Current Paediatric Coeliac Disease Screening Strategies and Relevance of Questionnaire Survey

Lyudmila V. Savvateeva^a Svetlana I. Erdes^b Anton S. Antishin^b
Andrey A. Zamyatnin Jr.^{a, c}

^aInstitute of Molecular Medicine, Sechenov First Moscow State Medical University, Moscow, Russian Federation;

^bFaculty of Pediatrics, Sechenov First Moscow State Medical University, Moscow, Russian Federation; ^cBelozersky Institute of Physico-Chemical Biology, Lomonosov Moscow State University, Moscow, Russian Federation

Keywords

Coeliac disease · Paediatric population · Symptoms · Screening · Questionnaire

Abstract

Coeliac disease (CD) is an autoimmune enteropathy triggered by the ingestion of gluten-containing grains in genetically predisposed individuals. Identification of CD in clinical practice is often difficult due to the manifestation of non-specific symptoms and signs, so a relatively significant proportion of CD cases remain undiagnosed. Timely detection of the disease is necessary to provide an appropriate approach to control of the disease treatment, in order to avoid potential complications. This is even more important in the case of children and adolescents, to ensure their proper growth and development. In this review, we discuss the data on the current strategies for CD detection among paediatric populations and the role of questionnaire-based discovery of CD cases in the area of interest. We assume that mass screening is a preferable strategy for finding CD cases within the paediatric population because this could uncover symptomatic, oligosymptomatic, and asymptomatic CD

cases. However, under conditions of limited financial resources, screening for CD in risk groups, members of which can be identified using questionnaires, is essential. The pros and cons of CD screening in paediatric populations are presented. These depend on a number of situational criteria (cost-effectiveness, lack of awareness), but screening is designed to improve the detection of the disease and therefore improve the quality of life of patients.

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Introduction

Coeliac disease (CD) is an immune-mediated systemic disorder caused by ingestion of gluten and related prolamines from wheat, barley, and rye cereals in genetically susceptible individuals [1, 2]. The genetic component is determined by the presence of well-established HLA-DQ2 and/or HLA-DQ8 haplotypes and some non-human leucocyte antigen (HLA) genetic variants [3, 4]. The

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Table 1. Common clinical manifestations of CD and associated conditions

Symptoms
Gastrointestinal
Diarrhoea
Abdominal pain
Constipation
Gas/bloating/distention
Poor weight gain
Malodorous fatty stools
Vomiting, etc.
Extraintestinal
Pubertal delay
Unexplained weight loss
Poor height gain
Bone/joint pain
Eczema
Hives/atopic dermatitis
Dermatitis herpetiformis
Fatigue
Headache/migraine
Foggy mind, etc.
Iron deficiency anaemia, etc.
Associated condition (risk group)
Genetic predisposition
First-degree relatives of coeliac patients
T1DM
Autoimmune thyroid disease
Autoimmune liver disease
Trisomy 21 (Down syndrome)
Williams syndrome
Turner syndrome
IgA deficiency
Hashimoto thyroiditis, etc.
Juvenile chronic arthritis, etc.
CD, coeliac disease; T1DM, type 1 diabetes mellitus; IgA, immunoglobulin A.

disease is accompanied by small intestinal enteropathy with variable degrees of severity and the presence of coeliac-specific autoantibodies against tissue transglutaminase type 2 and deamidated forms of gliadin peptides [5]. The clinical manifestations of CD are extremely diverse, varying from gastrointestinal complaints to a broad spectrum of non-specific signs and symptoms and associated conditions (Table 1).

Among the paediatric population it has been observed that gastrointestinal symptoms are usually predominant in young children, and non-gastrointestinal signs are more common in older children and adolescents [6–8]. Moreover, the disease can be oligosymptomatic or asymptomatic, and therefore it is important to diagnose CD

in a timely manner to avoid or reduce probable complications and negative health consequences (e.g., osteopenia, which is the most common problem) [5, 9–13].

