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The clinical and genetic features of SCN1A, SCN2A gene related phenotypes in patients with epilepsy and intellectual/developmental disability

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Relevance: In nowadays, the problems of epilepsy in children still lead a huge place in pediatric neurology, caused by many controversies in the understanding of the essential problem, approaches in determining the priory diagnostic methods, and, of course, the treatment. For the neurologist in the inspection of a physician with epilepsy, the problem is not in the choice and calculation of the correct dose of the AED, but rather the differential diagnosis and the secondary conditions arising from epilepsy. The consequence of chronic seizures in the case of epilepsy is a gross cognitive deficit, possible physical damage (resulting from sudden seizures), economic damage from the constantly using of AEDs, a high risk of disability with low social status, and finally, low quality of life for the patient, his family and for the whole society [1].

Keywords: SCN1A, SCN2A, patients, epilepsy.

The development of genetic technologies leads to the identification of a large number of gene-associated epilepsies. In the database indicated (OMIM, HGMD, PubMed, EpilepsyGene) 977 genes associated with epilepsy [2].

Epilepsy which traditionally classified as idiopathic (by etiology) with the widespread availability of genetic research methods in 70% was confirmed by its genetic nature [3].

The past 15 years was a significant breakthrough for the genetic possibilities in the science and research methods. This period named as “golden” for the idiopathic epilepsies genes discovery [4]. But despite the extraordinary period of the epileptogenesis discoveries and elucidation of the new neurobiological mechanisms, there are still many cases without genetic explanations and it is opens new opportunities for the future discoveries in the study of epilepsy [5].

The most cited from the 84 genes causing epilepsy is the SCN1A gene, noted as the most common mutated gene associated with a wide phenotypic range and severity [6].

SCN1A is the most clinically relevant gene responsible for a wide range of epilepsy phenotypes. And the first generally accepted step according to the International League Against of Epilepsy (ILAE) [7] is the DNA diagnosis of the patients with suspected Dravet syndrome, GEFS + and epileptic encephalopathy is to "check" the patients for the SCN1A mutation. Reported that 80% of patients with Dravet syndrome have a mutation in the SCN1A gene [8].

The SCN1A gene was first described as a cause of epilepsy in 2001 [9]. Since 2009 incessant researches made possible identifying more than 1200 mutations in these gene. But despite considerable efforts, there is no clear phenotype-genotype correlation in hundreds of identified SCN1A gene mutations [3].

The SCN2A gene also encoding the alpha subunits of sodium channels is highly expressed in the early stages of postnatal brain formation. Long-term studies of SCN2A gene mutations have revealed a wide range of possible clinical manifestations in patients, there are ranging from the benign familial infantile seizures, autism to the intractable forms of epilepsy, infantile spasms and severe myoclonic epilepsy of infancy [10].

Approximately 70-80% of all patients with epilepsy without an obvious cause, and those cases predominantly suggests to have the genetic basis. The number of genes and families genes associated with epilepsy has rapidly increased with the advances in technology and gene mutations diagnosis [11]. The heterogeneity of the mutations underlying in idiopathic epilepsy make a trouble in the rational choice of the target therapy which specific for the ion channels [12]. Pharmacogenetic studies not yet explained why 30% of patients are still resistant to the antiepileptic therapy. [13].

The aim of the work: to determinate the phenotypic signs of the SCN1A, SCN2A gene mutations in Uzbek population with epilepsy and intellectual/developmental disability.

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Materials and research methods:

The research work produced according with the research plan of the Center for the Development of Professional Qualifications of Medical Workers, in the frame of the young scientists project "Development of clinical and genetic diagnostic methods with identification of the causes of psychomotor and speech development delay in children with epilepsy" (contract No. PZ- 20170928638 dated 4.01.2018). In this project, for the first time in Uzbekistan developed and implemented a specific test system for epilepsy and intellectual/developmental disability. For the first time we proved molecular genetic mechanisms, the unfavorable course and prognosis of the disease.

