minor cerebellar abnormalities later in the disease course have been described) and the MCPs sign is not present [26]. PD is characterized by asymmetrical resting tremor, most often in hands, rigidity, bradykinesia, postural instability and no motor symptoms like sleep disorders, depression and reduced olfactory sense [26]. Patients with symptoms of idiopathic primary PD have not specific diagnostic neuroradiological findings, therefore the diagnosis is exclusively based on the clinical signs and the purpose of the MRI study consists in the overall assessment of regressive-atrophic encephalic phenomena, of the extent of any signs of subcortical ischemic encephalopathy and finally in the exclusion of secondary forms [27]. Movement disorder in SCAs is characterized by intention tremor and slowly progressive ataxia. Unsteady gait is the first symptom. Parkinsonism may be seen in some SCA type. Examination of eye movements often reveals fragmented, jerky trekking movements and slow saccades [26]. SCA VI with clinical symptoms of an autosomal dominant cerebellar ataxia type III has been described as occurring in a single patient in association with increased T2 signal intensity in the MCPs and mild atrophy of the pons and cerebellum [28]. Three separately reported cases of SCA VI have not had the alteration in posterior fossa white matter T2 signal intensity [29]. Patients with SCA type I, II, III, V, VIII, XII, and XIII have been shown to have volume loss of varying severity involving the cerebellar hemispheres, vermis, and pons [30-36]. In PSP tremor and cerebellar ataxia are not usually present, while we can find parkinsonism characterized by axial rigidity, vertical gaze palsy, slow saccades and executive dysfunction [26]. The MRI finding is characterized by the volumetric reduction of the midbrain, predominantly at the tegument, with consequent deepening of the posterior portion of the III ventricle that dilates as a "funnel", like observable in the sagittal scans with thin thickness. When the atrophy is very pronounced the MRI investigation in the axial scans documents the atrophy of the superior colliculi and a deepening of the interpeduncular cistern. With the long TR sequences, it is possible to highlight the astrogliosis as hyperintensities of the periaqueductal region, of the red nuclei and of the Globus pallidus. Because of the increased deposition of iron, the putamina may appear, contrary to the norm, hypointense with respect to the Globus pallidus, in the T2 and T2* weighted sequences [27]. In patients with PSP increased signal intensity has been described as occurring in the superior cerebellar peduncles on proton diffusion-weighted images [37], although normal signal intensity can be seen in the deep cerebellar wm and MCPs. Alterations involving the superior cerebellar peduncles were not shown to occur in the patients with FXTAS. MSA represents three diseases, previously considered as distinct syndrome: Nigro-striatal degeneration (NSD), olivo-Ponto-cerebellar atrophy (OPCA) and Shy-Drager syndrome (SDS). We can speak about forms or variants of MSA: in

