

# Epidemiology of Coeliac Disease in Children in One Croatian County: Possible Factors That Could Affect the Incidence of Coeliac Disease and Adherence to a Gluten-free Diet (Part II)

Z. Matek, M. Jungvirth-Hegeduš and S. Kolaček

Referral Centre for Paediatric Gastroenterology and Nutrition, Children's Hospital Zagreb, Zagreb, Croatia

## ABSTRACT

*Coeliac disease is a life-long disorder characterised by small-intestinal mucosal damage caused by gluten. The treatment, gluten-free diet, leads to mucosal restoration and reduces the risk of malignant and non-malignant complications. According to our recent results, cumulative incidence in Croatian children is 1:519 life-births. Coeliac disease presents early, mostly with typical symptoms. We investigated possible influences of breast-feeding duration and time of gluten introduction on such presentation of the disease. Study included coeliacs born in Medimurje between 1985 and 1994 (N = 31). Patients' adherence to treatment was also studied. Although short breast-feeding (mean 2.9 months) and early gluten introduction (mean 4.9 months) were shown, no correlation was found between those factors and time of the disease presentation. Concerning adherence to gluten-free diet, only 50% of patients maintained it strictly, 23% irregularly, while 27% were on normal diet. In order to improve it, regular follow-ups are recommended.*

## Introduction

Coeliac disease is a life-long chronic non-infectious disorder characterised by severe small-intestinal mucosal damage

caused by gluten, a protein found in wheat, rye and barley. After gluten withdrawal, a full histological and clinical remission occurs<sup>1</sup>.

Received for publication May 10, 1999.

For the expression of the disease, the interaction of genetic, immunological and environmental factors is necessary. It is known that a genetic factor constitute a strong determinant for coeliac disease. The disorder is closely associated with human leukocyte antigen (HLA) class II alleles and explains most of the increased risk seen in relatives of coeliac patients. Nonetheless, since considerable changes of the incidence of coeliac disease have been observed during the past few decades which could not be ascribed to possible changes in inheritance, other factors, such as environment, have been sought as being of relevance<sup>2,3</sup>. According to the results of recent studies, there are several factors which could influence and change the clinical presentation of coeliac disease. Some have been verified in studies, such as gluten quantity, while other have not, such as infantile gastroenteritis. For some factors (duration of breastfeeding, the age of introduction of cow's milk formulas, the age of gluten introduction) different studies have shown contradictory results<sup>4</sup>.

In Croatia, according to our recent study, the cumulative incidence of coeliac disease is 1.9 per 1000 life births, which, in comparison to other countries, is one of the highest in Europe<sup>5</sup>. Opposite to recent trends in most European countries<sup>3,6</sup>, majority of our patients presented with typical clinical symptoms (diarrhoea, failure to thrive and/or loss of weight) already in the course of first year of life<sup>5</sup>. The reasons for this are unknown.

Therefore, the aim of this study was to investigate the role of two important environmental factors, which could influence the presentation of coeliac disease in our patients: i. the age of gluten introduction; ii. the importance of breast feeding.

Adherence to a gluten-free diet presents yet another major problem in the treatment of patients with coeliac disease<sup>7</sup>. As the gluten-free diet may significantly improve prognosis in respect to development of various malignant and non-malignant complications<sup>8</sup>, we have also studied if our patients followed the prescribed diet and their attitudes towards it.

## Patients and Methods

The study was performed in Međimurje, a county in Croatia with 119.866 inhabitants. All children born during the period 1985–1994 who had coeliac disease diagnosed according to strict ESPGAN criteria were included<sup>9</sup>. Patients with coeliac disease born outside Međimurje were excluded from the study. In total, there were 31 coeliac children (17 girls and 14 boys) diagnosed in that ten-year period, who entered this study.