According to the database of the Pediatric Neurology Department, for the period from 2018 to 2020, we examined 159 children with epilepsy and intellectual/developmental disability (IDD) at the age from 0 to 6 years 11 months 29 days. From 159 number, 118 patients were selected to the molecular genetic study to exclude SCN1A, SCN2A genes pathology. 118 patients constituted the main study group. Seizures were detected in 85 of 118 (72.0%) children. 41 patients from the 159 were excluded from the study: due to hemolysis of blood during DNA extraction - 14 patients, due to refusal from the genetic study - 18 patients, 9 patients were excluded from the study due to insufficiency of anamnestic, laboratory-instrumental and neuro-imaging data.

Thus, we examined 118 pediatric patients with epileptic seizures and/or intellectual/developmental disability, 91 of which identified with polymorphism/mutation of SCN1A, SCN2A genes, $\chi 2$ (10) = 20.032, p = 0.029 ($\leq$ 0.05).

In general, epileptic encephalopathies are merciless in their sudden appearance in early childhood. At first glance, they are appeared suddenly in an absolutely healthy child with normal psychomotor development, manifest with febrile seizures, often no specific EEG patterns at first, the absence of structural changes on MRI even after the clinical picture is fully developed. It is important to examine each patient

with the described condition as early as possible, to confirm or exclude epileptic encephalopathy, with followed by its correct management [14]. It is the reason to search phenotypic manifestations of SCN1A, SCN2A gene mutations in the Uzbek population.

Statistical analysis: Data was analyzed using IBM SPSS 27.0.

Statistical analysis was performed using SPSS software (v27, IBM, Chicago, IL, USA). Descriptive statistics for the studied variables are presented as mean M ± SD (standard deviation) for normally distributed continuous variables, median with interquartile range for abnormally distributed continuous variables, and frequency with percentage for categorical variables. The variables were compared with Student's independent t-test for normally distributed continuous data and Chi-square test for categorical data. Differences between groups were determined by one-way analysis of variance (ANOVA) followed by a Tukey/Dunnett C post hoc test.

The association of the risk factors and seizure onset was assessed using Cox proportional hazards models to examine how the variables predict outcome. A one-way (unadjusted) analysis of each risk factor was assessed separately for stepwise addition to the predictive model. A P value of less than 0.05 was considered statistically significant.

Stepwise logistic regression was performed by injecting variables into blocks to predict seizure onset, which was coded as a continuum variable. Step 1 contained control indicators (age, gender). Due to the wide distribution of ages among patients, square ages were also analyzed. Step 2 contained age, gender, and genetic parameters. To reduce the problem of multicollinearity, a separate statistical analysis was performed in the following models by adding variables for age, sex, and genetic parameters at baseline. Step 3: risk factors. In step 4, the number of comorbidities was included. Step 5 represented the severity of the seizures. Step 6 cognitive and motor pathology.

Research results:

To solve the tasks set in the research all the patients according to the results of the genetic research, were divided into 6 genetic combinations group. Among the

patients were 75 (63.5%) boys, 43 (36.4%) girls, there was no statistical difference in sex between the subjects $\chi 2$ (10) = 4.95, p = 0.422. Patient's age ranged from the birth to 6 years 11 months 29 days. The average age of the patients was 49.05 ± 23.16 months (Minimum-2; Maximum-102).

The average age of seizures onset was 13.0±15.8 (Min 0.03; Max 96.0) months of life.

All patients were divided into the following groups depending on the results of genetic study:

Group 1 NN included 27 patients with epilepsy and intellectual/developmental disability, in whom the result of molecular genetic research was a normal genotype for the SCN1A, SCN2A genes. In this study group there was 18 (67% of this group) males and 9 (33% of this group) females. The average age of the study group was 59.4 ± 20.7 (Max 3; Max 102) months of life (4 years 9 months). From the 27 patients' active seizures had 16 (59.2%). The average age of the epilepsy manifestation was 20.6 ± 25.05 (Min 0.70; Max 96.0) months of life.

