Defining the phenotype of FHF1 developmental and epileptic encephalopathy

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Original Article

Pathogenic variants in *FHF1* gene cause developmental and epileptic encephalopathy.

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Abstract

Objective: Fibroblast-growth-factor homologous factor (*FHF1*) gene variants have recently been associated with developmental and epileptic encephalopathy (DEE). *FHF1* gene encodes a cytosolic protein that interacts with neuronal sodium channel. Aim of this study is to report the largest series of patients with pathogenic *FHF1* genetic variants in order to define electro-clinical phenotype, genotype-phenotype correlation, and information about management and prognosis.

Methods: Through an international collaboration, we retrospectively collected detailed clinical, genetic, neurophysiologic and neuroimaging data of 17 patients with *FHF1*-related epilepsy.

Results: Fourteen patients carried heterozygous missense variant c.341G>A (p.Arg114His) in *FHF1* gene, two patients heterozygous missense variant c.334G>A (p.Gly112Ser) and one patient carried a chromosomal microduplication involving *FHF1* gene. The majority of variants were *de novo*, although in 29% of cases somatic or germline parent mosaicism occurred. Patients with c.341G>A variant presented with a phenotype consisting of early onset DEE. Drug resistant epilepsy, intellectual disability, psychiatric features and status epilepticus were also common features. Tonic seizures were the most frequent seizure type. Patients who carried c.334G>A variant and *FHF1* gene duplication showed a delayed epilepsy onset compared with patients carring the hotspot variant (c.341G>A). Brain MRI was normal at onset while a mild cerebral and/or cerebellar atrophy appeared during follow-up in 8 out of 17 patients (47%).

Conclusion: *FHF1*-related DEE is characterized by an almost homogeneous clinical phenotype characterized by early-onset and drug-resistant epilepsy, intellectual disability, and psychiatric features in patients with c.334G>A variant. Few cases with a milder phenotype can occur, although a genotype-phenotype correlation had been identified. Because of the possibility of germline or somatic mosaicism, it is appropriate to offer prenatal diagnosis to couples with a child with *FHF1*-related DEE.

Introduction

Developmental and epileptic encephalopathies (DEEs) are clinically and genetically heterogeneous severe neurodevelopmental disorders [1]. These conditions often start in infancy or early childhood and include a large group of severe epilepsies characterized by multiple seizure types, frequent epileptiform activity on EEG, and developmental slowing or regression [2]. With the application of next-generation sequencing approaches, the number of known monogenic determinants underlying DEEs has grown rapidly. To date, a genetic etiology can be identified in upward of 30% of case (60-80% for epilepsies with neonatal onset) [3,4] and it consists mainly of *de novo* variants in genes encoding neuronal ion channels or proteins involved in synaptic transmission, regulatory, and developmental functions [5,6].

Once a gene is identified, electro-clinical studies of patients who have a specific gene variants are needed to facilitate the recognition of the phenotypic spectrum of that specific genetic DEE [7].

Recently, *de novo* mutations in fibroblast-growth-factor homologous factor 1 (*FHF1*) gene, encoding a voltage-gate sodium channel subunit (Nav1.6) binding protein, have been reported in patients with severe epilepsies [8-14], although a definite clinical phenotype has not clearly emerged. *FHF1* gene is located on the long arm of chromosome 3 (3q28-q29) and c.334G>A (p.Gly112Ser) *FHF1* missense variant has been demonstrated to lead to a gain-of-function of voltage-gate sodium channel (Nav1.6), predicting an increasing of neuronal excitability [12].

Aim of this study is to report the largest series of patients with pathogenic *FHF1* mutations in order to delineate the electro-clinical features of *FHF1*-related DEE, identify genotype-phenotype correlation, improve management and define prognosis.

Methods

This is an international retrospective multicenter study. We collected 17 patients with *FHF1*-related epilepsy, followed-up in 14 epilepsy centers across the world (Belgium, Canada, China, France, Italy, Japan, Poland, United Kingdom, and United States of America).

For every patient, the referring physician filled out a detailed medical questionnaire. We collected data on gender, family and clinical history, age at epilepsy onset, age at study, *FHF1* genetic variant, morphologic details, neurologic and neuropsychological assessments in terms of cognitive and behavioral disorders, seizure semiology and frequency, occurrence of status epilepticus (SE), ictal and interictal EEG abnormalities, brain imaging and treatment during the follow-up.
Patients #A-K and #Q have been previously reported [8-14]. Epileptic seizures were classified according to the current International League Against Epilepsy (ILAE) Classification [15,16]. The authors confirm that they approved the final draft of the manuscript.

