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EDITORIAL

Indian task force for celiac disease: Current status

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Abstract

There are limited data on celiac disease (CD) from India. The limited knowledge about CD in India might be attributed to several factors. The first meeting of the Indian Task Force for Celiac Disease was held in the Asian Institute of Gastroenterology, Hyderabad, India in December 2008. The objectives of the meeting were to focus research on prevalence of CD in the wheat-eating Northern *vs* the rice-eating Southern Indian population, low-budget serological assays to study the underprivileged population, to involve other medical subspecialties in CD, to suggest proper legislation regarding wheat food labeling, and to organize affordable food substitutes for patients with celiac disease.

Key words: Celiac disease; Food labeling; Gluten-free diet; India; Legislation; Malnutrition; Rice; Wheat

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INTRODUCTION

Celiac disease (CD) is an autoimmune disease that is caused by interaction of gluten in genetically predisposed individuals[1]. The diagnosis is based upon European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN)/United European Gastroenterology Foundation (UEGF) criteria[2].

CD in India is submerged in an ocean of malnutrition. The limited research on CD in India can be attributed to several factors: (1) a common belief that CD is uncommon in India; (2) recognition of tropical sprue and gastrointestinal tuberculosis as major causes of chronic diarrhea and malabsorption syndromes; (3) non-realization that partial villous atrophy (PVA) may be a feature of CD; (4) more pressing problems of malnutrition; (5) lack of awareness regarding non-diarrheal manifestations of CD[3-5].

The first meeting of Indian Task Force for Celiac Disease was held in the Asian Institute of

Gastroenterology, Hyderabad, India on December 6, 2008. The main objectives of this meeting were to evaluate the Indian data on CD and discuss future research. A panel of experts from different parts of India, who have special interest in CD, took part in this Task Force. Professor Mulder CJJ, VU University Medical Center, Amsterdam, also participated in the meeting as an international expert. All the participants addressed issues specific to CD and discussed the area of future research and the strategies to carry out these objectives. In addition, legal issues related to food labeling and availability of gluten-free food items in India were also discussed.

EPIDEMIOLOGY OF CD IN INDIA

Based on epidemiological studies from Europe and the United States, 90% of CD remains undiagnosed. There are limited data on prevalence of CD from India[6-9]. The majority of data are from Northern India. The incidence of CD is increasing[10]. The prevalence of CD in India is probably not different from that in western Caucasian populations[11]. In a field study conducted among school children in Punjab, the estimated frequency of disease was 1 in 310 (0.3%)[12]. This prevalence is probably an underestimation. The siblings of CD patients have a high prevalence of CD (22%). In other studies, the prevalence of CD among the first-degree relatives has been reported to be 8%-25%[13-15]. There are regional variations in the prevalence of CD due to genetic and dietary factors, that is, the wheat-rice shift from the North to the South in India, which will be discussed in the next section.

REGIONAL DIFFERENCES AND CHANGING EPIDEMIOLOGY IN INDIA

CD has a strong genetic predisposition. The main genetic factors are *HLA-DQ* genes, that is, the genes encoding DQ2 or DQ8 in the HLA complex. In the West, approximately 95% of CD patients have a DQ2 heterodimer comprised of DQB1*02 and DQA1*05, and most of the remaining 5% have a DQ8 heterodimer comprised of DQB1*302 and DQA1*03. Adequate data about DQ2 and DQ8 distribution in India are lacking[16-19].

Regional differences in CD can be explained by genetic, dietary and immunological factors. High prevalence areas of CD such as Saharawis (North Africa, up to 5%) and Europe (1%) have a very high carrier rate of DQ2 and DQ8. On the other hand, Japan and Burkina Faso, which have very low prevalence of CD, have low or absent DQ2 and DQ8 carriage.

Dietary patterns also contribute to geographical differences in CD. Wheat consumption broadly parallels CD prevalence, being particularly low in the Far East and Sub-Saharan Africa. In India also, CD is reported frequently in high wheat-consuming states in Northern India.

Immune conditioning might also influence the development of CD. Dose of gluten in early childhood may be an important determinant of lifelong susceptibility. Breast feeding during gluten induction probably reduces susceptibility[20]. Increased exposure to enteric infections in infancy confers modest increase (1.5 RR) in susceptibility to CD[21] .

