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Alimentary Tract

Epidemiological and clinical features in immigrant children with coeliac disease: an Italian multicentre study

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See related commentary on pages 712–713

Abstract

Background. There are no available data concerning the incidence and the clinical pattern of coeliac disease in immigrant children coming to Italy from developing countries.

Aims. To evaluate the epidemiological and clinical features of coeliac immigrant children coming to Italy.

Patients and methods. Hospital records of 1917 children diagnosed in 22 Italian Centres from 1999 to 2001 as having coeliac disease were retrospectively reviewed, comparing immigrant patients versus Italian ones.

Results. 36/1917 (1.9%) coeliac children were immigrant. This prevalence was similar to that of the immigrant children among the whole paediatric population living in Italy. Prevalence was influenced by geographical factors, being higher in Northern Italy (1.7%) and in Central Italy (2.5%) than in Southern–Insular Italy (1.5%), as consequence of a higher proportion of immigrants in these regions. The native areas of the immigrant children were East Europe (15/36), Northern Africa (14/36), Southern Asia (4/36), West Africa (1/36), East Africa (1/36) and the Middle East (1/36). The clinical spectrum and dietary habits in immigrant patients were similar to those of the Italian children.

Conclusions. Coeliac disease among the immigrant children coming from developing countries is an emerging problem, and physicians need to be fully aware of it. An important risk factor for coeliac disease in immigrant children appears to be sharing of the same dietary habits with the Italian population. The finding of coeliac disease in children coming from many countries worldwide suggests that coeliac disease is a global public health problem.

Keywords: Coeliac disease; Immigrant children

1. Introduction

Coeliac disease (CD) is a permanent enteropathy caused by the ingestion of gluten, a protein occurring in wheat, rye and barley, in genetic-susceptible individuals. Epidemiological knowledge concerning CD saw great changes at the end of the 20th century, and the condition is now being seen as a worldwide health problem. Indeed, until about a decade ago the prevalence of gluten intolerance appeared to be 1/1000 in Europe [1], and CD was considered a very uncommon disease in the United States [2,3], in South America [4,5] and in developing countries [6–12]. However, more recently, several serological population screenings have shown that the prevalence of CD in Europe is 1/200 or greater [13–18]. Similarly, in the United States [19–21], in Latin America [22–25] and in Australia [26,27], it is more common than previously consid-

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ered, probably because the majority of Caucasian American, Latin American and Australian people share a common European ancestry. Furthermore, a very high incidence of CD has been recently reported in some developing areas of the World, such as North Africa [28–32], South Asia [33–36], the Middle East [37–41], while in the Old World there have been some sporadic case reports on native coeliac patients from developing countries [42,43].

In the last 25 years, the migratory flow from developing countries towards Italy has progressively increased. In December 2001, in our country the number of adult immigrants with regular residence permits was 1,362,630 [44]. A large proportion of them have permanent residence in Italy and get married. The direct consequence has been an increase in the number of infants born in Italy to immigrant parents, as well as of children coming from their native countries to join their original families. In December 2001, the number of immigrant children living in our nation was 326,101, mainly in Northern and Central Italy (respectively, 200,264, 61.4% and 82,742, 25.4%) and less in Southern–Insular Italy (43,095, 13.2%), amounting to 2% of the entire paediatric population living in Italy [44]. These children share the same environment and the same dietary habits as the Italian children. Therefore, if they have predisposing CD genetic factors (i.e. HLA DQ and non-DQ alleles), they may be at risk of gluten intolerance.

To our knowledge, there are no available data concerning the prevalence and the clinical pattern of CD, as well as the predisposing environmental risk factors for CD, in immigrant children coming to Italy from developing countries. The aims of the present study were to evaluate: (1) the prevalence of immigrant children with CD in our country; (2) the clinical findings of CD in these patients; and (3) the possible relationship between immigration, dietary habits and CD in childhood.

2. Patients and methods

This was a nationwide study with the co-operation of 22 paediatric Centres of Gastroenterology or Immigration Centres. It was retrospective, with a review of the hospital medical records from January 1999 to December 2001 of 1917 patients (both Italian and immigrant), consecutively diagnosed as having CD. The revised criteria of the European Society of Paediatric Gastroenterology and Nutrition (ESPGAN) for CD diagnosis were used [45]. The study was carried out under the auspices of both the 'Gruppo di Lavoro Nazionale per il Bambino Immigrato' (GLNBI), affiliated to the Italian Society of Paediatrics and the Italian Society of Paediatric Gastroenterology Nutrition and Hepatology (SIGENP).

