UNFAVOURABLE PROGNOSIS MARKERS IN THE ASSOCIATION OF TYPE I SUGAR DIABETES WITH THE CELIAC DISEASE

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Abstract: *The association of the celiac disease with sugar diabetes has been demonstrated by the common genetic aspect (HLA-DR3,) which correlates with the serious evolution of the type I diabetes. Object and method: During 2008-2009, we followed the quantification of the associated autoimmune phenomena through immunoenzymatic reactions on a group of 40 children with sugar diabetes of type I. Results: The immunologic markers' prevalence was: liver-kidney anti-microsomal antibodies 2.5%, soluble liver antigen 0%, glutamic acid* anti-decarboxylase antibodies *35%, anti-tyrosine phosphatase antibodies 55%, anti-insulin antibodies 50%, cytoplasmic anti-insulin antibodies 2.5%, anti-thyroglobulin antibodies 11.1%, antithyroidperoxidase antibodies 23.1% and tissular antitransglutaminase antibodies IgA 25.7%. The main associations of the IgA tissular antitransglutaminase antibodies were with the glutamic acid* anti-decarboxylase antibodies *r=0.33 (p=0.027). Conclusion: Since the presence of the glutamic acid* anti-decarboxylase antibodies *was associated with the tissular antitransglutaminase antibodies IgA, these could be used as predictive markers in the unfavourable development of the type I sugar diabetes.*

Cuvinte cheie: *markeri imunologici, asociere diabet-boală celiacă*

Rezumat: *Asocierea bolii celiace cu diabetul zaharat a fost demonstrată prin aspectul genetic comun (HLA-DR3), care se corelează cu evoluţia severă a diabetului de tip 1. Scop şi metodă. Pe parcursul anului 2008-2009 am urmărit cuantificarea fenomenelor autoimune asociate, prin reacţii imunoenzimatice, pe un lot de 40 copii cu diabet zaharat tip 1. Rezultate. Prevalenţa markerilor imunologici a fost: anticorpi antimicrozomi hepato-renali 2.5%, antigen solubil hepatic 0%, anticorpi antidecarboxilază acid glutamic 35%, a*nticorpi *antitirozinfosfatază 55%,* anticorpi *antiinsulină 50%,* anticorpi *antiinsulari citoplasmatici 2.5%, anticorpi antitireoglobulină 11.1%,* anticorpi *antitiroidperoxidază 23.1% şi anticorpi antitransglutaminază tisulară IgA 25.7%. Principalele asocieri ale anticorpilor antitransglutaminază tisulară IgA găsite au fost cu anticorpii antidecarboxilază acid glutamic r=0.33 (p=0.027). Concluzii. Deoarece prezenţa anticorpilor antidecarboxilază acid glutamic s-a asociat cu anticorpii antitransglutaminază tisulară IgA, aceaştia ar putea servi ca marker predictiv în evoluţia nefavorabilă a diabetului zaharat tip 1.*

INTRODUCTION

The following were emphasized in an informative educational journal of April 2009, issued by the Group of Patients with Gluten Intolerance of North America: "There is a genetic connection between the sugar diabetes and the celiac disease. One disease's development increases the risk of the other one's evolution. If a family has two children with type I sugar diabetes, the risk is much higher. The prevalence of the celiac disease in persons with type I sugar diabetes is of about 60% in the world. The celiac disease' symptoms vary a lot but, many times they are absent in persons with sugar diabetes. The celiac disease can cause glycaemia dysfunctions."

The natural history of the type I sugar diabetes is strongly connected to the autoimmune manifestations. In 2003, Ziegler &collab (1) emphasized the importance of the genetic sensitiveness in the occurrence of the autoimmune manifestations associated to the type I sugar diabetes, as well as the extremely high prevalence, 1/30, of the autoimmune manifestations in the risk groups.

