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Classical and Non-Classical Celiac Disease Comparison: Ten Years of Study

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Abstract

Objective: Celiac disease (CD) is an immune-mediated systemic disorder triggered by gluten. It has a variable combination of clinical manifestations and changes that have been occurring in recent decades however they are not known in detail. The purpose of the article is to compare Classical and Non-Classical CD cases in terms of demographic characteristics, duodenal biopsy, extraintestinal manifestations, and associated comorbidities. **Materials and Methods:** A comparative retrospective cohort study from January 2008 to December 2018. **Results:** A total of 128 cases were included: 84 Classical (66%) and 44 Non-Classical CD (34%). The family history of CD was identified in 14% of cases without differences between groups. The age at diagnosis was distinct for Classical and Non-Classical CD (4.9 ± 4 and 8.3 ± 4 years old; $p < 0.001$), respectively. Important changes were found within the classical presentation, including mono symptoms and a significantly higher rate of intestinal atrophy; $p = 0.04$. The main Non-Classical CD symptom was recurrent abdominal pain. The extraintestinal manifestations (EIM) were identified in 42% and occurred in both groups. The comparison between groups showed differences in rates of migraine and vitamin D deficiency and was higher for Non-Classical CD ($p < 0.05$). Associated diseases occurred in 10.9%, and type 1 diabetes was significant for the Non-Classical CD group ($p = 0.04$). **Conclusion:** The classical CD was the most prevalent profile and presented a decrease in the severity of symptoms however remain a higher rate of intestinal atrophy. Recurrent abdominal pain was the main symptom of Non-Classical CD. Extraintestinal manifestations and associated diseases presented an increasing trend of occurrence among cases of Non-Classical CD.

Keywords

Celiac Disease, Gluten Allergy, Extra-Intestinal Manifestation, Disease Associated with Celiac Disease

1. Introduction

Celiac disease (CD) is one of the most prevalent permanent immune-mediated multisystem disorders affecting genetically predisposed people, which leads to a greater occurrence among first-degree family members [1] [2] [3]. It is triggered by eating gluten and other similar proteins such as wheat, rye, barley, and triticale (a mix of wheat and rye) [4] [5]. Patients present varying intestinal or extra-intestinal manifestations which can reflect or not degrees of intestinal mucosal atrophy [6]. Since 2011, the definitions proposed by the *Oslo Consensus* have been used to classify the spectrum of clinical manifestations ranging from asymptomatic to symptomatic CD [7] [8]. The symptomatic presentation is sub-classified as Classical CD (malabsorption syndrome), Non-Classical CD (absence of malabsorption syndrome with the presence of extraintestinal manifestation), or potential CD (positive serology and normal small intestinal biopsy) [9].

It has been recognized that important changes have occurred in the CD presentation in the last decades. The severity of malabsorption syndrome has decreased and the rate of non-classical/asymptomatic cases has increased in pediatric and non-pediatric populations [10] [11]. Details about these changes are scarce. It is not clear whether the changes also affect the presentation of classic CDs or if there are important differences between classical and non-classical CDs. In addition, CD researchers continue to emphasize the importance of clinical studies, especially those that focus on the clinical manifestations of CD, to identify these changes in detail [12] [13].

The objective of this study is to show in detail the comparison between Classical and Non-Classical CD cases over ten years.

2. Materials and Methods

A retrospective CD cohort study in the pediatric population at a Spanish University hospital. The data for each selected patient was obtained retrospectively by the medical records from January 2008 to December 2018. The cases have confirmed diagnosis according to the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) criteria: suggestive symptoms, serum levels 10 times the upper limit of normal transglutaminase IgA, and positive endomysial antibodies IgA [14]. Patients with wheat sensitivity were excluded. The participants were classified according to the Oslo Consensus criteria. The groups (Classical and Non-Classical CD) were compared and the main variables analyzed were sex, age at diagnosis, age of symptom onset, family history, main symptoms, extra-intestinal manifestations, duodenal biopsy, and as-

