

## Adult celiac disease with acetylcholine receptor antibody positive myasthenia gravis

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### Abstract

Celiac disease has been associated with some autoimmune disorders. A 40-year-old competitive strongman with celiac disease responded to a gluten-free diet, but developed profound and generalized motor weakness with acetylcholine receptor antibody positive myasthenia gravis, a disorder reported to occur in about 1 in 5000. This possible relationship between myasthenia gravis and celiac disease was further explored in serological studies. Frozen stored serum samples from 23 acetylcholine receptor antibody positive myasthenia gravis patients with no intestinal symptoms were used to screen for celiac disease. Both endomysial and tissue transglutaminase antibodies were examined. One of 23 (or, about 4.3%) was positive for both IgA-endomysial and IgA tissue transglutaminase antibodies. Endoscopic studies subsequently showed duodenal mucosal scalloping and biopsies confirmed the histopathological changes of celiac disease. Celiac disease and myasthenia gravis may occur together more often than is currently appreciated. The presence of motor weakness in celiac disease may be a clue to occult myasthenia gravis, even in the absence of intestinal symptoms.

**Key words:** Acetylcholine receptor antibodies; Celiac disease; Myasthenia gravis; Transglutaminase antibodies

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### INTRODUCTION

A range of neurological disorders have been identified in patients suffering from celiac disease<sup>[1]</sup>. Occasionally, neurological changes first occur and celiac disease is only recognized later<sup>[2]</sup>. Celiac disease is considered an immune-mediated disorder that affects the proximal small intestine and leads to reduced nutrient absorption, diarrhea and weight loss. Treatment with a gluten-free diet is usually sufficient. Marked fatigue and weakness may also occur in many chronic disorders, including celiac disease. However, here, concomitant myasthenia gravis was also discovered<sup>[3]</sup>.

Serological screening for celiac disease antibodies using stored frozen samples from a serum bank of 23 additional patients with acetylcholine receptor positive myasthenia gravis was also completed. From these banked serum samples, one was discovered with both positive IgA endomysial (EMA) and IgA tissue transglutaminase (tTG) antibodies. Subsequent clinical evaluation, including endoscopic biopsy studies, confirmed the findings of celiac disease.

Although rare and estimated to occur in only about 1 in 5000, myasthenia gravis may occur more frequently than is currently appreciated if celiac disease is also present. Ongoing fatigue and profound muscle weakness in celiac disease may be a clinical clue that this unusual immune-mediated neurological disorder, myasthenia gravis, is present.

## CLINICAL CASE STUDY

A 40-year-old male orchidist was initially investigated in 2001 for diarrhea and weight loss of 10 kg with intermittent generalized fatigue. His IgA tTG antibody assay was increased to 89 units (normal, < 20 units). Gastroscopy and colonoscopy were visually normal, but small bowel biopsies showed changes of celiac disease with crypt hyperplastic villus atrophy (i.e. severe "flat" lesion, Marsh 3 lesion). Treatment with a gluten-free diet led to rapid resolution of diarrhea and weight loss. His IgA tTG antibody assay also subsequently normalized completely to 10.2 units.

By July 2003, however, his fatigue was persistent and his weakness became progressive and generalized. Although his physical attributes were well known locally, having previously been placed 6th in an international strongman competition, he stumbled and fell easily with weakness notably exacerbated by exertion. Marked leg fatigue developed, especially while standing on a ladder picking peaches. Once fatigue occurred, he was unable to step up to the next rung on the ladder, holding on with both arms.

While picking peaches, he also noted that he could only lift his arms above shoulder level for 15 min before he could no longer lift his arms. During the previous year, fatigue with chewing also developed along with right eyelid ptosis and diplopia.

Detailed neurological examination showed rapid muscle fatigue on repetitive exercise. Bilateral ptosis with a flattened facial expression, but normal speech function, was noted. Extra-ocular movements were abnormal with progressive eye elevation weakness after 20 to 30 s of sustained upward gaze along with worsening ptosis. Diplopia was also evident. After a minute of voluntary upward gaze, he was unable to elevate his eyes beyond the primary position. Facial muscles were strong. Examination of his upper extremities revealed deltoid fatigue after 10 to 15 repetitive movements, and examination of his lower extremities revealed that 9 stand-ups from a sitting position produced complete fatigue and an inability to stand upright. Reflexes and sensory studies were normal. His Quantitative Myasthenia Gravis (QMG) examination was at 18 (normal, 0; maximum deficit, 39)<sup>[4]</sup>. A Mestinon test produced an evident response with return to normal strength. Repeated stimulation confirmed the existence of decrement. Computerized tomography of his chest revealed no evidence of a thymoma. Acetylcholine receptor antibodies were 22.0 nm/L (normal, < 0.1 nm/L). The final diagnosis was acetylcholine-receptor-antibody-positive, generalized myasthenia gravis class IIIb (Osserman classification)<sup>[5]</sup>.

Subsequent prednisone and Mestinon treatment provided partial improvement in motor weakness. Thymectomy was performed and the resected thymus was noted to be large (10 cm × 9 cm × 2 cm). Microscopic evaluation noted normal thymic tissue with no hyperplasia or evidence of thymoma. Post-operatively, his weakness on exertion persisted and his acetylcholine receptor antibodies increased by November

2004 to 38.4 nmol/L. Over the next 3 years, his symptoms improved with infusions of immunoglobulin along with the addition of mycophenolate mofetil and cyclosporin. His QMG score normalized to 3 with some persistent diplopia and minor facial weakness. This clinical improvement was accompanied by serological improvement with reduced levels of acetylcholine-receptor antibodies to 23 nmol/L.

