Effect of intravenous immunoglobulin on cerebellar ataxia and neuropathic pain associated with celiac disease

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Background: Cerebellar syndrome and small fiber neuropathy may complicate celiac disease (CD) and may be resistant to a strict gluten-free diet. *Methods:* Case series. *Results:* We report three patients with biopsy-proven CD who developed cerebellar ataxia and neuropathic pain despite strict adherence to a gluten-free diet. A small fiber neuropathy was suggested by skin biopsy findings in two patients. All patients' symptoms, including small fiber neuropathy symptoms, responded to treatment with intravenous immunoglobulin (IVIG). Discontinuation of IVIG in two patients resulted in worsened ataxia that reversed after resumption of IVIG. *Conclusion:* Intravenous immunoglobulin may be effective in treating cerebellar ataxia and small fiber neuropathy associated with CD, suggesting an immune pathogenesis. Further prospective, controlled studies are necessary to determine the long-term response to IVIG or other immunomodulation therapy.

Introduction

Celiac disease (CD) enteropathy is one of the diverse manifestations related to gluten sensitivity with abnormal immunological response in genetically susceptible patients [1]. Neurological complications, particularly cerebellar ataxia and peripheral neuropathy, are estimated to occur in 6–10% of adults with CD [2–4]. They may precede or occur without enteropathy and may be resistant to a strict gluten-free diet [5–7]. Their treatment is not well standardized. Intravenous immunoglobulin (IVIG) has been reported to be effective in one patient with ataxia and CD [6] and in four patients with ataxia and gluten sensitivity [8]. However, in both studies the follow-up was short and the effectiveness of IVIG in treating CD-associated neuropathy was not established.

We report the occurrence of ataxia ± small fiber neuropathy in three patients, in whom IVIG was effective in treating the gait ataxia and neuropathic symptoms.

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Methods

Case series

All three patients were screened for other causes of neuropathy and ataxia. Glutamic acid decarboxylase (GAD) antibodies were elevated in Patient 1 only. Genetic testing for hereditary ataxias [spinocerebellar ataxia (SCA) 1, 2, 3, 6, 7, 8, 10, 17, dentatorubropallidoluysian atrophy, or FRDA1 gene], tested in Patients 1 and 3, was negative. The following immunological studies were negative: GD1a, GD1b, GQ1b, myelin-associated glycoprotein, GM1 antibodies, quantative immunoglobulins, serum immunofixation electrophoresis, erythrocyte sedimentation rate, antinuclear antibodies, double-stranded DNA antibodies, SS-A, SS-B antibodies, anti-neutrophil cytoplasmic antibodies, rapid plasma reagin, rheumatoid factor and Lyme studies.

Results

Patient 1

This case was previously reported [6]. A 37-year-old woman presented in July 2002 with a 12-year history of progressive dysarthria and ataxia. She was

diagnosed with CD in 1997. She had elevated gliadin (IgG and IgA) and endomysial antibody titers with a duodenal biopsy revealing subtotal villous atrophy. She strictly adhered to a gluten-free diet.

On examination in 2002, she had severe dysarthria, left finger-to-nose dysmetria, impaired right rapid alternating and fine finger movements, diminished pedal pin perception, ankle areflexia, and a severely ataxic, wide-based gait. A modified International Cooperative Ataxia Rating Scale (ICARS) score [9] (without Archimedes Spiral) was 31/96. Her Modified Total Neuropathy Score (MTNS) [10] was 5/36. Transglutaminase (IgA) antibodies were elevated (= 44 units; > 30 units = 'positive'), whilst gliadin antibodies (IgG and IgA) were negative. GAD antibodies were elevated (= 3.5, normal ≤ 1 U/ml). Testing for hereditary ataxias (SCA 1, 2, 6–8) was negative. Cerebral MRI showed superior vermian atrophy; lumbosacral MRI was normal. Electrodiagnostic studies revealed low amplitude sensory responses and prolonged duration distal motor unit potentials on needle electromyography.

