IDENTIFICATION AND ANALYSIS OF GENETIC EPILEPSY AND EPILEPTIC ENCEPHALOPATHIES IN THE OUTPATIENT PRACTICE OF EPILEPSY SPECIALISTS

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ABSTRACT

Background: Given the significant share of gene mutations in the etiology of epilepsy, it is important for the practitioners to evaluate progress in this area.

Objective: To describe the spectrum of being detected gene mutations in patients with epilepsy or epileptic encephalopathy in clinical practice of neurologists specializing in epilepsy with an analysis of diagnosed epileptic syndromes, the characteristics of seizures, the timing of a genetic diagnosis, options and treatment efficacy.

Methods: The study included 100 patients (40 boys, 60 girls) with epilepsy/epileptic encephalopathy and a gene mutation identified. The average age was 6.9±5.1 years. Through remote access, epilepsy specialists filled out a specially designed unified table containing information from outpatient case history.

Results: In the outpatient practice of epilepsy specialists, there are patients with a wide range of gene mutations, the leading of which is a mutation in the SCN1A gene (15%). Nowadays, the main method (85%) of detection remains the next generation sequencing in the “Hereditary Epilepsy” panel. Years pass from the onset of the disease to the genetic diagnosis (Me - 3 years). In most cases, patients with severe (52% have epileptic encephalopathy, 88% have developmental disorders) and pharmacoresistant (mean amount of anti-epileptic drugs - 3.8±2.2, multitherapy -70%) syndromes have undergone genetic testing. In the treatment of these patients epileptologists are increasingly (52%) use alternative methods: steroids, ketogenic diet and others. The absence of seizures was observed only in 46% of patients.

Conclusion: Thus, in the outpatient practice of epileptologists of Russia, patients with a wide range of gene mutations are found. As a rule, these are patients with severe, therapy-resistant epileptic syndromes.

Keywords: Epilepsy, epileptic encephalopathy, genetics

Introduction

There is no doubt about the relevance of genetic testing in epilepsy.1,2,3 In Russia, there is also an increase in the number of genetic studies in epilepsy.7 However, the path from the onset of the disease to the genetic diagnosis remains sophisticated. Many patients with epileptic seizures fail or do not receive genetic testing at all.1 From a practical point of view, on-time diagnosis can limit the diagnostic search, the duration of which often provokes parental anxiety and unnecessary financial expenditures, it is necessary for calculating the risk of giving birth to a sick child in a burdened family and planning of preventive measures, improves the prognosis accuracy and can lead to targeted therapy.4,5,6

The interpretation of the results is believed to be carried out in collaboration with geneticists, only if the treating neurologist doesn’t have the sufficient experience and understanding of genetics.3 Russian practice shows that the management of these patients, including the selection and interpretation of genetic testing, often falls on the shoulders of neurologists-epileptologists. Therefore, it is important for the practitioner to evaluate progress in this area and prepare for the use of genetic testing in clinical practice.9

The aim of the study was to describe the spectrum of detectable gene mutations in patients with epilepsy or epileptic encephalopathy in everyday clinical practice, including analysis of diagnosed epileptic syndromes, characteristics of seizures, timing of the genetic diagnosis, treatment options and efficacy.

Methods

A multicenter descriptive retrospective study was conducted. Epileptologists from five cities of the Russian Federation (Tyumen, Novosibirsk, Yekaterinburg, Omsk, Volgograd)
Analysis of epileptic syndromes before and after genetic testing showed several significant points (Figure 1). In most cases, children with various epileptic encephalopathies underwent this investigation, and after the mutation was detected, the number of patients with this diagnosis increased. In the group of syndromes with febrile seizures, a redistribution towards the more severe Dravet syndrome also occurred. After investigation, the number of structural focal epilepsies, focal epilepsies of unknown etiology decreased. In general, the statement of the diagnosis changed: the term “genetic” was added, the prefix “probable” was removed. Specific names of the syndromes appeared, for example, autosomal dominant nocturnal frontal epilepsy and others (Pic. 1). Moreover, many etiological syndromes were established: Angelman syndrome - 4, Cornelia de Lange syndrome of various types - 4, Rett syndrome (typical / atypical) - 6 (4/2), neuronal ceroid lipofuscinosis of various types - 3, Lafor’s disease - 2, Boring-Opitz, Gallerwarden-Spatz, Coulin de Vries, Prader-Willi, Smith-Kingsmore, Phelan-Mtsermid syndromes - 1 each, autosomal recessive tape heterotopy -1, neurodegenerative disease with an accumulation of iron in the brain - 1.

