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والصيدلة - مراكش
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ET DE PHARMACIE - MARRAKECH
MARRAKECH
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The Immunological and Histopathological Profile of Celiac Disease in Children

THESIS

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BY

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Born on August 9th1998in Rabat

TO OBTAIN THE DEGREE OF DOCTOR OF MEDICINE

KEYWORDS:

Celiac disease- Children- Serological tests - tTGA-IgA - Histology - Villous atrophy

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بسم الله الرحمن الرحيم

Oath of Hippocrates

At the time of being admitted as a member of the medical profession:

I solemnly pledge to dedicate my life to the service of humanity

The health and well-being of my patient will be my first consideration

I will respect the autonomy and dignity of my patient

I will maintain the utmost respect for human life

I will not permit considerations of age, disease or disability, creed, ethnic origin, gender, nationality, political affiliation, race, sexual orientation, social standing or any other factor to intervene between my duty and my patient

I will respect the secrets that are confided in me, even after the patient has died

I will practise my profession with conscience and dignity and in accordance with good medical practice

I will foster the honour and noble traditions of the medical profession

I will give to my teachers, colleagues, and students the respect and gratitude that is their due

I will share my medical knowledge for the benefit of the patient and the advancement of healthcare

I will attend to my own health, well-being, and abilities in order to provide care of the highest standard

I will not use my medical knowledge to violate human rights and civil liberties even under threat

I make these promises solemnly, freely, and upon my honour.

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324	ABAINOU Lahoussaine	Pr Ass	Endocrinologie et maladies métaboliques
325	BENCHANNA Rachid	Pr Ass	Pneumo-phtisiologie
326	TITOU Hicham	Pr Ass	Dermatologie
327	EL GHOUL Naoufal	Pr Ass	Traumato-orthopédie
328	BAHI Mohammed	Pr Ass	Anesthésie-réanimation
329	RAITEB Mohammed	Pr Ass	Maladies infectieuses
330	DREF Maria	Pr Ass	Anatomiepathologique

331	ENNACIRI Zainab	Pr Ass	Psychiatrie
332	BOUSSAIDANE Mohammed	Pr Ass	Traumato-orthopédie
333	JENDOUZI Omar	Pr Ass	Urologie
334	MANSOURI Maria	Pr Ass	Génétique
335	ERRIFAIY Hayate	Pr Ass	Anesthésie-réanimation
336	BOUKOUB Naila	Pr Ass	Anesthésie-réanimation
337	OUACHAOU Jamal	Pr Ass	Anesthésie-réanimation
338	EL FARGANI Rania	Pr Ass	Maladies infectieuses
339	IJIM Mohamed	Pr Ass	Pneumo-phtisiologie
340	AKANOUR Adil	Pr Ass	Psychiatrie
341	ELHANAFI Fatima Ezzohra	Pr Ass	Pédiatrie
342	MERBOUH Manal	Pr Ass	Anesthésie-réanimation
343	BOUROUMANE Mohamed Rida	Pr Ass	Anatomie
344	IJDDA Sara	Pr Ass	Endocrinologie et maladies métaboliques

LISTE ARRETEE LE 09/01/2024

DEDICATIONS

*"My success comes only through Allah.In Him I trust and to Him I turn."**Quran 11-Hũd***

To Allah, the one who is uniquely glorious, honorable, praiseworthy, exalted, and great, the creatorof nothingness, who knows the subtleties of sins, and who hears my call secretly without words.May accept this work purely for your sake and benefit the nation through it, Ameen.3w5

وبآية الكُرسيّ سرّ كلّه ... في لفْظها وحرُوفهَا نلْقاه

Ayatul Kursi 2:255

"When is Allah's victory?" Unquestionably, Allah's victory is near."

Quran214-Al-Baqarah

To Palestine, a land of ancient stories etched in stone and resilience woven into the fabric of its olive groves. This thesis, offered as a humble apology for the inadequacy of words, and for the silence for too long, is a testament to the enduring of Palestinianspirits. May their stories of struggle and perseverance resonate within these pages, a call for a brighter tomorrow where peace replaces the weight of hardship.

" سلامٌ لأرْض خُلقت للسَّلاممَا رأَت يوْمًا سلامًا "

” And be humble with them out of mercy, and pray, “My Lord! Be merciful to them as they raised me when I was young.”

Quran-24 Al-Isra

To my hero Abi, Moulay Ali ELIDRISSI

My guiding light, my unwavering support, and my greatest inspiration. You have shown me the true meaning of compassion, selflessness, and constant support. Your words of wisdom, love, and encouragement propelled me forward, pushing me to overcome challenges and reach for the stars. Through your example, you instilled in me the values of empathy, perseverance, and a lifelong pursuit of knowledge.

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My confidante, my radiant beacon throughout this journey, my consistent pillar of strength, and my source of unconditional love and support. You are my rock, my guide, my friend, and my dearest mother and a shoulder to lean on.Watching you navigate life with patience, kindness, and tenderness has inspired me to dedicate myself to Allah's path.

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For your steady love, dedication, and sacrifices you have made for my sisters and I.Yourunparalleled devotion to our education and the countless prayers you have offered on our behalf have paved the way for our success. I pray that Allah continues to protect you, bless you with good health, and grant you long, pious lives so that we may all reap the rewards of your hard work and sacrifice. May this thesis stand as a testament to your exemplary parenting and good manners. May you always be proud of my sisters and me. This work belongs to you, as do I.

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Your presence has been a constant source of inspiration, reminding me of the importance of perseverance and dedication. Just like this thesis, you are a work in progress, full of potential and ready to blossom in unexpected ways.

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To my supportive sister-in-law, Zaineb, and my brothers-in-law, Amine and Oussama, your belief in me has been a gift beyond measure.

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This thesis may be mine, but the joy of life's little moments is something we share. As you take this leap into a new chapter, remember that laughter and aninspiring soul are always the best companions. May your journey be filled with endless possibilities, and may you find magic in every sunrise and sunset. Wishing you nothing but the best, my friend.

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Thesis Chairperson

Professor of Pathology

Head of the Pathology department and Vice Dean for Research and Cooperation

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To my professor ADMOU Brahim

Supervisor of my thesis

Professor of Immunology and Head of the Immunology department

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Judge of my thesis

Professor of Pediatrics in the pediatric "B" department

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LIST OF ABREVIATIONS

ACG: American college of gastroenterology

AD: Anno domini, latin for “in the year of the Lord”

BCR: B cell receptors

BSG: British society of gastroenterology

CeD: Celiac disease

CD:Cluster of differentiation CD71/CD41/CD3

COVID-19: Coronavirus disease 2019.

DGP: Deamidated gliadin antibodies

e.g.: Exempli Gratia meaning “for example “

EGD: Esophagogastroduodenoscopy

EMA: Anti-endomysium

ESPGHAN: European Society of Pediatric Gastroenterology, Hepatology, and Nutrition.

GI: Gastrointestinal

GIP: Gluten immunogenic peptides.

GWAS: Genome-wide association studies

HLA-DQ: Human Leukocyte Antigen – DQ

TIEL: Intraepithelial lymphocyte

I-FABP: Intestinal fatty acid binding protein

IFN-g:Interferon gamma

IL-15:Interleukin-15

IgA / IgG: Immunoglobin A/G

LPS: Lipopolysaccharides

MCH: Mean cell hemoglobin

MCV: Mean corpuscular volume.

MD2: Myeloid Differentiation factor 2

MHC: Major Histocompatibility Complex

NASPGHAN:North American Society for Pediatric Gastroenterology, Hepatology and Nutrition.

NPV: Negative predictive value

N/R: Not reported.

Non-GI: Non gastrointestinal

PPV:Positive predictive value

SCFAs: Like short-chain fatty acids

SD: Standard deviation

SNPs: Single-nucleotide polymorphisms

SPSS: Statistical Package for the Social Sciences.

T1D:Type 1 diabetes

TCRs: T cellreceptors

TG: Transglutaminase

TH1: T helper cell type 1

TLR3: Toll-like receptor 3

tTG: Tissue transglutaminase

tTGA:Tissue transglutaminase antibodies

ULN: Upper limit of normal

LIST OF FIGURES

Figure 1: Distribution of patients by age group.

Figure 2: Distribution of patients by gender.

Figure 3: Different types of feeding.

Figure 4: Consanguinity rateand its category in our patients.

Figure 5:Percentage of similar cases in the family of celiac patients.

Figure 6: Distribution of extraintestinal symptoms in celiac patients.

Figure 7:Categories of anemia observed in our series.

Figure 8: Distribution of patients according to tTGA-IgA titer.

Figure 9: V: Villi with normal height, C: normal sizes crypt, IEL<40%. Normal duodenum architecture.Pathology Department, Mohammed VI University Hospital of Marrakech (Hex20).

Figure 10: The ModifiedMarsh type 2, CH: Crypt hyperplasia, IEL: Intraepithelial lymphocytes >40%, Villi with normal height.Pathology Department, Mohammed VI University Hospital of Marrakech.

Figure 11: The Modified Marsh type 3a, PA: Partial Atrophy, CH: Crypt hyperplasia, IEL: Intraepithelial lymphocytes >40%.Pathology Department, Mohammed VI University Hospital of Marrakech.

Figure 12: The Modified Marsh type 3b, STA: subtotal atrophy, CH: crypt hyperplasia, IEL: intraepithelial lymphocyte >40% (Hex20).Pathology Department, Mohammed VI University Hospital of Marrakech.

Figure 13: The Modified Marsh type 3c, TA: total atrophy, CH: crypt hyperplasia, IEL: intraepithelial lymphocyte >40%.Pathology Department, Mohammed VI University Hospital of Marrakech.

Figure 14: Pathogenesis of celiac disease.

Figure 15: A: Normal endoscopic and morphological aspect of the duodenum. B: normal duodenal biopsy. C: endoscopic and morphological aspect of duodenum in celiac patient. D: duodenal biopsy of celiac patient with total atrophy, compensatory crypt hyperplasia and IEL >40%

LIST OF TABLES

SUMMARY

INTRODUCTION

Celiac disease (CeD) is an autoimmune disorder in which ingestion of dietary gluten triggers an immunological response in susceptible individuals, resulting in damage to the small intestine. CeD can manifest at any age, including within the pediatric population[1].

The overall prevalence of celiac disease is estimated to be 1.4% through serology and 0.7% through biopsy on a global scale, with a slight predominance of females (M: F ratio of 1:3). The prevalence in the pediatric population stands at 0.9%, higher than the 0.5% observed in adults[2].

Due to various clinical presentations, including a significant proportion of asymptomatic individuals, and limitations in accessibility to both definitive endoscopic biopsy and highly sensitive and specific serological testing in many regions globally, underdiagnosis and misdiagnosis of CeD persist as significant challenges on a worldwide scale[3].

In children, the classic presentation of CeD is typically associated with gastrointestinal manifestations such as diarrhea, constipation, abdominal pain, and distension. Additionally, CeD is linked to a range of extraintestinal symptoms, some of which (weight loss, failure to thrive, iron-deficient anemia, osteopenia/osteoporosis, and poor tooth enamel) are direct consequences of nutrient malabsorption[4].

Traditionally, CeD diagnosis has relied on serological testing for CeD-specific antibodies and small intestinal biopsies. A common approach utilizes serology for initial testing and screening, followed by biopsies from multiple duodenal locations, considered by some as the gold standard for CeD diagnosis[5]. Serologic tests for CeD offer advantages over biopsy, they are less time-consuming, less invasive, more cost-effective, and suitable for large-scale screening[6].

Despite the wide availability of serologic testing and increased disease awareness, diagnostic delays for CeD remain a significant issue, particularly for children. A European study conducted by

Whitburnet al. suggested that 83%–91% of children with CeD remain undiagnosed, with the greatest disparity observed in lower socioeconomic households [7]. Serological testing for CeD, specifically tTGA-IgA, demonstrates some of the highest sensitivity and specificity in autoimmune diagnostics. Consequently, a higher anti-tTGA titer correlates with a greater likelihood of an actual positive biopsy result [8]. tTGA-IgA plays a crucial role in most guidelines developed to aid in the evaluation of adults and children suspected of having CeD.

Biopsy constitutes another crucial component of CeD diagnostic testing. The earliest histological change indicative of active CeD in the duodenum is an increase in intraepithelial lymphocytes (IELs) exceeding 25 IELs/100 enterocytes.While this finding exhibits high sensitivity, it lacks specificity for CeD[9]. CeD also presents with inflammatory infiltration in the lamina propria, typically rich in plasma cells. Crypt hyperplasia and villous atrophy signify intermediate to advanced stages of CeD, ultimately progressing to villous flattening in severe disease. Histological findings are comparable in both adult and pediatric populations [10].

Over the years, improvements in sensitivity and specificity of serologic assays for anti-tTGA antibodies have been observed. This has led to growing interest in utilizing serology asa true diagnostic test for CeD, without the need for a confirmatory biopsy. This approach is particularly appealing in the pediatric population, where invasive procedures pose greater challenges.

In 2020, ESPGHAN issued updated guidelines on a non-biopsy diagnostic approach for a subset of patients including symptomatic and high-risk individuals. The same diagnostic algorithm was applied to both groups with testing beginning with total IgA and tTGA-IgA. For both groups, if tTGA-IgA is positive but <10x ULN, a biopsy was recommended. For tTGA-IgA levels exceeding 10 x ULN, a separate blood sample was required for EMA testing (as opposed to both EMA and HLADQ typing)[11].

Despite these advancements, knowledge regarding celiac disease in Moroccan childrenremains limited. Therefore, this study aimed to assess the clinical and biological characteristics ofceliac disease in Moroccan children, to define the immunological and histopathological profile of the disease in this population, and to establish the correlation between anti-transglutaminase antibodies and the clinical, biological, and histological findings of jejunal biopsy among Moroccan children.

MATERIALS AND METHODS

I. Type of study:

We conducted a descriptivecross-sectional study on patients with CeD. It was carried out at the Mohammed VI University Hospital of Marrakech, in the following departments: Immunology Laboratory, Pediatrics B department, and Pathology Laboratory, over 2 years (stretching from July 2021 to July 2023).

II. Patients and data collection:

Patients were selected from an initial sample of 300cases admitted to the Immunology laboratory for CeD screening. We included all patients under 16 years old at diagnosis and who had benefited from an anti-transglutaminase antibody assay and jejunal biopsy. A total of 66 patients met the criteria previously mentioned.

All patients over 16 years of age and children without a serological test or histologically proven biopsy were excluded from this study.Likewise, patients with known CeD who have been on a gluten-free diet for more than 6 monthsand those with unusable or lost medical records were also excluded.

The data were collected from the pediatrics B department'smedical records, the immunology and pathology laboratory registers. Concerning the missing information, they werelater supplemented by phoning some patients.

For each patient, we gathered:

→ **Epidemiological data:** age,year of CeD diagnosis, gender.

→ **Medical history**: feeding, age of introduction of gluten, consanguinity,associated pathologies (e.g. Type 1 diabetes, autoimmune thyroid…), similar cases in the family.

→ **Clinical findings**: typical signs of CeD (diarrhea, abdominal bloating, abdominal pain…) and atypical symptoms.

→ **Biological results:**resultsof biologicalparameters were collected for each child at the time of diagnosis when available, specifically blood hemoglobin (g/dl), mean corpuscular volume (MCV) (fl), mean cell hemoglobin(MCH), ferritin (ug/l), calcium (mg/l), protein (g/l), cholesterol (g/l) and phosphate (mg/l).

Biological abnormalities were defined according to the age- and sex-specific reference values used by the university laboratory.

→ **Immunological results**:Based on the medical prescription, the following analyses were carried out:

- Detection and titration of IgA anti-transglutaminase antibodies by Fully automated chemiluminescence assay (BIO-FLASH®, threshold: 20 CU/ml), supplemented by IgG anti-transglutaminase antibodies if needed.
- Detection of anti-endomysium antibodies by Immunofluorescence method, performed to corroborate the positivity of the tTGA test.
- Detection of anti-deamidated gliadin antibodies by chemiluminescence assay (BIO-FLASH®, threshold: 20 CU/ml), realized only for patients with non-contributory tTGA results.
- Measurement of total IgA isotype by turbidimetry was performed to exclude possible IgA deficiency that could mask CeD with negative tTGA-IgA.IgA deficiency was defined according to the age-specific reference values used by the local laboratory.

→ **Histopathological results and classification**:In cases of suspected CeD, the common local practice is based on at least four duodenal biopsy fragments during gastrointestinal endoscopy.

