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Research Article

Search of New Autoimmune Marker in Diagnostic Diabetes Mellitus Type 1

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Abstract

Background: For diabetes mellitus is characterized by increased immunogenicity, which triggers the development of autoimmune processes and leads to the production of various autoantibodies. In order to find a new marker of autoimmune accumulation in type I diabetes, using immunoassay method, the level of antibodies to the protein eEF1A1 in blood of patients with type 1 diabetes mellitus and those in the control group was performed.

Results: The main group consisted of 52 patients with type I diabetes who were hospitalized in the Lviv Regional Endocrinology Centrum (West Ukraine) from 2018 to 2019 years. The control group included 40 people of the appropriate age and sex, where the family denied the presence of diabetes. The gender and age structure of the study group was different: the group consisted of 32 (61.5%) women and 20 (38.5%) males.

Clinical examination and analysis of data from medical records shows that in the majority of patients with type 1 diabetes, endocrinologists diagnosed serious complications: polyneuropathy - in 32 (61,5%) patients, retinopathy - in 28 (53,8%) and nephropathy - in 14 (26,9%) cases. Naturally, many of the 34 (65,4%) patients from the main group of doctors found a combination of these complications, which depended on the severity of their course of diabetes.Diagnosed significantly higher rates of cardiovascular events 18 (34.6%), ophthalmic 28 (53.8%) and neurological pathologies 32 (61.5%) in the main group were considered to be the domination of complications of diabetes in patients in contrast to the control group.

Antibodies to the eEF1A1 protein were absent in 35 (67.3%) patients with type I diabetes and in 39 (97.5%) subjects. Low titers of autoantibodies (from 1:20 to 1:160) to the eEF1A1 protein were observed in 5 (9.6%) patients with type I diabetes and in 1 (2.5%) of the control group. In contrast to individuals without diabetes mellitus, diagnostically significant antibodies to eEF1A1 protein in higher concentrations (from 1: 320 to 1: 640) were recorded in 12 patients (23.1%) with type I diabetes from the main group, which differed significantly ($p < 0.05$) from data from the control group.

Conclusion: The level of antibodies to the protein eEF1A1 in blood patients with type I diabetes possible can consider as a new autoimmune marker in diagnostic diabetes mellitus type 1.

Keywords: *Diabetes Mellitus Type 1; New Autoimmune Marker; Ukraine*

Introduction

The diabetes prevalence in the world in 2019 is estimated to be 9.3% (463 million people), rising to 10.2% (578 million) by 2030 and 10.9% (700 million) by 2045. The prevalence is higher in urban (10.8%) than rural (7.2%) areas, and in high-income (10.4%) than low-income countries (4.0%). One in two (50.1%) people living with diabetes do not know that they have diabetes [1].

There were registered 1 million 234 thousand patients with diabetes in 2020 year in Ukraine [2]. Type 1 diabetes mellitus (T1DM) is an autoimmune disease that leads to the destruction of insulin-producing pancreatic beta cells. Insulin is an essential hormone that exerts multiple effects on glucose, lipid, protein, and mineral metabolism, as well as growth [3].

Type 1 diabetes mellitus (T1DM) results from immune mediated destruction of pancreatic β-cells. The presence of autoantibodies, such as anti-glutamic acid decarboxylase (GAD65) autoantibody (GADA), precedes clinical disease by months or even years and persists after the disease becomes clinically overt [4]. No gender difference in the incidence of type 1 diabetes is found. The frequency of antibodies against glutamic acid decarboxylase (GADA) in diabetes mellitus depends on gender at diagnosis and age also GADA-positive female diabetic patients with an age at diagnosis between 40 and 59 years have higher GADA levels and a more severe loss of beta-cell function than male patients with the same age at diagnosis. Female patients with high GADA levels also had a high prevalence of other autoimmune endocrine diseases, especially autoimmune thyroid disease, which further emphasises the need for screening of thyroid function in female patients with high GADA levels [5]. GADA is used not only to diagnose autoimmune-mediated T1DM, but also to predict the course of disease progression [6,7].