Results

We collected the electro-clinical data of 12 previously published patients (#A-K and #Q) [8-14] and 5 unpublished patients (#L-P). For all patients, both published and unpublished, more information has been collected directly contacting their referring physicians except for patients #C-E and #Q for whom only data coming from publications were available [11,14]. Median age at study was 8,7 ± 8,59 years (range 1 month - 33 years); seven patients were female (41%). Two were siblings (#A,B) and both died at the age of 7 and 3.5 years respectively for a SE and for unknown cause.
All patients were born at term except one who was born at 36 weeks of gestational age (#P). Birth was without complications and none of them had perinatal insults. Two patients (#K,M) had congenital microcephaly and the two patients (#A,B) had acquired microcephaly.
Clinical, EEG, neuroimaging and genetic details of all patients are briefly included in Table 1 and extensively in table e-1.

Genetic investigations

Fourteen patients carried the heterozygous missense variant c.341G>A (p.Arg114His) in *FHF1* gene, two patients the heterozygous missense variant c.334G>A (p.Gly112Ser) (#P,Q), and one patient carried a chromosomal microduplication involving the entire *FHF1* gene (0.58-Mb gain, arr[hg19] 3q28q29 (191876978_192454675)x1) (#I).

FHF1 genetic variants were *de novo* in 12 patients. Five patients (29%) inherited the variant from parents who had a germline or somatic mosaicism. In the two siblings (#A,B) it was supposed a germline mosaicism from an unaffected parent (father had one epileptic seizure when he was 5 years old). Patient #J inherited the *FHF1* variant from his healthy mother who had a somatic mosaicism (blood leukocyte with a mutant allele fraction of 11.7% - 11/94 clones). Two patients inherited the variant from their affected parents: patient #O from his 23 years-old father with epilepsy onset at the age of 8 months, treated with carbamazepine and phenobarbital with poor seizure control; patient #P from his mother for whom no clinical data are available.

Epilepsy

Seizures onset ranged from 1 day to 3 years and 5 months. In detail, seizures began within 42 days of life in all patient with c.341G>A variant (10 out 14 within the first eight days of life) and later for patients carrying c.334G>A variant (#P-Q), who started both at 4 month of age. Patient with *FHF1* duplication (#I) started at the age of 3 years and 5 months. Tonic seizures were the most common seizure type (15/17, 88,2%), mostly with impairment of awareness, associated with autonomic signs such as apnea (5/15, 33,3%) and bradycardia (2/15, 13.3%).

Fourteen out of 17 patients developed additional seizure types, including generalized tonic-clonic seizures (n=8), focal to bilateral tonic-clonic seizures (n=4), myoclonic seizures (n=2), atonic seizure (n=2), absence seizures (n=1) and epileptic spasms (n=2). SE occurred in 8 (47%) patients. Seizure frequency was highly variable, with multiple episodes per day and long seizure-free periods lasting up to several years (12 years in patient #J).

According with ILAE classification criteria [1,15], 10 individuals presented a combined generalized and focal epilepsy, 4 presented focal epilepsy, and 3 unknown epilepsy.

Twelve out 17 patients had refractory epilepsy, while 5 patients (#F,G,O,P,Q) reached a good seizure control with different AEDs combinations. Eleven patients were treated with phenobarbital as first line medication without significant efficacy (no reduction >50% in seizure frequency). Seven patients (#A,B,D,F,I,K,Q) reported an improvement in seizure frequency with phenytoin.

Phenytoin had no effect on seizure control in 5 patients and in the remaining 5 it was not tested. Data on response to other drugs (rufinamide, lamotrigine, carbamazepine and vigabatrin) were not conclusive. Ketogenic diet and vagal nerve stimulation were reported with some improvement in patients #N and #D respectively.

EEG investigations

Interictal EEG at the onset of seizure was highly variable. Data on background activity at epilepsy onset was available in 15 patients: it was reported to be slowed in 8 out of 15 (53%), discontinuous in 2, normal in 5 patients. In 13 patients multifocal spikes were reported in the first EEG, two patients had focal spikes (frontal) and two patients (#P,Q) had not epileptiform abnormalities. Four patients had diffused spikes and waves discharges. An increase of spike and waves discharges during sleep was reported in 4 patients and abnormal sleep architecture in 3 patients.