Biopsy samples are sent to the pathology laboratory, where they are processed and analyzed, andonly correctly oriented specimens are accepted for further microscopic analyses. The Intraepithelial lymphocyte count, the crypt hyperplasia,and the degree of villous atrophy were categorized based on the Marsh-Oberhuber grading[12].

Table 1: The Marsh-Oberhuber classification[12]:

	IEL	Crypts	Villi
Type 0	< 40	Normal	Normal
Type 1	> 40	Normal	Normal
Type 2	> 40	Hypertrophic	Normal
Type 3a	> 40	Hypertrophic	Partial atrophy
Type 3b	> 40	Hypertrophic	Subtotal atrophy
Type 3c	> 40	Hypertrophic	Total atrophy
Type 4	<40	Normal	Hypoplastic
IEL: Intraepithelial lymphocyte count/100 epithelial cells.			

A patient information form was made for each patient to facilitate the collection and analysis of the different clinical, para-clinical, and histopathological results(Appendix 1).

III. Statistical analysis:

We recorded the collected data with the Microsoft Excel 2021 version using the patient's information form. Afterward, statistical analyses were performed using Statistical Package for the Social Sciences (SPSS) statistical software (SPSS Inc., Chicago, IL, USA). The continuous variables were presented as mean and standard deviation, andthe categorical data were expressed as frequencies

and relative percentages. The analysis of collected data allowed us to express the statistical results found in diagrams and tables of frequency and subsequently their percentages.We defined the p-value as statistically significant when less than 0.05.

IV. Ethical aspects:

Patient privacy and data security were paramount throughout the data collection process, in line with ethical standards.

RESULTS

I. Epidemiological data:

Our study involved sixty-six children diagnosed with celiac disease who met the inclusion criteria.

1. Age:

1.1. At diagnosis:

The mean age of our series was 6.5 years, with a standard deviation of 4.18 ranging from 1 year to 15 years old.

The 2-4 age group was the most represented, with a frequency of 21.2%, followed by the 1-2 age group with 19.7%, whereas the least frequent age group was that between14 and 16 years, with a frequency of 1.5% (Figure 1).

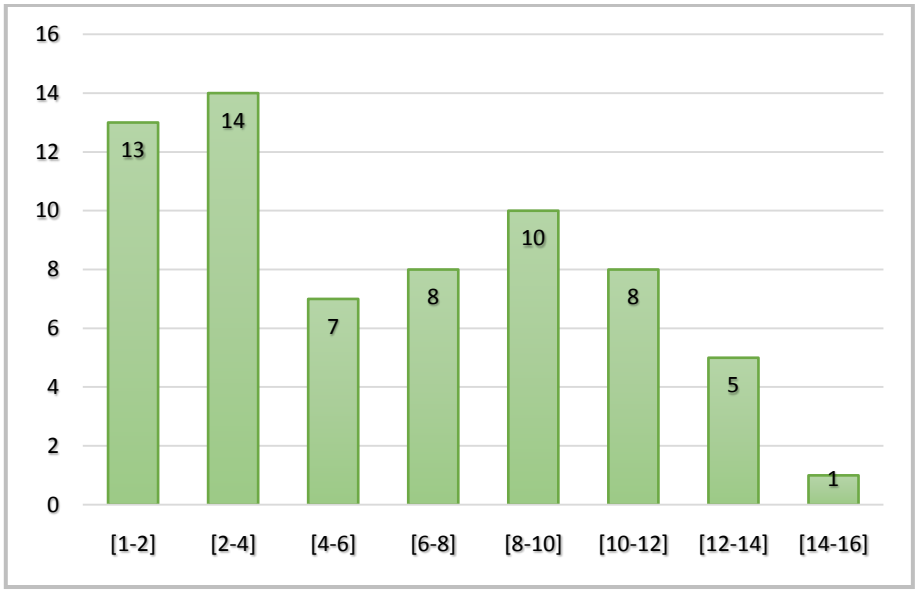

Figure 1:Distribution of patients by age group.

1.2. Age of introduction of gluten:

The mean age of introduction of gluten was5.56 months ranging from 3 months to 1 year.

1.3. Age of symptom's onset:

The mean age of appearance of symptoms was 6.14 years ranging from 3 months to 15 years.

→ The symptomatology appears about 2 years after the introduction of gluten.

→ The Diagnostic delay of about 5 months (between the onset of disorders and consultation).

2. Gender:

Our series included 37females (56.1%) and 29 males (43,9%) with a male to female sex-ratio of 0.78 (figure 2).

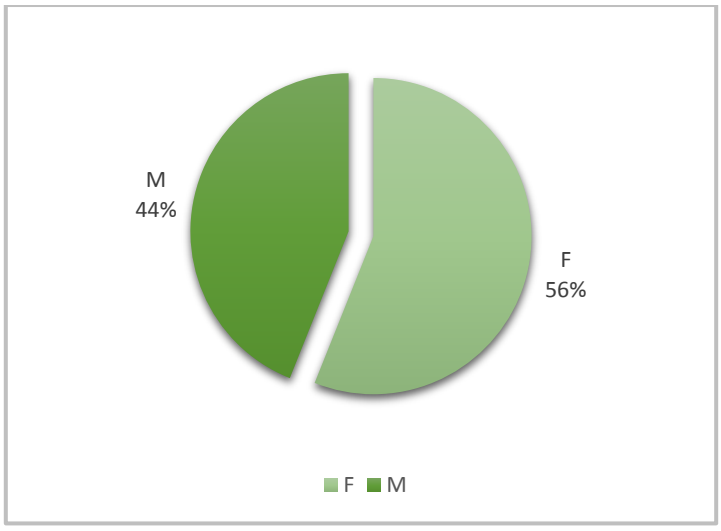

Figure 2:Distribution of patients by gender.

3. Case history:

3.1. Feeding:

Among our patients,mixed feeding is predominant with 44%, followed by Breastfeeding with 33 %. Formula feeding was the leastpracticed, with 23% (figure 3).

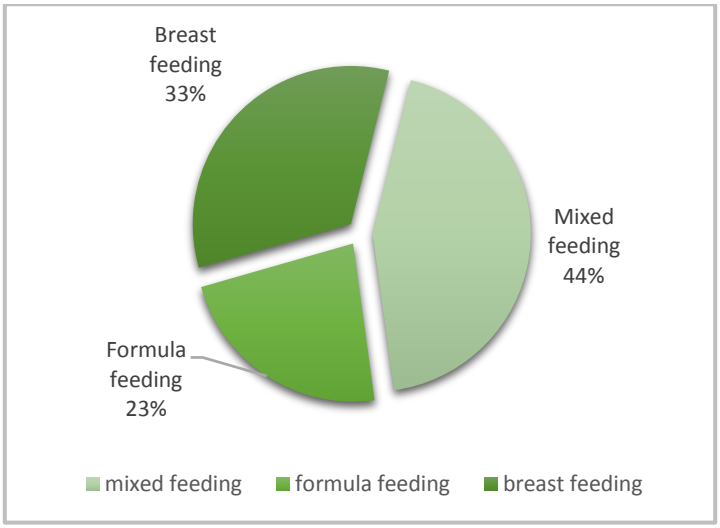

Figure 3:Different types of feeding.

3.2. Consanguinity:

The notion of consanguinity was noticed in 10 patients (12%), with 8 cases of 1st -degree and 2 cases of 2nd-degree consanguinity (figure4).

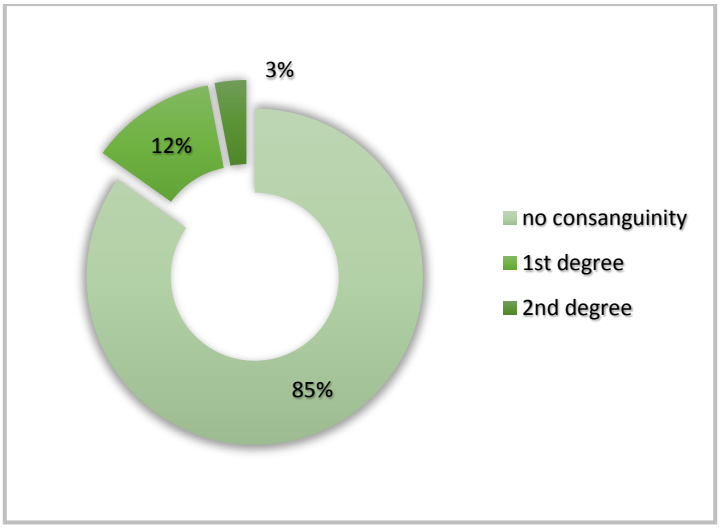

Figure 4: Consanguinity rateand its category in our patients.

3.3. Similar cases in the family:

Similar cases of CeD were found in 12% (8 cases) among the family members of our patients (figure5).

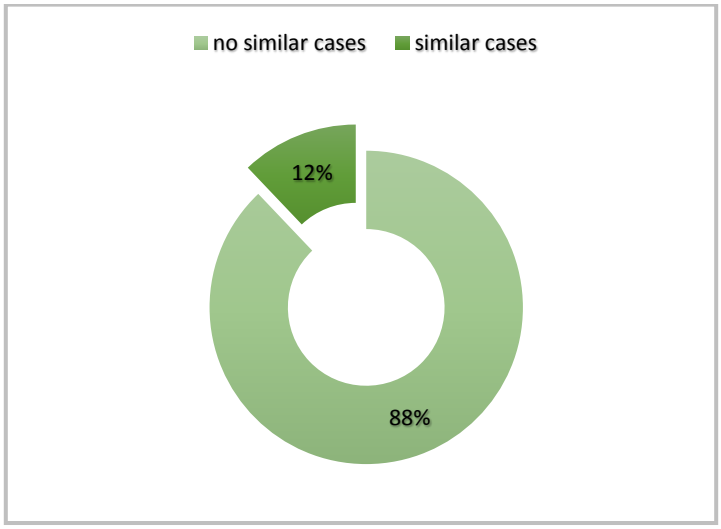

Figure 5:Percentage of similar cases in the family of celiac patients.

II. Clinical data:

1. Gastrointestinal signs:

The predominant symptom of the disease was transit disorder, which was reported by twenty-seven (41%) of our patients, dominated by diarrhea(29%), followed by constipation (9%), and alternating diarrhea-constipation (3%). The other clinical manifestations are reported in table 2.

Table 2: Distribution of gastrointestinal symptoms in our patients.

Symptom	Headcounts	Percentage
Transit disorder	27	41%
Abdominal pain	22	33%
Abdominal distention	17	26%
Vomiting	21	32%

2. Extraintestinal signs:

- Forty-one patients (62%) were diagnosed with growth retardationwith a mean average of -1.33 and a standard deviation of 1.47 in the height percentile and a mean average of -1.38 in the weight percentile with a standard deviation of 1.5.

→ Growth retardation was defined as an abnormal deceleration of growth development compared with ageand gender-matchedSD units.

→ The expected growth rate was considered abnormally low if the current height and weight differed from the expected more than −2 SD.

- Pallor, a clinical indicator of potential anemia, was observed in twenty-six (40%) of the patients in our study.
- Anorexia was manifestedin twenty-one (32%) cases and has a direct impact on malnutrition which was manifested in eighteen (27%) patientsof our series.
- Seven (11%) patients had dehydration whileedema syndrome was diagnosed in 7 (11%) patients too.
- Five (9%) patients were suffering fromfeverand current infection at diagnosis of celiac disease.
- Two patients (3%) experienced irritability as a Behavioral disorder.
- We also noted arthralgia and integumentary disorders presented by one of our studied patients (1.5%) (Figure 6).

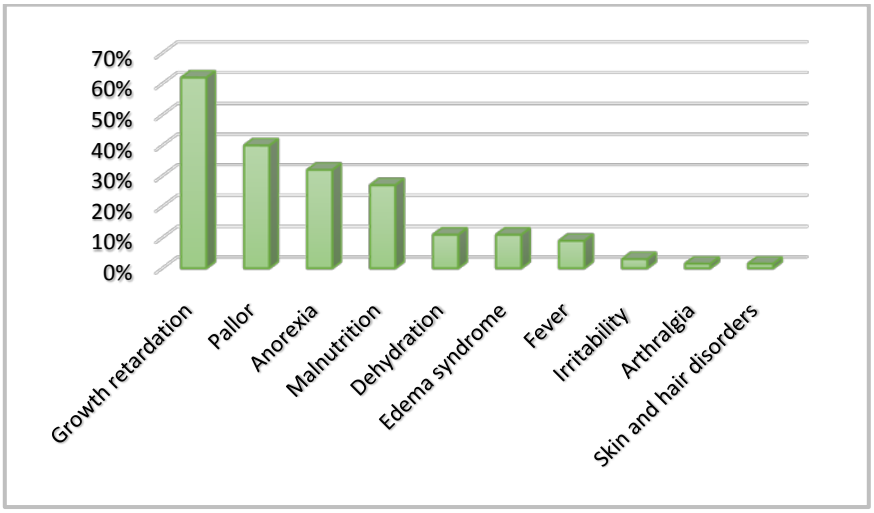

Figure 6:Distribution of extraintestinal symptoms in celiac patients.

3. Associated pathologies:

Celiac diseasewas associated with other clinical conditions in 42% of cases, represented by type 1 diabetes, hepatic cytolysis, lupus, hypothyroidism (Table 3).

Table 3: Frequency of different pathologies associated with celiac disease.

Associated pathologies	Headcounts	Percentage
Type 1 Diabetes	20	30%
Hepatic cytolysis	3	4.5%
Lupus	1	1.5%
Hypothyroidism	1	1.5%
Neutropenia	1	1.5%

III. Paraclinical data:

1. Biological results (Biological signs of malabsorption):

1.1. Anemia:

The complete blood count revealed anemia in 35 patients (53%), type microcytic hypochromic, normocytic hypochromic, and normocytic normochromic in 31, 2 and 2 casesrespectively(figure 7).

The hypochromicmicrocytic anemia was resistant to iron supplementsin 15 patients (23%).

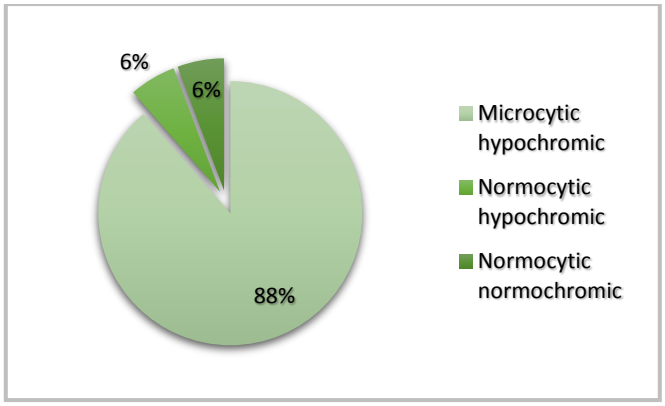

Figure 7:Categories of anemia observed in our series.

1.2. Hypoferritinemia:

The measurement of ferritinemia was realized in 31 patients (46.9%), showing Hypoferritinemia in 45 % of cases (n=30 cases).

1.3. Hypocalcemia:

Hypocalcemia was observed in 7 of the 43 patients who benefited from calcemia measurement.

1.4. Hypoproteinemia:

Serum protein assays carried out in 42 patients revealed hypoproteinemia in 11% of cases.

1.5. Hypocholesterolemia:

Total cholesterol was explored in 41 patients, showing hypocholesterolemia in 21 patients (32%), while it was normal in the other 20 patients.

The frequency of all the biological abnormalities encountered in our patients is shown in the table below (table 4).

Table 4: Frequency of biological abnormalities.

Biological results	Headcounts	Percentage
Anemia	35	53%
Hypoferritinemia	30	45%
Hypocalcemia	7	11%
Hypoproteinemia	7	11%
Hypocholesterolemia	21	32%

2. Radiological results (bone age):

X-ray of the left hand and wrist was taken for one child, displaying a low bone age. The difference between bone age and chronological age was 8 months.

3. Immunological results:

In our series, anti-transglutaminase antibodies were realized in all 66 cases, while anti-endomysium and deamidated gliadin peptide antibodies were tested in only one patient (1.5%).

The demand for total IgA quantification was issued in 21patients (32%).

3.1 Anti-transglutaminase antibodies(tTGA):

tTGA-IgA antibodies were positive in 82% of patients (n=54) and negative in 12 cases (18%).

The titers of the positive antibodies were considered very high (over 10 times the cut-off) in 36 patients (55%), moderate (between 3-10 times the Upper limit of normal) in 6 patients (9%), and low (under 3 times ULN) in 12 patients (18%) (figure8).

