CASE REPORT

Celiac disease association with other autoimmune disorders: Three case reports

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Abstract

Background: A 15 year period retrospective study at our celiac centre (Semmelweis University 2nd Department of Internal Medicine) has found, that 91 out of 248 coeliac patients (20 male, 71 female) also suffered from at least one autoimmune disease associated with celiac disease. The objective of the following case reports is to demonstrate the protean faces of celiac disease and the association tendency with other autoimmune disorders.

Case presentation: 34-years old male patients presented with peripheral neuropathy. Results of electrophysiological studies were normal. Immunpanel examination was detected elevated tissue Transglutaminase antibodies levels. Duodenal biopsy revealed villous atrophy. Patient was started on strict gluten free diet and one year later he had almost complete recovery. 46-years-old male diagnosed with Dermatitis herpetiformis Duhring and celiac disease 20-years ago. In the last few years in spite of the gluten-free diet, he newly presented intestinal symptoms and chronic iron deficiency anaemia. The control tissue Transglutaminase antibodies, and duodenal biopsies were negative. Colonoscopy found inflammation in terminal ileum; video capsule endoscopy detected multiple ulcerative lesions in whole small bowel. The results confirmed the diagnosis of Crohn's disease. A 22-years old female patient diagnosed with celiac disease during the puerperium. The patient had muscles weakness, swallowing dysfunction, diplopia and generalized fatigue too. Muscle biopsies were normal. The electromyography was specific to myasthenia gravis. Computed tomography found thymus persistent. After tymectomy she showed good clinical response to immunosuppressant and cholinesterase inhibitor therapy.

Conclusion: Autoimmune disorders have often been associated with celiac disease.

Keywords

Celiac disease, Autoimmunity, Inflammatory bowel disease, Neuropathy, Myasthenia gravis, Gluten-free diet

1 Introduction

According to the ESPGHAN definition, "Celiac disease is an immune-mediated systemic disorder elicited by gluten and related prolamines in genetically susceptible individuals, characterized by the presence of a variable combination of gluten dependent clinical manifestations, celiac disease specific antibodies, HLA-DQ2 and DQ8 haplotypes and enteropathy" [1].

However, celiac disease (CeD) may manifest itself at any age, with the potential involvement of any organs. The prevalence of CeD in Hungarian population ranges from 1% to 2% [2]. In adulthood, "classic symptoms" including diarrhea, abdominal distension, malabsorption syndrome as typical clinical feature are commonly absent. Patients may exhibit minor gastrointestinal complaints, as well as numerous extraintestinal manifestations. For the diagnosis of CeD in diet-naive adult patients serological and histological examination is necessary. After diagnosis, the basis of all the present treatments for CeD is the life-long gluten-free diet. Nowadays, the range of diseases that can be proven to occur more frequently in untreated CeD has expanded (see Table 1).

Table 1. Autoimmune disorders associated with celiac disease (modified after) [13]

Autoimmune disorders associated with celiac disease	
Proved link	**Hypothetical link**
• Autoimmune thyroid disorders • Type 1 diabetes mellitus • Dermatitis herpetiformis Duhring • Sjögren's syndrome • Selective IgA-deficiency • Juvenile chronic arthritis • Autoimmune myocarditis	• IBD • IgA nephropathy • Alopecia aerate • Autoimmune hepatitis • Primary biliary cirrhosis • Asthma bronchiale • Sclerosis multiplex • Myasthenia gravis • Turner syndrome • Down syndrome

Various autoimmune diseases show association with CeD, such as type-1 diabetes mellitus, autoimmune thyroid disorders and Sjögren's syndrome. A 15 year period (November 1997 to November 2013) retrospective study at the celiac centre of Semmelweis University 2nd Department of Internal Medicine has found, that 91 out of 248 coeliac patients (20 male, 71 female) also suffered from at least one autoimmune disease associated with celiac disease (see Table 2). The aims of these three case reports are to illustrate from these autoimmune diseases three rare ones, which can be associated with CeD.

