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Mathematical model of diabetic encephalopathy in diagnosis of complicated forms of diabetes mellitus

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Abstract. ***Background.*** *The purpose of this research is to optimize the methods for diagnosis of diabetic encephalopathy based on the study of indicators of cerebrovascular hemodynamics, functional state of the brain, metabolic disorders and morphological characteristics of the brain tissue.* ***Materials and methods.*** *A comprehensive survey was carried out in 537 patients with diabetes mellitus (DM), including 342 (63.7 %) persons with type 1 DM, and 195 (36.3 %) — with type 2 DM.* ***Results.*** *The article presents data on the integrated study of clinical, metabolic and functional indicators as risk factors for diabetic encephalopathy. Their diagnostic significance is argued. On the basis of a comprehensive assessment of the obtained data, which expanded the view on the pathogenesis of diabetic encephalopathy, the priority of metabolic disorders was confirmed. Diagnostic criteria of diabetic encephalopathy were established and its mathematical model was developed.* ***Conclusions.*** *The availability of informative indicators identified will allow the doctor to diagnose diabetic encephalopathy at the early stages or to predict its development and to detect at the preclinical stage.*

Keywords: *diabetes mellitus; diabetic encephalopathy; diagnosis; mathematical model*

Introduction

Diabetes mellitus (DM) leads to a significant increase in mortality and deterioration of the quality of life of patients, primarily due to the development therein of cardiovascular complications [1–3]. Ischemic stroke occurs in patients with DM are two to four times, coronary heart disease is two to three times more often than in the general population. The mortality rate for ischemic stroke is undergoing 50–60 % and 70–95 % of hemorrhagic form. The prognosis for patients with DM, stroke more pessimistic than in those not suffering from the disease.

Diabetic angiopathic encephalopathy precedes and accompanies acute stroke [4–6]. Diabetic encephalopathy (DE) is a symptom of various pathological processes associated with impaired hemodynamics and liquorodynamics, which is based on metabolic changes in the brain. Pathogenetic basis of brain damage in DM is diabetic micro- and macroangiopathy leading to degenerative, hypoxic changes, causing structural damage, sometimes irreversible. Many authors believe that the defeat of cerebrovascular cause of complex metabolic disorders, which are based on absolute or relative insulin deficiency. For others, the main role in the cerebral circulation plays atherosclerosis in patients with diabetes who develop earlier and progresses faster than in those without DM [7]. There is no doubt that an important place in the development of cerebrovascular events takes arterial hypertension, which is significantly more common in patients with DM [8]. It was found that cerebrovascular disorders in DM due to the change in arterioles, capillaries and venules, mainly cortical brain, characterized by the same histological features and diffuse form of diabetic microangiopathy [9]. Thus, various forms of DE is a frequent and dangerous complication of DM, but the issues of diagnosis, treatment and prognosis in these patients insufficiently developed and require further study.

The purpose of this research is to optimize the methods for diagnosis of diabetic encephalopathy based on a study of indicators of cerebrovascular hemodynamics, functional state of the brain, metabolic disorders and morphological characteristics of the brain tissue.

Materials and methods

It was carried out a comprehensive survey of 537 patients with DM, including type 1 DM is set to 342 (63.7 %), type 2 DM — in 195 (36.3 %) patients. In 108 (20.1 %) patients with DM, the clinical syndrome DE not identified in 429 (79.9 %) — found DE I, II and stage III disease, it

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should be noted that the clinical signs DE established on the basis of generally accepted classification [2]. Stage I installed in 56 (13.0 %) patients with type 1 DM and 28 (6.5 %) patients with type 2 DM, these were patients with moderate disease duration of 5–10 years. Stage II installed in 124 (28.9 %) patients with type 1 DM and 114 (26.6 %) patients with type 2 DM, these patients secondary and severe forms of the disease with a duration of 10–20 years. Stage III installed in 54 (12.6 %) patients with type 1 DM and 53 (12.4 %) patients with type 2 DM, these patients severe illness and disease duration of 20 years. Due to the heterogeneity of the groups in the distribution of patients according to the stage where the studied parameters were analyzed in patients according to the type of DM, duration and severity of the disease. Depending on the duration and severity distribution of patients into five groups. The degree of severity of diabetes was assessed in accordance with the applicable criteria [7].

Group I included 108 patients with type 1 DM of moderate severity with disease duration up to 5 years in age from 20 to 25 years. According to gender, patients in group I were as follows: women — 46, men — 62.

Group II consisted of 110 patients with type 1 DM of moderate severity with the experience of the disease 5–10 years, aged 20–35, had 56 women, 54 men.

Group III presented 124 patients with type 1 DM with severe aged 34–50 years with disease duration of 10–20 years, among them there were 69 men, women — 55.

