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Celiac Disease and Other Immunologically Mediated Disorders of the Gastrointestinal Tract: Working Group Report of the Second World Congress of Pediatric Gastroenterology, Hepatology, and Nutrition

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The gastrointestinal tract is exposed to a vast array of foreign antigens, such as ingested foods, microorganisms and toxins. It hosts the largest immunologic system in the human body and possesses unique properties. It must defend against pathogens while tolerating food antigens and commensal microorganisms. Mistakes in these dual functions (defense and oral tolerance) may play a role in the pathogenesis of a number of diseases of the gastrointestinal tract, such as celiac disease, food allergy and inflammatory bowel diseases.

OVERVIEW OF CELIAC DISEASE

Celiac disease is characterized by an enteropathy triggered in genetically susceptible individuals by the ingestion of gliadin and related prolamines found in wheat, barley and rye (1). The observation of a strong association between celiac disease and HLA class II genes is strengthened by the finding that DQ2 and DQ8 molecules present gliadin-derived peptides, some after deamidation by tissue transglutaminase (TG2), to intestinal T lymphocytes (2). The activated Th1 T cells secrete proinflammatory cytokines that are thought to produce the intestinal lesions of celiac disease. Such immune reactions might be driven by the interaction of gliadin peptides with the innate immune system (3).

Epidemiologic studies in some countries report prevalence rates of celiac disease of 1 in 100 to 250 in the general population (4,5), suggesting that celiac disease remains largely underdiagnosed (6). Untreated, the condition is associated with an increase in both mortality and morbidity. Conditions related to lack of treatment include failure to thrive, short stature, delayed puberty, nutritional deficiencies, osteoporosis, infertility, recur-

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rent spontaneous abortions, intestinal malignancies (lymphomas), neuropsychiatric disturbance, and possibly an increased risk of autoimmune diseases. Treatment with a gluten-free diet leads to symptom resolution and reduces the risk of long-term adverse health consequences.

PRIORITIES FOR CELIAC DISEASE

Priorities for celiac disease are revised diagnostic criteria, improved serologic testing, increased disease awareness, enhanced dietary compliance, better understanding of the pathogenic mechanisms involved in the disease, and development of new therapeutic strategies. Revised diagnostic criteria are needed to include cases detected through screening programs and those without typical small intestinal histologic findings, who do not meet the current diagnostic criteria established by the European Society of Paediatric Gastroenterology and Nutrition (ESPGAN) in 1990. Such criteria should incorporate the use of the new, highly accurate serologic assays for endomysial antibodies (EMA) and TG2 (7).

The overall goal of an education campaign is to enhance early identification and treatment of celiac disease by healthcare providers. The campaign will require a multidimensional approach to achieve the following specific objectives: (1) obtain additional prevalence data; (2) determine the cost/benefit/risk of active case finding; (3) educate physicians on the protean manifestations of celiac disease; (4) develop and promulgate algorithms for identifying cases on the basis of clinical presentation and through screening programs; and (5) maximize the benefits of early diagnosis and treatment.

To achieve these goals, there is a need for global collaborative research and consensus on the use of standardized, reasonably priced, high-quality serologic tests. Guidelines for the use of serologic tests are needed for several clinical scenarios (early identification of celiac disease in symptomatic patients; algorithms to screen asymptomatic at-risk groups, including those with IgA deficiency; management of patients diagnosed with celiac disease), and for epidemiologic research on celiac disease. Uniform standards are needed to define gluten-free products so that guidelines can be developed to maximize dietary compliance. Alternative forms of therapy are desirable. Work focused on the development of novel strategies is underway and should be encouraged. In particular, immunomodulatory strategies that specifically block the adverse immune reactions triggered by gliadin should be investigated as a potential alternative to the gluten-free diet.

OVERVIEW OF FOOD ALLERGY

According to a recent proposal by the European Academy of Allergy and Clinical Immunology (EAACI) (8), an adverse reaction to food should be called *food hypersensitivity*. When immunologic mechanisms are demonstrated, the appropriate term is *food allergy*. If the role of IgE is highlighted, the term is *IgE-mediated food allergy*. All other reactions, previously sometimes called "food intolerance," should be referred to as *non-allergic food hypersensitivity*. Despite the lack of uniform definitions, it is believed that the prevalence of food allergy is in the range of 1.9% to 2.8% for cow's milk, 0.5% to 1.9% for peanut, and up to 3.2% for egg. The prevalence of food allergy may be increasing, but in interpreting data, one should differentiate between estimates based on self-reporting, IgE sensitization (skin or RAST tests) and clinical challenge studies. Real and perceived gastrointestinal food intolerance has a significant medical, financial and social impact on young children and their families.

