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ARTICLE ORIGINAL

Vers une classification systémique de la maladie cœliaque : perspectives à partir des patients positifs aux anticorps anti-tTG2

Toward a Systemic Classification of Celiac Disease : Insights from Anti-tTG2 Positive Patients

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MOTS CLÉS

Maladie cœliaque

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KEYWORDS

Celiac disease,

Anti-tTG2,

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Résumé

Introduction : La maladie cœliaque est une entéropathie auto-immune induite par le gluten, caractérisée par des manifestations cliniques hétérogènes. **Méthodes :** Les anticorps anti-tTG2 ont été mesurés par ELISA manuel et automatisé (Alegria 2) chez des patients suspects de maladie cœliaque. Simultanément, le dosage des IgA totales sériques a été réalisé chez tous les patients. Les anticorps anti-endomysium ont été recherchés par immunofluorescence indirecte chez les patients présentant des taux élevés d'anticorps anti-tTG2. Les caractéristiques cliniques des patients positifs ont ensuite été analysées. **Résultats :** Soixante-dix patients étaient positifs aux anticorps anti-tTG2. Les anticorps anti-endomysium ont été testés chez 40 patients (54 %) et détectés dans 35 cas. L'âge moyen était de 28 ans (5-62 ans), avec une prédominance féminine (77 %). Les principales manifestations comprenaient des symptômes digestifs (59 %), une anémie (34 %), une asthénie (21 %), des arthralgies (16 %), une perte de poids (14 %) et un diabète de type 1 (14 %). Les formes isolées incluaient l'anémie (10 %), le diabète de type 1 (11 %), une thrombose veineuse cérébrale (3 cas), des troubles neurologiques (2 cas) et des fausses couches à répétition (1 cas). **Conclusion :** La maladie cœliaque se manifeste à la fois par des formes typiques et atypiques, soulignant son caractère systémique et la nécessité d'un dépistage élargi.

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Abstract

Introduction : Celiac disease is an autoimmune enteropathy induced by gluten, with heterogeneous clinical manifestations. **Methods :** Anti-tTG2 antibodies were measured by manual and automated ELISA (Alegria 2) in patients with suspected celiac disease, simultaneously we determined total IgA in serum for all patients. Anti-endomysium antibodies were tested by indirect immunofluorescence in cases with high anti-tTG2 titers. Clinical

features of positive patients were then analyzed. **Results** : Seventy patients were anti-tTG2 positive. Anti-endomysium antibodies were assessed in 40 patients (54%) and detected in 35 cases. Mean age was 28 years (5–62), with female predominance (77%). Main manifestations included digestive symptoms (59%), anemia (34%), asthenia (21%), arthralgia (16%), weight loss (14%), and type 1 diabetes (14%). Isolated forms included anemia (10%), type 1 diabetes (11%), cerebral venous thrombosis (3 cases), neurological disorders (2 cases), and recurrent miscarriage (1 case). **Conclusion** : Celiac disease presents with both typical and atypical features, underlining its systemic nature and the need for broad screening.

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Introduction

Celiac disease (CD) is a chronic autoimmune disorder triggered by gluten ingestion in genetically predisposed individuals. Traditionally regarded as a gastrointestinal disease, CD is now recognized as a systemic condition with multiple extra-digestive manifestations including hematologic, endocrine, neurologic, thromboembolic, and reproductive complications [2,4].

Despite advances in diagnostic tools, many cases remain unrecognized, particularly those without classical gastrointestinal symptoms [5].

The aim of this study was to describe the epidemiological profile and clinical spectrum of patients with positive anti-tTG 2 antibodies in our cohort.

Material and methods

All patients referred to our laboratory with suspected celiac disease underwent measurement of anti-tTG2 antibodies (IgA isotype), using either a manual ELISA or an automated platform (Alegria 2). Total serum IgA levels were also assessed using laser nephelometry assay to identify potential IgA deficiency. In patients with markedly elevated anti-tTG2 titers, anti-endomysium antibodies were investigated by indirect immunofluorescence, using primate esophagus or rat liver as substrates. Finally, we performed a descriptive analysis of the clinical characteristics of patients testing positive for anti-tTG2 antibodies.

Results

Demographic characteristics

Out of the 70 patients who tested positive for anti-tTG2 antibodies. The mean age of the cohort was 28 years (range : 5–62). The pediatric population (<18 years) accounted for 18 patients (25.7%), whereas 5 patients (7.1%) were older than 50 years. A marked female predominance was observed in the overall cohort (77%) as well as in the pediatric subgroup (78%) (**Figure 1**).

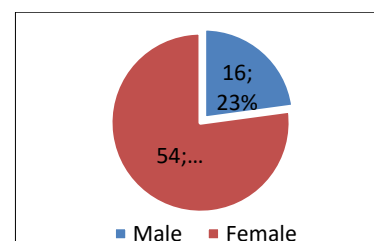


Figure 1. Distribution of patients according to sex

Laboratory findings

Among the 70 patients with positive anti-tTG2 antibodies in ELISA assay, anti-endomysium antibodies were further investigated in 40 cases (54%) and were found positive in 35 of them.

ELISA assays use human purified or recombinant tTG2, whereas the IFI technique (endomysium) detects the same enzyme in its native form, which confers slightly higher specificity to the latter method. The positivity of these antibodies could be sufficient for the diagnosis of celiac disease especially for children.

