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Iwona Terczyńska[1], Elżbieta Szczepanik[1], Kinga Duszyc[2,3], Paulina Górka[2], Renata Tataj[2] Dorota Hoffman-Zacharska[2,3]

GENETIC EPILEPSIES WITH FEBRILE SEIZURES PLUS: CLINICAL SPECTRUM OF POLISH PATIENTS WITH *SCN1A* MUTATION – PRELIMINARY REPORT*

PADACZKA GENETYCZNIE UWARUNKOWANA Z DRGAWKAMI GORĄCZKOWYMI PLUS: SPEKTRUM KLINICZNE U PACJENTÓW Z MUTACJĄ W GENIE *SCN1A* W POPULACJI POLSKIEJ – DONIESIENIE WSTĘPNE

[1]Neurology Clinic for Children and Adolescents; Institute of Mother and Child, Warsaw, Poland
[2]Department of Medical Genetics; Institute Mother and Child, Warsaw, Poland
[3]Institute of Genetics and Biotechnology, Warsaw University, Warsaw, Poland

Abstract

Diseases caused by mutations in SCN1A are currently named Genetic Epilepsies with Febrile Seizures Plus, and this term stands for expanded spectrum of syndrome previously called as GEFS+ (Generalized Epilepsy with Febrile Seizures Plus). SCN1A is the uniquely identified gene directly linked to specific type of epilepsy, and its testing has been included in the screening processes.

The aim: *To diagnose and describe epileptic syndromes caused by SCN1A mutations.*

Material and methods: *203 patients were included in the screening process with suspected SCN1A mutation, based on clinical features and family history. Study group was selected based on inclusion and exclusion criteria and then preliminary epilepsy diagnosis was verified using ILAE classification. Molecular testing to screen SCN1A mutations was performed in the study group.*

Results: *Mutations were detected in 57 cases. Majority of patients (50 cases – 87.5%) suffered from Dravet syndrome, 8.8% (5 cases) were diagnosed as GEFS+, 3% as vaccines encephalopathy and Panayotopoulous syndrome. Mutations were not detected in children with isolated febrile seizures, family febrile seizures nor in patients with myoclonic – astatic epilepsy.*

Conclusions: *Frequency of mutations in SCN1A in Dravet syndrome and GEFS+ in Polish populations are similar to other countries. Diagnostic clinical criteria are currently insufficient to draw precise diagnosis. There is a strong need to establish clinical criteria for molecular testing and this topic will be investigated in the future.*

Key words: Dravet Syndrome, GEFS+, phenotype variability, *SCN1A*

Streszczenie

Grupa jednostek chorobowych, których podłoże stanowią mutacje genu SCN1A określana jest jako padaczka genetycznie uwarunkowana z drgawkami gorączkowymi plus. SCN1A to w chwili obecnej jeden z nielicznych zidentyfikowanych genów sprawczych dla padaczki, którego analiza została włączona do grupy rutynowych badań diagnostycznych.

Celem *projektu była identyfikacja i charakterystyka kliniczna zespołów padaczkowych ze spektrum padaczek, u podłoża, których leżą mutacje w genie SCN1A.*

Materiał i metody: *Badaniem objęto 203 pacjentów, u których na podstawie obrazu klinicznego i wywiadu rodzinnego podejrzewano mutację w genie SCN1A. Grupę badaną wyłoniono w oparciu*

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kryteria włączenia/wyłączenia następnie zweryfikowano rozpoznanie wstępne padaczki w oparciu o Międzynarodową Klasyfikację Padaczek i Zespołów Padaczkowych. U wszystkich probandów przeprowadzono analizę molekularną genu SCN1A.

