Gluten sensitivity and neurological manifestations

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Abstract

The authors report on six cases of gluten-sensitivity, also defined non-celiac gluten sensitivity, characterized by abdominal features (diarrhea, bloating, pain), genetic positivity for predisposition to celiac disease (DQB1*02 in all cases; DQA1*05 in three; DQA1*02 in two, DQB1*03 in two), negative anti-t-Transglutaminase antibodies, normal mucosa on biopsy in four cases, type 1 of Marsh in one case. The subjects presented frequent central nervous system (CNS) symptoms: headache in three patients, somnolence in one, electroencephalogram aspecific alterations in three (in two of them with previous seizures), leptomeningeal cyst in one, intracranial calcification in one, cerebral gliosis in two. After a gluten-free diet, all intestinal and clinical CNS features remitted, but re-appeared after gluten reintroduction. On the basis of the neurological signs, the authors stress the relevance of immune innate system in the pathogenesis of these cases with possible subsequent evolution on immune adaptive system involvement.

Introduction

The individuals with human leukocyte antigens (HLA) DQ2 and DQ8 are genetically susceptible to an abnormal immune responsive-
ization after gluten-free diet. Instead, in subjects with high anti-\( t \)-Tg antibodies subjected to gluten-free diet, EEG showed some irregularity, a condition attributed to the persistence of chronic inflammatory processes in CNS due to a non-compliance of the subjects with the diet and/or to other unknown factors.\(^{15} \) In this paper, we report 6 cases responding to GS standards.

**Materials and Methods**

Six patients with essentially clinical diagnosis of GS and having intestinal features (abdominal pain, diarrhea, bloating, or both diarrhea and bloating), and sometimes other extra-intestinal symptoms, such as headache and somnolence, and/or EEG alterations after gluten ingestion, remission after gluten elimination from the diet, and relapse after gluten reintroduction have been included in the study. The patients were anti-tTg and anti-endomisium negatives with duodenal 0-1 grade biopsy according to Marsh classification. The gastrointestinal symptoms, the EEG recording and the neurological symptoms of these patients have been evaluated before and after gluten free diet administration.

**Results**

The results obtained in this research are reported in Table 1. In basal conditions, abdominal pain was observed in 3 patients, diarrhea in 3, bloating in 3. Extraintestinal CNS symptoms were also present; EEG pattern was aspecifically abnormal in 3 patients, with previous seizures in 2, headache in 3, gliosis in 2, leptomeningeal cyst in 1, and intracranial calcification in 1.

All cases presented the genetic HLA predisposition to CD. In all cases anti-tTg antibodies were normal on free diet, the duodenal mucosa was normal in 4 patients and with type 1 of Marsh alteration in one of them. After gluten-free diet introduction (1-2 weeks), the gastrointestinal symptoms as well as headache disappeared; convulsions necessitating EEG control were not observed.

**Table 1. Observed cases of gluten sensitivity.**

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age (years)</th>
<th>Genetics HLA</th>
<th>BCS</th>
<th>Anti-tTg</th>
<th>Duodenal biopsy</th>
<th>CNS symptoms</th>
<th>EEG</th>
<th>Other CNS symptoms</th>
<th>Gluten free diet results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>32</td>
<td>DQA1*0201</td>
<td>Diarrhea, abdominal pain</td>
<td>Negative</td>
<td>Type 1 (Marsh)</td>
<td>Headache</td>
<td>Negative</td>
<td>Leptomeningeal cyst</td>
<td>Positive</td>
</tr>
<tr>
<td>2</td>
<td>38</td>
<td>DQA1*05</td>
<td>Bloating</td>
<td>Negative</td>
<td>-</td>
<td>Somnolence</td>
<td>Fronto-temporal alterations (spikes)</td>
<td>Calcifications, convulsions</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>8</td>
<td>DQA1*05</td>
<td>Abdominal pain</td>
<td>Negative</td>
<td>Normal</td>
<td>-</td>
<td>Centro-temporal alterations</td>
<td>Convolusions</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>41</td>
<td>DQA1*0201</td>
<td>Diarrhea, bloating</td>
<td>Negative</td>
<td>Normal</td>
<td>Headache</td>
<td>Normal</td>
<td>Pontine gliosis</td>
<td>Positive</td>
</tr>
<tr>
<td>5</td>
<td>48</td>
<td>DQB1*02</td>
<td>Abdominal pain</td>
<td>Negative</td>
<td>Normal</td>
<td>-</td>
<td>Normal</td>
<td>-</td>
<td>Positive</td>
</tr>
<tr>
<td>6</td>
<td>37</td>
<td>DQA1*05</td>
<td>Diarrhea, bloating</td>
<td>Negative</td>
<td>Normal</td>
<td>Headache</td>
<td>Temporolateral R alterations</td>
<td>Frontal gliosis L, fronto-temporal R gliosis</td>
<td>Positive</td>
</tr>
</tbody>
</table>

HLA, human leukocyte antigen; BCS, bowel clinical symptoms; Anti-tTg, anti-t-Transglutaminase; CNS, central nervous system; EEG, electroencephalography; R, right; L, left. \(^{°}\)Only \( \beta \) chain.

