

**ABSTRACT:** Celiac disease is usually associated with autoimmune disorders and has occasionally been reported in patients with inflammatory myopathies. Our aim was to determine the presence of celiac disease and antibodies associated with celiac disease in patients with inflammatory myopathies and to investigate their relationship. Serum antigliadin, anti-tissue transglutaminase, and antiendomysial antibodies were determined in 51 patients with inflammatory myopathies. HLA-DQ2 and -DQ8 alleles were studied to assess their complementary diagnostic value. Jejunal biopsy was performed in patients with moderate to high levels of antigliadin antibodies. Patients with jejunal histology consistent with celiac disease initiated a gluten-free diet. Seventeen patients (31%) were positive for antigliadin antibodies, which were significantly more frequent in patients with inclusion-body myositis than dermatomyositis ( $P < 0.001$ ). Positive status to HLA-DQ2 and/or -DQ8 did not differ between antigliadin-positive (75% and 12.5%) or -negative (60% and 15%) patients. Three of five jejunal biopsies were diagnostic for celiac disease with histological normalization after a gluten-free diet. Thus, celiac disease is more prevalent in patients with inflammatory myopathies than in the general population. Positive status to HLA-DQ2 allele, which is known to be more frequent in patients with inflammatory myopathies, could explain the high prevalence of antigliadin antibodies in this population. The diagnostic value of HLA-DQ2 or -DQ8 haplotypes to detect celiac disease in patients with inflammatory myopathy is limited.

*Muscle Nerve* 35: 49–54, 2007

## CELIAC DISEASE AND ANTIBODIES ASSOCIATED WITH CELIAC DISEASE IN PATIENTS WITH INFLAMMATORY MYOPATHY

ALBERT SELVA-O'CALLAGHAN, MD, PhD,<sup>1</sup> FRANCESC CASELLAS, MD, PhD,<sup>2</sup>  
INES de TORRES, MD, PhD,<sup>3</sup> EDUARD PALOU, MD, PhD,<sup>4</sup> JOSEP M. GRAU-JUNYENT, MD, PhD,<sup>5</sup>  
and MIQUEL VILARDELL-TARRÉS, MD, PhD<sup>1</sup>

<sup>1</sup> Internal Medicine Department, Vall D'Hebron General Hospital, Universitat Autònoma Barcelona, C/Siracusa No. 12 Bis A, Barcelona, Spain

<sup>2</sup> Digestive System Research Unit, Vall D'Hebron General Hospital, Universitat Autònoma Barcelona, Barcelona, Spain

<sup>3</sup> General Pathology Department, Vall D'Hebron General Hospital, Universitat Autònoma Barcelona, Barcelona, Spain

<sup>4</sup> Lirad, Banc Sang i Teixits, Barcelona, Spain

<sup>5</sup> Muscle Research Group, Hospital Clínic Provincial, Institut d'Investigacions Biomèdiques August Pi i Sunyer, Universitat de Barcelona, Barcelona, Spain

Accepted 28 July 2006

**I**diopathic inflammatory myopathies (IIM) are a group of acquired, heterogeneous, systemic diseases characterized by progressive symmetrical muscle

weakness, elevated serum levels of muscle enzymes, electromyographic abnormalities, and inflammatory infiltrates on muscle biopsy.<sup>7</sup> Characteristic histopathological features allow classification of IIM into polymyositis (PM), dermatomyositis (DM), and sporadic inclusion-body myositis (sIBM).<sup>6</sup> These are commonly regarded as autoimmune disorders, and various autoantibodies directed to specific nuclear and cytoplasmic antigens are found in up to 55% of patients with PM or DM.<sup>31</sup>

Celiac disease (CD) is a chronic intestinal disorder with an estimated prevalence of 1 in 389 adults in Spain.<sup>4</sup> A strong association with the human leu-

**Abbreviations:** AGA, antigliadin; CD, celiac disease; DM, dermatomyositis; ELISA, enzyme-linked immunoassay; EMA, antiendomysial; HLA, human leukocyte antigen; IIM, idiopathic inflammatory myopathy; PCR, polymerase chain reaction; PM, polymyositis; sIBM, sporadic inclusion-body myositis; TTG, tissue transglutaminase

**Key words:** antigliadin antibodies; anti-transglutaminase antibodies; celiac disease; dermatomyositis; inflammatory myopathy; polymyositis

**Correspondence to:** A. Selva-O'Callaghan; e-mail: aselva@vhebron.net

© 2006 Wiley Periodicals, Inc.

