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MRI ANOMALIES AMONG ASYMPTOMATIC MALE CARRIERS OF THE FRAGILE X PREMUTATION

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Fragile X-associated tremor/ataxia syndrome (FXTAS) is a progressive movement disorder accompanied by cognitive impairment, affecting persons who carry the fragile X premutation (a CGG trinucleotide expansion with 55 - 200 repeats). Males are more commonly affected than females. Mean age of onset of neurologic symptoms is the early 60s. FXTAS is neurodegenerative, but also may be a neurodevelopmental disorder that manifests after decades of what is thought to be an mRNA toxic gain of function process. We tested the hypothesis that premutation carriers may show preclinical radiologic signs associated with FXTAS, but no clinical neurological findings. We compared blinded clinical and volumetric MRI data for 29 asymptomatic male carriers (mean age = 59.1, mean CGG repeat = 81.8, range 57-150) with those for 39 males with normal *fmr1* alleles (mean age = 64.1, mean CGG repeat = 30.2, range 15-47). Three carriers (10.7%) showed bilateral hyperintensities in the middle cerebellar peduncles (MCPs); no controls showed the MCP sign (chi-square = 4.37, $p < 0.05$). Clinically, there were no differences in distribution or location of cerebral white matter hyperintensities. On every measure of volume (whole brain, cerebrum, cerebellum, left/right hippocampus, total hippocampus, third and lateral ventricles combined), z-scores for volumes of asymptomatic carriers were below the mean, while z-scores for controls were above the mean. However, using OLS regression controlling for age and education, there were no significant differences for any volumetric measure. The MCP sign is observed in a significant number of asymptomatic carriers, and given that it is only present in 50% to 70% of individuals with FXTAS, the results suggest that neuropathologic changes might be identified prior to onset of FXTAS in 20% of apparently unaffected carriers. More sensitive imaging techniques, such as diffusion tensor imaging, may a higher prevalence of white matter anomalies among asymptomatic premutation carriers.

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