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Focus
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auto-immune intestinal diseases

Excerpts from the Bio Rad day seminar on auto-immune intestinal diseases on 19 September 2008.

The following presentations were made at this seminar:
- **Auto-immune diseases:**
- Coeliac disease
- Auto-immune enteropathies
- **Dysimmune diseases:**
- IBD (Crohn's disease and UC)
- Microscopic colitis
- Immune deficiencies: CVID+++

Auto-immune enteropathies

- In the first year of life in infants and in exceptional adult cases, this condition is characterised by chronic diarrhoea and malabsorption syndrome +++ (villous atrophy). The associated auto-immune diseases are IDD, auto-immune thyroiditis, and AIHA.
- IPEX syndrome is a rare, severe and exclusively paediatric enteropathy (profuse diarrhoea occurring in the first days of life) with auto-immune symptoms similar to auto-immune diabetes, and AIHA. Extensive destruction of the intestinal epithelium occurs; the disease is caused by a mutation of the FOXP3 gene, inducing regulator T-cell dysfunction. The survival time is less than 8 years.

Coeliac disease

Définition

- This disease consists of an auto-immune enteropathy induced by a dietary antigen: gliadin, in genetically predisposed subjects. It is the most frequent cause of malabsorption in adults and children. The duodenal biopsy procedure detects partial or sub-total atrophy of the intestinal villosities causing the malabsorption syndrome. It takes a conventional form or the form of isolated signs (in asymptomatic forms).
- Abnormal immune reactions to gliadin induce villous atrophy; there are two types of immune responses: adaptive and innate.
- Coeliac disease is a gluten intolerance. Gluten is a viscous elastic mixture of a large number of proteins contained in cereals (wheat, barley, rye, oats).

Genetics

Coeliac disease is associated with the HLA system, although other environmental factors are involved. This results in the following type of genetic predisposition:
- HLA DQ2 (DQA1* 05 and DQB1* 02): in 90 to 95% of patients
- HLA DQ8 (DQA1* 03 and DQB1* 03): in 5 to 10% of patients

Furthermore, some subjects are at a higher risk of developing celiac disease: dermatitis herpetiformis, identical twins, siblings with identical HLA haplotypes, Trisomy 21, IDD, PBC, Auto-immune conditions.

Epidemiology

This concerns:
- Populations of Northern Europe, Northern Africa, Australia and the United States. It is very rare in Asia and sub-Saharan Africa.
- The sex ratio for CD in adults in 2-3 women for 1 man.
- 2 frequency peaks: onset during childhood, generally between 6 months and 2 years after introduction of dietary gluten. The adult-onset form is generally detected between 20 and 40 years. Late-onset forms (after 65 years) are not exceptional. Only 10 to 20% of patients show characteristic clinical signs.

Clinical profile

- Symptomatic conventional form.
- Atypical mono- or pauci-symptomatic form.
- Silent or asymptomatic form essentially in at-risk populations.

Conventional coeliac disease: concerns infants and young children (between 6 and 24 months) after introduction of gluten. The symptoms are retarded growth, chronic diarrhoea, abdominal distension, decrease in muscle mass, hypotonicity, lack of appetite, irritability. In adults (between 20 and 40 years): diarrhoea, weight loss, abdominal pains, biological signs of malabsorption (iron, Ca, Mg, vit ADEK, folates, B12).
Atypical coeliac disease: in 90% of cases. The form is mono or pauci-symptomatic; it affects children but particularly adults. The symptoms are digestive with recurrent abdominal pains and nausea, vomiting, abdominal bloating, recurrent mouth ulcers. Extra-digestive symptoms may or may not be caused by malabsorption syndrome (anaemia, frequently severe osteopenia, osteoporosis with or without fracture, migraine, tetany, epilepsy, severe depression, alopecia, myocarditis, small stature, delayed puberty, amenorrhoea, recurrent miscarriages, sterility, etc.).
Silent or asymptomatic coeliac disease: fortuitous detection of gluten enteropathy in an asymptomatic patient following an endoscopy performed for other reasons or as part of a systematic investigation in at-risk subjects.

The two complications described are osteoporosis and malignant tumour growth: NHML of the small intestine, epithelial carcinoma (oropharynx, oesophagus), adenocarcinoma (small intestine, breast, testicle).

Diagnosis of coeliac disease

- screening diagnosis: serology
- confirmation diagnosis: intestinal biopsy
- definitive diagnosis: clinical and histological improvement after GFD
- diagnostic aid: HLA DQ2 and DQ8 (genotyping)

The antibodies of coeliac disease (CD) are, in decreasing order of sensitivity and specificity:

- Anti-transglutaminase TTG antibody (IgA and IgG) detected using Elis
- Anti-endomysium EMA antibody (IgA and IgG) detected by IFI on monkey oesophagus
- Anti-gliadin antibody (IgA and IgG) detected using Elisa
- Anti-reticulin (IgA) detected by IFI on rat tissue
- Anti-jejunum antibody (IgA) also prescribed, detected by IFI on rat jejunum.
- Other antibodies: anti-F actin antibody (IgA) described as of 2000 in CD, the frequency of which is closely dependent on the identification techniques used (IFI on Hep2, Elisa, etc.). The antibody titre is correlated with the severity of the villous atrophy, the primary benefit is to form an argument in favour of diffuse villous atrophy lesions in the case of an association of clinical symptoms and positive serology with a normal biopsy.

The screening strategy proposed by the French Higher Health Authority (HAS) was updated in January 2007.
Only the screening test for anti-endomysium antibodies and anti-transglutaminase antibodies is relevant in the diagnosis of CD. If it is positive, it confirms the clinical suspicion and enables the decision to perform a biopsy of the small intestine. The screening test for anti-reticulin and anti-gliadin antibodies, which has lower performances, is no longer relevant in the diagnosis of CD.

According to the good medical technology practices updated in June 2008, the disappearance of anti-endomysium and anti-transglutaminase antibodies is associated with observance of treatment and encourages patients to follow treatment. Treatment observance is evaluated by testing for the antibodies used for the diagnosis. The French health insurance scheme now reimburses anti-transglutaminase antibodies and continues to partially reimburse anti-endomysium antibodies. However, it no longer reimburses anti-reticulin and anti-gliadin antibodies.

HLA genotyping: HLA DQ2 AND DQ8
Genotyping is of interest for IgA-deficient patients or patients with a negative serology. The genotype test may be useful but should not be used as a routine test. It has a high negative predictive value (99%).

Confirmation diagnosis: intestinal biopsy.

Treatment

- Strict Gluten-free diet (GFD) for life
- Sometimes necessary initially to correct some deficiencies (calcium, iron, vit B12)
- Dietician
- Cost (ECP €45/month)
- Observance< 50%
- Support group (AFDIAG, GERMC, etc.)
- Significance: control symptoms and prevent the two major complications of CD, osteoporosis and neoplasia.

GFD:

- Elimination of foods and medicinal products containing wheat, rye, barley flours.
- Corn, rice, buckwheat, meat, fish, poultry, vegetables, fruit, egg, milk and yogurts are allowed.

Gluten is a widely used additive in processed foods and ready meals.

Prospective alternatives to the GFD are emerging:

- Bacterial PEP (Propyl EndoPeptidase) administered orally, targeted against the primary immunogenic peptide of gliadin, inducing its destruction; trials are currently in phase 3.
- Anti-IL-15, anti-IFN, anti-TTG monoclonal antibodies
- GMOs