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IgA Tissue Transglutaminase Antibodies at Different cut-offs in the Evaluation of Possible Celiac Patients

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Abstract The celiac disease screening with IgA tissue transglutaminase antibodies depends on the cut-off reaction, therefore many patients with values less but close to the cut-off may be undiagnosed. Material and Method. We conducted the CD screening with IgA tissue transglutaminase antibodies in a group of 1616 children during 2014 at a cut-off of 25 U/ml and at a cut-off of 10 U/ml. We also wanted to compare our results with IgA tissue transglutaminase antibodies prevalence from other countries. Results. We found a IgA tissue transglutaminase antibodies prevalence rate of 3% for values higher 25 U/ml and a IgA tissue transglutaminase antibodies prevalence rate of 1.6% for values between 10-25 U/ml. A prevalence of 13.6% for IgA tissue transglutaminase antibodies was observed in Germany, Finland and Sweden. Conclusions. We observed a 4.6% IgA tissue transglutaminase antibodies prevalence at a cut-off of 10 U/ml. Prevalence of IgA tissue transglutaminase antibodies from Romania is lowered compared with other European countries.

Keywords: *celiac disease, screening, cut-off*

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1. Introduction

The European Society for Paediatric Gastroenterology Hepatology and Nutrition guidance from 2012 emphasized the role of serological tests in the diagnosis of celiac disease (CD). If IgA tissue transglutaminase antibodies (IgA tTG) are more than 10 times the normal level, the diagnosis of CD is performed without duodenal biopsy [1]. A recent study confirms that these criteria may be useful in screening of CD in the pediatric population [2].

IgA tTG was universally recommended as a screening test for CD [3,4]. The researchers have found correlations between high levels of IgA tTG and intestinal mucosal lesions [5]. The importance of IgA tTG in CD screening was revealed in risk groups, like Type 1 Diabetes Mellitus [6] and mildly elevated IgA tTG levels were more important compared to duodenal biopsy in Type 1 Diabetes Mellitus [7]. But the researchers agreed that positive results of IgA tTG need a second confirmatory method [8]. Therefore, the IgA tTG performance and characterization of the population where they are tested are discussed [9,10].

The main goal of our study was to find the IgA tTG prevalence in the pediatric population to a standard cut-off given by an ELISA kit and to a lower cut-off given by us. The secondary goal was to compare our IgA tTG prevalence with IgA tTG prevalence from other countries.

2. Material and Method

2.1. Study Design

The patients' sera were taken during the course of 2014 from children coming from the Regional Centre for the Management of Celiac Disease in Transylvania, organized within the structure of the Clinical Emergency Pediatric Hospital Cluj-Napoca, Pediatrics Clinic II. The patients were examined for serological CD screening. All serum samples were stored at -20°C, until testing. Type of study was analytical observation.

2.2. Patients

The study group consisted of 1616 pediatric patients aged between 0 and 18 years. We performed IgA tTG to all children where clinical physician suspected CD. Inclusion criteria were pediatric patients with symptoms like: chronic diarrhoea, weight loss, stature growth retardation, malabsorption syndrome, frequent anaemia, as well as patients with any disorders with primary or secondary intestinal involvement.

2.3. Methods

The tests included the IgA tTG measurement. INOVA Diagnostics Inc. (San Diego, USA) provided the

serological tests. An ELISA Dynex Technology Inc. analyser evidenced IgA tTG. We validated the results obtained only after internal quality control. The main interferences of IgA tTG were with free bilirubin (19.3 mg/dl), conjugated bilirubin (19.9 mg/dl), hemolysis haemoglobin (485 mg/dl) and rheumatoid factor (45 IU/ml), such sera being avoided during testing. The method had 25 U/ml as cut-off value, samples with a higher concentration being considered positive, and samples with a lower concentration being considered negative. But, we also analyzed the results with values between 10 to 25 U/ml, as a novelty in our research. Patients with selective IgA deficiencies were excluded from our study due to false negative results that can give IgA tTG.

We analyzed the data with Portable IBM SPSS Statistics v19.

3. Results

3.1. Demographic and Clinical Characteristics of the Studied Subjects

The geographical coverage area included patients from Cluj county and the counties of North-Western and Central Transylvania: Maramureş, Sălaj, Bistrița-Năsăud, Satu-Mare, Bihor, Alba, Mureş, Braşov, Hunedoara, Harghita, Suceava. Distribution by gender was 51 % boys and 49 % girls.

