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THE ROLE OF AUTONOMIC DISORDERS IN THE PROGRESSION OF CHRONIC KIDNEY DISEASE IN CHILDREN

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Анотація. *У роботі розглядається взаємозв'язок між дисбалансом вегетативної регуляції та прогресуванням ХХН у дітей з початковими її стадіями. Обстежено 214 дітей 6 - 17 років з ХХН I-III стадій. Використовували метод добового моніторування електрокардіограми з визначенням показників варіабельності серцевого ритму та кардіоінтервалографію в поєднанні з клиноортостатичною пробою. У 76,6% дітей із ХХН реєструвалися розлади вегетативного статусу, які характеризувались зсувом ваго - симпатичного балансу в напрямку послаблення парасимпатичного та домінуванням симпатикотонії. Такі зміни розглядаються як послаблення загальних адаптаційних можливостей організму, що по мірі прогресування ХХН є підґрунтям для розвитку й прогресування кардіоваскулярних порушень у даного контингенту дітей та ускладнюють перебіг ХХН.*

Ключові слова: *хронічна хвороба нирок, симпатикотонія, діагностика, діти.*

Introduction. It is incontrovertible today that renal dysfunction is an independent risk factor and pathogenetic mechanism of accelerated development of cardiovascular disease [1]. Increased cardiovascular risks are associated with the sympathetic autonomic nervous system (ANS) hyperactivity, which occurs with the progression of chronic kidney disease (CKD) [2]. That is, an autonomic imbalance with hypersympathicotonia is the first stage in the renal continuum [2-4]. Understanding the role of sympathetic nervous hyperactivity in the development and driving renal damage can help in the treatment and prevention of CKD, irrespective of its severity [5].

The aim of this study was to determine the relationship between the autonomic regulation imbalance and early-stage CKD progression in children.

Materials and methods. A total of 214 children aged between 6 and 17 years with stage I-III CKD were examined. The control group consisted of 60 healthy age-matched children. The 1st group included 153 patients with stage I CKD, the 2nd group - 39 patients with stage II CKD, the 3rd group - 22 children with stage III CKD.

The methods of daily electrocardiogram (ECG) monitoring with an analysis of heart rate variability (HRV) and cardiointervalography (CIG) combined with clinoorthostatic test (COT) were used [6, 7]. For time-domain assessment of HRV, the following parameters were used: SDNN (ms) – standard (mean-square) deviation of all normal sinus RR intervals over 24 hours, SDNN index (ms) - the mean of the standard deviations of all normal sinus RR intervals for all 5-min segments, SDANN (ms) – the standard deviation of all 5 minutes average normal RR intervals, RMSSD

(ms) – the root-mean-square of the successive normal sinus RR interval difference (parasympathetic activity index), pNN50 (%) - the percentage of successive normal sinus RR intervals more than 50 ms (ms^2). Spectral analysis was performed using the algorithm of fast Fourier transform with the calculation of the total power spectrum - TP (ms^2) and its three components - very low frequencies (VLF), low frequencies (LF), high frequencies (HF), and LF/HF index.

Analyzing the CIG with COT, the initial autonomic tone (IAT), the autonomic reactivity (AR) and autonomic support (AS) were determined.

Results. HRV analysis found unidirectional changes in the time-domain and spectral indicators. SDNN values were statistically significantly lower than normal in the 1st, 2nd and 3rd groups, representing -1.37; -1.42; -2.6, $p_{1-2} = 0.4121$, $p_{1-3} = 0.0232$, $p_{2-3} = 0.062$, respectively, for 24-hour measurements, due to the predominant daytime values of the indicator: -1.43; -1.45; -2.78, $p_{1-2} = 0.4651$; $p_{1-3} = 0.0273$; $p_{2-3} = 0.057$, respectively. A sharp decrease in SDNN (more than 3 S) was detected in 4.26% of patients in the 1st group, in 13.3% - of the 2nd group and in 35.3% - of the 3rd group. RMSSD and pNN50 parameters, which indicate the parasympathetic arm of the ANS activity, tended to decrease (RMSSD: -0.97, -0.49, -1.40, $p_{1-2} = 0.0355$ $p_{1-3} = 0.3791$ $p_{2-3} = 0.0371$), NN50 over the 24 hour-period: - 2.80; - 0.99; - 3.50, $p_{1-2} = 0.0730$, $p_{1-3} = 0.4123$, $p_{2-3} = 0.0348$, respectively, mainly due to the nighttime values: - 2.84 - 1.63 -3.54, $p_{1-2} = 0.0881$, $p_{1-3} = 0.4536$, $p_{2-3} = 0.0443$. A significant decrease in RMSSD values was revealed in the 3rd group of patients, and in the pNN50 values - in the 1st and 3rd group patients as compared to the control group.