To date, a proven effective treatment for CD has been a lifelong gluten-free diet (GFD). Strict adherence to a GFD is complicated by a number of factors (nutrient deficiency, high cost and low availability of gluten-free products and contamination with “hidden” gluten) and is especially problematic for children. Therefore, there are non-dietary CD treatments are in various stages of development, using exogenous gluten-degrading enzymes, substrates regulating intestinal permeability, various forms of immunotherapy, etc. [14].

At present, the global CD prevalence is estimated at approximately 1% with a clear tendency to increase based on data from various locations [15–17]. This lifelong disorder should be identified promptly, but the availability of screening strategies for CD is debatable. The aim of this review is to analyze the available data on CD screening strategies among paediatric populations and to discuss their pros and cons.

CD Diagnostic Strategies in Paediatric Populations

The diagnosis of CD remains a clinical challenge for many physicians due to the diversity of CD manifestations. Currently, CD diagnosis is based on the results of specific serology tests, duodenal biopsy, and HLA typing, as well as the response to temporary GFD.

HLA typing is recommended to identify the HLA class II haplotypes DQ2 and DQ8, which are involved in the presentation of gluten antigens to T cells, triggering the process of cell tissue damage [4]. The lack of HLA-DQ2 and HLA-DQ8 heterodimers is currently considered to be an indication of a negative predictive value for CD [5].

Among the serological tests used are those for anti-gliadin antibodies (AGA, IgA/IgG; now obsolescent), anti-tissue transglutaminase (ATTG, IgA/IgG), endomysial antibodies (EMA, IgA/IgG), and deamidated gliadin peptides (DGP, IgA/IgG). Due to the high sensitivity and specificity of the ATTG and EMA tests, their combination identifies suspected CD in children with the highest accuracy [18]. However, to prevent false results, the subjects should not be on a gluten-restricted diet, and the immunoglobulin A (IgA)-deficient individuals should be tested via IgG-based assays (i.e., IgG-ATTG) [19]. Recently, the usefulness of the major CD-specific wheat antigen gamma-gliadin 1 (GG1) has been evaluated [20].

Due to its high sensitivity and specificity, recombinant GG1 could be an important CD-specific antigen in the ELISA-based test for identifying patients with CD as well as in monitoring treatment and studying the pathomechanisms of CD.

Endoscopic duodenal biopsy is often considered to be the gold standard in CD diagnosis. CD lesions in the small bowel may present in various histological forms. The lesion gradation is often subdivided according to the Marsh-Oberhuber classification, using architectural changes in villi and crypts, an increase in lamina propria cell density and an increase in counts of intraepithelial lymphocytes [21]. The interpretation of duodenal biopsies depends on a number of variables (biopsy specimen orientation, handling and processing, awareness of histological similarity with other diseases), and therefore, in order to avoid a CD misdiagnosis, proper manipulation techniques should be used [22]. The method of obtaining intestinal mucosal specimens may also vary, from using forceps from the distal duodenum to using a suction capsule from the jejunum [23] (as recommended by paediatric societies). The role of capsule endoscopy in establishing CD diagnosis is also evaluated [24, 25]. Such procedures, in addition to being quite expensive and time-consuming, are painful and uncomfortable for patients, especially for children (with a risk of adverse reactions such as bleeding). Therefore, it is necessary to attempt to establish the CD diagnosis in alternative ways, bypassing biopsy and endoscopy if possible.