Regarding the EEG during the follow-up, in 12 patients a further deterioration of background activity was observed, and in one case a severe suppression has been detected (#J). An increase of interictal focal or multifocal spikes was reported in 11 patients. Hypsarrhythmia was reported in patient #A.

Ictal EEGs were reported as focal (with quick spread to bilateral regions) or generalized with low voltage fast activity, followed by diffuse rhythmic spikes with postictal suppression of cerebral activity (Fig.1). In two patients (#L,O) ictal bradycardia has been documented (Fig.1).

Other neurologic findings

Development prior to seizure onset was reported as normal in 11 patients, abnormal in 6. At follow-up, psychomotor delay/intellectual disability (ID) was severe in 7 patients, moderate in six, and mild in one (#H). Three patients had normal development (#F,I,P) at last follow-up (respectively at 3, 15 and 4 years). Psychomotor regression was observed in 8 patients in association with onset of seizures. Diffuse hypotonia was found in 4 patients and limb hypertonia was reported in two. Eight patients had feeding difficulties, and four of them required tube feeding. Among 14 patients older

than 18 months, nine of them reached unassisted gait (five without any delay). Gait was ataxic in 6 patients.

Seven patients achieved normal language skill, 3 of them with some delay; nine patients were no-verbal, and there are no information regarding the remaining one. Normal developmental milestones were reported in patients #F, #I, #P, with different genotype respectively c.341G>A, gene duplication, c.334G>A. Movement disorders were not reported, except for stereotypes present in 6 patients. Psychiatric features were observed in 11 patients. Nine patients had autistic features such as poor/absent eye contact (n=7) and no active interaction (n=2); three patients had sleep disturbances; one had quick mood changes, and one presented with severe obsessive behavior (table e-1).

Brain MR findings

Brain MR was normal in 10 out 14 patients who performed brain MR within the first year of life. The remaining 4 patients (#G,H,K,L) had respectively a Mild Chiari I malformation (#G), a tight T2 weighted hyperintensity of the parietal areas, cerebellum and brainstem (#H), and a mild cerebral atrophy (#K,L) (Fig.2).

Three patients performed first brain MR after the first years of life: two of them (#I,J) (Fig.2) had mild cerebral and cerebellar atrophy; one of them (#E), with a previously normal brain MR during childhood, developed a bilateral mesial temporal sclerosis and mild prominence of cerebellar folia at the age of 12 years.

Overall 8 out of 17 patients (47%) presented cerebral and/or cerebellar atrophy at brain MR, which was progressive in 6 patients. Neither major cortical malformations nor focal cortical dysplasia were observed.

Other systems

Six patients had mild dysmorphic features (table e-1). No cardiovascular problems were mentioned except for a pulmonary stenosis diagnosed a one month of age in patient #O.

Constipation was reported in 5 patients (#A-E) and chronic diarrhea without etiology since birth in one (#O). Regarding skin abnormalities, frequent eczema was reported in one patient (#N).

Two patients had cortical visual impairment (#A,B,G,O); one patient nystagmus and astigmatism (#G), one only astigmatism (#H), and one mild myopia (#I). None had conductive and sensorineural hearing loss. Excessive drooling was observed in 4 patients (#A,B,J,K).

Discussion

This is the largest reported cohort of individuals with *FHF1*-related DEE. The prevalence of these *FHF1*-related DEE has not been estimated, however it seems to be ultra-rare as far as since the first description [12] only 12 patients have been reported [8-14]. Furthermore, complex chromosomal rearrangements with 9p deletion and the 3q28q29 microduplication involving *FHF1* have been recently described in 16 patients. However, only 3 out16 patients had epilepsy [17].

As previously reported, c.341G>A missense mutation, is an hotspot locus and acts in a gain-of-function manner on voltage-gate sodium channel, predicting an increasing of neuronal excitability [12]. This mechanism of gain-of-function, it has been supposed also for the c.334G>A variant and *FHF1* gene duplication [14,17].

Thanks to an international collaboration, we collected a huge amount of clinical, genetic, neurophysiological and radiological data, and we were able to better delineate the phenotype of *FHF1*-related DEE, which consists of drug-resistant epilepsy with neonatal onset (mostly within the first eight days of life), severe developmental impairment, and psychiatric features. Axial hypotonia, ataxia and feeding difficulties are also reported.

In an effort to identify a genotype-phenotype correlation, we found that patients with c.334G>A and *FHF1* gene duplication had a later epilepsy onset (after the 4^{th} month of life), if compared with patients with the c.341G>A hotspot mutation who had a neonatal onset.