sociated comorbidities. The biopsy findings were described according to the Marsh classification as atrophic (Marsh 3 grade) and non-atrophic (Marsh 0 - 2 grades) profile [15]. Obstipation and heartburn have been described as other digestive disorders. Growth failure was classified according to the World Health Organization growth charts for the pediatric population [16]. Only patients with at least one year of follow-up (FU) after starting a gluten-free diet (GFD) were considered in this study. The Ethics Committee at Hospital de la Santa Creu I Sant Pau (Barcelona, Spain) approved this study, understudy protocol number IIBSP-CEL-2019-32.

For the quantitative variables, the mean ± SD (standard deviation) or median with interquartile was used according to the normality of the distribution. Student t-test was used for quantitative variables in comparison between groups (Classical and Non-Classical CD). The Chi-square was used to compare frequencies (categorical data). Fisher's exact test was used for events with a low frequency of occurrence (< 5 cases). A 95% confidence interval (CI) was calculated for some dependent variables. A 2-tailed $p < 0.05$ was considered as having statistical significance. The analysis was performed using SPSS v.26 (Chicago, Illinois) and graphics were performed by Prism 8.4.2 (GraphPad Software Inc, California).

3. Results

One hundred and twenty-eight pediatric cases confirmed diagnosis of CD between 2008 and 2018. Based on the Oslo Consensus, 84 patients (66%) presented Classical CD and 44 cases (34%) Non-Classical CD. Initially, ten patients were classified as asymptomatic cases; however, in the primary clinical evaluation, extra-intestinal manifestations were found and they were classified as symptomatic cases type Non-Classical CD. The main characteristics between groups are summarized in Table 1.

The prevalent gender was female (57.8%), however, differences were found between groups 51.2% *versus* 70.5% for Classical and Non-Classical groups respectively; $p = 0.036$.

Table 1. The main characteristics between classical and non-classical celiac disease.

Main Characteristics	Overall cohort n = 128 (%)	Classical n = 84 (%)	Non-classical n = 44 (%)	*P value*
Gender (female)	74 (57.8)	43 (51.2)	31 (70.5)	0.036
More than two years of symptoms *	90 (70)	35 (27.4)	55 (43.2)	<0.01
Growth failure	19 (14.8)	15 (17.8)	4 (9.1)	ns
Family history	18 (14.1)	15 (17.9)	3 (6.8)	ns
Duodenal biopsy (Marsh classification)	82 (64.1)	54 (64.3)	28 (63.6)	-
Non-atrophic (Marsh 0 - 2 grades)	34 (41.5)	17 (31.5)	17 (60.7)	ns
Atrophic (Marsh 3 grade)	48 (58.5)	37 (68.5)	11 (39.3)	0.04

*Before the diagnosis of CD.

Overall, the mean age at diagnosis was 6.1 ± 4 years and the age per group showed a difference of three years greater for the Non-Classical CD group (Figure 1). Classical CD presented two picks of diagnosed cases (2 - 3 and 6 - 10 years old) (Figure 2(a)). A distinct pattern was found for the Non-classical CD group (Figure 2(b)). In addition, the relation of range ages by groups showed an opposite distribution between them (Figure 3).

The number of cases per year showed the prevalence of the Classical group over the first eight years and an inversion with the increase of Non-Classical in the last two years of the study (Figure 4).

The duodenal biopsy was performed in 64.1% of patients as a diagnosis evaluation. The Classical CD presented a higher rate of duodenal atrophy (68.5% against 39.3%); p = 0.040.

Overall, the adherence to a gluten-free diet (GFD) decreased by 37.5% from the diagnosis to one-year follow-up and no difference was found between groups.

