ECRONICON OPEN ACCESS

EC PSYCHOLOGY AND PSYCHIATRY
Research Article

Three Russian Cases of Epilepsy in Infancy with Migrating Focal Seizures due to KCNT1 Mutations (Early Infantile Epileptic Encephalopathy Type 14)

Kholin AA[1,2]*, Zavadenko NN[1], Kholina EA[1], Fedonyuk ID[1,2], Il`ina ES[1,2], Antonets AV[3], Mukhin K Yu[4] and Malov AG[5]

[1]Neurology, Neurosurgery and Medical Genetics Department of Pediatric Faculty, Pirogov Russian National Research Medical University of the Russia Ministry of Health, Moscow, Russia

[2]Department of Psychoneurology N2, Russian Children Clinical Hospital of Pirogov Russian National Research Medical University of the Russia Ministry of Health, Moscow, Russia

[3]Center of Medical Genetics "Genomed", Moscow, Russia

[4]Svt. Luka's Institute of Child Neurology and Epilepsy, Moscow, Russia

[5]Department of Neurology named after V.P. Pervushin, Perm State Medical University named after Academician E.A. Wagner (PSMU), Perm, Russia

***Corresponding Author**: Kholin AA, Neurology, Neurosurgery and Medical Genetics Department of Pediatric Faculty, Pirogov Russian National Research Medical University of the Russia Ministry of Health, Moscow, Russia.

Received: October 17, 2019; **Published:** October 31, 2019

Abstract

Early infantile epileptic encephalopathy type 14 due to KCNT1 gene mutations had clinical and EEG manifestation of epilepsy of infancy with migrating focal seizures (EIMFS). In three unrelated Russian girls - M.V., 3 years and 3 month old, T.V., 9 month old and M.U., 5 month old were newly identified de novo mutations in KCNT1 gene. The first girl has previously not described mutation in 12 exome KCNT1 gene (chr9:138656907C>T) with amino acid substitution Arg356Trp. The second girl has renowned mutation in 11 exome KCNT1 gene (chr9:138651532G>A) with amino acid substitution Gly288Ser (OMIM: 608167.0010). And the third girl has previously not described mutation in 15 exome KCNT1 gene (chr9:138660712A>G) with amino acid substitution in 480 protein position (Asp480Gly). Girl M.V. had seizure onset at the age of 4 month with seizures of behavior arrest and tonic versive. Girl T.V. developed seizures at 4,5 month in the manner of behavior arrest and ophthalmo-clonic seizures with hyperemia of face. Girl M.U. had neonatal seizures with bilateral tonic-clonic seizures, cyanosis and then developing status epilepticus of alternant hemiconvulsive seizures. Further all the presented children developed polymorphic seizures of multiregional genesis up to migrating status epilepticus with typical electro-clinical pattern of EIMFS. So, it seems that KCNT1 is a major disease-associated gene for this rare severe epileptic syndrome.

Keywords: *Epilepsy of Infancy with Migrating Focal Seizures; Early Infantile Epileptic Encephalopathy Type 14; KCNT1 Gene*

Introduction

Epileptic encephalopathies are the group of pathological conditions of various etiologies, which are manifested by neurocognitive deficiency and in which the epileptiform abnormalities themselves are believed to contribute to the progressive disturbance in cerebral function [1]. The most severe forms of epileptic encephalopathies are their early infantile forms, leading not only to intellectual, but often to pronounced disturbances of motor functions. Until relatively recently several decades ago, infantile epileptic encephalopathies had exclusively clinical-electroencephalographic classification. By the time 2016 were identified and OMIM database had contained 35 genes responsible for the occurrence of early infantile epileptic encephalopathy (EIEE), and also differentiated approaches to therapy were

developed for a number of mutations [2]. Currently, by 2019, the International database of Online Mendelian Inheritance in Man (OMIM) has already included 75 genetic variants of EIEE with an identified monogenic type of inheritance, their search is constantly ongoing, and the OMIM database is constantly updated. Of the 75 types of EIEE, 38 variants with autosomal dominant inheritance type, 30 variants with autosomal recessive type, 4 variants have X-linked recessive and 3 variants have X-linked dominant inheritance type [3].

Early infantile epileptic encephalopathy (EIEE) type 14 with the phenotype number #614959 according to the OMIM classification, is caused by a mutation of the gene KCNT1. The KCNT1 gene encodes a sodium-activated potassium channel that is widely expressed in the nervous system. Activity of this channel contributes to the slow hyperpolarization that follows repetitive firing. KCNT1 gene is assigned the Gene/Locus MIM number #608167 and is located at locus 9q34.3. The first clinical description of EIEE 14 type and the first four variants of identified mutations of the KCNT1 gene belong to Barcia G., *et al*. (2012) [4]. Mutations of the KCNT1 gene have an autosomal dominant type of inheritance and the clinical cases described in the world literature are caused by de novo mutations. Clinically EIEE 14 type is manifested by migrating focal seizures in infancy.