Seizure semiology was highly variable during disease history, however focal and generalized tonic seizures were the most common seizure type, sometime with progression to apnea and bradycardia. Possible evolution into SE was also frequently seen.

The *FHF1* gene encodes for protein interacting with a sodium channel subunit of SCN8A and the mutations of these two genes acts in a gain of function manner on sodium channel [12]. Early epilepsy onset and tonic seizure with bradycardia may be common features of these two related genetic disorders.

The clinical outcome of patients with *FHF1* variants/deletion was poor in most of patients. Psychomotor delay/ID was moderate-severe in 75% of patients, mild in 6,5% and development was normal in 12,5%. Psychomotor regression was described in 43,7% of patients, often in association with seizure onset. More than half of patients had autistic features; poor/absent eye contact, sleep problems, and rapid mood change for no obvious reason have been also reported.

As regard the management, currently there are no specific treatments that could heal or reverse the progression of the *FHF1*-related DEE. As a consequence, the management is mainly symptomatic and aims to maximizing developmental and cognitive potential. Such as other DEEs, *FHF1*-related disorder requires a multidisciplinary approach, involving physicians, psychiatrists, neuropsychologists, pharmacists, dietitians, and specialist nurses. Attention to comorbid psychiatric and other diseases is paramount, given the higher prevalence in this cohort and associated poorer health outcomes [18,19].

The retrospective nature of this study does not allow any firm conclusions about efficacy of specific AEDs, but it is worthwhile to mention that drugs with effects on gain of function sodium channelopathies (mostly phenytoin, but also lamotrigine, carbamazepine and rufinamide) appeared to be more effective if compared with others [13,14]. The observation that sodium channel blockers may be effective in these cases underlie the importance of an early molecular diagnosis [20-23]. As concerns feeding difficulties, careful evaluation of nutritional problems may have a significant impact on quality of life in these patients [24]. Psychosocial support for families is an integral part of the management [25,26].

With regard to inheritance, as observed in other gene related DEEs [27-31], the majority of mutations arise *de novo*; although it is remarkable that in 29% of cases somatic or germline

mosaicisms were detected in parents. In this study we included only affected patients, not considering asymptomatic or affected carrier parents, however affected parents of #O and #P patients might have had a drug-responsive epilepsy with normal intellectual skills, even if information are scares and we cannot confirm this assumption. Because of the possibility of germline or somatic mosaicism, it is appropriate to offer prenatal diagnosis to couples who had a child with *FHF1*-related DEE regardless of whether the disease-causing mutation has been detected in a parent or not [32,33].

Brain MR showed no significant/remarkable abnormalities at seizure onset, and cerebellar and/or cerebral atrophy became evident in subsequent neuroimaging in 47% of patients. Cerebellar atrophy has previously been reported in DEEs caused by mutations in several other genes including those encoding voltage-gated sodium channels such as *SCN8A* [22,34-36]. Currently, it is not clear the pathological mechanism, even if a possible mechanism of hyperexcitotoxic has been supposed [12], however we cannot exclude also a secondary effect due to treatment with AEDs.

Overall, our findings expand and refine the clinical and EEG phenotype of patients with *FHF1*-related DEE and confirm that the hallmark of this disorder is the neonatal onset epilepsy with mainly tonic seizures, associated with ID and psychiatric features. Patients with the hotspot variant c.341G>A seems to have an earlier (neonatal) onset if compared with patients with the different genotype. Further experimental evidences are needed to shed light on the underlying pathophysiology of *FHF1*-DEE therefore improving management and treatment, define the natural history, and prognostic factors for outcome.

Conclusions

This article provides further evidences for a causative gene for DEEs and expands the phenotypic spectrum of *FHF1*-related DEE characterized by a drug-resistant epilepsy with neonatal-onset, neurodevelopmental impairment, and psychiatric features. The clinical features are distinguishable from most of the other common genetic causes of DEEs and bear some similarity with those of

SCN8A-related DEE. Mutations frequently arise *de novo* but inherited mutations from a mosaic parent can also occur, and genetic counseling is essential in these cases.

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Conflict of interest

The authors have no financial or personal relation that could pose a conflict of interest.

[to be completed]

Figure Legends

Figure 1

Ictal EEG of patient #L at the age of 42-days.

Ictal discharge starts with a diffuse low-voltage fast activity, increasing in amplitude and decreasing in frequency, bilateral and symmetrical. The clinical counterpart is characterized by a massive tonic contraction with perioral cyanosis and sialorrhea. Polygraphic recording shows ictal bradycardia at seizure onset for about 5 seconds concomitant with the beginning of the tonic phase (see bilateral contraction of upper limb in deltoids). Afterwards, there is a hypotonia and pallor associated with a brief compensative tachycardia. Seizure spontaneously ends after 86 seconds.

