ACCIDENTAL FINDING OF IMMUNODEFICIENCY AND CELIAC DISEASE

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An online version of this case, can be found at:
http://www.eaaci.net/site/content.php?artid=1633
A 42-year old truck driver was checked up because his sister and her daughter were treated for celiac disease (CD). Familial prevalence of CD is approximately 10% in first degree relatives. Examination of patients with positive family history as to the celiac disease even if there are no obvious gastrointestinal symptoms is recommended.

The mother of the patient died at the age of 40 after an accident, the father and grandfather died of urinary tract carcinoma. The father’s brother died at the age of 12 years of failing to thrive. The sister of this patient and the daughter were treated for celiac disease, the son is healthy. The patient has two children, without any symptoms associated with CD by now.

The patient gave a history of scarlatina and frequent tonsillitis in childhood, recurrent upper and lower airway infections, sinusitis and otitis media after tonsilectomy at the age of 14 years. In 2004 he was treated for pneumonia. During the last years he had several episodes of diarrhea.

The physical examination revealed a normally nourished man (BMI 22) without visible abnormalities.

He underwent upper gastrointestinal endoscopy: histological assessment of duodenal specimens revealed the presence of villous atrophy with crypt hyperplasia, increased plasma cells and increased intraepithelial lymphocytes (IELs) - typical pattern for celiac disease was found. (Fig.1, 2, 3, 4). Low activity of enzymes of the brush border cells was confirmed.

Fig. 1: Small intestinal mucosa showing moderate atrophy of the villi, crypt hyperplasia, mild chronic inflammatory infiltrate containing numerous plasma cells, and elevated intraepithelial lymphocytes.

Fig. 2: Lymphoid aggregate in the small intestinal mucosa with flat surface and numerous intraepithelial lymphocytes.
Fig. 3: Flat small intestinal mucosa with severe villous atrophy, crypt hyperplasia, chronic inflammatory infiltrate and intraepithelial lymphocytosis.

Fig. 4: Detail of the mucosal surface showing elevated intraepithelial lymphocytes.

**LABORATORY ANALYSIS**

Biochemical blood determinations were normal except slight elevation of AP (3.27 μkat/l) and C-reactive protein (CRP) (50 mg/l). ESR was 35 mm/h. Blood count revealed elevated numbers of leucocytes (17.5 × 10⁹/l) and platelets (455.10⁹/l). (Table 1). Antinuclear antibodies, anti-gliadin, anti-endomysial and anti-tissue transglutaminase antibodies were negative.
Significant depression of CD4⁺ T-lymphocytes (16.0%) was found, number of CD19⁺ B-lymphocytes was in normal range (15.0%). (Table 2).

WHICH DIAGNOSTIC STEPS MIGHT BE HELPFUL TO SPECIFY THE DIAGNOSIS?

Suspicion for immunodeficiency was expressed because of the discrepancy between typical histological findings and negativity of antinuclear anti-tissue transglutaminase, anti-gliadin and anti-endomysial antibodies. Serologic tests for CD are falsely negative in patients with antibody deficiency. Depression of all immunoglobulin classes IgG (0.49), IgA (0.06) and IgM (0.19 g/l) (Table 3) and poor response to immunization (undetectable IgG antibodies for tetanus and pneumococcus) were confirmed. Presence of immunoglobuline deficiency could explain the negative findings of autoantibodies.
Table 3: Laboratory findings

<table>
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<th>September 07</th>
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<tr>
<td>IgG</td>
<td>0.49</td>
<td>1.56</td>
<td>8.5-15.5 g/l</td>
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<tr>
<td>IgA</td>
<td>0.06</td>
<td>0.24</td>
<td>1.7-3.5 g/l</td>
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<td>IgM</td>
<td>0.19</td>
<td>0.17</td>
<td>0.8-1.4 g/l</td>
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<td>IgE</td>
<td>14.2</td>
<td>19.2</td>
<td>0.0-200 kIU/l</td>
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<td>IgG1</td>
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<td></td>
<td>4.9-11.4 g/l</td>
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<tr>
<td>IgG2</td>
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<td>IgG3</td>
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<tr>
<td>IgG4</td>
<td>0.003</td>
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</table>

**WHAT IS YOUR DIAGNOSIS NOW?**

Diagnoses of common variable immunodeficiency and celiac disease were set up.