In order to improve current CD diagnostics, a number of novel methods are in the process of development and validation. Notable non-invasive markers include serum intestinal fatty acid-binding protein (I-FABP), autoantibodies against exocrine pancreatic secretory granule membrane glycoprotein 2 (anti-GP2), the substrate of intestinal cytochrome P450 3A4 (CYP3A4) and some volatile organic compounds (VOCs). I-FABP is a sensitive marker for small intestinal epithelial damage and its measurement level, in addition to being the standard diagnostic procedure for CD, enables duodenal biopsy to be avoided in children at non-extreme values of ATTG [26, 27]. The Crohn's disease marker anti-GP2 has been found recently in coeliac patients, probably due to the loss of tolerance to GP2 resulting from increased permeability of the injured intestine. However, parallel testing of CD-specific ATTG or EMA is still needed for differentiating CD from Crohn's disease [28]. A metabolism control approach was proposed by Morón et al. [29], using the measurement of the serum concentration of an orally admin-

istered CYP3A4 substrate, simvastatin (cholesterol-lowering drug), for non-invasive assessment of the patient's small intestinal health. Another tool for the non-invasive detection of various diseases is detection of specific patterns of VOCs in urine, breath, sweat, and faeces. Since several gastrointestinal disorders are characterized by an altered gut microbiome, the detection of certain VOCs (e.g., cyclooctatetraene), using electronic nose technology analysis and/or field asymmetric ion mobility spectrometry, allows identification of urinary patterns associated with possible CD [30]. All these markers may also be suitable for evaluating intestinal healing in patients with GFD compliance.

Meanwhile, significant advances in genetics and genomics allow clarification of the molecular pathophysiology of CD. The use of the Immunochip genotyping platform contributed to the detection of non-HLA loci associated with CD. These data, according to Ricaño-Ponce et al. [31], are crucial, providing leads for the development of alternative therapies to the current GFD and the construction of genetic risk profiles to reveal genetic CD-associated factors which may be used for the stratification of patients. Moreover, the study of the cell types implicated in CD and the effects of CD-associated single-nucleotide polymorphism is aimed at determining the genetic make-up of individual patients so that appropriate therapies can be selected to target only the pathways that are deregulated in that particular patient [32].

Thus, the obvious progress in CD diagnostics via the development of immunobiological trials and genetics/genomics as well as the modernization of gastrointestinal endoscopic techniques are leading to improvements in establishing CD diagnoses and in the frequency of CD detection in patients, whether symptoms are clear or vague.

Meanwhile, it should be taken into account that CD diagnostic strategies and interpretation of the results may differ in patients with or without various symptoms. Currently, the choice of diagnostic criteria for certain groups of paediatric patients is stipulated by guidelines for the diagnosis of CD, e.g., those of the European Society for Paediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) [5], the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN) [33], the World Gastroenterology Organisation (WGO-OMGE) [34], the British Society of Gastroenterology [35], and the American College of Gastroenterology [19]. In general, it is recommended to test for CD in persons with gastrointestinal manifestation and extraintestinal symptoms without another con-

Table 2. Mass screening studies of the paediatric CD

Region	Study period	Number of people surveyed	Age	Screening methods			Prevalence of CD (%)	Ref. No.
				serology	HLA typing	gastro-intestinal endoscopy		
Karelia, Russia	1997–2001	1,988	6–18	ATTG, EMA	+	+	1:496 (0.2)	[42]
Finland	1994–2001	3,654	7–16	ATTG, EMA	+	+	1:99 (1.0)	[43]
Trieste, Northeast Italy	1999–2000	3,188	6–12	AGA, ATTG, EMA	+	+	1:96 (1.0)	[44]
Republic of San Marino	1993–2009	6,383	6, 10, 14	AGA, ATTG, EMA	–	+	1:125 (0.8)	[39]
Western Sahara	1998	1,005	2–18	ATTG, EMA	–	+	1:18 (5.6)	[45]
Ariana, Tunisia	2004–2005	6,286	6.7–12.7	ATTG, EMA	–	+	1:157 (0.6)	[46]
Ludhiana District of Punjab, North India	2003–2004	4,347	3–17	ATTG	–	+	1:310 (0.3)	[47]
Turkey	2006–2008	20,190	6–17	ATTG, EMA	–	+	1:212 (0.5)	[48]

