TISSUE TRANSGLUTAMINASE IgG ANTIBODIES AS A SCREENING TEST FOR CELIAC DISEASE IN SHORT CHILDREN

Thesis submitted for partial fulfillment of M.Sc degree in pediatrics

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٢٠٠٧

LIST OF CONTENTS

LIST OF FIGURES

LIST OF ABBREVIATIONS

AGA	Antigliadin antibodies
CD	Celiac disease
CNS	Central nervous system
CSF	Cerebrospinal fluids
CTLA-٤	Cytotoxic T lymphocyte-associated protein-٤
ELISA	Enzyme linked immunosorbant assay
EMA	Endomysial antibody
ESPGAN	Europeon Society of Pediatric Gastroenterology and Nutrition
FSS	Familial short stature
GFD	Gluten free diet
GHD	Growth hormone deficiency
Hb	Hemoglobin
HLA	Human leukocyte antigen
HPF	High power field
IEL	Intraepithelial lymphocyte
Ig	Immunoglobulin
IGF	Insulin-like growth factor
ISS	Idiopathic short stature
MAS	Malabsorption syndrome
MHC	Major histocompatibility complex
MPH	Mid-parental height
NIH	National institute of health
PAH	Projected adult height
PAS	Para-aminosalicylic acid
SD	Standard deviation
SDS	Standard deviation score
tTG	Tissue transglutaminase
VNTR	Variable number of tandem repeat

LIST OF TABLES

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INTRODUCTION

Celiac disease (CD) is a complex small intestinal disorder due to a dysregulated immune response to wheat gliadin and related proteins which leads to a small intestinal enteropathy **(Gianfrani et al., ٢٠٠٥).**

Celiac disease is an important cause of chronic diarrhoea, failure to thrive, and anaemia in children **(Mohindra et al., ٢٠٠١).**

Celiac disease must be considered in every child with failure to thrive and short stature regardless of whether diarrhea is present **(Walker-Smith, ٢٠٠٠).**

It is recommended that children and adolescents with symptoms of celiac disease or an increased risk for celiac disease have a blood test for antibody to tissue transglutaminase (TTG), that those with an elevated TTG be referred to a pediatric gastroenterologist for an intestinal biopsy and that those with the characteristics of celiac disease on intestinal histopathology be treated with a strict gluten-free diet **(Hill et al., ٢٠٠٥).**

Antigliadin and anti endomyseal antibodies and assays for tissue transglutaminase are very useful as screening assays for celiac disease , but they are neither ١٠٠٪ sensitive or specific and abnormal serological result should always be followed by histological confirmation of villous atrophy **(Smart and Nolan, ٢٠٠٠).**

AIM OF THE WORK

The aim of this study is to determine the prevalence of celiac disease (CD) in children presenting with short stature.

CELIAC DISEASE

Celiac disease is an immune-mediated enteropathy caused by a permanent sensitivity to gluten in genetically susceptible individuals. It presents in children and adolescents with gastrointestinal symptoms, dermatitis herpetiformis, dental enamel defects, osteoporosis, short stature, delayed puberty and persistent iron deficiency anemia. It occurs asymptomatic in individuals with type ١ diabetes, Down syndrome, Turner syndrome, Williams syndrome, selective immunoglobulin (Ig)A deficiency and first degree relatives of individuals with celiac disease **(Hill et al., ٢٠٠٥)**.

Although celiac disease can present at any age, including the elderly, typical cases often manifest in early childhood. The clinical spectrum in children is wide and includes: (١) typical cases presenting early in life with signs of intestinal malabsorption (chronic diarrhea, weight loss, abdominal distention, etc); (٢) atypical cases showing milder, often extra-intestinal, symptoms; (٣) silent cases that are occasionally discovered because of serological screening; (٤) potential/latent cases showing isolated positivity of celiac serology at first testing and eventually the typical intestinal damage later in life. Many celiac disease associated problems, which were originally described mostly in adults, can indeed be observed in children or adolescents, e.g. reduced bone mineral density, neurological problems and associated autoimmune disorders. Pediatricians and pediatric subspecialists

should have a high degree of awareness and embrace a 'liberal' use of serological celiac disease tests in order to identify these cases in a timely fashion to prevent serious complications secondary to untreated celiac disease **(Fasano and Catassi, ٢٠٠٥)**.

The clinical presentation of celiac disease varies greatly depending on patient's age, duration and extent of the disease, and the presence of extraintestinal manifestations. Unfortunately, most of patients with celiac disease have either silent or atypical presentations, thus escaping diagnosis for several years **(Chand and Mihas, ٢٠٠٦)**.

Serologic screening studies that use sensitive and specific antibody tests have revealed the disease to be common. Clinical presentations are diverse and atypical; the majority of patients lack diarrhea. Therapy is a gluten-free diet that requires avoidance of wheat, rye, and barley, although there is potential for other therapies based on our understanding of the pathophysiology of the disease **(Green and Jabri, ٢٠٠٦)**.

Epidemiology

Epidemiologic studies reveal celiac disease to be common, occurring in approximately ١٪ of the population. It is being diagnosed worldwide, even in developing countries **(Lee and Green, ٢٠٠٦)**.

