

Celiac Disease And Associated Autoimmune Diseases University Department Experience

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Abstract:

Celiac disease (CD) is an autoimmune disorder triggered by the ingestion of gluten, in genetically predisposed patients. The association with other autoimmune diseases is frequent, which makes it necessary to systematically search for them. Our study had for objective to evaluate the prevalence of these autoimmune diseases in CD adult patients, insisting on the importance of systematic screening given their frequent asymptomatic character.

It was a retrospective and descriptive study spread over 27 years, and including a total of 347 celiac patients with 72 among them had an associated autoimmune disease, a prevalence of 20,74%.

These autoimmune diseases (AIDs) were multiple, dominated mainly by autoimmune thyroiditis in 40.8% of cases, of which 19 patients were euthyroid, 9 patients hypothyroid and 2 patients hyperthyroid (Graves' disease), type I diabetes, Gougerot-Sjögren syndrome, autoimmune hepatitis, dermatitis herpetiformis and psoriasis. These autoimmune diseases should be systematically investigated to avoid diagnosis and therapeutic delays, and improve prognosis.

Keywords: *Celiac disease, autoimmune diseases, autoimmune thyroiditis*

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I. Introduction:

Celiac disease (CD) is an autoimmune disorder triggered by the ingestion of gluten, in genetically predisposed patients [1]. Like other autoimmune diseases, CD is a polygenic disorder in which the major histocompatibility complex locus is the most important genetic factor. It is the result of an immune response to self-antigens leading to tissue destruction and production of autoantibodies [2].

The association with other autoimmune diseases is frequent, which makes it necessary to systematically search for them [3].

The objective of our study is to evaluate the prevalence of these autoimmune diseases in CD adult patients, insisting on the importance of systematic screening given their frequent asymptomatic character

II. Patients And Methods:

This is a retrospective and descriptive study of all adult patients followed for celiac disease in a hepato-gastroenterology department.

The study period spanned 27 years, from January 1995 to December 2022.

During this period, we systematically looked for the existence of associated autoimmune disease or autoimmune marker.

III. Results:

Of a total of 347 celiac patients, 72 patients had autoimmune disease associated with CD, a prevalence of 20.74%.

The mean age of our patients was 44.75 years, with extremes ranging from 18 to 79 years.

The sex ratio F/M was 2.6, with a clear female predominance in 72.2% (n=52).

The diagnosis of celiac disease was based on clinical (malabsorption diarrhoea and/or deficiency syndrome), serological (positive IgA anti-transglutaminase antibodies) and histological (intraepithelial lymphocytosis > 30% and total, subtotal or partial villous atrophy) criteria, with a systematic search for the existence of an autoimmune disease or an associated autoimmune marker.

The diagnosis of associated autoimmune diseases preceded that of CD in 27.8% of cases (n=20), followed it in 33.4% of cases (n=24), and was concomitant in 38.8% of cases (n=28). CD was associated with only one autoimmune disease (AD) in 90,2% cases (n=65), with 2 AD in 8,4 % cases (n=6), and in only one patient was the combination of 3 autoimmune diseases noted.

These autoimmune diseases (AIDs) were multiple, dominated mainly by autoimmune thyroiditis in 40.8% of cases, of which 19 patients were euthyroid, 9 patients hypothyroid and 2 patients hyperthyroid (Graves' disease), Gougerot-Sjögren's syndrome in 15.4% of cases, insulin-dependent diabetes type 1 in 14% of cases, and illustrated in the following table (Table 1).

Autoimmune thyroiditis	40,8%	(n=29)
Gougerot-Sjogren Syndrome	15,4%	(n=11)
Type I Diabetes	14%	(n=10)
Autoimmune Hepatitis Type I	9,85	(n=7)
Immune Deficiency	7%	(n=5)
Dermatitis Herpetiformis	5,6%	(n=4)
Palmoplantar Psoriasis	5,6	(n=4)
Hepatic Sarcoidosis	4,2%	(n=3)
Biermer's Disease	4,2%	(n=3)
Primary Biliary Cholangitis	2,8%	(n=2)
Rheumatoid Arthritis	1,4%	(n=1)
Ankylosing Spondylitis	1,4%	(n=1)
Autoimmune Hypophysitis	1,4%	(n=1)
Vitiligo	1,4%	(n=1)

Table 1: Distribution of different autoimmune diseases associated with CD

All our patients were on a well monitored gluten free diet (GFD) in addition to the specific treatment of the associated AD.