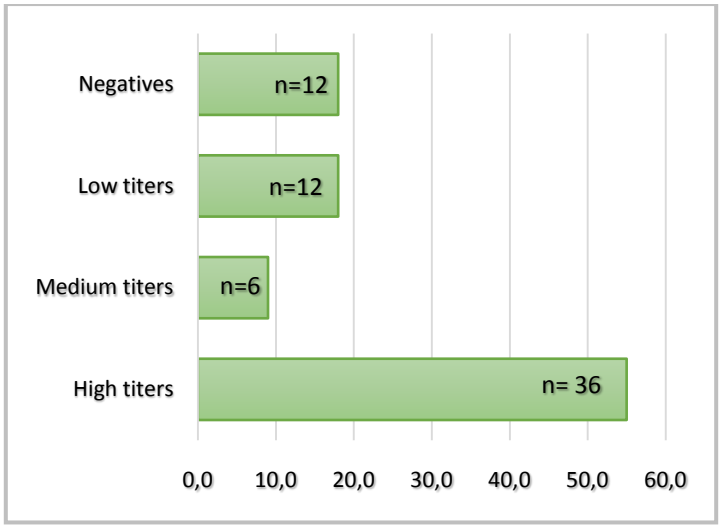

Figure 8:Distribution of patients according to tTGA-IgAtiter.

Based on these results, the sensitivity of the tTGA-IgA test was estimated at 97.2%. However, due to a limited number of negative cases (n=12), the specificity could not be reliably determined in our study.The positive predictive value (PPV) was estimated to be 64.8% and the negative predictive value (NPV) was 91.6% (table 5).

Table 5: Biological characteristics of the tTGA test.

	Biopsy +	Biopsy -	Total
tTGA-IgA +	35	19	54
tTGA-IgA -	1	11	12
Total	36	30	66

Interestingly, patients with negative tTGA-IgA and negative biopsy presented with significant clinical symptoms and a positive tTGA-IgG test.

Furthermore, tTGA-IgG antibodies were effectuated in 14 patients. They were positive in 19.5% of patients (n=13) and negative in one case. The titer of these antibodies was considered very high in 10 patients (15%), moderate in 2 patients (3%), and low in 1patient (1.5%).

3.2 Deamidated gliadin antibodies (DGP):

The only patient tested for DGP antibodies was positive with very high titers (>100 IU/ml) both for IgA and IgG antibodies.

3.3 Anti-endomysium (EMA):

EMA-IgA test was performed on one patient and was positive with a moderate titer.

3.4 Total IgA immunoglobulins:

The total IgA test was effectuated to rule out selective IgA deficiency. Low levels of IgA were found in 8 patients among 21, corresponding to 12% of frequency.

4. Histological results:

4.1 Villous atrophy grading:

Histopathological study of biopsies revealed the presence of total, subtotal, and partial villous atrophy in 14% (9 cases), 20% (13 cases), and 17% (11 cases) of patients respectively. It was absent in 50% (n=33) of cases.

4.2 Intraepithelial lymphocyte count:

As mentioned in pathological reports, intraepithelial lymphocyte count was above 40% in 21 patients (n=31.8%) and was less than 40% in 45 (n=68.2%) patients of our series.

4.3 Crypt hyperplasia:

Crypt hyperplasia was found on histopathology results in 34 cases (51.5%) and was absent in 32 patients (48.5%).

4.4 Histopathological findings according to the modified Marsh classification:

The results of histopathological abnormalities according to the modified MARSH classification are as follows (table 6):

Table 6: Distribution of Biopsy Results according to the Modified MARSH Classification.

Type	Number of cases	%
0	30	45%
2	3	4.5%
3a	10	15%
3b	13	20%
3c	9	14%
4	1	1.5%

The main histopathological abnormalities observed in some patients of our series are illustrated by pictures below, registered with the kind agreement of the pathology department of Mohammed VI University Hospital (figures 9,10,11,12 and 13).

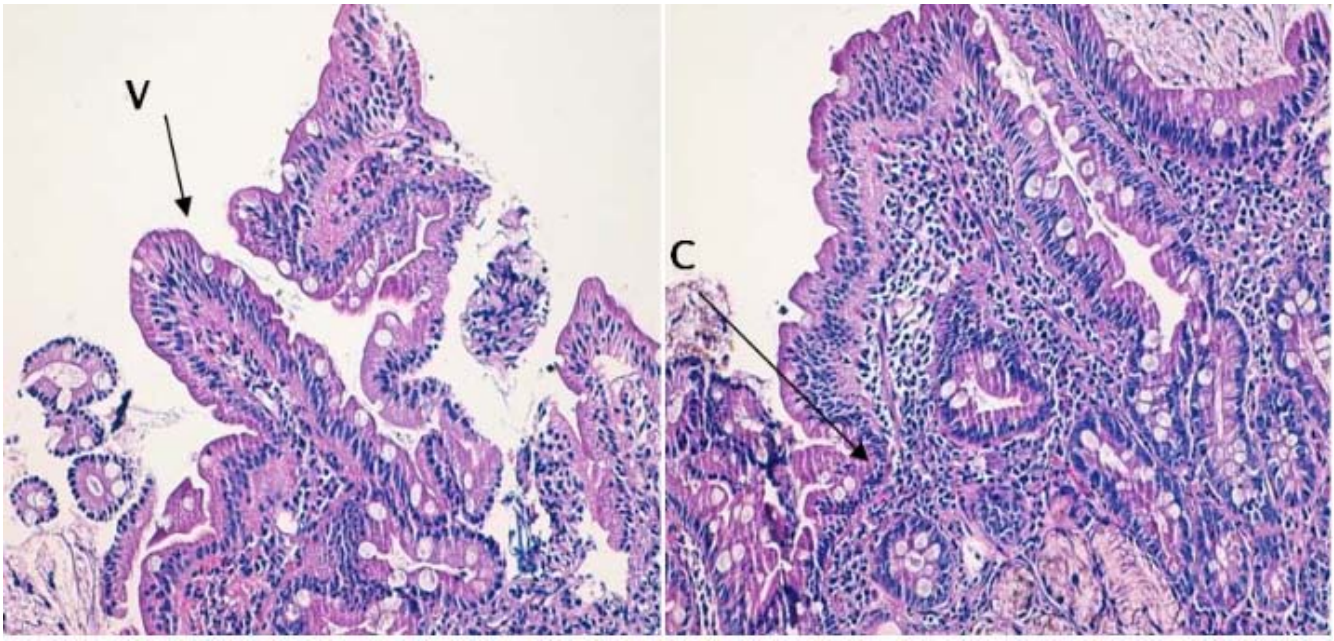

Figure 9: V: Villi with normal height, C: normal sizes crypt, IEL<40%. Normal duodenum architecture. Pathology Department, Mohammed VI University Hospital of Marrakech (Hex20).

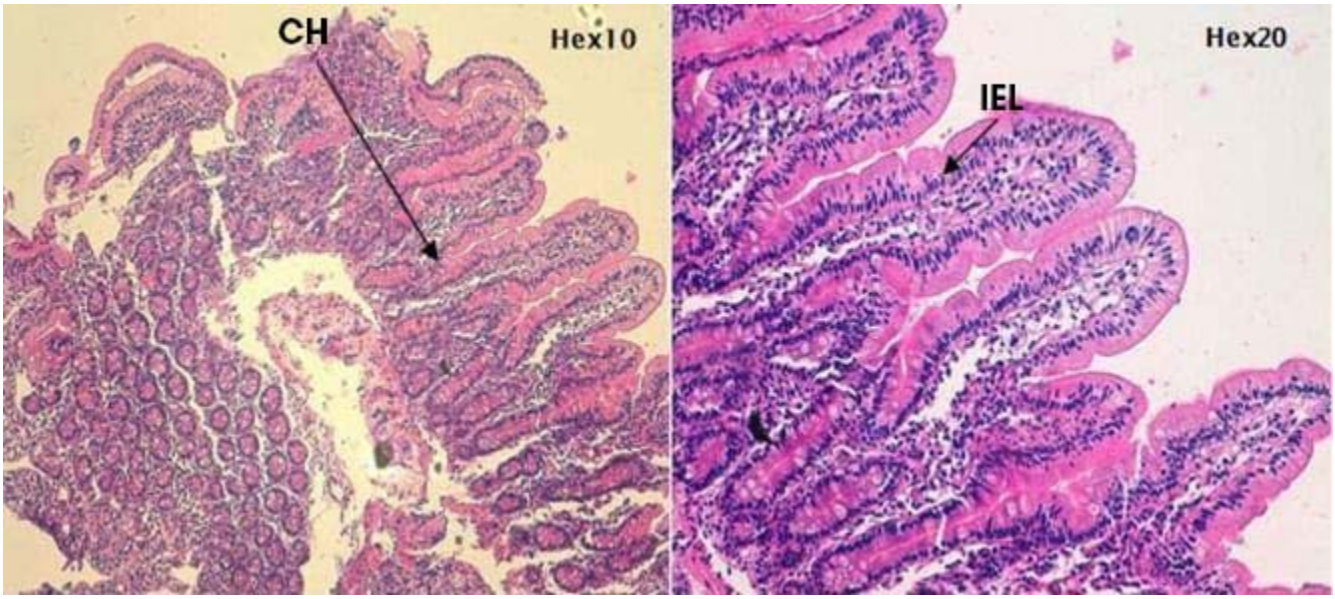

Figure 10: The ModifiedMarsh type 2, CH: Crypt hyperplasia, IEL: Intraepithelial lymphocytes >40%, Villi with normal height.

Pathology Department, Mohammed VI University Hospital of Marrakech.

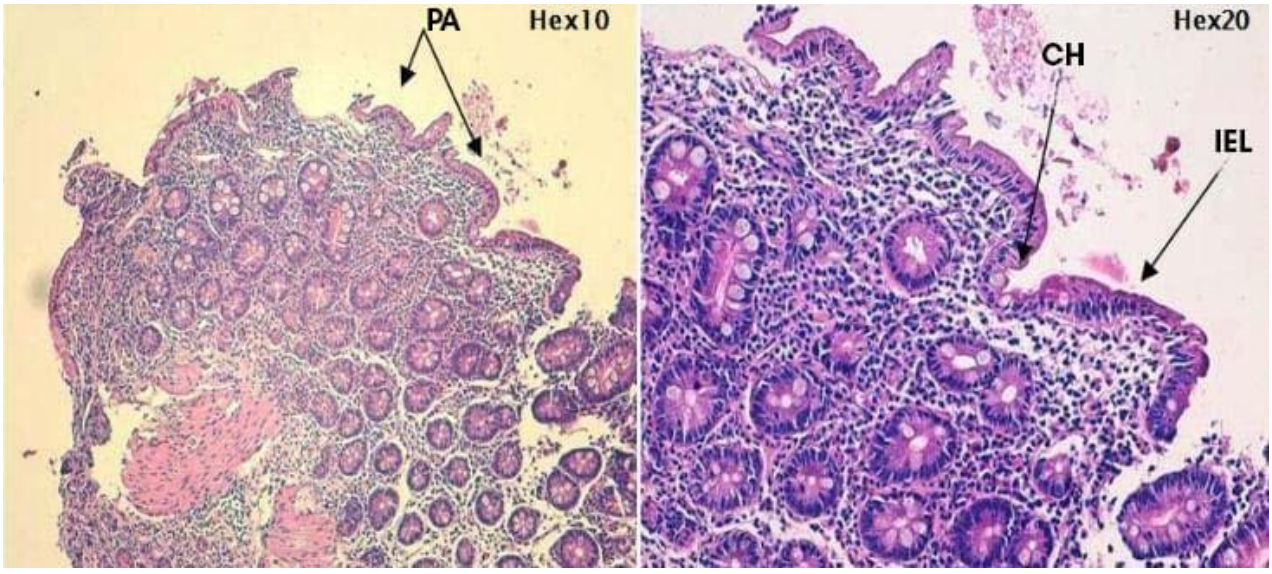

Figure 11: The Modified Marsh type 3a, PA: Partial Atrophy, CH: Crypt hyperplasia, IEL: Intraepithelial lymphocytes >40%.

Pathology Department, Mohammed VI University Hospital of Marrakech.

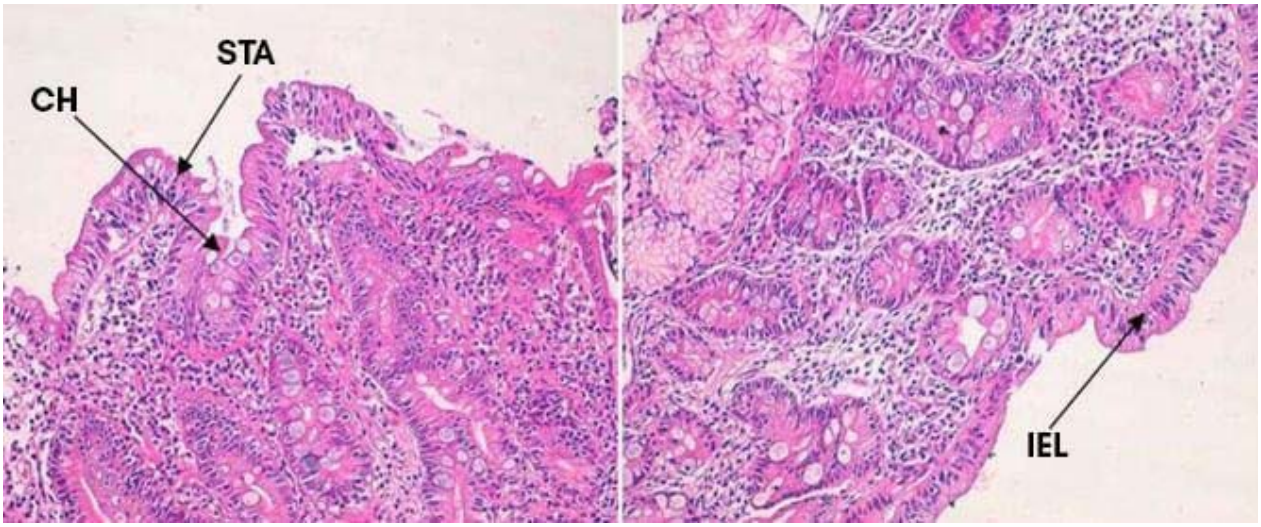

Figure 12: The Modified Marsh type 3b, STA: subtotal atrophy, CH: crypt hyperplasia, IEL: intraepithelial lymphocyte >40% (Hex20).

Pathology Department, Mohammed VI University Hospital of Marrakech.

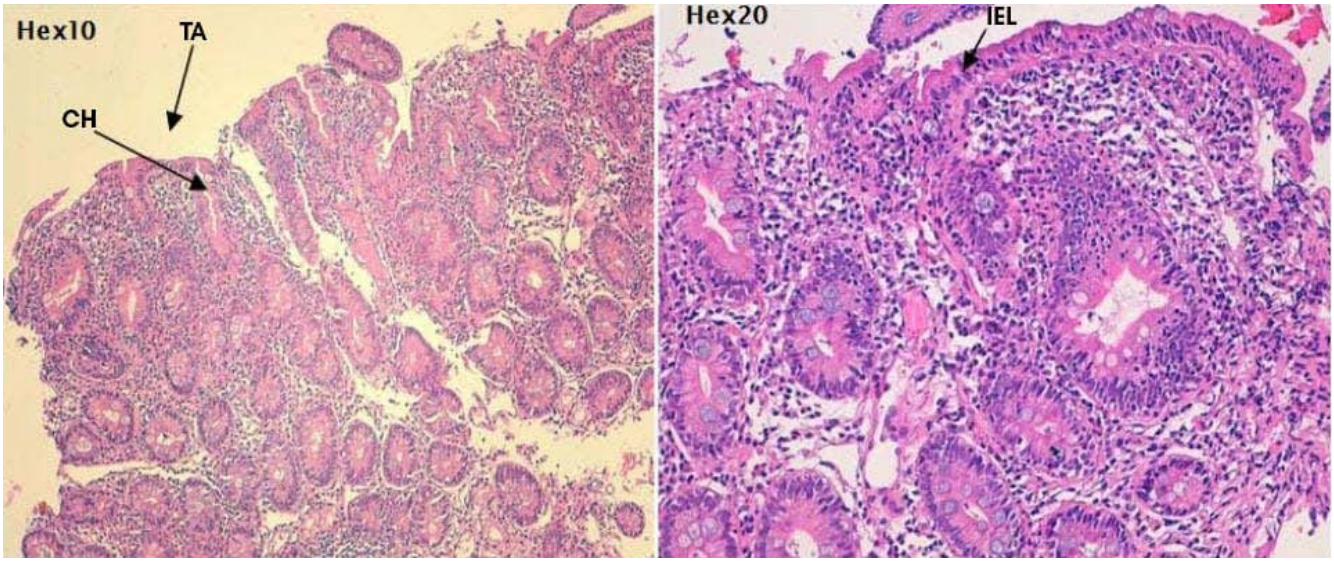

Figure 13: The Modified Marsh type 3c, TA: total atrophy, CH: crypt hyperplasia, IEL: intraepithelial lymphocyte >40%.

