ARTÍCULO ORIGINAL

Trends in the clinical presentation of celiac disease over time: a study from a national university hospital in Uruguay

Tendencias en la presentación clínica de la enfermedad celíaca a lo largo del tiempo: estudio de un hospital universitario de Uruguay

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ABSTRACT
The clinical presentation of celiac disease (CD) has evolved over recent decades. Understanding these shifts is essential to strengthen diagnostic suspicion and improve detection. **Objectives:** To evaluate temporal trends in the clinical presentation of CD at a university hospital in Uruguay. **Materials and methods:** A retrospective cross-sectional study, approved by the institutional ethics committee, was conducted. It included patients diagnosed with CD between 1970 and 2023 who presented positive IgA anti-tissue transglutaminase antibodies and compatible duodenal histology (Marsh III). Patients were categorized by diagnostic period: before 1986, 1986-1995, 1996-2005, 2006-2015, and 2016-2023. Clinical presentation was classified according to the Oslo criteria as classical, non-classical, or asymptomatic. **Results:** A total of 331 patients were included; 84% were female. The mean age at diagnosis was 32 years (range 0-77), showing a progressive shift toward adulthood diagnosis. Overall, 61% presented with classical CD, 27% with non-classical CD, and 12% were asymptomatic. Linear trend analysis demonstrated a significant decrease in classical CD (slope -15.7, p=0.0003), accompanied by an increase in non-classical (slope 12.5, p=0.00267) and asymptomatic presentations (slope 3.15, p=0.042). **Conclusions:** Over the past four decades, CD presentation has shifted toward later diagnosis and away from classical phenotypes, with an increasing recognition of non-classical and asymptomatic forms. These findings underscore the importance of maintaining clinical suspicion beyond traditional malabsorptive presentations.
Keywords: *Celiac Disease; Autoimmune Diseases; Uruguay (source: MeSH NLM).*

RESUMEN
La presentación clínica de la enfermedad celíaca (EC) ha evolucionado en las últimas décadas. Comprender estos cambios es esencial para fortalecer la sospecha diagnóstica y mejorar la detección. **Objetivos:** Evaluar las tendencias temporales en la presentación clínica de la EC en un hospital universitario de Uruguay. **Materiales y métodos:** Estudio transversal retrospectivo, aprobado por el comité de ética institucional, que incluyó pacientes diagnosticados con EC entre 1970 y 2023 con anti-transglutaminasa IgA positivo e histología duodenal compatible (Marsh III). Los pacientes se categorizaron por período diagnóstico: antes de 1986, 1986-1995, 1996-2005, 2006-2015 y 2016-2023. La presentación clínica se clasificó según los criterios de Oslo en clásica, no clásica o asintomática. **Resultados:** Se incluyeron 331 pacientes; el 84% eran mujeres. La edad media al diagnóstico fue 32 años (rango 0-77), con un desplazamiento progresivo hacia el diagnóstico en la edad adulta. En general, 61% presentó EC clásica, 27% EC no clásica y 12% fueron asintomáticos. El análisis de tendencia lineal mostró una disminución significativa de la EC clásica (pendiente -15,7, p=0,0003), acompañada de un aumento de las presentaciones no clásicas (pendiente 12,5, p=0,00267) y asintomáticas (pendiente 3,15, p=0,042). **Conclusiones:** Durante las últimas cuatro décadas, la presentación de la EC se ha desplazado hacia un diagnóstico más tardío y se ha alejado de los fenotipos clásicos, con un reconocimiento creciente de las formas no clásicas y asintomáticas. Estos hallazgos resaltan la importancia de mantener la sospecha clínica más allá de las presentaciones malabsortivas tradicionales.
Palabras clave: *Enfermedad Celíaca; Enfermedades Autoinmunes; Uruguay (fuente: DeCS BIREME).*

INTRODUCTION

Celiac disease (CD) is a chronic, systemic autoimmune disorder triggered by gluten ingestion in genetically predisposed individuals [1-4]. According to the Oslo criteria, CD can present as classical, predominantly involving malabsorption, or non-classical, characterized by extraintestinal manifestations or the absence of malabsorptive signs. Asymptomatic CD refers to patients without symptoms, even after targeted questioning, and is typically identified through endoscopy, screening of at-risk populations, or abnormal laboratory findings [1]. Currently, the diagnosis is most frequently established during adulthood, and extraintestinal manifestations account for more than half of the presentations in many series [5-7].