PRIORITIES FOR FOOD ALLERGY

Priorities for food allergy include characterization of the spectrum of food allergies, definition of diagnostic criteria, development of educational tools and implementation of preventive strategies. Specific examples are further assessment of a number of emerging conditions that could be allergy-based, such as multiple food protein intolerance in infants and young children, eosinophilic conditions of the gastrointestinal tract and aberrant gastrointestinal motility conditions (gastroesophageal reflux, constipation, abdominal pain and irritable bowel syndrome), and clarification of the role of specific food antigens and epitopes (including potential new ones in genetically modified foods) as a cause of multiple food allergy. Better tests for delayed reactions need to be developed. Educational tools need to be created to enhance public and professional understanding and to highlight the inconsistency of unorthodox diagnostic tests so as to prevent the inappropriate use of unnecessarily restricted diets in children. Finally, primary prevention, which aims to inhibit IgE and other immunologic sensitization, will be a priority for the future.

CELIAC DISEASE

Research Goals

Treatment Alternatives to the Gluten-Free Diet

Significant progress has been made in recent years in the understanding of the cellular and molecular basis of celiac disease and in the consequent identification of possible targets for therapy. It has recently been shown that, because of their high proline content, gliadin peptides are highly resistant to digestive processing by pancreatic and brush border proteases. Enzyme supplement therapy using bacterial endopeptidases has been proposed to promote complete digestion of cereal proteins and thus destroy T-cell multipotent epitopes. The identification of gliadin peptide sequences that have biologic effects, either through non-immune-mediated mechanisms (e.g., on differentiation of fetal intestine, on CaCo2 cell apoptosis, on enterocyte cytoskeleton), or by

activation of T cells, is important. Breeding programs and/or transgenic technology may lead to the production of wheat that is devoid of biologically active peptide sequences. The identification of specific epitopes may also provide a target for immunomodulation of antigenic peptides. Engineered peptides may potentially bind to HLA molecules but not T-cell receptors, or bind to T-cell receptors but switch a proinflammatory Th1 to a Th2 or a protective Th3 response. Other promising areas of research involve inhibiting the innate immune response activated by gliadin peptides, preventing gliadin presentation to T cells by blocking HLA binding sites, using TG2 inhibitors, and interleukin-10 assessment as a tool to promote tolerance. An immunomodulatory approach will need to have a safety profile equivalent to that of the gluten-free diet, but might have the advantage of increased compliance.

Plans to Achieve Goal

Collaboration with investigators in other fields should be increased. Researchers investigating type 1 diabetes and multiple sclerosis are already testing immunomodulatory strategies and have developed animal models; in vivo models of celiac disease are needed to test immunomodulatory strategies. Interaction with geneticists is important. Identification of genes involved in the pathogenesis of celiac disease using genome-wide screening, candidate gene studies or microarray technology, and studies addressing the molecular basis of the biologic effects mediated by gliadin peptides, may identify potential target molecules for alternative therapies. Furthermore, the characterization of susceptibility genes other than HLA genes may improve risk stratification and identify a population (e.g., first-degree relatives) that could benefit from primary prevention strategies (dietary or immunomodulatory interventions). Collaboration with national and international celiac organizations, as well as with organizations dealing with other immunologic diseases such as type 1 diabetes and multiple sclerosis, could provide opportunities for increasing resources, cost-sharing, enhancing awareness, and increasing the involvement of industry in managing celiac disease.

Definition of New Diagnostic Criteria

Currently, the gold standard for the diagnosis of celiac disease is the presence of the typical gluten-dependent small intestinal mucosal lesion, as characterized by villous atrophy with crypt hyperplasia and increased intraepithelial lymphocytes. Recent clinical evidence suggests that this criterion needs to be redefined. Interpretation of histologic findings is subjective and requires experience. Some patients are reluctant to undergo intestinal biopsy; thus, a noninvasive method of diagnosing celiac disease is desirable. The identification through screening programs of clinically silent, autoantibody-positive (EMA, TG2) individuals, and individuals without typical mucosal lesions, has become a problem, as they do not fulfill current criteria for the diagnosis of celiac disease. This issue highlights the need for a better understanding of the natural history of celiac disease and celiac autoimmunity.

