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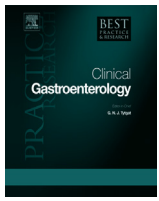

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Complications of coeliac disease

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A B S T R A C T

Within the past 20 years the spectrum of complications of coeliac disease (CD) has been considerably extended. Besides the classic complications, autoimmune diseases and osteopenia, numerous forms of CD non-responsive to a gluten-free diet have been recently identified. Among the non-responsive CD, the majority of patients presents as long term responders. However a small subset of CD patients becomes refractory to a gluten-free diet with persistent malabsorption and intestinal villous atrophy. Whereas refractory coeliac disease type I (RCDI) is hardly distinguishable from active CD, the type II (RCDII) has a severe clinical presentation and a very poor prognosis. Enteropathy Associated T cell Lymphoma (EATL) is even more aggressive with a five year survival of 20%. Classic adriamycin-based chemotherapy is poorly efficient in the lymphomatous complications of CD and current therapeutic strategies focus on more intensive regimen with autologous or allogenic stem cell transplantation. Notable pathogenic advances let us to test targeted therapy both in low (RCDII) and high grade lymphomatous (EATL) complications associated with CD.

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Introduction

Coeliac disease (CD) is an inflammatory enteropathy induced by gluten in genetically predisposed individuals. Its prevalence is of 1% in Europe and USA. Treatment relies on a life-long gluten free diet which prevents bone, autoimmune and malignant complications. Different types of resistance to a gluten free diet (GFD) have been described within the past 20 years. The majority of those patients are long term responders whereas a small group of them develop an authentic refractory celiac disease. We describe below the panel of CD complications with a particular detailed description of malignant complications.

Bone complications

Fifty to seventy percent of CD patients suffer from a loss of bone mass at diagnosis. Conversely, increased prevalence of CD in osteoporotic patients was reported [1]. Consequently, bone densitometry is recommended for all CD patients at diagnosis. Mechanisms involve both calcium malabsorption and inflammatory factors related to intestinal mucosal inflammation [2,3].

Osteopenia is major in the forearm which is the most common fracture site [4]. Gluten free diet may partially correct osteopenia but normalization is rarely observed [5]. The risk of fracture is significantly increased before diagnosis of CD but not under gluten free-diet [6]. Besides gluten-free diet, clinical management of osteopenia includes a daily calcium intake of 1500 mg, and vitamin D supplementation, if inadequate serum levels.

Autoimmune complications

The link between CD and autoimmunity is now firmly established. Five to 10% of patients with type I diabetes develop CD, while conversely, 15–20% of CD patients have or will develop autoimmune disorders [7]. Besides dermatitis herpetiformis which appears more as an extra-intestinal manifestation of CD, type I diabetes and autoimmune thyroiditis appear as the most frequent autoimmune diseases associated with CD, before Rheumatoid arthritis, autoimmune hepatitis, Sjögren's syndrome, systemic lupus, addison's disease, antiphospholipid syndrome or myasthenia gravis [7–9]. Indeed, type I diabetes and CD share frequently susceptibility HLA-type II genotypes DQ2/DQ8. Individuals who are heterozygous for DQ2.5 (DQA1*05:01/DQB1*02:01) and DQ8 (DQA1*03:01/DQB1*03:02) are also susceptible to type I diabetes with an almost five-fold higher risk than those who are homozygous for either of the DQ variants [10,11]. Besides HLA genes, some CD-associated variants within coding sequences have also been found in association with other autoimmune diseases. One such interesting variant is an SNP in *SH2B3* that is associated with other autoimmune, type I diabetes and rheumatoid arthritis [12]. Autoimmune diseases such as type I diabetes and thyroiditis are not clearly improved by gluten free diet, not surprisingly as pancreatic and thyroid lesions are irreversible, but GFD might reduce the risk to develop autoimmune diseases after diagnosis of CD, pointing to the link between exposure to gluten and onset of autoimmunity outside the gut [7,12,13].

Asymptomatic patients with persisting villous atrophy on a gluten free diet

Persisting villous atrophy despite a strict GFD is not a rare situation outside refractory coeliac disease. In our experience in Paris, villous atrophy was still present in 70 (44%) patients assessed after one year on GFD. Strict observance of the diet was comparable both in patients with or without full histological recovery (approximately 70% of the cases). Patients however differed significantly by the frequency of iron deficiency anaemia which was more often observed in patients with (20/70; 29%) than without (11/88; 12.5%) villous atrophy ($p = 0.015$; OR: 2.78). Similarly, low ferritinemia was more frequent in patients with (23; 33%) than without (21; 24%) villous atrophy ($p = 0.065$) [14]. Persistent villous atrophy does not seem to be associated with an increased mortality, but a higher risk for lymphoproliferative malignancies was reported among patients with persistent villous atrophy [15]. Further studies are necessary to better assess the long term follow-up of these coeliac