Movement Disorders
CLINICAL PRACTICE

CASE REPORT

High-Frequency Palatal Tremor and Stimulus-Sensitive Leg Myoclonus with Degeneration of Inferior Olivary Nuclei in Celiac Disease

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Classical "symptomatic palatal tremor" with a frequency of 2 to 3 Hz is often associated with ataxia and pseudo-hypertrophy of inferior olives on neuroimaging. Stimulus-sensitive foot myoclonus has been reported in a case series of celiac disease patients, but without palatal tremor.[1] Here we present a patient with biopsy-proven celiac disease and stimulus-sensitive leg myoclonus, case 2 in the previous series, who subsequently developed a unique high-frequency (approximately 7 Hz) palatal tremor and pharyngeal and laryngeal tremors. Neuropathological examination demonstrated inferior olivary nuclei degeneration without pseudo-hypertrophy.

Case Report

A 57-year-old man presented with intermittent twitching movements of the left toes that worsened during next few years to involve the left ankle, the leg, and eventually the left thigh. These movements were jerky, present at rest, increased with action, and occurred when sitting or when lying or during sleep. He subsequently developed similar involuntary movements in the right leg with progressive gait imbalance requiring full support for walking. At age of 68, the patient became aware of the development of tremor of his palate acutely for 1 day, followed by involvement of voice, cheek, and eyelids during the next few days (Video S1). The patient's medical history included refractory celiac disease type II (presence of abnormal intraepithelial lymphocyte despite a strict gluten-free diet for >1 year), but without malignancy, namely enteropathy-associated T-cell lymphoma.

Blood testing showed macrocytic megaloblastic anemia, elevated transglutaminase antibody (65 units/mL; normal <4 units/mL), and antiendomysial antibody (1:80; normal less than 1:5). Cerebrospinal fluid testing showed elevated protein 58 mg/dL, normal glucose of 31 mg/dL, cell count of 50 (74% lymphocytes,14% neutrophils, 12% monocytes), normal immunoglobulin G 4.89 mg/dL (0.5–6 mg/dL) without oligoclonal bands. Continuous electroencephalogram showed repetitive epileptiform discharges over the Cz electrodes (right worse than left), which were consistent with epilepsia partialis continua. Dopamine transporter scan was normal. Brain magnetic resonance imaging showed age-appropriate cerebral atrophy. Small intestinal biopsy revealed villous blunting and intraepithelial lymphocytes. A gluten-free diet and several medications, including clonazepam, levetiracetam, carbamazepine, mycophenolate, trihexyphenidyl, methylprednisolone, and intravenous immunoglobulins, were tried without benefit.

The patient died at the age of 69 after suffering from failure to thrive, requiring a feeding tube and tracheostomy, during his last year of life. Neuropathological evaluation of the brain showed degenerative changes involving the inferior olivary nuclei with marked myelin loss of the olivocerebellar fibers bilaterally, without features of pseudo-hypertrophy of the olives. The findings that stood out the most were the discrete segments of gliosis and absence of neurons in bilateral inferior olivary nuclei (Fig. 1). This was observed in both the ventral and dorsal arms of

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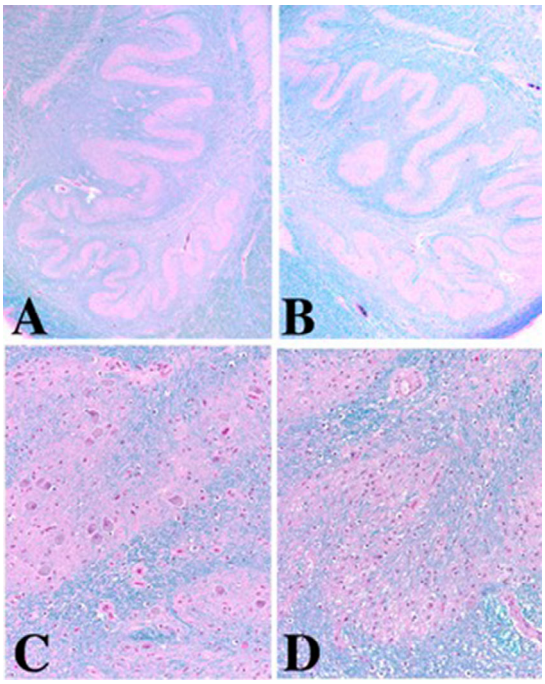