According to the results of genetic study, the 2nd GN group included 11 patients with a heterozygous carriage of SCN1A gene and a normal genotype of SCN2A gene. In the studied group there are 7 (64% of this group) males and 4 (36% of this group) females. The average age of the group was 35.2 ± 23.3 (Min 4; Max 78) months (2 years 9 months). Active seizures had 4 patients (36.6%). The average age of the seizure onset was 5.7 ± 3.2 (Max 2.0; Max 8.0) months of life.

Group 3 NG with a normal genotype of SCN1A gene and heterozygous carriage of the SCN2A gene, included the largest number of studied patients – 40. This study group include 22 (55%) males and 18 (45% of this group) females. The average age of the group was 47.8±23.9 (Min 2; Max 82) months (3 years 9 months). From all studied patients of this group (n = 40) active seizures had 33 (82.5%). The average age of seizures manifestation was 13.2 ± 14.1 months of life (Min 0.17; Max 60.0).

Group 4 GG with heterozygous carriage of both genes included 22 patients with epilepsy and intellectual/developmental disability. In the study group was 16

males (73% of this group) and 6 females (27% of this group). The average age of the patients was 50.9 ± 23.9 (Min 10; Max 83) months of life (4 years 2 months). Epilepsy in the study group was observed in 15 patients (68%) from 22. The average age of epilepsy manifestation was 8.7 ± 9.1 (0.03; 35.0) months of life.

The 5th MG group included 10 examined patients with SCN1A gene mutation and heterozygous carriage of the SCN2A gene. By gender, it consisted of 5 (50% of this group) males and 5 (50% of this group) females. The average age of the group was 39.8 ± 17.3 (Min 13; Max 60) months (3 years 3 months). Epilepsy was observed in all 10 (100%) patients in this group. The average age of seizures onset was 11.1 ± 6.08 (Min 5.0; Max 18.0) months of life.

As a result of a molecular genetic study, the 6th NM group included 8 patients with a normal genotype of SCN1A gene and mutated SCN2A gene. Among the studied patients there were 7 (88% of this group) males and 1 (12% of this group) female. The average age of the group in months was 46.1 ± 20.8 (Min 12; Max 59) (3 years 8 months). Convulsions were observed in each patient of this group - 8 (100%). The average age of epilepsy manifestation was 6.7 ± 3.19 months of life, with Min 0.23; Max 10.0

Group characteristics and the age of patients included in the study are presented in Table 1.

Table 1

Distribution of patients in the study groups by gender, age of the first examination and seizures onset.

Indicator, n (%)	NN (n=27)	GN (n=11)	NG (n=40)	GG (n=22)	MG (n=10)	NM (n=8)	Total (n=118)	Chi-square	P-value
Age at the time of examination, months M±SD	59.4±20.6	35.2±23.4	47.8±23.9	50.7±23.9	39.8±17.4	46.1±20.8	49.1±23.2		0, 45
Sex Males	18	7	22	16	5	7	75 (64%)	4.95	0.422
Females	9	4	18	6	5	1	43 (36%)		

History of seizures	16 (59.2)	4 (36.6)	32 (80)	15	10 (100)	8 (100)	85 (72%)	17.5	0.004
Age at the time of seizures onset, in month M±SD	20.6 ±25.05	5.7±3.2	13.2±14.1	8.7±9.1	11.1±6.08	6.7±3.19	13.0±15.9		0.001

Note: M- is average, SD- is standard deviation

The presented data confirm the idea of a high incidence of epilepsy and epileptic seizures in early age children. The youngest studied group was the GN group with a heterozygous carriage of the SCN1A gene 35.2 ± 23.4 months of life, in which the earliest manifestation of epilepsy among all the studied patients was - 5.7 ± 3.2 months. This suggests a connection between the SCN1A gene pathology and the early age of epilepsy manifestation p = 0.001.

