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Physiopathologie

Current status of celiac disease diagnosis in children and adolescents in West Algeria

État actuel du diagnostic de la maladie cœliaque chez les enfants et les adolescents dans l'Ouest algérien

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Abstract ***Introduction.*** The celiac disease is an autoimmune chronic inflammatory enteropathy caused by the gluten gliadin, a food antigen. ***Objective.*** To determine whether the epidemiology and the clinical presentation of celiac disease (CD) have changed during the last 30 years in children and adolescents in west Algeria. ***Subjects and methods.*** This was a retrospective analysis of all CD subjects listed in the regional reference center, the Department of Pediatrics « C » CHU Oran. Cases were enrolled in the whole west Algeria, from 1978 to December 31th 2010. The analyses focused on the study of clinical records. Only subjects who developed CD clinical and histological signs with a positive response to gluten-free diet were considered. ***Results.*** CD patients (4476 (2076 male and 2400 female, sex ratio 0.86) were identified. The evolution of CD incidence showed that the number of cases increased gradually since 1980 to 200 cases per year from 1990 to 1997, with peaks around 230 in 1990, 1993 and 1997, then stabilized at around 88 cases per year from 2006 to 2010. Although the mean age at introduction of gluten in the diet and the mean duration of breast feeding have not changed over the past 30 years, an increase in the mean age was noted at first symptoms and at diagnosis. Diarrhea remained the main symptom at diagnosis, its frequency was estimated at 86% until December 31th 2008, but non-diarrheal presentations were increased in recent years. ***Conclusion.*** A change in the clinical profile of CD was noted in the last decade, probably related to environmental factors still unidentified in our context.

Keywords: *Celiac disease, Gluten-free diet, Risk factors*

Résumé ***Introduction.*** La maladie cœliaque est une entéropathie inflammatoire chronique auto-immune provoquée par la gliadine du gluten, un antigènealimentaire. ***Objectif***. Déterminer si l'épidémiologie et la présentation clinique de la maladie cœliaque MC) ont changé au cours de ces 30 dernières années chez les enfants et les adolescents dans l'ouest algérien. ***Sujets et méthodes***. Une analyse rétrospective sur l'ensemble des sujets MC répertoriés au service de Pédiatrie « C » CHU Oran, provenant de tout l'Ouest algérien, de 1978 au 31 décembre 2010, a porté sur l'étude des dossiers cliniques. Tous les sujets ayant présenté des signes cliniques et /ou histologiques d'une MC, avec une réponse positive au régime sans gluten ont été retenus. ***Résultats.*** Des patients MC (n=4476 dont 2076 garçons et 2400 filles, sex-ratio de 0,86) ont été répertoriés. L'évolution du nombre de sujets MC recrutés dans le service a montré que le nombre de cas MC recrutés a augmenté progressivement pour atteindre 200 cas par an en moyenne de 1990 à 1997, avec des pics autour de 230 en 1990,1993 et 1997, puis une stabilité autour de 88 cas par an de 2006 à 2010. Bien que l'âge moyen à l'introduction du gluten dans l'alimentation ainsi que la durée moyenne de l'allaitement maternel, n'ont pas changé durant ces 30 dernières années, une augmentation de l'âge moyen a été constaté au début des troubles et au diagnostic. La diarrhée reste le maître symptôme au diagnostic, sa prévalence est évaluée à 86 % au 31 décembre 2008. Par contre, les formes non diarrhéiques sont de plus en plus fréquentes ces dernières années. ***Conclusion.*** Un changement de la physionomie de la MC a été noté cette dernière décennie, probablement lié à des facteurs environnementaux non encore identifiés dans notre contexte.

Mot- clés : *Maladie cœliaque, Régime sans gluten, Facteurs de risque*

Introduction

Celiac disease (CD) is a chronic, immunologically determined form of enteropathy affecting the small intestine in genetically predisposed children and adults [1]. The European Society for Paediatric Gastroenterology Hepatology and Nutrition (ESPGHAN) has produced new guidelines for the celiac disease diagnosis. Only children with symptoms or suggestive signs of CD are to be considered. The diagnosis of CD depends on gluten-dependent symptoms, CD-specific antibody levels, the presence of HLA-DQ2 and/or HLA-DQ8, and characteristic histological changes (villous atrophy and crypt hyperplasia) in the duodenal biopsy [2]. The clinical spectrum of CD has widened over the past decades, and clinical pattern and age at diagnosis of CD are still changing in children. Several investigators in recent decades have reported a decreasing prevalence of the classic celiac triad—failure to thrive, diarrhea, and abdominal distension—in children with CD [3,4]. The overall decrease in the prevalence of diarrheal presentations over the past 2 decades, accompanied by an increase in extra-intestinal symptoms manifestations of the disease [5,6], probably explained the older age at diagnosis. Indeed, children presenting typical symptoms were always younger, and their median age at diagnosis remained similar throughout the 20 years.

