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Non-Celiac Gluten Sensitivity: A New Member in the Family of Autoimmunity?

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Abstract

In the last years the attention of many scientists studying celiac disease has been attracted by novel gluten related disorder: non-celiac gluten sensitivity. As preliminary studies documented a role of the innate immune response in this condition, questions about its possible immune-mediated pathogenesis quickly arose. Non-celiac gluten sensitivity is currently classified as a "possible immunomediated disease": this review will focus on the most recent studies investigating the role of the immune system in this multifaceted medical condition.

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Introduction

Celiac disease (CD) is an immune-mediated reaction to gluten; it is characterized by an inappropriate T cell- mediated immune response that causes inflammatory injury to the small intestine in genetically predisposed subjects carrying the HLA-DQ2 and/or -DQ8 haplotypes [1].

CD is in many ways a prototypical autoimmune disease, of which both the genetic factors (HLA-DQ2 and -DQ8 predisposing antigens) and environmental triggers (ie, dietary gluten ingestion) are known [2].

Mechanisms leading from gluten ingestion to the formation of neo-antigens and to the activation of both innate and adaptive response in predisposed individuals have been largely investigated.

The activation of the adaptive response, in particular, leads to the formation of autoantibodies such as anti-transglutaminase (anti-tTGA), anti-endomysium (EmA) and anti-deamidated gliadin peptides (DGP), which are the main serological markers of disease [3].

Unlike other autoimmune conditions, in the case of CD a etiological therapy is available: the gluten-free diet (GFD) [2].

Most celiac patients following a GFD will negativize their autoantibody titer [2], an almost unique situation in the field of autoimmunity [2].

In recent times the scientific community has acknowledged non-celiac gluten sensitivity (NCGS) as a novel gluten-related disorder [3].

Originally described in the 1980s, NCGS is characterized by the occurrance of intestinal and extra-intestinal symptoms after the ingestion of gluten-containing food, in subjects that are not affected with either CD or wheat allergy [1].

Since both CD and NCGS share a common key ethiologic aspect (ingestion of gluten-containing foods) and similar clinical presentation, questions quickly arose about NCGS as a possible immuno-mediated disease.

Innate Immunity Alterations

In favour of the hypothesis of an immune-mediated origin, many studies suggested an activation of the innate immune response in patients with NCGS.

For instance, Carroccio et al. [4,5] demonstrated an increased number of eosinophils in the duodenal lamina propria, suggesting that basophil activation may be a useful marker for this form of wheat sensitivity

Toll-like receptors (TLRs) also seem to play an important role, as small-intestine expression of TLR2 and, to a lesser extent, of TLR1 and TLR4 in NCGS patients is even greater than in CD subjects [6].

Additionally, an increased number of intra-epithelial lymphocites of the classes α and β was found in NCGS [6].

It is not yet clear what the pathogenic mechanisms leading to the activation of the innate response, however it has been suggested a role of wheat amylase and trypsin inhibitors (ATIs) [7].

ATIs are a family of five or more homologous small proteins contained in wheat and highly resistant to intestinal proteolysis [1].

Preliminary in vitro studies suggested that the addition of 1 μg/mL to 20 μg/mL of ATIs to monocyte derived dendritic cells stimulates the release of IL-8 in a dose-dependent manner [1].

Adaptive Immunity Alterations

While studies documenting the activation of innate immunity are abundant, the role of adaptive immunity has initially been considered a minor contributor in NCGS pathogenesis.

Indeed, in contrast to CD, an overexpression of adaptive immunity

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markers has not been found in NCGS. In particular, IL17A, IL-6, interferon-c, IL-17 and IL-21 were not increased in intestinal biopsies of NCGS patients [6].

NCGS also differs from CD in the small bowel expression of FOXP-3, one of the most prominent markers of T-reg lymphocytes, which is markedly weaker in NCGS than in CD patients [6].

The little expression of this marker has been interpreted in the context of a reduced activation of adaptive immunity relative [1].