Wyniki: *Patogenne mutacje wykryto u 57 osób. Wśród nich przeważali pacjenci z zespołem Dravet – 50 dzieci (87,5%), 8,8% (5 dzieci) stanowili probanci z rozpoznaniem padaczka uogólniona z drgawkami gorączkowymi plus, a 3% z encefalopatią poszczepienną i zespołem Panayotopoulousa łącznie. Mutacji nie wykryto u dzieci z drgawkami gorączkowymi izolowanymi i rodzinnymi, ani u pacjentów z padaczką miokloniczno-astatyczną.*

Wnioski: *Wyniki badania wykazały, że częstość występowania mutacji w genie SCN1A w zespole Dravet i padaczce genetycznie uwarunkowanej z drgawkami gorączkowymi plus w populacji polskiej jest podobna jak w innych krajach, oraz że stosowane powszechnie w diagnostyce padaczki kryteria kliniczne są już za mało dokładne i nie zawsze wystarczające do postawienia precyzyjnego rozpoznania syndromologicznego, co rodzi konieczność ustalenia de novo kryteriów klinicznych kwalifikujących na badania molekularne.*

Słowa kluczowe: zespół Dravet, GEFS+, zmienność fenotypu, *SCN1A*

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INTRODUCTION

International Classification of Epilepsies and Epileptic syndromes is still developing, because of ongoing knowledge evolvement. Progress in clinical and laboratory diagnostics, neuroimaging, and first of all, in molecular diagnostics facilitates discovery and description of the new epileptic syndromes and the new features within already known syndromes (1).

SCN1A gene (MIM 182389), encoding type 1 voltage-gated sodium channel α-subunit ($Na_V1.1$), is one of the few identified causative epileptic genes, the analysis of which has been incorporated into routine diagnostic tests. This gene is located on chromosome 2 in *locus* 2q24.3. Diseases caused by *SCN1A* mutations are currently named Genetic Epilepsies with Febrile Seizures Plus (GEFS+), and this term stands for expanded spectrum of syndrome previously called Generalized Epilepsy with Febrile Seizures Plus, and includes the range of clinical spectrum from – benign febrile seizures (FS; MIM 604403), till – intractable epileptic syndromes (epileptic encephalopathies), such as Severe Myoclonic Epilepsy of Infancy/Dravet Syndrome (SMEI/DS) also called Early Infantile Epileptic Encephalopathy type 6 (EIEE6; MIM 60720), Intractable Childhood Epilepsy With Generalized Tonic-Clonic Seizures (ICE-GTC), cryptogenic generalized epilepsy and cryptogenic focal epilepsy. Doose syndrome, Lennox-Gastaut syndrome, West syndrome, Rassmusen syndrome, Panayiotopoulous syndrome and last but not least post-vaccination encephalopathies might be *SCN1A* gene mutation related (2,3). Additionally, mutations in this gene have been found in hemiplegic migraine and in familial autism (4).

Prevalence of *SCN1A* mutation related seizures are not precisely known. More than 700 types of mutations in this gene have been found, however the full clinical spectrum have not been described (5).

Detection of the molecular defect is crucial from diagnostic, prognostic, and therapeutic point of views. *SCN1A* mutations lead to dysfunction of inhibitory GABA neurons. Confirmation of this gene mutation is an indication to GABA receptor drugs introduction, such as clobazam, stiripentol, valproate, diazepam, topiramate. Sodium channel blockers such as carbamazepine, lamotrigine, oxcarbazepine are contraindicated, as well vigabatrine which might trigger epileptic seizures (6, 7).

Identification of the mutations in the *SCN1A* gene is also important from genetic counselling point of view. *SCN1A*-related disorders are autosomal dominant. Majority of mutations in the most severe syndromes (such as Dravet syndrome) are *de* novo and syndrome appearance in siblings might be caused by mosaicism in one of the parent. Therefore molecular testing in severe syndromes is crucial for the future family prognosis (8, 9). Extensive studies on *SCN1A*-related disorders have been run world-wide for several years and the presented research has been the first focused on this topic in Poland so far.

AIM

The aim of research was to identify and describe epileptic syndromes caused by *SCN1A* mutations.