3.1. Classical CD

The main symptoms were diarrhea (71.4%) and abdominal distension (61.3%). The principal association was diarrhea plus abdominal distension (48%), followed

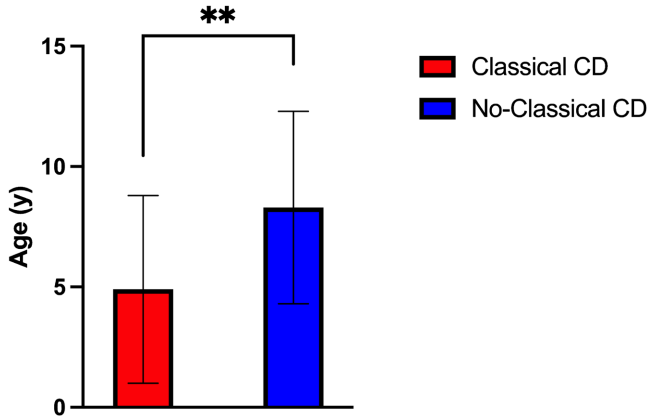

Figure 1. The age at diagnosis for Classical and Non-Classical CD cases (Mean ± SD).

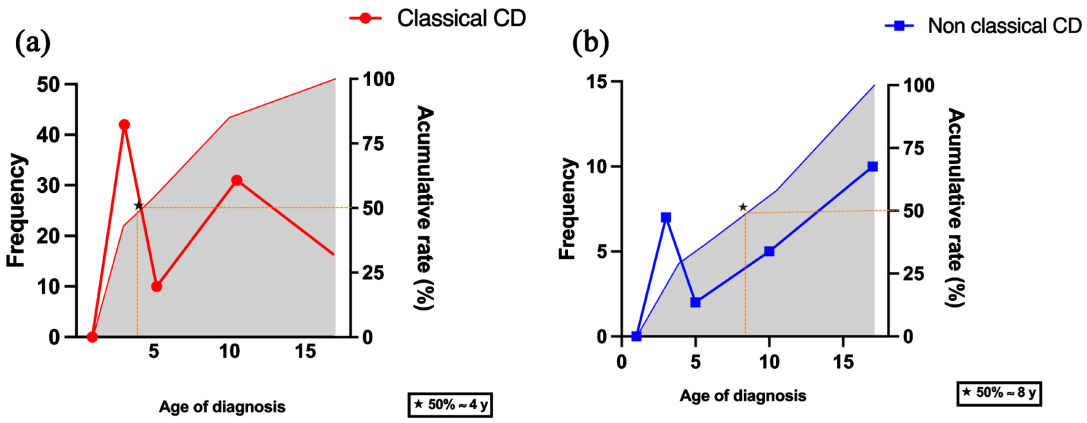

Figure 2. Classical and Non-Classical Celiac Disease frequency and accumulative rate by age of diagnosis and the mean age per group when 50% of cases are reached.

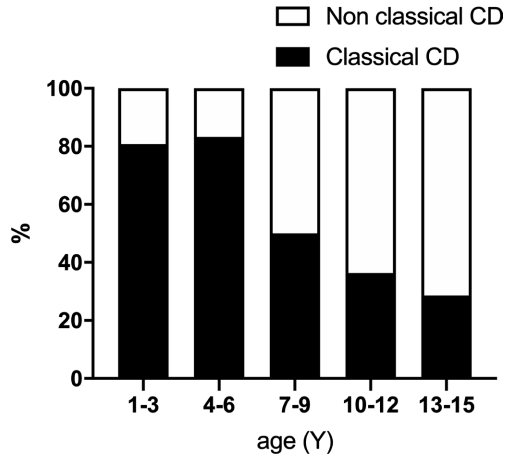

Figure 3. Distribution of cases by age range of Classical and Non-classical CD.