This table summarizes the data of the studies that roughly reflect the situation in different parts of the world. CD, coeliac disease; AGA, anti-gliadin antibodies; ATTG, anti-transglutaminase antibodies; EMA, anti-endomysial antibodies.

firmed diagnosis and individuals with conditions associated with CD (Table 1). According to the updated algorithms of ESPGHAN [5], the assessment of CD prevalence in children is commonly based on the results of screening performed within one of the following groups. The first group consists of children and adolescents with otherwise unexplained signs and symptoms suggestive of CD (e.g., chronic or intermittent diarrhoea, failure to thrive, weight loss, stunted growth, delayed puberty, amenorrhoea, iron-deficiency anaemia, nausea or vomiting, chronic abdominal pain, cramping or distension, chronic constipation, chronic fatigue, mouth ulcers, dermatitis herpetiformis-like rash, fracture with inadequate traumas and abnormal liver biochemistry). In this patient group, the algorithm provides an opportunity to forgo biopsy. Diagnosis of CD without biopsy could be considered in symptomatic patients with a combination of a tenfold excess of the upper limit of the normal ATTG level, positivity for EMA in serum, and HLA-DQ2/DQ8-positive haplotype. However, it should be borne in mind that without biopsy confirmation, false diagnosis cannot be completely ruled out. The second group consists of asymptomatic children and adolescents with an increased risk of CD (e.g., individuals suffering from type 1 diabetes mellitus, Down syndrome, autoimmune thyroid disease, Turner syndrome, Williams syndrome, selective IgA deficiency and autoimmune liver disease, and persons who have first-degree relatives with CD). In this group, screening for CD is recommended to start with HLA-DQ2 and HLA-DQ8 typing, with confirmation of CD diagnosis via biopsy [5].

CD Screening Strategies in Paediatric Populations

CD is a common disorder with a worldwide distribution and it has a significant impact on daily life. As mentioned above, earlier detection of CD is important to avoid an increased risk of long-term consequences from the untreated disease, in both children and adults. Currently, screening strategies are presented in the form of screening of the general population (mass screening or screening of low-risk groups) or screening of at-risk groups only. These strategies have their pros and cons and their supporters and opponents, and to date, opinions about who should be tested for CD remain controversial [36, 37]. Soon, however, it may be possible to predict an increasing tendency to switch to serological analysis of CD in the general population [16, 38]. For the present, it is a question of economic expediency: mass screening is quite expensive due to the large number of test subjects compared to smaller cohorts of at-risk groups, although screening in the latter case requires a certain periodicity of analysis. According to the few available data, an accurate assessment of the cost-effectiveness of a mass CD screening programme is difficult, though in some screening studies such spending is not considered to be critical [39]. Along with the direct costs of diagnostic tests, instrumental and medical procedures, the cost of CD screening strategies should also include the costs of raising the awareness of clinicians (care providers) and parents, for accurate prediction and timely prevention of CD. Indeed, in the study by Berti et al. [40], a successful attempt was made to increase the quality of the CD diagnosis in children after an educational intervention.

Table 3. Prevalence of pediatric CD at risk groups

Risk group	Region	Number of people surveyed	Screening methods			Prevalence of CD, %	Ref. No.
			serology	HLA typing	gastro-intestinal endoscopy		
<i>Autoimmune diseases</i>							
T1DM ^a	Brazil	111	ATTG, EMA	–	+	4.5	[52]
	India	126	ATTG	–	+	13.5	[53]
	Sistan and Baluchestan Province, Iran	344	ATTG	–	+	2.9	[53]
Thyroid disorders	Sweden	300	EMA	+	+	9.7	[54]
	Italy	331	EMA	–	+	6.6	[55]
	Turkey	80	ATTG	–	–	1.3	[56]
	Sweden	335	AGA, ATTG, EMA	+	+	4.3	[57]
	Italy	343	AGA, EMA	–	+	26.2	[59]
	USA	302	ATTG	–	+	1.3	[59]
	Sistan and Baluchestan Province, Iran	344	ATTG	–	+	3.7	[53]
	Turner syndrome	Ireland	35	ATTG, EMA	–	+	9.4
	Egypt	80	ATTG	–	+	12.5	[61]
<i>Syndromes</i>							
Down syndrome	Brazil	77	ATTG, EMA	–	+	13.0	[85]
	Estonia	134	AGA, ATTG, EMA	+	+	3.0	[62]
	Netherlands	137	AGA, ATTG, EMA	+	+	8.0	[63]
Williams-Beuren syndrome	Turkey	24	ATTG	+	+	4.2	[64]
<i>Family history</i>							
First-degree relatives	Portugal	111	AGA, ATTG	+	+	3.1	[65]
First-degree relatives	Iran	119	ATTG	–	+	6.5	[66]
First-degree relatives	India	202	ATTG	+	+	8.9	[67]

