Screening for Celiac Disease

In

Egyptian Children

Thesis

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بسم الله الرحمن الرحيم

To My Mother

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LIST OF ABBREVIATIONS

AGAs : Antigliadin antibodies.

BMD : Bone mineral density.

CBC : Complete blood count.

CD : Celiac disease.

DH : Dermatitis herpetiformis.

EATL : Enteropathy associated T-cell lymphoma.

EMAs : Antiendomysial antibodies.

GF : Gluten-free.

GFD : Gluten free diet.

HIV : Human Immunodeficiency Virus.

HLA : Human leukocyte antigens.

IEL : Intraepithelial lymphocyte.

IgA AGAs : Immunoglobulin A. antigliadin antibodies.

IgA : Immunoglobulin A.

IgE : Immunoglobulin E.

IgG AGAs : Immunoglobulin G antigliadin antibodies.

MHC : major histocompatibility complex.

MRI : Magnetic Resonance Imaging.

PREP : Prolyl Endopeptidases.

SBB : Small bowel biopsy.

SLE : Systemic Lupus Erythematosus.

TTG : Tissue transglutaminase.

ABSTRACT

Celiac disease (CD) is an immune-mediated enteropathy triggered by the ingestion of gluten in genetically susceptible individuals. It is one of the most common, lifelong disorders in both the US and Europe affecting approximately 1 % of the general population. The CD prevalence in developing countries is less clear, although occasional data suggest that CD prevalence could be high in Northern Africa and Middle East countries. In these areas, untreated CD may contribute to childhood mortality by worsening the vicious circle of diarrhea-malnutrition. The determination of anti-transglutaminase (tTG) antibodies (Ab) is considered a sensitive tool for detecting atypical and silent forms of CD. Aims of the study:- (1) to investigate for the prevalence of CD among children in Egypt, (2) to describe the main presenting symptoms of CD in the positive group. Methods: 1500 case was picked out from Abu El Reish hospital outpatient clinic. The screening test was serum class A anti-tTG Ab. Samples showing anti-tTG less than 0.5 U were further analyzed for IgG class anti-tTG and total IgA level (to rule out IgA deficiency). Serum antiendomysium Ab (EMA) determination was performed in subjects that tested positive for anti-tTG IgA Ab. Small intestinal biopsy was recommended to subjects showing IgA anti-tTG and EMA positivity or IgA deficiency plus IgG anti-tTG positivity. Results: Showed, prevalence of affection in the selected group was 1.4%, with a higher incidence of affection in females than males, and main presenting symptoms to be failure to thrive.

Conclusion: These results indicate that CD in the Egyptian pediatric population is as frequent as in Europe and North America.

Key words: Celiac disease, gluten, children.

INTRODUCTION

Celiac disease (CD) is an immune-mediated enteropathy triggered by the ingestion of gluten in genetically susceptible individuals. Gluten is a protein component in wheat, a staple food for most populations in the world, and other cereals (rye and barley). The major CD-predisposing genes are located in the HLA region, namely the HLA-DQ2 and/or DQ8 genotypes found in at least 98% of patients. CD is one of the most common lifelong disorders in Europe and in the United States. This condition can manifest with a previously unsuspected range of clinical presentations, including the typical malabsorption syndrome (chronic diarrhea, weight loss, abdominal distention) and a spectrum of symptoms potentially affecting any organ or body system. Because CD often is atypical or even clinically silent, many patients remain undiagnosed and are exposed to the risk of long-term complications, such as osteoporosis, infertility, or cancer (Fasano et al., 2001).

The burden of illness related to CD is doubtless higher than previously thought and there is growing interest in the social dimensions of this condition. Although CD can present at any age, including the elderly, typical cases often manifest in early childhood (Fasano, 2005).

In 1888, Samuel Gee, having drawn attention to the disorder in a lecture delivered on October 5, 1887, at the Hospital for Sick Children in London, produced his classic paper, On the Coeliac Affection (Gee, 1890). Dr. Gee described celiac disease as follows: “There is a kind of chronic indigestion which is met with in persons of all ages, yet is especially more likely to affect children between one and five years old. Signs of the disease are yielded by the faeces; being loose, not formed, but not watery; more bulky than the food taken would seem to account for-”. Remarkably, he already hypothesized that foodstuffs could be the trigger of the disease: “The causes of the disease are obscure. Children who suffer from it are not

all weak in constitution. Errors in diet may perhaps be a cause, but what error? Why, out of a family of children all brought up in much the same way, should one alone suffer? To regulate the food is the main part of treatment. The allowance of farinaceous food must be small; highly starchy food, rice, sago, corn-flour are unfit." (Gee, 1890).