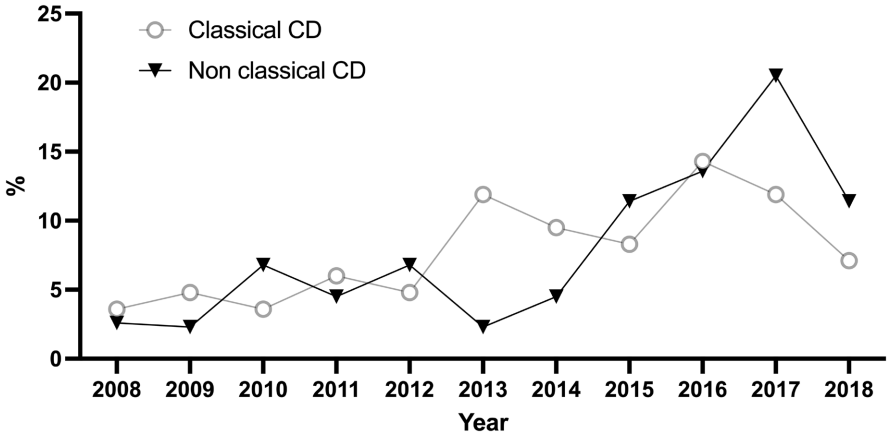

Figure 4. Numbers of cases by group per year during the 10 years of the study.

by abdominal distension plus growth failure (15%). Isolated symptoms were found in this group: isolated diarrhea (15%), growth failure (13%), and abdominal distension (9%). Constipation has been found among classical cases in association with other symptoms (failure to thrive and diarrhea alternating with constipation).

3.2. Non-Classical CD

The presence of symptoms for two years or more, prior to diagnosis, was significantly higher for the Non-Classical (43%) than the Classical CD group (27%); $p < 0.01$. Almost 50% of them presented recurrent abdominal pain (RAP) as the main symptom (34%) followed by constipation.

An interesting finding was the reasons that led to the diagnosis of CD in Non-Classical cases: recurrent abdominal pain (48%), family history of CD (23%), and presence of autoimmune disease (18%), especially type 1 diabetes.

3.3. Extra-Intestinal Manifestations (EIM) and Others Digestive Manifestations

Overall, they were found in 42% of CD cases, and the main IEMs were iron defi-

ciency (14.1%) and neuropsychiatric disorders (14.1%). Comparison between groups showed a statistically significant difference for vitamin D deficiency and neurological disorder (migraine). These extraintestinal manifestations were higher for non-classical CD cases with 10-fold higher vitamin D deficiency and 4-fold higher migraine than for the classic CD group (Table 2).

In terms of other digestive disorders, constipation was the main one and occurred in 25.8% of CD cases, followed by miscellaneous disorders (heartburn, gastritis, hemorrhoids, duodenitis, and associations), which were found in 8.6% of cases. Most patients with other digestive disorders (70%) reported improvement after starting a gluten-free diet (DGF). No differences were found between the compared groups.

3.4. Diseases Associated with CD

The autoimmune diseases were identified in 10.9%. Type 1 diabetes was the most prevalent followed by hypothyroidism. The diabetes rate was 4 fold higher in the Non-Classical than in the Classical CD group ($p = 0.047$). All diabetic patients had confirmed CD diagnosis after the diabetes diagnosis (Table 3). The mean age at CD diagnosis for diabetes cases was 9.6 ± 5 years (95% CI 6 - 13 years). Other dietary allergies were identified in 14.8%: milk allergy (5%) and multiple allergies (5%).

4. Discussion

Celiac disease is one of the most prevalent diseases and has a frequency between

Table 2. Comparison of extra-intestinal manifestation between Classical and Non-classical Celiac Disease.

Extra-Intestinal Manifestation	Overall cohort n = 128 (%)	Classical n = 84 (%)	Non-classical n = 44 (%)	*P value*
Neuropsychiatric Manifestations	18 (14.1)	12 (14.3)	6 (13.7)	ns
Irritability	8 (6.2)	7 (8.3)	1 (2.3)	ns
Migraine	7 (5.5)	2 (2.4)	5 (11.4)	0.034
Others*	3 (2.4)	3 (3.6)	0	ns
Skin Manifestations	17 (12.5)	11 (13.1)	6 (13.7)	ns
Dermatitis Herpetiformis	3 (2.3)	2 (1.6)	1 (0.8)	ns
Miscellaneous**	14 (10.9)	9 (10.7)	5 (11.4)	ns
Iron deficiency	18 (14.1)	14 (16.7)	4 (9.1)	ns
Vitamin D deficiency	6 (4.7)	1 (1.2)	5 (11.4)	0.01
Vitamin A deficiency	2 (1.6)	2 (2.4)	0	ns
Fatigue	11 (8.6)	8 (9.5)	3 (6.8)	ns

*Attention deficit disorder and Insomnia; **Prurigo nodularis , chronic urticaria, atopic dermatitis, sub-acute eczema.