She received IVIG 2 g/kg initially, and 0.5 g/kg 2 weeks later. Within 1 month, she reported substantial improvement of her speech and gait. Her ICARS score improved to 3/100 and there was modest improvement of her MTNS to 4/36. IVIG was held after she developed a rash and her condition worsened about 5 weeks later (ICARS score = 17). A different IVIG formulation was given and her condition improved (ICARS score = 3). She has received maintenance doses of IVIG (0.5–0.75 g/kg/2–4 weeks) and her ICARS score has remained stable (~5, range 3–13).

Patient 2

A 41-year-old woman presented with a 3-year history of progressive numbness, tingling, and electric-like pains affecting her upper extremities with later involvement of her lower extremities and face. A right rib resection, performed shortly following symptom onset, did not relieve any symptoms. She then developed diarrhea, fatigue, and weight loss.

Celiac disease was diagnosed 1.5 years following initial symptom onset. Gliadin (IgG = 115, IgA = 165) and transglutaminase (IgA = 139) antibodies were markedly elevated (normal ≤ 20) and a duodenal biopsy revealed complete villous atrophy and increased intraepithelial lymphocytosis. She began a gluten-free diet with rapid resolution of the diarrhea, weight restoration, and normalization of antibody levels (except for a gliadin IgG level of 78, about 6 months prior to initiation of IVIG). The numbness and pain; however, continued to progress. Electrodiagnostic studies were normal. Cerebrospinal fluid studies (including Lyme titers), performed 6 months after symptom onset, were normal.

Initial neurological examination revealed normal cranial nerve and motor functions. There was glove distribution pinprick loss up to the wrist level. There was mildly diminished pin and light touch perception throughout the legs, with accentuated stocking-distribution impairment up to the ankle level. There was patchy facial sensory involvement. Vibratory perception was absent in the feet, severely impaired at the knees, and normal in the fingers. Deep tendon reflexes were diffusely 3+. Plantar responses were flexor.

Her initial ICARS score was 3 with mild impairment of station (when standing with her feet together and eyes open), an inability to stand on one foot and mild incoordination with drawing of Archimedes' spiral. She had a slow, unsteady gait, and could not tandem walk. She had increased head and truncal swaying with eye closure. She had an increased base (distance between her feet) when standing in the neutral position. There was finger-to-finger instability. Four months later, her score worsened to 10 and she started using a cane for stability. Her neuropathic pain also significantly worsened (MTNS = 9/36).

Her immunological work up was normal except for non-specific total complement and beta-2 microglobulin levels. Skin biopsy revealed a low normal epidermal nerve fiber density in the thigh and mild qualitative changes (sparse fibers with small axonal swelling, increased branching, and uneven distribution of epidermal axons) in the calf and thigh suggestive of a small fiber polyneuropathy.

She received IVIG (2 g/kg divided over four doses over a 2-week period), followed by maintenance treatments (60 g) every 2 weeks for a total of 3 months. Dramatic improvement of her ataxia and neuropathy were noted at her follow-up examination 1 month after initiation of IVIG treatment. Her ICARS score improved from 10 to 0 and her MTNS improved from 9 to 5. Her ataxia and neuropathic pain worsened after IVIG was held for 3 months because of insurance issues. Maintenance IVIG (60 g every 2 weeks) was resumed, and her condition has remained stable after approximately 12 months of follow-up.

Patient 3

A 42-year-old right-handed woman presented with a 1-month history of progressive numbness and electric-like, tingling sensations in the fingers and then legs. She also reported 2 years of progressive gait ataxia resulting

in several falls. Despite adherence to a gluten-free diet since being diagnosed with CD at age 25, she had persistent diarrhea.

Neurological examination was significant for absent vibratory perception in the feet and moderately impaired vibratory perception at the knees. There was impaired pin perception in digits I and II bilaterally, characterized as 80% of unaffected areas. Joint position sensation was impaired in the toes. Deep tendon reflexes were 2+ and symmetric; plantar responses were flexor. She had ataxia (noted with bilateral heel-shin testing). She had an unsteady, wide-based gait and Romberg testing was positive. She was able to stand on her heels and toes with support. Her ICARS score was 16 and MTNS was 7.

