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STRATIFICATION OF CONTROLLED COURSE OF AUTOIMMUNE DIABETES MELLITUS AS A LOW-LEVEL INFLAMMATION IN CHILDREN

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Introduction. Diabetes mellitus (DM) in children - a chronic pathology that requires constant medical attention due to the labile course, the complexity of the treatment, a tendency to developing autoimmune processes, complications and disability. **Objective:** to identify predictors of controlled course of autoimmune diabetes in children for predicting its occurrence.

Materials and methods: among 100 children with first diagnosed type 1 diabetes aged from 1 to 18 years was confirmed autoimmune diabetes in 98 children by determining the level of antibodies to glutamic acid decarboxylase, tyrosine phosphatase (islet antigen-2), zinc transporters, by enzyme immunoassay (ELISA, «Euroimmun»). Using sequential analysis of Wald, was analyzed 100 clinical - immunological, molecular - genetic, instrumental - diagnostic parameters determining relative risk (RR) and diagnostic coefficient (DC) in patients with

uncontrolled (study group, n=23) and controlled course (control group, n=31) of autoimmune diabetes.

Results. Predictors of controlled course of autoimmune diabetes in children were selected 14 factors sufficiently informative prognostic significance (I≥0,5), which are suitable to use in clinical practice: the level of glycated hemoglobin less than 9% after 1 year of observation (I=5.4), transferred flu 1 year before debut of DM (I=1.58), no increase in antibodies to glutamic acid decarboxylase (I=1.2), alanine aminotransferase level more than 39.3 U/l (I=1.18), age of manifestation of the disease 4-6 years (I=1.02), alkaline phosphatase level less than 328 U/l (I=0.76), maximum glycemia less than 23 mmol/l (I=0.64), weight at birth less than 4 kg (I=0.63), the level of urea less than 4.3 mmol/L in the blood (I=0.61), related autoimmune diseases (I=0.56), concomitant cardiovascular pathology (I=0.56), hypoproteinemia less than 60 g/dL (I=0.55), observance of hourly diet in the first year of life (I=0.54), the absence of glycosuria (I=0.54).

Conclusion: to improve the quality of diagnosis, prognosis and personalized treatment of autoimmune diabetes mellitus, especially in patients with first diagnosed disease, is necessary to define specific autoantibodies against islet apparatus of the pancreas, a, namely, the study of the level of antibodies to glutamic acid decarboxylase.

Keywords: autoimmune diabetes, children, prognosis, predictors, Wald analysis

Introduction Diabetes mellitus (DM), a disease of civilization, stands one of the main causes of death in most developed countries, and there is substantial evidence that the increased prevalence of diabetes and its complications can take epidemic in developing countries. Uncontrolled course of DM is associated with the development of macrovascular complications, loss of vision, the development of chronic kidney failure, neuropathy, and increasing number of amputations of the lower limbs [1; 2].

The absolute insulin deficiency, majority children (90-97%) are the result of an autoimmune damage islet apparatus of the pancreas [3; 4]. Significant value as markers of autoimmune diabetes mellitus provide antibodies to glutamic acid

decarboxylase (GAD), protein 2 tyrosine phosphatase or antigen-2 insulinoma tyrosine phosphatase (insulinoma-antigen (IA) - 2α), zinc transporters (ZnT8) and C-end of zinc transporters (C-end of ZnT8). Interestingly, the prevalence of autoimmune process against islet antigens is higher in regions with increased incidence of type 1 diabetes, regardless of genetic predisposition [5].

The aim of the study: to identify predictors of controlled course of autoimmune diabetes mellitus in children for the stratification of its course.

Materials and methods

Clinical examination of patients during hospital stay at the children's department of Endocrinology CI «Dnepr City Clinical Hospital №1» DCC». List of additional paraclinical examination methods was compiled according to the MOH ordered Ukraine №254 from 27.04.2006, the «Protocol of care to children suffering from diabetes mellitus» and №864 from 10.07.2013 «About amendments to the protocol of caring to the children with diabetes mellitus».

Laboratory examination included a general clinical examination, determination of C-peptide and glycated hemoglobin ($HbA1_C$), markers of autoimmune DM using enzyme immunoassay (ELISA) in venous blood.

Research on contrinsular immunogenesis, was to determine the presence of autoantibodies to beta-cells of the pancreas, according to the recommendations of the Association of children endocrinologists of Ukraine, antibodies glutamic acid decarboxylase (GAD), tyrosine phosphatase (IA-2α), transporters of zinc (Zn8T) and the C-terminal end of the zinc transporter (C-end of TZn8) enzyme immunoassay using a set of «Euroimmun». According to various authors, methods of antibodies to IA-2α and ZnT8 have high specificity (100% and 97%) but low sensitivity (42% and 33.3%). The method of detection of antibodies to GAD less specific (70%), but it’s sensitivity higher (58.3%) [6; 7; 8; 9].