Published online 11 September 2006 in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/mus.20652

kocyte antigen (HLA)-DQ2 and -DQ8 alleles has been reported.<sup>10,24</sup> A definite diagnosis is only elicited when histological demonstration of typical intestinal alterations is achieved, together with clinical improvement when patients are on a gluten-free diet. Nevertheless, serologic study with antigliadin (AGA) IgA antibodies, antiendomysial (EMA) IgA antibodies, and anti-tissue transglutaminase (tTG) antibodies has demonstrated their utility in screening for CD.<sup>4,24</sup> Several studies have established a close association between CD and other autoimmune diseases, with primary biliary cirrhosis, primary Sjögren's syndrome, and lupus being the diseases most frequently assessed.<sup>1,21,29</sup> CD has occasionally been described in patients with IIM.<sup>3,8,9,18–20,25</sup> The aim of this study is to report the prevalence and significance of the various celiac autoantibodies in a series of patients with IIM and to investigate the association between these two diseases.

## PATIENTS AND METHODS

**Patient Population.** The study included 51 consecutive adult patients diagnosed with IIM who were regularly followed-up at our outpatient clinic in Barcelona, Spain. Our center is a single referral teaching hospital serving a population of nearly 450,000 inhabitants. All patients with myositis in this population are referred to our hospital for diagnosis and therapy, regardless of disease severity. The study protocol was approved by the hospital ethics committee.

The diagnosis of PM/DM was based on the criteria of Bohan and Peter,<sup>2</sup> which include symmetrical proximal muscle weakness, increased serum muscle enzymes, electromyographic abnormalities, typical histological findings on muscle biopsy, and characteristic dermatological manifestations (heliotrope rash and Gottron's papules). All patients included met the criteria for definite PM/DM. Patients with IIM who fulfilled the criteria for another defined connective tissue disease were included as myositis overlap syndrome, and those with a diagnosis of cancer within 3 years of the diagnosis of myositis were included as cancer-associated myositis. Characteristic clinical and histological features provided the diagnosis of inclusion-body myositis according to established criteria.<sup>6,13</sup> Patients were classified as having DM ( $n = 26$ ), PM ( $n = 9$ ), myositis overlap syndrome ( $n = 4$ ), cancer-associated myositis ( $n = 8$ ), or sIBM ( $n = 4$ ). Patients with myositis overlap syndrome and cancer-associated myositis were further classified as to whether they had PM, DM, or sIBM. In the group with myositis overlap syndrome,

3 patients were diagnosed with PM and 1 with DM; systemic sclerosis was present in 3 cases and systemic lupus erythematosus in 1. Patients with cancer-associated myositis (8 DM) had ovarian and breast cancer (2 patients each), or lung, colon, stomach, and bladder cancer (1 patient each). Immunosuppressive treatment was systematically recorded. Disease activity was retrospectively evaluated with a visual analog scale and the 5-point Likert scale at the time of the study.<sup>30</sup>

The patients' overall clinical course was defined as monophasic (full recovery within 2 years without relapse, with or without drug therapy), chronic polyphasic (prolonged, relapsing course with one or more relapses occurring between periods of inactive disease), chronic continuous (persistent disease activity for longer than 2 years despite drug therapy and which is never inactive), and undefined (illness of less than 2-year evolution). A drug trial was defined as a single course from the beginning of administration of a given drug to the time at which it was discontinued or, in the case of prednisone, the time at which the dose was reduced to 25% of the initial dose. Treatment response was defined as complete (patient totally recovered without evidence of active disease), partial (evidence of clinical improvement short of a complete clinical response), or none (no evidence of clinical improvement).