MATERIALS AND METHODS

203 patients, 103 girls and 100 boys from 4 months to 16 years old, referred to the Institute of Mother and Child in years 2011-2013 for *SCN1A* gene mutation testing, were included in the study. Study group was selected using inclusion and exclusion criteria (Table I), prepared by the authors based on current data from the literature (1, 2, 4, 8, 9). There was a need to run in-depth medical history and additional tests in some cases. Preliminary epilepsy diagnosis was verified using ILAE Classification (Table II) (10).

The *SCN1A* gene analysis covered the point mutations identification (direct sequencing of all exons and exons/

Table I. Inclusion and exclusion criteria to the research.

Tabela I. Kryteria włączenia/wyłączenia do badania.

Inclusion criteria: ***Kryteria włączenia:***	
1.	Generalized epilepsy with febrile seizures plus *Padaczka uogólniona z drgawkami gorączkowymi plus*
2.	Severe myoclonic epilepsy in infancy (Dravet syndrome) *Ciężka miokloniczna padaczka niemowląt (Zespół Dravet)*
3.	Severe myoclonic epilepsy in infancy with atypical clinical course *Ciężka mioklonicznа padaczka niemowląt o nietypowym przebiegu*
4.	Intractable epilepsy in infancy with generalized tonic-clonic seizures *Lekooporna padaczka dziecięca z napadami uogólnionymi toniczno-klonicznymi*
5.	Cryptogenic generalized epilepsy* *Skrytopochodna padaczka uogólniona**
6.	Cryptogenic focal epilepsy* *Skrytopochodna padaczka ogniskowa**
7.	Severe multifocal epilepsy in neonates *Ciężka niemowlęca padaczka wieloogniskowa*
8.	Post-vaccination epileptic encephalopathies *Encefalopatie padaczkowe poszczepienne*
9.	Epilepsy with myoclonic-astatic seizures (Doose syndrome) *Padaczka z napadami mioklonicznо-astatycznymi (zespół Doosego)*
10.	Epileptic syndromes with unknown etiology (criptogenic), such as Lennox-Gastaut syndrome, West syndrome, familial temporal epilepsy with febrile seizures, Rassmunsen syndrome, Panayiotopoulos syndrome* *Zespoły padaczkowe o nieustalonej etiologii (skrytopochodne), takie jak zespół Lennoxa-Gastaut, zespół Westa, rodzinna padaczka skroniowa z drgawkami gorączkowymi, zespół Rassmusena, zespół Panayiotopoulosa**
11.	Other epileptic encephalopathies with unknown etiology, not meeting above criteria, especially when syndrome onset occurs within first two years of life with existing tendency to trigger seizures during fever *Inne encefalopatie padaczkowe o nieustalonej przyczynie, nie spełniające kryteriów diagnostycznych ww. zespołów padaczkowych, szczególnie z początkiem zachorowania w pierwszych dwóch latach życia dziecka, jeśli istnieje tendencja do prowokowania napadów padaczkowych zwyżką ciepłoty ciała*
Exclusion criteria: ***Kryteria wyłączenia:*** **Epilepsy and epileptic syndromes with known etiology:** ***Padaczki i zespoły padaczkowe o znanej etiologii, m.in.:***	
1.	Post-traumatic epilepsies, post-infection epilepsies, epilepsies related to hypoxic-ischemic encephalopathies, epilepsies related to brain tumor or CNS defects or phakomatoses *Padaczki pourazowe, poinfekcyjne, w przebiegu encefalopatii niedotlenieniowo-niedokrwiennej, guza mózgu, wad OUN, fakomatoz*
2.	Epileptic encephalopathies in the course of metabolic, neurodegenerative disorders with known etiology: storage diseases, peroxisomal disorders, mitochondrial disorders, fatty acid oxidation disorders, disorders of ketolysis, creatine metabolism diseases, organic acidosis (i.e. Canavan disease), biotinidase deficiency, neurotransmitter disorders (i.e. folinic acid-responsive seizures, pyridoxine-dependent seizures), disorders of carbohydrate metabolism (GLUT1 deficiency syndrome), purine and pyrimidine disorders and nucleotide metabolism disorders *Encefalopatie padaczkowe w przebiegu chorób metabolicznych i neurozwyrodnieniowych o ustalonej etiologii: m. in. choroby spichrzeniowe, choroby peroksyzomalne, choroby mitochondrialne, zaburzenia oksydacji kwasów tłuszczowych, zaburzenia ketolizy, zaburzenia metabolizmu kreatyny, kwasice organiczne (np. choroba Canavana), niedobór biotynidazy, zaburzenia neurotransmiterów (np. drgawki odpowiadające na kwas folinowy, pirydoksynozależne), zaburzenia metabolizmu węglowodanów (np. zaburzenia transportu glukozy GLUT1), zaburzenia puryn i pirymidyn oraz metabolizmu nukleotydów*
3.	Benign, idiopathic epileptic syndromes during first 2 years of life i.e. benign infantile epilepsy, benign myoclonic infantile epilepsy *Łagodne, idiopatyczne zespoły padaczkowe ujawniające się w pierwszych 2 latach życia dziecka, jak np. łagodne drgawki niemowlęce, łagodna mioklonicznа padaczka niemowląt*

