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Research Paper

Celiac disease: An update on clinical presentation, epidemiological profile, diagnosis and treatment

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ABSTRACT: *Celiac disease (CD) is a common autoimmune disease, affecting approximately 1% with geographic variation and presents primarily intestinal and extra-intestinal manifestations or both. It is an immune-mediated enteropathy induced by gluten, characterized by a specific genetic genotype (HLA-DQ2 and HLA DQ8) and the production of autoantibodies (anti-tissue and anti-endomysia transglutaminase) caused by the recognition of the immune system with transglutaminase complexed to gliadin, which triggers the inflammatory process that specifically targets the intestinal mucosa. The diagnostic process consists of a serological test based on IgA anti-transglutaminase (tTG) antibodies combined with IgA quantification to exclude IgA deficiency, a potentially misleading factor in the diagnosis of CD. A positive tTG serology must be corroborated by an anti-endomysial antibody test before considering an intestinal biopsy. In this context, the aim of this review is to provide information on the clinical presentation, epidemiology profile. Pathophysiology, diagnosis and treatment of celiac disease.*
KEYWORDS: *Celiac disease, an update*

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I. INTRODUCTION

Celiac disease (CD) is an immune-mediated disease, known as celiac sprue or gluten-sensitive enteropathy, characterized by a specific serological and histological profile triggered by gluten ingestion in genetically predisposed individuals [1]. Gluten is a general term for the proteins found in various grains, including wheat, rye, barley, spelt and kamut [1,2]. In fact, itis a chronic inflammation caused by the ingestion of gluten, resulting in damage of the small intestinal mucosal membrane and leads to villous atrophy, crypt hyperplasia and intraepithelial lymphocytic infiltrate and consequently malabsorption of nutrients [3,4]. The first description of this disorder was made by Aretaea of Cappadociain the end century AD and he word "celiac" comes from the Greek "koeliakos" which means "suffering of the bowels "malabsorption [4].

II. CLINICAL PRESENTATION

Celiac disease has gradually moved from the status of a rare digestive disease in infants to that of a frequent systemic disease affecting all ages of life. Is can occurring, with two peaks of onset one shortly after weaning from gluten in the first 2 years of life, and the other in the second or third decade of life. However, the clinical manifestations are polymorphic with many silent or atypical clinical forms and can vary widely from patient to patient, this leads to difficulty in diagnosis. In fact, symptoms can be classified into categories: intestinal (classic) and extra-intestinal (non-classical) manifestations subclinical, refractory [1,5,6].

Intestinal (classic) symptoms: It corresponds to an extensive attack of the small intestine. Children under 3 years of age are more likely to have gastrointestinal symptoms including diarrhea, loss of appetite, abdominal distension and poor growth. Older children and adults may also present with diarrhea, bloating, constipation, abdominal pain or weight loss [1,5].

Extra-intestinal (non-classical) symptoms: due to a combination of chronic inflammation, nutrient deficiencies, and possibly an adaptive immune response spreading from the intestinal mucosa to other tissues and organs [5]. They may include Iron deficiency anemia, liver disease, Duhring's dermatitis herpetiformis, IgA nephropathy, neurological and psychiatric manifestations or both such as temporal lobe epilepsy, cerebellar ataxia and peripheral neuropathy. The pulmonary hemosiderosis, or nonspecific problems such as joint pain exhaustion, headaches, mood swings (depression) and constipation are also present [5,7,8].

Subclinical symptoms: This form includes CD-susceptible patients with symptoms that are not clinically significant, and are often only recognizable after GFD-induced benefit or screening. Indeed, patients undergoing antibody screening are related to patients with CD or to cases identified through a general population screening strategy [1,6].

refractory symptoms: It is the persistence or recurrence of malabsorption symptoms and villous atrophy despite strict adherence to a gluten-free diet for at least 6 to 12 months.

III. DISEASES ASSOCIATED AND COMPLICATIONS

The CD is an autoimmune pathology related to gluten intolerance. The mechanism of the immunological involvement is now well known [3]. The clinical form of CD is characterized by the association of diarrhea, weight loss, malabsorption. The latent forms are often frustrated that leads a difficulty of diagnostic [4].