Epilepsy of infancy with migrating focal seizures (EIMFS)-is rare and usually unrecognized epileptic syndrome of infancy with seizure onset in the first 6 months of life, characterized by the presence of almost constant seizures starting from various independent foci in both hemispheres and delayed psychomotor development. The first publication was presented by G. Coppola and colleagues in 1995 on the basis of neuropediatric Department of Rene Descartes University (Paris) with clinical observation of 14 infants of both sexes with previously undescribed epileptic syndrome characterized by almost continuous multifocal seizures [5]. O. Dulac in 2005 summarized 24 patients follow-up in the Saint Vincent de Paul hospital in Paris [6]. The authors who described the first cases, as well as in the most world publications, this form of epilepsy is defined as "malignant migrating partial seizures in infancy (MMPSI)". Taking into account the undesirability of using such terms as "malignant" and "partial" in the definition of epileptic syndromes, the International League Against Epilepsy (ILAE), according to the 2010 draft and the 2017 adopted classification, defines this form of epilepsy as "epilepsy of infancy with migrating focal seizures" in the group of developmental and epileptic encephalopathies, as well as in the subgroup of electro-clinical syndromes of infancy [7]. Taking into consideration the contributions of scientists who first described this form of epilepsy (G. Coppola) and gave the most detailed description of clinical and neurophysiological criteria (O. Dulac), the following definition is proposed: Coppola-Dulac syndrome [8].

Aim of the Study

The aim of the study was analysing the genetic, clinical and neurophysiological data of early infantile epileptic encephalopathy type 14 due to KCNT1 gene mutations in Russian population among the patients suffered from epilepsy of infancy with migrating focal seizures.

Material and Methods

At the period of 2017 - 2019 were revealed and investigated 3 non-relative Russian girls with clinical characteristics of epilepsy in infancy with migrating focal seizures (EIMFS) with identification of mutations in KCNT1 gene. Clinical, anamnesis and laboratory data were analyzed. Was obtained DNA sequencing - panel "Hereditary epilepsy" (Next Generation Sequencing on platform IlluminaNextSeq 500, USA). Dynamical video-EEG monitoring investigation was done by "Encephalan-Video" RM-19/26 ("Medicom MTD", Russia).

Results

In three unrelated Russian girls - M.V., 3 years and 3 month old, T.V., 9 month old and M.U., 5 month old were newly identified de novo mutations in KCNT1 gene. The girl M.V. has previously not described mutation in 12 exome KCNT1 gene (chr9:138656907C>T) with amino acid substitution of arginine on tryptophan in 356 position (Arg356Trp). The girl T.V. has renowned mutation in chromosome 9: 138651532G>A with amino acid substitution of glycine to serine in 288 position - Gly288Ser (OMIM: 608167.0010). The girl M.U. has previously not described mutation in 15 exome KCNT1 gene (chr9:138660712A>G) with amino acid substitution of asparagine to glycine in 480 protein position (Asp480Gly). Patients characteristics are combined in table 1.

Patients	M.V.	T.V.	M.U.
Gender	Female	Female	Female
Age at the last observation	3 years and 3 months	9 months	5 months
Defective gene	KCNT1	KCNT1	KCNT1
Mutation variant (position)	chr9:138656907C>T	chr9:138651532G>A	chr9:138660712A>G
Amino acid change	Arg356Trp	Gly288Ser	Asp480Gly
Exone	12	11	15
OMIM classification of allelic variant	Not previously described	608167.0010 Ishii., *et al*. (2013)	Not previously described
Age of seizure onset	4 months	4,5 months	1-st day
First seizure type	behavior arrest and tonic versive	behavior arrest and ophthalmo-clonic seizures with hyperemia of face	bilateral tonic-clonic
Seizure types	minor motor, dialeptic, versive, asymmetric tonic, serial extensor spasms, tonic-autonomic seizures with apnea and cyanosis, bilateral tonic with hyperemia, tonic seizures with alternating clonic component, bilateral tonic-clonic seizures	minor motor, dialeptic, ophthalmoclonic, focal myoclono-clonies in the left extremities, autonomic seizures, tonic spasms, asymmetric tonic versive seizures, inhibitor seizures with ictal paresis	bilateral tonic-clonic, tonic-autonomic seizures cyanosis, alternating hemiconvulsions, serial tonic spasms, ophthalmotonic, asymmetric tonic and versive seizures
Status neurologicus	Diffuse hypotonia, tetraparesis, severe delay of psycho-motor development	Plagiocephaly, diffuse hypotonia, delay of psycho-motor development	Diffuse hypotonia, delay of psycho-motor development
EEG	Multifocal ictal patterns, multifocal independent spike-wave foci (MISF) pattern	Continuous multifocal ictal patterns, predominantly from different regions of right hemisphere and also left frontal	Continuous multifocal ictal patterns, multifocal independent spike-wave foci (MISF) pattern
Neurovisualization	Moderate diffuse atrophy	Subatrophy with moderate delay in myelination	Subatrophy with moderate delay in myelination
Non-effective AEDs	valproates, lamotrigine, topiramate, levetiracetam, oxacarbazepine, ethosuximide, zonisamide, benzodiazepines (frisium) and corticosteroids	valproates and corticosteroids	valproates, levetiracetam and corticosteroids
Aggravation on AEDs	-	levetiracetam, oxcarbazepine, pagluferalum-1 (phenobarbital)	oxcarbazepine
Moderate effective AEDs combination	pagluferalum-1 (phenobarbital) + rufinamide	nitrazepam + topiramate	phenobarbital + topiramate

