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Coeliac Disease: A Food Allergy?

Jan Hed

Pharmacia AB, Diagnostics, Uppsala, Sweden

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Introduction

It was not until the introduction of the peroral biopsy capsule in the 50s that made it possible to make more detailed histological studies of the jejunal mucosa in coeliac disease (CD). After that time there was a shift in the diagnosis of CD to be based on morphological changes in an intestinal biopsy and its relation to gliadin exposure.

During the last 20 years several studies have shown different immunological phenomena associated to CD increasing the suspicion that the disease is based on an immunological mechanism and not due to a nonimmunological toxic reaction of gliadin peptides.

The aim of this paper is to describe these immunological phenomena and suggest how they can fit to an immunological model that indicate an allergic mechanism for CD. CD is often manifested with atypical, mild or no abdominal symptoms. It has been reported that 50% of first-degree relatives to CD patients are asymptomatic despite typical morphological alteration in intestinal biopsies [1] and in a Swedish population only 1 out of 5 adult CD patients had clinical symptoms [2] in contrast to early childhood when most patients have clinical symptoms. Therefore, when discussing immunological mechanisms in CD it is important to point out if it is discussed in relation to the morphological alteration in the intestinal mucosa or in relation to clinical symptoms.

Genetic Predisposition

It is well established that in first-degree relatives to CD patients the prevalence is increased 5–15 times compared to the general population indicating a genetic predisposition [3–6]. It has also been known for many years that CD is highly linked to MHC genes. The strongest association is with the HLA-DR3DQw2 haplotype which is often found in other diseases with autoimmune reactions [7, 8]. This association to autoimmune reactivity is believed to be of more biological relevance for CD than a possible role of the MHC genes for restricted antigen presentation in this disease. Despite all these results, environmental factors, except gliadin, may play a role since there is only 70% concordance for CD in monozygotic twins and 40% in HLA-identical siblings [9].

Lymphocyte Infiltration in Relation to Tissue Morphology

Infiltration of lymphocytes into the lamina propria and an increased density of intraepithelial lymphocytes (IEL) are characteristic pathological findings at biopsy in CD. However, this is not specific for CD and can be seen in food-sensitive enteropathies and Crohn's disease probably indicating an immunological hypersensitivity. In dermatitis herpetiformis (DH) about 5% of the patients have normal jejunal mucosa but it is infiltrated by lymphocytes which decreased after gluten-free diet [10]. In relation to that, recently an overrepresentation of one TCR variant [11] of the infiltrating lymphocytes was shown in CD suggesting a role of these cells in the disease.

The graft-versus-host (GvH) reaction has been used as an animal model to study the immune-mediated intestinal damage to explain the villus atrophy and lymphocyte infiltration. In this model it could be shown that the T lymphocytes were necessary for the typical mucosal changes [12, 13]. In another experimental design with milder GvH reaction the mucosal changes resembled the infiltrative lesions described in DH patients and CD first-degree relatives with normal villus morphology.

Sensitization to Gliadin

Gliadin in an aqueous solution binds [14] in a lectin-like manner to reticulin fibers in cryostat sections of mammalian tissue. The phenomenon has been used in an indirect immunofluorescence assay [15] to detect IgA antigliadin antibodies (AGA). The pattern obtained shows the same distribution as the R1 pattern described for reticulin antibodies by Rizetto and Doniach [16]. This pattern also

corresponds to antiendomysium antibodies (EMA) [17] and anti-human jejunum antibodies (JAB) [18] described later on. This shows a close relation between gliadin and reticulin fibres in connective tissue. It has also been shown that CD sera react with the gliadin-derived peptides that contain the sequences that have the most damaging properties in in vitro organ culture of coeliac small intestine [19] indicating that the sera may react with similar structures [20]. However, not all CD patients have AGA in their sera. In one study, 3 subjects with CD but without serum AGA had AGA in faeces, indicating that faecal antibodies may precede serum antibodies [21].