## SPECIAL SEROLOGICAL STUDIES

A total of 23 patients with acetylcholine receptor antibody positive myasthenia gravis were identified through the Neuroimmunology Laboratories in the UBC Brain Research Center (Dr. Joel Oger). Acetylcholine receptor antibodies were measured using a modified radioimmunoprecipitation assay<sup>[6]</sup>. Approval to test samples for endomysial antibodies and IgA tissue transglutaminase antibody concentrations was obtained through the Clinical Research Ethics Board at UBC as previously noted<sup>[7,8]</sup>.

Residual frozen and stored serum samples from this myasthenia serum bank were quantitatively evaluated for IgA EMA and IgA tTG antibodies. IgA EMA was detected using indirect immunofluorescence against human umbilical cord using the method described by Ladinsker *et al*<sup>[9]</sup>, measuring the serum at an initial dilution of 1:5. With this method, positive sera were repeated at increasing dilutions until they became negative. Titers of IgA tTG antibody were measured using an ELISA method based on that reported by Dieterich *et al*<sup>[10]</sup> but modified to account for local differences in scientific supplies. During the initial evaluation of this assay, a reference range of up to 140 U/mL (3 SDs above the mean, 99% confidence limits) was calculated from titers on adult intestinal disease controls with normal small intestinal biopsies, and on sera from adults with biopsy-defined celiac disease as previously noted by Gillett and Freeman<sup>[11]</sup>. During validation, all IgA-deficient patients were found to have tTG titers of 5 U/mL or lower. For this study, therefore, samples with titers of 5 U/mL or lower were tested for IgA deficiency using NOR-Partigen Total IgA kit (Behring Diagnostics Inc, USA).

## RESULTS OF SCREENING

All 23 samples were examined for both IgA EMA and IgA tTG. One sample was EmA positive and tTG quantitation measured 1160 U/mL. All other serum samples were negative for EmA. For tTG quantitation using this assay method, all other serum samples were less than 95 U/mL. The single positive patient, a 16-year-old female, had endoscopic evaluation that revealed mucosal scalloping in the duodenum, consistent with celiac disease. Findings were confirmed on histologic evaluation of small intestinal biopsies and a gluten-free diet was initiated.

## DISCUSSION

These studies suggest that myasthenia gravis, an

autoimmune neuromuscular disorder, may occur more often in adult celiac disease than is currently appreciated. In most patients with myasthenia gravis, circulating antibodies are thought to block acetylcholine receptors at the post-synaptic neuromuscular junction, inhibiting stimulatory effects of the neurotransmitter, acetylcholine, causing muscle weakness. Both generalized or localized muscle weakness with fatigue occur, particularly with exertion, but these might conceivably be ascribed to various chronic medical disorders, including celiac disease. In adults with celiac disease, weakness and fatigue could also result from changes in nerves (e.g. peripheral nerve lesion)<sup>[12]</sup>, or alternatively, skeletal muscle (e.g. rhabdomyolysis, myositis)<sup>[13,14]</sup>. Alternatively, nutritional depletion associated with electrolyte alterations such as hypokalemia<sup>[15]</sup> or a protein deficiency state such as hypoalbuminemia might be responsible. The present report further emphasizes that myasthenia gravis should also be considered as a specific association with both symptomatic or classical celiac disease as well as subclinical disease initially defined with screening measures.

Myasthenia gravis is uncommon, with estimates of about 1 in 5000 in the United States, while celiac disease has been estimated to occur in about 1 in 200. Although the appearance of these two disorders together could be coincidental, there is now other evidence available to suggest that these two distinct immune-mediated disorders occur together more frequently than is currently appreciated. First, early case reports from Europe recorded myasthenia gravis in celiac disease<sup>[16-18]</sup>. Second, similar human leukocyte antigen (HLA) types (B8 and DR3) appear to independently predispose to both myasthenia gravis and celiac disease. Third, other historical serological survey studies with different, but less specific antibodies have been positive. For example, anti-reticulon antibodies (present in celiac disease) were previously recorded in myasthenia gravis<sup>[19]</sup>. Finally, acetylcholine receptor antibodies have been recently detected by others in celiac disease<sup>[20]</sup>. In the present study, both IgA EMA and IgA tTG antibodies in celiac disease were found in myasthenia gravis patients, while antibodies to acetylcholine receptors were defined in celiac disease before and after gluten-free diet treatment. In this case, seropositive patients were confirmed to have positive intestinal biopsies.

Celiac disease will have to be added to the increasing list of other autoimmune disorders that have been associated with myasthenia gravis, including diabetes mellitus, rheumatoid arthritis, thyroid disease, neuromyelitis optica (post-thymectomy myasthenia gravis)<sup>[21]</sup> and multiple sclerosis<sup>[22]</sup>. The suspicion of a common mechanism between these diseases is well supported by common HLA haplotypes, co-occurrence in the same families and confirmed by their occurrence in the same patients.

## CONCLUSION

In conclusion, these studies suggest that celiac disease and myasthenia gravis may occur together

more frequently than is currently appreciated, in part because clinical changes may be subtle and difficult to recognize. The precise frequency of celiac disease in this local myasthenia population is unknown as serum was collected during the previous decade and additional celiac disease cases may have been subsequently detected. Future antibody screening studies exploring the frequency of celiac disease in myasthenia gravis, and *vice versa*, as well as their relatives remains to be elucidated.

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