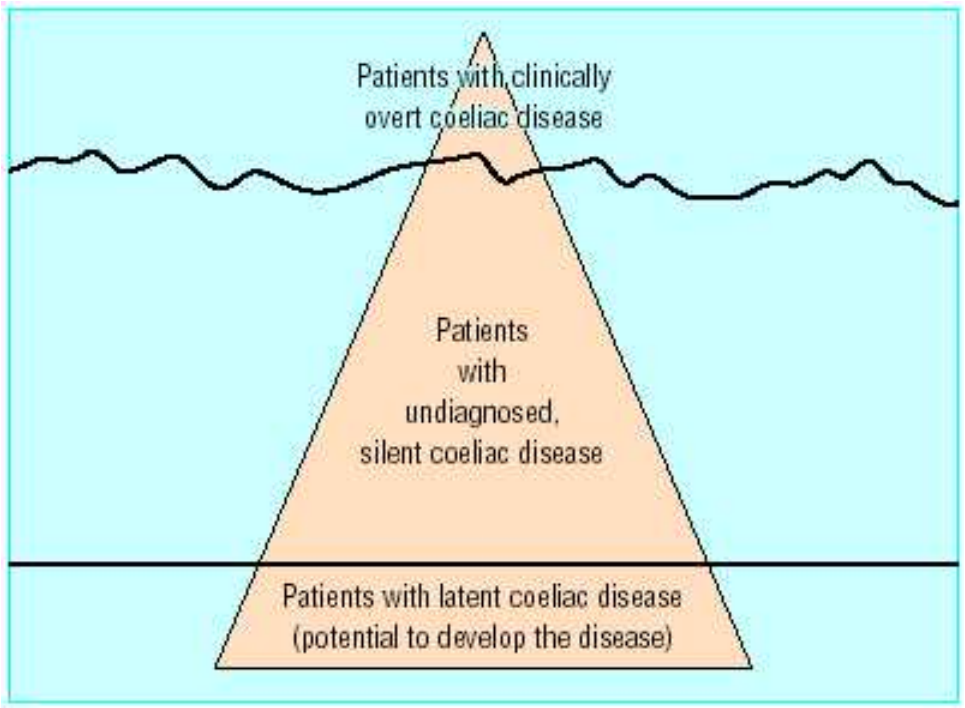
Silent celiac disease is reported in ١٪ of Caucasian populations, but there is a lack of knowledge of its

natural course and the risk of complications (**Verkasalo et al., ٢٠٠٥**).

Prevalence of clinically overt celiac disease varies from ١/٢٧٠ in Finland to ١/٥،٠٠٠ in North America. However, since celiac disease can be asymptomatic, most subjects are not diagnosed or they can present with atypical symptoms. In epidemiological studies that aimed to assess celiac disease prevalence, large cohorts in North America and Europe were screened for highly-sensitive endomysium or tissue transglutaminase antibodies. Besides, they underwent subsequent small intestinal biopsies when antibody testing was positive. The celiac disease prevalence was found to be much higher than expected. Approximately ١/١٠٠ to ١/٥٠٠ were found to be positive for antibodies and had villous atrophy of the small intestine. Thus, up to ١٪ of a western population tests are positive for celiac disease. Furthermore, approximately ١٠٪ of the first-degree relatives also have celiac disease **(Holtmeier and Caspary, ٢٠٠٦)**.

Several epidemiological studies showed that celiac disease with extraintestinal manifestations is ١٥ times more frequent than celiac disease with intestinal symptoms. Fifteen years ago, the iceberg model was proposed to explain the epidemiology of this disease (Fig. ١). On one hand, there is a quantifiable number of patients who are correctly diagnosed since they have symptoms suggestive of this disease and who form the visible part of the iceberg. However, several studies using screening serology demonstrated that for each

patient diagnosed, there is a mean of ٥-١٠ patients without a diagnosis. These patients form the submerged part of the iceberg (monosymptomatic or silent celiac disease). The most widely accepted strategy to investigate the submerged part of the "celiac iceberg" is screening of known risk groups through a systematic search for celiac disease in these groups **(Fernandez-Banares et al., ٢٠٠٥)**.



(Fig. ١): Iceberg model depicting prevalence of celiac disease **(Fernandez-Banares et al., ٢٠٠٥)**

Pathophysiology

Celiac disease is the end result of ٣ processes that culminate in intestinal mucosal damage **(Marsh, ١٩٩٢)**: genetic predisposition, environmental factors, and immunologically based inflammation. Celiac disease

may be the result of an evolutionary collision between the cultivation of wheat and the human immune system, in particular between the human leukocyte antigen (HLA) system of self identification and the specific deleterious peptide sequences in wheat **(Greco, ١٩٩٧)**.

Genetics

As gluten acts as an essential factor in the pathogenesis of celiac disease, this raises the question of what makes a particular individual susceptible to gluten. Evidence suggests that hereditary factors play a significant role, and celiac disease is diagnosed in around ١٠٪ of first degree relatives of an individual with celiac disease **(Feighery, ١٩٩٩)**.

Celiac disease is a heritable condition. It seems to be more common in whites and family co-occurrence is common (Table ١) **(Talal et al., ١٩٩٧)**.

(Table ١): Risk for celiac disease in specific populations **(Talal et al., ١٩٩٧)**

Population	Risk
	%
Family member of affected patient	5–20
Persons with type 1 diabetes	5–7
Persons with Sjögren disease	3
Persons with thyroid disease	4
Persons with selective immunoglobulin A deficiency	7