Data on infant nutrition were collected retrospectively from interviews (according to the questionnaire) with patients and their parents and from medical documentation. The questionnaire contained questions on the type of infant diet (whether a child was breast-fed or not and for how long) and on time of introduc-

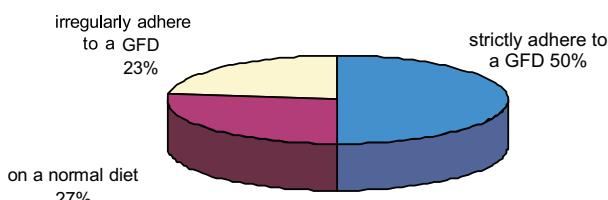


Fig. 1. Adherence to a gluten-free diet (GFD) (N=26)

**TABLE 1**  
THE AGE OF THE FIRST SYMPTOMS OF COELIAC DISEASE COMPARED TO  
THE DURATION OF BREAST-FEEDING

Duration of breast-feeding	No. of patients (percentage)	Median value of the age of first symptoms of coeliac disease in years (range)
< 1 month	2 ( 8.33%)	0.50 (0.50–0.50)
1–6 months	19 (79.17%)	1.46 (0.33–8.00)
> 6 months	3 (12.50%)	1.375 (1.33–1.42)

No correlation was found,  $r=0.07$

**TABLE 2**  
THE AGE OF THE FIRST SYMPTOMS OF COELIAC DISEASE COMPARED TO  
THE TIME OF INTRODUCING GLUTEN INTO INFANTS' DIET

Time of introducing gluten	No. of patients (percentage)	Median of the age of first symptoms of the disease in years (range)
< 1 month	0	—
1–6 months	19 (86%)	1.33 (0.33–10)
> 6 months	3 (14%)	1.42 (0.58– 2)

No correlation was found,  $r=0.14$

ing gluten into the diet. Concerning adherence to the gluten-free diet, it also inquired information on the type of patients' everyday diet and on how much the gluten-free diet affected theirs life (it is impossible to adhere to it, it affects patient's life greatly, it moderately affects patient's life, patient does not feel affected at all). Collected data were entered into a data base at a PC. Spearman's correlation coefficient was used for the statistical analysis. The study was approved by the Ethical Committee of the Children's Hospital Zagreb.

## Results

### *Environmental factors that could affect the incidence of coeliac disease*

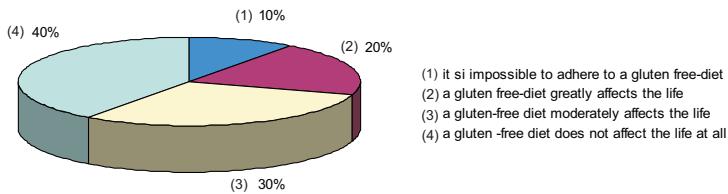
Information on infant diet were obtained from 27 patients (87%). Twenty-four of our patients were breast fed dur-

ing their infancy with the average duration of breast feeding of 2.9 months, while 3 patients were not breast-fed at all (Table 1). In almost 80% of breast-fed patients, breast-feeding lasted for 1 to 6 months whereas only 12.5% were breast-fed for more than 6 months. Using the Spearman's correlation coefficient we studied whether there was a correlation between the duration of breast feeding and the age of first symptoms of coeliac disease, but it was not found to be significant ( $r = 0.07$ ).

Reliable information on the time of introduction of gluten into infant's diet were obtained in 22 cases (71%). The average time of gluten introduction was 4.9 months (median value 4.75 months, mode 5) (Table 2). No significant correlation was found between the time of the introduction of gluten and the age of first

**TABLE 3**  
**THE AGE AT INTRODUCING GLUTEN AND THE AGE OF FIRST SYMPTOMS OF COELIAC DISEASE ACCORDING TO WHETHER THE PATIENT WAS BREAST-FED OR NOT**

	No. of patients	Median of the age of introducing gluten in months (range)	Median of the age of first symptoms of coeliac disease in years (range)
Breast-fed	24	5 (2–8)	1.33 (0.33–8)
Not breast-fed	3	4 (3–5)	1 (1–10)



*Fig. 2. How does a gluten-free diet affect the life of our patients (N=18)*

symptoms of the disease (Spearman correlation coefficient was used,  $r = 0.14$ ).