Nowadays, many authors have emphasized the clinical relation between the celiac disease and type I sugar diabetes. McGowan & collab (2) said that the population antibodies testing for the celiac disease tripled the celiac disease occurrence but increased the average age four times from the diagnosis. Narula & collab (3) stated that the patients with type I sugar diabetes and celiac disease had a higher frequency of the gastro-intestinal symptoms than the diabetics with negative serology for Gee's disease and were not really asymptomatic. Vicuña & collab (4) noticed these symptoms decreased at an adult age. Galicka-Latala & collab (5) observed that the diarrhoea, abdominal pains were more frequent in the patients with villous atrophy and the introduction of diet without gluten led to the improvement of life quality and of these symptoms but they recommended the control of IgA tissular antitransglutaminase antibodies titer.

Paraclinically, the relation between the celiac disease and the type I sugar diabetes was proven by the laboratories that determined the HLA, by emphasizing the common histocompatibility antigens, respective HLA DR3, which, in the case of diabetics, are correlated with the diabetes' more severe evolution, being a risk factor.

PURPOSE OF THE PAPER

Because the histocompatibility testing through molecular biology comes within the competence of the specialized laboratories and has not been available yet in the

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clinical diagnosis, our goal was to look for other immunologic markers with unfavourable prognosis value in diabetics with associated celiac disease by quantifying the autoimmune phenomena associated with type I sugar diabetes.

MATERIAL AND METHOD

The researched group included a representative group of 40 patients diagnosed with type I sugar diabetes, who, during 2008-2009, were serologically tested in order to determine the associated autoimmune manifestations. The group's distribution per sexes was: 65% boys and 35% girls. The patients were divided into three age groups: 10% between 0-3 years old, 45% between 3-10 years old and 45% between 10-18 years old. The testing included the determination of liver-kidney anti-microsomal antibodies (LKM), soluble liver anti-antigen antibodies (SLA), glutamic acid *anti-decarboxylase antibodies* (GAD), anti-tyrosine phosphatase antibodies (IA2), anti-insulin antibodies (*IAA*), cytoplasmic anti-insulin antibodies (ICA), anti-thyroglobulin antibodies (TT), antithyroidperoxidase antibodies (TPO) and tissular antitransglutaminase antibodies IgA (tTG IgA).

The testing was done through ELISA immunoenzymatic reactions, to detect the antigen and antibodies, using *in vitro* diagnosis kits produced by Inova Diagnostics Inc. (San Diego, USA) for anti-LKM, anti-SLA, anti-TT, anti-TPO and anti-TG, by Biomerica Inc.(Newport Beach, USA) for anti-GAD and by DRG Diagnostics Inc. (Marburg, Germany) for anti-IA2, anti-IAA and anti-ICA.

Statistic Analysis

The statistical analysis was done using the SPSS-PC+ soft, version 13, statistical packet of high dimensions used for scientific medical and social research, capable to execute a high range of tests. The relation between the numerical data was described with Pearson's correlation coefficient and the autoimmune manifestations association quantification was done with the square Hi test. The applied tests were considered statistically significant only for $p<0.05$.

RESULTS

I. Demographic and clinical characteristics of the studied patients

The geographical area of the investigated patients covered the county of Cluj and the neighbouring areas: Bistrița-Năsăud, Maramureș, Alba, Sălaj, Harghita.

Our group's clinical characteristics included several manifestations of the type 1 sugar diabetes, i.e.: patients without complications but also patients with acidocetosis without coma, with diabetic neuropathy, with non-specific complications, with repeated hypoglycaemia, with low control and other forms of type 1 sugar diabetes without complications. The study's type was analytic observational.

II. Quantification of Autoimmune Manifestations

The immunologic markers prevalence in our group was the following: anti-LKM 2.5%, anti-SLA 0%, anti-GAD 35%, anti-IA2 55%, anti-IAA 50%, anti-ICA 2.5%, anti-TT 11.1%, anti-TPO 23,1% and anti-tTG IgA 25.7%.