All 51 patients were prospectively examined and tested for serum AGA, tTG, and EMA antibodies. Patients positive for tTG or AEM and those with AGA concentrations greater than 7 mg/L were studied for the presence of the histological hallmark of CD by jejunal biopsy using a Watson capsule. Patients found to have villous atrophy and crypt hyperplasia consistent with CD were prescribed a gluten-free diet, and a control biopsy was taken 6 months later to assess mucosal recovery.

**Laboratory Tests and Serological Assays.** AGA-IgA antibodies were analyzed by enzyme-linked immunosorbent assay (ELISA; UniCAP-100; Pharmacia, Uppsala, Sweden); positive status was defined as a value of greater than 3 mg/L. Anti-tissue transglutaminase antibody was analyzed by ELISA with human recombinant antigen, and EMA antibodies were determined using indirect immunofluorescence with monkey esophagus as the substrate (ImmunoGlo [EMA], IFA; Immco Diagnostics, Buffalo, New York). The results of these tests were reported as positive or negative. Thyroid autoantibodies (anti-thyroglobulin and anti-peroxidase) were analyzed by an ELISA method (Immunitite 2500; DPC, Los Angeles, Cali-

fornia); values of less than 40 IU/L were considered normal.

Serum samples from each patient were screened by indirect immunofluorescence for antinuclear antibodies using HEp-2 cells, and by ELISA for antibodies against extractable nuclear antigens (Ro, La, RNP, Sm) and anti-histidyl-tRNA synthetase (anti-Jo-1). Sera from all 51 patients in this series were tested by protein and RNA immunoprecipitation, which allows detection of other synthetases and myositis-specific and myositis-associated antibodies (anti-Mi-2, anti-SRP, anti-Ro 52, anti-Ro 60, anti-La, anti-PM/Scl, and anti-RNP) that may have been overlooked by the ELISA test, and also serves to confirm the ELISA results.

Immunoglobulin types were measured in all patients to exclude congenital IgA deficit, as well as serum concentrations of vitamins D (25-hydroxycholecalciferol) and E in the patients with histologically confirmed CD.

**Histology and Morphometric Techniques.** Paraffin-embedded sections (4  $\mu\text{m}$ ) from formalin-fixed jejunal mucosa were stained with hematoxylin and eosin (H&E). Immunohistochemical studies were performed in each case. The villous height and crypt depth ratio was measured under a light microscope in each H&E-stained biopsy specimen. The number of CD3<sup>+</sup> and CD8<sup>+</sup> intraepithelial T cells per 100 enterocytes was counted, applying the modified Marsh classification of celiac disease.<sup>27</sup> All histological examinations were performed by an expert gastrointestinal pathologist (I.D.T.), who was blinded to the disease history and laboratory findings.

**Genetic Markers.** A class II HLA study was performed with polymerase chain reaction (PCR)-sequence-specific primer as a routine determination in our hospital laboratory.

**Statistical Analysis.** The various clinical and immunological associations were compared by the chi-square and Fisher exact test for qualitative variables. All statistical analyses were performed with SPSS 6.0 software (SPSS, Inc., Chicago, Illinois). Significance was set at  $P < 0.05$ . Results are expressed as the median and range.

## RESULTS

During the past 2 years (2004–2005), 51 consecutive patients (40 women, 11 men; mean age 45.7 years, SD 16.2) diagnosed with IIM and followed up in our outpatient clinic were prospectively examined and

tested for serum IgA-class AGA, tGT, and IgA EMA antibodies. All patients diagnosed with PM/DM received identical therapy based on reported regimens and our own experience. Briefly, this consisted of prednisone (1 mg/kg/day) for 1 month with slow tapering over the next 12 months. Other immunosuppressive agents were added when only a partial therapeutic response was obtained by the second month. Azathioprine (1–2 mg/kg/day) and cyclosporine (3–5 mg/kg/day) were prescribed most often. Sporadic IBM patients received a tentative course of prednisone and intravenous immunoglobulins without clinical response.