The highest rates of the seizures presence (100%) were in children with a complete mutation of the SCN1A and SCN2A genes, which confirms the 100% specificity of seizures with pathology of the genes encoding sodium channels, p = 0.004.

Among the genetic groups, there was no statistically significant difference in gender, p = 0.422. The results of the molecular genetic study did not reveal gender differences.

According to the main clinical diagnosis, the studied patients were divided into 3 disease categories (Table 2).

Table 2

Clinical diagnosis of the studied patients

	NN	GN	NG	GG	MG	NM	Total	Chi-square	P-value
Epilepsy without IDD	1	0	6	1	3	1	12	20.03	0.029
Epilepsy with IDD	17	3	23	13	5	7	68		
IDD without epilepsy	9	8	11	8	2	0	38		

As can be seen from the table, most of the patients were in the group with Epilepsy and developmental intellectual disability 68/118 (57.6%), which once again shows the presence of two pathological conditions simultaneously. In the group of epilepsy and IDD, cases of NG- heterozygous carriage of the SCN2A gene, prevail. The category of patients without epilepsy but with IDD was 38/118 (32.2%). The data confirmed the correct choice of SCN1A, SCN2A genes investigations in the searching of both conditions- epilepsy and IDD, $\square^2$ (10) = 20.032, p = 0.029 (≤0.05).

At the time of examination, the leading complaints in patients (Table 3) were seizures 78/118 (66%) $\square^2$ = 13.721, p = 0.017, speech impairment 66/118 (56%) $\square^2$ = 15.332, p = 0.009, developmental delay according to parents 90/118 (76%), $\square^2$ = 12.686, p = 0.027, ARP 49/118 (42%), $\square^2$ = 40.306, p = 0.0001, behavioral disorders 59/118 (50 %), $\square^2$ = 23.581, p = 0.0001, as well as fears and sleep disturbances, which did not reveal statistical significance. The fact of the majority of complaints in the group with heterozygous carriage of the SCN2A gene turned out to be obvious. Behavioral disorders were observed in the older age group GG with heterozygous carriage for both genes.

Table 3

Analysis of the complaints during the initial examination

Complaint, n (%)	NN (n=27)	GN (n=11)	NG (n=40)	GG (n=22)	MG (n=10)	NM (n=8)	Total (n=118)	Chi-square	P-value
Жалобы при поступлении									
Seizures	16	3	29	14	8	8	78/118 (66%)	13.721	0.017
Speech delay	20	6	24	13	2	1	66/118 (56%)	15.332	0.009
Developmental delay	17	11	28	16	10	8	90 (76%)	12.686	0.027
Affective-respiratory paroxysm	2	1	17	12	10	7	49 (42%)	40.306	0.0001
Behavioral disorder	8	4	19	10	10	8	59 (50%)	23.581	0.0001

Analysis of complaints with using Pearson's correlation, determined that the presence of the SCN1A gene mutation positively correlated with complaints on developmental delay, Pearson r = 0.203, p = 0.028; and ARP Pearson r = 0.293, p = 0.001. There were no other statistically significant associations with complaints.

None of the genes were associated with autism, deafness, eye disorders, somatic pathology, or ADHD. However, in patients with a mutation of the SCN2A gene, the phenomena of enuresis prevailed $\chi^2 = 28.939$, $p = 0.0001$.

The SCN2A gene mutation positively correlated with the presence of enuresis in children, Pearson r=0.306, p =0.001. Moreover, enuresis was also positively associated with a history of seizures, Pearson r=0.233, p=0.003. This may mean that seizures are an important and statistically significant factor in the presence of bedwetting in children, which may also be due to the expression of the SCN2A gene.

The criterion for the presence of comorbidity in the cases of our studies was the fact of the presence of certain disorders (delayed psychomotor development, developmental anomalies, eye disorders) before the manifestation of epilepsy and epileptic seizures.