At least 20-30% of CD patients have extraintestinal manifestations [5]; liver lesions, are most often described [6]. They are often asymptomatic. The pathophysiological mechanisms implicated in liver damage in CD are still lousily understood [7].

The hepatic cirrhosis in this case was suggested by the following clinical and biological signs: splenomegaly, dilatation of the portal trunk, tuberous varices and disorders of the hepatic tests. And CD was retained based on the positivity of anti-transglutaminase tissue antibodies and the result of intestinal biopsy [11]. However, hepatic involvement is frequent in CD. It is essentially depicted by atypical signs (15 to 61%). These abnormalities are generally resolved after the installation of a diet without gluten [11-12].

However, CD is associated with more others liver diseases like as primary biliary cirrhosis (3-7%), sclerosing cholangitis (2-3%), hepatic steatosis, autoimmune hepatitis (3- 6%), viral hepatitis C (1.2%) [13-14].

IV. CELIAC DISEASE EPIDEMIOLOGY

Prevalence, the proportion of individuals with CD in a population at a given time, depends is variable [14]. In fact, this prevalence has increased in recent years due to an increase in the sensitivity of the diagnostic test in determining serum IgA class anti-tTG antibodies, as well as early dietary habits, gluten composition, dough fermentation, early changes in the microbiome, intestinal infections and drug use [7,15,16].On the other hand, serum IgA antibodies against tissue transglutaminase are reliable markers of celiac CD, these antibodies, while anti-tTG IgG and IgM antibodies have been found less frequent[17]. However, some studies have suggested that these autoantibodies may be less useful in early-onset celiac disease, because these antibodies only enter into the circulation after severe villous atrophy has developed [18, 19,20,21].

Globally the prevalence of CD is 1%, with variation between populations (Table1) [7].

Table 1: Prevalence of celiac disease worldwide [7].

Region	Period	Prevalence %	Reference
Italy	1991-1992	Sero-p (0.57%) Biop-p (0.49%)	(Grandgirard et al., 2002)
Italy (Sassari and Ancona)	2000-2002	Adults (0.7%) children (1.1%)	(Mustalahti et al., 2010
Italy	1999-2001	Immigrant children (1,9%)	(Cataldo et al., 2004)
Finland	2004-2006	0.55%	(Virta et al., 2009)
Finland	2000-2001	Adults (2%)	(Mustalahti et al., 2010)
Germany (Augsburg)	1989-1990 1999-2001	Adults (0.2%) Adults (0.3%)	(Mustalahti et al., 2010)
Sweden	2001	Children (1.3%)	(Carlsson et al., 2001)
UK	1986-1987 2000	Adults (1,5%) Children (0.9%)	(Mustalahti et al., 2010)
Russie (Karelia)	1997–2001	Children (0.2%)	(Kondrashova et al., 2008)
Poland (Bydgoszcz)		children Sero-p (0.8%) Biop-p (0.22%)	(Szaflarska-Popławska et al., 2009)
Spain (Catalonia)	2004-2007	Total population (0.49%) Adults (0.28%) children (1.41%)	(Mariné et al., 2011)
Spain (Madrid)	2001-2002	Sero-p (0.63%) Biop-p (0.27%)	(García Novo et al., 2007)
(Spain) Granada	2009-2012	Children (3%)	(Almazán et al., 2015)
Spain (Biscay)	1998-1999	Children (0.85%)	(Castaño et al., 2004)
USA	2009– 2010	6 – 80 years (0.71%)	(Rubio-Tapia et al., 2012)
USA (Wyoming)	2003	Adults Sero-p (0.8 %)	(Katz et al., 2011)
USA (Maryland)	1974-1989	1974 Sero-p (0.21%)	(Catassi et al., 2010)