Figure 2

Brain magnetic resonance images of patients #L and #I.

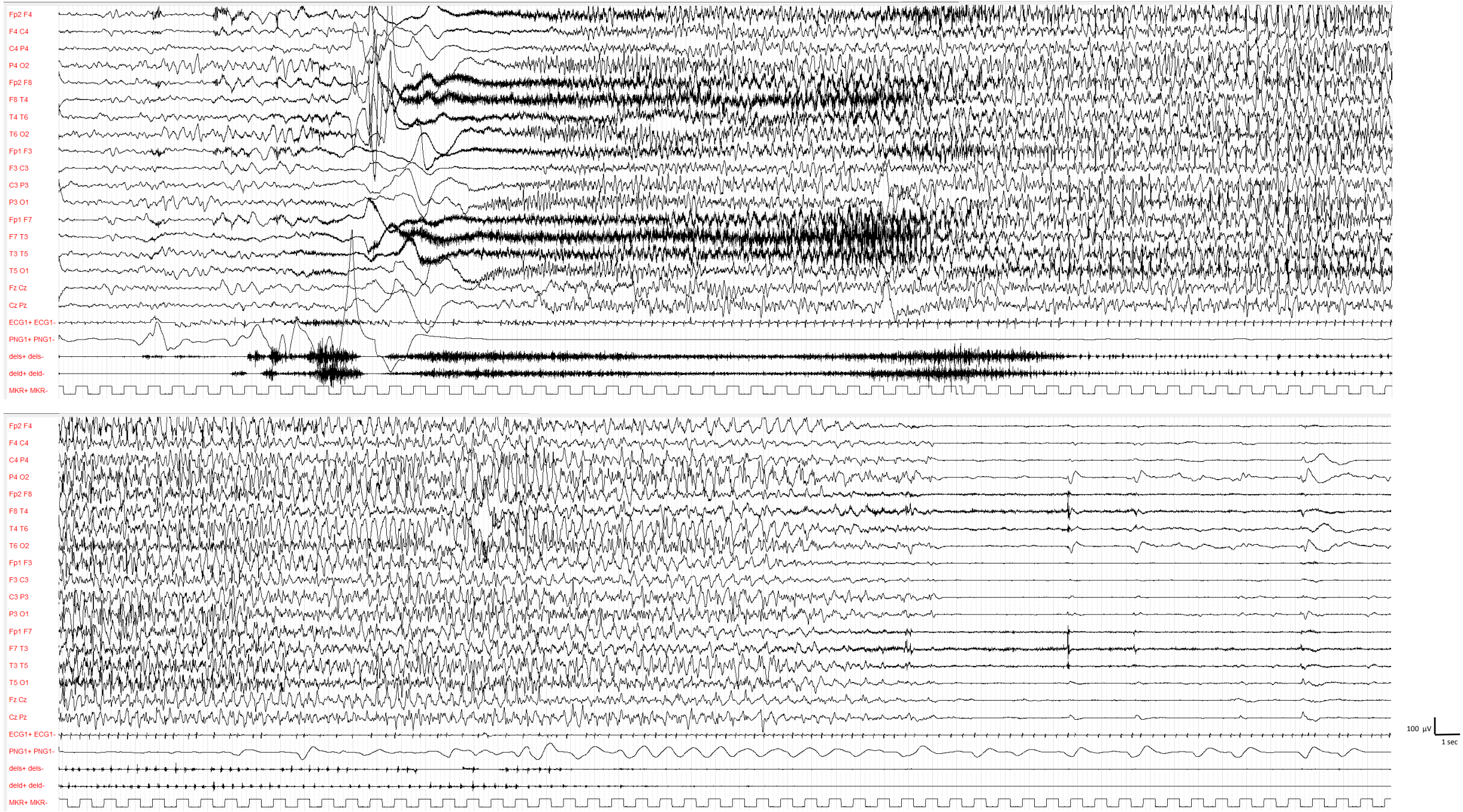
Patient #L at the age of 2,3 months (a-c) and at the age of 2,7 years (d-f): signs of cerebral brain atrophy, with enlarged subarachnoid space around frontal and insular lobes, without a significant progression of the atrophy. Patient #I at the age of 8 years (g-i): mild cerebral and cerebellar atrophy with an enlarged subarachnoid space around frontal and insular lobes and cerebellar folia.