Plans to Achieve Goal

Disease-related definitions should not be altered without appropriate scientific evidence. Therefore, research aimed at widening and revising the current biopsy-based criteria for diagnosis is a priority. Most cases with positive EMA and TG2 autoantibodies have celiac disease with a manifest gluten-dependent mucosal lesion, and are DQ2- or DQ8-positive. In future, a diagnosis of "genetic" gluten intolerance may include patients with gluten-dependent symptoms or signs of celiac disease, a positive test for the autoantibodies, and the correct celiac-type HLA DQ type, even though they have an equivocal or normal small intestinal mucosa on biopsy. A multicenter study within the Federation of International Societies for Pediatric Gastroenterology, Hepatology and Nutrition (FISPGHAN) should determine the natural history of celiac disease in such patients who choose to remain untreated. This study could provide the experimental basis for new diagnostic criteria that combine autoantibody positivity with correct genetics without the need for invasive small intestinal biopsy. However, while it is important to diagnose celiac disease correctly, it is equally important to avoid a false-positive diagnosis and unnecessary treatment with a gluten-free diet.

Practical Intervention Goals to Improve Child Health

Serologic Testing for Celiac Disease

With the advent of more sophisticated, diverse and commercially available "celiac disease screening" panels and tests, healthcare providers need updating on their rational use and interpretation. Because of the varying accuracy of the tests in different clinical settings, evidence-based guidelines are needed for the use and interpretation of the tests in each of these settings. Research is also needed to evaluate the cost/risk/benefit of algorithms for each clinical scenario, and should include the role of DQ2/DQ8 testing.

Research is also required to determine: (1) whether early identification and treatment leads to a significant benefit; (2) the clinical significance of persistent seropositivity to antigens associated with celiac disease (TG2) in the absence of frank enteropathy; and (3) whether serologic testing is a useful tool for monitoring the gluten-free diet.

Plans to Achieve Goal

Success in this campaign will require collaboration with industry, professional medical societies, funding agencies and support groups.

Standardization of Serologic Tests (Techniques and Panels). The development of worldwide consistency in serologic testing techniques and reporting standards is a necessary first step, as it will greatly improve acceptance and interpretation of testing by healthcare providers and lay communities. Professional medical societies should provide position statements on the preferred components for inclusion in "celiac panels," on whether gliadin antibody testing should continue to be used, on the role of HLA DQ2/DQ8 testing, and on age-specific recommendations for testing for IgA deficiency and celiac disease. Organizations representing clinical laboratories, surgical pathology groups, and adult and pediatric gastroenterologist societies need to collaborate to promote this process.

Research on Benefits of Serologic Testing for Celiac Disease. Cost-effective algorithms to screen for celiac disease need development and validation. These algorithms should be designed for the evaluation of: (1) the symptomatic patient; (2) the asymptomatic at-risk patient; (3) the symptomatic and asymptomatic IgA-deficient patient; (4) dietary compliance monitoring; and (5) research on general populations.

Research is needed to obtain data for recommendations on the age at which to begin screening, and the frequency of repeat screening, of asymptomatic at-risk individuals. Additional research is required to determine whether serologic tests in specific clinical settings are sufficient to confirm the diagnosis of celiac disease without the need for a biopsy.

Reaching these goals will require collaboration among professional medical societies, including member organizations of FISPGHAN and adult gastroenterology, immunology, endocrinology, and public health societies. This endeavor may first need validation by computer modeling followed by large-scale studies. The research would benefit from multicenter collaboration and should involve different age groups.

Funding and Support. National celiac organizations need to focus fundraising and lobbying on larger scale research and educational programs. Collaboration among researchers, celiac associations and industry is needed to promote the development of accurate and cost-effective screening panels. Government support for collaborative initiatives would assist in this endeavor.

Worldwide Accepted Definition of Gluten-Free Labeling Issues, Availability and Measures to Monitor and Ensure Compliance

It has been noted that 7% to 55% of patients with celiac disease do not adhere to a strict gluten-free diet. This figure may be even higher because many claiming to be on a gluten-free diet had histologic abnormalities.

Worldwide Definition of Gluten-Free and Methods for the Analysis of Gluten in Foods. The definition of "gluten-free" varies among countries and regions:

1. No residual gluten in foods or zero gluten.
2. No detectable gluten by a laboratory test.
3. The Codex Alimentarius standard.