*especially in cases with positive febrile seizures history, with GEFS+ epileptic syndromes, familial hemiplegic migraine, familial autism

**szczególnie w tych przypadkach, gdzie wywiad osobniczy i rodzinny obciążony jest występowaniem drgawek gorączkowych, zespołami padaczkowymi ze spektrum GEFS +, rodzinną migreną hemiplegiczną, rodzinnym autyzmem*

Table II. Preliminary and after verification diagnosis, number of mutations.

Tabela II. Rozpoznania wstępne i po weryfikacji, liczba patogennych mutacji.

Diagnosis ***Rozpoznanie***	**Preliminary** ***Wstępne***	**After verification** ***Po weryfikacji***	***SCN1A* mutations** ***Mutacje w genie SCN1A***
	n	**n**	**n**
Severe myoclonic epilepsy of infancy/Dravet syndrome *Ciężka mioklonicza padaczka niemowląt, Z. Dravet*	144	69	50 (+2?)
Febrile seizures *Drgawki gorączkowe*	10	3	–
Febrile seizures plus *Drgawki gorączkowe plus*	6	14	–
Familial febrile seizures *Drgawki gorączkowe rodzinne*	8	2	–
Generalized epilepsy with febrile seizures plus *Padaczka uogólniona z drgawkami gorączkowymi plus*	17	32	5
Myoclonic-astatic epilepsy, Doose syndrome *Padaczka miokloniczno-astatyczna, Z. Doose*	4	7	–
Benign occipital epilepsy, Panayotopoulous syndrome *Łagodna padaczka potyliczna, Z. Panayotopoulousa*	1	3	1
Temporal epilepsy *Padaczka płata skroniowego*	1	1	–
Hemiplegic migraine *Migrena połowiczo-porażna*	1	1	–
Post-vaccination encephalopathy *Encefalopatia poszczepienna*	1	5	1
Juvenile myoclonic epilepsy, Janz syndrome *Młodzieńcza padaczka mioklonicza, Z. Janza*	3	5	–
Absence epilepsy *Padaczka z napadami nieświadomości*	1	1	–
West syndrome – Lennox-Gastaut syndrome *Z. Westa - Z. Lennoxa-Gastaut*	1	9	–
Pseudo Lennox *Pseudo Lennox*	1	–	–
Rassmusen syndrome *Z. Rassmusena*	1	1	–
Unclassified intractable epilepsy *Padaczka oporna na leczenie, niesklasyfikowana*	2	19	–
Epilepsy with continuous spike-waves during slow-wave sleep *Padaczka z ciągłymi wyładowaniami we śnie*	–	1	–
Benign neonatal febrile seizures *Łagodne drgawki niemowlęce*	–	4	–
Nocturnal frontal lobe epilepsy *Padaczka czołowa nocna*	–	1	–
Early-onset neonatal epileptic encephalopathy *Wczesnoniemowlęca encefalopatia padaczkowa*	–	15	–
Rolandic epilepsy *Padaczka rolandyczna*	–	1	–
Cryptogenic focal epilepsy *Skrytopochodna padaczka ogniskowa*	–	1	–
Fejerman syndrome *Zespół Fejermana*	–	1	–
Autoimmunologic encephalitis *Autoimmunologiczne zapalenie mózgu*	–	3	–
CNS defect *Wada OUN*	–	2	–
Other genetic diseases *Inne zespoły uwarunkowane genetycznie*	–	2	–