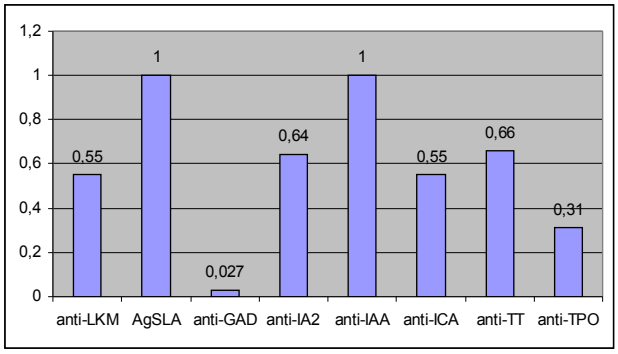
III. Possible Associations of the anti-tTG IgA

Statistically speaking, the most relevant association is the one between the anti-GAD and anti-tTG IgA variables *(Figure I)*. From the quantitative analysis of the two variables expressed through the Pearson coefficient r=0.33 it results the existence of a moderate correlation and the square Hi test value p=0.027, statistically significant ($p<0.05$) confirms the association between the anti-GAD and anti-tTG IgA variables.

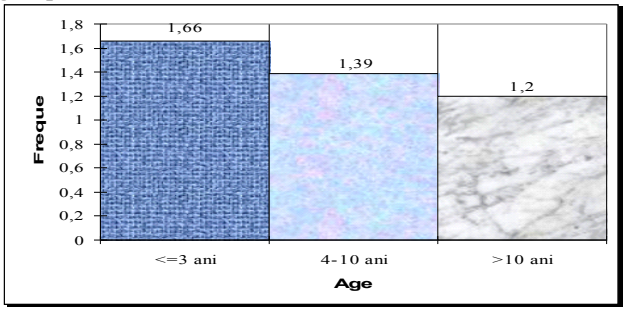
IV. The Analysis of the Anti-GAD Numerical Values

The analysis of the anti-GAD numerical values reported on age groups shows a distribution of the positive values on all age groups, values that decrease with the advancing in years *(Picture no. 2)*.

Picture no. 1. Values of p Hi square test ($p<0.05$) in association with other immunological markers of anti-TTG IgA



Picture no. 2. Distribution of anti-GAD reported in age groups



The analysis of the anti-GAD numerical values correlation with the numerical values of other immunologic markers shows significant values of the Pearson coefficient in association with the anti-TT r=0.23 and in association with anti-TPO r=0.21.

DISCUSSION

Starting with the common genetic aspect of type 1 sugar diabetes and celiac disease, emphasized through HLA-DR3 as unfavourable predictive marker, the statistical analysis of the possible immunologic associations of anti-tTG IgA within the type 1 sugar diabetes confirmed us as unique association the one with anti-GAD, as well as their 35% prevalence.

It is well-known in literature the coexistence of the type 1 sugar diabetes with other specific autoimmune diseases like thyroiditis, gastritis, celiac disease and Addison disease, associated with the production of specific auto antibodies.(6) The first antibodies described in association with the type 1sugar diabetes development were anti-ICA. The anti-IAA, anti-GAD and anti-IA2 were described later.(7) Among the most recent studies on autoimmune manifestations we mention the one of Karavanaki & collab (8), who, in the case of 144 children with type 1 sugar diabetes obtained a prevalence of 53.2% of anti-GAD, 11.1% of anti-TT, 17.4% of anti-TPO and 7.6% of anti-tTG IgA. At the same time, they admitted the connection between anti-GAD and anti-TPO (p=0,01) and recommended the use of anti-GAD as marker in the development of autoimmune manifestations associated with type 1 sugar diabetes at children. Kakleas & collab (9) associated the thyroid autoimmune phenomena in the female sex with the long duration of the type 1 sugar diabetes and with the anti-GAD persistence. Uibo and Lernmark (10) commenting on the anti-

GAD56 role, said these could be present for years before the hyperglycaemia debut and represented a marker of the beta-pancreatic cells loss.

CONCLUSION

1. The association between anti-GAD and anti-tTG IgA shows that these can function as predictive marker in the unfavourable development of the type 1 sugar diabetes in the absence of the HLA-DR3 determining;
2. The anti-GAD and anti-TT association, respective anti-TPO shows that these can function as a marker of the autoimmune disease development associated with the type 1 sugar diabetes.

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