IV group consisted of 102 patients with type 2 DM at the age of 45–50 years, suffering from diabetes for 10 years, from them women — 58, men — 44.

Group V included 93 patients with type 2 DM with severe disease at the age of 53–67 years and 10–20 years duration. In the group there were 65 women and 28 men.

All patients were on the examination and treatment in the regional endocrinology department of Donetsk Regional Clinical Territorial Medical Center.

A comprehensive study of carbohydrate metabolism (glucose fasting, glycated haemoglobin — HbA1c), lipid status (cholesterol, alpha-cholesterol, triglycerides, lipoprotein low density lipoproteins of very low density lipoprotein, high density level apoprotein — Apo-A, Apo-B, calculated atherogenic index). The state of lipid peroxidation (malonic aldehyde, diene conjugate peroxide hemolysis of erythrocytes, concentration of vitamin E), blood coagulation system (prothrombin index, recalcification time, tolerance plasma heparin, fibrinogen, fibrinolytic activity, factor XIII). In addition, research conducted instrumental, studied the cerebral vascular system by transcranial Doppler and rheoencephalography (extracranial and intracranial sonography). Functional brain activity was studied by electroencephalography. The nature of pathological changes in the brain was evaluated by intravital imaging — CT.

The material for the morphological study were 11 cases section, persons who were ill during the life of diabetes and were diagnosed diabetic encephalopathy.

Statistical analysis of the results obtained from the use of variations, correlation, regression, single and multivariate analysis of variance was carried out using computer programs. In order to construct a mathematical model that describes the disease process (presence of diabetic encephalopathy). Neural Networks methods used modeling methods for constructing logical regression models. Evaluation of diagnostic characteristics of the models carried out by calculating the sensitivity of the model and its specificity.

Results

At the time of the survey patients with DM of all groups were able to sub- and decompensation. No significant differences between groups in the level HbA1c were found.

In the study conducted an analysis of the lipid metabolism in diabetic patients allowed to install these laws. In patients without clinical evidence of DE (I group) with type 1 DM disease duration of five years, hyperlipidemia was not found. In patients with DE suffering from type 1 DM, moderate, with disease duration more than 5 years (group II) hypoalphacholesterynemia with normal cholesterol (Ch) led to increased atherogenic index (AI). For this group was also characterized by hypertriglyceridemia and increase the level of low density lipoprotein (LDL). Patients with DE with severe type 1 DM, suffering more than 10 years (group III) and type 2 DM (IV, V group) set unidirectional changes in lipid metabolism. High concentrations of LDL and low HDL alpha-IA identified significant growth. In these groups, found a significant increase in atherogenic lipoprotein fractions, but significant differences between the groups were found. Grossest changes in lipid profile in patients with established DE suffering from type 2 DM (IV, V group), but they were not statistically significant compared to the third group. Thus, lipid metabolism is an important factor in the formation DE in diabetic patients.

In the study of coagulation parameters in diabetic patients without clinical signs of DE, it found no violation of the blood coagulation system. With an increase in the duration and severity of the disease on the background of the development of DE progressed hemostatic disorders. Most rough change of blood coagulation in patients with DE, with severe type 1 DM, with disease duration of 10 years (III group). In patients with type 2 DM accounted for IV and V group, figures on the degree of coagulation abnormalities consistent with group III, with significant differences between the groups IV and V were not found. It was conducted a multivariate analysis of correlation between coagulation parameters and indicators rheoencephalography. There was an inverse correlation ($p < 0.05$) between the geographic index (PI), which determines the relative value of the pulse volume and fibrinogen ($r = -0.37$). Dicrotic index (DI), reflecting mainly the tone of the arteries, also correlated with fibrinogen ($r = -0.39$). It was established connection between the diastolic index (DTI), which mainly characterizes the state of the outflow of blood from the arteries to the veins and venous tone, with fibrinogen ($r = -0.39$). Noted an inverse correlation ($p < 0.05$) elastic modulus (MP), which reflects the elastic properties of the of blood vessels, and fibrinogen ($r = -0.36$). The direct dependence ($p < 0.05$) of the asymmetry coefficient (AC), the index of hemispheric asymmetry pulse volume, and fibrinogen

(r = +0.58). So, high levels of fibrinogen, as a manifestation of hypercoagulable reduces pulse blood filling, shock microcirculation, venous discirculation development, increasing rigidity and heterogeneity of cerebral vascular blood supply of the brain. The correlation with indicators of fibrinogen rheoencephalography (REG) suggests that hyperfibrinogenemia is one of the essential factors in the development of vascular encephalopathy in patients with DM, which is the basis of formation of DE.