Over time, the clinical phenotype of CD has changed significantly [2,8,9]. Understanding these trends is essential to improve diagnostic suspicion, particularly in regions with scarce local evidence. This study aimed to evaluate temporal changes in CD presentation and to compare clinical characteristics at diagnosis across the years.

MATERIALS AND METHODS

A retrospective cross-sectional study was conducted at the University Hospital of Montevideo, Uruguay.

Ethical considerations

Data extracted from medical records were anonymized in compliance with national and international ethical standards. The protocol was approved by the institutional ethics committee.

Patients diagnosed with CD between 1970 and 2023 were included. Diagnosis required ≥1 positive CD-specific serological test and compatible histology (Marsh III). Patients with insufficient diagnostic or clinical data were excluded. To evaluate temporal changes, patients were stratified into five periods: before 1986, 1986-1995, 1996-2005, 2006-2015, and 2016-2023.

These data were anonymized in accordance with national and international ethical standards.

The clinical presentation was classified as follows:

- Classical CD: Symptoms of malabsorption
- Non-classical CD: Symptomatic without evident malabsorption
- Asymptomatic CD: Absence of symptoms despite targeted questioning

Laboratory variables included hemoglobin, ferritin, vitamin B12, folic acid, AST, and ALT.

The main study variables were summarized using measures of central tendency and dispersion, such as mean and range for quantitative variables (age), and relative percentage frequencies for qualitative variables (clinical presentation, sex, diagnostic period). Trend analysis evaluated the temporal evolution of the three distinct clinical presentations, considering the frequency distribution of the presentation types across the diagnostic periods.

Finally, a binary logistic regression model was fitted using the classical clinical presentation of CD (yes/no) as the dependent variable. Non-classical and asymptomatic forms were pooled into a single comparative category. As independent variables, age at diagnosis, sex, and diagnostic period were included. Due to the small number of patients diagnosed before 1986, the periods "before 1986" and "1986-1995" were combined into a single category (≤1995). Regression estimators are presented as odds ratios (ORs) with their respective 95% confidence intervals (95% CIs).

Statistical significance was defined as a p-value<0.05. Data management, graphical visualizations, and statistical analyses were performed using R software, version 4.3.1.

RESULTS

A total of 331 patients with biopsy-confirmed CD were included; 84% were female. The mean age at diagnosis was 32 years (range 0-77); 21% were diagnosed before age 15, and 20% after age 50 (Table 1). Diarrhea was the most frequent initial manifestation (50%), followed by anemia (17%) and abdominal distension (8%). Family screening accounted for 7% of diagnoses. Malignancy was documented in 1%. In total, 61% presented with classical CD, 27% with non-classical CD, and 12% were asymptomatic. A progressive temporal shift in the clinical phenotype was observed, with a significant decrease in classical CD (slope -15.7; p=0.0003) and an increase in non-classical (slope 12.5; p=0.00267) and asymptomatic forms (slope 3.15; p=0.042). Among patients with available laboratory data, anemia was present in 41%, mostly mild to moderate. Approximately one-quarter of the sample exhibited elevated transaminases, which were predominantly mild.

In the multivariate analysis, more recent diagnostic periods were independently associated with a lower probability of classical presentation after adjusting for age and sex. Compared with patients diagnosed up to 1995, the probability of classical presentation progressively decreased in the periods 1996-2005 (OR 0.24; 95% CI 0.07-0.74; p=0.014), 2006-2015 (OR 0.16; 95% CI 0.05-0.51; p=0.002), and 2016-2023 (OR 0.08; 95% CI 0.02-0.27; p<0.001) (Figure 1). Age at diagnosis and sex showed no independent association with classical presentation.

DISCUSSION

This study demonstrates significant changes in the clinical presentation of CD over more than five decades in a cohort from a university hospital in Uruguay. The main

Table 1. Clinical features by decades.