**Celiac Disease Antibodies.** IgA-class AGA antibodies were found in 17 patients (31%) (5.9; range 3.5–13.1 mg/L), including 3 of 26 (11%) DM patients, 4 of 9 (44%) PM cases, 4 of 4 (100%) sIBM patients, 2 of 4 (50%) in the overlap group, and 4 of 8 (50%) in the cancer-associated myositis group. Clinical outcome of these patients in relation to different treatments including gluten-free diet or immunosuppression is summarized in Table 1. No patient studied was positive for anti-tTG or IgA-class AEM antibodies. Positive IgA-class AGA was significantly more frequent in patients with sIBM than DM (100% vs. 11%;  $P < 0.001$ ) and less frequent in DM patients (11%) than in the remaining patients (56%) ( $P < 0.001$ ). None of the patients had a selective IgA deficit. A non-significant association was observed between specific or associated myositis antibodies and celiac disease antibodies, with the exception of anti-Ro antibodies, which were positive in the two patients with sIBM who had histologically proven celiac disease. No association was found between AGA or overall disease activity and positive status to thyroid autoantibodies, which were present in only 5 of the 51 patients (10%). None of the patients with proven celiac disease had low serum concentrations of vitamins D or E.

**Small Bowel Biopsy Findings and Genetics.** Three of the five patients undergoing jejunal biopsy (one with DM and two with sIBM) were found to have subtotal villous atrophy and crypt hyperplasia consistent with celiac disease. This represents 6% of all patients with inflammatory myopathy, 18% of the patients positive for IgA-class AGA antibodies, and 60% of the patients positive for IgA-class AGA antibodies at moderate values ( $>7$  mg/L).

Immunohistochemical staining showed increased intraepithelial CD3<sup>+</sup> and CD8<sup>+</sup> T-cell counts ( $>40$  lymphocytes per 100 enterocytes), with destructive lesions in all three cases. Histologically

**Table 1.** Clinical, epidemiological, and laboratory data of the 17 patients with positive antigliadin antibodies.

Patient	Gender/age	Diagnosis	CDA	CD	Treatment	Clinical course	Outcome
1	F/26	DM	AGA <sup>+</sup> /EMA <sup>-</sup> /tTG <sup>-</sup>	Yes	Cs/GFD	Monophasic	Asymptomatic
2	M/56	PM	AGA <sup>+</sup> /EMA <sup>-</sup> /tTG <sup>-</sup>	ND	Cs	Polyphasic	Partial response
3	F/67	CAM(DM)	AGA <sup>+</sup> /EMA <sup>-</sup> /tTG <sup>-</sup>	ND	Cs/CHT	Undefined	Asymptomatic
4	F/42	CAM(DM)	AGA <sup>+</sup> /EMA <sup>-</sup> /tTG <sup>-</sup>	ND	Cs/CHT	Undefined	Asymptomatic
5	M/50	PM	AGA <sup>+</sup> /EMA <sup>-</sup> /tTG <sup>-</sup>	ND	Cs	Monophasic	Asymptomatic
6	M/76	sIBM	AGA <sup>+</sup> /EMA <sup>-</sup> /tTG <sup>-</sup>	ND	Cs/AZA/MTX	Chronic	Deceased
7	M/45	sIBM	AGA <sup>+</sup> /EMA <sup>-</sup> /tTG <sup>-</sup>	Yes	IVIg/GFD	Chronic	No response
8	F/22	PM	AGA <sup>+</sup> /EMA <sup>-</sup> /tTG <sup>-</sup>	No	Cs	Monophasic	Asymptomatic
9	F/37	DM	AGA <sup>+</sup> /EMA <sup>-</sup> /tTG <sup>-</sup>	ND	Cs	Monophasic	Asymptomatic
10	F/47	sIBM	AGA <sup>+</sup> /EMA <sup>-</sup> /tTG <sup>-</sup>	ND	Cs/IVIg	Chronic	Wheelchair
11	M/64	sIBM	AGA <sup>+</sup> /EMA <sup>-</sup> /tTG <sup>-</sup>	Yes	Cs/IVIg/GFD	Chronic	No response
12	F/50	DM	AGA <sup>+</sup> /EMA <sup>-</sup> /tTG <sup>-</sup>	ND	Cs/AZA/CyA/IVIg	Chronic	Partial response
13	F/43	CAM(DM)	AGA <sup>+</sup> /EMA <sup>-</sup> /tTG <sup>-</sup>	ND	Cs/AZA/CyA	Polyphasic	Partial response
14	F/34	Overlap	AGA <sup>+</sup> /EMA <sup>-</sup> /tTG <sup>-</sup>	No	Cs	Polyphasic	Asymptomatic
15	F/79	PM	AGA <sup>+</sup> /EMA <sup>-</sup> /tTG <sup>-</sup>	ND	Cs	Monophasic	Asymptomatic
16	F/50	PM	AGA <sup>+</sup> /EMA <sup>-</sup> /tTG <sup>-</sup>	ND	Cs/MF/IVIg	Undefined	Partial response
17	F/51	PM	AGA <sup>+</sup> /EMA <sup>-</sup> /tTG <sup>-</sup>	ND	Cs/AZA/CyA	Polyphasic	Partial response