More widespread use of serologic markers has facilitated the diagnosis of celiac disease in children. This fact alone did not entirely explain the decrease

in diarrheal manifestations, as many long-term studies in adult and pediatric patients predating the use of these markers have documented this shift in clinical presentation [7,8].

The objective of this study was to determine whether the epidemiology and the clinical presentation of celiac disease have changed during the last 30 years in children and adolescents in west Algeria.

Subjects and methods

Subjects

This was a retrospective analysis of cases recruited from 1978 up to December 31th 2010: all the CD subjects diagnosed at the Department of Pediatrics « C » CHU Oran were considered. The latter being considered the referral center for care of CD children from west Algeria. The west of Algeria is bordered by the Mediterranean Sea in the north, Mauritania, West Sahara and Mali in the south Region which extends over an area of 2 114 km^2. Oran province is located in the north-west of Algeria and its population is 1.584.607. The new cases came from all the West of Algeria for consulting units primary care, pediatric offices of Oran province, and Pediatric Hospital of Oran. All the patients were followed by the Department of Pediatrics « C » CHU Oran. Oran register was used to retrieve the data. In 1978, a prospective incidence register was established in Oran province. The register enables a continuous epidemiological surveillance of celiac disease children.

Methods

The analysis focused on the study of clinical records, namely, the demographic characteristics, the age at first symptoms, the breastfeeding duration, symptoms leading to the diagnosis, the age at introduction of gluten, the results of the intestinal biopsy and the starting date of gluten-free diet. In our study, the diagnosis of CD was performed according to the ESPGHAN criteria published in 1970. Marsh-Oberhuber classification was used to classify the intensity of mucosal damage. All the patients had villous atrophy. A positive response to gluten-free diet was evaluated by the disappearance of clinical signs and histological improvement.

Statistical analysis

The comparison of two means was made by the t-test, while the comparison of percentages was made by Chi-square test using EXCEL software. Not normally distributed data were compared by Wilcoxon rank sum test. Results were considered statistically significant at $p \leq 0.05$.

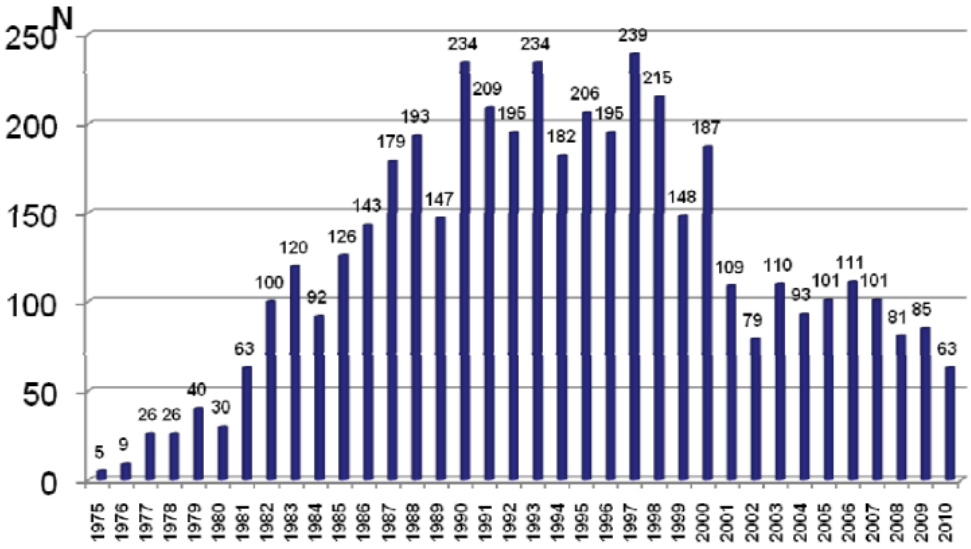

Fig. 1. Evolution of celiac disease number recruited in our department since 1975 to december 31th 2010 (n = 4476)

