Gastroenterology and Hepatology From Bed to Bench

EDITORIAL

Immunogenetics of non celiac gluten sensitivity

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The immunogenetics of coeliac disease (CD) has advanced from "Bench to Bed" in the sense that HLA-DQ typing is now an established part of the diagnostic armamentarium. The configuration characteristics and the specificity of the HLA-DQ2, (1) -DQ8 (2, 3) and –DQ9 (4, 5) allow the binding of small peptides that cannot be further digested by the absence of specific human intestinal enzymes (6, 7). These peptides are derived from wheat (gliadins and glutenins), barley (hordeins), rye (secalins), oats (avenines) and hybrids of these grains, such as kamut and triticale and bind to HLA molecules, in particular when deamidated by tissue transglutaminase (8, 9).The stimulation of dendritic and T cells contribute to produce the spectrum of the characteristic changes of the duodenal and jejunal mucosa present in (CD). These changes lead to intestinal symptoms and autoimmune reactions that may affect extraintestinal organs. It is also known that the immune response can remain dormant. Environmental elements trigger the disease and, as opposed to what was thought to be a lifelong disease, it may be transitory (10, 11). Genomics studies have revealed that many other genes are involved in the modulation of the immune response but these findings have not yet transcended into the clinic workup, although 57 additional non HLA variants have improved the identification of potential CD patients (12).

In the past 10 years it has become clear that there is a group of conditions related to gluten consumption. Foremost among them are three types: a) the least common is wheat allergy; although the estimated prevalence of food allergy among adults in Western Europe is thought to be between 1 and 2%, with the frequency in infants being greater (approximately 5%). b) The autoimmune form, the best characterized, includes CD, dermatitis herpetiformis, and gluten ataxia and c) sensitivity to gluten, which is possibly immune-mediated and now the most common (13).

Recent studies of the immunogenetics of different forms of wheat allergy have implicated beta adrenergic receptor polymorphisms (14) and Toll-receptor 4 (15). IL-18 polymorphisms were significant associated with the rate of sensitization to wheat flour (16) and more recently IL-4 receptor alpha polymorphisms have been found to be associated in bakery workers (17, 18).

The immunogenetics of non celiac gluten sensitivity are non–existent and in order to advance in this field we need to go from "Bed to Bench".

The first time the term non-celiac gluten sensitivity was used probably was in 1978, by Ellis and Linaker (19) even though a few months before Hemmings (20) had reported two patients with satisfactory response to a gluten-free diet. In both cases, as in others later on, in Israel and England, it was more a case of allergy to dietary wheat (21). These isolated cases preceded the first double-blind study in 9 non-celiac patients who clearly showed the

deleterious effects of 20g of gluten per day (22, 23). G. Holmes, one of the authors of the original publication in 1980 has recently written an Editorial in the summer issue of this journal and masterly put into context this "entity" with recent literature already pointing to the possibility of a syndrome (24, 25). Since then, a few randomized, placebo-controlled studies have shown that it is increasingly clear that this it is not an entity but a syndrome. It has to be remembered that the published studies cannot be securely compared to each other since their patient selection is not uniform; besides, the protocols followed to establish the effects of gluten in each case are different.

Many of the described observations have helped to define non celiac gluten sensitivity as a reaction to gluten in which allergic and autoimmune mechanisms are excluded. That is to say, anti-EMA and/or anti-tTG tests are negative although antigliadin antibodies may be present but the duodenal mucosa is normal. Symptoms disappear with GFD and reappear with gluten challenge. As Sapone et al. have written, so far, this is essentially a diagnosis of exclusion (13). Therefore, it is fair to state that several immunological differences in patients with so called wheat (26) or non celiac gluten sensitivity (27, 28) justify the division of subgroups of patients that are begging for the presence of an immunogenetic marker. This vision is not only of semantic interest but it is crucial in the planning of immunogenetic studies. At this stage of the game, the clinical presentation is not enough to define subgroups of patients, many biological and immunological parameters are available and therefore this can be used when planning modern genomics studies.

