Movement Disorders
CLINICAL PRACTICE
CASE SERIES

Stimulus Sensitive Foot Myoclonus: A Clue to Coeliac Disease

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ABSTRACT: Background: Coeliac disease (CD) is an autoimmune enteropathy that may feature extraintestinal manifestations including cerebellar ataxia and myoclonus.
Methods and Results: A descriptive series of five patients with CD who presented with prominent stimulus-sensitive foot myoclonus.
Conclusions: Stimulus-sensitive foot myoclonus is a distinct clinical sign and may be a useful clue to the diagnosis of CD.

Introduction

Stimulus-sensitive foot myoclonus is a distinct neurological sign and can be the presenting or predominant feature in a limited number of differential diagnoses. These encompass mitochondrial disease,[1] corticobasal syndrome,[2] structural lesions,[3] and, as we present here, coeliac disease (CD).[4] Here, we report an illustrative case series in order to highlight the association of stimulus-sensitive foot myoclonus and CD, and to emphasize the red flags pointing to the correct diagnosis.

Case One

After an episode of diarrhea and stomach cramps that lasted two months, a 48-year-old man developed jerks of his left-foot that were most noticeable when trying to put on his socks. He also noted a shaking of his hands. One year later, he developed speech and walking difficulties. Examination at this time showed generalized spontaneous and stimulus-sensitive myoclonus, most prominently affecting the left-foot. Cerebellar signs included limb dysmetria, dysdiadochokinesia, and a broad-based gait with difficulties on tandem walking (Video 1). There was generalized hyperreflexia with downgoing plantars, and we noticed a rash on both elbows. Video EEG-EMG recording of the left-leg showed muscle jerks of short duration (25–50 ms), brief and sudden interruption of tonic activity, a definite pyramidal pattern of muscle activation, and a clear response to tactile stimulation; EEG jerk-locked back averaging was impossible to interpret due to muscular EEG artifacts. The findings were consistent with cortical myoclonus (positive and negative). The diagnosis was also supported by the presence of giant cortical somatosensory evoked potentials and C-reflex. Brain MRI showed generalized atrophy with prominent cerebellar involvement. Gliadin and transglutaminase antibodies were negative, but a duodenal biopsy showed total villous atrophy and raised intraepithelial lymphocyte count in keeping with a diagnosis of CD. Treatment with clonazepam, a gluten-free diet (GFD), and immunosuppressants did not ameliorate the symptoms. Levetiracetam provided partial benefit, but the neurological symptoms progressed.

Case Two

A 65-year-old man noticed intermittent twitching movements of his left toes around the age of 57. Five years later, they progressed to involve the whole foot and calf, and became larger in amplitude. Moving the leg, or even thinking of moving it,

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consistently prompted the jerks, but they also occurred at rest. Subsequently, the jerks became more violent and disabling. He had multiple falls without any obvious precipitant or loss of consciousness. The patient then noticed a symptom spread to the right foot. Examination revealed myoclonus affecting both feet. Any active or passive attempt to move the legs elicited myoclonus (Video 2). An extensive diagnostic workup in blood and CSF was positive only for blood tissue transglutaminase and endomysial antibodies. A small intestine biopsy showed villous blunting and intraepithelial lymphocytes compatible with CD. Continuous EEG monitoring showed nonstop spikes and polyspikes in the paracentral cortex over the leg area, present when the patient was awake and asleep, in keeping with the leg myoclonus being present during sleep. Discharges preceded the myoclonus at a fixed interval as demonstrated by bipolar surface EMG leads. A diagnosis of cortical myoclonus, secondary to CD, was made. GFD was ineffective to control the neurological symptoms, and treatment with levetiracetam provided partial improvement.

Case Three (Previously Reported in 5)

This woman developed diarrhea and severe weight loss at the age of 60, and received a diagnosis of CD based on a duodenal biopsy. At age 67, she complained about spontaneous jerky movements in the left foot. These were triggered whenever she tried to put her shoes on or place the foot on the floor. Examination showed walking difficulties due to flurries of myoclonic jerks in the left leg, as well as spontaneous and stimulus-sensitive foot myoclonus. There was also mild dysdiadochokinesia in the upper limbs, and a distal loss of touch and vibration sense in a glove and stocking distribution. Complementary tests proved a cortical origin of the myoclonus and mild sensory neuropathy. GFD improved the digestive symptoms at onset without any effect on neurological manifestations.