cases with prevalence of parkinsonian signs the disease is the MSA-p (MSA-Parkinson type, identifiable with DNS), while in cases with prevalent cerebellar and brain-encephalic dysfunction it is the MSA-c (MSA-cerebellar type, identifiable with the OPCA). The SDS, characterized by Parkinsonian type movement disorders and severe dysregulation of the autonomic nervous system, has no reason to exist as a disease, as its characteristics are present in varying degrees in all forms of MSA [27]. The patients with MSA can show tremor, cerebellar ataxia (MSA-c), parkinsonism (MSA-p), other non-motor symptoms like autonomic dysfunction, dystonia and REM sleep disturbance [26]. The findings of the MR study do not have high sensitivity, especially at an early stage, but, when present, they reflect neuropathological alterations and can make an essential contribution to the diagnosis of the specific form of the disease. In MSA-P atrophy, gliotic degeneration and ferritin iron deposition in putamina involves a typical and specific alteration, the linear signal rim (hyperintense in T2 / DP and FLAIR weighted sequences and hypointense in T2* weighted sequences), in correspondence of the postero-lateral portion of the putamen [38]. A careful examination can also reveal a reduction, sometimes asymmetrical, of the transverse diameter of the putamen, and the atrophy of the head of the caudate nucleus, better visible in the coronal plane, with loss of the typical indentation on the lateral wall of the ventricular frontal horns [27]. While the MRI findings at the basal ganglia are more frequent in case of MSA-P, or MSA-C (predominantly cerebellar symptomatology), the essential neuropathological element is represented by the degeneration of the pontine nuclei and therefore of the transverse fibers of the pons, cerebellar peduncles, wm of the cerebellar hemispheres and olives. On these cases, sometimes associated with basal ganglia findings already described, a typical picture is observed, characterized by the reduction of the pontine volume and T2 hyperintense signal, which highlights the cross-sectional fibers of the pons which can extend to the average cerebellar peduncles, with a cross arrangement, from which the sign of the "hot cross buns" [27]. Among the mentioned and described neurodegenerative diseases, MSA type C can mimic clinically FXTAS more than the others one. In fact, Maureen A. Leehey, et al. [39] recommended genetic testing for FMR1 premutation even in suspected cases of MSA type C. In any case, the presence of the MCPs sign can help a correct diagnostic classification in a patient with movement disorders similar to that described in our case. However, on the other hand there are many other diseases with involvement of MCPs: this is the reason why a differential diagnosis needs to be considered adequately. When approaching abnormal T2 signal in the MCP, entities such Multiple Sclerosis (MS), PML (Progressive Multifocal Leukoencephalopathy), PRES (Posterior Reversible Encephalopathy Syndrome) and certain toxic/metabolic or vascular states should be entertained. Careful evaluation of concomitant correlation with key clinical findings discussed would yield an appropriate and accurate differential diagnosis in most cases. Cerebellar symptoms and signs are reported in 50%80% of MS patients and on conventional MRI frequency of brainstem lesions and cerebellar lesions is 68% and 49%88% respectively [40]. Posterior fossa involvement of JC virus has been reported in 58% of cases [41], when present there is MCP involvement in 64%100% of cases [42]. Involvement of the brainstem by PRES has been documented in 18% of cases [43]. Isolated involvement of the brainstem or basal ganglia was seen in 4% of cases (central variant of PRES) [44] and this "atypical distribution patterns" of PRES can be more common than expected [45]. Toxic/drug induced involvement of the MCP has been reported after heroin inhalation ("chasing the dragon") [46]. Other toxic drug induced abnormalities, such as toluene and methotrexate toxicity, involving the cerebellum and

MCP have also been described [47-49]. MCP is supplied by the anterior inferior cerebellar artery (AICA) and in lesser degree by the superior cerebellar artery. In AICA infarction, that represents an uncommon event (thromboembolic or secondary to severe atherosclerotic disease of basilar artery and branches), specific restricted diffusion is seen in the involved cerebellar peduncle. Wallerian Degeneration (WD) in the MCP can occur in the setting of pontine ischemia or hemorrhage. Increased T2 signal caused by gliosis would correspond to the third of four stages in the evolution of WD, as described by Kuhn, et al. [50]. Increased signal on DWI in the corticospinal tract (CST) have been documented in about 20% of cases of MCA/ACA infarcts as early as 72 h [51] and similarly, restricted diffusion in the CST has been reported at 48 h after MCA ischemia in the pediatric population [52] and in the bilateral MCP at 34 week after acute pontine insult [53-56]. In all cases the changes are attributed to early WD, representing different phases in the development of WD and should not be misinterpreted as ischemic insults. At the end the MCPs can be affected in inherited metabolic disorders represented by Leuco Distrophy (LD). However, there is concomitant, usually symmetric involvement of the supratentorial wm, with sparing of subcortical u-fibers [57].

Conclusion

FXTAS is a relatively rare movement disorder with diverse clinical symptoms including motor, sensory, and cognitive findings that first must be clinically valued. The disorder may mimic other ND, especially MSA C. MRI typically reveals generalized brain atrophy, characteristic bilateral MCPs T2 hyper-intensity (often referred to as the MCPs sign), and sometime T2 hyper-intensity of posterior region of the corpus callosum. However, in order to establish a possible, probable and definitive diagnosis of the disease, a genetic test is always necessary to evaluate the presence of the pre-mutation. Finally, it is mandatory a genetic counselling for the patient and her/his family, due to the potential incidence of this genetic syndrome in children born from the female relatives of the patient carrier.

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