IV. Discussion:

Celiac disease is a chronic enteropathy, markedly increasing in the general population [7], of autoimmune origin with both a genetic component illustrated by the strong dependence on the presence of the HLA-DQ2 and DQ8 haplotypes [8], and an environmental component, the main trigger of which is the ingestion of gluten, the protein fraction of wheat, barley and rye. Its clinical manifestations are highly variable, and include both gastrointestinal and non-gastrointestinal features. Currently there is interest in the role of the gut microbiome as an additional trigger contributing to the development of CD [9].

It has been suggested that the intestinal barrier dysfunction associated with undiagnosed CD may promote the development of other autoimmune disorders by increasing intestinal permeability to certain triggers [10], thus the tendency for multiple autoimmune disorders to develop over the lifetime of a celiac patient has been well described, and several autoimmune diseases tend to coexist. The prevalence of these diseases in CD patients is estimated to be 3 to 10 times higher than in the general population, reaching up to 15 to 20% in the literature [6]; in our series, this prevalence was 20.74%. (Table 2).

STUDIES	TOTAL PATIENT	PREVALENCE OF AD	TYPE I DIABETES	AUTOIMMUNE THYROIDITIS	GS SYNDROME	AUTOIMMUNE HEPATITIS TYPE I	PRIMARY BILIARY CHOLANGITIS	BIERMER'S DISEASE	VITILIGO
O.Gharbi et al (Tunisia 2016)	78	17,9% (n=14)	60% (n=9)	-	7,14% (n=1)	14,2% (n=2)	7,14% (n=1)	7,14% (n=1)	7,14% (n=1)
S.Mrabet et al (Tunisia 2017)	65	46,1% (n=30)	23,1% (n=15)	12,3% (n=8)	1,6% (n=1)	3,1% (n=2)	-	3,1% (n=2)	-
F.Frikha et al (Tunisia 2019)	43	32,5% (n=14)	11,6% (n=5)	9,3% (n=4)	7% (n=3)	2,4% (n=1)	-	-	2,4% (n=1)

S.Souissi et al (Tunisia 2021)	58	1,8% (n=10)	5,1% (n=3)	6,8% (n=4)	1,7% (n=1)	-	-	-	-
Our series (Morocco 2022)	347	20,74% (n=72)	14% (n=10)	41,6% (n=30)	15,4% (n=11)	9,85% (n=7)	2,8% (n=2)	4,2% (n=3)	1,4% (n=1)

Table 2: Distribution of the prevalence of different autoimmune diseases in CD according to studies

The association between CD and thyroid disorders is well documented. Numerous studies confirm an increased prevalence of autoimmune thyroiditis (Hashimoto's) and Graves' disease in the adult celiac population [11-12]. The reverse also appears to be true, with CD occurring in individuals with autoimmune thyroid disorders at higher rates than in the general population [12-13]. In their series of 90 patients with thyroid disorders, Larizza et al. reported a higher prevalence of autoimmune thyroiditis (AIT) with CD compared to patients with isolated AIT in the general population. A Tunisian series by F.Frikha [4], including 15 celiac patients, showed a rate of associated AIT of 26.6%. In our study, autoimmune thyroiditis represented a percentage of 41.6%. (Table 3)

STUDIES	PREVALENCE OF AUTOIMMUNE THYROIDITIS
Sategna-Guidetti C et al (Italy 2001)	30,3%
Hadiithi M et al (Neerlande 2007)	21%
F.Frikha (Tunisia 2019)	26,6%
S.Souissi et al (Tunisia 2021)	6,8%
Our Series	41,6%

Table 3: Distribution of the prevalence of autoimmune thyroiditis in CD

The association between CD and type I diabetes (T1D) is well established. A recent review of the literature reports a prevalence between 4.4 and 11% in adults with T1D [31]. Other studies have shown that, in the majority of cases (90%), the diagnosis of T1D precedes that of celiac disease [32], and that the two conditions share similar HLA and non-HLA genetic loci [33-34]. Cohort studies have shown that the early introduction of gluten in the diet before the age of 3 months increases the prevalence of diabetic autoantibodies in high-risk individuals, with an improvement in insulin sensitivity and secretion in the GFD group compared with the normal diet group [35]. Our series shows an association T1D with CD of 14% (Table 4).

