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Tremor and Other Hyperkinetic Movements

Case Reports

A Treatable Rare Cause of Progressive Ataxia and Palatal Tremor

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Abstract

Background: Cerebrotendinous xanthomatosis is a rare autosomal recessive neurometabolic disorder characterized by chronic diarrhea, tendon xanthomas, juvenile cataracts, and neurological symptoms.

Case Report: An adult patient with cerebrotendinous xanthomatosis exhibited ataxia and palatal tremor in the absence of tendon xanthomas and cataracts.

Discussion: The importance of this case resides on the fact that cerebrotendinous xanthomatosis should be considered as a possible etiology of the syndrome of progressive ataxia with palatal tremor, even in the absence of tendon xanthomas and cataracts. Early diagnosis is critical to the institution of specific treatment with chenodeoxycholic acid.

Keywords: Palatal tremor, ataxia, cerebrotendinous xanthomatosis, diagnosis

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Introduction

Cerebrotendinous xanthomatosis (CTX) is a rare autosomal recessive neurometabolic disorder characterized by infantile or early childhood onset of chronic diarrhea, tendon xanthomas, cataracts, and neurological problems, such as behavioral disorders, cognitive impairment, peripheral neuropathy, dystonia, parkinsonism, epilepsy, myoclonus, and progressive cerebellar ataxia, that usually start in the second or third decades of life.[1,2] This disease is caused by mutations in the *CYP27A1* gene that result in decreased production of chenodeoxycholic acid and elevated levels of cholestanol and bile alcohols.[3] Chenodeoxycholic acid is an established treatment that restores metabolic abnormalities and may improve or even prevent neurological deterioration,[4] especially if it is instituted at the early stages of the disease process.[5]

Case report

A 31-year-old female with no family history of neurological disease or consanguinity was evaluated after a 4-year history of gait instability, dysarthria, and dysphagia. She had a relevant history of chronic diarrhea at early childhood and depression since 20 years of age. Physical examination disclosed spasmodic-like dysphonia, altered saccadic eye movements, pyramidal signs, proximal and distal muscle wasting in the upper and lower limbs, palatal tremor at low frequency without ear or throat clicks, and mild limb and gait ataxia (Video 1). The Scale for the Assessment and Rating of Ataxia (SARA) score was 15. No tendon xanthomas were present (Figure 1). Electromyography and a nerve conduction study revealed a sensorimotor axonal polyneuropathy. Brain magnetic resonance imaging (MRI) displayed mild cerebellar atrophy and bilateral hyperintensity of the dentate nuclei on fluid-attenuated inversion recovery and T2-weighted images, with a central hypointensity suggestive of calcification (Figure 2A, left and central) and bilateral hyperintensity of the basal ganglia (Figure 2A, right). The olivary nuclei showed a serpiginous abnormal signal, although there was no classic olivary hypertrophy (Figure 2B, left). A brain computed tomography scan showed subtle calcifications in the white matter surrounding the dentate nucleus (Figure 2B, right). Routine work-up studies for ataxia, such

as alpha-fetoprotein, thyroid function and anti-thyroid peroxidase antibodies, celiac disease antibodies (transglutaminase, anti-gliadin, and anti-endomysial), anti-neuronal antibodies, ceruloplasmin, human immunodeficiency virus, cupruria, vitamin B1, B12, and vitamin E levels were normal or negative, except for plasmatic cholesterol levels, which were low (111 mg/dL). CAG repeat determination in the *ATXN1*, *ATXN2*, *ATXN3*, *CACNA1A*, and *ATXN7* genes were negative. Whole-exome sequencing detected two heterozygous variants (c.1183C>T p.(Arg395Cys) and c.1184+1G>A) in the *trans*-phase in the *CYP27A1* gene consistent with a diagnosis of CTX. Cholestanol levels in the serum and tendons were not available for evaluation in our patient. Treatment with chenodeoxycholic acid was started, with improvement of irritability and gait instability (SARA scores slightly improved from 15 to 14 points because of a change in the item that measures stance) and weight gain.