#### *Adherence to a gluten-free diet*

Reliable data were obtained from 26 of our patients (84%). Half of them strictly adhered to a gluten-free diet, while 23% adhered to a gluten-free diet irregularly, consuming gluten containing food from time to time. Seven patients (27%) ate normal, gluten-containing diet.

Eighteen patients (58%) have answered the question how does the gluten-free diet affect their lives. Two patients (10%) said that it is impossible to adhere to such a diet while 4 (20%) thought that it greatly affected their lives. The rest thought that the gluten-free diet either affects their life moderately (30%) or does not affect it at all (40%).

#### **Discussion**

Major changes in the clinical picture and in the age of the appearance of symptoms have been recorded in patients with

coeliac disease all over Europe. Most of them presented atypically in older ages, or were discovered by screening studies<sup>3,6,10,11</sup>. Since the understanding of this change could widen the knowledge of pathophysiology of coeliac disease, numerous studies on the influence of environmental factors were performed<sup>3</sup>. Most often, breast-feeding and the introduction of cow's milk formulas, the age of gluten introduction, the quantity and the quality of gluten and infantile gastroenteritis have been studied<sup>4</sup>.

We have recently showed that the incidence of coeliac disease in Croatia is exceptionally high and that coeliac disease presents very early. In nearly 50% of cases coeliac disease was diagnosed during the first two years of life, and it presented with typical clinical symptoms<sup>5</sup>. This differs Croatia from the majority of European countries, where, as stated above, decrease in incidence of clinically typical cases has been reported<sup>3,6</sup>.

However, the concept of coeliac disease in Croatia is similar to Swedish ex-

perience, where the age of introduction and quantity of gluten were identified as the most important environmental factors affecting early presentation of the disease and higher incidence of clinically typical cases<sup>12</sup>. Therefore, in this study we have tried to establish if infant nutrition has also influenced the presentation of coeliac disease in our patients.

According to results obtained in our study neither the introduction of gluten, nor the duration of breast-feeding had a major effect. However, many recent studies have shown the opposite results. Concerning breast-feeding, already in 1953 Andersen and di Sant'Agnese found that, if longer than two months, it delayed the onset of diarrhoea in coeliacs<sup>13</sup>. During 60's it was shown that even 80–90% of children with coeliac disease in Finland at the time of diagnosis were younger than 2 years, presenting with typical classical symptoms<sup>3,10,14</sup>. This was ascribed to diminished breast feeding and earlier introduction of humanized infant formulas and wheat into infants' diet<sup>3,4</sup>. During 80s and 90s coeliac disease in Finland started to be diagnosed later, mostly in children over 2 years of age, often with mild or even absent gastrointestinal symptoms what coincided with the revival of prolonged breast-feeding<sup>3,10,14</sup>.

The age at which gluten is introduced in diet has also been studied as an important factor in precipitating clinical disease. Some studies showed a positive correlation between the time of first wheat cereal ingestion and the mean age at diagnosis of coeliac disease<sup>15</sup> whereas in the others no correlation was found<sup>14,16</sup>. In Sweden, for example, the incidence of clinically recognized coeliacs is considerably higher than in its neighbouring countries and it was shown that the cereal consumption of healthy Swedish infants was significantly higher in comparison with Finland and Denmark<sup>17–19</sup>. Therefore, it was the amount of ingested

wheat gluten during infancy which was suggested to have a special role in triggering the development of enteropathy in genetically susceptible individuals<sup>4</sup>.

Since the pattern of coeliac disease in Croatia is similar to that in Sweden, we assumed that the habit of introducing gluten early, even in first few months of life, in a form of flour added to a diluted cow's milk may be the incriminating cause for early presentation of the disease. However, although short duration of breast-feeding (mean 2.9 months) and early gluten introduction (mean age 4.9 months) were confirmed by our study, no correlation was found between these factors and the age of disease presentation.