Pathology Department, Mohammed VI University Hospital of Marrakech.

5. HLA-genotyping:

The HLADQ2/DQ8analysis was not conducted on any of our study participants.

IV. Correlation between antibody titers with clinical, biological, and histopathological results:

1. Correlation between tTGA-IgA titers and clinical symptoms of celiac disease:

As shown in tables 7 and 8, the clinical symptoms of celiac disease were significantly more manifested in patients with high titers of tTGA-IgA antibodies.

Table 7: Titers of tTGA-IgA according to gastrointestinal signs.

tTGA-IgA titers		Gastro-intestinal symptoms					
		Diarrhea	Constipation	Alternating diarrhea and constipation	Abdominal bloating	Abdominal pain	Vomiting
Negatives	Count	2	1	0	2	5	3
	% within the symptom	10.50%	16.70%	0%	11.80%	22.70%	14.30%
Low titers	Count	3	0	0	0	5	4
	% within the symptom	15.80%	0%	0%	0%	22.70%	19%
Moderate titers	Count	3	2	0	3	1	0
	% within the symptom	15.80%	33.30%	0%	17.60%	4.50%	0%
High titers	Count	11	3	2	12	11	14
	% within the symptom	57.90%	50%	100%	70.60%	50%	66.70%
Total	Count	19	6	2	17	22	21
	% within the symptom	100%	100%	100%	100%	100%	100%
P value		0.17			0.001	0.011	0.003

Table 8: Titers of tTGA-IgA according to extraintestinal signs.

tTGA-IgA titers	Extraintestinal symptoms								
	Growth retardation	Anorexia	Dehydration	Pallor	Malnutrition	Edema	Integumentary disorders	Arthralgia	Neurological manifestations
Negatives	6	2	0	8	2	2	0	0	0
	14.6%	9.5%	0%	30.8 %	11.1%	28.6%	0%	0%	0%
Low titers	5	4	1	2	1	2	0	0	0
	12.2%	19%	14.3%	7.7%	5.6%	28.6%	0%	0%	0%
Moderate titers	5	1	0	2	3	0	0	0	0
	12.2%	4.8%	0%	7.7%	16.7%	0%	0%	0%	0%
High titers	25	14	6	14	12	3	1	1	2
	61%	66.7%	85.7%	53.8 %	66.7%	42.9%	100%	100%	100%
Total	41	21	7	26	18	7	1	1	2
	100%	100%	100%	100%	100%	100%	100%	100%	100%
P value	0.003	0.007	0.003	0.002	0.003	0.009	0.013	0.01	0.009

2. Correlation between tTGA-IgA titers and biological signs of malabsorption:

There was no statistically significant correlation between the titers of anti-transglutaminase antibodies and the biological signs (table 9).

Table 9: Titers of tTGA-IgA according to biological signs.

tTGA_IgA titers		Anemia	Hypo-ferritinemia	Hypo-calcemia	Hypo-proteinemia	Hypo-cholesterolemia
Negatives	Count	4	6	0	1	8
	% within the biological result	14.3%	20%	0%	14.4%	40.0%
Low titers	Count	9	2	1	1	3
	% within the biological result	32.1%	7%	14.4%	14.4%	15.0%
Moderate titers	Count	2	6	2	2	2
	% within the biological result	7.1%	20%	28.5%	28.5%	10.0%
High titers	Count	13	16	4	3	7
	% within the biological result	46.4%	53%	57.1%	42.7%	35.0%
Total	Count	28	30	7	7	20
	% within the biological result	100.0%	100.0%	100.0%	100.0%	100.0%
P-value		0.111	0.347	0.395	0.201	0.304

3. Correlation between tTGA-IgA titers and histopathological grade (Marsh-Oberhuber classification):

tTGA titers were significantly higher in patients with subtotal and total villous atrophy than in those with partial atrophy as shown in table 10 (p=0.001).

Table 10: Titers of tTGA according to villous atrophy grade.

tTGA_IgA titers		The modified Marsh classification / villous atrophy					
		Normal 0	Normal 2	Partial 3a	Subtotal 3b	Total 3c	Hypoplastic 4
Negatives	Count	11	1	0	0	0	0
	% within the modified Marsh classification	36.6%	33.3%	0.0%	0.0%	0.0%	0.0%
Low titers	Count	10	0	2	0	0	0
	% within the modified Marsh classification	33.3%	0.0%	20.0%	0.0%	0.0%	0.0%
Moderate titers	Count	3	0	3	0	0	0
	% within the modified Marsh classification	10.0%	0.0%	30.0%	0.0%	0.0%	0.0%
High titers	Count	6	2	5	13	9	1
	% within the modified Marsh classification	20.0%	66.7%	50.0%	100.0%	100.0%	100.0%

4. Correlationofvillous atrophy and intraepithelial lymphocyte rates:

The rate of intraepithelial lymphocytes was significantly higher in patients with subtotal and total villous atrophy than in those with partial atrophy (p=0.005), (table 11).

Table 11: Intraepithelial lymphocyte rates by villous atrophy grade.

Intraepithelial lymphocyte		Villi			
		Normal	Partial atrophy	Subtotal atrophy	Total atrophy
<40	Count	32	7	3	3
	% within Intraepithelial lymphocyte	71.1%	15.6%	6.7%	6.7%
>40	Count	1	4	10	6
	% within Intraepithelial lymphocyte	4.8%	19%	47.6%	28.6%

5. Correlation between tTGA-IgA titersand intraepithelial lymphocyte rates:

We have noted a significant correlation between the level of intraepithelial lymphocytes (IEL) and the titers of transglutaminase antibodies. the rate IEL was above 40 in high titers of tTGA-IgA, in comparison with moderate and low titers (table 12), with a p-value of 0.01.

Table 12: Titers of tTGA according to Intraepithelial lymphocyte rates.

Intraepithelial Lymphocytes		tTGA_IgA titers:			
		Negatives	Low titers	Moderate titers	High titers
<40	Count	11	11	6	17
	% within Intraepithelial lymphocyte	24.4%	24.4%	13.3%	37.8%
>40	Count	1	1	0	19
	% within Intraepithelial lymphocyte	4.8%	4.8%	0.0%	90.5%

DISCUSSION

I. General aspects:

Celiac disease, alternatively referred to as gluten-sensitive enteropathy, is an autoimmune disorder affecting the small intestine. The condition occurs when the body reacts inappropriately to gluten, triggering an immune response that results in inflammation and harm to the small intestine[13]. The disease displays a range of gluten-related signs and symptoms, as well as the presence of CeD-specific antibodies, HLA-DQ2 or HLA-DQ8 haplotypes, and enteropathy[14].

1. History:

In 250 AD, the ancient Roman physician and philosopher Areteus Cappadocia first described a disease characterized by symptoms of exhaustion, weakness, and diarrhea that he called "koiliakos" which comes from "koelia", in Greek "abdominal cavity"[15].

In 1856, Francis Adams translated Aretheus' observations into English, and in 1888, Samuel Gee Britishpediatrician published a monograph on celiac disease, establishing the link between the disease and diet[16].

The true causes of celiac disease remained unknown until the Second World War when Willem-Karel Dicke noticed that children with the disease recovered during periods of food shortage. After the war, in the 1950s Dr. Dicke conducted further research and found that wheat and rye flour exacerbate celiac symptoms. He also associated gluten with celiac disease and introduced gluten-free food as a standard treatment[17].

However, new methods of studying the small intestine have shown that not only the response of the immune system but also the deformation of the intestinal walls lies at the heart of celiac disease. Paulley conclusively demonstrated histological abnormalities in the lining of the small

intestine in 1954. The reliable diagnosis was made possible by the per-oral biopsy techniques described by Royer in 1955 and Shiner in 1956 [18].

Celiac disease was originally thought to be a type of food allergy, but it was later discovered to be an autoimmune disease. In the early 1970s, Dr. Daniel Leffer found that the HLA-DQ2 and HLA-DQ8 genes were linked to celiac disease[19].

Circulating antibodies to gluten were first reported in 1958. Even though, these antibodies are not specific to celiac disease and can be found in other conditions with mucosal damage. In 1971, there was disagreement about the specificity of antibodies to reticulin. The discovery of anti-endomysium antibodies in 1971 proved to be highly sensitive and specific for CeD but had limitations in availability and interpretation. Later, the use of human umbilical cord tissue helped address some of these issues. Further advancements occurred when tissue transglutaminase was identified as the autoantigen responsible for CeD in 1997. The ELISA method made screening with anti-transglutaminase antibodies simpler, more economical, and faster[20].

Research into the effects of gluten began in the 1980s and continues today. Celiac disease is now defined as an autoimmune disease that affects the small intestine, caused by a reaction to gliadin in wheat, barley, rye, and oats. This reaction leads to inflammation and damage to the small intestine, reducing nutrient absorption. The exact mechanism of immune response is not fully understood, but it involves T-cell and immune response in the intestinal epithelium[21].

2. Epidemiology:

Celiac disease is estimated to affect approximately 1% of the global population[4], with recent studies showing an overall seroprevalence of 1.4%. Biopsy-confirmed cases have a slightly lower global prevalence at 0.7%. The specific prevalence varies across different regions with Europe and Oceania having the highest rates at 0.8%, followed by Asia at 0.6%. Africa and North America have a

prevalence at 0.5%, while South America has the lowest prevalence at 0.4%[2]. The incidence of celiac disease has been increasing in recent years, particularly among children[22]. Albeit, the pediatric population shows a prevalence of 0.9% compared to that of 0.5% of adults[10].

In Arab countries, Saudi Arabia has the highest reported prevalence at 3.2%, while Tunisia has the lowest at 0.1%[23]. Less is known about the prevalence of celiac disease in Africa, but seroprevalence in North African countries such as Morocco, Algeria, and Egypt is similar to the global average of 1.1%[24].

3. Physiopathology:

Celiac disease stands out from other autoimmune disorders due to its distinctive features: it has a well-known environmental trigger (gluten), a significant contribution of certain HLA types (DQ2 or DQ8) is necessary for the disease to manifest, and autoantibodies against TG can be detected[25].The pathogenesis of CeD involves a complex interplay of genetic and environmental factors.

3.1. Genetic factors:

Studies on twins showed a significantly higher concordance in monozygotic twins than in dizygotic twins. Monozygotic and dizygotic twins had 70% and 9% cumulative probability of having symptomatic or silent forms of CeD, respectively, within 5 years[26].

a. HLA Genes:

The HLA-DQA1 and HLA-DQB1 genes play a crucial role in presenting gluten peptides as antigens, making the MHC-HLA locus the most significant genetic factor in the development of CeD. Most CeD patients (around 90-95%) carry HLA-DQ2.5 heterodimers, which are encoded by DQA1*05 and DQB1*02 alleles. These alleles can be inherited together on the same chromosome or separately

on two homologous chromosomes. There is a small percentage (about 5-10%) of CeD patients who carry HLA-DQ8 heterodimers encoded by DQA1*03 with DQB1*03:02 or HLA-DQ2.2. A minority (<1%) of CeD patients do not carry these heterodimers but express the other half of the DQ2.5 heterodimer (DQ7.5). Homozygous DQ2.5 carriers have the highest risk of developing CeD, up to 30%, compared to a 3% risk in those with a heterozygous genotype. Homozygosity for HLA-DQ2.5 is linked to a more classical presentation and complicated CeD. However, having the human leukocyte antigen (HLA) risk alleles alone is necessary but not sufficient for the development of CeD. About 35-40% of the genetic risk for CeD is attributed to HLA haplotypes alone, indicating that additional non-HLA genomic regions identified as associated with CeD contribute to the overall genetic heritability of the disease[26].

b. Non-HLA Genes:

In total, more than 40 non-HLA risk loci have been identified in CeD throughGenome-wide association studies(GWAS). Many of these loci contain genes that play a role in the immune system's T cells and B cells. Furthermore, a distinct characteristic of these non-HLA sites is that numerous single-nucleotide polymorphisms (SNPs) with the most substantial associations are found in noncoding regions and exert their influence by regulating gene expression[27].It should be acknowledged that GWAS chip arrays have detected a relatively small quantity of SNPswithin the genetic regions responsible for encoding B cell receptors (BCRs) and T cell receptors (TCRs) when compared to SNPs associated with HLA. However, it would be hasty to assert that these genes do not play a role in celiac disease. As a result, these regions have not received sufficient investigation [28]. Given the emerging understanding of their genetic variability, it is plausible that genes in the TCR and BCR regions do play a role in the genetic risk for CeD. This effect could be influenced by variations in exons that directly impact antigen recognition or, more likely, by SNPs or structural variations (e.g.,

gene duplications or deletions) that affect the representation of these genes in the TCR/BCR repertoires[27].

3.2. Environmental factors:

a. Gluten:

Gluten was identified as the trigger for coeliac disease almost 70 years ago. It is a proteinaceous mass that remains after washing a dough made from wheat flour and water to remove starch and soluble material. This molecule is classified as a prolamin, a group of proteins that are soluble in alcohol and present in other cereals as well[29].These proteins, known as gliadin and glutenin, are rich in proline and glutamine residues, which make them resistant to digestive proteases.Similar proteins called hordeins and secalins are found in barley and rye, respectively, although they do not form gluten balls like wheat proteins. However, they are also referred to as gluten proteins[27]. It has been suggested that gluten proteinsincrease gut permeability and stimulate both the adaptive and innate immune systems[30]. The evidence for the harmful effects of gluten proteins on the adaptive immune system is substantial, but there is still limited evidence regarding the stimulation of innate immunity. T cell epitopes have been defined for gliadins, glutenins, hordeins, secalins, and avenin, indicating that these gluten proteins are harmful to individuals with celiac disease[31]. There is ongoing debate regarding the harmfulness of oats, which contain avenin proteins similar to gluten. While some CeD patients show sensitivity and immune responses to avenin epitopes, oats are generally considered safe for most CeD patients[32–34].

b. Non-Gluten factors:

The development of celiac disease is not solely attributed to gluten, as other environmental factors are suspected to play a role[35], comprising gastrointestinal infections, medications, alpha-interferon administration, and surgical interventions, occurring at any stage of an individual's life[36]. In

particular, early life infections, such as*rotavirus*, have been identified as potential triggers for CeD, with some studies suggesting that *rotavirus* vaccination may protect against the disease[37][38]. Other infectious agents, such as *Helicobacter pylori*, *adenovirus*, *enterovirus*,have also been associated with CeD. The viral infectioninteracts with Toll-like receptor 3 (TLR3) may trigger gut inflammation, contributing to disease development. Although, the role of bacteria in CeD is still unclear, with limited cross-sectional studies available[35]. Mechanistic studies suggest that certain microbes may be involved, with evidence of cross-reactivity between gluten epitopes and bacterial peptides. It is proposed that microbial exposure could initiate an anti-gluten T-cell response[39]. Additionally, bacteria, such as *Pseudomonas aeruginosa*, have been shown to influence sensitivity to gluten in mice by generating T cell epitopes and upregulating inflammatory pathways[40].

3.3. Gut microbiota:

The rising prevalence of celiac disease suggests factors beyond genetics are at play. Recent research points to the gut microbiome, the community of bacteria in our intestines, as a potential culprit. Studies show alterations in the gut bacteria of CeD patients, with lower levels of beneficial bacteria like *Bifidobacterium*[41] and *Lactobacillus*[42], and higher levels of potentially harmful bacteria like *Bacteroides* and specific strains of *Escherichia coli*[43].

These changes might contribute to CeD in several ways. Some bacteria mimic gluten, triggering an immune attack[39]. Others release substances that promote gut inflammation or make the gut lining more permeable. Additionally, the microbiome can influence how gluten is digested, potentially producing harmful fragments[43]. Even the bacteria's metabolic products, like short-chain fatty acids(SCFAs) derived from fiber fermentation, seem to play a role in immune response and gluten tolerance[44]. Moreover, the presence of lipopolysaccharides (LPS) on certain gut bacteria

activates both innate and adaptive immune systems, leading to the production of the inflammatory molecule IL-15[45].