	Total	Before 1986	1986-1995	1996-2005	2006-2015	2016-2023
n	331	8	31	104	145	43
Female, n(%)	277 (84)	7 (88)	23 (74)	88 (85)	126 (87)	33 (77)
Age at diagnosis (mean)	32	3	9	30	39	39
Diagnosis before 15 years, n(%)	70 (21)	8 (100)	25 (81)	29 (28)	7 (5)	1 (2)
Diagnosis after 50 years, n(%)	66 (20)	0	0	15 (14)	38 (26)	13 (30)
Symptoms at diagnosis						
Diarrhea, n(%)	167 (50)	8 (100)	26 (84)	55 (53)	67 (46)	11 (25,5)
Incidental diagnosis, n(%)	15 (5)	0	0	2 (2)	10 (7)	3 (7)
Family screening, n(%)	23 (7)	0	2 (6,5)	9 (9)	10 (7)	2 (5)
Anemia, n(%)	56 (17)	0	2 (6,5)	15 (14)	28 (19)	11 (25,5)
Bloating, n(%)	27 (8)	0	0	9 (9)	14 (10)	4 (9)
Others*, n(%)	43 (13)	0	1 (3)	14 (13)	16 (11)	12 (28)
Presentation based on the Oslo criteria						
Classical, n(%)	202 (61)	8 (100)	27 (87)	69 (66)	82 (56)	16 (37)
Non classical, n(%)	91 (27)	0	2 (6,5)	24 (23)	43 (30)	22 (51)
Asymptomatic, n(%)	38 (12)	0	2 (6,5)	11 (11)	20 (14)	5 (12)

*Others: nausea/vomits, abdominal pain, dyspepsia, GERD, constipation, failure to thrive, weight loss, severe malnutrition, fatigue, dermatitis herpetiformis, osteoporosis, oral aphthae, anxiety, depression, ataxia, infertility, miscarriage, another autoimmune disease, hypertransaminasemia, neoplasia.

findings were a progressive shift toward diagnosis in adulthood and a marked decline in classical malabsorptive forms, accompanied by an increase in non-classical and asymptomatic presentations. Furthermore, in the multivariate analysis, more recent diagnostic periods were independently associated with a lower probability of classical presentation after adjusting for age and sex.

These findings are consistent with the shifting clinical profile of CD described in European and North American cohorts [2,8-18]. Several studies have shown that CD is increasingly recognized outside the traditional malabsorptive phenotype, with more frequent diagnoses in adults and in patients with subtle gastrointestinal or extraintestinal manifestations [5,8,14]. Our results confirm that

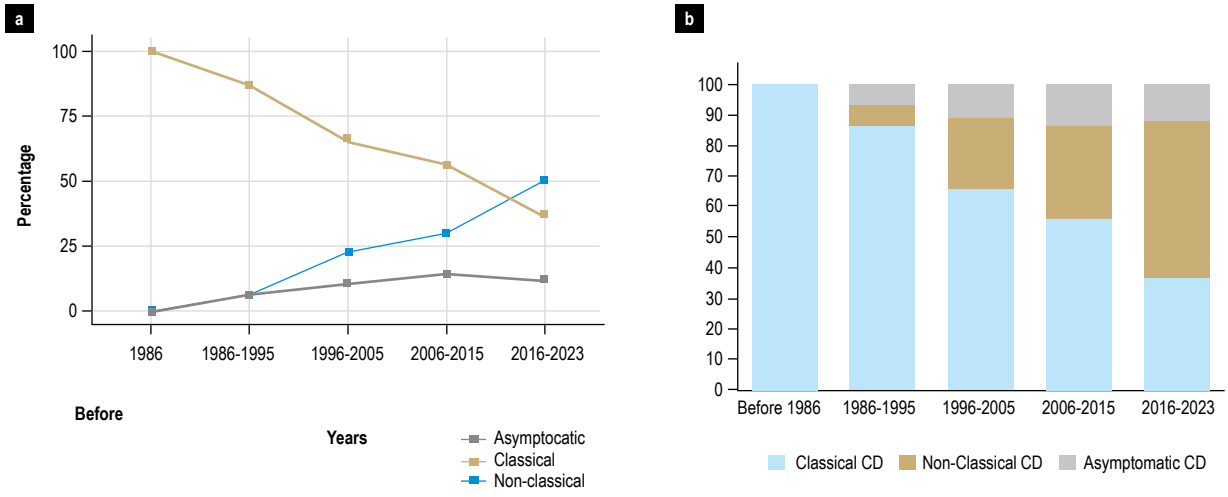

Figure 1. a) Clinical presentation (Oslo classification) over the decades. **b**) Trends in clinical presentation over time – note the increase in non-classical presentations after 1986.

this epidemiological and clinical transition is also occurring in Uruguay, providing one of the few Latin American series with a longitudinal evaluation of these trends spanning more than five decades. The female predominance observed in our cohort aligns with previous reports [10-13].