The analysis of the patients age, age of the seizure onset, made possible to determine the duration of the epilepsy (Table 4).

Table 4

Analysis of the duration of epilepsy

Sign n (%)	NN (n=27)	GN (n=11)	NG (n=40)	GG (n=22)	MG (n=10)	NM (n=8)	Total (n=118)	P-value
Average age of the patients, мес M±SD	59.4±20.6	35.2±23.4	47.8±23.9	50.7±23.9	39.8±17.4	46.1±20.8	49.1±23.2	0, 45
Age of the seizures onset, M±SD	20.6 ±25.05	5.7±3.2	13.2±14.1	8.7±9.1	11.1±6.08	6.7±3.19	13.0±15.9	0.001
Duration of epilepsy, M±SD	34.51±27.9	0.98±0.99	31.31±25.9	48.5±26.9	29.2±13.6	39.40±18.02	34.61±25.69	0.033

As described earlier, the average age of seizures onset was 13 months of life (Min 0.03; Max 96.0), p = 0.001. The earliest onset was at the age of 5.7 ± 3.2 months in the 2nd study group GN. The latest onset of seizures was at the age of 20.6 ± 25.05 months in group 1 NN.

The onset of seizures was classified according to the age range. So, seizures were manifested in infancy (up to 6 months) at 35/85, 9 from them were manifested in the neonatal period. At the age of up to one year - 21 cases, up to 3 years - 22 patients, after 3 years old seizures were manifested in 7 patients.

The presence of the SCN2A gene mutation negatively correlated with the age of seizures onset, Pearson r = -0.223, p = 0.035 (Table 5). It means, that in cases of heterozygous carriage or mutation in SCN2A gene, the earliest seizures onset is possible. Whereas the correlation of the SCN1A gene mutation with the age of onset revealed unreliable data, Pearson r = -0.135, p = 0.219.

Table 5

Sign	Statistical data	SCN1A gene mutation	SCN2A gene mutation
Age of the seizure's onset	Pearson Correlation	-0.135	-0.230
	Sig0. (2-tailed)	0.219	0.035

As noted earlier, any individual contains mutations/polymorphisms of some genes in his genotype, which can be in "silence" state for a long time until the moment of a specific trigger action (Table 6).

Table 6

Trigger, n (%)	NN (n=27)	GN (n=11)	NG (n=40)	GG (n=22)	MG (n=10)	NM (n=8)	Bcero (n=118)	Chi-square	P-value
Damage	0	0	2	0	0	2	4	9.670	0.085
Diarrhea	0	0	3	1	0	5	9	26.318	0.0001
Vaccination	4	0	4	2	0	0	10	4.142	0.529
Hyperthermia	6	0	7	6	11	0	30	29.137	0.0001
Noise	1	0	1	0	0	0	2	1.604	0.901
Without cause	9	2	15	6	1	1	34	7.233	0.204

According to all the studies carried out in the field of the genes encoding sodium channels, the main triggers are hyperthermia, taking a hot bath, and their

occurrence without an established cause. As a result of our study, the largest number of seizures manifested without a cause 34/118 (29%), but the data turned out to be statistically unreliable χ^2 =7.233, p =0.204. A strong statistical effect in our study was such triggers as diarrhea 9/118 (8%) χ^2 = 26.318, p = 0.0001 and hyperthermia against the background of virus infection 30/118 (25.4%) χ^2 =29.137, p =0.0001. Also, according to the parents, such a trigger as touch and a flash of light was noted, in 1 case, which did not lend itself to statistical analysis.

The analysis of seizure types according to the ILAE classification 2017 was carried out in 85 of patients (72%) from 118 subjects [15]. According to this classification, a table provided that clearly demonstrate the prevalence of types of seizures.