Eight of the participant centres, with 768 patients, were in Northern Italy (Cuneo, Milano 1, Milano 2, Novara, Padova, Parma, Reggio Emilia, Venezia-Mirano), eight with 603 patients were in Central Italy (Ascoli Piceno, Bologna, L'Aquila, Lucca, Modena, Pisa, Roma 1, Roma 2) and six with 546 patients were in Southern and Insular Italy (Bari, Catania, Messina 1, Messina 2, Palermo 1, Palermo 2).

Thirty-six CD-affected immigrant children (ages ranging from 6 months to 15 years, mean age 7.3 years, 15 males and 21 females) were recruited. From the clinical histories of these immigrant patients we recorded: (1) parents' native countries; (2) patients' country of birth; (3) reasons for their presence in Italy (adoption, family rejoining, birth in Italy, casual presence in our country); (4) clinical findings of CD at diagnosis (classic, atypical, silent or latent forms), comparing them to those of the control group. The control group consisted of Italian CD children, matched for sex and age with immigrant CD children (1881 patients, ages ranging from 6 months to15 years, mean age 7.9 years; 891 males and 990 females), diagnosed in the same period, using the same criteria, in the same centres; (5) feeding practices of immigrant CD children by means of a non-quantitative dietary recall. In this regard, the parents of the immigrant CD children were called in each centre participating to the study, in order to request in the same manner and using the same criteria by means of the same standardised questionnaire notices on breast or bottle-feeding practices, duration of breast-feeding, age of the weaning, age at introduction of gluten-containing diets; (6) age of the onset of symptoms compared to the age of their coming to Italy; (7) age at diagnosis of CD, compared to the age of the onset of symptoms (diagnostic delay); (8) compliance to the gluten-free diet (GFD).

3. Results

36/1917 CD patients (1.9%) were immigrant. Table 1 shows their distribution through the Italian geographical areas (Northern, Central, Southern–Insular Italy), and Table 2 shows the native continents and the native countries of their parents. 5/36 of the immigrant CD children had only one immigrant parent.

Table 1
Geographic distribution of immigrant children in Italy (December 2001, source: Caritas, Rome) and geographic distribution in our country of the immigrant CD patients

Italian areas	Immigrant children (n = 326,101)	Immigrant CD patients (n = 36)	Total CD patients (n = 1917)	Prevalence of immigrant CD patients/total CD patients
Northern	200,264 (61.4%)	13	768	1.7%
Central	82,742 (25.4%)	15	603	2.5%
Southern–Insular	43,095 (13.2%)	8	546	1.5%

Table 2
Native continents and native countries of the parents' CD immigrant children (number of the immigrant CD children in the brackets)

East Europe (n = 15/36)	Macedonia (1), Rumania (4), Poland (2), Russia (1), Serbia (1), Albania (5), Ukraine (1)
North Africa (n = 14/36)	Egypt (1), Morocco (6), Tunisia (5), Saharawi (2)
West Africa (n = 1/36)	Cape Verde (1)
East Africa (n = 1/36)	Somalia (1)
Middle East (n = 1/36)	Syria (1)
Southern Asia (n = 4/36)	Sri Lanka (1), Pakistan (3)

Table 3
Parents' native countries of the immigrant children living in Italy

Countries	Immigrant children (n = 326,101)	Immigrant CD cases	Children/case
Morocco	49,567 (15.2%)	6	8,261
Albania	45,002 (13.8%)	5	9,000
China	22,827 (7%)	0	0
Rumania	16,305 (5%)	4	4,076
Yugoslavia	15,001 (4.6%)	1	15,000
India	11,740 (3.6%)	0	0
Macedonia	11,087 (3.4%)	1	11,000
Philippine Islands	10,761 (3.3%)	0	0
USA	9,131 (2.8%)	0	0
Peru	8,153 (2.5%)	0	0
Russia	7,501 (2.3%)	1	7,500
Ukraine	7,175 (2.2%)	1	7,100
Sri Lanka	6,849 (2.1%)	1	6,850
Tunisia	6,523 (2%)	5	1,305
Dominican Republic	6,523 (2%)	0	0
Pakistan	5,871 (1.8%)	3	1,848
Ghana	5,545 (1.7%)	0	0
Bangladesh	4,567 (1.4%)	0	0
Brazil	4,240 (1.3%)	0	0
Columbia	3,914 (1.2%)	0	0
Total of these 20 countries	**258,272 (79.2%)**	**28**	**10,000**
Other countries	**67,829 (20.8%)**	**8**	**8,478**