This table summarizes the data from the studies that roughly reflect the situation in different parts of the world. CD, coeliac disease; T1DM, type 1 diabetes mellitus; AGA, anti-gliadin antibodies; ATTG, anti-transglutaminase antibodies; EMA, anti-endomysial antibodies. ^a More detailed information can be found in a recent review [74].

The undeniable advantage of mass screening is the identification of CD cases with oligosymptomatic and asymptomatic manifestations, which can otherwise often remain undiagnosed. It is also well established that only between 1 in 3 and 1 in 7 patients with CD are symptomatic [41]. Mass CD screening among the paediatric population is easy to implement via CD-specific analyses of IgA ATTG in serum samples collected for ordinary paediatric medical examination. However, false-positive serology may result in unnecessary and traumatic biopsy for healthy children, and this represents a significant disadvantage of CD screening in the general population until the procedure will have been replaced by non-invasive tests.

Since CD is a genetic and autoimmune disease, relatives of CD patients and sufferers from autoimmune diseases have an increased risk of CD development. There is also a correlation between the risk of CD development and some other disorders (Table 1). Screening for CD in at-risk groups is less costly and is justified, since it is known that the frequency of the disease in these groups is much higher than in the general population (Tables 2, 3). These patients should be tested periodically, at least for ATTG, to monitor for the emergence of CD, but the periodicity of tests is not indicated anywhere in the guidelines.

However, the identification of at-risk groups also requires a proper approach. Questionnaires may be suitable for this purpose, as well as for detecting emerging CD-

specific symptoms and signs. For a cohort identified by means of a questionnaire-based survey, a serological analysis should be carried out.

These strategies are described in more detail below. Ultimately, the optimal CD screening strategy is a personalized, preventive diagnosis capable of identifying potential CD patients at any age via the definition of CD-specific genetic markers.

Mass Screening in Children

The current strategy for mass screening for CD is to collect a pool of serum samples for subsequent instrumental analysis among the general paediatric population, usually represented by schoolchildren and adolescents from different geographical areas. To date, a number of paediatric population studies have been carried out on the spread of CD and screening for CD (some of these are given by country in Table 2). The set of samples currently available with respect to large-scale screening for CD and the determination of CD-specific antibody titres in these samples is carried out, as a rule, over a long period of time (a year or longer, see Table 2 [39, 42–48]). For instance, in Finland, large-scale CD screening was conducted using collected serum samples obtained from children for HLA typing and analysis for the presence of EMA and tissue transglutaminase antibodies. The prevalence of the combination of antibody positivity and an HLA haplotype associated with CD was 1 in 67, while the estimated biopsy-proved prevalence of CD among Finnish schoolchildren was reported as at least 1 case in 99 children (1.0%) [43]. The authors of the study noted that one-third of the subjects in whom CD was detected by screening had no symptoms and did not have any risk factors for CD. The same criteria were assessed in schoolchildren in the neighbouring Russian region of Karelia, but here the prevalence was lower – about 0.2% [42]. In the Republic of San Marino, instrumental analysis was used to determine levels of IgA AGA, IgG AGA or ATTG antibodies. Anti-EMA tests were performed if the result of the previous test was positive or borderline. If the EMA test was positive, then an endoscopy with histological examination was performed to confirm the final diagnosis. It is significant that when screening was performed with the AGA serological test in San Marino, the prevalence of CD was 1:169 or 0.6%, but later in the study the ATTG test was used for CD screening and the value of the overall CD prevalence increased to about 0.8% [39]. Screening for CD prevalence via the ATTG assay was carried out in a large paediatric population in Trieste; the prevalence in biopsy-proven coeliac subjects was found to be 1:106