M, male; F, female; CDA, celiac disease antibodies; CD, histologically proven celiac disease; ND, not done; DM, dermatomyositis; PM, polymyositis; sIBM, sporadic inclusion-body myositis; CAM, cancer-associated myositis; AGA, antigliadin antibodies; EMA, antiendomysial antibodies; tTG, transglutaminase antibodies; CHT, chemotherapy; Cs, corticosteroids; AZA, azathioprine; MTX, methotrexate; CyA, cyclosporine; IVIg, intravenous immunoglobulin; GFD, gluten-free diet.

destructive lesions with mild atrophy and hyperplastic crypts were observed in two cases (DM and sIBM), classified as type IIIa celiac disease, and marked atrophy in one case (sIBM), classified as type IIIb celiac disease.

Twelve (75%) of the 17 patients with IIM and positive AGA antibody status were positive for the DQ2 allele, and two (12%) for the DQ8 allele. There were no statistically significant differences relative to the remaining patients with IIM and negative AGA status [20 of 33 patients (60%) positive for DQ2, and 5 of 33 patients (15%) positive for DQ8]. Two of the three patients with histologically proven CD (66%) were positive for DQ2 and the other was negative for both alleles. Mucosal recovery occurred in all three patients after following a gluten-free diet. The two patients with sIBM and celiac disease have not shown improved muscle weakness in response to the gluten-free diet up to the time of this writing (2 years and 6 months, respectively, of follow-up since the diagnosis of celiac disease). The other patient, a DM case, has remained free of cutaneous and muscle symptoms after a gluten-free diet, but she had initially received glucocorticoids (1 mg/kg/day).

## DISCUSSION

Celiac disease is a complex autoimmune disease that is frequently underdiagnosed, particularly in adults. Several neuromuscular disorders have been associated with CD. Proximal myopathy due to deficiency of vitamin E,<sup>22</sup> osteomalacia due to vitamin D defi-

ciency,<sup>23</sup> sensorimotor axonal peripheral neuropathy and ataxia,<sup>14-17</sup> PM,<sup>8,18,19</sup> and sIBM<sup>32</sup> have been described in relation to AGA antibodies, with no intestinal symptoms in most cases. Few cases associated with DM have been reported to date<sup>3,9,20,25</sup> and these were mainly in the juvenile form, a fact that encourages prospective studies to evaluate the frequency of CD in patients with adult PM/DM.

Celiac disease resembles a multisystem disorder more than a primary gastrointestinal disease. Up to 50% of patients with histologically proven CD have no gastrointestinal symptoms.<sup>24</sup> Gluten sensitivity, as defined by Marsh,<sup>26</sup> refers to a state of heightened immunological responsiveness to ingested gluten in genetically susceptible individuals. The clinical spectrum of gluten sensitivity includes dermatitis herpetiformis and gluten ataxia, in addition to classic CD or gluten-sensitivity enteropathy. Most patients with gluten sensitivity are positive for AGA, but not necessarily to serum anti-tTG antibodies, as was found in our sIBM patients.