In the study of lipid peroxidation (LPO) in patients with no clinical manifestations DE (I group) the level of malon dialdehyde (MDA), the peroxide hemolysis of red blood cells (PHE) and vitamin E did not differ from controls, but there was a significant increase of conjugated diene (CC) . Patients with ED, which amounted II, III, IV and V marked activation of LPO that apparent increase in MDA, CC PHE compared with the control group and, and. Strengthening contributed inhibition of lipid peroxidation antioxidant that demonstrated decreased levels of vitamin E. The most pronounced changes in the indices of lipid peroxidation and the level of vitamin E, set in groups III and V, in diabetic patients with severe, significant differences between the groups III and V were not found.

Discussion

Thus, the activation of lipid peroxidation and inhibition antioxidant protection, first of all, determining of the severity disease. Among the indicators characterizing the LPO, the most significant changes have been an indicator of a conjugated diene.

When ultrasound extracranial department of the main arteries of the head (MAG) in patients without clinical manifestations DE (I group) pathological disorders were not found. In diabetic patients with the presence of DE, the following changes in cerebral blood flow. In Group II, revealed a tendency to decrease speed indicators of arteries, against the background of a slight thickening of the vascular wall. In the third group of patients were found changes in the vascular wall, characteristic of early stages of atherosclerosis (changing contours of blood vessels, increased intima-media complex (IMC). Patients groups IV and V were found changes in the vascular wall, the appropriate dissemination of atherosclerosis.

Thus, the expressed atherosclerotic changes of the vessel wall and a significant downward trend in high-speed performance established in patients with type 2 DM, defines a part of the development of cerebrovascular disease in these patients.

Analysis of cerebral hemodynamics in patients with diabetes according to the intracranial Doppler, revealed the following patterns. In patients without clinical symptoms of DE (I group), systolic blood flow velocity (SBFV) for the intracranial arteries do not differ from the age norm. Speed characteristics of cerebral blood flow in patients with DE, who were included in the II–V group were significantly reduced compared to age norm. Reduction of systolic blood flow velocity in the intracranial arteries in patients with DE due to the development of diabetic macroangiopathy. A significant deviation from the SBFV age norm due to the fact that diabetes contributes to early and progressive development of atherosclerosis, which is a risk factor for DE. It should be noted that the rate of decline in the rate of cerebral blood flow grew depending on the severity and duration of diabetes.

In determining the functional state of the brain in diabetic patients with DE established the dominance of the brain changes the background rhythm, the presence of moderately disturbed electroencephalogram (EEG), altered reactivity in functional studies.

Computer tomography (CT) in diabetic patients examined revealed indirect signs of cerebral vascular pathology, such as: diffuse white matter density reduction, mainly in the frontal, the presence of small hypointense lesions extension of the ventricular system. There was a direct relationship between the CT changes and the type of diabetes, duration of disease, stage of compensation, the age of patients.

A study morphological study of the brain in people with diabetes showed that the main manifestations of DE is a diffuse alteration of the basal membrane and vascular endothelial microvasculature as white, and the cortex: capillaries precapillaries, venules and, to a lesser extent, arterioles, intracerebral arteries and veins.

A large number of subjective characteristics of the DE, the lack of clear criteria for differential diagnosis of diabetic encephalopathy, greatly complicates the diagnosis in each case. To identify the factors that most associated with the development of diabetic encephalopathy, used genetic algorithm selection. As a result of the algorithm, which consists of 31 investigated the clinical and metabolic parameters were selected five attributes, such as the severity of diabetes (X1), the duration of disease (X2), total cholesterol (X3), glycosylated hemoglobin (X4), diastolic blood pressure (X5). According to the specified set of features developed diagnostic model of diabetic encephalopathy.

The model is described by the equation:

$$Y = 0.117 \times X1 + 1.042 \times X2 + 0.029 \times X3 + 0.017 \times \times X4 + 0.0061 \times X5 - 1.00,$$

X1 — the severity of DM; X2 — the duration of the disease; X3 — total cholesterol; X4 — glycosylated hemoglobin, X5 — diastolic blood pressure.

Diagnostics of the diabetic encephalopathy using this model are shown in Table 1.

Table 1. Diagnostics of the diabetic encephalopathy using the model

Indication	Training set		Test set	
	Positive assessment	Negative assessment	Positive assessment	Negative assessment
Total cases	105	124	29	21
True diagnosis	95	114	27	19
Wrong diagnosis	10	10	2	2

As a result, in calculating the constructed model with meaning Y ≥ 0.468 diagnosed negative assessment (presence DE), otherwise diagnosed positive assessment of (lack DE). The sensitivity of the model to the training set was 91.1 % (CI 85.5–95.5 %), specificity — 91.4 % (CI 85.3–96.0 %).