Discussion

This patient with CTX exhibited palatal tremor and progressive ataxia as the most prominent clinical signs, but without tendon xanthomas and juvenile cataracts, which are clinical hallmarks of CTX. The frequency of juvenile cataracts and tendon xanthomas in CTX patients averages 88% and 78%, respectively.[6] We cannot rule out the possibility that both problems can appear later in the course of the disease. However, this possibility would be very low, as approximately 75% of CTX patients present with cataracts, often appearing in the first decade of life, whereas xanthomas commonly develop in the second or third decade.[6,7] Large deposits of cholesterol and cholestanol, the 5-alpha-dihydro derivative of cholesterol, are found in virtually every tissue, particularly the Achilles tendons.[7] Low cholesterol and high cholestanol levels in the serum and tendons support the diagnosis of this entity, besides genetic testing.[3,7] Reports of palatal tremor (also referred previously as palatal myoclonus) in genetically confirmed patients with CTX are rare.[8,9] This atypical case combines palatal tremor and ataxia in the absence of the most characteristic clinical features of CTX, thus highlighting the phenotypic variability of this genetic entity. The syndrome of familial or sporadic progressive ataxia and palatal tremor (PAPT) is rare in clinical practice and the cause usually remains uncertain.[10,11] In the sporadic form, brain MRI frequently shows hyperintensity in the inferior olivary nuclei.[10] Even though no classic olivary hypertrophy was found in the patient described here, the olivary nuclei contained a serpiginous abnormal signal suggestive of a "forme fruste" or variant of olivary hypertrophic degeneration. Also, olivary hypertrophy may not be evident with routine MRI sequences, and its presence depends on the stage of olivary degeneration.[12] Despite the subtle olivary nuclei abnormalities, the clinical picture may exceed the classical PAPT syndrome.

A number of differential diagnoses must be considered in patients with progressive ataxia and palatal tremor. For example, the combination of ataxia, palatal tremor, dysphonia resembling spasmodic dysphonia, and dentate calcifications may orient to spinocerebellar ataxia type 20.[13] The hyperintensities observed in the dentate nucleus and the surrounding white matter are common features reported in CTX.[14] Other entities that present with progressive ataxia and palatal

Video 1. Cerebrotendinous xanthomatosis revealed by ataxia and palatal tremor in the absence of tendon xanthomas and cataracts. A 30-year-old female with genetically confirmed cerebrotendinous xanthomatosis showing mild limb and gait ataxia (**Segment 1A and 1B**) and palatal tremor at low frequency (**Segment 1C).**

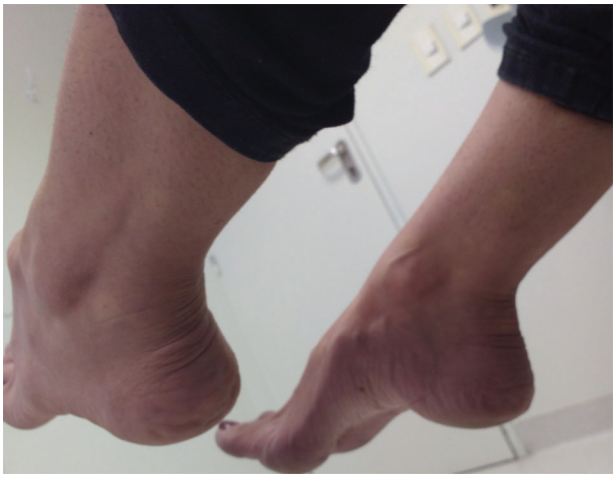

Figure 1. **Imaging of both feet**. Atrophy of the distal foot muscles and absence of xanthomas in the Achilles tendons. There were also no xanthomas in other body parts.