Overall, the evidence suggests the gut microbiome is not just a bystander in CeD, but potentially a key player in its development and progression. Understanding this intricate relationship could pave the way for new therapeutic approaches for this increasingly common condition.

3.4. Gluten movement from gut to tissue:

Gliadin, a gluten protein,disrupts the integrity of the intestinal barrier through multiple mechanisms.It loosens the intercellular tight junctions of epithelial cells, increasing gut permeability.This effect is triggered by gliadin binding to chemokine receptor 3, leading to zonulin release and disruption of interepithelial tight junctions.Gliadin also enhances paracellular permeability and causes an increase in gut mucosa permeability irrespective of disease status, immediately and transiently. Genetic studies have shown an association between certain tight junction genes and celiac disease[46].

Beyond paracellular pathways, gluten can breach the barrier directly (transcellularly) in individuals with established gluten intolerance. During the acute phase of CeD, the basolateral transferrin receptor CD71 is overexpressed on the luminal side of enterocytes, resulting in retro transcytosis(transported backwards) of secretory IgA-gliadin complexes. This allows harmful gliadin peptides to enter the lamina propria, perpetuating intestinal inflammation. The gluten immunogenic peptides (GIP) are resistant to degradation and can cross the defective epithelial lining, enter the bloodstream, and be excreted in urine[30].

3.5. Gut immune response:

Celiac disease unfolds in a coordinated dance between the body's innate and adaptive immune systems. In the first act, Key players in the innate immune response include cytokines such as IL-15 and interferon α, gliadin peptides inducing structural and signaling changes in enterocytes, and alpha-amylase/trypsin inhibitors activating the Toll-like receptor 4-MD2-CD14 complex pathway. These factors, along with zonulin-mediated barrier disruption and neutrophil activation, create a "perfect storm" leading to CeD enteropathy[30].

The adaptive immune responseinvolves a highly specific interaction between gluten peptides and HLA-DQ2/8-restricted T cells. Transglutaminase (TG) mediated deamidation of gluten and IL-15-driven imprinting influence this interaction. Activated T cells (CD41 TH1 cells) in the lamina propria release pro-inflammatory cytokines such as IFN-gand growth factors, inducing cryptal hyperplasia and villous blunting. Additionally, overexpression of IL-15 on enterocytes contributes to IEL activation. [36]. Moreover, the immune response can also occur outside of the gut, leading to extraintestinal manifestations of CeD [27].

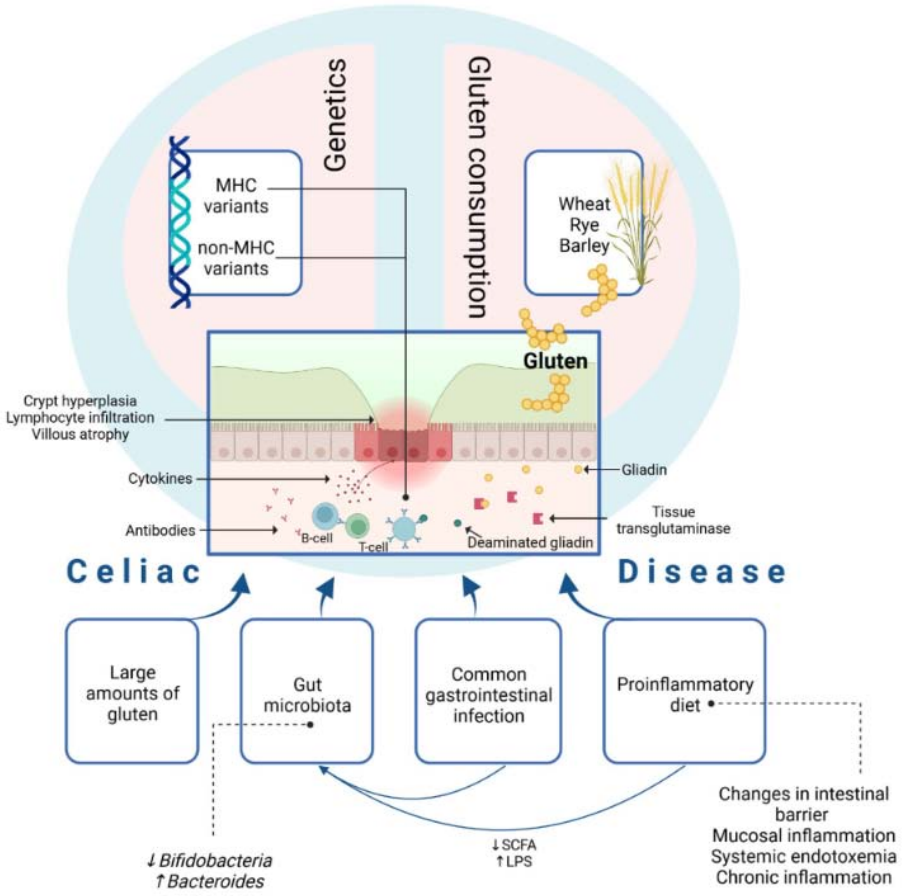

Figure 14: Pathogenesis of celiac disease.

*MHC-major histocompatibility complex; HLA-human leukocyte antigen; SCFA-short chain fatty acids;LPS-lipopolysaccharide.*In genetically predisposed individuals, exposure to gluten can trigger both cell-mediated and humoral immune responses, leading to characteristic pathological changes in the small intestine. These changes include crypt hyperplasia, lymphocyte infiltration, and villous atrophy. Tissue transglutaminase deaminates gliadin, a component of gluten, resulting in a heightened proliferative response by gliadinspecific T cells. This enhanced response ultimately leads to mucosal inflammation and activation of B cells, contributing to the clinical manifestations of celiac disease[47].

4. Immunology:

In the past two decades, routine serological tests have become a key tool, significantly increasing diagnoses of celiac disease. These tests detect related antibodies in individuals suspected of having CeD.While histological evaluation remains the gold standard for confirmation, some cases can be diagnosed based on serological results alone[48]. In the early 1980s, anti-gliadin antibodies were the first serological marker used to screen for CeD. However, due to their low accuracy, this test is no longer recommended. Its current role is limited to potentially identifying a subset of cases with non-celiac gluten or wheat sensitivity[49].

Currently, highly predictive and validated serological tests Including anti-tTGA, EMA, and DGP are used.CeD-related antibodies belong to IgA and IgG classes, but only IgA antibodies are highly specific for CeD. IgG markers (except DGP) are often misleading and should only be used for patients with IgA deficiency[48].

DGPs (deamidated gliadin peptides) play a crucial role in celiac disease. They bind strongly to HLA-DQ2 or DQ8 molecules on antigen-presenting cells of patients. This binding potently stimulates inflammatory T cells within the small intestine's mucosal lining, leading to the characteristic inflammation observed in CeD[26]. However, isolated positivity for IgA or IgG anti-DGP in low-risk individuals for CeD is predictive of CeD only in 15% of cases, being a false positive result in the remaining cases (85%)[50]. IgG DGPs are useful for identifying CeD in young children (<2 years old). On the other hand, IgA DGPsare not recommended for diagnosis[51]

The development of autoantibody testing revolutionized celiac disease diagnosis. Initially, tests targeted reticulin, followed by EMA (endomysial antibody), and finally the highly specific tissue transglutaminase (TG) antibodies. Identifying TG as the target antigen for IgA-EMA antibodies was a breakthrough[26].

TG antibody testing boasts impressive accuracy, with a sensitivity and specificity of around 95% for untreated celiac disease. Higher antibody titers in the test indicate a greater chance of a true positive result. The test utilizes a cost-effective and widely available enzyme-linked immunosorbent assay (ELISA) format. Compared to the less common radioimmunoassay (RIA), ELISA-TG tests offer superior sensitivity, specificity, reproducibility, and affordability. These advantages have propelled TG testing to become the gold standard for both diagnosing and monitoring celiac disease[52]. While the anti-TG test is the most sensitive, IgA-EMA offers the highest specificity. Therefore, serological testing typically starts with anti-TG[48]. If the anti-TG titer is low (less than twice the upper limit of normal), a confirmatory IgA-EMA test might be used. However, in such cases, a duodenal biopsy is often recommended for definitive diagnosis[53].

The revised ESPGHAN 2020 guidelines recommend two main diagnostic approaches for CeD detection depending on age. In children, both symptomatic and asymptomatic children can be diagnosed with CeD based on high anti-tTGA IgA levels (more than 10 times the cut-off) and positive EMA tests, without needing a duodenal biopsy or HLA typing. While high anti-tTGA IgA levels confirmed by positive EMA IgA tests correlate with villous atrophy, an intestinal biopsy remains mandatory for confirming CeD diagnosis in adults. Currently, a targeted case-finding approach focusing on at-risk groups is preferred over mass screening for CeD detection [48]

5. Histology:

For over five decades, small intestinal biopsies have been the cornerstone for diagnosing celiac disease. Even with the development of sensitive and specific serological tests, duodenal mucosal biopsies continue to be obtainedin the vast majority of patients for whom a diagnosis of celiac disease is being considered. To ensure optimal accuracy, biopsies require coordinated efforts and

information exchange between gastroenterologists, laboratories, and pathologists. This collaboration optimizes tissue sampling, preparation, and interpretation[54].

Interpreting biopsies for celiac disease can be challenging. Patchy involvement of the mucosal surface and the risk of false-positive or negative results can make diagnosis difficult. Therefore, it's crucial to take biopsies regardless of the endoscopic appearance. At least four specimens should be obtained from the distal (post-bulbar) duodenum and two from the duodenal bulb, as 13% of patients may only show abnormalities in this area. To ensure tissue integrity, using one biopsy per pass is the recommended endoscopic technique[55].

Clinicians play a vital role in accurate diagnosis by providing relevant clinical information when submitting tissue for histological evaluation, especially if their electronic medical records are not readily accessible to the pathologist. This information is extremely helpful for the pathologist to make a definitive diagnosis[56].

Taking enough biopsy samples and examining multiple sections (serial sectioning) are crucial for accurate diagnosis of celiac disease. Special attention is paid to the number of intraepithelial lymphocytes (IELs) in different scenarios:

- **Normal:** Occasional IELs (up to 25 per 100 enterocytes) are present mainly on the sides of the villi, decreasing towards the tips ("decrescendo pattern").
- **Celiac Disease (Normal Villi):** More than 25 IELs per 100 enterocytes are evenly distributed or concentrated in the villous tips (over 6 per 20 enterocytes).
- **Celiac Disease (Abnormal Villi):** IEL count is very high, almost always exceeding 40 per 100 enterocytes.

Importantly, a specific staining technique (CD3) is not routinely used for IEL counting. Pathologists should also be aware of unusual histological changes that might indicate other conditions and cautious when interpreting abnormalities near Brunner glands or lymphoid tissues[12].

Following these standardized guidelines for biopsy sampling, IEL counting, and histological evaluation helps improve the accuracy of celiac disease diagnosis.

The histological appearance of celiac disease can vary widely. It can range from a simple increase in intraepithelial lymphocytes (IELs) without villous atrophy (latent or asymptomatic form) to near-complete flattening of the villi (villous atrophy). This atrophy is often accompanied by increased IELs, compensatory growth of the crypts (hyperplasia), and a more cellular lamina propria (the connective tissue layer). The lamina propria may also show increased inflammatory cells, particularly IgA+ plasma cells. These findings can indicate silent or active disease [57].

Diagnosing CeD can be challenging, especially in children. It's often a multidisciplinary effort, and clinicians should be aware of the possibility of celiac disease. The degree of villous atrophy (VA) can vary significantly and should be assessed using a classification system like the Marsh-Oberhuber classification.

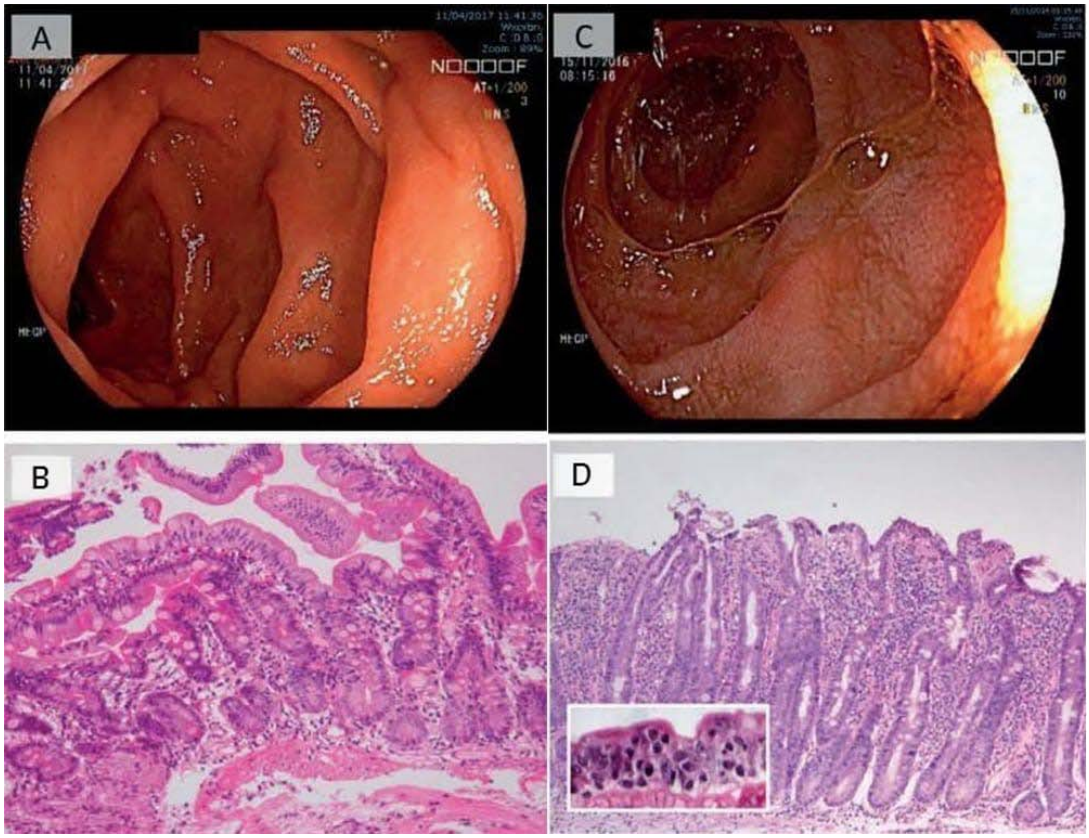

Figure 15: A: Normal endoscopic and morphological aspect of the duodenum. B: normal duodenal biopsy.C:endoscopic and morphological aspectof duodenum in celiac patient. D: duodenal biopsy of celiac patient with total atrophy, compensatory crypt hyperplasia and IEL>40% [57].

II. Epidemiological data:

1. Age:

Celiac disease has been observed to manifest at any age, including among elderly populations [58]. Nevertheless, recent prospective cohort studies have indicated that the majority of patients are diagnosed with celiac disease before reaching the age of 10 [59,60].

Our study observed a mean age of celiac disease diagnosis at 6.5 years old ± 4.18consistent with the findings of comparable studies.However, there are some variations in the data.Specifically, our findings demonstrate a higher mean age compared to the studiesofYafi [61], and Villanuevaetal.[62]. Conversely, the mean age reported by the other studies: OLIVEIRA et al.[63], Krauthammer etal.[64],Rizniket al. [65],andAlNababtehet al.[66]exceeded our observations.

While our study demonstrates closer alignment with some research in terms of mean age, the comparable standard deviations among studies imply similarities in the distribution of age patterns.

Table 13:Comparison of mean age according to the literature.

Author	Country	Year of publication	Time of study	Number of patients	Mean age ± SD (year)	Range
Yafi.I [61]	Marrakech, Morocco	2017	2015-2016	47	6.47±4.46	1-16
OLIVEIRA et al.[63]	Manchester, United Kingdom	2018	2014-2016	159	8.5±4.5	1-17
Villanueva et al.[62]	Chile,South America	2020	2010-2017	98	5.7±4.3	N/R
Krauthammer et al.[64]	Occupied Palestine	2021	1999-2018	932	7±4.2	1-18
Rizniket al. [65]	Central Europe	2021	2016	653	7	1-19
AlNababtehet al. [66]	Dubai, United Arab Emirates	2023	2018-2021	23	6.7±3.3	2.5-18
Our study	Marrakech, Morocco	2024	2021-2023	66	6.5±4.18	1-15

It is crucial to acknowledge that direct comparisons between studies might be subject to limitations imposed by diverse factors, including where the study was conducted, the specific

timeframe of data collection, the sample size involved, and potential discrepancies in diagnostic protocols employed.