The 20 countries with higher frequencies are shown according to the decreasing order of presences (December 2001, source: Caritas, Rome).
Native continents of the immigrant children placed in Italian public hospitals: North Africa: 36%, East Europe: 25.9%, South Asia: 20%, Central Africa: 8%, Latin America: 5.8%, Giepsies: 4%, Australia, United States, Middle East (0.3%) (reference [46]).

Table 3 shows the native countries of the immigrant children living in Italy in December 2001, the immigrant CD patients observed for each country in our study and the rates of the immigrant children placed in Italian public hospitals during the observed years (1999–2001) in relation to their native continents.

Table 5
Clinical pattern at diagnosis in Italian and in immigrant CD children

	Italian CD children (n = 1881)	Immigrant CD children (n = 36)
Classical forms	1276 (67.8%)	25 (69.4%)
Atypical forms	510 (27.1%)	9 (25%)
Silent forms	95 (5.1%)	2 (5.5%)

No significant differences were observed between the two groups (χ^2 test).

20/36 (55.5%) of the immigrant coeliac children were living in Italy since birth (19 were born in our country and one had been adopted at birth). Fourteen immigrant CD children had been residing in Italy for several years because they had joined their families since their 2nd and 3rd year of childhood (11 patients), or because they have been adopted (three patients: one at the age of 2 years, one at the age of 3 years and 6 months, and one at the age of 6 years). Finally, two Saharawi patients coming from Saharan Africa were in our country on holiday, as part of a humanitarian programme.

Table 4 shows the clinical pattern and the presenting symptoms at diagnosis in the immigrant coeliac children. At diagnosis, their clinical pattern (classic, atypical and silent forms of CD) was similar to the one in the control group (Table 5). The two silent forms observed in these patients include a casual diagnosis (loss of the Kerckring folds observed during an upper gastrointestinal endoscopy performed for a suspected *Helicobacter pylori* gastritis), and an asymptomatic first-degree relative of a CD patient who tested IgA antiendomysium antibody (EMA) positive at serological familiar screening.

All the 20 immigrant CD children living in our country since birth had a short period of breast-feeding (less than 2 months) or formula-feeding since birth, and an early weaning (from the 4th month of life) with a consistent gluten intake. The onset of CD in these children was before 18 months of age in 15 cases (all classic forms with gastrointestinal symptoms), or after 4 years of age in four cases (all atypical forms without gastrointestinal symptoms). One of these patients (the asymptomatic first degree relative of a CD patient with positive EMA at a familial serological screening) had a silent form of CD.

Ten of the 16 immigrant CD children who came to Italy after birth (since their 2nd and 3rd year of childhood), previously, in their native country, used to eat products contain-

Table 4
Clinical pattern and presenting symptoms at diagnosis in immigrant CD patients

Presenting symptoms		
Classical forms 25/36 (69.4%)	Atypical forms 9/36 (25%)	Silent forms 2/36 (5.5%)
Chronic diarrhoea: 25/25	Iron-deficient anaemia: 3/9	Serological screening in first degree relative: 1/2
Weight loss: 25/25	Short stature: 2/9	Loss of Kerckring folds at endoscopy: 1/2
Abdominal distention: 24/25	Delayed puberty: 1/9	
Vomit: 22/25	Recurrent oral aphthae: 1/9	
	Abdominal pains with constipation: 2/9	