Table 1. The spectrum and the ratio of genes with mutations (n=100, abs. numbers=%)

| Gene          | The number of patients |
|---------------|------------------------|
| SCN1A         | 15                     |
| CDKL5, PCDH19 | 5                      |
| MECP2, SMC1A, UBE3A | 4                   |
| GABRA1        | 3                      |
| CACNA1H, EPM2A, GRIN2B, KCNQ2, KIAA2022, MEF2C, PIQV, SCN2A, SCN5A, SCN8A, SLC2A1, SNRPN, TTP1, TRPM6 | 2   |
| ALDH7A1, ALG6, ASXL1, BPTF, CACNA1A, CASK, CHRNA4, CM14248, COL13A1, CSN2A, CYR4A4, DEPDPC3, DNM1, DYRK1A, EEF1A2, EML1, FLNA, FOLR1, GABRA6, GABRB3, GLDC, GLRA1, GNAO1, GRIA4, KANS1L1, KCNT1, MTOC, MYCPC, NSUN2, PTS, SCM2A, SNAR3, SETBP1, SNIP1, SPTAN1, SRPX2, STX1B, STXBP1, SYN1, SYNGAP1, SZT2, TBX1, TSC1, TSC2, WDR45, WWOX | 1   |

Table 2. Some clinical features of the observed group of patients (n=100, abs. number=%)

| Febrile seizures in debut                                      | 24 |
|----------------------------------------------------------------|----|
| Epileptic spasms (focal / generalized)                        | 43 |
| Bilateral tonic-clonic seizures                                | 42 |
| Focal motor seizures                                          | 23 |
| Tonic                                                           | 23 |
| Focal non-motor seizures                                      | 23 |
| With cessation of activity                                     | 32 |
| Myoclonic (focal / generalized)                                | 32 |
| The presence of epileptic statuses                            | 25 |
| Focal neurological symptoms                                    | 73 |
| Cognitive impairment                                           | 88 |
| Emotional & behavioral disorder                                | 61 |
| Brain MRI NIL                                                  | 63 |
| Slowing the main background activity                          | 65 |
| The presence of epileptiform activity                         | 90 |
| (regional - 34, diffuse - 26, combined - 30)                  |    |

Table 3. General efficacy of the therapy

| Level of effect                                            | Criterium                  | n=100 (abs. numbers=%) | Duration of effect |
|------------------------------------------------------------|----------------------------|------------------------|-------------------|
| Remission of attacks                                       | Absence ≥12 months         | 24                     | 2.8±2.0 years     |
| Control of attacks                                         | Absence <12 months         | 22                     | 4.4±2.8 months    |
| Significant reduction of frequency of attacks              | ≥50%                       | 20                     | -                 |
| No effect                                                  |                            | 34                     | -                 |
At the time of inclusion to the research, 97 patients were receiving antiepileptic drugs (AEDs), 2 had planned cancelation and 1 did not receive AEDs. Of these, only 30% are on monotherapy, 34% receive 2 AEDs, 30% 3 AEDs and 6% 4 antiepileptic drugs. On average, the number of AEDs used in patients in past medical history was 3.8 ± 2.2. Alternative therapies were used in half (52) patients. Of these, steroids were used in 37 patients (synthetic ACTH derivatives - 17, glucocorticosteroids - 20), with repeated courses - 20. A ketogenic diet was used in 20 patients, other types of diets (gluten-free casein-free / gluten-free / casein-free) - 10, vagus nerve stimulation - 6; resection surgery - 1, others (B6, folic acid, magnesium, acetazolamide) - 7.