Autoimmune Reaction to Connective Tissue Constituents

Antireticulin antibodies (ARA) in CD was first described in the early 70s using indirect immunofluorescence [22]. Cryostat sections from liver and kidney were used as substrates showing typical reticulin staining of connective tissue fibres surrounding the renal tubules, glomeruli and hepatic sinusoids [23]. When cryostat sections from the primate gastrointestinal tract were used as substrate, the immunofluorescence patterns were described as antiendomysial antibodies (EMA) [17] in oesophagus sections and as JAB in human jejunal sections [18]. With indirect immunoelectron microscopy it could be shown that these antibodies do not bind to the collagen fibres but to amorphous material surrounding these fibres [24]. Later on, Mäki et al. [25] identified extracellular matrix non-collagenous protein molecules that specifically react with CD patient sera IgA and they could isolate these antigens from a fibroblast line [26]. The antigens isolated from the fibroblast line absorb both ARA and EMA. Different tissue absorption studies show a high degree of cross-reactivity between ARA, EMA and JAB [18, 23, 27].

These tissue autoantibodies are not related to clinical symptoms since they could be shown in asymptomatic CD patients [29]. In a follow-up study of 7 ARA-positive relatives to CD patients but with normal mucosa revealed 2 further cases of CD and 1 of DH during the next 3 years [30]. Furthermore, in children these autoantibodies showed a lower sensitivity than antigliadin antibodies to identify CD in children below 2 years of age [31].

Toxicity to Biopsies

When intestine from a patient with untreated CD was cultured with gluten the disease state was continued [32] in contrast to intestinal tissue from CD patients in remission is cultured with gluten [33]. This suggests that gluten is not

directly cytotoxic to coeliac jejunal mucosa but requires an effector mechanism. In co-culture experiments [34] it has been demonstrated that jejunal tissue from a CD patient in remission becomes susceptible to the toxic effect of gluten if it is co-cultured with diseased tissue. This indicates that the mucosa of CD produces mediators or activated cells that induce the typical CD changes. This has been taken as strong evidence for a role of immune mechanisms in the pathogenesis of CD [35].

IgG Antibodies to Food Antigens

Precipitating antibodies to a variety of food antigens have been shown since the 70s in both children and adults with CD. The incidence falls after a period with gluten withdrawal [1, 2] and morphological improvement [36, 37]. The IgG subclass profile is similar to food antibodies [38] in other non-CD patients. This increased production of IgG food antibodies is accompanied with a raised number of IgG-producing cells present in the coeliac lesion reflecting an imbalanced immune response to gluten and probably also to other dietary antigens [39]. IgG antibodies to gliadin have higher sensitivity to CD in most studies and has been suggested to be related to clinical symptoms. Moreover, IgG food antibodies are increased in early childhood in both CD patients and normal subjects.

Immune Complexes

The sequential morphological changes which take place in the CD intestinal mucosa after gluten challenge have been studied to elucidate the role of immunological mechanisms in CD. Lamina propria [40, 41] was infiltrated by eosinophils and neutrophils after 4 h. This time course is more compatible with a type III reaction than type I or type IV and this is in agreement with immunofluorescent studies showing deposition of complement and immunoglobulins in the region of basement membrane [42–44].

Conclusion

Increasing evidence shows that immunological and inflammatory factors are involved in the mucosal destruction of CD but there is no clear specificity for this enteropathy. During recent years, interest has focused on the mucosal infiltration of lymphocytes. These lymphocytes seem to infiltrate the tissue before clinical symptoms and atrophy of the villus develop and can be recruited after

gluten challenge. However, the specific correlation to gliadin or tissue antigens has not been proven since the reaction can be obtained despite absence of AGA and EMA. The mucosal alterations seen in CD have many similarities to other T-cell-mediated injuries of the intestinal mucosa such as GvH reaction. A type IV reaction seems to be the most likely allergic reaction type for this tissue reaction but would not explain the variability in clinical symptoms. The affinity of gliadin to reticulin fibres would induce a T-cell-dependent hapten reaction with an autoimmune reaction as a secondary phenomenon. This is further indicated by the decrease of both these antibodies after instruction of gluten-free diet.

Since it is known that increased permeability is a basic feature of CD, all factors for a type III allergic reaction are present in CD to explain one important mechanism for the clinical symptom in the disease. IgG food antibodies are related to clinical symptoms and immune deposits can be detected in the mucosal tissue in CD.

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Jan Hed, Pharmacia AB, Diagnostics, S-757 55 Uppsala (Sweden)