A repeat intestinal biopsy, performed around the time of her initial presentation to us, revealed total villous atrophy suggestive of refractory CD. Transglutaminase antibody levels were mildly elevated (= 13.4, normal < 4) with normal gliadin and endomysial antibody levels; all antibodies were negative with repeat testing 7 months later, just prior to initiation of IVIG therapy. She had a positive ANA titer (1:640, homogenous). A brain MRI showed mild superior vermian atrophy. Electrodiagnostic studies were normal. Skin biopsy revealed morphologic abnormalities suggestive of a small fiber polyneuropathy (increased axon branching, horizontally oriented fibers, a few small axonal swellings, and a low normal intra-epidermal nerve fiber density).

Four months after her initial evaluation, the patient was treated with IVIG (2 g/kg, divided over four doses, given over a 2-week period), followed by maintenance doses (40 g each) every 2 weeks for 3 months. Upon reevaluation, she demonstrated significant improvement of her ICARS (16–7) and MTNS scores (7–2). The diarrhea resolved.

She continued to receive maintenance IVIG doses every 2 weeks for four more months with progressive clinical improvement. The dose was then increased to 50 g every 2 weeks. Twenty months after initiation of IVIG treatment her ICARS and MTNS scores were 3 and 2, respectively.

Discussion

Celiac disease is considered a T cell-mediated, autoimmune, multi-system disorder with the small intestine as the main target of the immunological processes [1]. Ataxia and peripheral neuropathy are the most common neurological manifestations associated with CD, and may precede or occur without gastrointestinal symptoms [2,3,5,7,11,12]. The effect of a gluten-free diet on ataxia and peripheral neuropathy associated with CD has been variable. Disease onset or progression despite adherence to a gluten-free diet has been reported [2,7,11], whilst others have reported a benefit to the diet [12–14]. The diet has also been found to be beneficial in prospective studies of patients with gluten sensitivity (i.e. the presence of positive antibody serologies with or without enteropathy) and ataxia [15] or neuropathy [16].

A chronic distal symmetric predominantly sensory neuropathy has been the most commonly reported neuropathy; however, mononeuritis multiplex, a Guillain–Barre like syndrome, autonomic neuropathy and small fiber neuropathy have also been described [3,5].

In our study, two patients presented with neuropathic signs or symptoms before the diagnosis of CD was made (patients 1 and 2). In Patients 2 and 3, the diagnosis of a small fiber neuropathy was supported by morphological changes in the skin biopsy. Despite improvement or normalization of gastrointestinal symptoms with adherence to a gluten-free diet, the painful neuropathy symptoms continued to progress in these two patients.

Intravenous immunoglobulin has been reported to be effective in the treatment of one patient with ataxia and CD [5], and four patients with ataxia and gluten sensitivity in whom intestinal biopsy data are not available [6], with a follow-up period of 2–14 weeks. In our study, IVIG showed a beneficial and continuous effect on CD ataxia over a follow-up period of 16–36 months. Suspension of IVIG in two patients resulted in worsened ataxia that was reversed after resumption of treatment. Worsening of neuropathic pain paralleled the exacerbation of ataxia in Patient 2 after temporary IVIG suspension. In addition to improvement of the ataxia, the pain also improved with restoration of IVIG treatment.

To our knowledge, the effect of IVIG on peripheral neuropathy symptoms has not been reported. In this study, two patients with additional evidence of small fiber neuropathy demonstrated a beneficial response to IVIG over a follow-up period of 16–20 months in two patients.

Maintenance IVIG treatment may be needed for long-term management for CD ataxia and small fiber neuropathy. The reversibility or improvement of these neurological manifestations in response to IVIG suggest an immune-mediated process that may be occurring independent of gluten exposure.

Conclusion

Intravenous immunoglobulin treatment may be effective in treating cerebellar ataxia and small fiber

neuropathy associated with CD, suggesting an immune pathogenesis. Further prospective, controlled studies are necessary to determine the long-term response to IVIG or other immunomodulatory therapy.

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