There is currently a Draft Revised Standard for Gluten-Free Foods that redefines the amount of gluten that is allowed in a food designated "gluten-free." Based on the revised standard, gluten-free foods made from naturally gluten-free ingredients should not contain more than 20 parts per million (ppm) gluten (10 ppm gliadin or 1 mg gliadin per 100 g). Gluten-free foods made from ingredients that contain gluten (or the equivalent), such as wheat, rye and barley, should not contain more than 200 ppm gluten (100 ppm gliadin or 10 mg gliadin per 100 g). Clinical heterogeneity and inconclusive clinical challenge data suggest a variable threshold of gluten sensitivity such that a single definition for "gluten-free" is not valid for all individuals with celiac disease. It is necessary to establish the minimum dose of wheat gluten-gliadin and related prolamins sufficient to cause inflammatory and morphologic changes in celiac patients (9). The effort should be to keep the diet as gluten-free as possible. The best recommendation today may be to prescribe a naturally gluten-free diet. The role of oats requires further definition. While there are data on the safety of pure oats, many dietitians and celiac disease societies still advocate the exclusion of oats because of concerns about cross-contamination with gluten-containing grains. The long-term safety of oats needs to be firmly established and the definition of gluten-free diet modified accordingly.

Social Factors Associated with Poor Compliance. Older mean age at diagnosis, poorer baseline parent education and lower family social class significantly predicts poor dietary compliance. Poor knowledge about the disease and lack of efforts to understand its immediate and long-term health effects also correlates with poor adherence to a gluten-free diet.

Labeling of Gluten-Free Food. Avoidance may not always be easy because of inadvertent contamination of food, which may be present in unexpected sources, and due to a lack of proper labeling of available foods. The Codex Alimentarius Commission in 1999 adopted that "cereals containing gluten: i.e. wheat, rye, barley, oats, spelt or their hybridized strains, and products of these" and a further seven groups of ingredients shall always be declared. The European Commission adopted that "starch and modified starch must always be complemented by the indication of its specific vegetable origin, when that ingredient may contain gluten." However, in other areas of the world there is no legislation on labeling of gluten-free foods.

Measures to Assess Dietary Compliance. Assessment of dietary response has been based on the morphologic recovery of small intestinal mucosa. Neither enzyme-linked immunosorbent assay TG2 nor indirect fluorescence antibody EMA are sensitive enough to reveal slight dietary transgressions.

Plans to Achieve Goal

Several strategies will have to be used to encourage strict adherence to the gluten-free diet:

Measures to Improve Follow-up. Guidelines for the short- and long-term follow-up after the diagnosis of celiac disease need to be developed. These should address a team approach that involve physicians, nutritionists and psychologists and include monitoring for decreased bone mineralization, nutritional deficiencies, knowledge assessment and compliance among patients and their families. Endorsement from appropriate medical societies, including FISPGHAN member organizations, should be sought.

Measures to Improve Education. Emphasis should be placed on educating family members and developing new and improved educational tools such as videos, electronic media, support group participation and activities, summer camps, and relationships with gluten-free product producers and marketers. The knowledge imparted should be appropriate to the social and educational background of affected individuals. Lists of safe and forbidden foods, specific to the local settings, should be provided and adapted to individual needs. The websites of various support groups such as the national academies of pediatrics, gastroenterologists, nutritionists and celiac foundations should provide updates on the disease for the patients.

Measures to Improve Dietary Assessment. An accurate dietary evaluation remains the most noninvasive practical method of identifying patients not adhering to a gluten-free diet. Uniform and well-standardized tools for dietary assessments need to be developed and validated.

Measures to Improve Labeling and Quantifying Gluten Content in Food Products. It is imperative to implement standards for the definition of a gluten-free diet and labeling of ingredients in food products in national laws so as to make producers adhere to rules and so protect the health of individuals with celiac disease. Member organizations of FISPGHAN, adult gastroenterology societies and celiac societies can play an important role in achieving this goal.

Future Research Issues. The development of better enzyme-linked immunosorbent assay methods accompanied by nonimmunologic chemical standard methods (high-performance liquid chromatography, mass spectrometry, capillary electrophoresis) is required to detect trace amounts of prolamines in food. Evidence is needed to determine the amount of gluten-gliadin and related prolamines, if any, that can be safely consumed by individuals with celiac disease. Further microchallenge studies are necessary.

Educational Needs and Strategies to Improve Medical Knowledge

Celiac Disease Awareness Campaign

Although celiac disease is one of the most common genetically predetermined diseases known, it remains grossly underdiagnosed. There may also be a considerable delay in diagnosis, with studies reporting an average of 9 to 11 years between the onset of symptoms and diagnosis in adults. A major reason for this delay is the failure of physicians to appreciate the frequency of celiac disease and its variable clinical manifestations. This problem can be aggravated by outdated and inaccurate data in reference textbooks. Correction of these deficiencies is seen as a priority.