Table 2. Characteristics of coeliac disease associated disorders in our celiac centre

Disease	n	male/female	% prevalence in our centre
Dermatitis herpetiformis Duhring (DHD)	29	10/19	12%
Hyperthyroidism	16	2/14	6.4%
Hypothyreodism	15	1/14	6.04%
IBD(Crohn disease,ulcerative colitis)	8	4/4	3.2%
Selective IgA deficiency	8	2/6	3.2%
Gilbert's syndrome	4	2/2	1.6%
Type I. diabetes mellitus	3	0/3	1.2%
Scheuermann's syndrome	3	0/3	1.2%
Endometriosis	2	0/2	<1%
Systemic lupus erythematosus	1	0/1	<1%
Myasthanenia gravis	1	0/1	<1%
Autoimmune neuropathy	1	1/0	<1%

2 Case presentation

2.1 First case: Celiac disease associated with autoimmune peripheral neuropathy

A 34-years old male patient started to have weakness in his arms, and numb on the third-fourth fingers both of his hands. He was unable to perform his work as a dentist. Neurological tests were conducted at Semmelweis University Department of Neurology. Results of electrophysiological studies were normal, nerve root injury, motoneuron disease was not found. Due to suspect peripheral neuropathy, complete immunpanel examination was performed. The examinations excluded hereditary neuropathy (Charcot-Marie Tooth Disease, Hereditary Neuropathy with liability to Pressure Palsies) and from the acquired neuropathies the toxic and metabolic types (diabetic, uremic, alcoholic, B12 or B1 deficiency, hypothyroid, medical) and more immune mediated forms like multifocal motor neuropathy, Sarcoidosis, Sjögren syndrome, Polyarteritis Nodosa, Churg-Strauss syndrome, Systemic lupus erythematosus). Furthermore high levels of tissue transglutaminase antibodies were detected (tTG IgA: >200 IU and tTG IgG: 85 IU). He had no gastrointestinal complaints. Upper gastrointestinal endoscopy demonstrated the presence of pale and atrophic duodenal mucosa. Duodenal biopsy revealed villous atrophy, crypt elongation, increased intraepithelial lymphocytes and the patients was diagnosed with CeD type Marsh-3b. Osteodensitometry was found osteopenia. Patient was started on strict gluten free diet. Followed up at around one year, patient had almost complete recovery, numb and weaknesses of his arms were eliminated, he was able to work again. Beside gluten free diet immunosuppressant therapy was not necessary, which is an indirect proof of the CeD indicated autoimmune neuropathy.

2.2 Second case: Celiac disease associated with Crohn disease

We report the case of 46-years-old male patients, with history of skin lesions-itchy erythematous plaques, grouped vesicles on the elbows-has been diagnosed with Dermatitis herpetiformis Duhring 20-years ago. His serological findings revealed high levels of antiendomysial IgA antibodies (EMA) titer, histological examination demonstrated the presence of Marsh-1 lesion in his duodenum samples. A gluten-free diet for CeD was prescribed. In the last few years in spite of the gluten-free diet, he newly presented diarrhea, meteorism, and abdominal pain. He has chronic iron deficiency anaemia; he claimed to have received iron supplementation several times over the years. Control tissue transglutaminase IgA- and IgG-antibodies, and duodenal biopsies were negative, thereby indicating observed gluten-free diet. Laboratory findings revealed latent hypochromic microcytic anaemia. Femur neck and lumbar vertebrae were osteoporotic revealed by bone mineral density measurement with dual-energy X-ray absorptiometry (DEXA). Identification of the cause of anaemia colonoscopy found inflamed Bauchin's valve and small ulcers in the terminal ileum. Video capsule endoscopy (VCE) detected multiple ulcerative lesions in the whole small bowel (see Figure 1). These results confirmed the diagnosis of Crohn disease (CD). The initial management of CD patient has to take metilprednisolon (Medrol 24 mg minus 4 mg/5 dies) with Pantoprazole (1×40 mg/die) and potassium (Kaldyum 1×600 mg/die), and budesonid (Budenofalk 3×3 mg/2 months, 2×3 mg/2 weeks, 1×3 mg/2 weeks), azatioprin (Imuran 3×50 mg/die). At the one month control medical examination patient's symptoms were partly reduced.

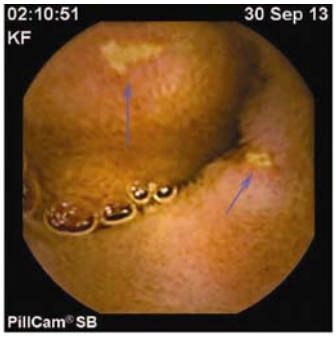

Figure 1. The video capsule endoscopy (VCE) detected ulcerative lesions in the patient's jejunum and ileum too.