Table 6

Case	Native country	Coming to Italy	Age of CD onset	Age at diagnosis	Diagnosis delay	Clinical form
1	Albania	Since birth	15 months	1 year and 6/12	3 months	Classical
2	Albania	2 years and 6/12[a]	12 months	4 years and 6/12	3 years and 6/12	Classical
3	Albania	Since birth	12 months	21 months	9 months	Classical
4[b]	Albania	Since birth	10 months	14 months	4 months	Classical
5	Albania	10 years		15 years		Silent[c]
6[b]	Rumania	Since birth	4 years	4 years and 6/12	6 months	Classical
7[d]	Rumania	3 years and 6/12	4 years and 6/12	5 years	6 months	Classical
8	Rumania	Since birth	14 months	2 years and 2/12	12 months	Classical
9[d]	Rumania	5 years and 6/12[a]	12 months	6 years	5 years	Classical
10[e]	Poland	Since birth	4 years	8 years	4 years	Atypical
11	Poland	Since birth	11 months	15 months	4 months	Classical
12[b]	Russia	Since birth	6 months	11 months	5 months	Classical
13[d]	Ukraine	3 years and 7/12[a]	10 months	3 years and 10/12	3 years	Classical
14	Serbia	18 months[a]	12 months	18 months	6 months	Classical
15	Macedonia	Since birth	18 months	20 months	2 months	Classical
16	Morocco	2 years and 6/12	3 years	3 years and 6/12	6 months	Classical
17	Morocco	Since birth	12 months	6 years	5 years	Classical
18	Morocco	6 years and 6/12[a]	2 years	10 years and 6/12	8 years and 6/12	Classical
19	Morocco	4 years	8 years	9 years	12 months	Atypical
20	Morocco	14 years and 6/12[a]	12 years	15 years	3 years	Atypical
21	Morocco	9 years and 10/12[a]	6 years	10 years and 10/12	4 years and 10/12	Atypical
22[b]	Tunisia	Since birth	7 months	13 months	6 months	Classical
23[b]	Tunisia	Since birth	5 years	5 years and 6/12	6 months	Atypical
24	Tunisia	Since birth	14 months	18 months	4 months	Classical
25	Tunisia	Since birth		2 years and 10/12		Silent[f]
26	Tunisia	Since birth	12 months	4 years	3 years	Classical
27[g]	Saharawi	10 years[a]	2 years	10 years	8 years	Classical
28[g]	Saharawi	9 years[a]	18 months	10 years and 6/12	9 years	Classical
29	Egypt	Since birth	8 months	11 months	3 months	Classical
30	Pakistan	3 years	5 years	5 years and 6/12	6 months	Atypical
31	Pakistan	5 years and 6/12	7 years and 6/12	8 years and 6/12	12 months	Atypical
32	Pakistan	Since birth	5 years and 6/12	6 years and 6/12	12 months	Atypical
33	Sri Lanka	Since birth	6 months	10 months	4 months	Classical
34	Syria	Since birth	8 months	16 months	8 months	Classical
35	Cape Verde	Since birth	7 years	8 years	12 months	Atypical
36	Somalia	8 years[a]	12 months	9 years	8 years	Classical

[a] Patient with CD symptoms at the moment of the arrival to Italy.
[b] Only one immigrant parent.
[c] Upper gastrointestinal biopsy.
[d] Adopted child.
[e] Adopted child since birth.
[f] Serological familiar screening.
[g] In Italy on holiday.

ing wheat flour, especially bread (three patients coming from Morocco, two from West Algeria, one from Somalia, one from Ukraine, one from Serbia, one from Rumania and one from Albania). 8/10 had a clear CD clinical pattern with gastrointestinal symptoms (classic forms) on their arrival in our country and 2/10 an atypical form.

The remaining 6 of the 16 immigrant CD children who came to Italy after their birth began to eat gluten-containing foods immediately after their arrival in our country. In two of them the onset of CD (classical forms with gastrointestinal symptoms) was early (after 6 months), while in other three it was later, after 2–4 years (atypical forms without gastrointestinal symptoms). The last of these immigrant CD children (the patient diagnosed during an upper gastrointestinal endoscopy by loss of Kerckring folds) had a silent form.

Table 6 shows, for each immigrant coeliac child, his/her native country, the age of coming to Italy, the age of CD onset, the age at diagnosis, the diagnosis delay and the clinical form. Excluding the two patients with the silent form, the age of onset was early in 25/34 cases, regardless of their native country. Furthermore, excluding the two patients with silent form and 10 who arrived in our country already displaying clear symptoms of CD, the diagnostic delay was short (less than 1 year) in 22/24 cases, regardless of their native country.

