HLA HAPLOTYPES IN THE INFANTILE POPULATION WITH DIABETOGENIC RISK

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Abstract
Aim of the study. The present study attempted to find out class II - HLA alleles in a group of children with diabetogenic risk.
Material and method. The studied lot included 38 children (aged 3 months - 18 years) grouped as follows: group A = 32 children (siblings of type 1 DM kids), group B = 5 children followed-up for impaired fasting glucose, group C = one 3 months old infant of a diabetic mother. We determined the anthropometric indexes (weight, height, waist) and, biologically, we evaluated the glucidic metabolism through fasting glycemia and HbA1c and the metabolism of lipids through serum lipids, cholesterol, triglycerides and HDLc. In the same time we determined the markers of humoral autoimmunity by measuring the: titre of anti-glutamic acid decarboxilase antibodies (GADA) and the islet cell antibodies (ICA). Of the metabolic markers we used the evaluation of C peptid concentration (normal ranges between 0,5–3 ng/ml). Class II HLA alleles were typed in 20 patients from this subgroup. HLA typing used INNO-LIPA HLA-B DRB1 tests for the allele group between DRB1*01 and DRB1*16. For the interpretation of the results we used the "Dynal Biotech pattern Matching Program S42" soft.
Results. In the studied lot, typing of class II HLA alleles revealed that of the 20 subjects evaluated, 25% were DRB1*04 while 15% were DRB1*03. In all typed cases serum C peptide and also the glycated hemoglobin ranged between normal limits.
Conclusions. Genetic predisposition represents the backgroud for the development of the autoimmune beta-cell destructive process, but the occurence of type 1 DM requires also the involvement of some trigger factors which are often hardly to distiguish.
Key words: *genetic, risk, diabetes mellitus, childhood.*

Introduction

Diabetes mellitus has become a real burden for the human society. Paradoxically, at present more resourses are spent for complications, comparatively with those used for prevention in diabetes. Following the new data concerning the susceptibility markers and the variable asymptomatic period in type 1 diabetes mellitus (type 1 DM), the prevention of the disease became a permanent preoccupation of the specialists, especially because this reffers preponderently to children and young subjects.

Today it is accepted that the short time prior to diagnosis in type 1 DM is just the peak of a huge iceberg, just partially explored by the immunogenetic modern studies. Genetically speaking, diabetes is a complex polygenic disease, for the developing of which, a variable number of susceptibility and protective genes, with incomplete penetrance, are contributing (1).

The presence of markers in association, in some subjects serum, both in the general population and in some belonging to subgroups with increased risk for type 1 DM, increases the probability for developing this disease (2).

Clinical manifestation of type 1 diabetes before the age of 20 years is associated with a strong HLA defined genetic susceptibility, an intensive humoral immune response to various beta cell antigens, a higher frequency of preceding infections and a shorter duration of symptoms and more severe metabolic decompensation of diagnosis (3).

Aim of the study

To determine the risk of occurence of diabetes mellitus in children from the western part of our country; determination of genetic susceptibility through identification of HLA class II genes that predispose to the occurence of type 1 DM.

Patients and method

The studied lot included 38 children (aged 3 months - 18 years) grouped as follows: group A = 32 children (siblings of type 1 DM kids), group B = 5 children followed-up for impaired fasting glucose, group C = one 3 months old infant of a diabetic mother. We determined the anthropometric indexes (weight, height, waist) and, biologically, we evaluated the glucidic metabolism through fasting glycemia and

HbA1c and the metabolism of lipids through serum lipids, cholesterol, triglycerides and HDLc. Of the metabolic markers we used the evaluation of C peptid concentration (normal ranges between 0,5–3 ng/ml). Class II HLA alleles were typed in 20 patients from this subgroup. HLA typing used INNO-LIPA HLA-B DRB1 tests for the allele group level DRB1*01 to DRB1*16. For the interpretation of the results we used the "Dynal Biotech pattern Matching Program S42" soft.

Results

All cases had a normal basal C peptide level while HbA1c levels also ranged between normal limits (fig. nr.1, fig. nr.2, fig. nr.3).