Results

Until December 31th 2010, 4476 CD patients were identified, (female/male, 2400/2076; sex ratio 0.86. Fifty eight % of them were from the Department of Pediatrics « C » CHU Oran . The consanguinity rate (specified in 3044 of the subjects) was of 26%. The number of CD subjects recruited in our Department showed a gradual increase from about 30 cases in 1980 to 200 cases per year from 1990 to 1997, with peaks around 230 in 1990, 1993 and 1997, then lowered to about 88 cases per year from 2002 to 2010 (Fig. 1).

In addition, analysis of age evolution at diagnosis compared to that at gluten introduction and duration of breastfeeding showed that the mean age at introduction of gluten (5.9 ± 4.5 months) in the diet as well as the mean duration of breastfeeding (4.8 ± 6.6 months) did not change over the past 30 years 1979-2008 and the mean age at first symptoms raised from a average of 20 months in the period 1979-1983 to an average of 28 months in the period 2004-2008 (Fig.2).

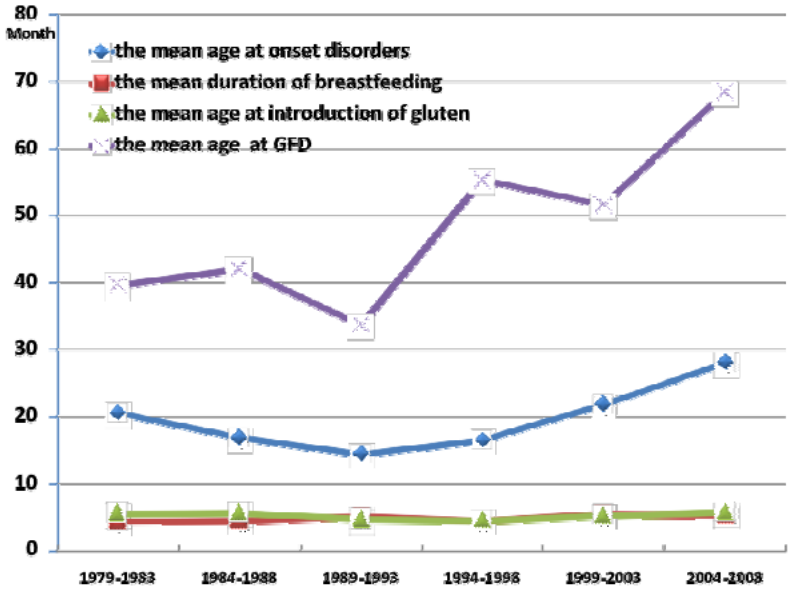

Fig. 2. Evolution of the mean age at GFD (n = 4262), at the introduction of gluten (n= 3355), at onset of disorders (n= 3127) and the mean duration of breastfeeding (n= 3426)