introns boundaries) and the gene rearrangements – deletion/duplication investigation (Multiplex Ligation Probe Amplification, using the commercially available MLPA test SALSA P137-*SCN1A,* MRC-Holland*).* Sequencing was performed for all referred patients, MLPA analysis only for the patients with clinical diagnosis of Dravet or Dravet Borderline Syndrome.

The pathogenicity of identified mutations was checked by analysis of its occurrence in the Human Gene Mutation Database Professional (http://www.biobase-international.com) and specialistic *SCN1A* Variation Database (http://www.molgen.ua.ac.be/SCN1AMutations) and *SCN1A*-InfoDataBase (http://www.scn1a.info). The impact of the new missense mutations on protein structure and function were analyzed by PolyPhen-2 v2.1/HumanVar model (http://genetics.bwh.harvard.edu/pph2) and Mutation Taster (http://www.mutationtaster.org) software.

RESULTS

SCN1A gene mutations were detected in 59 patients, including two cases with mutations of unknown role (the latter has been withdrawn from final statistical analysis). The final assessment was performed in 57 patients – most of these patients suffered from Dravet syndrome (n=50; 28% of total included patients, 35% of the group with preliminary SMEI diagnosis and 87.5% of the group with finally verified Dravet syndrome). GEFS+ was found in 5 patients (8.8%), including one (from pair of twins) with febrile seizures plus. Febrile seizures, febrile seizures plus, epilepsy and migraine were observed in remaining four families. *SCN1A* mutations were also detected in one patient with post-vaccination encephalopathy (1.75% of total included patients and 20% with the final diagnosis) and in one with Panayotopoulous syndrome (1.75%). Mutations were not found in patients with isolated febrile seizures and familial febrile seizures, nor in patients with myoclonic-astatic epilepsy and other rare cases.

DISCUSSION

Epileptic syndromes caused by *SCN1A* mutation are heterogenic clinical group with broad range of symptoms, from – febrile seizures, generalized epilepsy with febrile seizures plus, until SMEI/Dravet syndrome, intractable child epilepsy with generalized tonic-clonic seizures. The latter two, with poor clinical prognosis, are accompanied by mental retardation.

The phenotype of the *SCN1A*-related seizure disorders is not specific enough, especially at the onset of disease, to allow confident diagnosis. Gene molecular testing may help in differential diagnosis of epileptic syndromes, although they might be not always informative, especially in relation to the syndrome severity. Diagnosis should be confirmed within joint clinical and genetic team, taking into account EEG findings, clinical features in the context of the type of identified mutation, its heritability and patient's family history (11).

SCN1A gene mutations incidence in GEFS+ is estimated between 8 to 10% and in Dravet syndrome – 70-85% (11, 12, 13). Similar results were revealed in this research – 8.8% and 87.5% respectively – but as shown in Table II, these data correspond to assessed research group after additional, final syndromology verification.