Table 1: *Clinical and genetic finding in three Russian cases of EIMFS/MMPSI due to KCNT1 mutations (EIEE type 14).*

Girl M.V. had seizure onset at the age of 4 month with seizures of behavior arrest and tonic versive. Girl T.V. developed seizures at 4,5 month in the manner of behavior arrest and ophthalmo-clonic seizures with hyperemia of face. Girl M.U. had neonatal seizures with bilateral tonic-clonic seizures, cyanosis and then developing status epilepticus of alternant hemiconvulsive seizures. Further all the presented children developed polymorphic seizures of multiregional genesis up to migrating status epilepticus with typical electro-clinical pattern of EIMFS/MMPSI.

The typical electroencephalographic pattern is presented on figure 1.

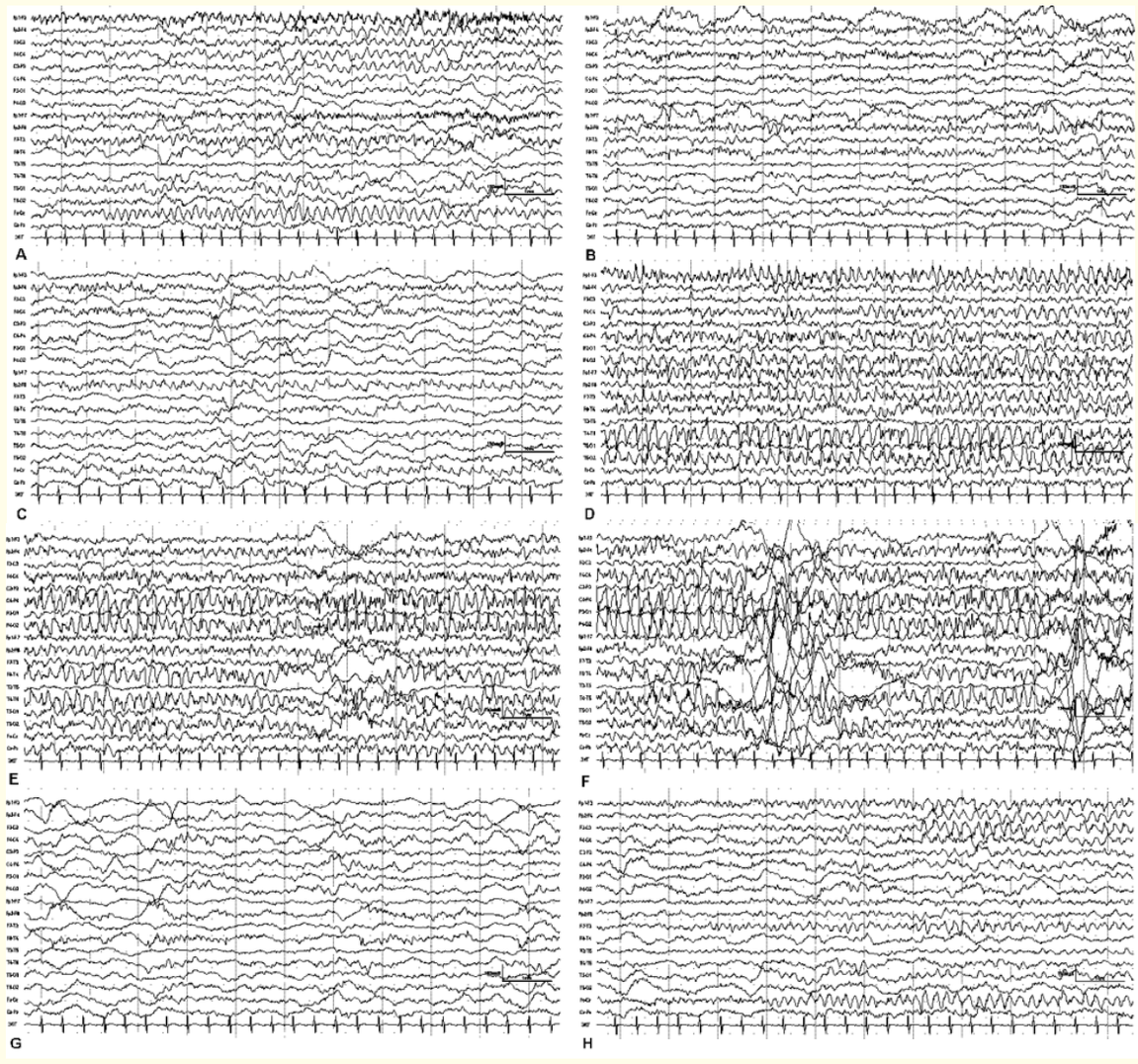

Figure 1: *Patient T.V., girl, 9 months old. Early infantile epileptic encephalopathy type 14. EEG recording during status epilepticus of focal seizures inhibitor, minor motor types and also tonic with versive left-side component.*

A: Appearance of regional ictal EEG pattern in left frontal region in the manner of regular sawtooth activity of the alpha-1-subdiapasone with transition to the theta-diapasone with bilateral spreading.