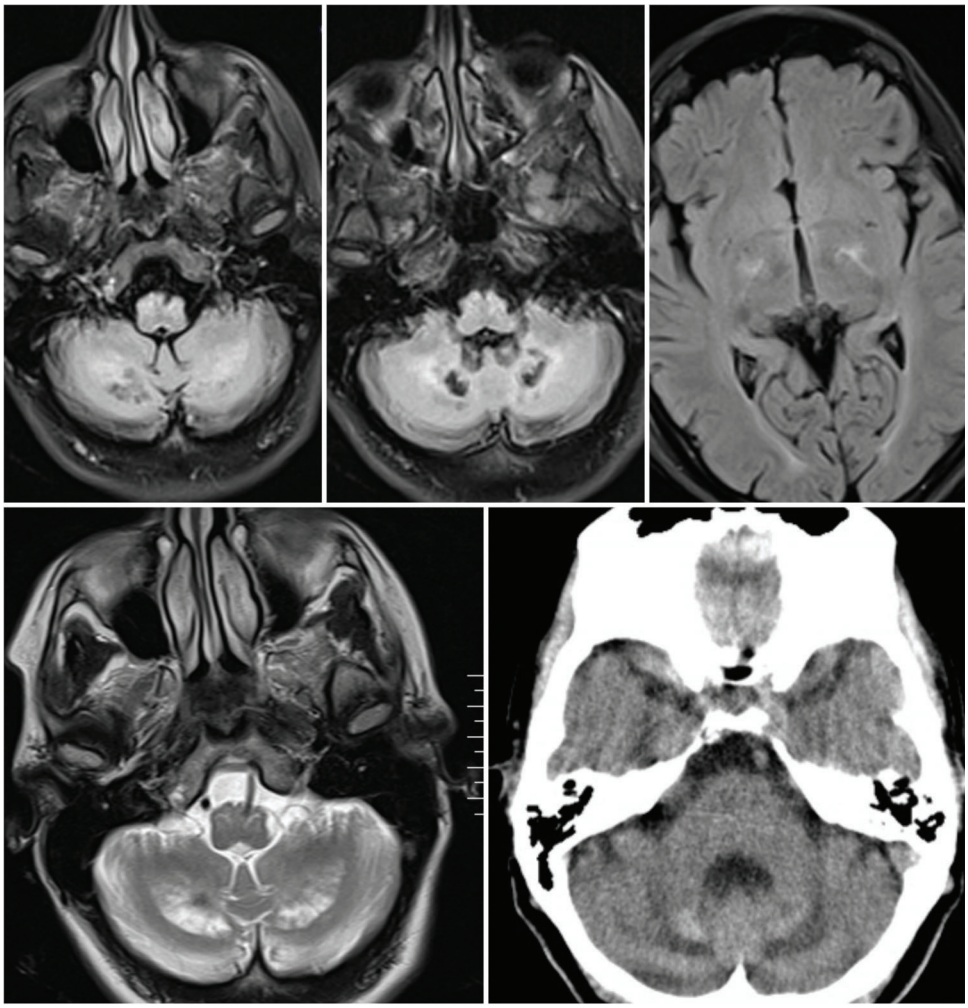

Figure 2. **Brain Magnetic Resonance Imaging**. (A) Flair and T2-weighted images display mild cerebellar atrophy and bilateral hyperintensity of the dentate nuclei on Flair and T2-weighted images with a central hypointensity suggestive of calcification (left and central). Bilateral hyperintensity of the basal ganglia (right). (B) Olivary nuclei with a serpingous abnormal signal (left). Subtle calcifications in the white matter surrounding the dentate nucleus (right).

