

# FEATURES OF DIAGNOSTICS OF CARDIOVASCULAR AUTONOMOUS NEUROPATHY OF CHILDREN WITH DIABETES MELLITUS TYPE 1

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**Abstract.** *The presence of cardiovascular autonomic neuropathy (CAN) significantly worsens the prognosis and course of the underlying disease. So in patients with diabetes mellitus (DM) and CAN, the mortality rate for 5 years is five times higher compared to patients without this complication. Due to the fact that CAN is closely associated with cardiovascular pathology, many authors consider CAN as a significant factor in cardiovascular risk. Purpose. To establish clinical, functional and metabolic changes in diabetic autonomic cardiovascular neuropathy in children with type 1 diabetes. Materials and methods research. The total number of patients studied by us was 114 children with type 1 diabetes mellitus aged 4 to 18 years. We conducted laboratory and instrumental research methods. Laboratory methods: general clinical research (general analysis of blood and urine, studies of blood sugar), biochemical methods (total blood protein, bilirubin, cholesterol, triglycerides, creatinine, urea, electrolytes, glycated hemoglobin), 24-hour heart rate monitoring with circadian index estimation was used and parameters of time and frequency analysis of heart rate variability. Conclusion diabetic autonomic cardiovascular neuropathy in children with type 1 diabetes is characterized by the development of tachyarrhythmic rhythm disturbances, as well as the formation of rigidity of the heart rhythm and a decrease in the sensitivity of the sinus node to parasympathetic influences according to a temporary analysis of daily monitoring of heart rhythm.*

**Keywords:** *diabetes mellitus, cardiovascular system, cardiovascular autonomic neuropathy, complication, 24-hour heart monitoring.*

**Introduction.** In recent years, there has been a significant increase in the incidence of diabetes mellitus (DM) worldwide. According to the World Diabetes Federation (WDF), there are currently about 425 million people with diabetes, more than three times more than in 1990, with a projected increase of up to 629 million by 2045. Of the total number of patients with diabetes in the world, more than one million people are children with type 1 diabetes (type 1 diabetes), the incidence of which is steadily increasing in this population, increasing annually by about 3%. The main causes of disability and mortality in patients with type 1 diabetes are micro- and macro-vascular complications (1.4).

According to the World Health Organization (WHO), over the past 15 years, CVD has remained the leading cause of morbidity and mortality worldwide. In turn, patients with T1DM have a higher risk of cardiovascular morbidity and mortality compared with the general population, which is one of the reasons for a significant decrease in the life expectancy of patients with T1DM. In patients with type 1 diabetes, cardiovascular events occur on average 10-15 years earlier than in the comparable control group without diabetes, and the age-adjusted relative risk of cardiovascular disease is about 10 times higher than in the general population (6).

The presence of cardiovascular autonomic neuropathy (CAN) significantly worsens the prognosis and course of the underlying disease. So, in patients with diabetes and CAN, the mortality rate for 5 years is five times higher compared to patients without this complication. Due to the fact that CAN is closely associated with cardiovascular pathology, many authors consider CAN as a significant factor in cardiovascular risk. Despite this, the exact pathophysiological mechanisms responsible for the relationship between adverse cardiovascular events and CAN are not clear enough. At the same time, early signs of cardiovascular pathology and preclinical manifestations of CAN can be detected already in childhood (5,7,8). Obviously, in addition to the fact that the formation of CAN and cardiovascular disease (CVD) has common pathogenetic mechanisms, CAN is an independent risk factor for cardiovascular morbidity and mortality, contributing to its formation and leading to disruption of cardiovascular regulation. In children and adolescents with T1DM, the literature on the association of CAN with general risk factors for CVD is described in the available literature, while there are only a few publications that study the functional changes in cardiovascular activity against the background of CAS. Hyperglycemia is the main risk factor for the formation and progression of micro- and macrovascular complications of diabetes, and hence CVD. Glycemia is associated with the severity of atherosclerosis, left ventricular function, and the thickness of the intima-media complex. Epidemiological data indicate a relationship between hyperglycemia and the clinical manifestations of CVD in patients with type 1 diabetes. (7,9,10). Thus, a high level of HbA1c is associated with a higher frequency of events in coronary heart disease (CHD), mortality due to coronary heart disease, and overall cardiovascular mortality. Despite the fact that the main indicator of glycemic control is the level of HbA1c, it does not reflect daily fluctuations in blood glucose - glycemic variability (GV). And recently, evidence has emerged indicating the role of hepatitis B and hypoglycemia in the pathogenesis of CVD and chronic complications of diabetes. Even with target levels of HbA1c in patients with type 1 diabetes, the risk of total and cardiovascular mortality is approximately 2.38 and 2.92 times higher compared to with a healthy population. In addition, there is strong evidence that DM, even in a population without diabetes, is an independent risk factor for cardiovascular disease. In turn, in patients with diabetes, DM GV is a predictor of mortality from all causes and from CVD, in particular, DM is associated with markers of oxidative stress, endothelial and cardiovascular damage and is associated with endothelial dysfunction (13).