Evaluation of the efficacy of therapy (table 3) showed that only 46% of patients managed to achieve the absence of seizures (24 - remission for more than a year, 22 - less than 1 year). In 54% of patients, seizures persist. Moreover, 26% of patients have never had a significant effect of therapy, the other 26% have had periods of absence of attacks, and the median relapse occurred in 0.6 years.

![Figure 1](image_url)

**Figure 1.** The statement of diagnoses and their ratio (%) before and after mutation detection

Note: EE - epileptic encephalopathy, FEUE - focal epilepsy of unknown etiology, GFE - genetic focal epilepsy, SFE - structural focal epilepsy, GEFS+ - genetic epilepsy, febrile seizures plus, E with MAA – epilepsy with myotonic-atomic attacks, GE with MAA – genetic epilepsy with myotonic-atomic attacks, GGE - genetic generalized epilepsy, PME - progressive myoclonus-epilepsy, NCL - neuronal ceroid lipofuscinosis, GE - genetic epilepsy, FA - febrile attacks, specific (autosomal dominant nocturnal frontal epilepsy, familial focal epilepsy with variable foci, X-linked epilepsy with behavioral disorders, B6-convulsions)

**Discussion**

In the described population, mutations in the SCN1A gene were most frequently detected, and were in 15 patients, which is consistent with all world and other Russian data. On the second place are the mutations in the CDKL5, PCDH19 genes, which were detected in 5 patients each, MECP2, SMC1A, UBEZA were in 4 patients each and GABRA1 were in 3 patients. Other Russian data showed that with epileptic encephalopathies, the second most detectable were mutations in the genes MECP2, responsible for the development of Rett syndrome, and TPP1, responsible for the development of neuronal ceroid lipofuscinosis. Foreign authors during EE show the leading mutations in the genes CDKL5, STXB1, KCNQ2.

Discussing the leadership in the use of sequencing on the diagnostic panel is most likely associated with economic feasibility, which is shown in many Russian publications. But changes in the ratio of diagnostic efficiency / cost of full-exome sequencing taking place in the world will probably lead this method to leading positions in Russia in the future too. The lack of confirmation of the mutation and its origin according to Sanger (inherited from parents / de novo) is also mainly due to the economic aspect. However, this fact indicates the possibility of errors in the interpretation of the clinical significance of the detected mutations by epileptologists, since in most patients it was carried out only by the similarity of the clinical picture.

Most of the obtained clinical data indicates that mostly children with a severe course of the disease underwent genetic testing: the prevalence of children with epileptic encephalopathies in the group; complicating the diagnosis after genetic testing: 73% of patients had focal neurological symptoms, 88% had cognitive impairment, 61% had emotional-behavioral disorders; all children had several types of seizures, 42% had bilateral tonic-clonic seizures, and 25% had convulsive status epilepticus. Pharmacological history shows that many of the patients included in the study met the criteria for pharmacoresistance.

The obtained figures of the efficacy of the treatment of genetic epilepsy and EE in everyday clinical practice are far from the target ILAE in 60-70%. Which also testifies in favor of the severity and resistance of genetic epilepsies and
EE in the observed group, despite the applied AED polytherapy (70%); alternative therapies; observation in specialized epileptological centers.

**Conclusion**

Thus, in the outpatient practice of epileptologists of the Russian Federation, patients with a wide range of gene mutations are found. To date, the leading detection method remains the NG-sequencing in the form of a diagnostic panel. Unfortunately, years pass from the onset of the disease to the genetic diagnosis. Given that in Russia, the main source of funding for genetic examinations is the personal funds of patients and their families, as a rule, these are patients with severe, therapy-resistant epileptic syndromes. Epileptologists use AEDs and, increasingly, alternative methods in the treatment of these patients. The authors believe that this analysis will improve the clinicians understanding in this field, since genetic testing can play an important role in taking care of patients with epilepsy.

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