STUDIES	PREVALENCE OF TYPE I DIABETES
Cerutti et al (Italy 2004)	6,8%
Larsson et al (Sweden 2008)	10%
Karavanaki et al (Grece 2009)	4,8%
Djuric et al (Serbia 2010)	5,79%
Bhadada et al (India 2011)	11,1%
Gabriel S et al (Romania 2011)	9,2%
S.Mrabet et al (Tunisia 2017)	23,1%
Our Studies	14%

Table 4: Distribution of the prevalence of type I diabetes in CD

Gougerot-Sjögren syndrome (SS) is an autoimmune exocrinopathy characterized by dry mouth and dry eyes, and whose association with celiac disease was reported as early as 1965 [36]. Since then, two series have reported prevalence rates of CD in adults with SS between 12% and 15% [37-38], with 66% of adult patients with SS also having HLA-DQ2, the haplotype most frequently encountered in celiac disease [37]. In our study we report a percentage of 15.4%. (Table 5).

STUDIES	PREVALENCE OF GOUGEROT-SJOGREN SYNDROME
Sari Iltanen et al (Finland 2003)	14,7%
O.Gharbi et al (Tunisia 2016)	7,14%
F.Frikha et al (Tunisia 2018)	7%
Notre série	15,4%

Table 5: Distribution of the prevalence of dry syndrome (SS) in CD

Cryptogenic hepatitis is the most common hepatic manifestation of CD [18], followed by autoimmune hepatitis (AIH) [14-15], characterized by isolated mild transaminases with mild lobular and portal inflammation on liver biopsy puncture (LBP) [16-17]. An increased prevalence of AIH has been documented in cohorts of adults with CD ranging from 2 to 11.5% [14-19].

In our series the percentage of AIH was 9.85%, all were type I (Table 6).

STUDIES	PREVALENCE OF AUTOIMMUNE HEPATITIS
Volta U et al (Italy 2000)	15%
Danilo V et al (Italy 2005)	6,4%
Joseph A.Murray et al (United-States 2007)	4%
Caprai S et al (Italy 2008)	13,5%
S.Mrabet et al (Tunisia 2017)	3,1%
Our Series	9,85%

Table 6: Distribution of the prevalence of autoimmune hepatitis in CD

Among the adult population of South Wales, Kingham et al [20] reported a relative prevalence of 3% for primary biliary cholangitis (PBC) in 143 patients with CD, and in 67 celiac patients, a relative prevalence of 6% for primary sclerosing cholangitis (PSC) [21]. In our study, PBC accounted for a percentage of 2.8%, however, no cases of PSD were reported. (Table 7).

STUDIES	PREVALENCE OF PRIMARY BILIARY CHOLANGITIS
JGC.Kingam et al (Wales 2000)	3%
Volta U et al (Italy 2000)	38%
Caprai S et al (Italy 2008)	1,5%
O.Gharbi et al (Tunisia 2016)	7,14%
Our Series	2,8%

Table 7: Distribution of the prevalence of primary biliary cholangitis in CD

Dermatitis herpetiformis (DH) is the dermatological manifestation of celiac disease [22], characterized by 1-3mm papules and vesicles presenting in young to middle-aged adults [22-23-24]. Although it resolves spontaneously in up to 12% of patients [25], GFD remains the standard treatment with resolution in 100% of patients. In their Tunisian series of 10 celiac patients, K. Agar and M.L. Hamzaoui [5], reported a prevalence of 9% for DH. Our study shows a percentage of 5.6%. (Table 8).

STUDIES	PREVALENCE OF DERMATITIS HERPETIFORMIS
K.Agar et al (Tunisia 2019)	9%
Our Series	5,6%

Table 8: Distribution of the prevalence of dermatitis herpetiformis in CD

Psoriasis is an autoimmune disease causing skin erythema and scaling [26], whose association with celiac disease is still not very clear, related to the fact that psoriasis is known to increase intestinal permeability, which is one of the first steps in the pathogenesis of CD [27-28-30]. A very large Swedish study, of 28,958 adults

and children with CD, showed a risk ratio of 1.72 for the development of psoriasis over the course of a lifetime in adults and 2.05 in children [29]. Our study reports a percentage of 5.6% (Table 9).

STUDIES	PREVALENCE OF PSORIASIS
Lindqvist et al (Sweden 2002)	4,4%
Ojetti et al (Italy 2003)	4,3%
Woo et al (UK 2004)	2,3%
C.Dube et al (Canada 2005)	1%
Montesu et al (Italy 2011)	2%
Our Series	5,6%

Table 9: Distribution of the prevalence of psoriasis in CD

V. Conclusion:

Celiac disease in adults is often associated with other autoimmune diseases. In our study, this prevalence represented 20.9%. The analysis of the literature shows that this disease is most strongly associated with autoimmune thyroiditis, type I diabetes, Gougerot-Sjögren syndrome, autoimmune hepatitis, dermatitis herpetiformis and psoriasis.

These autoimmune diseases should be systematically investigated to avoid diagnosis and therapeutic delays, and improve prognosis.

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