It is possible that the number of our patients was too small to establish a significant relations, so further studies in some other part of Croatia should be undertaken, using the same methodology.

For almost 5 decades it is well recognised that there is no coeliac disease without gluten<sup>10</sup> and for the last 20 years strict, life-long gluten-free diet has been advocated as the basic treatment for patients with coeliac disease<sup>7</sup>. Moreover, it has been clearly shown that adherence to a gluten-free diet may diminish the rate of various malignant and non-malignant complications of coeliac disease<sup>20</sup>. Compared to general population, untreated adults with coeliac disease have a 43-fold increased risk of non-Hodgkin's small bowel lymphoma, a 12-fold increase in the risk of oesophageal carcinoma and a 10-fold increased risk of carcinoma of the oropharynx<sup>21</sup>. Also, children with untreated coeliac disease show increased chromosomal instability which could be related to the predisposition to cancer<sup>22</sup>. Therefore, it has been suggested that coeliac disease should be regarded as a pre-malignant condition<sup>23</sup>. Holmes showed the decreasing trend of the excess morbidity rate (observed minus expected number of tumours divided by person

years at risk) over increasing adherence to a gluten-free diet was significant<sup>24</sup>. Moreover, it has been indicated that patients adhering to a strict gluten-free diet for at least five years have a similar risk of developing malignancy to this of general population<sup>8</sup>. Failure to implement a strict diet or failure to respond to dietary treatment may result in some other complications such as osteoporosis, gynaecological and obstetric problems and some other non-malignant complications<sup>20,25</sup>.

Despite all mentioned above, compliance to the diet has not improved over the years<sup>7</sup>. Studies have shown that as much as 6 to 48% of patients do not adhere to a gluten-free diet<sup>7,26–28</sup>.

Our study has shown even worse results. Every third patient thought it was either impossible to adhere to a gluten-free diet or that such diet greatly affected their lives. Half of our patients did not adhere to the gluten free diet: 23% allowed themselves gluten-containing food from time to time, while as much as 27% were on a normal diet. As suggested in other studies, this may be partly due to the fact that, after achieving remission, patients often feel well and are without any major symptom of the disease on a gluten-containing diet<sup>7</sup>. Ljungman et al. showed that the compliance to a gluten-free diet correlated well to a patients' knowledge of the disease<sup>29</sup>, while others have confirmed the same effect of a regular follow-up of patients by a physi-

cian<sup>7,30</sup>. Therefore, it is important to repeatedly inform the patients, medical workers and general population of the importance of life-long adhering to the gluten-free diet.

Another problem is that besides voluntarily non-compliance to gluten-free diet, coeliacs can unintentionally take gluten-containing food because of several reasons: i. lack of knowledge of the gluten-free diet; ii. list of ingredients on food products is not always available; iii. labelling may be inadequate; iv. possibility of gluten contamination of originally gluten-free food<sup>31–33</sup>.

Compared to an average European country, in Croatia the situation on the market is much worse; food labeling in respect to gluten is very poor, gluten-free products are sparse and are very expensive. These may be the additional explanations for poor compliance of our patients to the gluten-free diet, and their negative attitudes towards it. Therefore, a special support and regular follow-ups of patients are advised. Labelling directives should be improved to enable coeliacs to distinguish between gluten-free and gluten-containing food, as well as contamination of the gluten-free products should be avoided. It is also necessary to repeatedly increase awareness of patients, medical workers and population on coeliac disease in general, and about the importance of gluten-free diet in particular.