CASE FINDING IN HIGH-RISK GROUPS

A wide gap exists in India between the CD prevalence in the population (1%) and the prevalence based on diagnosis (0.02%-0.27%). Thus 90%-95% of CD remains undetected[22]. Several complications might occur among untreated CD subjects. Among non-diarrheal adult cases with gastrointestinal symptoms, diagnosis of CD and treatment with gluten-free diet results in a significant improvement in symptoms of abdominal pain, bloating and lactose intolerance. A twofold increase in standard mortality ratio has been reported in adult CD[23]. Excess mortality occurs in the first 5-10 years after diagnosis among subgroups of patients with malabsorption, delayed diagnosis and poor compliance. Enteropathy-associated T-cell lymphoma (EATL) is an important mortality risk in patients diagnosed above 50 years of age. There is a higher frequency of so-called associated disorders in CD in comparison to controls, such as endocrine disorders, type 1 diabetes mellitus and connective tissue disorders. Higher risk of malignancy in adult CD is known. Over-presentation of cancer occurs in the small bowel, esophagus and T-cell lymphoma. After diagnosis, despite dietary compliance, an increased risk was observed for EATL[24]. On the contrary, a protective role of gluten-free diet has been reported for these so-called associated malignancies[25]. The risk of breast cancer seems lower in CD. A higher frequency of CD occurs with autoimmune disorders. The incidence of autoimmune disorders in CD seems to be related to duration of gluten exposure[26].

Targeted screening of CD might be important[27]. Among children, screening for CD in India is not indicated before age 1-3 years. Compliance with gluten-free diet and giving consent for small bowel biopsy are problems, because the subjects usually are not convinced about investigations and treatment in the absence of severe symptoms. Serological tests like tissue transglutaminase (tTGA) have a positive predictive value of 75%-80%, however, seronegative CD is well-recognized in milder degrees of villous atrophy[28]. In future, we have to define how to interpret serology positivity when biopsies are normal. There is no consensus regarding treating subjects with silent disease with positive serology.

CD IN CHILDREN IN INDIA

CD was first reported in India in 1966[29]. The triad of symptoms of chronic diarrhea/malabsorption, failure to thrive and anemia were common until 2000 in India. However, the presentation of disease seems to have changed over the past few years. An upsurge has been observed by clinicians from North-West India. The so-called typical presentation is now below 50%[30-32].

Symptomatic disease is just the tip of the iceberg but, because of the availability of new serological tests,

we are exploring the hidden CD groups in India. The demographic profile of CD in children in India is different from that in the West[33]. In one Indian study, the male/female ratio was 3:2. The sole atypical presentations were short stature in 20%, anemia in 14%, constipation in 5%, family history of CD in 5%, and rickets in 1.5% of patients. Common associations observed in children were IgA deficiency in 6%, asthma in 2%, type 1 diabetes in 1.5%, autoimmune hepatitis in 1.5%, seizures in 1.5%, juvenile rheumatoid arthritis in 0.7%, Down syndrome in 0.7%, and nephrotic syndrome in 0.7% of patients. The recent upsurge is due to factors like improved awareness among pediatricians, cost-effectiveness of serological tests, and increasing pediatric endoscopic facilities.

CAPSULE ENDOSCOPY IN CD

Video capsule endoscopy (VCE) provides high resolution views of the small intestinal mucosa in a noninvasive manner. Characteristic mucosal abnormalities are seen on capsule endoscopy in CD, which include scalloping of mucosal folds, fissures or grooves, mosaic pattern, and absent or reduced mucosal folds[34]. Although esophagogastroduodenoscopy (EGD) and multiple duodenal biopsies continue to remain the gold standard, VCE may be used for initial diagnosis and follow-up of CD patients. VCE may be a reasonable alternative to upper gastrointestinal endoscopy in those patients who are strongly positive for tTGA or endomysial antibodies (EMAs), who are unwilling to undergo EGD. In patients with positive serology for CD and negative histology, VCE might be of help. VCE is useful in follow-up of patients of CD who remain symptomatic despite being on a gluten-free diet[35].

MAGNIFICATION ENDOSCOPY IN CD

The role of conventional endoscopy in the diagnosis of CD has been limited because of low and varying sensitivity and specificity. The small bowel mucosal damage associated with CD can be distributed unevenly and present as patchy villous atrophy, with some parts appearing normal and others severely diseased[36]. Endoscopic markers are not adequate to target biopsy sampling to sites of villous damage in the duodenum .

In the past few years, newly developed procedures and technologies have improved endoscopic recognition of the duodenum. These new technologies include the water immersion technique, chromoendoscopy, high-resolution magnification endoscopy, narrow band imaging, and optimal band imaging[37]. These new endoscopic techniques have increased the accuracy of CD diagnosis in patients with patchy villous atrophy, and achieve optimal accuracy for the recognition of severe villous atrophy[38].