FIG. 1. Degenerative changes involving the inferior olivary nucleus (ION) with marked myelin loss of the olivocerebellar fibers bilaterally without features of pseudo-hypertrophy of the olives. (**A**) Left ION. (**B**) Right ION. (**C**) Relatively spared dorsal arm of the left ION. (**D**) Ventral arm of the left ION showing severe neuronal loss.Luxol fast blue counterstained with hematoxylin and eosin (A–D). Original magnification: A and B, 25×; C and D, 200×.

the right inferior olive, and the ventral arm was more severely affected on the left side. Marked myelin loss was noted at the hili of the inferior olivary nuclei and the olivocerebellar fibers. Interestingly, there was no myelin loss in bilateral central tegmental tracts. We did not identify features of inferior olivary hypertrophy, for example, vacuolated neurons and prominent bizarre fibrillary astrocytes.

Discussion

Palatal tremor is defined as a rhythmic movement disorder of palate, and subcategorized as (1) symptomatic palatal tremor (SPT), which is associated with changes involving the brainstem or cerebellum (within the Guillain-Mollaret triangle) and as (2) essential palatal tremor of unknown etiology.[2] Lesions resulting in SPT are often associated with ataxia (typically static). In a subset of SPT cases, the syndrome of progressive ataxia and palatal tremor[3] has been described in the settings of tauopathy,[4] a number of genetic disorders including polymerase gamma (*POLG*) gene mutations,[5] and rarely gluten sensitivity (see below).[6] Hypertrophic olivary degeneration (on magnetic resonance imaging or postmortem) is a common feature of many but not all causes of SPT, including those presenting with the progressive ataxia and palatal tremor syndrome.[7,8]

The pathologic findings described in patients with celiac disease with neurological complications include the loss of Purkinje cells; spongiform demyelination in the posterior and lateral columns; lymphocytic infiltrates involving the spinal cord, hypothalamus, cerebellum, and brainstem; and neuronal loss and gliosis involving the neostriatum and brainstem.[9] One case report described a patient with celiac disease with encephalitis and unilateral pseudohypertrophy of the inferior olivary nucleus.[10] Our patient had bilateral and discrete segmental atrophy of the inferior olivary nuclei, but no other detected changes that could be related to celiac disease. We hypothesize that the neuropathological findings in this patient are remnants of remote episodes of focal autoimmune damage targeted to the inferior olivary nuclei in the setting of celiac disease. This hypothesis is supported by the qualitative and topographic spectrum of damages recorded in patients with established celiac disease in addition to the involvement of the inferior olivary nuclei as the target for inflammatory infiltrate in patients with paraneoplastic etiology.[11,12]

Celiac disease is an autoimmune enteropathy that can present with variable neurological syndromes,[13] including cortical myoclonus and ataxia.[14] Recently, stimulus-sensitive foot myoclonus was identified as a distinct clinical sign for celiac disease with neurological involvement.[1] Three cases of celiac disease with classic 2 to 3 Hz palatal tremor/myoclonus have been reported previously.[6,15,16]The high-frequency palatal tremor (approximately 7 Hz; see supplemental materials for supportive data from electromyography recording) observed in our patient was significantly faster (7 Hz compared with 2–3 Hz) than the previously reported cases of palatal tremor, with or without celiac disease. Furthermore, our patient had similar high-frequency tremor in additional branchial arch structures (pharynx and larynx). To our knowledge, this unique high-frequency branchial tremor has not been reported previously.

This case report expands the phenomenology and neuropathology of SPT, celiac disease–associated neurological syndrome, and inferior olivary nuclei degeneration. This case report also adds to the literature[17] that degeneration of inferior olive may contribute to the pathophysiology of palatal tremor.

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Author Roles

(1) Research Project: A. Conception, B. Organization, C. Execution; (2) Manuscript Preparation: A. Writing of the First Draft, B. Review and Critique.

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Disclosures

Ethical Compliance Statement: The authors confirm that the approval of an institutional review board was not required for this work. The patients have given written and informed consent for online publication of their videos. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines.

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Supporting Information

Supporting information may be found in the online version of this article.

Appendix S1. Supporting Information

Video S1. Stimulus-sensitive leg myoclonus, gait impairment (slow and careful steps with wide-base gait and imbalance in both standing and walking) and high-frequency tremor (palatal, pharyngeal, laryngeal, and voice) observed in this patient, and comparison of this patient's high-frequency (approximately 7 Hz) palatal tremor with low-frequency (2–3 Hz) palatal tremor previously reported in literature.