All cases typed for HLA had the basal level of the C peptide between normal limits and HbA1c was also normal (*Tabel I*)

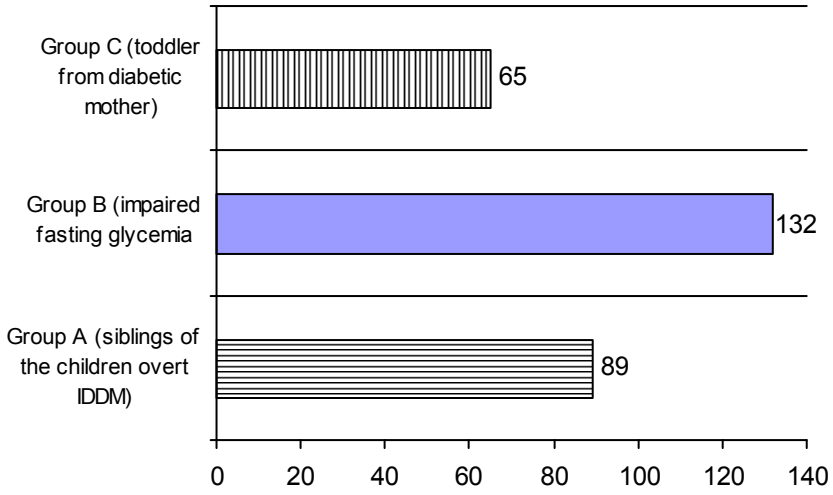

Fig. nr. 1 - Fasting glycemia (mg / dl).