HISTOLOGICAL FEATURES AND PROBLEMS IN INTERPRETATION

Diagnosis of CD is confirmed by biopsy, with a characteristic mucosal injury in association with a clinical response to a gluten-free diet. Biopsy of the small bowel remains the gold standard for the diagnosis of CD[39]. Normal small intestinal mucosa contains long villi, varying in length depending on orientation and depth of biopsy. Histological features of CD comprise small intestinal mucosal injury, surface enterocyte damage, increased intraepithelial lymphocytes, crypt hyperplasia and villous blunting or flattening. A reliable histological diagnosis of CD requires lifelong adherence to a gluten-free diet, which is expensive, socially limiting and difficult on a contemporary diet with manufactured food stuffs. Pathologists should avoid overdiagnosis based on minimal nonspecific histological changes. The uniform classification according to Marsh and its modification as described by Rostami should be applied, which includes Marsh I lesion (lymphocytic enteritis); Marsh II (lymphocytic enteritis with crypt hyperplasia; Marsh IIIA in addition shows partial villous atrophy; Marsh IIIB, subtotal villous atrophy; and Marsh IIIC, total villous atrophy.

Jejunal biopsies are not necessary anymore if adequate duodenal biopsies are taken. Numerous intestinal disorders can present with a CD-like histology but are not responsive to a gluten-free diet, and therefore, are not CD cases. Villous atrophy is noted in various infections such as giardiasis, tropical sprue, HIV, Whipple's disease, and immune-mediated diseases. In the same way, increased intraepithelial lymphocytes (IELs) are seen in tropical sprue, after nonsteroidal anti-inflammatory use, Crohn's disease, and bacterial overgrowth. In cases of histological features suggestive of CD, the diagnosis should be based on ESPGHAN criteria.

Diagnosis of refractory CD, ulcerative jejunitis and EATL requires multiple biopsies. Identification of the two categories of refractory CD (RCD), Marsh type I without aberrant T cells and type II with aberrant T cells requires correlation with T-cell immunophenotyping by flow cytometric analysis and immunohistology. An increase in IELs in uncomplicated CD shows a phenotype of sCD3+, CD8+, γ^+ population of T cells, which contrasts with RCD II, which shows an aberrant immunophenotype of sCD3- cCD3+, CD8-. Immunostaining methods using anti-CD3 and anti-CD8 antibodies distinguish active CD from RCD.

Pathologists should be attentive to recognize the less severe histopathological abnormalities of Marsh type I and II CD, and must be aware of the pitfalls in the assessment of mucosal biopsy specimens[40]. In general, we do not advise a gluten-free diet for Marsh type I lesions, unless serology (tTGA and EMA) is positive and the patients are symptomatic for CD.

ATYPICAL CD

Atypical presentations of CD are on the rise in children and adults[41]. Patients may present with CD-related symptoms in other specialties, such as cardiology, hematology, ENT, endocrinology, dermatology and dental services. Clinicians should be aware of CD. Screening for CD should be considered in unexplained anemia, unexplained gastrointestinal symptoms, idiopathic

osteoporosis, unexplained infertility, first-degree relatives of CD patients, and autoimmune diseases.

DIETARY COMPLIANCE IN CD

CD is well recognized in most parts of the world where wheat is the staple diet. Irrespective of the manifestations of CD, the mainstay of treatment is a gluten-free diet. Proper dietary compliance leads to alleviation of symptoms, improvement of anthropometry, improvement in quality of life, and prevention of EATL and osteoporosis. It is important to determine factors that affect dietary compliance. Non-compliance to any dietary modification is multifactorial and is determined by several socioeconomic and cultural factors. Dietary compliance can be assessed by questionnaires, serology or histology, or a combination of these methods.

In a study to determine factors to assess gluten-free dietary compliance, strict compliance was seen in 45%, 50% and 35% in pediatric, adolescent and adult populations, respectively. Temptation was the main reason for default in children. Ignorance combined with temptation were major problems in adolescents, whereas digression in adults was mainly due to sociocultural and economic factors. Overall compliance rates to GFD vary from 45% to 80%. tTGA normalizes in 75% of the compliant patients at 1 year and serves as a useful marker for medium-term compliance and beyond. Histological improvement lags behind serological response. Overall non-compliance was seen in 58% at 2 years[42].

MANAGEMENT PROBLEMS OF CD IN INDIA

The only treatment available for CD is strict adherence to a gluten-free diet for life. Data suggest that diagnosed but untreated patients with CD have significantly higher morbidity and mortality.

Gluten-free diet

A gluten-free diet is defined as one that excludes wheat, rye and barley. Even small quantities of gluten may be harmful. The strict definition of a gluten-free diet remains controversial because of the lack of an accurate method to detect gluten in food, and the lack of evidence for what constitutes a safe amount of gluten ingestion. The patients and their relatives should be counseled by a trained dietician. Vitamin and mineral deficiencies, including iron, calcium, phosphorus, folate, B12, and fat-soluble vitamins should be looked for. It is important to have a team-based approach to management. In addition to treatment by a physician and participation in a local support group, consultation with a skilled dietitian is essential (Table 1).