To date (2 years and 6 months, respectively, of follow-up), the myositis manifestations of the two patients with sIBM and histologically proven CD have not responded to a gluten-free diet. This might be because the damage incurred is irreversible, as seems to be the case with ataxia, a condition in which treatment efforts, for the most part, only succeed in preventing further clinical deterioration. The highly favorable clinical response obtained in the patient with DM and CD after 8 years of follow-up with a

gluten-free diet must be viewed with caution because she was initially treated with glucocorticoids, which may have contributed to the outcome.

Tissue transglutaminase is reported to be the main antigen in patients with CD, and blood determination of anti-tTG antibodies is considered the best screening parameter for patients with suspected disease. None of our patients were positive for serum anti-tTG antibodies, even those with histologically confirmed CD. The following factors could contribute to explain these findings. Low positive values of IgA-class AGA antibodies can be present in patients with autoimmune disease, as has been demonstrated in Sjögren's syndrome and lupus<sup>21,29</sup>; therefore, it is plausible that autoimmune myositis patients might show similar findings. In a study<sup>21</sup> of 40 patients diagnosed with Sjögren's syndrome, 9 (22%) had low positive IgA-class AGA antibody values with negative histological findings. The prevalence of true CD (histologically proven and positive EMA antibodies) was 14.7%, a value higher than that seen in the general population. In a large prospective study<sup>29</sup> of 103 patients with systemic lupus erythematosus, 24 (22.3%) patients tested positive for AGA antibodies, but none were positive for EMA antibodies. Furthermore, none were found to have histological evidence of CD. In our group of patients with myositis, those with higher AGA antibody values and histologically proven CD were not positive for EMA or anti-tTG antibodies. The majority of these patients were on immunosuppressive treatment, and the possibility that anti-tTG antibodies are more sensitive to this treatment cannot be excluded. Another reason for their negative status could be that anti-tTG antibodies are bound to the antigen in the bowel mucosa and cannot be detected in serum, as has recently been reported in some patients with gluten ataxia.<sup>17</sup> Moreover, patients with ataxia due to gluten sensitivity are usually positive for AGA, but not necessarily to serum anti-tTG antibodies.<sup>16</sup>

Elevated expression of tTG, as compared with normal muscle, has recently been reported<sup>5</sup> in patients with sIBM, suggesting that this could contribute to the pathogenesis of myopathy. Furthermore, this ubiquitous enzyme has also been proposed as a marker of IIM.<sup>12</sup> Cellular infiltrates of CD8<sup>+</sup> T cells, restricted to MHC I cells, are typically detected in sIBM and PM, and also in the bowel mucosa in CD. Thus, the participation of tissue transglutaminase as the antigen responsible for the immune response against the bowel and muscle cannot be excluded. Studies directed to confirm or reject this hypothesis are needed.

On the basis of our findings in these patients, we offer some practical observations. First, CD seems to be more prevalent in patients with IIM than in the general population, perhaps because of the marked association that exists between the HLA class II haplotypes (DQ2) in both diseases.<sup>10,28</sup> The DQ2 haplotype in healthy controls in Barcelona is approximately 24%,<sup>11,33</sup> a notably lower frequency than that seen in patients with IIM, regardless of whether they are positive for AGA. As is recognized, genetic susceptibility may be an additional marker for gluten sensitivity.

Second, a high degree of suspicion is necessary to detect CD in patients with IIM. Intestinal symptoms are usually absent, AGA antibodies are mildly positive, and anti-tTG antibody, the most specific and sensitive serological screening test for CD, is usually negative. The HLA-DQ2 haplotype does not seem to help in the diagnosis of CD in these patients because of the shared HLA alleles in both diseases. Thus, moderate AGA values (>7 mg/L) in these patients may warrant a bowel biopsy to exclude CD. An accurate diagnosis and implementation of a gluten-free diet can be important to avoid malnutrition. Moreover, the risk of cancer, which is increased in patients with PM/DM, may be even higher in patients with associated CD, particularly gastrointestinal cancer. A correct diagnosis of CD may help to reduce this risk.