The development of oxidative stress is associated with the development of complications of diabetes. Thus, it is obvious that hepatitis B contributes to the formation and progression of CVD and microvascular complications of T1DM, including CAN. In turn, the resulting autonomous dysfunction exacerbates counter-regulation and leads to more frequent episodes of hypoglycemia and increased VH, closing the vicious circle. Recent studies have shown the association of hypoglycemia with various rhythm disturbances and prolongation of the QT

interval in adult patients with type 1 diabetes. To date, no such studies have been conducted in children and adolescents (14).

CAN develops as a result of damage to autonomic nerve fibers that innervate the heart and blood vessels, which is clinically manifested in impaired regulation of cardiac activity and vascular dynamics. Early signs of CAN are a decrease in heart rate variability (HRV) and a prolongation of the QT interval as a result of autonomous dysfunction, which in turn is also a risk factor for the development of life-threatening rhythm disturbances and sudden death (11,12).

Currently, contradictions remain regarding the pathogenesis of vascular complications of diabetes in general and DAN in particular. Traditionally, oxidative stress is considered as the main mechanism leading to nerve damage in patients with diabetes. Starting most likely through vascular disorders and the associated microangiopathy, oxidative stress is a key pathogenetic mechanism in nerve damage.

As in the case of other microvascular complications of T1DM, the main risk factor for CAN is chronic hyperglycemia, which is determined by a longer duration of the disease and a high level of glycated hemoglobin (17,18).

Heart rate variability (HRV) is represented by differences in the duration of the cardio intervals between them. It is based on the balance of the sympathetic and parasympathetic nervous system. A decrease in HRV is considered one of the earliest manifestations of diabetic autonomic cardiovascular neuropathy (DACN). To evaluate HRV, most researchers use a 24-hour recording of an electrocardiogram (ECG). In this case, daily ECG monitoring allows us to evaluate not only cardiac arrhythmias, but also its variability, which is especially important in the diagnosis of DACN (15). During analyzing HRV, indicators of temporary (statistical) analysis are used, such as:

SDNN (ms) - standard deviation of all RR intervals - characterizes the whole HRV in the form of increase or decrease;

rMSSD (ms) is the square root of the sum of the differences of consecutive RR intervals — PNS activity in the form of sinus arrhythmia;

pNN50 (%) episodes of difference in consecutive RR intervals of more than 50 ms, expressed as a percentage - PNS activity.

Recently, the influence of sharp fluctuations in glycemia in children with type 1 diabetes on the development of cardiac complications has been widely discussed. The effect of hypoglycemia and hyperglycemia on the cardiovascular system (CVS) in children is considered separately, however, the effect of hepatitis B remains uncertain.