A multidimensional celiac disease awareness campaign would be expected to

1. Ensure that educational materials contain accurate data on prevalence, clinical manifestations and diagnostic tests for celiac disease in the future.
2. Educate primary healthcare providers on the variable clinical manifestations of celiac disease, the value of serologic tests and the potential benefits of early diagnosis and treatment.
3. Encourage primary healthcare providers to adopt a strategy of active case finding in celiac disease.

Plans to Achieve Goal

Success in this campaign will require both research and the development of educational programs.

Research Needs. Additional data on the prevalence of celiac disease are needed to demonstrate the magnitude of the problem and the benefit of treatment. Without such data, it will be difficult to convince physicians of the importance of the condition.

Education Needs. Programs need to be developed to educate healthcare providers, at-risk groups and the general public about the importance and mechanics of celiac disease screening, as well as the health benefits of treating patients with celiac disease. These programs may incorporate lectures, web-based learning materials, advertising and other awareness programs. Celiac disease associations and pediatric gastroenterology professional organizations should take the lead in these initiatives.

Programs for education of health care providers need to be consistent across geographic regions and time. These programs should highlight current knowledge and recommendations regarding serologic testing but should also openly discuss gaps in knowledge.

Effort is needed to improve awareness about celiac disease-related complications. This includes strategies to encourage and improve compliance, such as the development of improved serologic tests for monitoring dietary compliance as well as improved testing of "gluten-free" products. Tests to do this would ideally be home-based, inexpensive and easy to perform.

FOOD ALLERGY

Research Goals

Identification of the Whole Spectrum of Disorders Due to Food Allergy

Clinical patterns attributed to food allergy fall into three groups (10,11). Immediate reactions such as anaphylaxis, rashes, swelling and respiratory symptoms are clearly related to IgE and mast-cell mediated responses. Gastrointestinal reactions are usually more intermediate, occurring within 1 to 24 hours, and including acute onset nausea, vomiting, abdominal pain and, perhaps later, diarrhea. Delayed reactions beyond 24 hours are due to T-cell sensitization (with varying degrees of IgE sensitization) and include exacerbation of atopic dermatitis, failure to thrive, vomiting and diarrhea. While there is no doubt about the patient who develops vomiting, rash and respiratory symptoms within minutes or hours of ingesting milk and who has positive skin and RAST tests, there remains considerable debate about the role of allergy in a number of other gastrointestinal conditions (Table 1).

Infant Colitis

The clinical pattern of infantile colitis is well recognized. Infants develop varying degrees of rectal blood, mucus and diarrhea within the first few weeks of life. Peripheral blood eosinophilia and hypoalbuminemia are variable. Colon biopsies usually demonstrate an eosinophilic inflammatory response. The colitis is self-limited and usually resolves by about 6 months of age. Dietary protein antigens in breast milk or bottled formula milk are likely causative (although the exact mechanism remains obscure) and the colitis responds to antigen withdrawal in most cases. Allergic gastroenterocolitis is a more severe and prolonged form. It may persist beyond the first year or may develop later upon the introduction of new foodstuffs in the diet and is associated with variable degrees of failure to thrive, malaise, vomiting, diarrhea and pain.

TABLE 1. *Allergy and gastrointestinal conditions*

Generally accepted allergic conditions (mechanism not necessarily clear)
Immediate reactions
Infantile proctitis/colitis
Allergic gastroenterocolitis
Emerging allergic conditions
Multiple food protein intolerance in infancy
Allergy and gastro-esophageal reflux/esophagitis
Infantile "colic," infant distress
Food allergy and atopic dermatitis
Conditions that may have an allergic component
Primary eosinophilic esophagitis
Eosinophilic enteropathy
Allergy and gastrointestinal motility disturbances
Gastroesophageal reflux
Constipation
Irritable bowel syndrome

Multiple Food Protein Intolerance

Some infants and young children are intolerant to a wide variety of foods. These reactions are not associated with positive IgE-based tests (skin, RAST) but are diagnosed by careful history-taking, elimination diet and clinical challenge (preferably double-blind placebo-controlled food challenge [DBPCFC]). The majority of children attain tolerance to most foods by 2 to 3 years of age but may require extensively hydrolyzed or elemental formulas in the meantime.