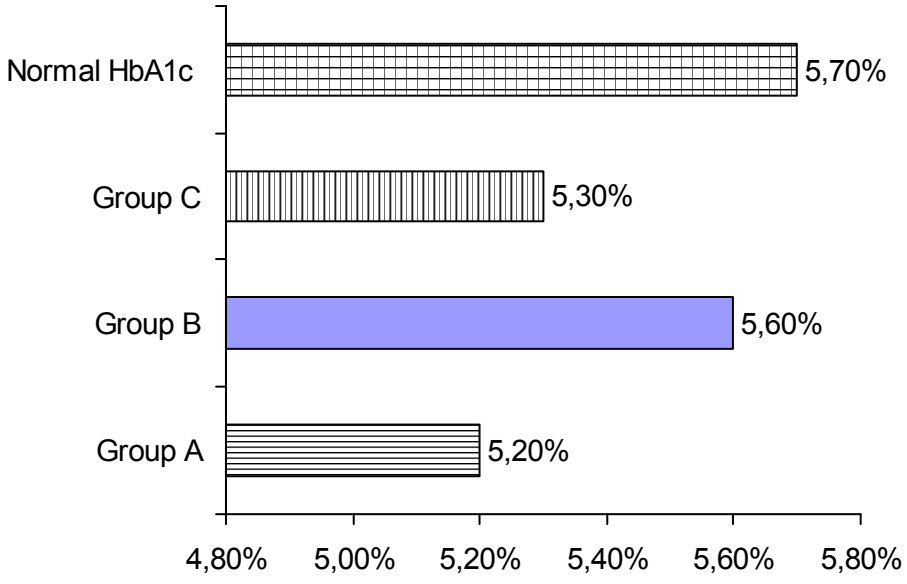

Fig. nr. 2 – HbA1c value in the studied lot

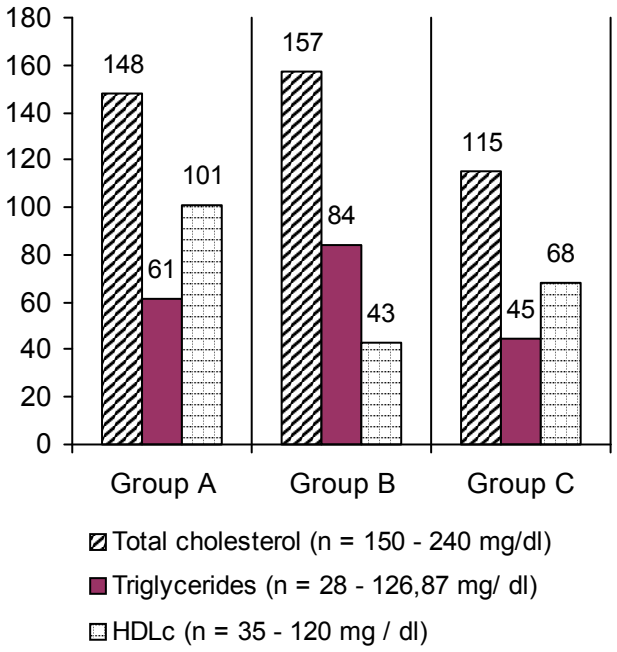

Fig. nr. 3 – Serum lipids values (cholesterol, triglycerides and HDLc) in the studied lot.

Table I. Class II HLA alleles.

Nr.Crt.	Name	Typed allele	Basal C peptide	HbA1c
1.	B.A.	DRB1*07, DRB1*11	0,8	3,55
2.	B.C	DRB1*01, DRB1*04 DRB1*04, DRB1*04	1,4	3,5
3.	B.D.	?	1,4	3,5
4.	C.A.	DRB1*04, DRB1*04	1,8	3,5
5.	C.A.	DRB1*11	2,9	3,5
6.	F.P.	DRB1*01, DRB1*11	2,0	3,6
7.	G.D.	DRB1*11, DRB1*16	0,9	3,7
8.	H.C.	DRB1*14, DRB1*15	1,0	3,5
9.	I.R.	?	0,8	3,9
10.	P.A.	?	2,7	3,9
11.	R.A.	DRB1*11, DRB1*13	1,2	3,6
12.	S.N.	DRB1*01, DRB1*04 DRB1*04, DRB1*04	2,2	3,5
13.	T.L.	DRB1*03, DRB1*16	0,7	3,52
14.	T.S.	DRB1*04, DRB1*16	0,5	3,5
15.	T.D.E.	DRB1*15, DRB1*16	1,9	3,6
16.	T.B.A.	DRB1*11, DRB1*16	1,5	3,9
17.	T.I.	DRB1*03, DRB1*04	2,9	3,8
18.	T.L.	DRB1*04, DRB1*13	2,5	3,9
19.	V.A.	DRB1*03, DRB1*13	2,9	3,9
20.	W.L	?	2,3	3,8

In the studied lot, typing of HLA class II shown 25% patients positive for DRB1*04 while 15% are DRB1*03.

Discussions

Type 1 diabetes results from the autoimmune destruction of insulin-producing beta cells and is characterized by the presence of multiple islet autoantibodies and high risk HLA haplotypes for type 1 diabetes.

The risk associated with type 1 diabetes HLA haplotypes differs between continents (4).

Presently is accepted that type 1 DM in children is associated with HLA DR3, DQB1 0201 and DR4, DQB1 0302 (3), and the decreased frequence might explain the reduced incidence of diabetes mellitus in some countries like Romania (5).

Recent studies revealed the independent role of some gene variants HLA-DRB1, especially DRB1*04 allele subtypes, that sometimes may even cancel the predisposing /protective effect of HLA-DQ allele. Various studies shown that HLA-DRB1*04 (DR4 antigen) is associated with type 1 DM in all ethnic groups except for the chinese population (Pennz et all, 1992).

HLA DRB1*04-DQB1*0302 and / or HLA DRB1*03-DQB1*0201 are observed in > 90% of affected children and in only 40% of the general population (6).

In the studied lot, typing of HLA class II shown 25% patients positive for DRB1*04 while 15% are DRB1*03. All cases typed for HLA had a normal basal C peptide level while HbA1c levels also ranged between normal limits.

The results found in our study group seem to confirm the theory sugesting that genetic predisposition plays an important role in developing DM.

Conclusions

1. Our results are not allowing us to make considerations upon the diabetogenic risk in the studied group.
2. The following evolution of these subjects will prove if these allele are really predisposing for type1 DM also in the population we have studied.
3. Genetic predisposition represents the backgroud for the development of the autoimmune beta-cell destructive process, but the occurence of type 1 DM requires also the involvement of some trigger factors which are often hardly to distiguish.

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