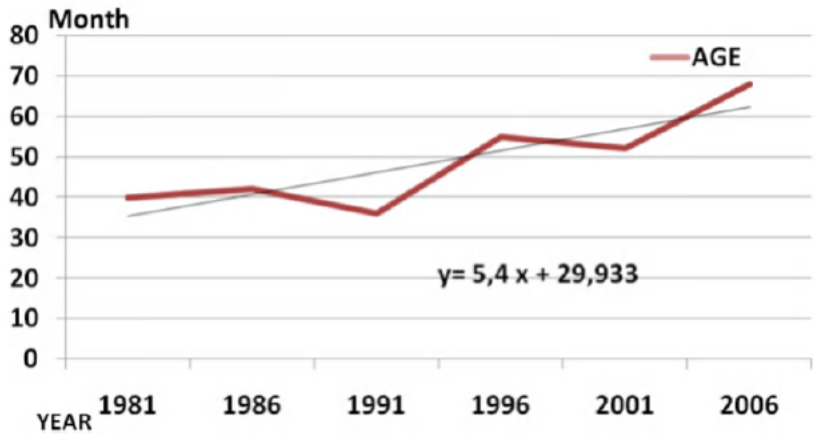

Fig. 3. Evolution of age at Gluten Free Diet

The GFD age enhanced from a mean of 40 months in the 80ties to 70 months in 2008. A linear function fitted to the observed data (Fig. 3) showed that at every 5 years, there was an increase of 5.4 months for the age at GFD, indeed, there was an overall increase of about one month more each year from the 80 ties to the 2008. Moreover, the difference between the age at GFD (e.g. the age at diagnosis) and the age at onset of disorders moved with an increasing trend , exactly parallel to the age at GFD, from an average of 20-25 months before 1988 to an average of 30-40 months after 1999. Also, the pattern of the age evolution at diagnosis of new cases according to age classes is presented in Fig. 4. The age-group 10-15 years increased from 10% in the five year period 1979-1983 to 21.4% in 2004-2008 (p = 0.2) (Fig. 4).

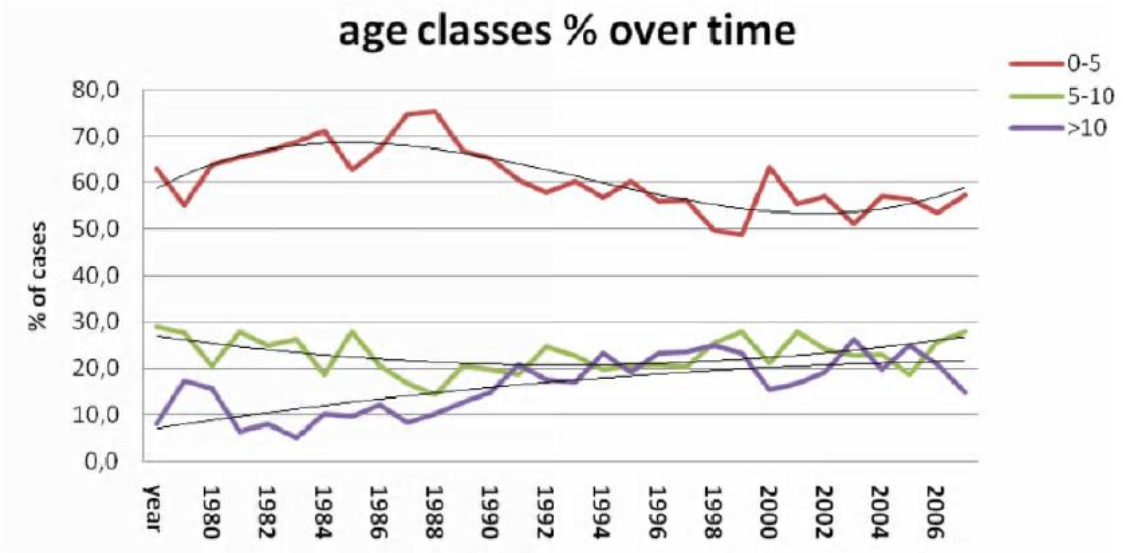

Fig. 4. Evolution of the age at GFD according to age classes (n = 4262) from 1979 to 2008. A 2nd degree polynomial function was fitted to the observed data.