Case Four[5]

This man developed first symptoms at the age of 41, when he noticed tingling in the left fingers and jerks in his left hand. Subsequently, jerks affecting his left leg, precipitated by touching the floor, interfered with walking. Examination revealed marked spontaneous and stimulus-sensitive myoclonus, more pronounced in the left leg, and additional gait ataxia. The diagnostic workup confirmed a cortical origin of myoclonus by electrophysiology. Serum gliadin antibodies were negative, but a suspected diagnosis of CD was corroborated by duodenal biopsy. GFD was ineffective, and the neurological symptoms were progressive.

Case Five[6]

At the age of 60, this 73-year-old woman observed that her left foot would jump when she attempted to put on shoes or socks. Over the ensuing months, she also noted a twitching of the left side of her face. At age 63, neurological examination showed involuntary twitches of the orbicularis oris that worsened when speaking, and myoclonus of the left foot during tactile stimulation or when walking. Poly-EMG and EEG with back averaging confirmed cortical myoclonus. An extensive diagnostic workup at that time (see Supporting Information), also comprising brain and spine MRI, was unremarkable. A gut biopsy showed normal small intestinal mucosa with normal intraepithelial lymphocyte count. Two years later, another brain MRI showed generalized volume loss, including the cerebellum. During her disease, she was occasionally tested positive for tissue transglutaminase IgA antibodies (8.1–9 U/ml, normal range 0–6.99 U/ml), and endomysium and gliadin IgG and IgA antibodies. Because of the serological signature of CD-related antibodies and the fact that her clinical picture closely resembles the other cases, a diagnosis of possible CD-related myoclonus was made. The patient refused a second biopsy, but tried GFD, resulting in the disappearance of CD-related antibodies. That disappearance, however, did not improve her symptoms, which also progressed to mildly involve the right side (Video 3). Symptomatic treatment with levetiracetam (750 mg BD) and valproate (400 mg BD) proved mildly effective.

Discussion

Here, we present five patients with prominent stimulus-sensitive and action-induced foot myoclonus as the initial neurological presentation of CD. Myoclonus was mostly unilateral, and occurred either in isolation or associated with other neurological signs (cerebellar ataxia more frequently than neuropathy). Whereas some patients had symptoms of enteropathy or a diagnosis of CD before the onset of myoclonus, in some cases,[2,4,5] it was the characteristic foot myoclonus that prompted the diagnosis.

CD is a chronic immune-mediated enteropathy precipitated by exposure to dietary gluten and strongly associated with certain HLA types. It has become clear that various extraintestinal symptoms may occur unrelated to intestinal malabsorption, including dermatitis herpetiformis, as seen in case one.

Neurological involvement is relatively frequent, occurring in up to one-third of the cases.[4] Cerebellar ataxia, sometimes associated with progressive myoclonus, is the most frequent movement disorder presentation.[4,5] While there is a link between cerebellar pathology and cortical myoclonus in CD,[7] and antibodies against a brain expressed transglutaminase, TG6, have been found in patients with cerebellar ataxia,[8,9] the pathophysiological link between CD and the neurological presentation is not fully understood.[10,11] It has been suggested that tissue transglutaminase antibodies may cross-react with neuronal antigens,[12–14] but it remains unclear how the antibodies should access their intracellular targets in vivo.

The fact that GFD seems not to consistently improve CD-related neurological symptoms,[5,11] and the concept of extraintestinal manifestations without enteropathy,[15] suggests that the autoimmunity to the gut and the neurological manifestations may not be closely linked, especially in cases with myoclonus. Indeed, refractory CD can be severely disabling, despite GFD and poly-immunotherapy and the normalization of gut mucosa under this regime.[11]

In our patients, GFD did not improve the neurological manifestation, albeit seronegativity as confirmation of adherence to GFD was only available in case five. In this patient, despite adherence to GFD, neurological symptoms still progressed. Longitudinal biopsies to investigate for refractory CD were not available. The main aim of this paper, however, is to highlight the phenomenology and its implication for differential diagnostic considerations.