3.2. Evaluation of IgA tTG Values Higher than 25 U/ml in Our Pediatric Population

IgA tTG was positive in 49 children, which means a 3% prevalence of IgA tTG. Analysis by gender revealed positive results for IgA tTG in 26 boys and 23 girls. We found a mean positive IgA tTG values at 70 U/ml and we also found a mean age of children with positive IgA tTG at eight years (Table 1). Five children from 49 children with IgA tTG positive values had values more than 10 times than the normal level 25 U/ml.

Table 1. The means compare of values higher 25 U/ml

Statistical evaluation		tTG +	Age
Mean		70.6	8.0
95% Confidence Interval for Mean	Lower Bound	58.3	6.6
	Upper Bound	82.9	9.5
5% Trimmed Mean		66.8	7.8
Median		61.2	8.0
Variance		1844.6	24.9
Std. Deviation		42.9	5.0
Minimum		25.5	0.0
Maximum		204.0	20.0
Range		178.5	20.0
Interquartile Range		61.6	7.0
Skewness		1.1	0.5
Kurtosis		1.1	-0.2

3.3. Evaluation of IgA tTG Values between 10-25 U/ml in Our Pediatric Population

IgA tTG was positive in 25 children, which means a 1.6% prevalence of IgA tTG. Analysis by gender revealed positive results for IgA tTG in 15 boys and 10 girls. We found a mean positive IgA tTG values at 15.7 U/ml and we also found a mean age of children with positive IgA tTG at 9.1 years (Table 2).

Table 2. The means compare to values between 10-25 U/ml

Statistical evaluation		tTG +	Age
Mean		15.7	9.1
95% Confidence Interval for Mean	Lower Bound	13.7	7.2
	Upper Bound	17.7	11.0
5% Trimmed Mean		15.5	9.0
Median		13.4	8.0
Variance		23.9	21.0
Std. Deviation		4.9	4.6
Minimum		10.6	3.0
Maximum		24.6	17.0
Range		14.0	14.0
Interquartile Range		9.2	7.5
Skewness		0.6	0.4
Kurtosis		-1.2	-1.2

4. Discussions

Compared to 2011 when we found a 13.8% prevalence of IgA tTG [8], in 2014 we obtained a lower prevalence of IgA tTG. But if we get down cut-off reaction at 10 U/ml, the prevalence was 4.6%. There are not major differences among IgA tTG values in boys or girls. The CD screening showed us a high average age of eight years for IgA tTG positive results. So, CD is a major problem to school age. Although new guidelines for the diagnosis of CD from 2012 recommend giving up intestinal biopsy in patients with IgA tTG values greater than 10 times the normal values, our study shows a few such cases.

Evaluation of ELISA serological tests for CD has always been a major problem [11,12]. A 1.33% prevalence of IgA tTG was found in healthy Turkish school children [13] and in Iranian children with recurrent abdominal pain referred to a pediatric referral centre [14]. A 1.62% prevalence of IgA tTG, with female gender predominance ($p < 0.023$) was found in Argentina [15]. IgA tTG IgA showed 1.8% prevalence in children from the Republic of San Marino [16] and 3.18% prevalence in children from Canada [17]. Therefore, IgA tTG ELISA was needed in CD screening from Italian Apulian Family Pediatricians [18]. A 2.56% prevalence of IgA tTG was found in 1679 Dutch children who were positive for human leukocyte antigen (HLA) DQ2/DQ8 [19]. A 13.6% prevalence of IgA tTG was found in children from six clinical centres in four countries positive for HLA-DR3-DQ2 or DR4-DQ8 from the USA and Europe [20].

But IgA tTG screening at a cut-off of 25 U/ml and at IgA tTG screening a cut-off of 10 U/ml is an important problem that requires further laboratory and clinical studies.

5. Conclusions

We obtained a 3% prevalence of IgA tTG with a high average age of eight years for IgA tTG positive results. Both sexes at school age are equally susceptible to CD. Prevalence of IgA tTG from Romania is lowered compared with other European countries, such as Germany, Finland and Sweden.

Conflicts of Interest

The authors report no conflicts of interest.

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