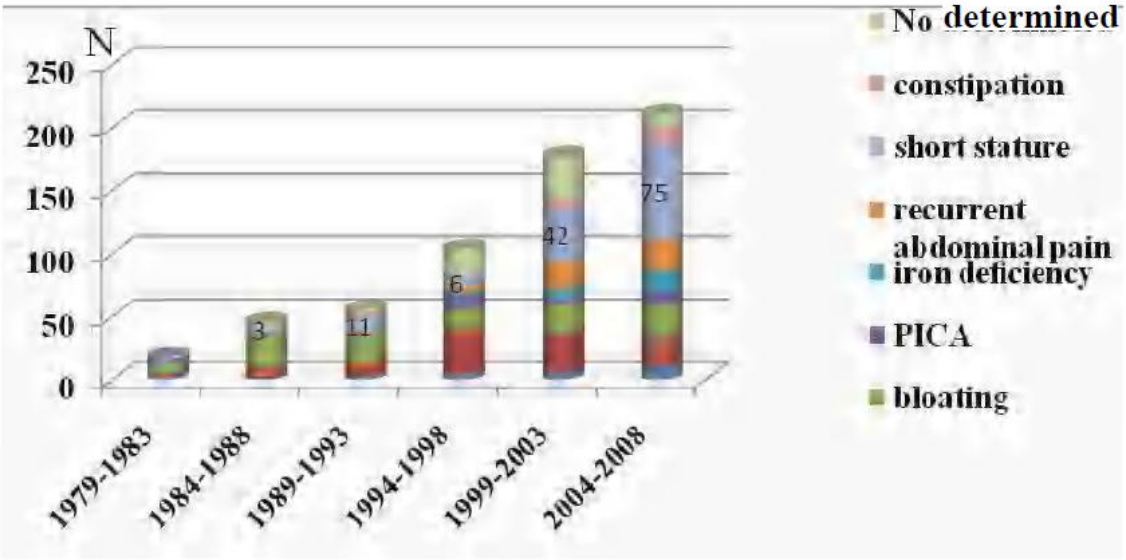

Fig. 5: Atypical presentations of celiac disease in children and adolescents

Regarding the symptoms at presentation, diarrhea was the main symptom, its prevalence was estimated at 86% until December 31th 2008 among 3056 cases. The diarrhea frequency decreased from 94% in the period 1979-1983 to 72% in 2004-2008 ($p < 0.001$). Currently, there was a general trend to delayed onset of symptomatic CD. These children had a tendency to experience unusual intestinal complaints (e.g. recurrent abdominal pain, nausea, vomiting, bloating, and constipation) or extra-intestinal manifestations (e.g. short stature, iron deficiency (Fig. 5).

Discussion

The analysis focused on 4476 CD patients listed in the Department of Pediatrics "C" CHU Oran since 1975 until December 31th 2010. The high number of these patients were diagnosed before 2000, with annual peaks around 230 in 1990, 1993 and 1997. Then the number of CD cases stabilized around 88 cases per year from 2006 to 2010. This decrease could probably not be explained by the fact that a number of patients might have escaped our records since our data were crossed with those of the pediatric offices in Oran and we could not find any other source of diagnosis.

In our cohort, the changes in the age at introduction of gluten in the diet and in the duration of breastfeeding were not observed over the past 30 years. Despite the unchanged pattern of nutritional risk factors, we noted either a decreased incidence as well as a rise of the age at diagnosis, and some changes in the symptoms. An epidemiological study from Sweden [9] suggested that the introduction of small amounts of gluten during breastfeeding protected infants against the risk to develop CD. Conversely, the absence of breastfeeding and the early introduction of gluten were proposed as the cause of the Swedish epidemic. These both latter arguments seemed to be the most important risk factors in subjects genetically predisposed. In our context, we were not able to examine the amount of gluten introduced in our patients, but there was any modification in the infant feeding practices over the last 30 years.

It would therefore appear that there are other environmental factors, as age at gluten introduction and breastfeeding which can influence the changing phenotype.

In this study, an increase in the average age at diagnosis was found. In particular, a progressive decrease in the mean age at diagnosis until 1993, then an increase from 2.8 years during the 1989-1993, 5-year period to 5.5 years in 2004-2008. The diagnosis of CD was progressively delayed. The mean age at onset of digestive disorders increased from 20 months (1979-1983) to 28 months between 2004 and 2008. Our data are supported by those of Vella [10], who reported that the median age at diagnosis of CD increased from 14 months in the 1985-1989 period to 48 months during 1995-1999 period.

For over 30 years, CD patients treated in our department were essentially the classical gastrointestinal forms characterized by diarrhea. However, the frequency of diarrhea decreased from 90% during 1979-1983 to 70% in 2004-2008. These data were comparable to those found in the literature [11-17]. Maki [18] reported a regression of the classic form that was present in less than 50% of newly diagnosed patients. This result was also described by Green [15]: 73% were of classical forms before 1993 *vs* 43% after 1993. Murray [19] in the USA also noted that the prevalence of diarrhea changed from 100% of cases during the period 1950-1996 to 54% of cases during 2000-2001.

Conclusion

The evolution of CD incidence show that the new cases number gradually increases since 1980 to 200 cases per year from 1990 to 1997, then remains stable at around 88 cases per year from 2006 to 2010. The clinical spectrum of CD has widened over the last decades. Diarrhea remains the main symptom at diagnosis, its frequency is estimated at 86% until december 31th 2008, but non-diarrheal presentations are increased in recent years.

Clinical pattern and age at diagnosis of CD are still changing in our children, probably related to environmental factors unidentified in our context.

Conflict of interest

The authors declare no conflict of interests in preparing this article.

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