Allergy and Motility

Gastroesophageal Reflux/Esophagitis. The presence of eosinophils in esophageal biopsies has traditionally been considered to indicate reflux esophagitis due to exposure to acid and pepsin. However, recent studies have shown a poor correlation between the amount of acid reflux as measured by prolonged esophageal pH monitoring and the presence of esophagitis in infants presenting with distressed behavior attributed to reflux esophagitis. Many of these babies have mild inflammatory changes not only in esophageal biopsies but also in biopsies taken from the stomach and duodenum. Although skin and RAST tests may be negative, there is frequently a family history of atopy. In one study, about two-thirds of these babies responded to antigen exclusion using an elemental formula, and two-thirds reacted to the reintroduction of formula milk on DBPCFC.

Colic. Similarly, a role for food allergy in so-called "infant colic" or infant distress has been proposed. The relative role of food allergy in these conditions, and whether the mechanism is direct inflammation or disturbed motility, remains to be determined.

Allergy and Constipation. Chronic constipation is common in young children. Fewer than 5% have any definable anatomic, endocrine or neuromuscular abnormality. In recent years, the role of mucosal inflammation and allergy in children with constipation refractory to normal treatment has received increasing attention. Atopy is common in these children, and they may respond to a cow's milk–free diet. Further studies are required to assess the prevalence of constipation in atopic individuals and the role of food allergy in constipation

and to clarify the role of mucosal mast cells in the pathogenesis of these disorders.

Other Motility Disturbances. Mucosal inflammation may lead to neuromotor disturbance in atopic individuals. Whether this concept can be extended to other conditions associated with gastrointestinal motility disturbances remains to be established but may be of importance in cases of chronic abdominal pain, irritable bowel syndrome, constipation and gastroesophageal reflux.

Food Allergy and Atopic Dermatitis

The role of food protein hypersensitivity in cases of atopic dermatitis (eczema) is controversial, with estimates ranging from "food allergy affects only a minority" to "most infantile eczema is due to an IgE-mediated adverse reaction to foods." A positive skin and/or RAST test is present in 80% of cases but does not necessarily indicate that food allergy is the cause of atopy or, conversely, that atopy is always associated with food allergy. The use of elimination diets in patients with atopic dermatitis should be undertaken only when the diagnosis of allergy has been clearly established.

Eosinophilic Conditions

Primary eosinophilic esophagitis has emerged in the past 10 years as a distinct entity characterized by marked basal cell hyperplasia and intense eosinophilic infiltration of esophageal biopsy samples. The typical endoscopic appearance is of longitudinal furrows or "wrinkling" of the esophageal mucosa, often along its entire length. Characteristically, eosinophilic esophagitis manifests with dysphagia or food impaction. Food refusal, pain and vomiting are less frequent. Twenty-four-hour esophageal pH monitoring may yield normal results, and symptoms do not respond to acid blockade. A family history of eosinophilic esophagitis is common, as is a history of allergy and atopy in the patient or family. The condition responds to topical or systemic corticosteroids but usually not to an elimination diet. This intriguing condition requires a much greater awareness, recognition and further research. The role, if any, of food allergy, or ingestion of aeroallergens, remains to be established. Eosinophilic enteropathies are rare conditions that may affect part or all of the gut (gastritis, enteritis and gastroenterocolitis), and different layers of the intestine, such as the mucosa, submucosa, muscular layer or serosa. The primary pathogenic role of eosinophils in these conditions remains unclear, as does the role of food allergy.

Definition of the Goal

The prevalence of food allergy in children remains unclear because different studies have used different entry criteria and methods. There is a need for standardization of definitions, diagnostic procedures, test methods and careful categorization of cases into immediate, intermediate and delayed type reactions for a meaningful description and outcome comparison.

Food antigens and epitopes need to be further subdivided and the mechanisms of multiple food allergies identified. The impact of genetically modified food needs to be assessed.

Better tests are needed, particularly for delayed reactions, and may come from the better identification of specific epitopes, and lead to more specific RAST and skin tests. The role of inflammatory markers in blood and stool may provide predictive information but have so far met with limited success. Quantification of IgE and other cells in the mucosa and assessment of mucosal responses to allergen installation during endoscopy might be developed. At present, food challenge (preferably as DBPCFC) remains the gold standard.

The majority of children achieve tolerance by 2 to 4 years of age. Studies should address the mechanisms by which intolerance develops and by which tolerance is achieved. The role of the eosinophil and eotaxin in gastrointestinal disease needs clarification.