Table 1

Summary of molecular, clinical, EEG, and neuroimaging features of all published and unpublished patients with *FHF1*-related developmental and epileptic encephalopathies.

Table e-1

Clinical, EEG, neuroimaging and genetic details of all patients extensively reported.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T5 O1
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Cz Pz
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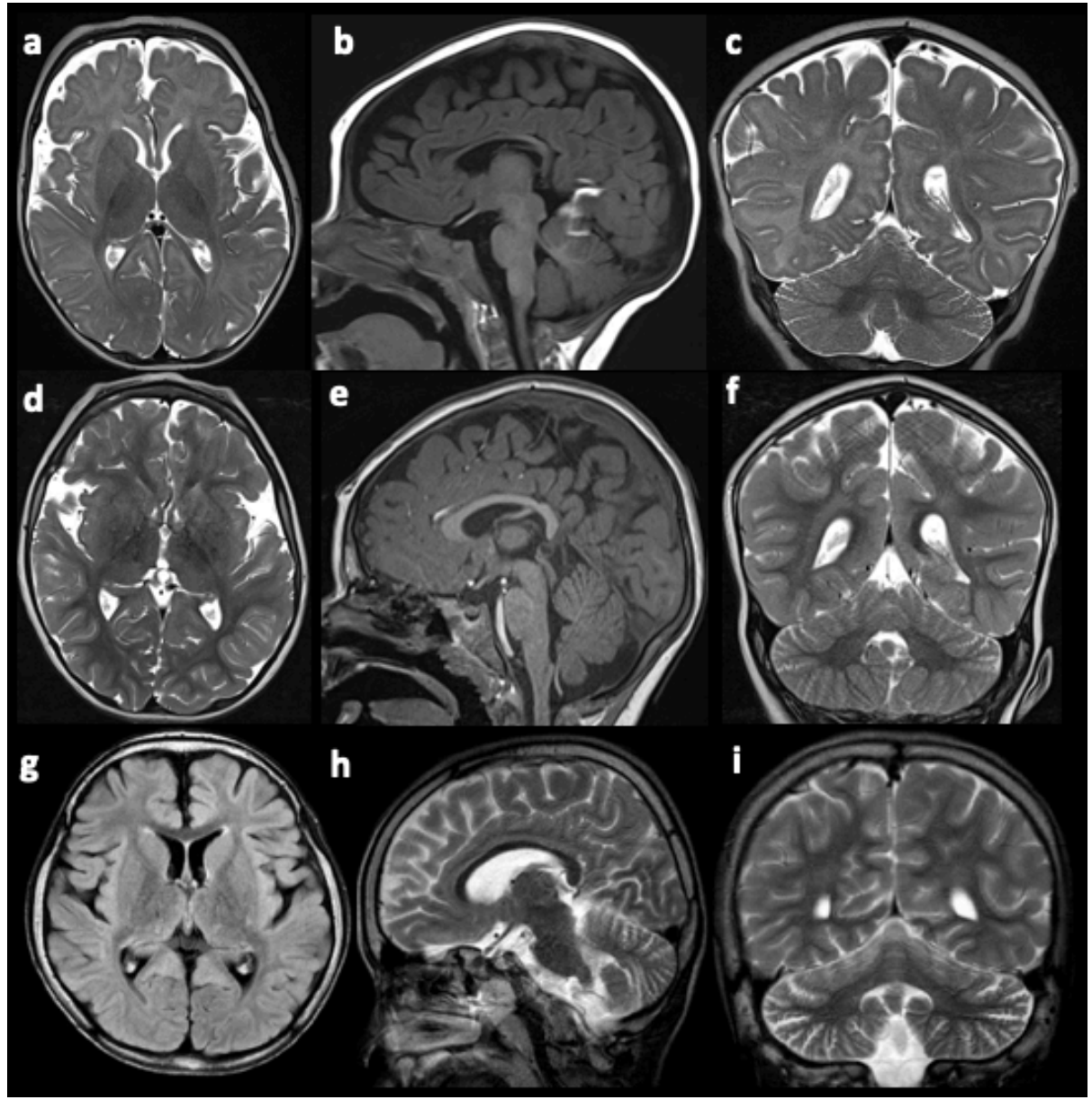
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eference	Siekierska et al. 2016	Siekierska et al. 2016	Al-mehmadi et al. 2016	Al-mehmadi et al. 2016	Al-mehmadi et al. 2016	Guella et al. 2016	Guella I. et al. 2016	Villeneuve et al. 2017	Shi RM. et al. 2017	Takeguchi R. et al. 2018	Takeguchi R. et al. 2018	unpublished	unpublished	unpublished	unpublished	unpublished	Paprocka et al. 2019
ender/ ge at last bservation/death ause)	F/died age 7y (SE)	M/died age 3y6m (unknow cause)	M/3y	F/16y	F/8y	F/3y3m	F/15y	M/9y	M/15y1m	M/33y3m	M/2y6m	M/5y8m	F/1 m	F/13y	M/2y10m	M/4y2m	M/4y6m
***HF1* variant, heritance**	c.341G>A, probable germline mosaicism. At age of 5 y the father had one epileptic seizure	c.341G>A, probable germline mosaicism. At age of 5 y the father had one epileptic seizure	c.341G>A, *de novo*	c.341G>A, *de novo*	c.341G>A, *de novo*	c.341G>A, *de novo*	c.341G>A, *de novo*	c.341G>A, *de novo*	0.58-Mb gain, arr[hg19] 3q28q29 x1, including FHF1 gene, *de novo*	c.341G>A, inherited from healthy mother (blood leukocyte with a mutant allele fraction of 11.7% - 11/94 clones)	c.341G>A, *de novo*	c.341G>A, *de novo*	c.341G>A, *de novo*	c.341G>A, *de novo*	c.341G>A, inherited from affected father with somatic mosaicism	c.334G>A, inherited from affected mother with somatic mosaicism	c.334G>A, *de novo*
EPILEPSY															-		
pilepsy onset	14d	28d	2d	42d	2d	2d	2d	1d	3y5m	7d	1d	31d	2d	3d	8d	4m	4m
izure type	TS	TS	FTS, GTCS	FTS, GTCS, MS	FTS, FS	FTS	GTCS, FS	AS, FS	GTCS; FS, FTS	TS, ES	FTS; FS, GTCE	TS	FS FTS	GTCS; A. FTS	FS, TS, GTCS	TS, GTCS	TS, MS, ES, GTCS, FTS
pilepsy Type	Combined generalized and focal epilepsy	Combined generalized and focal epilepsy	Combined generalized and focal epilepsy	Combined generalized and focal epilepsy	Focal epilepsy	Focal epilepsy	Combined generalized and focal epilepsy	Combined generalized and focal epilepsy	Combined generalized and focal epilepsy	Unknown	Combined generalized and focal epilepsy	Focal epilepsy	Focal epilepsy	Combined generalized and focal epilepsy	Unknown	Unknown	Combined generalized and focal epilepsy