The effect of hyperglycemia on the vascular wall is well known due to the activation of lipid peroxidation and excessive protein glycosylation, which ultimately leads to the development of endothelial dysfunction and tissue hypoxia. Hypoglycemia, according to research, also leads to impaired functioning of the CVS. As a result of activation of the sympathoadrenal system, the load on the myocardium increases, repolarization processes are disrupted, which ultimately can lead to the development of life-threatening arrhythmias and sudden death syndrome. The lengthening of the QT interval and the decrease in HRV parameters that occur with hypoglycemia, according to previous studies, are some of the indicators of DACN in children with type 1 diabetes. Hypoglycemia leads to impaired vascular endothelial function in children with type 1 diabetes, which can also become an additional risk factor for

early cardiovascular diseases (12.19%). Single studies are aimed at studying the effect of hepatitis B on the development of DACN in children with type 1 diabetes.

**Purpose of the study.** To establish clinical, functional and metabolic changes in diabetic autonomic cardiovascular neuropathy in children with type 1 diabetes.

Research work was carried out in the children's department of the Republican Specialized Scientific and Practical Medical Center of Endocrinology in Tashkent. The study included 114 children with type 1 diabetes. During the examination period, none of the children showed ketoacidotic and hypoglycemic conditions. All children were divided into three groups depending on the duration of the disease. The first consisted of 72 children with diabetes lasting less than 5 years (63%), the second group - 42 children with a disease duration of more than 5 years (37%). The control group consisted of 30 healthy children, comparable to sick children by gender and age.

Fig. 1

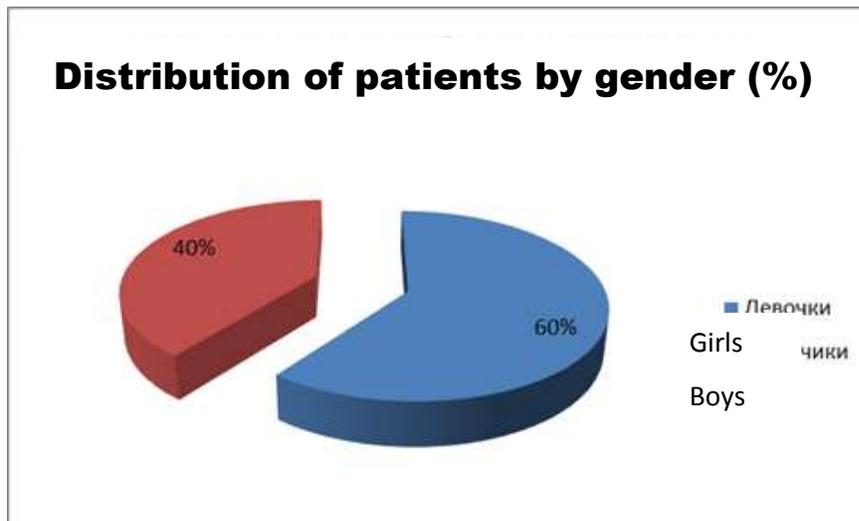
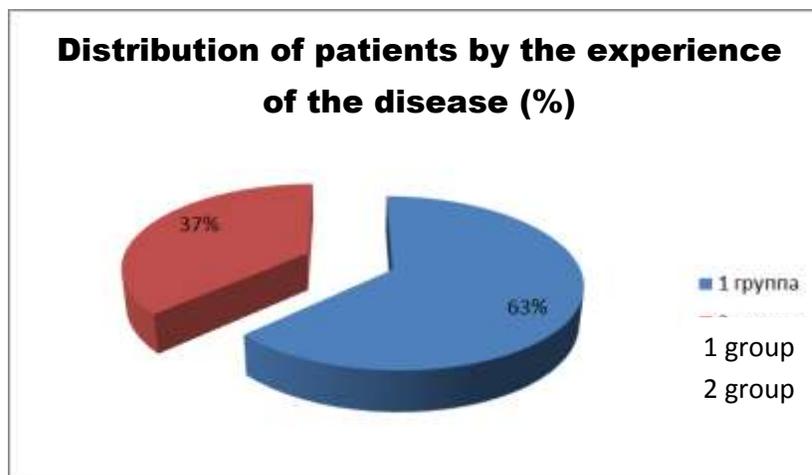


Fig.2



In addition to the standard clinical and anamnestic research method, electrocardiography, 24-hour heart rate monitoring was used with an assessment of the circadian index and parameters of the time and frequency analysis of heart rate variability.