Regarding the clinical course and the compliance with the GFD, the follow-up of the immigrant CD children was possible in 33 cases, since the remaining three went back to their native country. If we exclude the four adopted children living in Italian families who paid special attention to the health problems of their adopted children, a strict GFD was followed

Table 7
Prevalence of CD in different areas of the world (data obtained with population's serological screening and not with retrospective search of previously identified cases)

Geographic areas	Prevalence of CD	Reference
Europe		
Estonia	1:88	[48]
Finland	1:99	[18]
Germany	1:500	[60]
Hungary	1:85	[13]
Ireland	1:122	[17]
Italy	1:184	[14]
Norway	1:250	[61]
Portugal	1:134	[62]
Spain	1:389	[63]
Sweden	1:190	[16]
Switzerland	1:132	[64]
The Netherlands	1:198	[65]
United Kingdom	1:100	[66]
United States	1:133	[21]
Australia	1:251	[26]
North Africa	1:18	[28]
Latin America		
Brazil	1:681	[22]
Argentina	1:167	[23]
Middle East		
Israel	1:157	[40]
Iran	1:166	[41]

by 25/29 (86.2%) of these patients. No relationship was observed between adherence to GFD and their parents' native country, whereas the four immigrant patients who did not adhere to a strict GFD were members of families with a very low income. All the immigrant coeliac patients who adhered to a strict GFD showed a remission of their symptoms.

4. Considerations and conclusions

This is the first study on immigrant coeliac children coming from developing countries to Italy, and shows that they, compared to the Italian children, can similarly be affected by gluten intolerance. The majority of the immigrant CD children were residing in Italy since birth (20/36) or since several years (14/36). This finding shows that the migratory flow of children from developing countries towards Italy is permanent and suggests that in the next future, CD will be a new and emerging healthy problem also among immigrant children, because their presence in Italy is quickly increasing [44].

It is likely that the cases presented here do not fully represent all immigrant coeliac children residing in our country. Indeed, our findings are the result of a retrospective search of previously identified cases and not a longitudinal serological prospective screening of the immigrant population. On the contrary, the advent of serological tests for population screening has shown in several studies, both in Europe and in the other continents (Table 7), many undiagnosed (subclinical or asymptomatic) cases of CD. Consequently, our study might have underestimated the true prevalence of CD in the immigrant children because, being retrospective and cross-sectional, it has probably missed some of the silent/subclinical immigrant coeliac patients.

As Table 2 shows, our patients mainly come from Eastern Europe (15/36) and from North Africa (14/36). This finding is not surprising because CD is very common in these areas of the world [13,28–32,47–49] and because the immigrant children living in Italy and placed in Italian public hospitals are mainly native to these countries (Table 3). On the other hand, we observed only one CD patient from the Middle East (Syria) where CD probably originated [50], and no CD children coming from the United States, South America and Australia, where there is a high prevalence of CD [21–23,26,27]. As Table 3 shows, these findings appear to be related to the low number of immigrant children coming to Italy from Middle East, United States, South America and Australia, who are placed in Italian public hospitals [46].

We have not observed coeliac children coming from Central Africa. The reason for our finding might again be the low number of immigrant children coming to Italy from this part of the world and placed in Italian public hospitals. Nevertheless**,** a genetic cause might also account for this finding. Indeed, in some populations of Central Africa (i.e. the Mossi people, living in Burkina Faso, formerly Upper Volta) the risk of CD, despite the consumption of wheat foodstuffs, seems to be low probably because they have a very low frequency of the HLA CD predisposing genes [51]. In this regard, however, further studies are needed, because the frequencies of the HLA predisposing CD genes in the populations of the Central Africa are not yet well known.

CD seems to be very uncommon in the Far East (China, Japan, Korea, Philippine Islands, Malaysia, etc.) [52,53], where it is not clear whether CD does not exist because wheat products are not the staple diet, or because these populations do not have a genetic risk for CD (in the Far East the frequencies of the HLA predisposing CD genes are unknown). We have not observed coeliac children coming from this area of the world. However, the immigrant children coming to Italy from the Far East are mainly Chinese and natives of Philippine Islands (Table 3). Chinese immigrants form enclosed and exclusive communities, keeping their diet based on a non-gluten-containing foods and preferring to go to their own physicians rather than to the Italian Public Health Services [44]. Furthermore, Chinese and native Philippine Islands children rarely live for a long time in Italy with their parents, tending instead go back to their native countries [44]. These could quite possibly be the reasons for the lack of coeliac children coming from the Far East in our survey. Nevertheless, three cases of CD patients have been recently described in adult descents of Japanese and Chinese immigrants living in Canada [54], and this finding suggests that genetic susceptibility to CD also exists in these populations.