The condition is characterized by villous atrophy, a lowering of the villous height to crypt depth ratio (normal, 3–5:1), an increase in intraepithelial lymphocytes (normal, 10–30 per 100 epithelial cells), and extensive surface cell damage and infiltration of the lamina propria with inflammatory cells (Ciclitira, 1999).

Both the symptoms and abnormal small intestinal mucosal morphology resolve on removal of gluten from the diet (Ciclitira, 1999).

Aim of the work

The aim of this study is to screen for the prevalence of celiac disease among Egyptian children. In the study, serological tests have been used for identifying many patients with CD including some who are totally free of symptoms despite having significant histological features of small intestinal mucosal damage.

General Introduction

Diseases of the small intestine have long been affecting children. In recent years there has been a much wider understanding of the physiology and pathology of the small intestine in humans. This has been due both to new diagnostic techniques, such as intestinal biopsy, and to increasingly sophisticated animal modeling techniques (Smith et al., 1999).

Of particular importance in the development of pediatric gastroenterology was the demonstration by Sakula and Shiner in 1957of a flat, small intestinal mucosa on biopsy of the small bowel of a child with celiac disease (Smith et al., 1999).

Anatomy and Histology of the Digestive tract:

The structure of the gastrointestinal tract conforms of a general plan which is clearly evident from the esophagus to the anus.

The gastrointestinal system is essentially a muscular tube lined by a mucous membrane which exhibits regional variations reflecting the changing functions of the system from the mouth to the anus.

The arrangement of the major muscular component remains relatively constant throughout the tract, whereas the mucosa shows marked variations in the different regions of the tract.

The gastrointestinal tract has four distinct functional layers: mucosa, submucosa, muscularis propria and adventitia.

Mucosa:

It is made up of three components: the epithelium, a supporting lamina propria and muscularis mucosa which is a thin smooth muscle layer. Muscularis mucosa produces local movement and folding of the mucosa.

At four points along the tract the mucosa undergoes abrupt transition from one form to another: the gastro-esophageal junction, the gastro duodenal junction, the ileocaecal junction and the recto-anal junction.

Submucosa:

This layer of loose collagenous tissue supports the mucosa and contains the larger blood vessels, lymphatics and nerves.

Muscularis propria:

The muscular wall proper consists of smooth muscle which is usually arranged as an inner circular layer and an outer longitudinal layer. In the stomach only, there is an inner oblique layer of muscle. The action of the two layers, at right angles at one another, is the bases of peristaltic contraction.

Adventitia:

This outer layer of loose supporting tissue conducts the major vessels and nerves; in obese individuals it contains a large amount of adipose tissue. Where the gut lies within the abdominal cavity (peritoneal cavity), the adventitia is referred to as the serosa (visceral peritoneum) and is lined by a simple squamous epithelium (mesothelium). Elsewhere, the adventitial layer merges with retroperitoneal tissues.

Anatomy and Histology of the small intestine:

The small intestine consists of the duodenum, jejunum and ileum. It is the main site for absorption of digestion products from the gastrointestinal tract. Digestion begins in the stomach and is completed in the small intestine in association with the absorptive process.

Four factors combine to provide an enormous surface area:

- The small intestine is extremely long (4-6 meters in humans).
- The mucosa and submucosa are thrown up into circularly arranged folds called plicae circulares or valves of Kerkring which are particularly numerous in the jejunum.
- The mucosal surface is made up of numerous finger-like projections called villi, whilst the mucosa between the bases of the villi is formed into crypts, called crypts of Lieberkühn.
- Plentiful microvilli are present at the luminal surface of the enterocytes, the columnar cells covering the villi and crypts; these cells are responsible for the processes of digestion and absorption (Young et al., 2000).

The muscularis mucosa lies immediately beneath the mucosal crypts and separates the mucosa from the submucosa. The vascular submucosa extends into, and forms the core of, the plicae circulares. Inner circular and outer longitudinal layers of the muscularis are responsible for the continuous peristaltic activity of the small intestine. The peritoneal aspect of the muscularis is invested by the loose collagenous serosa, which is lined on its peritoneal surface by mesothelium identical in appearance to the mesothelial lining of the pleura (Young et al., 2000).

Because of its continuity with the external environment, the gastrointestinal system is a potential portal of entry of pathogens. Thus the system incorporates a number of defense mechanisms, which include prominent aggregations of lymphoid tissue known as the gut associated lymphoid system (GALT), distributed through out the tract. GALT is part of the mucosa associated lymphoid tissue (MALT). Lymphoid tissue is distributed throughout the gastrointestinal tract both as diffusely scattered cells, particularly in the lamina propria, and as dense aggregates which may form follicles (Peyer's patches) (Young et al., 2000).

Racial and Climatic Differences in Small Bowel Mucosa