B: Change of lateralization of ictal activity in frontal regions on right-side in the manner of fast epileptiform activity with inclusion of spikes and joining the arcuate and sawtooth alpha- and theta-forms; in the left frontal region ictal pattern is superimposed on the irregular delta-slowing.

C: Temporary "subsiding" of ictal pattern in the left frontal region. Ictal arcuate and sawtooth activity in right hemisphere with frontal accentuation involves temporal regions, and also observed a diffuse increasing of delta-waves.

D: Diffuse spreading of ictal epileptiform activity with the inclusion of multiple spikes and regular fast spike-wave complexes. Is observed an independent combination of regional ictal patterns in right posterior temporal region and in left frontal regions.

E: Ictal pattern dominates in the right parietal-temporal region with the clinical expression in left-sided versive component of the seizure.

F: Ictal pattern in the right parietal-temporal-frontal region with the appearance of cluster spasms with the left-sided versive component.

G: Fragmentation of ictal pattern in the right frontal-temporal-parietal region with the appearance of irregular delta-slowing.

H: Reactivation of ictal activity in the left frontal region with the right-side versive component of the seizure.

The following variants were noted in the structure of seizures kinematics: Patient M.V., female, developed minor motor, dialeptic, tonic versive seizures with alternative lateralization (predominantly right side with raising of right hand and version of head to the right), serial extensor tonic spasms, tonic-autonomic seizures with apnea and cyanosis, bilateral tonic with flushing of the skin, hypomotor with oral automatisms, asymmetric tonic seizures with clonic component of alternating lateralization and transfer into a bilateral tonic-clonic seizures, as well as the so-called tonic-vibratory seizures following the clusters of tonic spasms.

The girl T.V. had hypomotor seizures with ophthalmoclonia and facial hyperemia, focal myoclono-clonies in the left extremities, asymmetric tonic versive seizures with alternative lateralization, tonic spasms, inhibitor seizures with ictal paresis of the extremities.

And the girl M.U. had neonatal convulsions with bilateral tonic-clonic seizures, cyanosis, with the subsequent developing of status epilepticus with alternating hemiconvulsions, serial tonic spasms, ophthalmotonic and alternating asymmetric tonic and versive seizures.

Magnetic resonance imaging on 1,5 Tl devices in our patients did not reveal dysplastic changes in the brain, as well as any gross structural changes-only subatrophy with moderate delay in myelination parameters was observed.

Antiepileptic drug therapy in our patients demonstrated pharmacoresistance with the inability to achieve clinical remission of seizures. Nevertheless, we are trying continue attempts of AEDs taking into account domestic and international experience, including the possibility of using quinidine. Girl M.V. (3 years and 3 month old) demonstrated resistance to valproate, lamotrigine, topiramate, levetiracetam, oxacarbazepine, ethosuximide, zonisamide, benzodiazepines and corticosteroids, but a moderate positive effect on the combination of barbiturates (pagluferal I) 37,5 mg x 2 times daily in combination with rufinamide (inovelon) 150 mg x 2 times daily. T.V. (9 month old) showed resistance to valproates and corticosteroids, aggravation on levetiracetam, oxcarbazepine and barbaturates (pagluferal I), but moderate positive effect on the combination of benzodiazepine (nitrazepam 2,5 mg x 2 times daily) and topiramate (topamax 12,5 mg x 2 times daily). M.U. (5 month old) had a temporary positive response to valproates (depakine in syrup) and levetiracetam (keppra in syrup) with the subsequent effect of "eluding" from therapy. There was a temporary positive effect on hormonal pulse therapy (dexamethasone). At oxcarbazepine therapy (trileptal in syrup) after a temporary period of improvement the aggravation of epileptic seizures was recorded and their moderate decreasing on the background of drug withdrawal. Currently takes a combination of barbiturate and topiramate (phenobarbital 75 mg x 3 times daily + topamax 12,5 mg x 2 times daily) with a moderate positive effect, alternating of "bad" and "good" days.

Discussion

Epilepsy of infancy with migrating focal seizures is a rare form of epilepsy with not much more than a hundred cases described in the world literature. However, the number of publications has steadily increased in recent years. It should be emphasized again that in the vast majority of world publications (before the entry of the ILAE Congress resolution in Barcelona in 2017), the predominant definition of these clinical cases were "malignant migrating partial seizures in infancy" (MMPSI). It is obvious that this severe form of epilepsy is more common than diagnosed due to the low popularity among the clinicians. Thus, in the structure of patients in infancy and early childhood with status epilepticus onset up to 3 years of age (n = 267), the group of children with EIMFS/MMPSI was 4,9% (n = 13), and in the structure of infantile status epilepticus (n = 147) -8,8% [9].