Plans to Achieve Goal

Collaborative protocols and definitions need to be established to further clarify the range of allergic and eosinophilic gastrointestinal disease, following from the work of the 2000 FISPGHAN World Congress Working Group on Allergy and Immunologically Related Diseases. A better definition of eosinophil-associated gastrointestinal disorders warrants special attention.

Intervention Goals

Identification and Implementation of Prevention Strategies for Food Allergy

Allergy prevention has been classified as primary prevention, which inhibits IgE and other immunologic sensitization; secondary prevention, which avoids disease expression in spite of immunologic sensitization; and tertiary prevention, which suppresses symptoms after disease expression.

Primary prevention should be directed at identifying patients at risk of developing food allergy (12,13). Identification of the allergy-prone infant in the perinatal period is desirable. This identification is not easy, because tools such as elevated IgE levels in umbilical cord blood do not discriminate the risk of developing food hypersensitivity. A series of genetic and immunologic markers related to the development of allergic disease has been established, but at this point they can be used only in certain settings, and none has a greater predictive value for the practical screening of "at-risk" neonates than a

family history of atopy. Efforts should be directed toward developing accurate and practical tests for identifying patients at risk of food allergies.

The development of food allergy depends on genetic predisposition, early exposure to allergenic proteins, food protein uptake and handling, and the development of tolerance. Alteration of maternal diet during pregnancy has been proposed as a strategy to avoid in utero sensitization of the genetically predisposed infant. However, current evidence suggests that food allergen avoidance during pregnancy does not affect the development of allergic sensitization. Food proteins ingested by the mother have been found in breast milk in an immunologically intact form, and sensitization of infants to food proteins during exclusive breast-feeding has been reported. It is not entirely clear whether the small amounts of foreign protein found in breast milk are responsible for the sensitization, or if other sources of allergens play a role. Primary prevention through hypoallergenic diets in newborns and infants may reduce the prevalence of food allergy. Breast-feeding, delayed introduction of solid foods and the use of hypoallergenic formulas for supplementation are at present the recommended prevention strategy in "high-risk" patients, as this approach seems to be associated with a reduction of atopic disease.

A matter that needs to be settled is whether these measures result in true long-term prevention or merely delay the development of food allergy as long as the allergen avoidance is maintained. Definitive conclusions regarding the potential benefits of breast-feeding in reducing allergic disease are lacking. If supplementation is needed in the allergy-prone baby, then extensively hydrolyzed formulas are likely the better choice, although definitive data are lacking. Multicenter, randomized studies, performed in well-defined high-risk infants, in whom the assessment of allergy at the end of the study period is determined by DBPCFC, are required to address this question.

Secondary prevention methods for food allergy are (1) elaboration, promotion and regular use of screening protocols for the detection of the already sensitized infant; and (2) raising awareness through education of primary healthcare workers and pediatricians. Early and accurate diagnosis of food allergy is necessary to institute appropriate treatment (tertiary prevention) and to avoid unnecessary diets in patients with other conditions. Controversial areas that need to be addressed are the safety and efficacy of soy formulas, which are an available, less costly and more palatable alternative to protein hydrolysates (14).

Avoidance of allergenic foods is the only currently available method for allergy prevention. Other therapeutic options under investigation are the use of humanized antibodies against IgE; immunotherapy with engineered proteins; vaccination with DNA sequences that encode food allergens; and the use of immunomodulators that can direct the immune response away from allergy. In this context, the role of probiotics warrants further investigation.

Plans to Achieve Goal

It is essential to clarify and unify concepts, both for the medical community and for the general public, so that food allergy can be correctly diagnosed, to improve medical knowledge and diagnostic tests, and to better define those individuals "at risk." These steps are a prerequisite to the development of strategies for the prevention and evaluation of intervention studies. Improvement of medical knowledge through collaborative work, consensus and education should be considered the starting point.

Educational Needs and Strategies to Improve Medical Knowledge

Diagnosis of Food Allergy

There appears to have been an increase in gastrointestinal food allergy, but prevalence data are confounded by a lack of uniform definitions and of standardization of the tests used in different studies. Comparative data need to be interpreted with caution, and one should differentiate between diagnoses made by self-reporting, by measurements of IgE sensitization (skin or RAST tests), and by clinical challenge.