Dietary counseling of the patient and the family is the cornerstone of the treatment of CD. In India, it is common practice for families to purchase whole grain and have the flour processed at a small neighborhood flourmill, where other cereals like corn and rice are ground separately at a different time slot after cleaning the grinding machine. Despite cleaning of the flour-making machine, there may be mixing during grinding of cereals. The mixing occurs in the initial part of cereal grinding, therefore, initial flour should not be used by the patients with CD. These measures are inadequate, and some quantity of wheat becomes mixed with other cereals and may be a factor for non-response in a strictly compliant patient. It might make sense for patients to use solely home grinding for gluten-free flour. The major problem is faced by the patients and families on certain occasions: birthday cakes, chocolates, ice creams, biscuits, social functions, and traveling (Table 2).

Table 1 Key elements in the management of celiac disease (CD)

Consultation with a skilled dietitian
Education about the disease
Lifelong adherence to a gluten-free diet
Identification and treatment of nutritional deficiencies
Access to a support group
Continuous long-term follow-up by a multidisciplinary team

Table 2 Factors to improve compliance

Learning about CD
Identify gluten-containing products
Improved self-management
Trust in physicians and dietitians
Proactive follow-up measures
Understanding the risk factors and serious complications
Ability to reinforce positive changes internally
Positive coping skills
Participation in a support groups

CD has come to attention of physicians in the past two decades. The number of patients diagnosed with CD is also limited. Therefore, the market value of gluten-free products and food items has not been properly realized. With time, the exact number of patients with CD is going to rise and there will be a requirement for commercially available food items. Besides, there is no legislation for gluten labeling in India, therefore, a patient with CD will not be able to know if any of the food items is safe.

MANAGEMENT OF RCD

A small subset of CD patients fails to respond to a gluten-free diet. This condition is referred to as RCD, which can be either primary or secondary. There is no standard definition of RCD. Currently, RCD is defined as persisting or recurrent villous atrophy with crypt hyperplasia and increased IELs, in spite of a strict gluten-free diet for more than 12 mo[43].

Before making a diagnosis of RCD, the following causes must be ruled out: (1) dietary non-compliance; (2) ubiquitous gluten source (pill capsules); (3) wrong initial diagnosis; and (4) associated disease, such as collagenous colitis, lactose intolerance, or bacterial overgrowth syndrome.

There are no clear clinical or biological markers that

predict the development of RCD. This disorder usually manifests in patients diagnosed in adulthood, and all reported cases have been patients diagnosed over the age of 40-50 years. The exact incidence of RCD amongst CD is not known. However, in a small subgroup of patients, the clinical and histological abnormalities persist or recur while taking a gluten-free diet. This non-responsiveness leaves a poorly understood syndrome known as RCD[4,38,40]. RCD may appear in a subgroup of CD patients with persistent histological abnormalities. In all patients screened for RCD, DQ2 and DQ8 need to be checked. In non-DQ2/DQ8 patients, the diagnosis of CD has to be reconsidered and differentiated from diseases such as autoimmune enteropathy. Most of the patients referred for RCD are affected by other diseases. Probably, the commonest cause of non-responsiveness is continued gluten intake. Exocrine pancreas insufficiency, hyperthyroid disease and collagenous colitis are other common explanations. Immunosuppressive treatment might moderate this. We suggest azathioprine and steroids in RCD- I (without aberrant T lymphocytes). However, in RCD-Ⅱ (with aberrant T lymphocytes), we suggest chemotherapy. As the prognosis of EATL is extremely poor, the early detection of CD is crucial[44].

CONCLUSION

The spectrum of CD in India is changing. There is a need to start studies to estimate prevalence of CD all over India. This task can be accomplished by establishing nodal centers in different parts of the country. In addition, competent authorities must be approached with specific recommendations to make food labeling regarding gluten content legally mandatory. Based on available data and discussion, the following recommendations are made. (1) Common questionnaire to collect data at different centers needs to be developed. (2) Studies to estimate community prevalence of CD must be started. (3) Prevalence of CD in high-risk groups should be studied. (4) Simple and low-budget serological assays should be developed for studies in underprivileged individuals. (5) Genetic studies to identify HLA typing of CD patients in India can be taken up in a small sub set of patients. (6) Subspecialties like endocrinology and neurology must be approached and involved in the Indian Task Force. (7) Rapid assays for CD serology need studies among populations suffering from parasitic infections to look for interference with CD. (8) Proper legislation about wheat food labeling should be framed.

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