In our survey 4/36 (11.1%) immigrant coeliac children were native to South Asia (three patients came from Pakistan and one from Sri Lanka, formerly Ceylon, in Southern India).

During recent years, several epidemiological studies [33–36] have shown a high incidence of CD in some areas of South Asia (i.e. Northern India). Instead, except for sporadic cases reported several years ago [55], no available epidemiological data exists concerning the prevalence of CD in other areas of South Asia (i.e. Pakistan, South India, etc.). However, our findings show that CD is present (and probably underestimated because under-diagnosed) in these people, suggesting that greater attention to gluten intolerance is also needed in South Asia.

During the years studied (1999–2001), the prevalence of immigrant CD children among CD patients (36/1917, 1.9%) appeared similar to that (2%) of the immigrant children among the whole paediatric population living in Italy [44]. This finding suggests that the presence of CD in immigrant children may be related to some environmental risk factors shared with the Italian childhood population. In this respect, in most developing countries infants' diets are based on prolonged breast-feeding and on delayed weaning, without or with small amounts of gluten-containing cereals, conditions described as having a protective effect against the development of CD [1]. On the contrary, all the 20 immigrant CD children living in our country since birth had, similarly to the Italian childhood population [56,57], a short period of breast-feeding or a formula-feeding since birth and an early weaning with a consistent dietary gluten intake. Likewise, the six asymptomatic immigrant CD patients who came to Italy to join their parents, began eating gluten-containing foods immediately after their arrival in our country. In the same way, the 10 immigrant CD patients who came to Italy with clear clinical signs of CD, in their native country had previously ingested products containing wheat flour. Therefore, this sharing of similar dietary habits among immigrant and Italian children might represent the same environmental CD risk factor.

It is well known that CD is a complex disease that has a strong genetic component related to HLA and non-HLA alleles [53,58]. In the cases presented here of immigrant CD patients we have not looked for the genetic CD risk factors (i.e. HLA genes). However, the reliability of the CD diagnosis, based on revised ESPGAN criteria [45] provides an indirect confirmation that the immigrant children presented here have the predisposing CD genes. This suggests that distant and apparently different populations have the same genetic predisposing CD background and that gluten intolerance is widespread in the world as in a common 'global village' [67], involving not only people of European ancestry but also population of the developing countries. Consequently, CD should be seen as a worldwide public health problem.

In the immigrant children, the clinical presentation of CD (classical, atypical and silent forms) was similar to that observed both in the control group (Table 5) and in a recent multicentre study on the clinical pattern of CD in Italy [59]. In the same way, as with the well-known clinical pattern of CD in the children of the Old World, the age of onset of symptoms in the immigrant CD children appears to modify the clinical picture: an earlier onset is associated with classic forms with gastrointestinal symptoms, and a delayed onset with atypical forms, without gastrointestinal symptoms. Therefore, since the coeliac children under study come from different continents and countries of the world, our findings show that in childhood the clinical spectrum of CD tends to be the same in each race and in each ethnic group, regardless of the areas of origin.

In the majority of the CD immigrant children, the diagnostic delay was short and the compliance to GFD strict, regardless the families' native country. This findings suggest that immigrant CD children are not at risk of being neglected in relation to the cultural differences and traditions of their families.

In conclusion, the prevalence of CD in the immigrant children coming to Italy from the developing countries is high and similar to the one of the immigrant children among the whole paediatric population living in Italy. It appears an emerging health problem because there is a large and increasing number of immigrant children with permanent residence in our nation. The clinical picture of CD in these patients, despite the wide differences in their countries of origin, is the same as the one known in the coeliac children of the Old World. An important environmental risk factor for CD in immigrant children may be the sharing of dietary habits with Italian children. The finding of CD patients native to different countries suggests that CD has a wide distribution in the world as in a common global village and that it should be seen as a worldwide public health problem.

Conflict of interest statement

None declared.

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Appendix A

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