The degree of disease compensation was assessed by the level of glycosylated hemoglobin (HbA1c), determined by the method of borate affinity analysis using an Nycocard Reader II analyzer. Statistical processing of the material was carried out on a personal computer using Microsoft Excel programs.

## Results

The examined children were analyzed complaints presented by them. Complaints were nonspecific and were represented by pain in the heart (17 children, 18.9%), palpitations (20 children, 22.2%), interruptions in the heart (12 children, 13.3%) and dizziness (13 children, 14.4%).

The analysis of anamnestic data revealed a significant prevalence of hereditary burden of diabetes in sick children. So, in 25 families (27.8%), when assessing the family history, diabetes was detected, which significantly distinguished them from children in the control group (1 child, 3.3%;  $p < 0.01$ ).

Pathological changes in the metabolism could not but affect the physical development of the examined children. There was a certain relationship between the level of physical development and somatotype and the duration and severity of the underlying disease. A low level of physical development was more often detected in children with diabetes lasting more than 5 years compared with children with less than 5 years of age and healthy children. In children with severe diabetes, a low level of physical development was also more often detected. Changes in the somatotype of the examined children had the same orientation depending on the duration and severity of the course of diabetes. This fact indicates a gross metabolic shift in children with a longer and more severe course of the underlying disease.

In children with type 1 diabetes mellitus, as the underlying disease progressed, an increase in the number of late complications and their severity was noted.

Among all the late complications, retinopathy (8 children, 7%), peripheral sensory-motor polyneuropathy (59 children, 52%), encephalopathy (23 children, 20.7%), and neuropathy (25 children, 21.9%) were most often detected. ) Rarely enough - nephropathy, it was detected (2 children, 1.7%). It was found that only with a long and severe course of the disease were nephropathy diagnosed (2 children, 1.7%). The increase in the frequency of occurrence and severity of complications amid an increase in the duration of diabetes mellitus indicates a deepening of metabolic-dystrophic changes and a failure of adaptation in the body of a sick child.

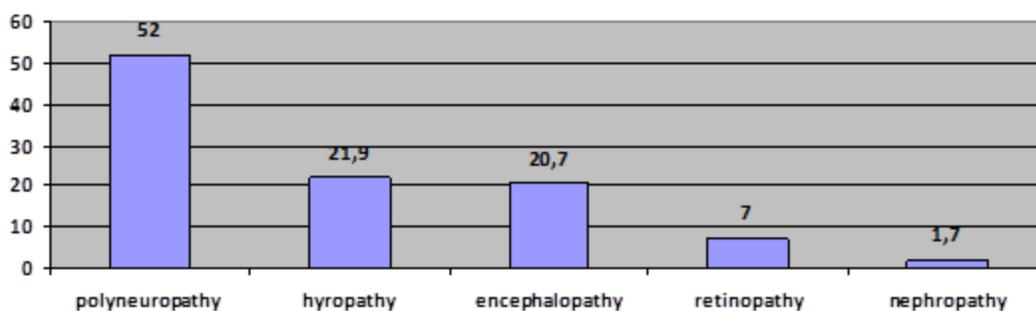


Figure. 3

According to our data, in children with type 1 diabetes mellitus there is a vegetative imbalance with a predominance of the tone of the sympathetic nervous system. So, in children with a long and severe course of the disease, a tendency to tachycardia and an increase in systolic and diastolic blood pressure was noted. Sympathicotonia was detected in 60 children (52.3%), while vagotonia was observed only in 19 children (16.6%), eutonia - in 35 children with diabetes (30.7%). According to the observation, it was found that the initial vegetative tone in children with diabetes depended on the duration and severity of the course of the disease. Thus, in children with diabetes lasting more than 5 years, compared with children with less than 5 years of age and healthy children, sympathicotonia was more often detected ( $p < 0.05$  and  $p < 0.01$ , respectively). In severe cases of the disease in children of group II, sympathicotonia was also more often determined in comparison with children of group I and the control group ( $p < 0.05$  and  $p < 0.01$ , respectively).