Diarrhea remained the most frequent manifestation, although its relative predominance decreased over time, while anemia and other non-classical manifestations gained greater diagnostic relevance. This agrees with prior studies showing that iron deficiency anemia and other mild extraintestinal manifestations currently constitute frequent scenarios for CD diagnosis [19-24]. Similarly, the progressive shift toward diagnosis in adulthood since the mid-1990s mirrors international trends and likely reflects wider availability of serological testing, greater awareness of non-classical phenotypes, and changes in diagnostic practices [13,16].

The observed shifts in clinical presentation must also be interpreted within the historical context of evolving diagnostic tools and healthcare access during the analyzed period. In the earliest decades included in this cohort, the availability of serological testing was limited, and diagnosis relied primarily on overt malabsorption syndromes and compatible histology. During the 1980s, antigliadin antibodies (AGA) were the first widely used serological tools, although they exhibited moderate sensitivity and specificity, which were particularly variable in adults. Subsequently, in the late 1980s and early 1990s, anti-endomysial antibodies (EMA) were introduced, characterized by a high specificity close to 98-100%, albeit with lower sensitivity in mild forms and operator dependence. Later, from the late 1990s and especially during the 2000s, the progressive introduction of anti-tissue transglutaminase (tTG) antibodies significantly improved diagnostic performance, with sensitivities and specificities generally exceeding 90-95%, as well as high positive and negative predictive values in populations with appropriate clinical suspicion [1,2,8,16,18]. The gradual integration of these tools, alongside wider dissemination of international diagnostic guidelines, likely contributed to the rising recognition of non-classical and asymptomatic forms. Likewise, improvements in access to specialized care, increased availability of gastrointestinal endoscopy, and enhanced medical awareness regarding contemporary disease phenotypes may have favored earlier and more heterogeneous case detection in recent decades.

The growing predominance of non-classical and asymptomatic forms carries relevant clinical implications. Our findings reinforce the necessity of maintaining a high index of diagnostic suspicion beyond traditional malabsorptive presentations, particularly in adults and in patients with subtle extraintestinal manifestations, such as iron deficiency anemia or mild hypertransaminasemia. Furthermore, they support the importance of optimizing screening strategies in at-risk populations, including first-degree relatives and patients with associated autoimmune diseases [8,9,14,16,18].

This study has certain limitations. Its retrospective and single-center design may limit the generalizability of the findings; however, the University Hospital serves as a national reference center, which partially mitigates this constraint. Data completeness varied across decades due to shifts in medical documentation and the availability of diagnostic tools. Classification of clinical presentation depended on the information recorded in medical charts; thus, older cohorts might have underestimated non-classical or asymptomatic forms. Likewise, the multivariate analysis must be interpreted with caution, as some subgroups, particularly asymptomatic patients and earlier diagnostic periods, included a small number of cases, limiting the stability of more complex statistical models.

Despite these limitations, the study possesses substantial strengths, including a large cohort of patients with biopsy-confirmed CD, strict diagnostic criteria, a structured temporal stratification, and an observation period spanning more than five decades. To our knowledge, this is the first Uruguayan study to comprehensively evaluate longitudinal changes in the clinical presentation of CD, contributing relevant regional evidence that supports the global concept of an evolving clinical phenotype.

In conclusion, the clinical presentation of CD in Uruguay has progressively shifted from classical malabsorptive forms toward non-classical and asymptomatic phenotypes, with diagnoses becoming increasingly frequent in adulthood. These findings underscore the importance of maintaining diagnostic suspicion beyond traditional presentations and support the need to enhance detection and screening strategies in contemporary clinical practice.

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