Foot myoclonus, either isolated or combined with other signs, is a rather distinct clinical sign and is seen with a limited number of conditions.[16] Structural lesions, in particular of the posterior or posterolateral thalamus and less frequently of the posterolateral putamen, can cause focal myoclonus.[3,17] The origin of the myoclonus due to basal ganglia lesions is subcortical, and the response to external stimuli is typically not as prominent, as observed in our cases with cortical myoclonus due to CD.

Cortical lesions can cause epilepsia partialis continua (EPC), a simple focal motor status epileptics resulting in spontaneous and repetitive jerks restricted to a specific body region, which may be aggravated by action, or be stimulus-sensitive. CD patients can display focal, continuous, and spontaneous myoclonus of cortical origin, fulfilling the definition of EPC.[11] Indeed, patient two presented with spontaneous jerks that persisted during sleep, a feature frequently seen in EPC. However, EPC more frequently affects the upper body, and often features other signs such as hemiparesis or other cortically generated deficits.[18] Of course, EPC can be caused by various other etiologies, for example vascular, inflammatory, or neoplastic, with a corresponding structural lesion on imaging. Another cause of EPC and cortical myoclonus are mitochondrial disorders, and muscle biopsy and/or genetic testing should be considered in the workup of such cases, although isolated presentations are probably rare.[1,19] Similarly, although distal focal myoclonus, spontaneous or triggered by movement or sensory stimulation, is seen in up to 57% of cases of corticobasal degeneration,[20] additional signs like apraxia or cortical sensory deficits are typically present.[18] In contrast, isolated foot myoclonus can be seen in "primary progressive myoclonus of aging,"[6] which is defined by a cortical origin of myoclonus in the absence of secondary causes or other clinical features. The diagnostic criteria include age older than 65 years; however, reports of younger patients with a similar phenotype query this definition.[6] It seems conceivable that this is a syndrome, rather than an entity, and it may be that CD may be underlying in some of these cases, as illustrated by case five.

In summary, stimulus-sensitive foot myoclonus can be a manifestation of CD and occur either in isolation or associated predominantly with signs of cerebellar ataxia. Of note, it may manifest in the absence of CD-enteropathy, and therefore, a high index of suspicion is required.

Author Roles

1. Research Project: A. Conception, B. Organization, C. Execution; 2. Statistical Analysis: A. Design, B. Execution, C. Review and Critique; 3. Manuscript Preparation: A. Writing the First Draft, B. Review and Critique.

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Disclosures

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Supporting Information

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

Supporting Video 1 This video shows patient one. The initial segment shows that this man has great difficulties in putting his sock due to stimulus-sensitive myoclonic jerks of his right foot. The stimulus-sensitivity is demonstrated by touch. In addition, there is some mild action myoclonus affecting the face when he moves or opens his eyes, and stimulus-sensitive myoclonus of his hands (right more than left). When walking, he is unsteady and shows cerebellar signs on the heel shin test.

Supporting Video 2 This video shows patient two, with prominent myoclonus mainly of the left leg that is spontaneous and also induced by touch and action, thereby, also interfering with gait. In addition, he has some dysmetria and increased tone in the left leg and a wide-based, unsteady gait.

Supporting Video 3 This video shows patient five with myoclonus involving the left more than the right side of the face. There is very subtle stimulus-sensitive myoclonus of the left more than the right hand. Myoclonus is most prominently affecting the left leg, with stimulus-sensitive myoclonus of the foot. When attempting to put the left shoe on, there is action's myoclonus of the left leg, but also less pronounced on the right. She is in a wheelchair as the leg myoclonus prevents safe stance and gait.

Supporting Table 1. Ancillary investigations.

Supporting Table 2. Prescribed treatments during follow-up.