Finally, the possibility should be considered that sIBM, a disease that has no effective treatment, may be, to some extent, a clinical expression of gluten sensitivity. Hence, implementation of a gluten-free diet, which has been successful in other gluten-sensitivity diseases or syndromes, such as ataxia, might be accompanied by clinical improvement or, at least, long-term stability of the condition.

This work was supported in part by a research grant FIS/2004 PI040464. The authors thank Rosa Maria Ras for her kind assistance in the determination of celiac disease autoantibodies.

## REFERENCES

1. Bizzaro N, Villalta D, Tonutti E, Tampona M, Bassetti D, Tozzoli R. Association of celiac disease with connective tissue diseases and autoimmune diseases of the digestive tract. *Autoimmun Rev* 2003;2:358-363.
2. Bohan A, Peter JB. Polymyositis and dermatomyositis. *N Engl J Med* 1975;292:344-347.
3. Buderus S, Wagner N, Lentze MJ. Concurrence of celiac disease and juvenile dermatomyositis: result of a specific immunogenetic susceptibility? *J Pediatr Gastroenterol Nutr* 1997;25:101-103.
4. Casellas F. Celiac disease. *Med Clin (Barc)* 2006;126:137-142.
5. Choi Y-C, Park GT, Kim T-S, Sunwoo I-N, Steinert PM, Kim S-Y. Sporadic inclusion body myositis correlates with in-