We consider a result as positive anti-endomysium if we observe the following aspects of fluorescence (Figure 2).

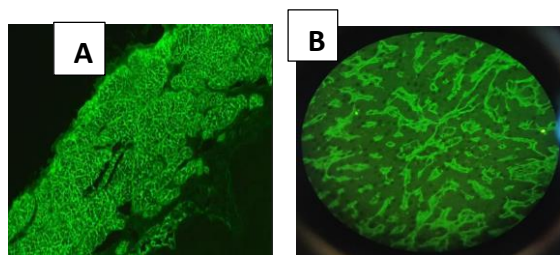


Figure 2. Positive anti-endomysium result : (A) primate esophagus or (B) rat liver as substrates

Clinical manifestations

Digestive symptoms (diarrhea, abdominal pain, and/or constipation) were the predominant clinical presentation, affecting 59% of patients. Extra-digestive features were also frequent : anemia in 24 patients (34%), asthenia in 15 patients (21%), arthralgia in 11 patients (16%), weight loss in 10 patients (14%), and type 1 diabetes in 10 patients (14%). In contrast, cutaneous manifestations, liver disease, failure to thrive, myalgia and neurological disorders were less commonly observed (Figure 3).

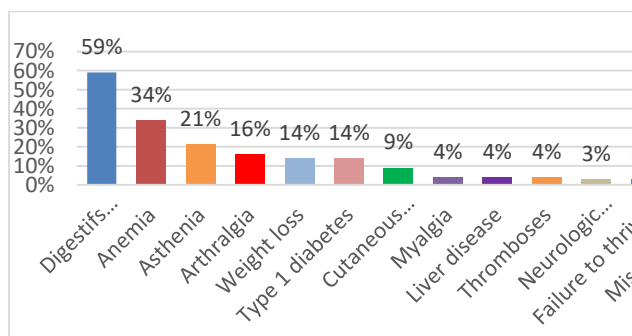


Figure 3. Frequencies of different clinical manifestations

Several atypical or isolated presentations were identified. Anemia was isolated in 7 patients (10%), and type 1 diabetes in 8 patients (11%). Rare but noteworthy findings included cerebral venous thrombosis (3 cases), and recurrent miscarriage (1 case), all occurring as isolated manifestations.

All patients with isolated Type 1 diabetes are asymptomatic children send for systematic screening for celiac disease, their mean age is 9 years (range : 3–13). Meanwhile the 3 patients with isolated cerebral venous thrombosis are adults. In the other hand isolated anemia is found in children as well as in adult patients (Table 1).

Table 1. Main isolated extradigestive symptoms

Manifestations	Number of patients (%)	Mean age (%)
Anemia	7 (10%)	28 years [5-45]
Type1 diabetes	8 (11%)	9 years [3-13]
Cerebral venous thrombosis	3 (4%)	29 years [24 - 33]

Discussion

The female predominance and the mean age of 28 years observed in our cohort are consistent with findings from other studies [4,5].

Recent reports have emphasized the wide clinical spectrum of celiac manifestations : digestive, hepatic, vascular, musculoskeletal, cardiac and neuro-psychiatric involvement [2, 3]. Our results reinforce the marked heterogeneity in the clinical presentation of this condition :

Absence of digestive manifestations

CD is not limited to the classical triad of diarrhea, weight loss, and abdominal pain. A substantial proportion of patients remain asymptomatic from a gastrointestinal standpoint. This may be explained by :

- Mild or patchy villous atrophy of the intestinal mucosa, insufficient to cause overt malabsorptive symptoms.
- Compensatory mechanisms, whereby unaffected intestinal segments enhance nutrient absorption, masking digestive signs.

Anemia

Anemia was observed in 34% of our patients, in line with previous reports [7]. It is generally multifactorial, resulting from iron, folate, or vitamin B12 deficiencies secondary to malabsorption.

Type 1 diabetes

Type 1 diabetes was found in 14% of cases, often in isolation, consistent with the shared genetic **background** of both autoimmune diseases. This well-established association has been widely documented in the literature [1,2].

Thrombosis

Three adult patients presented with isolated cerebral venous thrombosis. This complication has

also been described in other cohorts, with different mechanisms proposed [6] :

- **Vitamin K deficiency** impairs the γ -carboxylation of glutamic acid, reducing the synthesis of protein C and protein S. Their deficiency leads to uncontrolled coagulation and thrombosis.
- **Vitamins B12, B6, and folate** are crucial for homocysteine metabolism. Their deficiency causes **hyperhomocysteinemia**, associated with platelet activation, endothelial dysfunction, oxidative stress, and reduced anticoagulant activity (protein C, antithrombin).
- **Dehydration and hyperviscosity**, particularly in patients with profuse diarrhea, may further increase the risk of thrombotic events.

Miscarriages

Recurrent miscarriages, as described in previous studies [6,8], further illustrate the **systemic nature** of CD and highlight the risks associated with delayed diagnosis.

Conclusion

Celiac disease is a systemic condition with both digestive and extra-digestive polymorphic manifestations. Anemia, type 1 diabetes, as well as rare complications such as thrombosis and miscarriages, should prompt serological screening. Early detection is crucial to prevent complications and initiate a gluten-free diet promptly.

Conflict of interests

There is no conflict of interest.

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