The degree of changes in the HRV power spectrum demonstrated significant intergroup differences in both the low-frequency LF ($H = 23.22$ $p = 0.0001$) and the high-frequency HF ($H = 14.45$, $p = 0.0023$) components. A statistically significant decrease in the HF power component with an increase in the LF component resulted in a statistically significant increase in the LF/HF ratio in the patients of all groups compared to the controls, without intergroup differences ($H = 1.67$, $p = 0.8725$). An increased VLF values, that indicates an overstrain of the compensatory mechanisms and may be responsible for body adaptive reserves depletion, was defined in 21.3% of the 1st group patients, in 20.0% - of the 2nd group and in 11.8% - of the 3rd group. Additionally used Spearman's correlation analysis showed the presence of significant intercorrelations between GFR levels and HRV parameters, namely GFR and SDNN ($r = + 0.564$, $p = 0.023$), GFR and pNN50 ($r = + 0.492$, $p = 0.037$), GFR and TP, LF, HF ($r = –0.591$, $p = 0.030$; $r = –0.662$, $p = 0.012$; $r = + 0.627$, $p = 0.018$, respectively).

An analysis of IAT revealed statistically significant decrease in the frequency of euthonia (40.9%) and an increase of sympathicotonia (39.1%) in all the groups of CKD patients. The maximum changes occurred in the 3rd group, where sympathicotonia was identified 2.3 times more often than in the 1st group (27.8% and 63.7%, respectively). Such changes demonstrated the intensive mechanisms of cardiovascular system adaptation and were considered as a risk factor for subsequent development of arterial hypertension (AH).

Most of the 1st group patients had the hypersympathicotonic type of AR (57.4%). At the same time, the proportion of asympathicotonic variant increased with

the progression of CKD (from 16.7% in the 1st group to 54.5% in the 3rd group, p <0.05), confirming a substantial decrease in the level of compensatory-adaptive potential. Indicators of AS were also characterized by a decrease in the proportion of normal reactions to the COT due to an increase in pathological ones: the excessive (hypersympathicotonic) variant dominated in the 1st group (38.9%), while the 2nd and 3rd groups exhibited insufficient variant (48,7% and 68.2%, respectively). The most maladaptive type of cardiovascular response to the COT – hyperdiastolic, was found in the 2nd and 3rd groups of patients (23.1% and 36.4%, respectively).

Conclusions. Thus, disorders of autonomic status were revealed in 76.6% of children with stage I-III CKD. The changes were characterized by a shift in the vagosympathetic balance towards reducing parasympathetic tone and the sympathetic arm of the ANS dominance. Such changes can be regarded as a general adaptive capacity weakening, which is responsible for the development and acceleration of cardiovascular disorders with the progression of CKD, complicating the disease course in this group of children.

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Abstract. *The study examines the relationship between the imbalance of autonomic regulation and initial stages CKD progression in children. 214 children aged 6-17 years with stage I-III CKD were enrolled. The methods of daily electrocardiogram monitoring with the analysis of heart rate variability and cardiointervalography combined with clinoorthostatic test were used. In 76.6% of children with CKD, disorders of autonomic status were revealed, being characterized by a shift in the vagosympathetic balance towards reducing parasympathetic tone and the sympathetic arm of the ANS dominance. Such changes can be regarded as a general adaptive capacity weakening, which is responsible for the development and acceleration of cardiovascular disorders with the progression of CKD, complicating the disease course in this group of children.*

Key words: *chronic kidney disease, sympathicotonia, diagnosis, children.*

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