Opsoclonus-Myoclonus Associated With Celiac Disease

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Celiac disease may be associated with various neurologic manifestations, most commonly cerebellar ataxia. This report describes a 2-year-old male who presented with opsoclonus-myoclonus syndrome including action myoclonus, palpebral flutter, opsoclonus, and ataxia. Given the severity of ataxia, the child was unable to sit or walk independently. Brain magnetic resonance imaging was normal on two occasions (4-week interval). Oligoclonal bands were found in the cerebrospinal fluid. Blood and serum examinations were unremarkable, with no evidence of infectious seroconversion. However, autoantibody testing indicated the presence of antigliadin antibodies of immunoglobulin A subtype, anti-endomysial antibodies, and anti-CV2 antibodies that were not, however, detected in the cerebrospinal fluid. Duodenal biopsy documented villous atrophy confirming the diagnosis of celiac disease. This case confirms that initial presentation of celiac disease may be restricted to neurologic features. We suggest that a search for evidence for celiac disease should be included in the evaluation of opsoclonus-myoclonus.

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Introduction

Celiac disease is a genetic [1], immunologically mediated disease [2]. The classical consequence of the abnormal response of the immune system to the ingestion of gluten is an enteropathy. Symptoms occur commonly weeks or months after gluten introduction in the diet, with a malabsorption syndrome, but the diagnosis is sometimes delayed up to adulthood [3]. The Working Group of the European Society of Paediatric Hepatology, Gastroenterology, and Nutrition has defined diagnostic criteria for celiac disease including the histologic lesions of intestinal villous atrophy, crypt hyperplasia, and intra-epithelial lymphocytic infiltration. The immune response to gluten may also occur in other tissues [4]. Antigliadin, antireticulin and, more specifically, anti-endomysium and immunoglobulin A anti-transglutaminase antibodies are detected in the serum of the patients [4,5]. With serologic testing, asymptomatic or atypical presentations are now recognized. Associated conditions such as Down syndrome, autoimmune diseases, and nonintestinal involvement have been described [6]. Neurologic manifestations occur in 8% to 10% of the patients with celiac disease [7]. Neurologic involvement includes cerebellar ataxia, myelopathy, brainstem encephalitis, progressive multifocal leukoencephalopathy, encephalopathy, dementia, seizures, progressive myoclonic ataxia, peripheral neuropathy, and internuclear ophthalmoplegia [2,8,9]. This report presents a child who developed opsoclonus-myoclonus syndrome together with gastrointestinal symptoms of malabsorption and evidence for celiac disease.

Case Report

A 2-year-old male of Italian origin with no remarkable past medical, developmental, or family history progressively developed cerebellar ataxia, action myoclonus, palpebral flutter, and opsoclonus of increasing severity over a 3-week-period (Fig 1). He had diarrhea during the days preceding the occurrence of these symptoms. The child became unable to sit or walk independently. His voice changed (dysphonia), and he manifested dysarthria that evolved into anarthria. In addition, marked lower limb myoclonus was persistent during sleep.

Routine blood examination, protein electrophoresis, urine analysis, thyroid and parathyroid function tests, serum levels of vitamin B12, folate and vitamin E were normal. Blood lactate and pyruvate, blood and urine amino acids, and urine organic acids were normal. Cerebrospinal fluid was normal in a 24-hour urine sample. Serologic examinations revealed no evidence of seroconversion for cytomegalovirus, Epstein-Bar virus, mycoplasma, or mumps. Cerebrospinal fluid disclosed no abnormalities except for the presence of oligoclonal bands (which were absent in serum). Brain magnetic resonance imaging was normal on two occasions (4-week interval). Awake and sleep electroencephalogram was normal. In particular, myoclonic jerks were not associated with electroencephalographic changes.

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Jerk-locked back-averaging of electroencephalogram revealed no spikes or other consistent elements preceding the jerks.

Nerve conduction studies, electromyography, brainstem evoked potentials, and visual evoked potentials were normal. Abdominal ultrasonography, thoraco-abdominal magnetic resonance imaging, and metaiodobenzylguanidine scintigraphy did not detect any abnormalities, and in particular no features suggestive of neuroblastoma. Autoantibody testing indicated the presence of antigliadin antibodies of immunoglobulin A subtype, anti-endomysial antibodies together with anti-CV2 antibodies in blood but not in the cerebrospinal fluid. Duodenal biopsy disclosed subtotal villous atrophy, confirming the diagnosis of celiac disease (Fig 2).

The patient began a gluten-free diet and after 4 weeks stools became normal and serology revealed a decrease of anti-endomysium and antigliadin immunoglobulin A. In addition, he received prednisolone (2 mg/kg/day for 2 months), coupled with intravenous gamma globulin infusions (MULTIGAM; Croix Rouge de Belgique; 2 gm/kg; 2 sessions). Within this period, opsoclonus and myoclonus symptomatology improved significantly. He recovered independent walking after 5 months.

**Discussion**

Association of opsoclonus-myoclonus syndrome with the occurrence of celiac disease is unusual. Opsoclonus-myoclonus syndrome is a rare, autoimmune neurologic disorder [10]. In a recent survey of 105 cases, neuroblastoma was present in one half of the cases [11]. Because the appearance of the syndrome can herald occult neuroblastoma, most symptomatic children are screened for tumors by various markers [11]. In the patient discussed in the present report, extensive screening was negative. In children without evidence of tumor, a viral etiology is inferred, often based on “prodromes” consisting of upper respiratory or gastrointestinal symptoms. This patient had diarrhea during the days preceding the occurrence of opsoclonus-myoclonus syndrome, but the infectious sero-
logic testing was negative for common enteropathogenic germs. In contrast, serologic and histopathologic evidence for celiac disease was found.

The most prevalent neurologic manifestation related to celiac disease is cerebellar ataxia [12]. Several mechanisms have been suggested to explain this association [1]: (1) Cerebellar dysfunction could be due to vitamin E malabsorption, as hypovitaminosis E is known to cause cerebellar ataxia. In the patient described herein, vitamin E level was normal. (2) Alternatively, abnormal immunologic reactions may be responsible for the occurrence of the neurologic complications as antigliadin antibodies are thought to be neurotoxic [13]. However, the effectiveness of a gluten-free diet in the treatment of the neurologic complications of the disease is not clear. Some reports demonstrated a clinical and electrophysiologic improvement in neurologic complications in celiac disease patients on diet [14]. (3) A patient-specific immunologic (autoimmune) process resulting in both celiac disease and neurologic complications could be the explanation. The dramatic improvement of symptomatology in our patient after immunomodulator treatment supports hypotheses (2) and (3) for the explanation of the symptomatology.

In conclusion, although gluten sensitivity is known as a malabsorption syndrome, neurologic symptoms may sometimes dominate the clinical picture, as opsoclonus-myoclonus syndrome in the case of this patient. Therefore, just as for individuals with isolated chronic ataxia or polyneuropathy, we suggest screening patients with opsoclonus-myoclonus syndrome for the presence of antigliadin or endomysium antibodies for celiac disease.

References