Table 1. **Differential Diagnosis of Progressive Ataxia and Palatal Tremor**

Disease Name (Gene)	Inheritance	Main Clinical Features Besides Ataxia and Palatal Tremor	MRI Findings
Spinocerebellar ataxia type 20 (SCA20)[13,17]	AD	Dysphonia resembling spasmodic dysphonia, dysarthria, hypermetric saccades, postural tremor, pyramidal signs	Dentate calcifications and cerebellar atrophy
Spastic paraplegia type 7 or HSP/ATX-SPG7 (SPG7)[18]	AR/AD	Spastic paraparesis, optic atrophy, nystagmus, chronic external ophthalmoplegia-like phenotype, pes cavus, decreased vibratory sense in the lower limbs, scoliosis	Cerebellar and spinal cord atrophy
Neuroferritinopathy or NBIA/CHOR-FTL (FTL)[19,20]	AD	Chorea, oromandibular dyskinesia, dystonia, parkinsonism, dysphagia, psychiatric symptoms, cognitive impairment	Iron accumulation in globus pallidus, caudate, putamen, substantia nigra, red nucleus; cystic basal ganglia changes and pallidal necrosis

Table 1. Continued

Disease Name (Gene)	Inheritance	Main Clinical Features Besides Ataxia and Palatal Tremor	MRI Findings
Alexander disease (GFAP)[10,21–23]	AD	Psychomotor regression, spasticity, seizures, pyramidal signs, pseudobulbar signs, macrocephaly	Extensive cerebral white-matter abnormalities with a frontal preponderance, periventricular rim, basal ganglia abnormalities, hydrocephalus
POLG-related disorders (POLG)[24–27]	AR	Dystonia, chorea, myoclonus, tremor, progressive external ophthalmoplegia, seizures, cognitive impairment, psychiatric symptoms, cataracts, optic atrophy, peripheral neuropathy, muscle weakness and atrophy, hypogonadism, stroke-like episodes	Cerebellar atrophy or normal
GM2-gangliosidosis type II or Sandhoff disease (HEXB)[28]	AR	Progressive mental and motor deterioration, macular cherry red spot, blindness, spastic paraparesis, muscular atrophy, fasciculations, dysmorphic features, startle reaction, cardiomegaly, episodic abdominal pain, chronic diarrhea, hepatosplenomegaly	Bilateral symmetric thalamic lesions, hyperintensities in the periventricular, deep, and subcortical white matter, delayed myelination
Progressive ataxia and palatal tremor due to a four-repeat tauopathy[29,30]	Sporadic	Dysarthria, dysphagia, hearing loss, blurring vision, nystagmus	T2 hyperintensities in the bilateral inferior olivary nuclei and cerebellar atrophy
Progressive ataxia and palatal tremor syndrome[10,31,32]	Sporadic (rarely familial)	Dysarthria, nystagmus	T2 hyperintensity and hypertrophy of the bilateral inferior olivary nuclei and cerebellar atrophy
Gluten sensitivity ataxia[33]	Sporadic	Dysarthria	T2 hyperintensity and hypertrophy of the bilateral inferior olivary nuclei and cerebellar atrophy
Multiple system atrophy (cerebellar subtype)[19]	Sporadic	Autonomic failure, action tremor, nystagmus, pyramidal signs, dysarthria, dysphagia	Atrophy of the putamen, middle cerebellar peduncle, or pons. The "hot-cross-bun sign" (cruciform hyperintensity in the pons) in T2-weighted sequences

Abbreviations: AD, Autosomal Dominant; AR, Autosomal Recessive; MRI, Magnetic Resonance Imaging.

tremor are listed in Table 1. A functional disruption in the "Mollaret's triangle", formed by the red, dentate, and inferior olivary nuclei has been postulated as the cause of palatal tremor.[15] Presumably, in this patient, the palatal tremor arose because of a disruption of the dentatorubroolivary circuit secondary to the lesions in the olivary nuclei and dentate nuclei.

Neurologists should consider CTX when ataxia, palatal tremor, and dentate nuclei hyperintensities are present, even in the absence of tendon xanthomas and cataracts. Patients with progressive ataxia and palatal tremor should be exhaustively studied, because some cases, as the one described here, are not sporadic, but of genetic origin and also susceptible to specific treatment.[16] CTX should be added to the differential diagnosis of progressive ataxia and palatal tremor.

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