**IS IT REALLY CELIAC DISEASE OR ONLY HISTOLOGICAL CHANGES IN A CVID PATIENT?**

Histological findings of CVID enteropathy are similar to those found in patients with celiac disease, but with some differences. In CVID, plasma cells are absent from the intestinal lamina propria, and the crypt epithelium is not hyperplastic. Nodular lymphoid hyperplasia (NLH) in CVID patients is usually generalized, involving the proximal small intestine as well as the distal ileum and proximal colon. Duodenal villous atrophy has been described in 24-50% of CVID patients with chronic diarrhea. This histological alteration is significantly associated with anemia, malnutrition, and low blood CD4+ lymphocyte counts. Low number of circulating CD4+ T lymphocytes is related to an increased risk of contracting bacterial infections, predominantly along the upper and lower respiratory and gastrointestinal (GI) tracts. An increased prevalence of malignancies and autoimmune diseases of the GI tract has been observed in these patients. CVID patients with such enteropathy respond to a gluten-free diet in only 50% of cases.

Villous atrophy with the presence of endoscopic features of duodenal fold loss or scalloping--both have been asserted to be major macroscopic findings suggestive of celiac disease in nonimmunodeficient subjects. Classification of histological mucosal damage in celiac disease is performed according to the MARSH criteria. It does not only take the architecture of the villi into account but also the infiltration of inflammatory cells in early stages. Infiltration stage (I) is characterized by increase of intraepithelial lymphocytes (> 3 IEL/10 epithelial cells (EC)). In hyperplasia stage (II) in addition to the infiltration of lymphocytes, a hyperplasia of crypts exists with branching and elongation and a reduced mitosis rate. Villous are normal. In destruction stage (III) atrophy of the villi is found. For hypoplastic stage (IV) is typical flat atrophic mucosa with irreversible damage. Low activity of enzymes of the brush border cells is a typical histochemical finding.
WHICH FURTHER INVESTIGATIONS SHOULD BE PERFORMED TO CONFIRM THE DIAGNOSIS OF CD?

Genetics testing was performed. Genetic predisposition to CD is strongly associated with HLA-DQ alleles. The majority (90-95%) of patients carry HLA-DQ2 (α1*0501, β1*02) heterodimer encoded by DQA1*0501 and DQB1*02 genes. The remaining patients (5-10%) carry HLA-DQ8 (α1*0301, β1*0302) heterodimer encoded by HLA-DQ A1*0301, B1*0302 genes. Presence of HLA-DQA1*0501-DQB1*02 genes has a low specificity, frequency is about 20% of the healthy population. HLA determination is useful in ruling out celiac disease in questionable cases, if the patient is found to be neither DQ2 nor DQ8 positive.

In our patient by means of HLA typing predisposition to develop celiac disease was found: HLA-DQA1*0501-DQB1*02 genes were found also in patient’s sister and her daughter and in both children of this patient. (Fig. 5)
Mutation in TACI (transmembrane activator and CAML interactor) carried in only 8% of CVID patients was not found.

**WHAT ACTION SHOULD BE TAKEN?**

Gluten-free diet resulted in partial improvement of III B type (subtotal atrophy of the villous) by endoscopy. Laboratory results after the diet revealed decrease in CRP (26.4 mg/l), number of leucocytes (11.9.10⁹/l) and platelets (447.10⁹/l) and increase in percentage of CD⁴⁺ T-lymphocytes (25.0%), but persistent low level of serum iron (3.5 µmol/l).

**WHAT OTHER TREATMENT FOR GAINING CONTROL OVER THE DISEASE DO YOU SUGGEST?**
Treatment with oral iron was started. After 6 months, simultaneously with an improvement of intestinal mucous, slowly increasing in level of serum iron was seen (6.8 µmol/l).

**SHOULD BE PERFORMED AN INTRAVENOUS SUBSTITUTION OF IMMUNOGLOBULINS?**

Low level of IgG (below 2g/l) is an absolute indication for decision to administer IVIG. Intravenous immunoglobulins at a dose of 400 mg/kg/month was started, the treatment was well tolerated.

**DISCUSSION**

An increased prevalence of celiac disease is present in patient with CVID. Duodenal villous atrophy is very frequent in symptomatic CVID patients. This histological alteration is significantly associated with anemia, malnutrition, and low blood CD4⁺ lymphocyte numbers. The only treatment currently available for CVID patients is life-long substitution of IgG. The decision to treat a patient by means of immunoglobulin replacement therapy is not based on the level of serum IgG alone, but on the frequency and severity of infections and on the kind and severity of other autoimmune manifestations. In addition to immunoglobulin therapy, patient management should include early and aggressive antibiotic therapy of infections and close monitoring for the development of autoimmune and inflammatory diseases. Benefits of IVIG replacement therapy include fewer and less severe infections and lessening the frequency of the chronic diarrhea.

Patients with asymptomatic form of CD are often first and second-degree relatives of a patient with CD. Often a family history of gastrointestinal cancers or other autoimmune disorders is present. Very slow improvement of villous atrophy despite a rigorous gluten-free diet lasting more than 6 months, iron deficiency and high risk of T-cell lymphomas (complication of long-standing CD) require immunosuppressive treatment, including steroids, azathioprine, and cyclosporine. This treatment in patient without gastrointestinal symptoms and with CVID is very controversial.

