Cœliac Disease: An Important Clinical Entity Reveals Its Secrets

Scientific current evidence concerning gluten enteropathy

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Molecular Basis of the Toxic Action of Grain Proteins

Cœliac disease represents the only autoimmune disease where the environmental factor that triggers the immune response is perfectly well known, i.e. gluten [1]. It is an autoimmune pathology due to the interaction of genetically susceptible individuals (it is associated with HLA-DQ8 and especially with HLA-DQ2 [2]) and of the ingestion of gluten-containing grains (especially wheat, rye and barley [3]). Although these HLA class II alleles could only be found in 39.5% of the general population, almost 100% of affected individuals have them [1].

Surprisingly, oats - however rich in gluten - do not usually induce the lesions on the intestinal mucosa that are typical of the disease, i.e. the atrophy of the villi and the hyperplasia of the crypts [4, 5]. A fundamental discovery, published in the reputable journal *Science* on 27 September 2002, finally allows us to understand the toxicity of certain glutens present in

grains, in spite of the great biological diversity of this group of proteins [6].

The molecular basis of these grains' toxicity seems to come from a 33 amino acid peptide, which is the result of incomplete digestion of **gliadin**. This sub-protein of gluten is found in **wheat** (*Latin*: *Triticum*).

The above-mentioned peptide, called *33-mer gliadin*, contains a large quantity of proline (13 residues) and a fair amount of glutamine (10 residues) [6]. This peculiarity explains its strenuous resistance to any form of digestion by our proteolytic enzymes present in gastric and pancreatic juices, as well as in the intestinal brush-border membrane (loaded with proteases to complete protein digestion).

The *33-mer gliadin* is a substrate for tissue transglutaminase [2]. This extracellular enzyme found in the lamina propria indirectly triggers the autoimmune reaction characteristic of cœliac disease. The action of this enzyme on the peptide in question is followed by complete endocytosis by antigen-presenting cells, where it is divided into three distinct epitopes, which are then sent to be presented on the cellular surface [3].

Each of these epitopes, sometimes repeated within the peptide (up to three copies [6]), are identified as ligands of the molecules HLA-DQ2 or DQ8 [3]. The epitopes presented by HLA molecules on the surface of the antigen-presenting cells are then recognised by the specific CD4+ lymphocytes receptors and bind to them. The activation of those CD4+ generates an immune response producing cytokines, which in turn triggers both the villous atrophy and the crypt hyperplasia [3].

Homologous peptides, gluten sub-proteins **secalins** and **hordeins**, were also discovered in rye (*Latin: Secale)* and in barley (*Latin: Hordeum*) respectively. However - here is finally the key to the mystery - an equivalent peptide is *not* detected in the **avenins**, a gluten sub-protein found in **oats** (*Latin: Avena)*, nor in any other gluten-free grain such as rice or maize.

The autoimmune mechanisms triggered by the disease are highlighted by the presence of IgA anti-gliadin antibodies, but also by the increase of IgA anti-endomysium antibodies [7]. The latter, in fact, takes as a target the enzyme already mentioned, i.e. extracellular transglutaminase [3].

It is necessary to take good care not to exclude toxic grains until there is evidence of cœliac disease provided by a duodenal-jejunal biopsy via endoscopy. Only a biopsy could confirm a suspected diagnosis based on serology, as blood tests relating to cœliac disease are not 100% definitive.

Molecular Basis for the Increase in Intestinal Permeability

A paper published by *The Lancet* in April 2000 revealed the discovery of a human protein that induces tight junction disassembly in the small intestine enterocytes [8]. This protein, called **zonulin**, rapidly came to be considered as playing a key role in certain pathological processes, especially those characterised by an intestinal hyper-permeability, such as inflammatory and autoimmune processes [9].

Initially, the opening of the paracellular pathway (as opposed to a transcellular pathway that crosses the brush-border in the enterocytes) provoked by zonulin secretion may have been a defence mechanism [10]. Indeed, any bacterial proliferation in the small intestine does generate an increased secretion of zonulin. This mechanism seems to be part of an innate immune response that might help by flushing microorganisms out of the system [10]. Such a beneficial mechanism, controlled by zonulin, has been preserved by evolution despite the arrival of grain proteins.