(0.9%) and the ratio of symptomatic to asymptomatic cases diagnosed was 1:2 [44].

The available epidemiological data indicate that CD is also not rare in North Africa. The screening study performed in the general population involving refugee children from the Western Sahara showed a 5.6% prevalence of serum anti-EMA-positive tests in samples of Saharawi children [45]. These data have not been confirmed in other surveys among the North African population. A mass survey among schoolchildren was held in Ariana, a Tunisian district. The blood samples were tested for ATTG followed by subjecting positive participants to intestinal biopsy, biological exploration, and bone mineral densitometry. The prevalence of CD in Tunisian schoolchildren was estimated to be about 1:157 (0.6%) [46], which is close to the values obtained for European prevalence. It is indicative that most of the screened children showed an atypical and asymptomatic form, but even the typical forms were underdiagnosed. The first study on mass CD screening was conducted among schoolchildren in North India, in the Ludhiana district of Punjab, by Sood et al. [47]. The screening for CD of suspected coeliacs (initially identified through a questionnaire collecting sociodemographic data and symptoms and signs related to CD) was performed by testing for ATTG. The “high-positive ATTG” children, whose parents consented, underwent upper gastrointestinal endoscopy. Ultimately, the disease prevalence was found to be 1 in 310 children (0.3%). Hence, this study showed that CD is not rare in wheat-eating areas of North India [47]. Apparently, the most extensive epidemiological studies of CD have been performed in some regions of Turkey, involving more than 20,000 healthy Turkish schoolchildren. After exhaustive serological analysis of CD-specific antibody titres and biopsy confirmation where appropriate, the prevalence of CD was found to be at least 0.5% [48]. The authors also found a positive correlation between serology (high levels of IgA-tTG and EMA positivity) and histopathology in patients, which makes biopsy an optional procedure.

Thus, it has been shown that CD does not only affect people of European descent. Nevertheless, in some Asian nations, CD is still considered to be either non-existent or very rare, but the incidence may be underestimated due to a lack of awareness and low suspicion of the disease [49]. In particular, official reports on CD prevalence in the paediatric Japanese population are absent, but among non-clinical adults the prevalence is about 0.05% [50].

Based on the above data from various geographical locations, it can be concluded that the paediatric general

Table 4. Comparative data of questionnaire-based studies

Region	Age	Number of people surveyed	Data collection methods	Response ratio, %	Questionnaire content			Criteria for selection	Risk group, n (%)	Prevalence of CD, %	Ref. No.
					gastro-intestinal manifestations	extra-intestinal manifestations	associated condition				
Finland	10–11	404	filled in by the parents and delivered to the school by school nurses	96	+	–	–	symptom severity of 1 or more criteria	110 (27.2)	1.20	[75]
Denmark	8–9	9,880	by mail to the families	70	+	+	–	1 or more criteria	2,835 (28.7)	1.22	[76]
US	5	1,234	by telephone interview or by a physician during the clinical evaluation	NA	+	+	–	NA	33 (2.67)	1.14	[77]
Italy	0–14	48,808	primary care paediatricians	NA	+	+	+	1 or more criteria	447 (0.9)	0.12	[40]
Sweden	12	7,567	questionnaires were completed at school; a questionnaire for parents brought home by the children	93	+	+	+	1 or more criteria	2,333 (30.8)	2.10	[78]

prevalence of CD does not exceed 1% (except in the case of the Saharawi population), and this can be considered comparable to the overall CD prevalence of most populations (about 1:100) [51], although different tests (kits) and interpretations were applied. Moreover, almost all the presented studies have the ability to identify asymptomatic coeliac children.