For example, many of Carroccio et al. (26, 29, 30) well studied patients in Italy showed that eosinophils in the duodenal lamina propria and colon are increased, suggesting that basophil activation may be a useful marker for this form of wheat sensitivity. Other approaches are being used. For example, in the U.S.A. Sapone et al., found that non celiac gluten sensitive patients had no increase in the expression of the IL-17 cytokine in comparison with a group of celiac patients who did show an increase of this same cytokine in the intestinal mucosa (31, 32). However, subsequent studies by the same group have shown that non-celiac gluten sensitivity is not associated with increased intestinal permeability and that, in these cases, the expression of the T FOXP3 regulatory cell marker is decreased. Conversely, in these patients there is a significant increase in the expression of claudin (CLDN) 4 and of the innate immunity marker for the Toll-like receptors (TLR) 2 (31). These studies suggest that the difference between these two groups of patients is that, in CD, both innate and acquired immunity are altered, whereas in non celiac gluten sensitive patients only the innate immunity is activated by gluten. Recent Norwegian studies indicate that the immune response is more complicated than is suggested by this hypothesis and that more studies are needed to understand the symptoms. Thus, 30 HLA-DQ2+ celiac patients and fifteen patients with non-celiac gluten sensitivity were studied before and after a gluten-free diet, then feeding them four slices of gluten-containing bread for three days. Duodenal biopsies were collected before and after exposure. In celiac patients the tumour necrosis factor alpha and interleukin-8 were increased after the *in vivo* gluten challenge. The gamma interferon level in treated celiac patients was increased both before and after exposure and did not increase significantly; IFN-alpha was also found to be activated upon stimulation with gluten. By contrast, in patients with non-celiac gluten sensitivity, only IFN-gamma was significantly increased. The intra-epithelial lymphocyte density was higher in patients compared with controls independently of gluten overload, although they were lower in the latter than in the former (33) The studies so far have concentrated more in separating CD from non celiac wheat or gluten sensitivity rather than focusing on the different subgroups of patients that represent this syndrome.

In summary, the immunogenetics of non celiac wheat or gluten sensitivity is ready to be explored.

With the recent advances in genomics and the spectacular reduction in the cost of DNA sequencing it is up to clinicians to characterize the different subgroups of patients with this syndrome. Provided the selection of patients is adequate, the genomic specialists may provide results that will not only help to find genetic markers but also help to develop a personalized approach to medicine. As I and others have written before, personalized medicine is inevitable. It is our responsibility to become educated in genomic medicine in order to help and to educate our patients. The old Chinese proverb "a journey of a thousand miles must begin with a single step" has proven its truth (34).

One final point for clinicians when studying patients with this syndrome is to remember that a new vision of placebo/nocebo exits and this may be applicable to the clinical response to a gluten-free diet. Until recently, the well-known therapeutic effect of placebo was based primarily on the fact that the patient did not know that what was being taken was an inert substance. However, placebos work even if the patient knows they are such. Regarding the nocebo effect, it generates negative expectations in the patient and, it exemplifies the old saying "fear makes you sick", and it also explains why an analysis of placebo-controlled trials shows that almost 25% of patients taking placebo reported side effects that should not exist. Although there is less research on nocebo and therefore less documentation, the results of the studies are consistent with the fact that the placebo and nocebo effects are real. This opens an interesting field in therapy and makes the ethical issue of deceiving the patient disappear, since the fact that he or she is being given a placebo is not being hidden from the patient. From now on conscious attempts to identify and exploit the characteristics of medical visits in order to increase the placebo's effects are an ethical way to use what is known about its mechanisms, to improve clinical outcomes. This new insight suggests the need to incorporate similar protocols to the effects that a gluten-free or non gluten-free diet may have in those particular patients where no biological abnormalities can be detected. It is clear that these two opposing mechanisms, placebo and nocebo, may be involved. Expectations can bias sensory evidence and therefore the patient and the physician must obtain an appropriate balance which will result in the updating of expectations of a procedure, a drug or a product involved in the prescribed diet (35-37).

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