According to the results of the research of contrinsulin immunogenesis among 100 children aged from 1 to 18 years with first diagnosed DM and 98 (98%) of them had autoimmune DM. Catamnestic observation was conducted among 54 individuals with autoimmune DM from 2018 to 2019.

To construct a mathematical model predicting the probability of a controlled course of autoimmune DM were formed into 2 groups of observation. The main group (n=23) presented children with uncontrolled course of autoimmune DM type 1, which, according to targets of glycemic control (Global IDF/ISPAD Guideline for Diabetes in Childhood and Adolescence), throughout 1 year of catamnestic observation, had a high risk of glycemic control and $HbA1_C$ level above 9%. The control group (n=31) included patients with controlled course of autoimmune type 1 DM, which had ideal, optimal and/or suboptimal glycemic control and level indicator $HbA1_C$ less than 9%.

Statistical analysis of the results was performed by using Microsoft Excel (Office Home Business 2KB4Y-6H9DB-BM47K-749PV-PG3KT), and software STATISTICA 6.1 (StatSoftInc., Serial № AGAR909E415822FA). Analysis of the data from the statistical probability estimate differences was conducted by para-, and non-parametric statistical methods, mathematical analysis Wald. The critical meaning of the level of statistical importance to the examination of all null hypothesis taken all equal 0.05 (5%) [10; 11; 12; 13].

Results

Availability of diverse effect on forecasting the uncontrolled course of autoimmune DM in children requires its assessment for an early diagnostic phase and within 1 year of observation by a combination of factors.

Predictors of controlled course of autoimmune diabetes in children were selected 14 factors sufficiently informative prognostic significance ($I \geq 0,5$), which are suitable to use in clinical practice: the level of glycated hemoglobin less than 9% after 1 year of observation (I=5.4; RR=17.8; DC=12.5), transferred flu 1 year before debut of DM (I=1.58; RR=0.16; DC=-7.82), no increase in antibodies to glutamic acid decarboxylase (I=1.2; RR=6.68; DC=8.24), alanine aminotransferase level more than 39.3 U/l (I=1.18; RR=0.12; DC=-9,08), age of manifestation of the disease 4-6 years (I=1.02; RR=1.02; DC=6.1), alkaline phosphatase level less than 328 U/l (I=0.76; RR=0.49; DC=-3.06), maximum glycemia less than 23 mmol/l (I=0.64; RR=0.56; DC=2.46), weight at birth less than 4 kg (I=0.63; RR=0.32; DC=1,13), the level of

urea less than 4.3 mmol/L in the blood (I=0.61; RR=2.23; DC=3.48), related autoimmune diseases (I=0.56; RR=0.19; DC=-7.32), concomitant cardiovascular pathology (I=0.56; RR=0.19; DC=-4.97), hypoproteinemia less than 60 g/dL (I=0.55; RR=0.5; DC=-3.05), observance of hourly diet in the first year of life (I=0.54; RR=4.45; DC=6.48), the absence of glycosuria (I=0.54; RR=4.45; DC=6.48).

Thus, the most significant factors in the controlled course of diabetes are the level of glycated hemoglobin less than 9% after 1 year of observation, body weight at birth less than 4 kg, adherence to the feeding regimen in the first year of life, age of manifestation of the disease 4-6 years, the absence of antibodies to glutamic acid decarboxylase and the absence of glucosuria during the onset of the disease, the level of glycemia in a random study is less than 23 mmol/l.

At the same time, factors worsening the controlled course of diabetes are transferred flu 1 year before debut of DM, alanine aminotransferase level more than 39.3 U/l, alkaline phosphatase level less than 328 U/l, related autoimmune diseases and concomitant cardiovascular pathology, hypoproteinemia less than 60 g/dL.

Conclusions

To improve the quality of diagnosis, prognosis and personalized treatment of autoimmune diabetes mellitus, especially in patients with first diagnosed disease, is necessary to define specific autoantibodies against islet apparatus of the pancreas, a, namely, the study of the level of antibodies to glutamic acid decarboxylase. In the case of a negative result, further guidance is recommended for molecular - genetic examination to exclude non autoimmunne types of diabetes, not requiring insulin replacement therapy.

Conflict of interest: The authors report no conflict of interest.

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