Conclusions

Construction of mathematical model allows to objectify the diagnosis where with the help of clinical and metabolic parameters without expensive equipment. At the same time, the availability of informative indicators identified will allow the doctor to diagnose DE the early stages or to predict its development and to discover at the preclinical stage.

Conflicts of interests. Authors declare the absence of any conflicts of interests that might be construed to influence the results or interpretation of their manuscript.

References

1. Sima AA. Encephalopathies: the emerging diabetic complications. Acta Diabetol. 2010 Dec;47(4):279-93. doi: 10.1007/s00592-010-0218-0.

2. Mijnhout GS, Scheltens P, Diamant M, et al. Diabetic encephalopathy: a concept in need of a definition. Diabetologia. 2006 Jun;49(6):1447-8. doi: 10.1007/s00125-006-0221-8.

3. Francis GJ, Martinez JA, Liu WQ, et al. Intranasal insulin prevents cognitive decline, cerebral atrophy and white matter changes in murine type 1 diabetic encephalopathy. Brain. 2008 Dec;131(Pt 12):3311-34. doi: 10.1093/brain/awn288.

4. Malone JI, Hanna S, Saporta S, et al. Hyperglycemia not hypoglycemia alters neuronal dendrites and impairs spatial memory. Pediatr Diabetes. 2008 Dec;9(6):531-9. doi: 10.1111/j.1399-5448.2008.00431.x.

5. Perantie DC, Wu J, Koller JM, et al. Regional brain volume differences associated with hyperglycemia and severe hypoglycemia in youth with type 1 diabetes. Diabetes Care. 2007 Sep;30(9):2331-7. doi: 10.2337/dc07-0351.

6. Musen G, Lyoo IK, Sparks CR, et al. Effects of type 1 diabetes on gray matter density as measured by voxel-based morphometry. Diabetes. 2006 Feb;55(2):326-33. PMID: 16443764.

7. Ho MS, Weller NJ, Ives FJ, et al. Prevalence of structural central nervous system abnormalities in early-onset type 1 diabetes mellitus. J Pediatr. 2008 Sep;153(3):385-90. doi: 10.1016/j.jpeds.2008.03.005.

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Математична модель діабетичної енцефалопатії в діагностиці ускладнених форм цукрового діабету

Резюме. ***Мета дослідження*** — оптимізувати методи діагностики діабетичної енцефалопатії, що ґрунтуються на вивченні індикаторів цереброваскулярної гемодинаміки, функціонального стану головного мозку, метаболічних порушень і морфологічних характеристик мозкової тканини. ***Матеріали та методи***. Під спостереженням перебувало 537 хворих на цукровий діабет (ЦД), у тому числі із ЦД 1-го типу — 342 (63,7 %) особи, 2-го типу — 195 (36,3 %). ***Результати.*** У статті наведені дані щодо комплексного вивчення клінічних, метаболічних і функціональних показників діабетичної енцефалопатії. Аргументована їх діагностична значимість. На підставі комплексної оцінки отримані дані, що розширили уявлення про патогенез діабетичної енцефалопатії та підтвердили пріоритетність метаболічних порушень. Встановлено діагностичні критерії діабетичної енцефалопатії та розроблено її математичну модель. ***Висновки.*** Використання розроблених інформативних індикаторів дозволяє діагностувати ранні стадії діабетичної енцефалопатії або передбачити її розвиток.

Ключові слова: цукровий діабет; діабетична енцефалопатія; діагностика; математична модель

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Математическая модель диабетической энцефалопатии в диагностике осложненных форм сахарного диабета

Резюме. ***Цель исследования*** — оптимизировать методы диагностики диабетической энцефалопатии, которые основываются на изучении индикаторов цереброваскулярной гемодинамики, функционального состояния головного мозга, метаболических нарушений и морфологических характеристик мозговой ткани. ***Материалы и методы.*** Под наблюдением находилось 537 больных сахарным диабетом (СД), в том числе СД 1-го типа — 342 (63,7 %) человека, 2-го типа — 195 (36,3 %). ***Результаты.*** В статье представлены данные по комплексному изучению клинических, метаболических и функциональных показателей диабетической энцефалопатии. Аргументирована их диагностическая значимость. На основании комплексной оценки получены данные, которые расширили представление о патогенезе диабетической энцефалопатии и подтвердили приоритетность метаболических нарушений. Установлены диагностические критерии диабетической энцефалопатии и разработана ее математическая модель. ***Выводы.*** Использование разработанных информативных индикаторов позволяет диагностировать ранние стадии диабетической энцефалопатии или предвидеть ее развитие.

Ключевые слова: сахарный диабет; диабетическая энцефалопатия; диагностика; математическая модель