Shifts in the autonomic provision of heart activity were confirmed by the evaluation of Ewing cardiovascular tests. Thus, only 35 children with diabetes (40.7%) noted normal autonomic support of heart activity, initial changes in autonomic provision were observed in 45 children (52.3%) and distinct involvement of autonomic provision in the pathological process in 6 children with diabetes (7.0%). Moreover, it was found that only in children with a duration of diabetes of more than 5 years there was a clear involvement of the autonomic support of the heart in the pathological process.

The increased activity of the sympathetic section of the autonomic nervous system reflects not only the process of adaptation of the cardiovascular system to metabolic changes, but also is a consequence of the weakening of parasympathetic influences due to vaginal denervation of the heart formed in patients with diabetes.

The predominance of the sympathetic orientation of autonomic homeokinesis in children with diabetes was confirmed by the analysis of electrocardiographic studies. So, as the underlying disease progressed, a higher incidence of tachyarrhythmias was detected compared with the control group. In addition to tachyarrhythmias in children with diabetes, there was an increase, compared with the control group, in the frequency of R wave alternation ( $p < 0.05$ ), repolarization process disturbances ( $p < 0.01$ ), and signs of left ventricular overload ( $p < 0.001$ ), which is regarded as a sign of metabolic-dystrophic and electrolyte changes in myocardiocytes.

In order to establish the diagnostic value of Holter monitoring in identifying violations of autonomic regulation in children with diabetes, an analysis was made of the daily variability of heart rhythm (HRV) in the examined children. We used temporal and spectral analyzes of HRV.

Assessment of heart rate variability was carried out by a temporary method in accordance with national recommendations for Holter ECG monitoring. Calculation of heart rate, duration of the corrected interval QT c (Buzzet's formula) was carried out automatically

Analysis of temporal indicators of heart rate variability revealed that in children, as the underlying disease progresses, the sensitivity of the sinus node to parasympathetic influences decreases and stiffness of the heart rhythm is formed. Thus, it was found that in children with diabetes lasting more than 5 years, the total average, average daily and average night pNN50 and rMSSD were significantly lower than in children of patients less than 5 years old and healthy children (table 1).

An analysis of the spectral indicators of heart rate variability showed that in children with signs of sympathicotonia (according to the results of the analysis of time indicators), the spectral analysis indicators are significantly lower compared to children with normal pNN50 and rMSSD values. These changes indicate a significant decrease in the influence of not only the parasympathetic, but also the sympathetic parts of the autonomic nervous system on the regulation of heart rhythm in these children.

An analysis of the relationship between the indicators of low-frequency (LF) and high-frequency (HF) wave spectra showed that in children with signs of diabetic autonomic cardiovascular neuropathy, this ratio was significantly higher ( $p < 0.001$ ) compared with the group with normal pNN50 and rMSSD, where this indicator was within normal limits. In our opinion, these changes indicate a predominant and more pronounced involvement of the autonomic nervous system in the pathological process of the parasympathetic department at the initial stages of the formation of diabetic autonomic cardiovascular neuropathy and can be used as a criterion for its early diagnosis.

Table 1.: Heart rate variability in children with diabetes, depending on the duration of the disease, M±m

Index	I group (n=72)	II group (n=42)	Control group (n=30)
pNN50 (total average),%	26,0±3,03*	14,0±2,1*** $p_1 < 0,01$	37,2 ± 1,14
pNN50 (average afternoon),%	18,6±2,69*	7,4±1,33*** $p_1 < 0,001$	22,5 ± 1,42
pNN50 (average at night),%	36,8±4,01*	25,8±3,54*** $p_1 < 0,05$	43,7 ± 1,95

rMSSD (total average), ms	54,2±5,04*	31,8±3,61*** p <sub>1</sub> <0,001	80,4 ± 1,86
rMSSD (average afternoon), ms	43,2±4,56*	21,6±2,23*** p <sub>1</sub> <0,001	59,4 ± 2,41
rMSSD (average at night), ms	70,3±6,51*	49,8±6,19*** p <sub>1</sub> <0,05	82,3 ± 2,10