E (frequency)	frequent	infrequent	frequent	frequent	frequent	no	n.a.	n.a.	no	no	no	yes (twice)	no	frequent	yes (twice)	no	no
EEG																	
nterictal EEG	Slow BG, multifocal SW (onset), hypsarrythmia (FU)	Slow BG, multifocal SW	Slow BG, multifocal SW	Slow BG, multifocal SW	Slow BG, multifocal SW	Discontinuous/slow BG, multifocal ad diffuse SW (onset); slow BG; increase of diffuse/multifocal SW; from 10m normal EEG (FU)	Slow BG left temporal SW (onset); slow BG and multifocal SW (onset)	Normal BG, multifocal spikes (onset); focal spikes (FU)	Frontal SW (onset); Slow BG, multifocal SW (FU)	Suppression burst (onset); slow BG with focal/multifocal SW (FU)	Slow BG, multifocal and diffuse SW (onset); slower BG and multifocal and diffuse SW (FU)	Normal multifocal SW (onset); slow BG and multifocal SW (FU)	Discontinuous and slow BG and multifocal ad diffuse SW (onset); slow BG with increase of diffuse/multifocal SW	Slow BG, multifocal and diffuse SW (onset); Slow BG and multifocal and diffuse SW (FU)	Normal BG multifocal SW (onset) Slow BG and posterior SW (FU)	Normal	Normal (onset); generalized and focal paroxysmal in temporal regions (FU)
tal EEG	Generalized onset (tonic seizure)	Generalized onset (tonic seizure)	Focal onset followed by secondary generalization	n.a.	n.a.	Generalized onset	Generalized onset (tonic seizure)	Generalized onset (tonic seizure)	Generalized onset (AS, TS, GTCS) Focal seizures: R or L hemisphere	n.a.	Generalized onset. Seizure activity migrated from one region to another	Diffuse onset	n.a.	L hemisphere; R frontal/frontotemporal	R central	n.a.	Generalized polyspikes, spike-SW complexes
TREATMENT																	
ED	PB, VPA, PHT, GVG, TPM, CZP; PN	PB, VPA, PHT, GVG, TPM	LEV, PB, KD	PHT, PER, VNS	PHT, PRG, PER, VNS	PB, LEV, TPM, PHT, CBZ	PB, TPM, LTG, RUF	PB, GVG, CBZ, CLB, ESM, KD	PB, CLB, VPA, KBr, PHT, LEV, NZP	VPA, PB, PHT, CZP, AZA, PHT, GBP	PB, PN, CBZ, CLB, VPA, ZNS, LEV, KBr, PHT	PB, PHT, CBZ, LEV, RTG, VPA	PB, LEV, PN/PLP, TPM, CBZ, PHT	PB, LEV, PHT, OXC, LCM, CLZ, PER, TPM, VNS, KD	VPA, CZP, LEV, GVG, CBZ, PN, PLP, PB, Lederfoline,	LEV, VPA, LTG	PB, CBZ, VPA, LEV, GVG, steroids, PHT