2.3 Third case: Celiac disease associated with myasthenia gravis

A 22-years old female patient presented with history of profuse diarrhea during the puerperium. Laboratory investigations revealed an elevated antiendomysial IgA antibody level. Lactose-, glucose- and starch- tolerance test showed plan curve. The duodenal biopsy was consistent with CeD (Marsh 3b). The patient had muscles weakness, swallowing dysfunction and generalized fatigue too. Nevertheless the first neurological examinations – electromyography (EMG) and electronystagmography (ENG) – did not find primary degenerative muscle disease, or neuromuscular lesion. Treatment with a gluten-free diet led to rapid resolution of diarrhea and increased 6 kg of her body weight. However, after one year, her fatigue was persistent and her weakness became progressive and she had difficulties with walking and defecation. Control antiendomysial IgA antibody level, and duodenal biopsies were negative. The results of hypophysis magnetic resonance imaging (MRI) examination and hormone level measurement of thyroid, cortisol and prolactin excluded the endocrine background of clinical symptoms. Detailed neurological examination showed diplopia, horizontal nystagmus and proximal weakness of her upper limbs. Muscle biopsies were normal. The control EMG and ENG with repetitive closely timed stimulation were specific to myasthenia gravis (see Figure 2). Human leukocyte antigen test showed HLA-DR3 and HLA-DQ2 positivity. Computed tomography found thymus persistent (see Figure 3). Serum acetylcholine receptor antibodies were elevated.

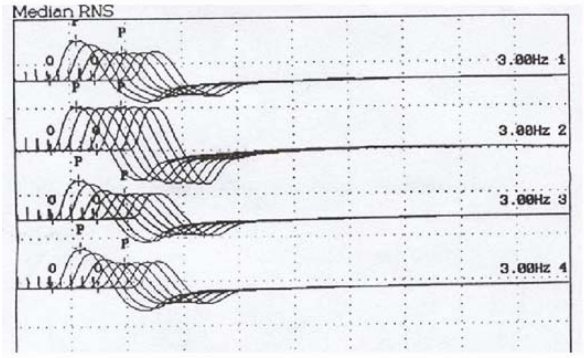

Figure 2. Result of electromyography (EMG) and electronystagmography (ENG) examination in myasthenia gravis. It demonstrates the electromyography (EMG) and electronystagmography (ENG) examination using 3 Hz repetitive stimulation. The amplitude of muscle potential is progressively decreasing, which is specific for myasthenia gravis (decrement).

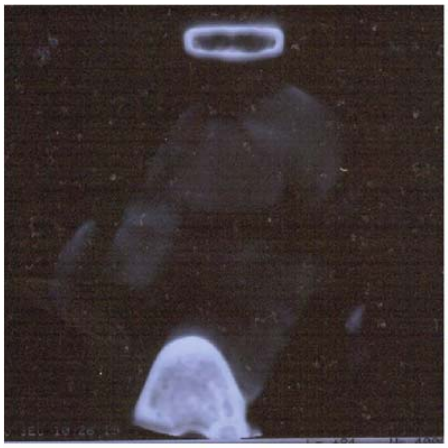

Figure 3. Thymus persistent detected by computed tomography (CT) increased thymus in patients thorax. By suspected myasthenia gravis thorax CT should be done due to thymus persistent or thymoma.

Before thymectomy, she was treated with immunosuppressant and cholinesterase inhibitor for nine days (azathioprin 100 mg/die, methylprednisolon 44 mg/die, pyridostigmin 240 mg/ die). Post-operatively, she has started basis therapy containing azathioprin (150 mg/die) and cholinesterase inhibitor (60-120 mg/die). She had good clinical response to therapy; her clinical improvement was maintained during the next year of follow-up.

3 Discussion

Several autoimmune diseases are associated with CeD. To date, no conclusive evidence is available that proves if the relationship between CeD and autoimmune diseases is mediated by gluten exposure, or if CeD and autoimmune diseases could occur together due to other causes, particularly the integrity injury of the intestinal barrier function and the common genetic background [3].