In most cases of EIMFS/MMPSI described in the international literature the etiology of epilepsy remains unknown; familial cases are rare. However, as it was initially assumed that this epileptic syndrome have a genetic nature, the introduction of genetic examinations in the diagnosis of epilepsy using new generation DNA sequencing techniques accumulates more and more data for the monogenic nature of this epileptic encephalopathy, but with a wide genetic polymorphism.

At the present date, mutations of the following genes have been described in the patients with EIMFS/MMPSI collected in the International database of Online Mendelian Inheritance in Man (OMIM) [3]:

- Gene SLC25A22, location 11p15.5, phenotype OMIM number #609304 (early infantile epileptic encephalopathy, type 3, modified variants) with autosomal recessive type of inheritance. The SLC25 gene family encodes mitochondrial carriers that transport a variety of metabolites across the inner mitochondrial membrane. SLC25A22, also known as GC1, is 1 of the 2 mitochondrial glutamate/H^+ symporters. Usually pathogenic mutations in SLC25A22 gene developed Ohtahara syndrome phenotypes with suppression-burst pattern. Nevertheless Poduri A., *et al*. (2013) reported about two sibs (brother and sister) with EIEE 3 type presenting as migrating partial seizures in infancy, born from consanguineous Saudi Arabian parents [10].
- Gene SCN1A, location 2q24.3, phenotype OMIM number #607208 (early infantile epileptic encephalopathy, type 6, modified variants), with autosomal dominant type of inheritance. SCN1A gene encodes alpha subunit of the brain voltage-gated sodium channels. Mutations in the SCN1A gene are the main etiology of severe myoclonic epilepsy of infancy (Dravet syndrome) and also responsible for autosomal dominant generalized epilepsy with febrile seizures plus (GEFS+) (GEFSP2; #604403). Freilich E.R., *et al*. in 2011 described a full-term female infant with seizure onset at age 10 weeks, progression of hemiclonic, apneic and multifocal migrating partial seizures leading to recurrent status epilepticus and death at age 9 months [11]. The same year Carranza Rojo D., *et al*. revealed two infants with malignant migrating partial seizures of infancy-one with de novo SCN1A missense mutation p.R862G that affects the voltage sensor segment of SCN1A and the second had a de novo 11.06 Mb deletion of chromosome 2q24.2q31.1 encompassing more than 40 genes that included SCN1A [12].
- Gene PLCB1, location 20p12.3, phenotype OMIM number #613722 (early infantile epileptic encephalopathy, type 12), with autosomal recessive type of inheritance. The PLCB1 gene encodes a mammalian phospholipase C-beta isoform that is expressed in select areas of the brain, including cerebral cortex, hippocampus, amygdala, lateral septum, and olfactory bulb. Poduri A., *et al*. in 2012 reported a boy, born of consanguineous Palestinian parents, with EIEE12 manifest clinically as malignant migrating partial seizures in infancy [13].
- Gene SCN8A, location 12q13.13, is responsible for voltage-dependent sodium channels, phenotype OMIM number #614558 (early infantile epileptic encephalopathy, type 13 типа), with autosomal dominant type of inheritance. Ohba C., *et al*. in 2014 revealed severely delayed Japanese boy with MMPSI and c.2537T>C (p.Phe846Ser) mutation in SCN8A [14].
- Gene KCNT1, location 9q34.3, encodes a sodium-activated potassium channel, phenotype OMIM number #614959 (early infantile epileptic encephalopathy, type 14), with autosomal dominant type of inheritance. Barcia G., *et al*. in 2012 described four mutation types KCNT1 of gene in 6 unrelated patients with MMPSI [4]. Then in 2013 Ishii A., *et al*. reported two unrelated girls with a de novo heterozygous c.862G-A transition in the KCNT1 gene, resulting in a gly288-to-ser (G288S) substitution at a highly conserved residue in the pore region of the channel presenting as malignant migrating partial seizures in infancy [15]. Vanderver A., *et al*. in 2014 identified the boy with de novo heterozygous c.2794T-A transversion in the KCNT1 gene, resulting in a phe932-to-ile (F932I) substitution at a highly conserved residue in the cytoplasmic C-terminal domain. Patient had mixed form of malignant migrating partial seizures in infancy in combination with myoclonic status and persistent of suppression-burst pattern [16].
- Gene TBC1D24, location 16p13.3, phenotype OMIM number #615338 (early infantile epileptic encephalopathy, type 16 типа), with autosomal recessive type of inheritance. The TBC1D24 gene plays an important role for the proper transport of intracellular vesicles and encodes a member of the Tre2-Bub2-Cdc16 (TBC) domain-containing Rab-specific guanosine triphosphatase (GTP)-activating proteins, which coordinate Rab proteins and other GTPases. Milh M., *et al*. (2913) identified two affected siblings with novel compound heterozygous mutations in TBC1D24 gene cause familial malignant migrating partial seizures of infancy. TBC1D24 loss of function has been also associated to idiopathic infantile myoclonic epilepsy, as well as to drug-resistant early-onset epilepsy with intellectual disability [17].
- Gene QARS, location 3p21.31, phenotype OMIM number #615760, determined progressive microcephaly, seizures, and cerebral and cerebellar atrophy (MSCCA), with autosomal recessive type of inheritance. The QARS gene encodes I aminoacyl-tRNA synthetase-enzyme that charge tRNAs with their cognate amino acids. Compound heterozygous mutation tyr57his + arg515trp in QARS gene developed MSCCA syndrome with migrating focal seizures in infancy in brother and sister born to healthy nonconsanguineous French parents of European descent [18].