Table 3. Comparison of comorbidities associated with CD between Classical and Non-classical Celiac Disease.

Comorbidities associated	Overall cohort n = 128 (%)	Classical n = 84 (%)	Non-classical n = 44 (%)	*P value*
Autoimmune Diseases (AID)	14 (10.9)	4 (4.8)	10 (22.7)	0.008
Diabetes type I*	7 (5.5)	2 (2.4)	5 (11.4)	0.047
Hypothyriodism	4 (3.1)	1 (1.2)	3 (6.8)	ns
Other**	4 (3.1)	1 (1.2)	3 (3.8)	ns
Other Dietary Allergies	19 (14.8)	13 (15.5)	5 (11.4)	ns
IgA deficiency	4 (3)	3 (3.6)	1 (2.3)	ns

*One case presented associated diabetes and hypothyroidism; **Psoriasis, Auto-Immune Hepatitis, Hemolytic Anemia, Sjogren' Syndrom

1:100 and 1:250 people in western countries [17]. In terms of global prevalence, Spain presents a low rate from 0.2% to 0.8% [13]. The Spanish National Registry of Celiac Disease (2014) identified the main age at diagnosis for CD population between 0 - 2 years and more than 80% are classical CD presentation. When compared, our study identified a lower rate for Classical CD (66%) and a higher rate for Non-Classical CD cases (44%) than the Spanish Registry. In terms of age at diagnosis for the classical group, we identified a bimodal peak: the first highest peak (between 1 - 3 years) and the second-lowest peak (between 6 - 10 years). We believe that the bimodal peak represents a change in the classical presentation of CD, where the first peak corresponds to patients with symptoms of malabsorption syndrome, and who have an early diagnosis. The second peak represents patients with mono symptoms with late diagnosis. Other authors have found the same results [18] [19].

The changes in CD clinical presentation started in the 1970s when the age of diagnosis was 2 years old. Nowadays the age is around 8 years old [18]. This change is increasing of asymptomatic and Non-Classical CD cases that lead to a later CD diagnosis. In our study, a distinct age at diagnosis between groups was found which was doubled for the Non-Classical CD than for the classical group.

The Oslo classification was an important accomplishment for the medical community despite doubts and different interpretations remain about the signs or symptoms of celiac disease [7]. The main symptoms of classical CD include diarrhea, steatorrhea, weight loss, or growth failure. Another important symptom, which can be associated with a classic CD, is abdominal distension. It can occur with or without other classical symptoms [17]. We identified isolated abdominal distension in 9% of the Classical group. According to the Oslo Consensus, these patients should be classified as Non-Classical CD due to the presentation of mono symptoms and the absence of malabsorption syndrome [14]. We consider abdominal distention a very important sign, which can lead pediatricians to suspect CD. Likewise, other authors consider abdominal distension as

one of the main signs of celiac disease and should be considered a Classical CD symptom [3] [17].

Growth failure is one of the most important findings that can lead to suspicion of CD in childhood [10]. In this study, we identified a general rate of growth failure of almost 15% and the comparison between groups showed a two-fold higher growth failure rate for the Classic group than for the Non-Classic group. Although not statistically significant, malabsorption syndrome is closely related to growth failure, which remains an important finding for Classical CD cases.