In the near future, it can be assumed that the tendency for CD mass screening to spread will be mediated by the development of available diagnostic tools, in particular available tests to determine the titres of CD serological markers with high specificity and sensitivity and non-invasive approaches that can substitute for biopsy.

Screening of Increased Risk Groups in Paediatric Populations

This screening is carried out among children having relatives with CD or children suffering from some autoimmune diseases and syndromes (Table 1), by analyzing serum samples for CD-specific antibodies and subsequent biopsy. Most screening studies on the prevalence of CD include diabetic children and adolescents, persons with thyroid disorders, persons with Down syn-

drome and those with close relations with CD (some of these are given by country in Table 3 [52–67]). The high prevalence of CD among patients with type 1 diabetes mellitus (up to 13.5%) is probably due to clinical and pathogenic overlap [68], and symptoms are often modest or absent. The results partially represented in Table 3 and found in meta-analyses [69, 70] of high CD prevalence in children with Down syndrome (more than 5%) and autoimmune thyroid disorders (about 6%) should motivate screening for CD in these cohorts. CD is also common in patients who have a first- and second-degree kinship with persons with CD, at 10 and 2.6%, respectively [71–73]. Meanwhile, progress in the understanding of CD pathogenesis leads to discovery of new CD-associated symptoms and syndromes, facilitating the diagnosis of CD.

Screening for CD once in a lifetime is not enough, especially for at-risk-group patients. It was shown that new CD cases can be detected a little later (1–3 years) after a first negative serological screening [74]. To bypass the indefinite periodicity of serological screening for CD in children, HLA-DQ2 and HLA-DQ8 typing should be performed [19].

Questionnaire-Based Survey as an Auxiliary Tool for Finding Paediatric CD Cases

The applicability of the mass screening strategy or the periodicity of the screening of at-risk groups among paediatric populations is conditioned mainly by the availability of funding from the regional health ministry. In this regard, for potential detection of arising CD symptoms and signs, CD case finding using questionnaires can be justified.

The questionnaires are usually addressed to respondents who are not experts in this field, so preliminary educational work can improve the detection of CD. Comprehensive information is included on educational websites for patients and their parents. In addition, special medical personnel may be involved in the questionnaire-based surveys for educational purposes, though this increases the cost of finding CD cases.

Some questionnaire-based survey studies are presented in Table 4, although there are as yet no relevant guidelines with approved recommendations. Nevertheless, it is clear that the content of the questionnaires should be based on an extensive list of CD symptoms, including a variety of gastrointestinal and extraintestinal manifestations as well as a list of associated diseases and the family history of the disease. Different sets of questions are usually used for research purposes, leading to the identification of heterogeneous groups of children for further testing. In the studies listed in Table 4 [40, 75–78], some authors included in the questionnaires only issues related to the gastrointestinal manifestations associated with CD (abdominal pain, diarrhoea, constipation, etc. [75, 76]). Other authors proposed questionnaires with extended questions regarding associated diseases (some autoimmune diseases, syndromes, IgA deficiency, anaemia, etc. [79]) and the family history (CD in a first-degree relative [77–79]). This questionnaire design clarifies the detection of the percentage of CD cases, since it is known that the frequency of CD is higher in groups of children with extraintestinal CD manifestations and associated conditions. However, the questionnaires are ineffectual in the case of asymptomatic CD patients lacking associated diseases. Kinoshita et al. [80] have shown that almost 50% of newly diagnosed CD patients who initially reported no symptoms experienced clinical improvement on a GFD.