Summarized data of genetically verified EIMFS/MMPSI cases and mutation types collected in the OMIM database is presented in table 2.

Phenotype OMIM series	Phenotype OMIM number	Gene name	Gene/ Locus OMIM number	Gene location	Mutation variants	Type of inheritance	References
EIEE 3 type	609304	SLC25A22	609302	11p15.5	gly110arg; (.0003)	AR	Poduri A., *et al*. 2013
EIEE 6 type	607208	SCN1A	182389	2q24.3	ala1669gly (.0023) arg862gly (.0024)	AD	Freilich E.R., *et al*. 2011 Carranza Rojo D., *et al*. 2011
EIEE 13 type	614558	SCN8A	600702	12q13.13	phe846ser	AD	Ohba C., *et al*. 2014
EIEE 14 type	614959	KCNT1	608167	9q34.3	arg428glm (.0001) ala934thr (.0002) arg474his (.0003) ile760met (.0004) phe932ile (.0009) gly288ser (.0010)	AD	Barcia G., *et al*. 2012 Vanderver A., *et al*. 2014 Ishii A., *et al*. 2013
EIEE 16 type	615338	TBC1D24	613577	16p13.3	phe229ser (.0005) + cys156ter (.0006)	AR	Milh M., *et al*. 2013
Microcephaly, progressive, seizures, and cerebral and cerebellar atrophy (MSCCA)	615760	QARS1	603727	3p21.31	tyr57his (.0003) + arg515trp (.0004)	AR	Zhang X., *et al*. 2014

Table 2: *Monogenic mutations as etiological factor in epilepsy of infancy with migrating focal seizures (EIMFS/MMPSI/Coppolo-Dulac syndrome) introduced in the OMIM database.*

EIEE: Early Infantile Epileptic Encephalopathy; AR: Autosomal Recessive Type of Inheritance; AD: Autosomal Dominant Type of Inheritance.

It should be noted that mutations in the KCNT1 gene also caused another form of epilepsy - nocturnal frontal lobe epilepsy, type 5 (OMIM#615005). However, the types of mutations in this form differ from those in EIEE type 14 and they are assigned numbers in the OMIM database 608167.0005 - .0008 (Arg928Cys, Tyr796His, Arg398Gln and Met896Ile appropriately).

In 2018 Madaan P., *et al*. from Child Neurology Division, Department of Pediatrics of All India Institute of Medical Sciences (New Delhi, India) revealed a novel pathogenic heterozygous missense mutation in exon 10 of the KCNT1 gene (chr9:138650308; c.808C > C/G (p.Q270E)) in infant with EIMFS/MMPSI. Neither quinidine nor ketogenic diet could control his seizures and the child succumbed to his illness at nine months of age [19].

It should be noted that both sexes are approximately equally susceptible to this disease. Thus, according to Dulac O (2005) observation, out of 20 children with EIMFS/MMPSI there were 9 girls and 11 boys [6]. According to our own observations, 36 cases of EIMFS/MMPSI were identified by such gender distribution: 16 boys and 20 girls. The fact that all the cases of EIEE type 14 manifested as epilepsy of infancy with migrating focal seizures we have found belonged to the female sex was probably accidental, since the mutation is autosomal dominant and assumes an equal probability of distribution by sex.

The age of seizure onset in EIMFS/MMPSI varies from 1 day of postnatal life to 6 months of life, on the average - about 3 months. Over the period from 1 to 10 months seizures become very frequent. Epileptic seizures has focal nature with different clinical characteristics starting from different cortical regions, and numerous epileptiform discharges have been observed on the EEG, occurring independently and moving from one cortical region to another during subsequent seizures. It should be kept in mind that many seizures are barely visible and often remain unrecognized for parents and medical staff. In particular, these are such "minimal" seizures as short-term breath holding, episodes of eyes deviations, face redness, etc. Along with the classic post-seizure Todd paresis, children with EIMFS could developed ictal paresis (inhibitory seizures). Only video-EEG monitoring can established the epileptic genesis of these paroxysmal phenomena. Patients demonstrated regress in psycho-motor development with developing of tetraparesis. There is observed a high mortality rate within a year after the debut of the disease [5,6,20-23].