**CONCLUSION**

In this patient CD and CVID were found as accidental findings. In regions where caloric intake is relatively high, approximately 50% of people with CD are asymptomatic despite typical changes in the small intestine. This condition is known as “silent CD”. Despite lack of CD symptoms, such patients are at risk for the complications of CD, including iron deficiency anemia, osteoporosis, and increased incidence of intestinal malignancies (particularly T-cell lymphomas arising in the small bowel). Examination of first degree relatives (parents, siblings, and children) as to the celiac disease even if there are no obvious gastrointestinal symptoms was recommended, so the damage done by undiagnosed disease can be reduced.

This is the first report of accidental finding of CVID and CD in asymptomatic patient.

**READ ABOUT CD AND CVID**

**Celiac disease (CD)** occurs in genetically predisposed individuals who demonstrate a permanent intolerance to gluten, found in wheat, barley and rye. This leads to the development of an autoimmune enteropathy, resulting in the malabsorption of critical vitamins, minerals, and calories. Signs and symptoms of the disease classically include diarrhoea, short stature, iron deficiency anemia and chronic abdominal pain. Serum antibodies anti-tissue transglutaminase, anti-gliadin and anti-endomysial antibodies can be utilized to screen for celiac disease, however, the keys to confirming the diagnosis remain a small intestinal biopsy, and the patient´s clinical response to a gluten-free diet. Anti-tissue transglutaminase antibodies (tTG IgA or IgG) have a high sensitivity (85-100%) and specificity (93-100%) for celiac disease. Anti-gliadin antibodies (AGA IgA or IgG) are not specific for CD. AGA IgA, resp. IgG assays are variable with respect to sensitivity (100 and 50%, resp.), and specificity (95 and 60%), respectively. Because there is a higher false-positive rate for gliadin antibodies, tTG antibodies are replacing them. AGA and anti-endomysial antibodies (EMA) are used for monitoring known celiac patients for dietary compliance. EMA disappears, along with
AGA, on a GFD and returns if there is a gluten challenge, even in the absence of overt symptoms.

Histological examination of duodenal samples often showed severe villous atrophy (grade III/IV), reduction in number or loss of Kerkring’s folds, mosaic pattern, scalloped folds and visibility of the underlying blood vessels.

Histological stage IV damage with complete atrophy of the villi in celiac disease refractory to therapy should be considered an early stage in the development of an enteropathy-associated T-cell lymphoma.

Histologic recovery usually takes several months but can take up to 1 year, even if the patient remains on a strict gluten-free diet. Refractory CD is defined as villous atrophy with crypt hyperplasia and increased IELs persisting for more than 12 months in spite of a strict gluten-free diet. If a patient is not responding well to a gluten-free diet, initial diagnosis of CD must be reassessed, diet must be checked for errors or compliance problems, and other reasons for persisting symptoms should be considered.

Familial prevalence of CD is approximately 10% in first degree relatives. Genetics testing (HLA-DQA1*0501-DQB1*02 alleles) is useful diagnostic support with a very high negative predictive value (99%).

**Common variable immunodeficiency (CVID)** is frequent primary immunodeficiency, with a bimodal distribution for the age at which the diagnosis is first made: with one peak between age 6 and 10 years, and another between age 26 and 30 years. An average period between the onset of symptoms and the diagnosis of CVID is 4-6 years. The predominant manifestation is hypogammaglobulinemia, poor response to immunization and increased incidence of recurrent infections. Up to 60% of CVID patients have diarrhea before starting therapy. Some gastrointestinal symptoms can be attributed to infection, about 25% of CVID patients develop clinical features suggestive of an autoimmune disease. Other patients may develop malabsorption with loss of weight and the typical laboratory signs of malnutrition. A small bowel biopsy usually reveals villous atrophy and generalized nodular lymphoid hyperplasia (hypertrophy of Peyer’s patches) involving the proximal small intestine as well as the distal ileum and proximal colon. These patients are at increased risk for gastric adenocarcinoma and small-bowel lymphoma arising in the setting of nodular lymphoid hyperplasia. Small bundles of lymphoid tissue in lamina propria mucosae are largely composed of B-lymphocytes. Unlike celiac disease, plasma cells are lacking. Adequate IVIG replacement therapy reduces the frequency of infections and, if started early enough, reduces the occurrence of pulmonary complications, frequency of the chronic diarrhea, and severity of autoimmune diseases.

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**References:**


**SUMMARY**

We describe the first accidental finding of common variable immunodeficiency (CVID) in patient with asymptomatic form of celiac disease.

**KEY WORDS**

Common variable immunodeficiency (CVID), celiac disease (CD)