2. Gender:

A 2021 systematic review[67] reported a higher prevalence of celiac disease in females compared to males (17.0 vs 7.8 per 100,000 person-years, pooled analysis). In line with this and other studies (Table 14), our study found a predominance of CeD in females, with 56.1% and a sex ratio of 0.78.

Females are more likely to develop celiac disease due to a combination of autoimmune susceptibility, X chromosome-linked genetics, and female-specific exposures like pregnancy and menstruation might contribute, potentially by affecting intestinal permeability[68]. The exact mechanism behind the observed female predominance in celiac disease remains unclear. Further research is needed to fully understand the relationship between gender and celiac disease.

Table 14: Sex-ratio by series.

Author	Country	Year of publication	Female n (%)	Sex ratio
OLIVEIRA et al.[63]	Manchester, United Kingdom	2018	109 (68.6)	0.45
Villanueva et al.[62]	Chile,South America	2020	63 (64.3%)	0.55
Dehbozorgi et al.[69]	Iran	2020	83(63.8%)	0.56
Krauthammer et al.[64]	Occupied Palestine	2021	585 (62.7%)	0.59
Alkhiari et al. [70]	Qassim, Saudi Arabia	2022	10(71.4%)	0.4
AlNababtehet al. [66]	Dubai, United Arab Emirates	2023	14 (61%)	0.64
Our study	Marrakech, Morocco	2024	37 (56.1%)	0.78

III. Clinical data:

The Oslo classification of celiac disease categorizes clinical presentations asclassic, non-classic, subclinical, potential and refractory[55]. However, in this thesis, we propose adopting a more relevant terminology based on symptom location: gastrointestinal/extraintestinal. This categorization reflects the two main clinical phenotypes of celiac disease, which can manifest individually (intestinal or extraintestinal) or concurrently [71].

1. Gastrointestinal symptoms:

In our study, the most common gastrointestinal symptom was transit disorder (41%), with diarrhea being the most frequent issue (29%). Constipation (9%) and alternating diarrhea-constipation (3%) were also observed. These findings are consistent with several studies in the literature, including those of Oliveira et al. (74.2%)[63], Villanueva et al. (76.5%)[62], Alkhiari et al. (71.4%)[70], Imran et al. (92.2%)[72], and Yafi I. (70.2%)[61], which all reported a high prevalence of transit disorder, often presenting as diarrhea, abdominal pain, abdominal distention, and vomiting followed in frequency.

In contrast, Dehbozorgi et al.[69] and Riznik et al.[65] found abdominal pain to be the predominant intestinal manifestation, with prevalences of 86% and 41.2%, respectively.

2. Extraintestinal symptoms:

Multiple studies[73–76]demonstrate a shift in the clinical presentation of celiac diseaseover recent decades. The classic symptoms of malabsorption, such as diarrhea and abdominal pain, are becoming less frequent. Conversely, extraintestinal presentations or even a complete absence of symptoms are on the rise.

This trend is reflected in our present study, where growthretardation was the primary reason (62%) for screening children for CeD.This finding aligns with Yafi's study [61]as well. As noted by AlNababteh et al. (2023) [66], gastrointestinal malabsorption associatedwith CeD can lead to nutritionaldeficiencies, ultimatelycontributing to stuntedgrowth and lowerweight in childrencompared to theirpeers.

Supporting this observation, researches conducted by Oliveira et al. (2018)[63], Villanueva et al. (2020)[62], and Imran et al. (2021)[72] identify growth retardation as the most prevalent extraintestinal manifestation of CeD.

Beyond growth concerns, we noted a variation in the prevalence and type of extraintestinal symptoms across different countries. Pallor and anorexia were the most frequent after growth delay in our study, similar to findings reported inCentral Europe[65] and United Kingdom[63]. However, studies from Pakistan[72] and Iran[69] reported a higher frequency ofarthralgia and skin/hair disorders.

These variations suggest potential differences in diagnostic practices between countries. Some symptoms may be more readily assessed at some centers compared to others, as noted by Lundin et al. (2021)[77].

3. Celiac disease and associated pathologies:

In patients with CeD, an increased prevalence of other autoimmune diseases has been observed, mainly due to a common genetic background [78,79].

Our findings are in accordance with existing literature, demonstrating Type 1 Diabetes (T1D) as the most frequent comorbidity in CeD patients [66,69,70].Previous studieshave indicated that T1D is often diagnosed before CeD.Additionally, our data revealed a prevalence of Hepatic Cytolysis at 4.5%,

mirroring the findings of Dehbozorgi et al. (2020) [69]who reported a prevalence of 3.1%.Other studies, including those of Alkhiari et al. [70]and AlNababteh et al.[66], have identified Hypothyroidism as another frequent comorbidity following T1D.

IV. Paraclinical data:

1. Biological signs:

Anemia is a well-documented biological finding reported in CeD worldwide.It has been observed that low hemoglobin may persist even after a year of a gluten-free diet[80,81].

In our study, all participants had a full blood count at diagnosis.Anemia,defined by age-appropriate hemoglobin levels for children,was identified in 53% of the patients. This prevalence was high and comparable to available data, where reported rates range from 8% to 93%[61,62,64,75]. Notably,a prospective study by Javed et al., documentedsevere anemia requiring blood transfusions in 26% of 323 children with CeD[75].

Unfortunately, ferritin levels were only measured in 46.9% of our participants, and 45%of themhad a low level.This limits our ability to definitively determine the prevalence of iron deficiency within our study population. However, a retrospective study driven bykrauthammer et al. , reportediron deficiency in 70% of CeD patients[64].

Our investigation identified hypocalcemia (11%) and hypoproteinemia (11%) as potential manifestations of micronutrient malabsorption in CeD patients. These findings align partially with those of Alkhiari et al., who observed hypocalcemia and hypoproteinemia in 3.2% and 40.3% of their patients, respectively[70].

Vitamin D deficiency, as another potential nutritional deficit, was not directly assessed in our study participants. Nonetheless, a wide range of vitamin D deficiency prevalences was reported in CeD patients, ranging from 20.4% to 77% across various studies[63,64,66,70].

2. Immunological tests:

Immuno-serological tests are valuable tools for diagnosing and monitoring celiac disease. These tests can identify patients at risk for the disease, help determine who needs an intestinal biopsy, and track adherence to a gluten-free diet. They detect auto-antibodies that target two main antigens: Transglutaminase (anti-TG) and Gliadin.Anti-tissue transglutaminase (anti-TG) and anti-endomysium (EMA) antibodies are highly sensitive and specific for CeD[73].While traditional antigliadin antibodies are no longer recommended due to low accuracy, antibodies against deamidated gliadin peptides (DGP) offer similar efficacy toanti-TG antibodies in detecting CeD[73,82].

In our population, anti-transglutaminase antibody testswereperformed in allcases, tTGA-IgA antibodies were positive in 82% of patients. This aligns with previous researchby Oliveira et al.[63] and Saeedet al.[83]. Only the study by Jansen et al.[84] reported a slightly lower prevalence of positive tTGA-IgA antibodies at 65%.

The antibody levels themselves varied,with 55% of patients showed very high titers (over 10 times the cut-off), and 18% with low titers (under 3 times the Upper Limit of Normal).This finding isconsistent with existing literature on the high prevalence of high antibody titers in CeD[66,72,77,84,85].

Our study found a sensitivity of 97.2% for tTGA-IgA antibodies, which is comparable to results from Bekdas et al. (98.7%)[86], Ciao et al. (96.8%)[30], and Al-Toma et al.(98%)[26].However, it's important to note, that this sensitivity can be lower in children under two years old. Therefore, testing for IgG-

deamidated gliadin peptide (DGP) antibodies in addition to IgA anti-TGA is recommendedfor this age groupto increase diagnostic sensitivity ofthe disease[87,88].

Our findings,supported byexistingliterature[67,71]suggest that measuring tTGA-IgA antibody concentration is a strong candidate for the first-line screening test for CeD.This recommendation is based on its high sensitivity, and its high negative predictive value. Additionally, compared to measuring endomysial antibodies (EMA), the tTGA-IgA test offers a less expensive option[89].

Selective IgA deficiency, a condition where individuals have low levels of IgA antibodies, is relatively common in CeD. In our study, 32% of the children underwent total IgA testing, with 12% showing low IgA levels.

To avoid false-negative results when using IgA-based serological tests for CeD, it's crucial to measure total IgA levels alongside the IgA-based test. In cases of IgA deficiency, alternative serological tests can be employed. These include tTGA-IgA, IgG-EMA, and IgG-deamidated gliadin peptide tests[11,83,89,90].

For patients without IgA deficiency, a negative tTGA-IgA test result holds a high negative predictive value, particularly when the initial suspicion of CeD is low or moderate[24]. This means that celiac disease can be confidently ruled out in such scenarios.

Measuring total IgA levels alongside IgA-based serological tests for CeD is crucial to avoid false-negative results, especially in individuals with a higher risk of selective IgA deficiency. This approach ensures a more accurate diagnosis of CeD.

3. Histological results:

Despite some challenges, examining small intestinal tissue through biopsy plays a critical role in diagnosing and managingCeD. Biopsy is especially crucial since nearly 40% of children with CeD might have a normal-appearing duodenum on endoscopy.Characteristic changes in the small intestine during active CeD include increased intraepithelial lymphocytes, inflammatory infiltration in the lamina propria, and changes in enterocyte appearance. The Marsh-Oberhuber classification system is commonly used to grade CeD based on histologic findings. Biopsy interpretation can be challenging due to patchy involvement of the mucosal surface and the potential for false positive or negative results. Adequate biopsy sampling and examination of serial histologic sections can help alleviate challenges in interpreting villous architecture in CeD diagnosis[10].

An analysis of biopsy samples revealed that nearly half (49%) of our patients displayed a modified Marshgrade 3. This breakdown further showed15% with Marsh 3a, 20% with Marsh 3b, and 14% with Marsh 3c. This aligns with findings from other studies, which have also reported a high prevalence of advanced histopathological changes in celiac disease patients.

For instance, studies conducted in the United Kingdom[63] and South America[62] reported that 73% and 89% of patients, respectively, presented modified Marsh grade 3 enteropathy. Similarly, research from Iran [69] andNorway[77]demonstrated a similar distribution of modified Marsh 3 grades (<90%), with comparable proportions of 3a, 3b, and 3c.

However, some regional variations emerged. Studies from Qassim, Saudi Arabia[70] and the Netherlands[84] showed a predominance of modified Marsh grade 3a, while those from Turkey[86] and the United Arab Emirates [66]found modified Marsh grade 3b to be more prevalent. Conversely, the study conducted in Riyadh, Saudi Arabia[83]reported a higher number of patients with Marsh grade 3c.

It is essential to recognize that some studies have observed a correlation between the severity of gastrointestinal symptoms and the grade of mucosal damage. Patients with predominantly gastrointestinal symptoms tend to have higher grade histopathology compared to those with extraintestinal presentations, where earlier grades are more common[72,86,91].

This emphasizes the need to consider a combination of clinical presentation, serological testing, and histological findings for a comprehensive diagnosis of CeD.

V. Correlation between antibody titers with clinical, biological, and histopathological results:

1. Correlation between tTGA-IgAtiters and clinical symptoms of celiac disease:

Our study found a significant correlation between high levels of tTGA-IgA antibodies and different clinical symptoms in celiac patients.Among gastrointestinal symptoms, patients with high tTGA-IgA titers frequently reported abdominal bloating (70.6%), followed by vomiting (66.7%) and transit disorders (59%). Throughout extraintestinal symptoms,dehydration affects 85.7% of patients with high tTGA-IgA levels. Additionally, growth retardation (61%) and a combination of anorexia and malnutrition (66.7%) were observed in a significant portion of these patients.

These findings align with Mubarak et al. who reported a similar association between high transglutaminase values and extra-intestinal manifestations in CeD[92]. Besides, Donaldson et al. highlighted the high accuracy of antibody testing, particularly inclinically symptomatic individuals [93].

Furthermore, Alkhiari et al.[70] and Saeed et al.[83] observed a significant link between higher tTGA-IgA levels and clinical symptoms of patients, and Saeed et al. reporting a 91.5% positivity rate

for anti-tTGA in both GI and non-GI patients[83]. Similarly, Imran et al.[72]found a significant elevation of tTGA-IgA titers in 80% of symptomatic patients.

However, it's important to acknowledge conflicting findings. Studies by Ziv-Baran et al. (2021) and Dehbozorgi et al. (2020) did not find a correlation between anti-tTGA titers and specific clinical manifestations in children with CeD[69,94].

While some studies, including those by Abdul Aziz et al., Bekdas et al. , and Imran et al. , suggest a higher prevalence of gastrointestinal symptoms in patients with severe intestinal damage[72,86,91]. On another note, Almallouhi et al. reported no significant association between the degree of villous atrophy and the type of clinical presentation[76].

These findings highlight the complexity of the relationship between anti-tTGA antibody levels and clinical symptoms in CeD. Further research is needed to better understand these variations and refine diagnostic approaches.

2. Correlation between tTGA-IgA titers and biological signs of malabsorption:

Our study did not reveal a statistically significant correlation between anti-tTGA antibody titers and biological signs in celiac patients. For instance, although anemia was present in 46.1% of patients with high tTGA-IgA titers, there was no statistically significant association.

This finding is somewhat in contrast to previous research. In fact, a recent study by Ziv-baran et al. [94]observed a positive correlation between anti-tTGA titers and various markers of CeD in children, including anemia, as well as that of Rajalahti et al. [81].

Similarly, Taneja et al.[95] reported a significant inverse correlation between hemoglobin levels and rising anti-tTGA antibody titers using Pearson's coefficient correlation.

These contrasting findings highlight the need for further investigation into the relationship between anti-tTGA antibody titers and biological signs in CeD.

3. Correlation between tTGA-IgA titers and histopathological grade (Marsh-Oberhuber classification):

Our study found a clear link between the severity of intestinal damage and anti-tTGA antibody levels. Patients with total or subtotal villous atrophy (Marsh 3b or 3c) had significantly higher tTGA titers compared to those with partial atrophy (Marsh 3a). This finding aligns with numerous other studies on both children and adults [8,61,86,88,93,94,96-104]. These studies consistently demonstrate a positive correlation between the degree of duodenal damage and elevated tTG antibody levels in the blood.

The classical algorithm for the diagnosis of CeD in both children and adults involves performing an esophagogastroduodenoscopy (EGD) with duodenal biopsies when symptoms of malabsorption or conditions related to CeD are present. However, advancements in reliable antibody testing have allowed for a combined diagnostic approach[105]. In 2016, The North American Society for Pediatric Gastroenterology Hepatology and Nutrition (NASPGHAN) recommended biopsies for all cases of suspected CeD in children[106](Table 15), while the European Society for Pediatric Gastroenterology Hepatology and Nutrition (ESPGHAN)guidelines suggested that intestinal biopsies may be avoided for symptomatic children meeting tTGA IgA levels $\geq$10 x upper limit of normal (confirmed with a positive EMA antibody in a different blood sample). This biopsy-free approach has been implemented in Europe since 2012 and was updated in 2020 to potentially include asymptomatic children without HLA

testing. The decision to pursue a non-biopsy diagnosis must be agreed upon by the family[11,105](Table 15). This strategy could reduce the need for EGD by 30-50% in practice[107].

In the United States, information on non-biopsy diagnosis of CeD is limited. The American College of Gastroenterology(ACG) recommends screening with celiac antibody testing followed by biopsy in populations with a low prevalence of CeD (<5%). However,for symptomatic patients with a high pretest suspicion for CeD, an upper gastrointestinal endoscopy with duodenal biopsy is still recommended regardless of serologic results [108](Table 15). This recommendation considers factors such as the imperfect sensitivity of serology, the risk of verification bias in studies assessing CeD testing, the possibility of seronegative CeD, and the need to rule out other enteropathies[90,109].

Table 15: Comparison of diagnostic guidelines for pediatric CeD published by NASPGHAN, ESPGHAN, and ACG.

	NASPGHAN Guidelines[106]	ESPGHAN updated guidelines[11]	ACG Guidelines[108]
Publication date:	2016	2020	2023
Target population:	Symptomatic patients (presenting with GI and non-GI signs) and asymptomatic patients at risk for celiac disease.		
Recommended First-line testing:	Anti-tTGAIgA	Anti-tTGAIgA with total IgA	Anti-tTGA IgA
Non-biopsy diagnosis criteria:	Not indicated	tTGA-IgA >10x ULN with positive anti-EMA	Not indicated
Indication of biopsy:	1. Positive tTGA. 2. Negative serology but high clinical suspicion for CeD. 3. Patients with inconclusive serology results.	1. Positive tTGA-IgA <10 ULN. 2. tTGA-IgA ≥ 10 ULN with negative anti-EMA. 3. Positive IgG isotype for any autoantibody in IgA deficient individuals.	Patients with suspicion of CeD.