Based on these results it has been postulated that CD is characterized by the activation of both innate and adaptive immunity, whereas in NCGS causes only the former is activated.

As always happens when relations seem simple enough, further studies have shown an actual more controversy role of the adaptive immunity

Abnormalities in adaptive unmoral response were documented by Brottveit et al [8] in a recent study on 30 CD and 15 NCGS patients, from whom duodenal biopsies from were obtained before and after a brief gluten challenge.

In CD subjects the gluten exposure led to an increase in interferon-alpha, interleukin-8 and tumour necrosis factor alpha. Interestingly, interferon-gamma was the only cytokine to be stimulated by the gluten challenge (however, treated CD subjects already had pre-challenge altered levels of gamma-interferon) [8].

Consistent with these findings interferon gamma-induced protein 10, also known as C-X-C motif chemokine 10 (CXCL10), has been shown to be over-produced by small intestinal mucosa and peripheral blood mononucleated cells of both CD and NCGS patients [9].

The magnitude of this overexpression is sharply prominent in CD (almost 10 times compared to NCGS), however NCGS subjects maintain elevated levels of this cytokine compared to controls. [9].

The activation of the adaptive response could be responsible for the frequent positivity of IgG antibodies to gliadin in NCGS.

These antibodies are present in approximately 50% of NCGS patients and almost always disappear after the GFD, unlike what occurs for the same serological marker in treated celiac subjects [10].

It is not entirely clear how gliadin may cause activation of IgG-mediated response in subjects who are not affected by celiac disease.

Initially, studies showed a reduced intestinal permeability in NCGS patients [6].

Intestinal permeability in NCGS is, however, a subject of controversy as other papers have instead described an increased permeability in a subgroup of NCGS patients carrying the HLA-DQ2+/DQ8+ [11].

The actual mechanisms at the origin of IgG response therefore remain elusive, however it is possible to speculate that changes in gut permeability could lead to an easier contact between gliadin and the antigen presenting cell located s in the lamina propria of the intestinal mucosa.

Finally, HLA genetics is another interesting topic. In contrast to CD, in fact, NCGS did not show any correlation with HLA-DQ2 and / or -DQ8, although two studies reported a slightly higher prevalence of these haplotypes in NCGS than that in the general population [1,12].

Genetic studies investigating non-HLA regions are still lacking and, in general, the immunogenetics of NCGS are still nonexistent [13].

Clinical Elements Suspect for an Immuno-Mediated Etiology

Adopting a clinical point-of-view, it is well known that autoimmune disorders often present in familiar cluster, privilege the female gender and associate with other autoimmune conditions.

It is interesting to note that in a previous study, NCGS rarely occurred in first degree relatives of CD patients (12.8%), who displayed immune responsiveness to gluten despite a normal small-intestine mucosa [13].

NCGS also seems to predominantly affect the female gender with a female: male ratio ranging from 3:1 to 6:1 [7].

Furthermore, an elegant analysis by Carroccio et al. [14] showed that similar portions of subjects with NCGS and CD (29% in both groups) develop autoimmune disease, mainly autoimmune thyroiditis. In the same study cohorts, a large portion of NCGS patients (46%) were found to be positive for antinuclear antibodies.

However it must be remembered that the aforementioned characteristics are frequently found in autoimmune conditions but are not specific for this kind of diseases.

Therefore, clinical elements alone should not be used to define a medical condition as an autoimmune disease.

Conclusion

Currently, NCGS should be regarded as a new clinical entity although with a possible overlap with other conditions, mainly with irritable bowel syndrome.

Evidences of alteration of innate and, to a lesser extent, adaptive immunity have been documented in NCGS. However, differently from CD, the immune system does not seem to play a pivotal role in the etiopathogenesis of this complex syndrome.

Nevertheless, at the state-of-the-art we can not frame the immune system as a simple innocent bystander. In particular, future studies should verify whether particular immunologic alterations are related to the different and manifold clinical subset of this complex syndrome, which include both intestinal and extra intestinal symptoms and still lacks a specific biomarker.

Competing Interests

The authors declare they have no competing interests.

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