Unfortunately, there is still no consensus about which mandatory questions should be included in the questionnaires used in CD screening. Nonetheless, it seems appropriate to identify all suspected persons via questions about a number of symptoms and signs which are com-

piled in the main conciliation documents (ESPGHAN, etc.). Certainly, it is important that the questionnaires should contain questions regarding both gastrointestinal and other common manifestations, as well as questions on related diseases and family history.

Certain difficulties and debates in the preparation of a CD questionnaire-based survey can be caused by the need to unify the following important parameters.

(i) Methods of Questionnaire Distribution and Collection of Information for Maximum Response Rate

The data may be collected by phone, by email, during a visit to the paediatrician or from questionnaires handed out by volunteers at schools or childcare facilities. It is obvious that the simultaneous distribution and direct collection of questionnaires in schools provide the highest response ratio; however, this method is hardly acceptable when parental involvement is required. It should be noted that the questionnaires collected by primary care paediatricians cannot be recommended for population studies on CD prevalence, because a visit to the paediatrician itself already indicates the presence of a medical problem. The most convenient way to distribute and collect questionnaires with a comparatively high response rate is likely to be via email (about 70%, see Table 4).

(ii) Age-Group of Respondents for Whom the Questions Are Intended (Children and/or Their Parents)

There is no consensus on the age of the children to be interviewed because CD can develop at any age (more than 70% of new patients are diagnosed above the age of 20 years [81]). Most of the paediatric CD screening strategy studies are aimed at school-age children [76, 82–84]. It may be reasonable, for example in terms of the convenience of questionnaire distribution/collection, to involve a relatively large number of children of a similar age in the studies, with the possibility of organized preliminary educational training of respondents regarding CD. Moreover, the most probable extraintestinal or oligo-symptomatic manifestations of CD appear at puberty.

(iii) Periodicity of the CD Questionnaire-Based Survey

This parameter should take account of the possibility of CD development at any age, so the survey should be carried out regularly, preferably every year. This is quite feasible due to the relatively low cost of the approach.

It is important to emphasize that a questionnaire-based survey is an auxiliary tool for paediatric CD case

finding, and it does not cover CD patients with some oligosymptomatic and asymptomatic clinical coeliac forms. Moreover, in the study by Rosen et al. [78], where prospective collection of questionnaire data was combined with CD serological marker testing of all children, it was shown that the symptoms or conditions presented within the questionnaire were as common among screening-detected CD cases as among non-CD children. Thus, it is possible to conclude that CD screening via a questionnaire-based survey cannot be applied for the accurate assessment of the prevalence of CD within the paediatric population. Nevertheless, questionnaire-based approaches are appropriate for studies with a restricted budget, at least for the purpose of identifying children with signs of increased risk of CD.

Conclusion

The continual updating of data on pathogenesis, genetics, and immunology leads to the identification of new signs and risk factors for CD that contribute to improved diagnosis. As a result, it becomes possible to refine the estimates of CD prevalence. Currently used screening strategies among paediatric populations include large-scale studies (CD mass screening) or studies performed on children in increased-risk groups according to the appropriate guidelines (e.g., ESPGHAN and NASPGHAN-ES). Evidently, CD mass screening is preferable due to detection of not only obviously symptomatic patients, but also oligosymptomatic and asymptomatic individuals.

However, the cost-effectiveness of mass screening programmes has not yet been estimated, and for many countries the costs of such studies are high, or even prohibitive. CD screening of at-risk groups captures children and adolescents with expressed symptoms and associated conditions; it reduces financial costs, but at the same time up to a third of potential CD patients are not detected. It is well known that the prevalence of CD in increased risk groups as well as the detection of new CD cases is significantly higher than in the general paediatric population and requires mandatory periodic screening for CD. Nevertheless, the identification of children belonging to the at-risk group is important for their further proper growth and development. The questionnaire-based survey of the paediatric population is designed to identify this group and is applicable to studies with a restricted budget. In this regard, it would be expedient to develop some guidelines with proper recommendations for questionnaire preparation, similar to the current guidelines for the diagnosis of CD.

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