An increased zonulin expression in intestinal tissues was also noted during an acute phase of cœliac disease [8]. Moreover, a paper published in *Gut* in February 2003, confirms that, *in vitro*, gliadin induces zonulin secretion in the enterocytes [11], a fact that has also been demonstrated *in vivo* more recently [12]. This explains the increased intestinal permeability to macromolecules characteristic of the disease [11, 12]. A functional test, based on the ingestion of a combined lactulose and mannitol powder, detects gut hyper-permeability amongst suspected patients.

The recent and extensive addition of gluten to the human diet, since the introduction of agriculture in the Neolithic era, seems to have caused, indirectly, a harmful effect on this defence mechanism and especially in relation to the onset of food allergies. Tight junction disassembly, due to the action of some of the gluten proteins, allows the entry into the organism of partially digested proteins, potentially resulting in food allergies.

Epidemiology and Clinical Manifestations of Cœliac Disease

The frequency of cœliac disease was initially greatly underestimated. It was only recognised in infants and adults presenting obvious signs of malabsorption: chronic diarrhoea, steatorrhea, abdominal distension, œdema, weight loss, and extreme lethargy [1]. However, the disease's classic mode of presentation has become less common: diarrhoea may be found in fewer than 50% of individuals [13] and gastrointestinal symptoms may even be totally absent [1].

Besides the great prevalence of its silent forms, cœliac disease seems to present a number of atypical symptoms, many more than previously thought. Several studies provide evidence regarding the extent of the disease, such that it will have to be considered, henceforth, as one of the most frequently found genetically based disorders in humankind [2].

A study that took place in the USA and that was published in February 2003 shows an overall prevalence of cœliac disease of 1 in 133 for those patients considered not-at-risk, i.e. asymptomatic and unrelated to cœliac-diagnosed patients [14]. The same author suggests that a systematic screening of North American and European population is needed [15]. Furthermore, recent findings relating to underachievement, in both education and work, amongst subjects with silent cœliac disease makes the need for global screening more urgent [16].

Another study, published on 19 June 2003 in the *New England Journal of Medicine*, estimated that the prevalence of cœliac disease amongst Finnish schoolchildren was at least 1 in 99 [17]. Two additional studies have confirmed that undetected cœliac

disease is likely to affect approximately 1% of the English population, both adults [18] and children [19]. These figures amply justify the term 'iceberg', frequently used in the literature since 1996 [20, 21], to characterise this very serious and underestimated disease.

These multiple and atypical clinical manifestations of cœliac disease are now beginning to be better described, if not as yet diagnosed [2]. Diagnosis should not just be limited to certain digestive signs (such as irritable colon) or cutaneous ones (dermatitis herpetiformis), but it should search for clinical signs and symptoms within the entire organism: liver, joints, uterus, brain, heart and other organs [1].

It is possible to find numerous autoimmune pathologies, amongst which we should include diabetes type I and autoimmune thyroiditis, as well as inflammatory bowel diseases, Sjögren's syndrome, primary biliary cirrhosis, primary sclerosing cholangitis, and rheumatoid arthritis. Autoimmune diseases occur as much as three to ten times more frequently in those with cœliac disease than in the general population [13].

We might also find a series of deficiency manifestations directly bound to assimilation disorders and due to the condition of the small intestine mucous membrane. They range from anaemia to osteoporosis -two pervasive conditions amongst cœliac patients- passing through neurological problems (ataxia), behavioural disorders and clinical depression. We could also mention the many cases of chronic fatigue, as well as miscarriages and digestive lymphomas. Finally, we should stress the fact that there is a frequent rise in hepatic transaminases.

Conclusion

Gluten enteropathy is a clinical entity much more important than we could ever imagine. First, its incidence is around 1% of the western world population and it is diagnosed worldwide, including in the developing countries [13]. In fact, it is becoming a common pathological occurrence for the general practitioner.

It seems that it is rather difficult to diagnose cœliac disease in current practice due to its extremely diversified clinical manifestations. Finally, the exclusion of incriminated grains is an effective treatment which would prevent pathological deficiencies and the auto-immune reactions generated by the disease, as well as protecting individuals from being haunted by its consequences which are, sometimes, even more dramatic.

Fortunately, several recent scientific discoveries allow us to improve our understanding of its molecular bases. Cœliac disease thus revisited will undoubtedly come to mind more easily, in spite of its misleading manifestations, when making a diagnosis.

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