**Discussion**

We think that gluten sensitivity may be referred to an immunologic condition. The immune system has evolved in animals and in humans into two parts, i.e. a part responsible for prompt immune action against external agents (infectious or non infectious), called the immune innate system, and another one which recognizes the antigen by specific antigen presenting cells (APCs) and antigen receptors, defined the adaptive immune system. The immune innate system utilizes phagocytic cells (monocytes, macrophages, microglia), and the adaptive immune system employs B and T lymphocytes. Cell-to-cell contact and soluble cytokines are the communication route of both immune systems. Gliadin has the power to induce the activation of both innate and adaptive immune system in bowel.\(^{5} \) In CD, the stimulation of innate immune system was demonstrated by production of interleukin 15.\(^{7} \) The activation of pathogenetic CD4+ T lymphocytes, and interferon gamma demonstrates the immune adaptive system response.\(^{7} \)

CNS is an immunologically specialized site in which inflammatory and immune reactions are locally originated (innate immunity). Immune reactions can also start in the peripheral tissue (bowel, lymph nodes) and be imported into the CNS by competent immune cells (acquired immunity).\(^{18} \) Innate and adaptive immunity can be transformed into each other by various cytokines and Toll-like receptors (TLRs).\(^{18} \) CNS may be involved in CD in association with bowel,\(^{4,11} \) with other tissues or alone.\(^{11} \) Gluten sensitivity was attributed to the possible involvement of innate immunity.\(^{5,14} \) In gluten sensitivity the CNS involvement was proposed for autism and schizophrenia,\(^{14,15} \) EEG abnormalities,\(^{16} \) and epilepsy.\(^{17} \)

In our subjects predisposed by (HLA) DQ2, the first reaction after gluten introduction could be supposed to occur in bowel, and gluten fractions production could have stimulated the activation of innate immune system with consequent bowel symptoms (diarrhea, bloating, abdominal pain) and minimal (grade 0-1) histologic manifestations. The cytokines/interferon production\(^{16} \) by immune system may have changed the blood-brain barrier, as was observed in some pathological conditions,\(^{18} \) and may have acted as a pro-inflammatory signal in CNS with excitotoxicity, possible TLRs production and microglia activation.\(^{20} \)

The activation of innate immune system at the periphery can recruit
inflammation cells into CNS via cytotoxic mediators, glutamic acid and cytokines production.\textsuperscript{14,20,23} The presence of neutrophils, macrophages and monocytes in areas of neuronal loss in human epileptic tissue demonstrates that these cells contribute to the neuronal damage by cytokines and glutamate.\textsuperscript{21} These phenomena and the production of glutamate from glutamine\textsuperscript{22} may have produced brain hyper excitability of neurons and the inflammatory process,\textsuperscript{8} demonstrated by EEG abnormalities in the absence of anti-tTg antibodies. The presence of headache, cerebral cyst and gliosis may be a consequence of the inflammatory processes.

On the other hand, Brottveit and colleagues\textsuperscript{16} demonstrated that gluten sensitive patients showed increased levels of gamma interferon and raised CD3+ T cell at baseline after gluten challenge. These findings indicate a possible activation of the immune adaptive component in GS. In these subjects the adaptive immune system activation could be subsequent and eventually signaled by the production of anti-tTg antibodies, and/or possibly of other autoantibodies, as demonstrated in other diseases and in other epilepsy-associated congenital diseases such as Kearns-Sayre Syndrome\textsuperscript{23} and Dravet Syndrome.\textsuperscript{24}

Alternatively, gluten fractions in GS may stimulate directly phagocytic cells (macrophages, monocytes) in bowel, with production of intestinal symptoms, and glia in CNS, with EEG abnormalities, headache and gliosis.

It will be important to re-evaluate in our patients the clinical symptoms, the anti-tTg antibodies (and, in case, also other autoantibodies), and the EEG even though in the absence of convulsions after a more prolonged period.

Conclusions

In our GS cases with genetic predisposition, the CNS involvement was frequent. This condition provided, to search for clinical, electrophysiological and radiological CNS features seems to be mandatory. Further studies could elucidate the significance of EEG alterations present in our cases and the relationships between gluten and CNS abnormalities in GS.

References