In our research, preliminary diagnosis of Dravet syndrome was amended in 75 children (36% of total assessed patients). During clinical assessment large group of patients were identified as unclassified intractable epilepsy (9.3%), and early infantile epileptic encephalopathy other than type 6 (7.3%). Above findings show distinctly, that currently used clinical criteria in medical practice are not precise and sufficient enough to perform differential diagnosis. It is complicated by the fact the boundaries between syndromes are sometimes blurred eg. between Dravet syndrome and GEFS+ or ICE-GTC. *SCN1A* mutations appear in approximately 70% of the latter (13), but they were not found in this research. Mutations were also not described in children with isolated febrile seizures, familial febrile seizures, myoclonic-astatic epilepsy, nor in rare cases with *SCN1A* gene mutation, except 1 case of Panayotopoulous syndrome.

It is currently not recommended to perform routine testing of the *SCN1A* gene in children with febrile seizures, because mutations of the gene in this disease are detected very rarely. It is worth to consider whether molecular testing should be considered in children with GEFS+ diagnosis since mutations are seen in 1/10 of patients suffering from this syndrome and in cases with less typical phenotype, even there is strict link between seizures and hyperthermia. Scientists views are mixed in this matter (13).

Another topic relates to co-occurrence of *SCN1A* mutations with post-vaccination encephalopathy. In recent years, many opinions presented direct causal relationship between vaccination and seizures and/or delay in psychomotor development, despite of the fact that such link was not confirmed (6, 11). This topic was elaborated by many researchers, including *Berkovic* et al. (14), who studied 14 cases (age: 2.5 to 47 years old) with suspected post-vaccination encephalopathy in which seizures appeared within 72 hours after vaccination. Seizures occurred in 13 patients after DTP vaccination and in 1 after immunization against polio. Re-assessment revealed that Dravet syndrome was present in 12 patients and Lennox-Gastaut syndrome in 2 cases. *SCN1A* mutations were confirmed in 11 patients with Dravet syndrome. Expanded genetic testing (including parents) was performed in 9 cases – all children carried *de novo* mutations. Such results provide the proof of not observing prior seizures, which was misinterpreted as direct link between immunization and encephalopathy. This study shows, that many cases of vaccination related epileptic encephalopathies were caused by the presence of the *SCN1A* gene mutation, and symptoms appearance would have happened independently of vaccination.

In the analyzed group, *SCN1A* mutations were found in 1 of 5 patients with post-vaccination encephalopathy diagnosis. This fact does not contradict above conclusions, but it is a strong recommendation for further in-depth analysis to look for underlying causes. Vaccination might be a trigger mechanism for encephalopathies in the course of different diseases, including these caused by mutations in other genes i.e. CDKL-5 or ARX (15).

Clinical features of diseases with underlying genetic pathology are dependent on existing 'molecular background', however confirmation of clinical phenotype in young children is often very difficult, especially in the initial phase, due to similar brain reaction for different damaging factors at this age. This fact may suggest appearance of patients with symptomatic epilepsy in studied group.

CONCLUSIONS

The full diagnosis of epilepsy and epileptic syndromes dependent on *SCN1A* mutations based on clinical features only is very tough, and is some case even impossible. This is caused, among other things, due to phenotypic diversity of epilepsy occurring within the same family, from mild cases (eg. febrile seizures) till severe cases (eg. Dravet syndrome) and the heterogeneity of epileptic syndromes.

The conducted study was preliminary, and the results revealed the incidence of *SCN1A* mutations in Dravet syndrome and GEFS+ in the Polish population is similar to that in other countries. Commonly used current clinical criteria in epilepsy diagnosis are too imprecise and, therefore, not always sufficient to confirm final accurate diagnosis. There is a strong need to develop new clinical criteria selecting eligible patients for molecular testing and this will be a topic for further studies.

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Address for correspondence:
Iwona Terczyńska
Klinika Neurologii Dzieci i Młodzieży,
Instytut Matki i Dziecka
ul. M. Kasprzaka 17a, 01-211 Warszawa, Poland
phone: (+48 22) 32-77-307
e-mail: iwonaterczynska@onet.eu