- creased expression and cross-linking by transglutaminases 1 and 2. *J Biol Chem* 1999;275:8703–8710.
6. Dalakas MC. Polymyositis, dermatomyositis, and inclusion body myositis. *N Engl J Med* 1991;325:1487–1498.
  7. Dalakas MC, Hohlfeld R. Polymyositis and dermatomyositis. *Lancet* 2003;362:971–982.
  8. Evron E, Abarbanel JM, Branski D, Sthoeger ZM. Polymyositis, arthritis, and proteinuria in a patient with adult celiac disease. *J Rheumatol* 1996;23:782–783.
  9. Falcini F, Porfirio B, Lionetti P. Juvenile dermatomyositis and celiac disease. *J Rheumatol* 1999;26:1419–1420.
  10. Farré C, Humbert P, Vilar P, Varea V, Aldeguer X, Carnicer J, et al. Serological markers and HLA-DQ2 haplotype among first-degree relatives of celiac patients. *Dig Dis Sci* 1999;44:2344–2349.
  11. Fernández-Bañares F, Esteve M, Farré C, Salas A, Alsina M, Casals J, et al. Predisposing HLA-DQ2 and HLA-DQ8 haplotypes of coeliac disease and associated enteropathy in microscopic colitis. *Eur J Gastroenterol Hepatol* 17:1333–1338.
  12. Gendek EG, Kedziora J, Gendek-Kubiak H. Can tissue transglutaminase be a marker of idiopathic inflammatory myopathies? *Immunol Lett* 2005;245–249.
  13. Griggs RC, Askanas V, DiMauro S, Engel A, Karpati G, Mendell JR, et al. Inclusion body myositis and myopathies. *Ann Neurol* 1995;38:705–713.
  14. Hadjivassiliou M, Chattopadhyay AK, Davies-Jones GAB, Gibson A, Grünewald RA, Lobo AJ. Neuromuscular disorders as a presenting feature of coeliac disease. *J Neurol Neurosurg Psychiatry* 1997;63:770–775.
  15. Hadjivassiliou M, Grünewald RA, Chattopadhyay AK, Davies-Jones GAB, Jarratt JA, Kandler RH, et al. Clinical, radiological, neurophysiological, and neuropathological characteristics of gluten ataxia. *Lancet* 1998;352:1582–1585.
  16. Hadjivassiliou M, Grünewald RA, Sharrack B, Sanders DS, Lobo A, Williamson C, et al. Gluten ataxia in perspective: epidemiology, genetic susceptibility and clinical characteristics. *Brain* 2003;126:685–691.
  17. Hadjivassiliou M, Mäki M, Sanders DS, Williamson CA, Grünewald RA, Woodroffe NM, et al. Autoantibody targeting of brain and intestinal transglutaminase in gluten ataxia. *Neurology* 2006;66:373–377.
  18. Henriksson KG, Hallert C, Norrby K, Walan A. Polymyositis and adult coeliac disease. *Acta Neurol Scand* 1982;65:301–319.
  19. Henriksson KG, Hallert C, Wallan A. Gluten sensitivity polymyositis and enteropathy. *Lancet* 1976;7980:317.
  20. Iannone F, Lapadula G. Dermatomyositis and celiac disease association: a further case. *Clin Exp Rheumatol* 2001;19:757–758.
  21. Iltanen S, Collin P, Korpela M, Holm K, Partanen J, Polvi, A, et al. Celiac disease and markers of celiac disease latency in patients with primary Sjögren's syndrome. *Am J Gastroenterol* 1999;94:1042–1046.
  22. Kleopa KA, Kyriacou K, Zamba-Papanicolaou E, Kyriakides T. Reversible inflammation and vacuolar myopathy with vitamin E deficiency in celiac disease. *Muscle Nerve* 2005;31:260–265.
  23. Kozanoglu E, Basaran S, Goncu MK. Proximal myopathy as an unusual presenting feature of celiac disease. *Clin Rheumatol* 2005;24:76–78.
  24. Lee SK, Green HR. Celiac sprue (the great modern-day imposter). *Curr Opin Rheumatol* 2006;18:101–107.
  25. Marie I, Lecomte F, Hachulla E, Antonietti M, François A, Levesque H, et al. An uncommon association: celiac disease and dermatomyositis in adults. *Clin Exp Rheumatol* 2001;19:201–203.
  26. Marsh MN. The natural history of gluten sensitivity: defining, refining and re-defining. *Q J Med* 1995;85:9–13.
  27. Marsh MN, Crowe PT. Morphology of the mucosal lesion in gluten sensitivity. *Bailliere's Clin Gastroenterol* 1995;9:273–293.
  28. O'Hanlon TP, Mercatante Carrick D, Arnett FC, Reveille JD, Carryngton M, Gao X, et al. Immunogenetic risk and protective factors for the idiopathic inflammatory myopathies. Distinct HLA-A, -B, -Cw, -DRB1 and -DQA1 allelic profiles and motifs define clinicopathologic groups in Caucasians. *Medicine* 2005;84:338–349.
  29. Rensch MJ, Szykowsky R, Shaffer RT, Fink S, Kopecky C, Grissmer L, et al. The prevalence of celiac disease autoantibodies in patients with systemic lupus erythematosus. *Am J Gastroenterol* 2001;96:1113–1115.
  30. Rider LG, Feldman BM, Perez MD, Rennebohm RM, Lindsley CB, Zemel LS, et al. Development of validated disease activity and damage indices for the juvenile idiopathic inflammatory myopathies: physician, parent, and patient global assessments. Juvenile Dermatomyositis Disease Activity Collaborative Study Group. *Arthritis Rheum* 1997;40:1976–1983.
  31. Selva-O'Callaghan A, Labrador-Horrillo M, Solans-Laque R, Simeon-Aznar CP, Martínez-Gómez X, Vilardell-Tarrés M. Myositis-specific and myositis-associated antibodies in a series of 88 Mediterranean patients with idiopathic inflammatory myopathy. *Arthritis Rheum* (in press).
  32. Williams SF, Mincey BA, Calamia KT. Inclusion body myositis associated with celiac sprue and idiopathic thrombocytopenic purpura. *South Med J* 2003;96:721–723.
  33. www.allelefreqencies.net.