															Biotine		
ED efficacy	Resistant to AEDs; best response to PHT	Resistant to AEDs; best response to PHT	Resistant to AEDs	Resistant to AEDs; partially responsive to PHT and VNS	Resistant to AEDs	Responsive to PHT and CBZ	Responsive: to RUF and LTG,	Partially responsive to CBZ	Best response to high dose of PHT	Resistant to AEDs	Best response to PHT and high-dose of PB	Partially responsive to VPA	Resistant to AEDs	Resistant to AEDs	AEDs-responsive	AEDs-responsive	Best response to PB and PHT
DEVELOPMENT																	
evelopment prior seizure onset	normal	normal	abnormal	abnormal	abnormal	normal	normal	abnormal	normal	abnormal	abnormal	normal	normal	normal	normal	normal	normal
D	severe	severe	severe	severe	moderate	no	moderate	mild	severe	severe	severe	moderate	n.a.	moderate	moderate	no	moderate
SD	n.a.	n.a.	n.a.	n.a.	yes	no	yes	very tight	yes	yes	no	yes	no	yes	yes	no	yes
BRAIN MR																	
irst brain MR/age	Normal/6m	Normal/4m	Normal/5d	Normal/1y	Normal/21d	Normal/3d	Mild chiari I malformation/14d	Tight T2 weighted hyper intensity of the parietal areas, cerebellum and brain stem/15d	Mild cerebral and cerebellar atrophy/3y	Mild enlargement of lateral ventricle/7y	Mild cerebral atrophy/6m	Mild cerebral atrophy/4m	Unspecific white matter abnormalities/5d	Normal/1y	Normal/21d	Normal/4m	Normal/4m
econd brain IR/age	Cerebellar atrophy/6y	Cerebellar atrophy/3y	Cerebral atrophy/2y	Cerebellar atrophy/8y	Bilateral mesial temporal sclerosis (R>L), mild prominence of cerebellar folia/12y	No	Mild chiari I malformation/2y	n.a.	Mild cerebral and cerebellar atrophy/8y	Mild enlargement of lateral ventricle/13 y	Diffuse cerebral atrophy/1y7 m	Mild cerebral atrophy/2y9 m	Normal/10d	Normal/4y	Normal/2y	Normal/3y4 m	No

Table Legend: A= Absences; AS= atonic seizure; ASD= autism spectrum disorder; AZA= acetazolamide; BG= background activity; CBZ= carbamazepine; CZP= clonazepam; d= days; ES= epileptic spasm; ESM= etosuximide; F= female; FS= focal seizure; FTS=focal tonic seizure; FU= follow-up; GBP= gabapentin; GTCS= generalized tonic-clonic seizure; GVG= vigabatrin; ID= intellectual disability; KBr= potassium bromide; KD= ketogenic diet; L= left; LEV= levetiracetam; LTG= lamotrigine; M= male; m= months; MS= myoclonic seizure; n.a.= not available; NZP= nitrazepam; OXC= oxcarbazepine; PB= phenobarbital; PER= perampanel; PHT= phenytoin; PLP= pyridoxal-5-phosphate; PN= pyridoxine; PRG= pregabalin; R= right; RTG= retigabine; RUF= rufinamide; SE=status epilepticus; SW= spike and wave; TPM= topiramate; TS= tonic seizure; VNS= vagal nerve stimulation; VPA= valproate; y=years; ZNS= zonisamide.