## REFRENCE S

1. WALKER-SMITH, J. A., S. GUANDALINI, J. SCHMITZ, Arch. Dis. Child., 65 (1990) 909. — 2. HALLERT, C., The epidemiology of coeliac disease: A continuous enigma. In: LOHINIEMI, S., P. COLLIN, M. MÄKI (Eds.): Changing features of coeliac disease. (The Finnish Coeliac Society, Tampere, 1998). — 3. VISAKORPI, J. K., Changing features of coeliac disease. In: MÄKI, M., P. COLLIN, J. K. VISAKORPI (Eds.): Coeliac disease. Proceedings of the Seventh International Symposium on Coeliac Disease. (Coeliac Study Group, Tampere, 1996). — 4. MÄKI, M., K. HOLM, H. ASCHER, L. GRECO, Factors affecting clinical presentation of coeliac disease: Role of type and amount of gluten-containing cereals in the diet. In: AURICCHIO, S., J. K. VISAKORPI: Common Food Intolerances 1: Epidemiology of Coeliac Disease. (Dyn. Nutr. Res., Karger, Basel, 1992). — 5. MATEK, Z., M. JUNGVIRTH-HEGEDÜS, S. KOLÁČEK, Coll. Antropol., 23 (1999) 621. — 6. GRECO, L., Evolution of coeliac disease. In: LOHINIEMI, S., P. COLLIN, M.

- MAKI (Eds.): Changing features of coeliac disease. (The Finnish Coeliac Society, Tampere, 1998). — 7. KUMAR, P. J., Dietary compliance and coeliac disease. In: LOHINIEMI, S., P. COLLIN, M. MÄKI (Eds.): Changing features of coeliac disease. (The Finnish Coeliac Society, Tampere, 1998). — 8. HOLMES, G. K., P. PRIOR, M. R. LANE, D. POPE, R. N. ALLAN, Gut, 30 (1989) 333. — 9. MÄKI, M., Changing features of coeliac disease. In: LOHINIEMI, S., P. COLLIN, M. MÄKI (Eds.): Changing features of coeliac disease. (The Finnish Coeliac Society, Tampere, 1998). — 10. CATASSI, C., I. M. RATTSCH, E. FABIANI, M. ROSSINI, F. BORDICCHIA, F. CANDELA, G. V. COPPA, P. L. GIORGI, Lancet, 343 (1994) 200. — 11. ASCHER, H.: Childhood coeliac disease in Sweden Changes in epidemiology, clinical pattern and diagnosis. Doctoral dissertation. (Göteborg University, Göteborg, 1996). — 12. ANDERSEN, D. H., P. A. DI SANT'AGNESE, Paediatrics, 11 (1953) 207. — 13. MÄKI, M., K. KALLONEN, M. L. LÄHDEaho, J. K. VISAKORPI, Acta Paediatr. Scan., 77 (1988) 408. — 14. STEVENS, F. M., B. EGAN-MITCHELL, E. CRYAN, C. F. McCARTHY, B. MCNICHOLL, Arch. Dis. Child., 62 (1987) 465. — 15. GRECO, L., A. E. TOZZI, M. MAYER, M. GRIMALDI, G. SILANO, S. AURICCHIO, Eur. J. Pediatr., 148 (1989) 610. — 16. ASCHER, H., The role of quantity and quality of gluten-containing cereals in the epidemiology of coeliac disease. In: MÄKI, M., P. COLLIN, J. K. VISAKORPI (Eds.): Coeliac disease. Proceedings of the Seventh International Symposium on Coeliac Disease. (Coeliac Study Group, Tampere, 1996). — 17. ASCHER, H., K. HOLM, B. KRISTIANSSON, M. MÄKI, Arch. Dis. Child., 69 (1993) 375. — 18. WEILE, B., B. CAVELL, K. NIVENIUS, P. A. KRASILNIKOFF, J. Paediatr. Gastroenterol. Nutr., 21 (1995) 64. — 19. HOLMES, G. K. T., Malignancy in coeliac disease. In: LOHINIEMI, S., P. COLLIN, M. MÄKI (Eds.): Changing features of coeliac disease. (The Finnish Coeliac Society, Tampere, 1998). — 20. HOLMES, G. K., P. L. STOKES, T. M. SORAHAN, P. PRIOR, J. A. WATERHOUSE, W. T. COOKE, Gut, 17 (1976) 612. — 21. KOLAČEK, S., I. PETKOVIC, I. W. BOOTH, Arch. Dis. Child., 78 (1998) 466. — 22. MARSH, M. N., J. Paediatr. Gastroenterol. Nutr., 24 (1997) S25. — 23. HOLMES, G. K. T., Annales Nestle, 51 (1993) 66. — 24. McCRAE, W. M., M. A. EASTWOOD, M. R. MARTIN, W. SIRCUS, Lancet, I (1978) 187. — 25. JACKSON, P. T., J. F. T. GLASGOW, R. THOM, Arch. Dis. Child., 60 (1985) 672. — 26. FABIANI, E., C. CATASSI, A. VILLARI, P. GISMODNDI, R. PIERDOME-NICO, I. M. RATTSCH, G. V. COPPA, P. L. GIORGI, Acta Paediatr. 412 Suppl (1996) 65. — 27. LJUNGMAN, G., U. MYRDAL, Acta Paediatr., 82 (1993) 235. — 28. BARDELLA, M. T., N. MOLTENI, L. PRAMPOLINI, A. M. GIUNTA, A. R. BALDASSARRI, D. MORGANTI, P. A. BIANCHI, Arch. Dis. Child., 70 (1994) 211. — 29. DEUTSCH, H., Food legislation and contamination. In: LOHINIEMI, S., P. COLLIN, M. MÄKI (Eds.): Changing features of coeliac disease. (The Finnish Coeliac Society, Tampere, 1998). — 30. JANSEN, F. W., Codex standard for gluten free products. In: LOHINIEMI, S., P. COLLIN, M. MÄKI (Eds.): Changing features of coeliac disease. (The Finnish Coeliac Society, Tampere, 1998). — 31. LOHINIEMI, S., K. MUSALAHTI, P. COLLIN, M. MÄKI, Measuring quality of life in coeliac disease patients. In: LOHINIEMI, S., P. COLLIN, M. MÄKI (Eds.): Changing features of coeliac disease. (The Finnish Coeliac Society, Tampere, 1998).