The most frequent type of seizure onset in EIMFS are tonic spasms (in 31,6% of cases), apnea seizures with cyanosis (21,1%), tonic versive (15,7%) and myoclonic seizures (15,7%); ophthalmic-tonic seizures (5,3%), dialeptic (5,3%) and bilateral tonic-clonic seizures (5,3%) also could be the first seizure type. Subsequently, there is a wide polymorphism of epileptic seizures (5 or more types) and their high frequency. In the expanded stage of the disease affected infants are in the state of migrating multifocal clinical and electroencephalographic status epilepticus (SE). Obligate type of SE is migrating status of minor motor seizures (100%), as well as the following variants: SE of serial tonic spasms -42,1%, SE of inhibitory seizures (prolonged > 30 minutes ictal paresis) -31,6%, myoclonic SE - 36,8%, ES of bilateral tonic-clonic seizures -21,1% and hemiconvulsive SE-in 15,8%. This form of epilepsy is almost a special form of infantile status epilepticus [23].

EIMFS is an epileptic syndrome characterized by pharmacoresistance and severe prognosis. In most cases, basic, old and new antiepileptic drugs in various combinations, as well as steroids are ineffective, while the drugs of carbamazepine group and vigabatrin had tendency for seizure aggravation [6]. Perez J., *et al*. (1999) has indicated the benefits of stiripentol and high doses of clonazepam [24]. Okuda K., *et al*. (2000) demonstrated the effectiveness of the drug of "pre-barbiturate epoch"-potassium bromide [25]. The seizures in EIMFS are also resistant to the ketogenic diet. Surgical treatment is impractical due to the diffuse nature of brain damage, genetic etiology and the absence of a clear local structural defect and dominant focus [6].

Previously observed cases of EIMFS/MMPSI also demonstrate pharmacoresistance. Antiepileptic drug (AED) monotherapy did not have a significant effect on the course of the disease in all the patients. No patient could become seizure free, while AEDs was completely ineffective in 57,9% of cases, seizure decreasing > 50% was observed in 31,6% of cases and seizure decreasing >75% was observed in only 10,5% of patients. Combinations of valproates with barbiturates (phenobarbital, hexamidine) and benzodiazepines were relatively effective. Among the drugs of the benzodiazepine group, the most effective was frizium at a dosage of 1 mg/kg/day. In 2 patients, a positive effect was noted on the background of combinations with levetiracetam, in one case-an improvement on the background of a combination of benzodiazepines with topiramate. In one patient, the reduction of seizures was noted on therapy with sodium bromide (30 mg/kg/day), but with side effects of hypersomnia. The use of high doses of vitamin B6 was moderately positive in 2 cases. The use of ethosuximide, lamotrigine and phenytoin did not have a significant positive effect. Was fixed the case of pharmacoinduced transformation into EIMFS/MMPSI of infant with a cryptogenic focal frontal epilepsy on application of carbamazepine treatment. Corticosteroids caused only a temporary moderate positive effect in 8 cases and in 5 cases was completely ineffective [9,22,23].

In cases of necessity of emergency treatment of convulsive status epilepticus (bilateral tonic-clonic and hemiconvulsive types) in EIMFS/MMPSI - benzodiazepines (relanium, midazolam) had for the most part of patients a temporary effect (n = 12, 63,2%), or were completely ineffective (n = 7, 36,8%). A positive effect was provided by the admission of sodium oxybate (natrium oxybutyricum) in doses of 100 - 150 mg/kg, that was carried out in 7 cases of convulsive SE - bilateral tonic-clonic (n = 4) and hemiconvulsive (n = 3), resistant to benzodiazepines. In 3 patients with EIMFS/MMPSI injectable valproates (convulex) had a significant positive effect in SE, especially in cases of tonic-vegetative attacks with apnea episodes previously with aggravation on the background of benzodiazepines [9].

In recent years, the experience of differentiated use of antiepileptic drugs in various genetic mutations has been accumulated. According to the number of studies, the use of quinidine may be effective in the cases of epilepsy with a mutation of the KCNT1 gene. However, this drug is not a panacea. In 2018 Abdelnour E., *et al*. along with the publication of their own experience in the use of quinidine in three children with EIEE type 14, summarized the data of the world literature on the effectiveness of this drug in mutation of the KCNT1 gene. From the 11 children, only one child was able to get seizures free (which certainly contrasts with the data of impossibility of achieving remission in this epileptic encephalopathy), and four children achieved a significant improvement in the clinical course of the disease; however, five children did not show significant improvement and one child had seizure aggravation with more than tenfold increasing of their frequency on quinidine treatment. Doses of quinidine with gradual titration of the dose from 10 mg/kg/day were applied with increasing up to 34 - 73 mg/kg/day with the drug serum concentration in the range of 0,4 - 5 mkg/ml; the daily dose was divided into 3 admission. Side effects included depigmentation of the skin and prolongation of the QT interval on the ECG, which required frequent dynamic ECG control [26].

Conclusion

KCNT1 is perhaps the main gene that determines the development of such a rare severe epileptic syndrome as EIMFS/MMPSI-Coppolo-Dulac syndrome. All children with pharmacoresistant epileptic encephalopathy need a comprehensive examination, including video EEG monitoring, good quality neuroimaging and mandatory genetic examination by new generation exomal sequencing techniques-such as the panel "hereditary epilepsy", clinical and whole-exome sequencing. The accumulation of international experience and future investigations on a differentiated approach to epilepsy treatment caused by various genetic mutations will increase the chances for recovery from epileptic seizures, for improving of mental and motor development, which will ultimately improve the quality of life of patients and their parents.