Table 7

Types of seizures according to ILAE 2017

Types of seizures n (%)	NN (n=27)	GN (n=11)	NG (n=40)	GG (n=22)	MG (n=10)	NM (n=8)	Bcero (n=118)	Chi-square	P-value
Focal with save consciousness	2	0	1	2	0	0	5	112.288	0.0001
Focal with disturbance consciousness	4	0	1	1	0	0	6		
Bilateral tonic-clonic seizures with focal onset	0	0	5	2	0	1	8		
Clonic seizures	3	1	3	3	1	0	11		
Tonic seizures	2	0	3	0	0	0	5		
Tonic-clonic seizures	0	1	1	0	3	0	5		
Myoclonic seizures	2	1	6	1	0	6	16		
Absence	1	0	3	0	0	0	4		
Atonic seizures	2	0	3	2	0	0	7		
Myoclonic-atonic	0	0	1	1	0	2	4		
Febrile seizures	3	0	2	3	0	0	8		
GEFS	0	0	0	0	4	0	4		
Polymorphic seizures	0	0	1	0	0	1	2		

Total	19	3	30	15	8	8	85		

In the studied groups, focal types of seizures 77/85 (90.5%) prevailed, myoclonic was in 16/85 (19%) and clonic 11/85 (13%) types of seizures were observed in most cases $\square^2 = 112.288$, $p = 0.0001$. These two types of seizures are most common in young children. The variety of seizure manifestations did not allow determining the specific characteristic types of seizures in genetic groups.

In our investigation, the duration of the epilepsy was previously analyzed to confirm the chronic nature of the biochemical pathomechanism, the consequence of which is the continuous effect of the epileptic activity on the young developing brain. To assess the severity of this chronic process, such characteristics of the seizures as duration, frequency and the usual time of seizures were analyzed (Table 8). Seizures lasting a few seconds, more precisely up to 1 minute, accounted for a greater specific weight among the entire duration of seizures - 33/85 (39%) $\square^2 = 33.176$, $p = 0.032$, which is typical for focal seizures. Daily convulsions several times a day had a statistical significance $\square^2 = 53.818$, $p = 0.005$. In the cases of childhood epilepsy, the brain is not able to take control under the epileptic focus, as a result brain controlled by this pathological focus, that is why, seizures not choose the usual time of realization. This study revealed a statistically reliable appearance of seizures at any time - 37/85 (43.5%) $\square^2 = 47.206$, $p = 0.005$.

Table 8

Seizures frequency									
Everyday/several times in a day	5	2	12	3	0	6	28	53.818 Chi-square	0.005 p-value
Once in week	1	1	2	2	0	0	6		
Several times in week or once in a month	2	0	2	2	0	0	6		
2 и более раз в месяц	2	0	5	0	0	1	8		
Several times in 6-12 month	5	0	3	0	4	0	12		
Once in 12 month	3	0	3	3	0	1	10		

Only once	1	0	2	5	0	0	8		
Total	19	3	29	15	4	8	78		

Conclusions:

This study confirmed the idea of a high incidence of epilepsy and epileptic seizures in early age children in Uzbek population. The youngest investigated group was the patients with heterozygous carriage of SCN1A gene. This suggests a connection between the SCN1A gene pathology and the early age of epilepsy manifestation, $p = 0.001$;

The highest rates of the seizures presence (100%) were in children with complete mutations of the SCN1A and SCN2A genes, which confirms the 100% specificity of seizures with pathology of genes encoding sodium channels, $p=0.004$;

Clinical and genetic analysis showed the simultaneous presence of two pathological conditions, such as epilepsy and intellectual/developmental disability;

The study confirmed a wide range of complaints in children with SCN1A, SCN2A genes abnormalities;

In the result of our study, the largest numbers of genetic associated epilepsies manifested without any cause;

These study revealed the phenotypic manifestations of SCN1A, SCN2A genes mutations in patients with epilepsy: the early age of onset, the wide range of complaints upon admission, the onset of seizures without apparent reason, the daily focal type of seizures that occurs at any time.

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