IMAGEM EM NEUROLOGIA/IMAGE IN NEUROLOGY

Fragile X-Associated Tremor/Ataxia Syndrome (FXTAS): Cardinal Radiological Signs

Síndrome de Ataxia/Tremor Associado ao X Frágil: Sinais Radiológicos Cardinais

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Fragile X spectrum disorders encompass a continuum of clinical conditions caused by expansions of cytosine-guanine-guanine (CGG) repeats in the *FMR1* gene on chromosome Xq27.3. Repeats over 200 lead to the most common single-gene cause of developmental delay and autism spectrum disorder - fragile X syndrome (FXS). A lower number of repeats, specifically between 55 and 200, is associated with a group of premutation syndromes, including fragile X-associated tremor/ataxia syndrome (FXTAS) and fragile-X associated primary ovarian insufficiency (FXPOI), among others. The prevalence of the *FMR1* premutation is approximately 1 in 400 males and 1 in 159-200 females in the general population.[1,2]

FXTAS is an adult-onset progressive neurodegenerative disorder that typically manifests after the age of 50, with a mean onset of 62 years. Major clinical criteria for diagnosis include cerebellar gait ataxia and intention tremor. Additional findings may include cognitive decline, neuropathy, parkinsonism and dysautonomia. Among male premutation carriers over the age of 50, approximately 40% develop FXTAS, with penetrance increasing to 75% in men aged 80 years or older; in female carriers, penetrance is lower, approximately 8%–16%.[1-4]

Adults, particularly over the age of 50, who present with otherwise unexplained cerebellar ataxia, intention tremor or mild parkinsonism, especially when accompanied by cognitive decline, peripheral neuropathy, or psychiatric symptoms, should prompt consideration of brain magnetic resonance imaging (MRI), particularly if there is a relevant family history.[1]

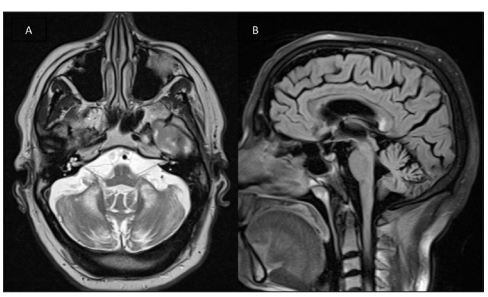

Figure 1. A) Axial T2 — symmetrical white matter lesions in the middle cerebellar peduncles (MCP sign). B) Sagittal FLAIR — white matter lesions in the splenium of the corpus callosum.

The brain MRI presented illustrates characteristic findings in FXTAS, namely T2-weighted symmetric hyperintensities in the middle cerebellar peduncles and white matter lesions in the corpus callosum. Additionally, cerebellar atrophy is present, along with extension of T2 hyperintensity to the brainstem, particularly the pons. Furthermore, there is global cerebral atrophy with ventricular enlargement consistent with ex vacuo dilatation. These were the diagnostic clues for a 62-year-old, previously healthy man with one year of progressive cerebellar gait and limb ataxia and intention tremor, as well as a confirmed fragile X premutation (97 CGG repeats). In carriers of the premutation with one major clinical criterion, these radiological signs have definitive diagnostic value.[1-5]

White matter lesions in the middle cerebellar peduncles are known as the "MCP sign" and are present in approximately 60% of men with

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FXTAS and much less common in women, being present in only 13% of women with this diagnosis. In addition to these radiological hallmarks, additional imaging features include T2 hyperintensity in the splenium of the corpus callosum, white matter T2 hyperintensities in the pons, insula and periventricular regions, T2 hyperintensities in the afferent projections of the middle and superior cerebellar peduncles. Disease progression may lead to moderate-to-severe generalized brain and cerebellar atrophy, with eventual ventricular enlargement.[1-5]

FXTAS is not the only diagnosis that should be considered when hyperintense lesions of the middle cerebellar peduncles (MCP) are present. Differential diagnosis includes demyelinating, toxic-metabolic, degenerative, genetic, vascular or neoplastic diseases. Demyelinating disorders such as multiple sclerosis typically show multifocal or periventricular lesions, rather than isolated MCP involvement. Toxic-metabolic conditions, such as hepatic encephalopathy or osmotic demyelination, often show symmetric involvement of deep nuclei or pontine hyperintensity. Degenerative diseases like multiple system atrophy (MSA) may feature the "hot-cross-bun" sign and pontocerebellar atrophy. Other genetic disorders, such as megalencephalic leukoencephalopathy (MLC) with subcortical cysts and spinocerebellar ataxia type 3 (SCA3), often show subcortical cysts or pronounced pontocerebellar atrophy. Vascular causes produce paramedian pontine hyperintensity related to stroke, while neoplastic lesions such as gliomas cause expansile T2 hyperintensity with mass effect in the MCPs.[6]

In addition, lesions involving the splenium of the corpus callosum have a broad differential diagnosis, including infectious etiologies, postictal changes related to epileptic seizures, metabolic disorders such as hypoglycemia and Marchiafava-Bignami disease, inflammatory conditions like acute disseminated encephalomyelitis, and neoplastic processes, particularly lymphoma. The coexistence of symmetric MCP involvement and splenial corpus callosum lesions significantly narrows the differential diagnosis, with FXTAS being a key consideration in the appropriate clinical context.

The diagnosis of FXTAS relies on genetic testing, clinical, radiologic and neuropathological criteria, and early identification is crucial for appropriate genetic counseling, family risk assessment, and multidisciplinary management to optimize outcomes and guide targeted interventions. ■

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