		1989 Sero-p (0.45%)	
Brazil	2010-2011	Adults ; 60 years or older (0.1%)	(Almeida, 2013)
China	2010-2013	Adults positive CD -anti-tTG-IgA (0.36%) -anti-DGP-IgG (1.88%) anti-tTG IgA and anti-DGP-IgG (0.06%)	(Yuan et al., 2017)
North India (Punjab)	2003 - 2004	School children anti-tTG (0.48%) Biop-p (0.32%)	(Sood et al., 2006)
Iran	1997-2003	Children (0.61%)	(Imanzadeh et al., 2005)
Turkey	2005	Children Sero-p (0.87%) Biop-p (0.63%)	(Ertekin et al., 2005)
Egypt	2001-2004	Children IgA anti-tTG (0.93%) Biop-p (0.53%)	(Abu-Zekry et al., 2008)
Tunisia	2003-2004	Schoolchildren IgA-tTGs (2.2%) Biop-p (0.45%)	(Hariz et al., 2007)
Libya	.2011	Children 0.79%	(Alarida et al., 2011)
Morocco		sample size (n=276) Sero-p 9.1%: [IgA-tTGA (8.7) ; IgG-tTGA 0.36%]	(Oujamaa et al., 2019)

The epidemiological profile of celiac disease throughout the world remains a bit ambiguous because of the diagnostic criteria used, in addition to that, we observe that a number of patients refuse to go all the way and to do a biopsy to confirm the disease. However, the prevalence in Europe is generally estimated to be between 0.2 and 3%, indeed, a high percentage is observed in children in the region of Granada (Spain) (3%) table 1[22]. In the United States, although CD is considered rare, epidemiological data show an increase in seroprevalence from 0.21% to 0.45% between the years 1974 and 1989 in the state of Maryland (USA) [23],while the survey of Rubio-Tapia et al. carried out between 2009 and 2010 reveals a prevalence of 0.71% in patients aged between 6 and 80 years [24].This disease also affects 0.1% of Brazilians aged over 60 years [25]. In Asia, 0.06% of adults have tested seropositive in China [26], while the prevalence among children in North India (Punjab), Iran and Turkey are around 0.32%, 0.61% and 0.45% respectively [27, 28, 29]. In North Africa, a prevalence of 0.53%; of 0.45% and 0.79% have been recorded among Egyptian, Tunisian and Libyan children respectively [30,31,32]. Regarding the Moroccan country, to our knowledge, few studies related to this disease, besides, the study of Oujamaa et al. on a sample of 276 diabetic patients showed a seroprevalence of 9.1% with 8.7% of IgA-tTG positive and 0.36% of IgG-tTG positive [33].

III. DIAGNOSTIC AND TREATMENT

CD is assured by a combination of clinical arguments: the positivity of immunological assessment (anti-tTG antibodies+ anti-endomysium antibodies (EmA)+ anti-deamidated gliadin antibodies (DGP)) and by intestinal biopsy [1,7,34]. Serological tests have completely transformed the conditions for the diagnosis of this disease, allowing pediatrics to easily relate both classical clinical forms and atypical or non-specific extradigestive symptomatology to CD. They allow to identify patients for whom intestinal biopsy is indicated, to screen CD patients with risk factors and to evaluate the adherence to the diet without gluten [9]. These tests include the search of IgA antibodies preferentially: anti-tissue Transglutaminase (tTG), anti-endomysium and anti-gliadin and anti- deaminated gliadin. Indeed, positive anti-tTG serology is an excellent screening procedure with a high sensitivity and specificity [7,34]. In addition, it is recommended to combine two serological tests in order to better detect CD [9]. The intestinal biopsy, considered as the "gold standard" of diagnosis, is more justified when the result of the serological tests is positive, or when these are negative, but the clinical picture is very evocative. In fact, the histological biopsy allowing to evoke the CD diagnosis are: a villous atrophy, a crypts hyperplasia and an increase in the chorion cell density. The association of villous atrophy with the positivity of serum anti-endomysium antibodies and anti-transglutaminase antibodies allows a diagnosis with near certainty [1,5,6].

Treatment for CD involves a diet without gluten. This diet can relieve symptoms, decrease autoantibodies and promote villus regrowth. But can also lead to mineral and vitamin deficiency and increase cardiovascular risk. Potential future therapeutics include dietary supplements to help digest gluten, targeted therapies to induce tolerance, and inhibition of gluten deamination by tTG.

IV. CONCLUSION

Celiac disease has a wide geographical distribution throughout the world, represents a prototype disease that science and medicine take advantage of, providing more and uninterrupted knowledge in genetic, clinical, diagnostic and management aspects. Understanding the pathophysiology of CD provides excellent opportunities for accurate diagnosis and therapy development to relieve infected individuals.

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