Conflict of Interest

The authors declare that there is no conflict of interest.

Bibliography

1. Engel JR. "A Proposed Diagnostic Schema for People with Epileptic Seizures and with Epilepsy". *Epilepsia* 42.6 (2001): 796-803.
2. Sharkov AA., *et al.* "Genetics and treatment of early infantile epileptic encephalopathies". *Zh Nevrol Psikhiatr Im S S Korsakova* 9.2 (2016): 67-73.
3. OMIM® (Online Mendelian Inheritance in Man) - An Online Catalog of Human Genes and Genetic Disorders (2019).
4. Barcia G., *et al.* "De novo gain-of-function KCNT1 channel mutations cause malignant migrating partial seizures of infancy". *Nature Genetics* 44.11 (2012): 1255-1259.
5. Coppola G., *et al.* "Migrating partial seizures in infancy: a malignant disorder with developmental arrest". *Epilepsia* 36.10 (1995): 1017-1024.

6. Dulac O. "Malignant migrating partial seizures in infancy". In: Eds: J Roger, M Bureau, Ch Dravet, P. Genton, CA Tassinari, P Wolf. Epileptic Syndromes in Infancy, Childhood and Adolescence (4th edition) (2005): 73-76.

7. Scheffer IE., *et al.* "ILAE classification of the epilepsies: Position paper of the ILAE Commission for Classification and Terminology". *Epilepsia* 58.4 (2017): 512-521.

8. Kholin AA. "Malignant migrating partial seizures in infancy or Coppola-Dulac syndrome". Materials of 29th International Epilepsy Congress, Rome (2011): 716.

9. Kholin AA. "Epileptic status in infancy and early childhood". Abstract of the dissertation of doctor medical sciences. Moscow (2000): 54.

10. Poduri A., *et al.* "SLC25A22 is a novel gene for migrating partial seizures in infancy". *Annals of Neurology* 74.6 (2013): 873-882.

11. Freilich ER., *et al.* "Novel SCN1A mutation in a proband with malignant migrating partial seizures of infancy". *Archives of Neurology* 68.5 (2011): 665-671.

12. Carranza Rojo D., *et al.* "De novo SCN1A mutations in migrating partial seizures of infancy". *Neurology* 77.4 (2011): 380-383.

13. Poduri A., *et al.* "Homozygous PLCB1 deletion associated with malignant migrating partial seizures in infancy". *Epilepsia* 53.8 (2012): e146-e150.

14. Ohba C., *et al.* "Early onset epileptic encephalopathy caused by de novo SCN8A mutations". *Epilepsia* 55.7 (2014): 994-1000.

15. Ishii A., *et al.* "A recurrent KCNT1 mutation in two sporadic cases with malignant migrating partial seizures in infancy". *Gene* 531.2 (2013): 467-471.

16. Vanderver A., *et al.* "Identification of a novel de novo p.Phe932Ile KCNT1 mutation in a patient with leukoencephalopathy and severe epilepsy". *Pediatric Neurology* 50.1 (2014): 112-114.

17. Milh M., *et al.* "Novel compound heterozygous mutations in TBC1D24 cause familial malignant migrating partial seizures of infancy". *Human Mutation* 34.6 (2013): 869-872.

18. Zhang X., *et al.* "Mutations in QARS, encoding glutaminyl-tRNA synthetase, cause progressive microcephaly, cerebral-cerebellar atrophy, and intractable seizures". *American Journal of Human Genetics* 94.4 (2014): 547-558.

19. Madaan P., *et al.* "A quinidine non responsive novel KCNT1 mutation in an Indian infant with epilepsy of infancy with migrating focal seizures". *Brain and Development* 40.3 (2018): 229-232.

20. Veneselli E., *et al.* "Malignant migrating partial seizures in infancy". *Epilepsy Research* 46.1 (2001): 27-32.

21. Coppola G. "Malignant migrating partial seizures in infancy: an epilepsy syndrome of unknown etiology". *Epilepsia* 50.5 (2009): 49-51.

22. Kholin AA., *et al.* "Malignant migrating partial seizures in infancy. Clinical observation of 6 cases". *Russian Journal of Child Neurology* 2.2 (2007): 25-38.

23. Kholin AA. "The syndrome of malignant migrating partial seizures in infancy or Coppola-Dulac syndrome (19 cases)". *Zh Nevrol Psikhiatr Im S S Korsakova* 113.3 (2013): 21-27.

24. Perez J., *et al.* "Stiripentol: efficacy and tolerability in epileptic children". *Epilepsia* 40.11 (1999): 1618-1612.

25. Okuda K., *et al.* "Successful control with bromide of two patients with malignant migrating partial seizures in infancy". *Brain and Development* 22.1 (2000): 56-59.

26. Abdelnour E., *et al.* "Does age affect response to quinidine in patients with KCNT1 mutations? Report of three new cases and review of the literature". *Seizure* 55 (2018): 1-3.

Volume 8 Issue 11 November 2019