Recurrent abdominal pain was the main symptom for the Non-Classical group in our study (48%). Two-thirds of RAP cases had this symptom for two years prior to the diagnosis and nearly 50% of cases had 5 years of symptom. A populational Swedish study about RAP (2020), in the pediatric population, identified 7.3% of CD among adolescents with persistent RAP [20]. Although RAP is a common childhood complaint for different reasons, it is important to include CD testing for children with persistent recurrent abdominal pain, especially in adolescence.

According to literature, constipation is a common finding in Non-Classical CD cases [19]. In this study, it was found in almost 26% of CD cases and was presented in both groups. Although diarrhea remains the main symptom of classical CD, constipation can be found in the classical cases. In this study, we identified obstipation associated with other classical symptoms such as distension, failure to thrive, and diarrhea alternating with constipation. It suggests changes within classical CD presentation, which means a new classical profile with less severity (oligosymptomatic or monosymptomatic form).

Another interesting finding was the significant rate of duodenal biopsies performed among the CD population (64%). Even though the rate of biopsies performed is decreasing in the European continent, mainly due to ESPGHAN recommendations [14]. We attribute this large number of biopsies due to the great number of Non-Classical CD cases with the symptom of recurrent abdominal pain. It led to the inclusion of endoscopy with duodenal biopsy as a diagnostic evaluation for these patients. We expected to find an increasing number of Marsh III cases for the Non-Classical group due to late diagnosis. Differently, the biopsy score showed a lower rate of severe atrophy (Marsh III) in this group. Indeed, the Non-Classical CD is a subtype with specific manifestations, less intestinal villous atrophy, and possible better tolerance to gluten intake. Some studies identified a progression of intestinal villous atrophy over time for undiagnosed CD cases [21] [22]. We believe that the progression of villous atrophy may occur in patients with classic CD and is less probable in Non-classic CD cases.

Autoimmune diseases have a risk of occurrence from 3 to 10-fold higher in the CD population than in the general population. The main diseases identified are diabetes and hypothyroidism which are estimated to occur in 4% and 10% of the CD population respectively [23]. We identified a similar rate of autoimmune diseases (10.9%) and type 1 diabetes in 5.5% of CD cases. The comparison between groups showed a significant rate for the Non-Classical CD group (22.7%

vs 4.5%). We attribute this finding to the oligosymptomatic manifestations for the non-classical CD and the confirmed CD after the diagnosis of autoimmune diseases. Although studies have suggested a potential pathogenic role for gluten in T1D, the exact mechanisms by which it may play a role in the onset and development of T1D are still not fully understood [24] [25].

Currently, the gluten-free diet is the only treatment available for CD patients. Adherence to the GFD is difficult, especially because of the emotional, economic, and social challenges associated with this dietary limitation. We identified a decrease in GFD adherence from the diagnosis to the one year of follow-up (37.5%). We expected to find fewer GFD adherence in the Non-Classical group due to oligosymptomatic manifestations, but it was similar for the Classical CD group. Adherence to GFD remains a challenge, mainly due to the decrease in symptom severity for classical and non-classical cases that can be reflected in increased gluten consumption by patients despite medical advice.

The limitation of this study is due to the design (a retrospective cohort study), in which the accuracy of reported information cannot be controlled. A potential limitation also is the data comes from a single center that represents a specific and restricted population.

5. Conclusions

Overall, the diagnosis of CD tends to be late for oligosymptomatic or Non-Classical cases. Regarding the number of cases per year, the Non-Classical cases exceed the Classical cases in the last two years of the study.

The Classical CD was the most prevalent profile and the diagnosis occurred mainly in early childhood. A decrease in the intensity of symptoms was found in this group, including the presence of mono symptoms however it presented a higher rate of severe intestinal atrophy.

The Non-Classical CD profile occurred mainly in adolescence and the principal symptom was recurrent abdominal pain. Extraintestinal manifestations and diseases associated with CD can be present in both groups; however, migraine, vitamin D deficiency, and type 1 diabetes were significantly higher in the Non-Classical CD group. Prospective studies are needed to confirm these findings.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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