In the absence of GADA antibodies in the blood of patients with type I diabetes, 31.8 % patients had autoantibodies to the eEF1A1 protein, which can be considered as a new marker for the diagnosis of type I diabetes. The quality of diagnostics increased from 76% - when detecting only GADA - to 86% when using GADA and a new marker. It has been shown that these autoantibodies are not detected in Graves' disease ($P < 0.005$) [8,9].

In 2014, the journal Diabetes published an article by Korean scientists on the discovery of a new marker of type I diabetes - autoantibodies to the eEF1A1 protein in the Korean population. Eukaryotic translation elongation factor 1 alpha 1 (eEF1A1) is a protein encoded by the gene of the same name located in humans on the short arm of chromosome 6 and found in patients with type II diabetes and in the control group [4,9].

Aim of the Study

The aim of the study was to search for a new autoimmune marker in the genesis of type I diabetes.

Object of Research

Cases of type I diabetes mellitus in patients who were hospitalized in the Lviv Regional Endocrinology Centrum (52 patients) and 40 people from the control group.

Materials and Methods

Examination of patients and the formation of the main and control groups was carried out using clinical and clinical-genealogical methods. To determine the level of autoantibodies of eEF1A1 in the blood of patients, the method of enzyme-linked immunosorbent assay. Statistical processing of the obtained research results was carried out according to generally accepted methods.

Research Results and their Discussion

The main group consisted of 52 patients with type I diabetes who were hospitalized in the Lviv Regional Endocrinology Centrum (Ukraine) from 2018 to 2019 years. The control group included 40 people of the appropriate age and sex, where the family denied the presence of diabetes. The gender and age structure of the study group was different: the group consisted of 32 (61.5%) women and 20 (38.5%) males. The age of patients ranged from 17 to 67 years, and the average age of manifestation of the disease in the main group was

15.7 ± 0.4 years (the period of treatment after confirmation of the diagnosis in patients with diabetes I ranged from 1 to 15 years).

In the main group in 46 (88.5%) patients the course of pathology was severe (severe juvenile form, labile course), and in the remaining 6 (11.5%) persons - moderate.

Clinical examination and analysis of data from medical records shows that in most patients with type I diabetes, endocrinologists have diagnosed serious complications: polyneuropathy - in 32 (61.5%) patients, retinopathy - in 28 (53.8%) and nephropathy - in 14 (26.9%) cases. In many -34 (65.4%) patients from the main group, doctors founded a combination of these complications, which depended on the severity of their diabetes.

Despite a significant percentage of cardiovascular diseases in the form of hypertension of II-III degrees in 18 (34.6%) patients with type I diabetes, the structure of concomitant somatic pathology in the main group was as follows: the most common diseases of the gastrointestinal tract (enteropathy), chronic cholecystitis) in 14 (26.9%) and endocrine system (autoimmune thyroiditis in 8 (15.4%) cases), musculoskeletal system (arthritis in 7 (13.5%) cases) and respiratory system (chronic bronchitis) in 1 (1.9%) case.

At the same time, the spectrum of concomitant somatic pathology in the control group was as follows: most often in the elderly were found diseases: cardiovascular system, including hypertension I degree in 3 (7.5%), endocrine system (diffuse goiter in 4 (10.0%) of persons and gastrointestinal tract (chronic gastroduodenitis and cholecystitis in 4 (10.0%) cases. In the control group were found one case (2.5%) of diseases of the respiratory, urinary systems and ophthalmic pathology.

Comparisons of clinical characteristics of individuals from the main and control groups are presented in table 1.