In response to the limitations on endoscopies during the COVID-19 pandemic, the British Society of Gastroenterology (BSG) advocated for a non-biopsy approach to diagnosing CeD in patients younger than 55. This method relies solely on serological testing[110].

Our study investigated the effectiveness of anti-tTGA antibody levels for identifying patients with severe intestinal damage (Marsh 3 lesions). We found that an anti-tTGA level exceeding 10 times the upper limit of normal (ULN) had a sensitivity of 84%, specificity of 74%, positive predictive value (PPV) of 75%, and negative predictive value (NPV) of 84% for detecting Marsh 3 lesions. These results align with the findings of Meena et al.[111], who studied 66 children with celiac disease. This study showed that high anti-tTGA titers had a perfect predictive value (100%) for identifying patients with intestinal changes. These findings support the potential of a non-biopsy approach for diagnosing the disease.

Wang et al. (2023) further investigated the diagnostic potential of anti-tTGA antibody levels and found that when these levels were at least five times the upper limit of normal (>5xULN), they offered good accuracy in diagnosing celiac disease, with a sensitivity of 83.9% and a specificity of 92.9%. Interestingly, a higher cut-off of eight times the ULN yielded even greater specificity (90%) for identifying villous atrophy, although with slightly lower sensitivity (67.9%)[112]. Therefore, their findings supported the strong predictive value of anti-tTGA levels, particularly when exceeding 10 times the ULN, for diagnosing celiac disease. This paves the way for combining anti-tTGA levels with clinical judgment to potentially reduce the need for invasive endoscopies.

A study in New Zealand involving 136 children found that using either a very high anti-tTGA IgA level (at least 10 times the upper limit of normal) alone or this level test combined with a positive EMA resulted in a 100% positive predictive value for diagnosing celiac disease. This non-biopsy

approach could have identified celiac disease in 18% (19 out of 103) of the children studied[113]. These findings add to the growing body of evidence supporting the potential for skipping biopsies in very high anti-tTGAlevels of children.

In children with both type 1 diabetes and potential celiac disease, studies by Wessels et al. (2020) and Joshi et al. (2019) suggest high anti-tissue transglutaminase antibody levels may be useful for diagnosing celiac disease without needing biopsies[85,114]. In the Joshi et al. study, all T1D patients with CeD who had both a biopsy and an anti-tTGA level exceeding 60 U/mL (56 out of 68 patients) had confirmation of CeD through the biopsy. This non-biopsy approach using anti-tTGA tests has the potential to reduce healthcare costs by eliminating unnecessary endoscopies and hospital admissions, while also avoiding the risks associated with anesthesia.

Our findings are further supported by Maglio et al. (2020), who explain the essential role of anti-tTGA antibodies. These antibodies, produced by the immune system in response to gluten exposure, contribute to intestinal damage in celiac disease. Their research aligns with our results, demonstrating that anti-tTGA antibodies produced in the small intestine increase during active disease, leading to intestinal injury. This connection strengthens the observed correlation between high serum anti-tTGA levels and the severity of celiac disease as seen in biopsies[52].

This aligns with the strong and consistent correlation observed in our study and a 2023 meta-analysis by Qureshi (analyzing 13 studies) between high serum anti-tTGA levels and the severity of celiac disease as revealed through biopsies.He compared anti-tTGA levels across different grades of the Marsh classification. He found that higher antibody levels consistently corresponded with greater degrees of mucosal atrophy across all Marsh grade comparisons. This finding underlines the potential of anti-tTGA antibody tests as a valuable tool for assessing celiac disease severity[115].

High anti-tTGA antibody levels are promising for a biopsy-free celiac disease diagnosis due to their association with severe intestinal damage (Marsh III). However, conditions like giardiasis can mimic CeD symptoms and serology, making biopsies crucial for differentiation as shown in a Rai et al. study (2022)[116]. To address this challenge, Taneja et al. (2021) suggest a simple stool microscopy for children with high anti-tTG levels to rule out giardiasis potentially avoid unnecessary biopsies for CeD patients[95].

While our study found a strong link between high anti-tTGA antibody levels and severe intestinal damage, some patients with Marsh IIIa had lower antibody levels (<10 ULN). This might be due to variations in gluten intake or the immune response of these patients. It highlights the importance of assessing gluten intake before interpreting antibody levels. Similarly, 6 (20%) patients with normal biopsies (Marsh 0) had high antibody levels, potentially because biopsies can miss patchy intestinal damage. As shown in our study and by Taneja et al., where some patients with Marsh III had low antibody levels, and by Saeed et al., where some patients with high antibody levels had normal biopsies[83,95].

Although the high accuracy of serology tests and Europe's experience with skipping biopsies in symptomatic children suggest a promising alternative for diagnosing celiac disease, limitations exist. The lack of standardized anti-tissue transglutaminase tests can lead to misdiagnosis if strict criteria aren't followed. Additionally, relying solely on a single antibody level threshold to identify who can avoid biopsies might not be ideal. Encouragingly, new research suggests that using different commercially available serology tests along with individual risk factors might still provide accurate diagnoses [117–119]. This highlights the importance of standardizing these tests, both in interpreting results and their strength. Unfortunately, achieving complete standardization is difficult due to

variations in test components, lab procedures, and platforms. These inconsistencies raise questions about the sole reliance on antibody levels for diagnosis[10].

Researchers are actively exploring the potential of blood tests to diagnose and monitor celiac disease. These tests would eliminate the need for intestinal biopsies, a more invasive procedure. Initial findings on biomarkers like plasma citrulline and I-FABP show promise in predicting villous abnormalities[98,120-122]. However, further validation is needed before they can be routinely used in clinical practice.

Despite all this debate, we concluded that biopsy could be reasonably avoided in the diagnosis of coeliac disease with reliable suspicion of coeliac disease and high serum tTGA-IgA,a biopsy would still be required for confirmation among patients with a lesser increase in tTGA titer and no improvement in symptoms following Gluten-FreeDiet.

4. Correlation of villous atrophy and intraepithelial lymphocyte rates:

Villous atrophy and intraepithelial lymphocyte (IEL) rates are both key histological features observed in celiac disease.Our study found that patients with subtotal or total villous atrophy had a significantly higher rate of intraepithelial lymphocytes (IELs) exceeding 40 compared to those with partial atrophy ($p=0.005$).

Indeed, research suggests that an increase in IELs contributes to predicting the progression towards villous atrophy[11].

Moreover, studies have shown a positive correlation between the severity of villous atrophy and the number of intraepithelial lymphocytes present in the small intestine of individuals with celiac disease. This means that as the villi becomes more flattened and damaged, the number of IELs in the

epithelium also tends to increase. Increased IELs are believed to be part of the immune response triggered by gluten in celiac disease[61,123,124].

It's important to note that the correlation between villous atrophy and IELs isn't always perfect. Some studies have reported cases with severe villous atrophy despite having a moderate IEL increase. However, other factors besides IELs can also contribute to villous damage[123,125,126].

In conclusion, a generally positive correlation exists between villous atrophy and IEL rates in celiac disease, suggesting the immune response plays a role in developing intestinal damage. Despite this, the correlation isn't absolute, and other factors might also be involved.

5. Correlation between tTGA-IgA titers and intraepithelial lymphocyte rates:

It's important to note that lymphocytic infiltration, also known as lymphocytic duodenosis (defined as more than 25 IELs per 100 epithelial cells), is relatively common in the general population, with a reported prevalence of 5.4% and potentially increasing. While most individuals with lymphocytic duodenosis do not have celiac disease, a workup to rule out CeD is still recommended[108].

Our study found a significant correlation between the level of intraepithelial lymphocytes (IELs) and the titers of transglutaminase antibodies (tTGA-IgA). However, the IEL count was>40 in patients with high tTGA-IgA titers (90.5%) compared to those with moderate and low titers ($p<0.05$).

Studies have shown thatcorrelation between lymphocytic duodenosiswith celiac disease associated serologic and/or genetic tests may be considered[9,108,127].Symptoms like diarrhea and weight loss occur at similar rates in patients with lymphocytic duodenosis and CeD. However, anemia, skin problems, positive tTGA-IgA results, and the presence of the HLA DQ2 genotype were more

frequent in patients with CeD[108]. Other factors can also contribute to lymphocytic duodenosis, including Helicobacter pylori infection, certain medications (e.g., nonsteroidal anti-inflammatory drugs), small intestinal bacterial overgrowth, non-celiac wheat/gluten sensitivity, and systemic autoimmune diseases[9].

Interestingly, research suggests that persistent IEL elevation can occur in up to 56% of patients with treated CeD, even if their villous architecture appears normal. The only factor associated with this finding was oat consumption [108].

Furthermore, a study of 43 children with lymphocytic duodenosis but no prior CeD diagnosis, evaluated at a referral center, found that only 10% were ultimately diagnosed with CeD[9,10]. These findings highlight that the increase in IELs, in the absence of villous atrophy, is sensitive but not specific to CeD, and other potential causes should be investigated.

VI. Limitations of the study:

The study dealt with all the constraints of a retrospective study based on the collection of data from files. The quality of the data was affected by the lackor insufficiency of some important information. Some files had missing pages, while others had a lot of information gaps.

Our laboratory's capabilities also limited the scope of the study. Anti-endomysial antibody (EMA) testing and HLA typing were rarely performed, both of which can be valuable tools in diagnosing or eliminating celiac disease. There were several reasons for not performing EMA and HLA typingas these tests are expensive and they were not always readily available at our local healthcare center. At the time, these tests were not considered essential for diagnosis according to prevailing practices.

Intestinal biopsy findings were not re-examined. Therefore, possible operator and pathologist biases cannot be excluded.Additionally,since it is a single-center observational study covering a small population, a largermulticenter observational study would enable us to analyze the influence of other variables on histopathological changes and anti-tTGA antibody titers.

Finally, A prospective study design is recommended for a more robust analysis. Following patients with suspected celiac disease from the time of diagnosis would allow us to assess the true incidence of asymptomatic patients and to validate the correlation between high anti-tTGA titers and positive duodenal biopsy results.

By addressing these limitations in future studies, we can gain a deeper understanding of celiac disease and improve diagnostic accuracy.

VII. Recommendations:

Our study has provided a comprehensive understanding of celiac disease in children within our specific context. We have highlighted the characteristic symptoms and the correlation between serological testing, clinical presentation, biological markers, and histopathological findings in diagnosing celiac disease. Based on our findings and a review of the literature, we propose the following steps to improve diagnostic accuracy and minimize the need for invasive biopsies:

Initial serological testing for Children:

- In the initial screening of children suspected of celiac disease, we recommend themeasurement of IgA-tTGA antibodies. It is important to note that the IgA-TGA antibody remains the preferred single test for CeD detection in patients of all ages, while endomysial IgA testing can be used as an alternative, antibodies directed against native gliadin (AGA) and deamidated gliadin peptides (DGP) are not recommended for initial diagnosis.
- **For optimal patient management**, we recommend the inclusion of regular celiac disease screening for individuals diagnosed with Type 1 diabetes.

Serological Testing Considerations:

- Tissue Transglutaminase-IgA (TGA-IgA) antibody levels significantly exceeding ten times the upper limit of normal offer strong diagnostic accuracy for identifying active celiac disease, hence potentially eliminating the need for biopsy.

- In cases where celiac disease is suspected despite negative serological test results, the measurement of total immunoglobulin A levels is recommended.
- For patients diagnosed with selective IgA deficiency, IgG-based testing (targeting deamidated gliadin peptides [DGPs] or tissue transglutaminase [tTG]) is recommended during celiac disease evaluation. A positive IgG-DGP or IgG-TGA antibody test result in this context suggests celiac disease with selective IgA deficiency, rather than seronegative celiac disease.
- To ensure reliable serological test results for CeD diagnosis, it is crucial that all testing be conducted during a period when patients are consuming a gluten-containing diet.

Duodenal Biopsy Considerations:

- In cases of persistent or relapsing symptoms suggestive of celiac disease, with no identifiable alternative etiology and negative serological test results, endoscopic biopsies are recommended to assess mucosal healing, even if endoscopic examination reveals a normal-appearing duodenum.
- In instances where discordance exists between tissue transglutaminase-IgA (tTGA-IgA) serological results and histopathological findings, a reevaluation of the biopsy specimens and/or consultation with an experienced pathologist is recommended.
- For optimal diagnostic accuracy during a gluten-containing diet, a minimum of four biopsies from the distal duodenum should be obtained for histological evaluation. Additionally, at least two biopsies from the duodenal bulb are recommended.
- The presence of isolated intraepithelial lymphocytosis (IEL) infiltration (Marsh 1) is not a specific diagnostic indicator for celiac disease. Further investigation is necessary to rule out alternative etiologies.

CONCLUSION

Celiac disease is a prevalent autoimmune disorder affecting the small intestine. It manifests with diverse clinical presentations, particularly in children, where early diagnosis is crucial to prevent severe and irreversible complications.

Our study highlighted the diverse clinical presentations and biological markers of pediatric celiac disease that should be considered regardless of age. The most prevalent clinical features were gastrointestinal (transit disorders and abdominal pain) and extra-intestinal (growth retardation and pallor). Type 1 diabetes was the most common associated disease. Anemia was the most frequent laboratory finding.

This study demonstrates a significant positive correlation between anti-TGA antibody levels and clinical symptoms. Children with pronounced symptoms had higher anti-TGA titers.We also found a strong association between anti-TGA antibody levels and the severity of duodenal mucosal lesions. Anti-TGA titers exceeding ten times the upper limit of normal (ULN) weresignificantly associated with modified Marsh grade greater than two, potentially allowing renunciation to biopsy in such cases.

Increased awareness of Celiac disease among clinicians can facilitate early diagnosis and management, leading to improved symptom management and nutritional status.

Overall, this study contributes to a better understanding of CeD in Moroccan children, potentially aiding in earlier diagnosis and improved management for this population.

APPENDIX

APPENDIX I: Medical sheet summary

(Patient's information summary):

I. Patient Identity:

1.**Full name:**

2. File number:

3. Entry Age:

4. Gender: female ☐male ☐

5. Admission date:

6. Phone number:

II. CeD Anamnesis:

1. Personal history:

- Feeding: Breastfeeding ☐ Formula feeding ☐ Mixed feeding ☐
- Age of introduction of gluten:
- Teething age in months:
- Associated pathology:

2**. Family History**:

- – Consanguinity: ☐YES ☐ NODegree of Consanguinity:
- – Similar cases in the family: ☐ YES ☐ NOThe relationship:

3. **Signs of CeD:**

- Transit disorder ☐ YES ☐ NO
- Abdominal bloating ☐ YES ☐ NO
- Abdominal pain ☐ YES ☐ NO
- Anorexia ☐ YES ☐ NO
- Vomiting ☐ YES ☐ NO

- Dehydration☐ YES ☐ NO
- Growth retardation ☐ YES ☐ NO
- Others:

III.CeD clinical examination:

- Weight (kg):
- Size(cm):
- Pallor☐ YES ☐ NO
- Dehydration☐ YES ☐ NO
- Malnutrition☐ YES ☐ NO
- Abdominal distension☐ YES ☐ NO
- Edema☐ YES ☐ NO
- Integumentary disorders☐ YES ☐ NO
- Arthralgia☐ YES ☐ NO
- Neurological manifestations☐ YES ☐ NO
- Others:

IV. CeD paraclinical examination:

1. **Complete blood count (CBS):**
   - Hb (g/dl):
   - Mean cell volume (MCV) (fl):
   - Mean cell hemoglobin (MCH):
   - White blood cells (WBC) (mm3):
   - Platelets (mm3):
2. **Serum electrolytes test:**
   - Calcium (mg/l):
   - Sodium (mmol/l):
   - Potassium (mmol/l):
3. **Kidney function test:**
   - Urea (g/l):
   - Creatinine (mg/l):
   - Protein (g/l):
4. **Lipid test (g/l):**
5. **Ferritin Test:**

6. **Erythrocyte sedimentation rate (ESR):**
7. **Hemostasis tests**:
    - Prothrombin Time:
    - Activated Partial Thromboplastin Time (APTT):
8. **Chest-X ray:**
9. **Bone age**:

V. Serology:

tTGA_ IgA	tTGA_ IgG	DGP_ IgA	DGP_ IgG	EMA	total IgA

VI. Jejunal biopsy:

Intraepithelial lymphocyte (IEL)	Crypts	Villi	The modified Marsh-Oberhuber classification

VII. HLA genotyping:

- HLA DQ2/ HLA DQ8:

VIII. Treatments:

- gluten-free diet:☐ YES ☐ NO
- blood transfusion:☐ YES ☐ NO
- Iron:☐ YES ☐ NO

IX. Evolution:

1. **Short-term:**
   - Normalization of transit:☐ YES ☐ NO
   - Gain of weight and size☐ YES ☐ NO
   - Negative serology☐ YES ☐ NO
   - Histological repair☐ YES ☐ NO
   - Therapeutic non-compliance☐ YES ☐ NO
   - Relapse☐ YES ☐ NO
2. **Long-term:**
   - Appearance of malignant pathology:☐ YES ☐ NO
   - Appearance of an autoimmune disease:☐ YES ☐ NO
   - Osteopenia:☐ YES ☐ NO

ABSTRACT

Abstract:

Introduction: Celiac disease is an immune-mediated systemic disorder triggered by gluten consumption, occurring in genetically predisposed individuals. It is characterized by clinical polymorphism, with intestinal and extra intestinal forms. Diagnosis involves serological tests for IgA anti-tissue transglutaminase antibodies and examination of a small intestinal biopsy. This study investigated celiac disease in a Moroccan pediatric population, looking at clinical symptoms, biological signs, immune response, tissue damage, and serological tests and their relationshipwith those factors.