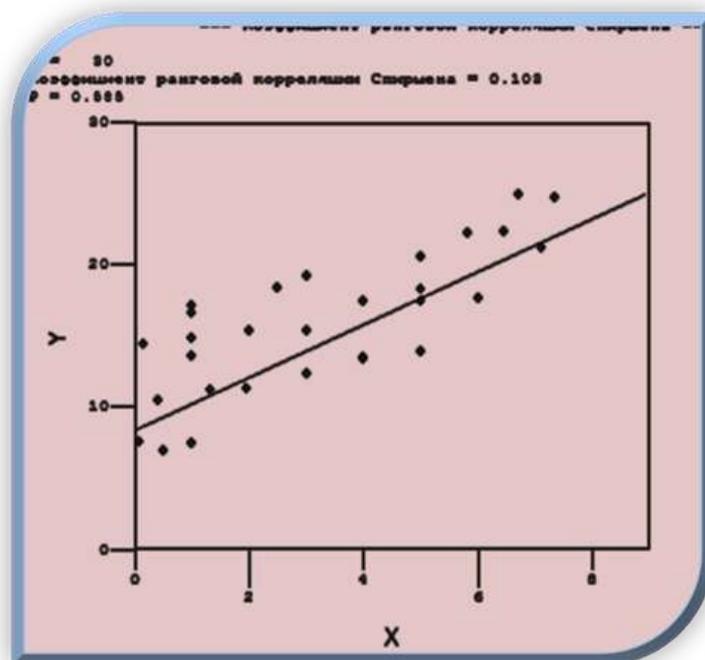
Note. Significance of differences: \*\*\* - p <0.001, \*\* - p <0.01, \* - p <0.05 - compared with the control group; p<sub>1</sub> - compared with group I.

In the course of the work, the diastolic function of the left ventricle was evaluated according to echocardiographic studies. For this, we used one of the main echocardiographic signs of impaired diastolic function of the myocardium - myocardial compliance index (MCI = ATE / DT1 / 2).

An analysis of the dynamics of MCI in children showed that in children with signs of diabetic autonomic cardiovascular neuropathy (according to the results of the analysis of temporary indicators), this indicator is significantly lower compared to children with normal pNN50 and rMSSD values. These changes indicate an increase in myocardial rigidity in the diastole phase and the emerging diastolic dysfunction in children with diabetes against the background of previously diagnosed autonomic diabetic cardiovascular neuropathy.

Thus, in most children with diabetes, the level of glycosylated hemoglobin (HbA1c) was higher than the permissible limits for compensating for the disease. Moreover, the average level of HbA1c in children with a long and severe course of the disease was significantly higher than in other children. The data obtained indicate insufficient compensation for the disease, unsatisfactory self-control of glycemic indicators and the labile course of the disease, especially with prolonged and severe course of diabetes.

The development of late complications of diabetes mellitus in children, including the cardiovascular system, is based on metabolic disorders associated with poor compensation for the disease, which, according to our data, gets out of control with diabetes lasting more than 5 years. This is confirmed by a close direct correlation between the level of HbA1c and the duration of the disease.



**Fig 4. Correlation between the experience of the disease and glycated Hb.**

*Notes: X axis - values of experience; Y - values of glycated hemoglobin.*

Given the above data, the duration of the disease and the level of HbA1c, as an indicator of metabolic imbalance, reliably correlates with organ and systemic complications. It can be assumed that the leading importance in the development of organ pathology is not the maximum peaks in the increase in blood glucose concentration, but long-lasting hyperglycemia.

### Conclusions

1. Diabetic autonomic cardiovascular neuropathy in children with type 1 diabetes is characterized by the development of tachyarrhythmic rhythm disturbances, as well as the formation of rigidity of the heart rhythm and a decrease in the sensitivity of the sinus node to parasympathetic influences according to a temporary analysis of daily monitoring of heart rhythm.
2. Thus, in our opinion, diabetic autonomic cardiovascular neuropathy can be considered as one of the stages in the formation of dystrophic myocardial damage in children with type 1 diabetes.

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