Overdiagnosis of food allergy by parents is well documented (15), but the factors involved are not well understood. Parents and primary healthcare providers also need to be aware of the diagnostic limitations of both conventional and alternative diagnostic methods and the risks of a spurious diagnosis. They should also be informed about the potential pitfalls of self-diagnosis, diagnosis by unqualified practitioners, and the limitations of alternative diagnostic techniques such as provocation-neutralization tests, "live blood analysis," leukocyte cytotoxicity, muscle strength testing, and electrodermal tests (Vega testing), none of which has shown efficacy in controlled settings. Similarly, patients and primary healthcare providers need to be aware of the potential problems with commercial advertising material and unreviewed information on the Internet.

Primary care providers should be able to direct families to appropriate medical resources for evaluation and treatment. At the specialist level, there is a need for standardized definitions and categorization of the whole range of gastrointestinal allergic and eosinophilic conditions.

The expected results are the following: (1) A better understanding and standardization of the spectrum of disorders by professionals; (2) better comparative data on which to base future recommendations; (3) better informed primary care professionals and parents; (4) fewer

children on unnecessarily restricted diets and more on appropriate diets for the right reasons; and (5) more children referred to appropriate practitioners.

Plans to Achieve Goal

Collaboration between gastroenterologists, allergists and pathologists will be required to provide uniform guidelines, protocols and strategies such as those developed by the ILSI (International Life Science Institute). Member organizations of FISPGHAN should develop close links with professional bodies in allergy and clinical immunology to develop locally applicable teaching materials for dissemination to physicians, nurses, dietitians and other primary healthcare providers. Consideration should be given to opening lines of communication with alternative medicine groups.

FISPGHAN could establish a standing committee to act as a central liaison resource with other professional groups and provide updated position statements on which to base teaching guidelines. This information should be developed in the form of Internet-based material that can be updated as required and downloaded and modified for local use at a reasonable cost. Internet links to other recommended sites could be provided.

Programs could be developed for primary caregivers, especially family doctors and pediatric nurses, providing them and their patients with reliable information about the conditions and appropriate referrals to specialist practitioners. This could take the form of leaflets, booklets and other teaching materials that could be distributed in local clinics and nurseries.

Pharmaceutical companies and manufacturers of special infant feeds could be approached to help support the costs of the standing committee, the maintenance of a website, and the production and distribution of printed material.

CONCLUSIONS

Priorities have been identified for education, research and interventions to improve child health in the areas of celiac disease and food allergy.

For celiac disease, new diagnostic criteria are required to address the needs of subjects identified through screening programs (asymptomatic), and of subjects without typical small intestinal histologic findings who do not meet the diagnostic criteria established by ESPGHAN in 1990. Patients' organizations have expressed the need for a less invasive diagnostic protocol than that based on small intestinal biopsy. Early identification and treatment of celiac disease by healthcare providers should be implemented. Uniform standards for defining gluten-free products should be developed, as should guidelines for maximizing dietary compliance. Alternative forms of therapy are desirable and efforts should focus on the development of conceptually amenable therapeutic strategies. National celiac organizations need to focus fundraising and lobbying on larger scale research and educational programs. Collaboration between researchers, celiac associations, and industry is needed to promote the development of accurate and cost-effective screening panels. Efforts to improve awareness about celiac disease–related complications and compliance need to be enhanced. In an effort to find new therapies for celiac disease, collaboration with national and international celiac organizations, as well as organizations devoted to other diseases such as type 1 diabetes and multiple sclerosis, could provide an avenue for increasing resources, cost-sharing, enhancing awareness, and increasing the involvement of industry in the management of celiac disease.

The priorities for food allergy are characterizing the spectrum of food intolerance, defining diagnostic criteria, developing educational tools and implementing preventive strategies. Specific examples include further characterization of a number of emerging conditions that could have an allergic basis, such as multiple food protein intolerance, eosinophilic conditions of the gastrointestinal tract and aberrant gastrointestinal motility. The role of specific food antigens and epitopes (including potential new ones in genetically modified foods) as a cause of multiple food allergy should be clarified. Better tests for delayed reactions need to be developed. At the same time, educational tools need to be created to enhance public and professional understanding and to highlight the inconsistency of unorthodox diagnostic tests so as to prevent the use of unnecessarily restricted diets in children. Finally, primary prevention, which aims at inhibiting IgE and other immunologic sensitizations, will represent a priority in forthcoming years. Collaboration between gastroenterologists, allergists and pathologists will be required to provide uniform guidelines, protocols and strategies. Programs for primary care providers and patients should be developed and should provide reliable information about food allergy and guidelines for appropriate evaluation and referrals to specialists.

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