Neurological manifestations can be seen in nearly 10%-36% of CeD patients, the most common being cerebellar ataxia and neuropathy; occipital calcifications with epilepsy and dementia are infrequent. The pathomechanism underlying of the neuropathy in patients with CeD is still unknown. Nowadays, there are several hypotheses about gluten toxic damage and vitamin malabsorption (B12, B6, E, D) [4, 5]. Neuropathy in celiac patients presumably mediated in part by antiganglioside antibodies or by antibodies that target transglutaminase bound to extracellular proteins such as fibronectin. However, these mechanisms have not yet been established [6, 7]. CeD is commonly associated with subclinical form of peripheral neuropathy without electrophysiological changes. According to another hypothesis, peripheral neuropathy is restricted to small neurologic fibre alone in which electro-diagnostic study is not sensitive enough to detect abnormalities of small fibre [8]. Numerous studies have reported neurological manifestations in CeD will also be improved by a gluten-free diet [6-8]. Like in our case report, CeD is commonly associated with peripheral neuropathy in adult patients and should be considered even in the absence of gastrointestinal symptoms. In idiopathic peripheral neuropathy, CeD should be suspected, when patients have anaemia, unexplained iron deficiency, diabetes type 1, steatorrhoea or positive family history of CeD. The take home message of this case of ours is by idiopathic peripheral neuropathy CeD serological testing is recommended.

Celiac disease and inflammatory bowel disease (IBD: Crohn disease, ulcerative colitis) are inflammatory disorders of the gastrointestinal tract with some common genetic, immunological and environmental factors involved in their pathogenesis. Several research shown that patients with CeD have 5-10-fold risk of developing IBD when compared with that of the general population. On the other hand, *Leeds at al.* found the prevalence of celiac disease in IBD was comparable with that in controls. Assumed cause of this difference is that the increased intestinal permeability in CeD may lead to increased antigen presentation and therefore generation of autoantibodies or increased bacterial translocation, which has been involved in IBD as a pathogenic mechanism [9, 10]. Genetic studies have identified four shared risk chromosomal loci: PTPN2, IL18RAP, TAGAP, and PUS10 in both diseases [11]. This considerable overlap between the associated genetic regions might indicate partial agreement of the pathogenesis both of two diseases. Patients with IBD and CeD have number of common symptoms like diarrhea, malabsorption, weight loss, long-standing history of iron deficiency anaemia, and loss of bone mineral density and this could cause problems in the differential diagnostics. The take home message of this case of ours is if patients have persistent intestinal symptoms despite adhering to a strict gluten-free diet, colonoscopy is highly recommended.

Myasthenia gravis is an autoimmune neuromuscular disease, leading to fluctuating muscle weakness and fatigue. Muscle weakness is caused by circulating antibodies, that block acetylcholine receptors at the postsynaptic neuromuscular junction, inhibiting the excitatory effects of the neurotransmitter acetylcholine on nicotinic receptors at neuromuscular junctions. Myasthenia gravis occurs at any age and in either gender, the prevalence is between 15 and 179 per million inhabitants [12]. The association of CeD and myasthenia gravis could be coincidental, but nowadays many evidence available to suggest that these two distinct immune-mediated disorders occur together more frequently than is currently appreciated. The cause of association may be the common genetically background. Human leukocyte antigen types

(HLA-DR3, -DQ2,-DQ8), appear to predispose to both myasthenia gravis and CeD. Molecular mimicry also plays role the emergence of both diseases [13, 14]. Serological survey studies have been detected acetylcholine receptor antibodies in CeD. CeD and myasthenia gravis also characterized by female predominance, and onset in the puerperium. The 20% of myasthenia gravis exacerbations are occur in the first trimester [15, 16]. Primary muscle diseases (polymyositis, dermatomyositis, and hereditary muscle disease) usually do not feature specific histological lesions, unlike neuromuscular disorders. Muscle biopsies have no diagnostic value in myasthenia gravis. In our patient, both diseases were beginning during puerperium, and the first EMG examination probably was false negative, these results postponed the diagnosis of myasthenia gravis. The main symptoms of myasthenia gravis are fluctuating weakness in skeletal muscles mainly in proximal region, generalized fatigue, bulbar disorders, diplopia, and ptosis. Generalized fatigue and weakness may also occur in CeD caused by malabsorption. In our case, the symptoms were ascribed to CeD, delaying thereby the diagnosis of accompanying myasthenia gravis. The take home message of this case of ours is that the presence of motor weakness and diplopia in treated CeD may be a clue to occult myasthenia gravis.

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