Patients and Methods: Our study involveda cross-sectional retrospective study at the Mohammed VI University Hospital of Marrakech from July 2021 to July 2023. Data from 300 patients with CeD were collected. All patients diagnosed with celiac disease aged 16 years or younger, and who have done serological tests and jejunal biopsy were included in this study. Patients older than 16, those without confirmed diagnosis through tests, and those with unavailable medical records were excluded. Children already on a gluten-free diet for over 6 months were also excluded. The tTGA IgA level was measured in CU/mL and was labeled as negative (<20 CU/mL) or positive (≥ 20 CU/mL) based on the cutoff value. Intestinal biopsy findings were identified using Marsh-Oberhuber classification stages.

Results: Sixty-six children diagnosed with celiac disease met the inclusion criteria. The mean age of our sample was 6.5 years (1-15 years),with a slight female predominance (56.1%, sex ratio 0.78). The most common presenting features were gastrointestinal symptoms like diarrhea (41%) and

abdominal pain (33%). Extra-intestinal manifestations included growth retardation (62%) and pallor (40%) which were more prevalent. Type 1 diabetes was the most frequently associated disease (30%). Blood tests revealed anemia (53%) and low cholesterol (32%), both of which were the most prominent abnormalities detected in celiac patients.Anti-tissue transglutaminaseIgA antibodies were positive in 82% of patients, with high, moderate, and low titers in 55%, 9%, and 18% respectively. The test demonstrated high sensitivity (97.2%) and negative predictive value (NPV) of 91.6%. Histological evaluation using the modified Marsh classification revealed varying degrees of intestinal damage. Marsh 0 (normal villi) was observed in 45% of patients, while Marsh 2 was present in 4.5%. The remaining patients exhibited varying degrees of villous atrophy: Marsh 3a (15%), Marsh 3b (20%), and Marsh 3c (14%). A significant correlation was noticed between high tTGA-IgA levels and clinical symptoms. Patients with high antibody titers had a higher prevalence of diarrhea (57.9%), abdominal bloating (70.6%), vomiting/anorexia (66.7%), and growth retardation (61%). However, no significant correlation was found between serological markers and biological signs of malabsorption. Interestingly, high tTGA-IgA titers were more prevalent in patients with advanced villous atrophy (100% in Marsh 3b and 3c), while Marsh 0 and 2 biopsies were associated with low or negative antibody levels. Additionally, increased intraepithelial lymphocytes (IELs) within the intestinal lining showed a significant association with higher antibody titers and villous atrophy.

Conclusion: Our findings suggest that positive anti-tissue transglutaminase antibody tests, particularly those with high titers (10 times the ULN), could potentially be used to diagnose celiac disease in symptomatic patients without a biopsy. However, larger prospective studies are needed to validate this approach. These studies should involve collecting duodenal biopsies according to recommended protocols,withan interpretation by experienced pathologists. Biopsy may still be

necessary for patients who do not improve on a gluten-free diet or those with mildly or moderately elevated tTGA-IgA levels.

Résumé:

Introduction: La maladie cœliaque est une entéropathie systémique secondaire à une réponse immunitaire déclenché par la consommation de gluten, qui survient chez des individus génétiquement prédisposés. Elle se caractérise par un polymorphisme clinique, avec des formes intestinales et extra-intestinales. Le diagnostic reposesur la mesure de la sérologiedes anticorps IgA anti-transglutaminase tissulaire et l'examen d'une biopsie de l'intestin grêle. Cette étude porte sur la maladie cœliaque chez les enfants marocains, en examinant les symptômes cliniques, les signes biologiques, la réponse immunitaire, les lésions tissulaires et les tests sérologiques et leurs relations avec ces facteurs.

Patients et méthodes: Notre étude a consisté en une étude rétrospective au CHU Mohammed VI de Marrakech de juillet 2021 à juillet 2023. Les données de 300 patients atteints de la maladie cœliaque ont été recueillies. Tous les patients diagnostiqués avec la maladie cœliaque âgés de 16 ans ou moins, et qui ont effectué un test sérologique et une biopsie jéjunale ont été inclus dans cette étude. Les patients âgés de plus de 16 ans, ceux dont le diagnostic n'a pas été confirmé par des tests et ceux dont les données médical n'était pas disponible ont été exclus. Les enfants suivant déjà un régime sans gluten depuis plus de 6 mois ont également été exclus. Le taux d'IgA tTG a été mesuré en UI/mL et a été qualifié de négatif (<20 UI/mL) ou de positif (≥ 20 UI/mL) sur la base de la valeur seuil. Cependant, les résultats de la biopsie intestinale ont été identifies selon la classification de Marsh-Oberhuber.

Résultats: Soixante-six enfants diagnostiqués avec une maladie cœliaque répondaient aux critères d'inclusion. L'âge moyen de notre échantillon était de 6,5 ans (1-15 ans), avec une légère prédominance féminine (56,1 %, sex-ratio 0,78). Les symptômes gastro-intestinaux tels que la diarrhée (41 %) et les douleurs abdominales (33 %) étaient les plus fréquents. Les manifestations extra-intestinales comprenaient un retard de croissance (62%) et une pâleur (40%) ont été plus présentés. Le diabète de type 1 était la maladie la plus fréquemment associée (30 %). Les analyses sanguines ont révélé une anémie (53 %) et un faible taux de cholestérol (32 %), les deux anomalies les plus détectées dans cette étude. Les anticorps IgA anti-transglutaminase tissulaire étaient positifs chez 82 % des patients, avec des titres élevés, modérés et faibles chez 55 %, 9 % et 18 % d'entre eux respectivement. Le test a montré une sensibilité élevée (97,2 %) et une valeur prédictive négative (VPN) de 91,6 %. L'évaluation histologique à l'aide de la classification de Marsh modifiée a révélé des degrés variables de lésions intestinales. Marsh 0 (villosités normales) a été observé chez 45 % des patients, tandis que Marsh 2 était présent chez 4,5 % d'entre eux. Les autres patients présentaient des degrés variables d'atrophie villositaire: Marsh 3a (15 %), Marsh 3b (20 %) et Marsh 3c (14 %). Une corrélation significative a été identifiée entre les niveaux élevés de tTG-IgA et la prévalence des symptômes cliniques. Les patients présentant des titres d'anticorps élevés avaient une prévalence plus élevée de diarrhée (57,9 %), de ballonnements abdominaux (70,6 %), de vomissements/anorexie (66,7 %) et de retard de croissance (61 %)... Cependant, aucune corrélation significative n'a été trouvée entre les marqueurs sérologiques et les signes biologiques de malabsorption. Il est intéressant de noter que des titres élevés de tTG-IgA étaient plus fréquents chez les patients présentant une atrophie villositaire avancée (100 % dans les Marsh 3b et 3c), alors que les biopsies Marsh 0 et 2 étaient associées à des niveaux d'anticorps faibles ou négatifs. En outre, l'augmentation des lymphocytes intra-épithéliaux (LIE) dans la muqueuse intestinale a montré une association significative avec des titres d'anticorps plus élevés et l'atrophie villositaire (valeur p $<0,05$).

Conclusion: Nos résultats suggèrent que les tests positifs aux anticorps anti-transglutaminase tissulaire, en particulier ceux dont les titres sont élevés (10 fois la LSN), pourraient potentiellement être utilisés pour diagnostiquer la maladie cœliaque chez les patients symptomatiques sans biopsie. Toutefois, des études prospectives de plus larges sont nécessaires pour valider cette approche. Ces études devraient prévoir le prélèvement de biopsies duodénales selon les protocoles recommandés et leur interprétation par des pathologistes expérimentés. Une biopsie peut rester nécessaire pour les patients dont l'état ne s'améliore pas avec un régime sans gluten ou qui présentent des taux de tTG-IgA légèrement ou modérément élevés

ملخص:

مقدمة: الداء الزلاقي هو مرض معوي ناتج عن استجابة مناعية ناتجة عن استهلاك الغلوتين، ويحدث لدى الأفراد المهيئين وراثياً. ويتميز بتعدد الأشكال السريرية، مع وجود أعراض هضميةٍ أو/و أخرى خارج الجهاز الهضمي. يعتمد التشخيص على قياس مصل الأجسام المضادة لناقالاتالغلوتامينوفحص خزعة الأمعاء الدقيقة . و الهدف من هذا العمل هو دراسة الداء الزلاقي لدى الأطفال المغاربة، وفحص الأعراض السريرية والعلامات البيولوجية والاستجابة المناعية وآفات الأنسجة والاختبارات المصلية وعلاقتها بهذه العوامل.

المرضى والطرق: شملت دراستنا دراسة ذات أثر رجعي في المستشفى الجامعي محمد السادس بمراكش من يو ليوز2021، الىيوليوز 2023. تم جمع بيانات 300 مريض مصاب بالداء الزلاقي. وشملت هذه الدراسة جميع المرضى الذين تم تشخيص إصابتهم بالمرض الزلاقي الذين تبلغ أعمارهم 16 عامًا أو أقل، والذين أجروا اختبارًا مصليًا وخزعة من الامعاء الدقيقة . تم استبعاد المرضى الذين تزيد أعمارهم عن 16 عامًا، وأولئك الذين لم يتم تأكيد تشخيصهم من خلال الاختبارات، وأولئك الذين لديهم معلومات طبية غير متوفرة. كما تم استبعاد الأطفال الذين اتبعوا بالفعل نظامًا غذائيًا خاليًا من الغلوتين لأكثر من 6 أشهر. تم قياس مستوى الأجسام المضادة لناقالاتالغلوتامين بوحدة دولية/ملليتر وتم تصنيفه على أنه سلبي (أقل من 20 وحدة دولية/ملليتر) أو إيجابيﮐ 20 وحدة دولية/ملليتر) بناءً على القيمة المحددة. إضافة الى ذلك، تم تحديد نتائج الخزعة المعوية كمجموعات تبعالتصنيفمارش-أوبيرهوبر.

النتائج: استوفى ستة وستون طفلاً تم تشخيص إصابتهم بالمرض الزلاقي معايير الشمول . كان متوسط عمر العينة لدينا 6.5 سنة (1-15 سنة)، مع هيمنة طفيفة للإناث (56.1%، نسبة الجنس 0.78). كانت الأعراض الأكثر شيوعًا هي أعراض الجهاز الهضمي مثل الإسهال (41%) وآلام البطن (33%). وشملت المظاهر غير الهضمية تأخر النمو (62%) وشحوب البشرة (40%) وكانت المظاهر الأكثر شيوعًا . كان داء السكري من النوع الأول أكثر الأمراض المصاحبة (30%). كشفت فحوصات الدم عن فقر الدم (53%) وانخفاض الكوليسترول (32%)، وكلاهما كانا أبرز الاعراض البيولوجية المكتشفة في هذه الدراسة. كانت الأجسام المضادة إيجابية في 82% من المرضى، مع وجود نسب مرتفعة ومتوسطة ومنخفضة في 55% و9% و18% على التوالي. أظهر الاختبار حساسية عالية

(97.2٪) وقيمة تنبؤية سلبية بنسبة 91.6٪. كشف الفحص النسيجي باستخدام تصنيف مارش المعدل عن درجات متفاوتة من التلف المعوي. لوحظت درجة مارش 0 (الزغابات الطبيعية) في 45% من المرضى، بينما كانت درجة مارش 2 موجودة في 4.5%.أظهر المرضى الباقون درجات متفاوتة من الضمور الزغبي : مارش 3" أ "(15%) ومارش 3 "ب" (20%) ومارش 3 "ج" (14%). تم تحديد ارتباط كبير بين ارتفاع مستويات مضادات الاجسام وانتشار الأعراض السريرية . كان المرضى الذين يعانون من ارتفاع نسبة الأجسام المضادة لديهم معدل انتشار أعلى للإسهال (57.9%)، وانتفاخ البطن (70.6%)، والقيء/فقدان الشهية (66.7%)، وتأخر النمو (61%)... ومع ذلك، لم يتم العثور على علاقة كبيرة بين العلامات المصلية والعلامات البيولوجية لسوء الامتصاص . ومن المثير للاهتمام، أن نسبة الأجساممضادة لناقلات الجلوتامين المرتفعة كانت أكثر انتشارًا في المرضى الذين يعانون من ضمور زغبي متقدم (100% في مارش 3ب و3ج)، بينما ارتبطت خزعات مارش 0 و2 بمستويات منخفضة أو سلبية من الأجسام المضادة . بالإضافة إلى ذلك، أظهرت زيادة الخلايا اللمفاوية داخل بطانة الأمعاء ارتباطًا كبيرًا بارتفاع نسبة الأجسام المضادة وضمور الزغاباتقيمة$p<0.05$.

<u>خاتمة:</u> تشير النتائج التي توصلنا إليها إلى أن اختبارات الأجسام المضادة لناقلات الجلوتامين الإيجابية، خاصة تلك التي تحتوي على نسبة مرتفعة (10 أضعاف الحد الأقصى المسموح به)، يمكن استخدامها لتشخيص الداء الزلاقي لدى المرضى الذين يعانون من الأعراض دون خزعة . ومع ذلك، هناك حاجة إلى إجراء دراسات مستقبلية أكبر للتحقق من صحة هذا النهج . يجب أن تتضمن هذه الدراسات جمع خزعات من الامعاء وفقًا للبروتوكولات الموصى بها وتفسيرها من قبل أخصائيين علم التشريح المرضي ذوي خبرة. قد لا تزال الخزعة ضرورية للمرضى الذين لا يتحسنون عند اتباع نظام غذائي خالٍ من الغلوتين أو أولئك الذين يعانون من ارتفاع طفيف أو معتدل في مستويات مضادات الاجسام لناقلات الجلوتامين.

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قسم الطبيب

أقسِم بِالله العَظِيم

أن أراقب الله في مهْنتي.

وأن أصُون حياة الإنسان في كافّة أطوارها في كل الظروف والأحوال باذلة وسْعي في إنقاذها من الهلاك والمرض و الألم والقلق.

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وأن أكون على الدوام من وسائل رحمة الله، باذلة رعايتي الطبية للقريب والبعيد، للصالح والطالح، والصديق والعدو.

وأن أثابر على طلب العلم، وأسخّره لنفْع الإنْسان لا لأذاه.

وأن أوقّر من علّمني، وأعلّم من يصغرني، وأكون أختا لكُلّ زميل في المهنة الطّبّية مُتعاونين على البرّ و التقوى.

وأن تكون حياتي مصْداق إيماني في سرّي وعلانيتي ،نقيّة ممّا يشينها تجاه الله ورسُوله والمؤمنين.

والله على ما أقول شهيد

كليـــــــة الـطب
والصيدلة - مراكش
FACULTÉ DE MÉDECINE
ET DE PHARMACIE - MARRAKECH

جامعة القاضي عياض
UNIVERSITÉ CADI AYYAD

أطروحة رقم 127سنة 2024

الخصائص المناعية والنسيجية للمرض الزلاقي عند الأطفال

الأطروحة

قدمت ونوقشت علانية يوم 2024/04/17

من طرف

السيدة**فاطمة الزهراء الادريسي**

المزدادة في 09غشت1998 بالرباط

لنيل شهادة الدكتوراه في الطب

الكلمات المفتاحية:

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