Groups	**Main group**		**Control group**		**P**
Pathology	**n = 52**	**%**	**n = 40**	**%**	
Cardiovascular system	18	34,6%	3	7,5%	< 0.05
Respiratory system	1	1,9%	1	2,5%	> 0.05
Gastrointestinal system	14	26,9%	4	10,0%	< 0.05
Urinary system	14	26,9%	1	2,5%	< 0.05
Endocrine system	8	15,4%	4	10,0%	> 0.05
Musculoskeletal system	7	13,5%	-	-	< 0.05
Nervous system	32	61.5%	-	-	< 0.05
Ophthalmic pathology	28	53.8%	1	2,5%	< 0.05

Table 1: *Clinical characteristics of patients with type I diabetes and persons from the control group.*

It should be noted a significantly higher percentage of cases and a statistically significant predominance ($p < 0.05$) of ophthalmic diseases (53.8%) in 28 patients with diabetes, lesions of the nervous system ($p < 0.05$) in 32 (61.5%) patients and cardiovascular 0.05) in 18 patients (34.6%) due to complications of diabetes mellitus in the main group.

Given the ever-increasing number of transient diabetes in our population and, accordingly, the dominant percentage of this diabetes in patients from the main group, the search for new markers for a more accurate diagnosis: persons from the control group.

In table 2 we present the distribution of titers of autoantibodies to the protein eEF1A1, found in the blood of patients with type I diabetes mellitus and in the control group.

Groups	Main group		Control group		P
Titers of autoantibodies	n = 52	%	n = 40	%	
From 1:20 to 1: 160	5	9,6%	1	2,5%	<0.05
From 1: 320 to 1: 640	12	23,1%	0	0	<0.05
All	17	32,7%	1	2,5%	<0.05

Table 2: *Comparison of the level of titer of autoantibodies to the protein eEF1A1 in the blood of patients with diabetes and in the control group.*

Antibodies to the eEF1A1 protein were absent in 35 (67.3%) patients with type I diabetes and in 39 (97.5%) subjects. Low titers of autoantibodies (from 1:20 to 1: 160) to the eEF1A1 protein were observed in 5 (9.6%) patients with type I diabetes and in 1 (2.5%) of the control group. In contrast to individuals without diabetes mellitus, diagnostically significant antibodies to eEF1A1 protein in higher concentrations (from 1: 320 to 1: 640) were recorded in 12 patients (23.1%) with type I diabetes from the main group, which differed significantly ($p < 0.05$) from data from the control group.

The prevalence of novel type 1 diabetes mellitus (T1DM) antibodies targeting eukaryote translation elongation factor 1 alpha 1 autoantibody (EEF1A1-AAb) and ubiquitin-conjugating enzyme 2L3 autoantibody (UBE2L3-AAb) has been shown to be negatively correlated with age in T1DM subjects [6].

Koo BK., *et al*. reported on two novel autoantibodies found through exploration of T1DM autoantibody repertoires using protein microarrays [4]. These two autoantibodies, eukaryote translation elongation factor 1 alpha 1 autoantibody (EEF1A1-AAb) and ubiquitin-conjugating enzyme 2L3 autoantibody (UBE2L3-AAb), were detected in 40% of GADA negative T1DM patients as well as in patients with fulminant T1DM [4]. The prevalence of EEF1A1-AAb and UBE2L3-AAb increased as the age of disease onset decreased, whilst EEF1A1-AAb and UBE2L3-AAb were only detected in T1DM patients < 40 years old [4]. Given that age may be associated with autoantibody positivity in T1DM subjects.

We will be interested in further study of the level of antibodies to the protein eEF1A1 in the young patients with Type 1 diabetes mellitus (up to 40 years) in the absence of GAD antibody in the blood living in our region.

Conclusion

1. The authors studied the eEF1A1 protein as an indicator of autoimmune accumulation in the genesis of type I diabetes and as a probable new marker for the diagnosis of this severe endocrine pathology.

2. Comparing the main clinical features of somatic diseases in both groups, the dominance of complications of diabetes in the main group revealed a significantly higher percentage of cases of cardiovascular pathology -18 (34.6%), ophthalmic pathology- 28 (53.8%) and lesions of the nervous system-32 (61.5%).

3. Analysis of the level of antibodies to the protein eEF1A1 in the blood of individuals from the comparison groups revealed a higher concentration of diagnostically significant antibodies (from 1: 320 to 1: 640) in 12 patients (23.1%) with diabetes mellitus, which is significant ($p <0.05$) exceeded the data from the control group.

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