S. Kolaček

Referral Centre for Paediatric Gastroenterology and Nutrition, Children's Hospital Zagreb, Klaićeva 16, 10000 Zagreb, Croatia

## EPIDEMIOLOGIJA CELIJAKIJE U DJECE JEDNE HRVATSKE ŽUPANIJE: MOGUĆI ČIMBENICI KOJI UTJEĆU NA INCIDENCIJU I PRIDRŽAVANJE BEZGLUTENSKE DIJETE (DRUGI DIO)

### S A Ž E T A K

Celijakija je doživotni poremećaj uzrokovani glutenom i označen teškim oštećenjem sluznice tankog crijeva. Liječenje, bezglutenska prehrana, dovodi do oporavka sluznice i smanjuje rizik razvoja malignih i ne-malignih komplikacija. Prema podacima našeg zadnjeg istraživanja, kumulativna incidencija celijakije u djece u Hrvatskoj je 1:519 živorođenih. Bolest se javlja rano, najčešće s tipičnim kliničkim simptomima. Istraži-

van je mogući utjecaj dojenja i dobi uvođenja glutena na takvu pojavnost bolesti. U ispitivanje su uključeni celijakičari rođeni u Međimurju u razdoblju 1985–1994 (N = 31). Pridržavanje liječenja također je proučavano. Iako je pokazano kratko trajanje dojenja (srednja vrijednost 2.9 mjeseci) i rano uvođenje glutena (srednja vrijednost 4.9 mjeseci), nije potvrđena korelacija između tih čimbenika i dobi pojave bolesti. Što se tiče pridržavanja bezglutenske dijete, samo 50% bolesnika strogo se pridržavalo, 23% činilo je to neredovito, a 27% bilo je na normalnoj prehrani. Kako bi se to poboljšalo preporuča se redovito pratiti bolesnike.