Epilepsy of Infancy With Migrating Focal Seizures (EIMFS): Expansion of Clinical Phenotypic And Genotypic Spectra

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Abstract

EIMFS is a rare early infantile epileptic encephalopathy with unknown etiology and poor prognosis. This study included 36 patients who were diagnosed with EIMFS. 17/36 cases had causative variants across 11 genes, including 6 novel EIMFS genes: *PCDH19*, *ALDH7A1*, *DOCK6*, *PRRT2*, *ALG1* and *ATP7A*. 13/36 patients had ineffective seizure control, 14/36 patients had severe retardation and 6/36 patients died. Of them, the genes for ineffective seizure control, severe retardation or death include *KCNT1*, *SCN2A*, *SCN1A*, *ALG1*, *ATP7A* and *WWOX*. 17 patients had abnormal MRI, of which 8 had ineffective seizure control, 7 had severe retardation and 4 died. 13 patients had hypsarrhythmia, of which 6 had ineffective seizure control, 6 had severe retardation and 2 died. Also, 7 patients had burst suppression, of which 1 had ineffective seizure control, 3 had severe retardation and 3 died. This study is the first to report that *ALDH7A1*, *ATP7A*, *DOCK6*, *PRRT2*, *ALG1*, and *PCDH19* mutations cause the phenotypic spectrum of EIMFS to expand the genotypic spectrum. The genes *KCNT1*, *SCN2A*, *SCN1A*, *ALG1*, *ATP7A* and *WWOX* may be associated with poor prognosis. The patients presenting with MRI abnormalities, hypsarrhythmia and burst suppression in EEG may be associated with poor prognosis.

Background

Epilepsy of infancy with migrating focal seizures (EIMFS) syndrome, which was first reported in 1995 [1], is a rare early infantile epileptic encephalopathy with poor prognosis, presenting with focal seizures in the first year of life. The main clinical features are seizure onset in the first 6 months of life, occurrence of almost continuous migrating polymorphous focal seizures, combined with multifocal ictal electroencephalography (EEG) discharges, and progressive deterioration of psychomotor development [2].

Previously, EIMFS was reported as an epilepsy syndrome with unknown etiology and poor prognosis [3]. Currently, in pace with the continuous development of genetic techniques, an increasing number of novel pathogenic genes have been shown to be related to EIMFS, including *GABRA1*, *GABRB1*, *GABRB3*, *KCNQ2*, *BRAT1*, *HCN1*, *SCN8A*, *SMC1A*, *TBC1D24*, *QARS*, *ATP1A3*, *CDKL5*, *PIGA*, *ITPA*, *AIMP1*, *KARS*, *WWOX*, *KCNT1*, *TBC1D24*, *SLC25A22*, *SCN1A*, *SCN2A*, *SLC12A5*, *PLCB1* and *PNPO* [2, 4–6]. Correspondingly, precision medicine treatments were adopted and partly improved patient outcomes. This study included 36 patients who were diagnosed with EIMFS; the clinical features, etiology, treatment strategies and outcomes of these patients were determined to explore new genetic etiology and new precision medicine treatment strategies.

Results

Clinical phenotypic spectrum

A total of 36 patients were enrolled in this study, and all patients fulfilled the inclusion criteria. We presented the phenotypic summary of the cohort (Table 1). Among them, 25 (69.4%) were male, and 11 (30.6%) were female. Eleven patients (30.6%) had seizure onset at 4 hours to 3 days after birth. Ten (27.8%) patients had a family history of epilepsy, febrile seizure or mental retardation, or stillbirth. There were 10 (27.8%) patients with congenital heart disease, 8 (22.2%) patients with perinatal history, 1 (2.8%) patients with intracranial hemorrhage, 1 (2.8%) patients with inguinal hernia, 3 (8.3%) patient with intracranial infection, 1 (2.8%) patient with Menkes disease and 1 (2.8%) patient with congenital disorder of glycosylation, type Ik.

Table 1
Clinical features of the 36 children with MMPSI

Feature	Incidence
Males: females	25:11 (2.3)
Age 4 hours to 3 days at onset	11/36 (30.6%)
Age≦6 months at onset	31/36 (86.1%)
Family history of epilepsy, febrile seizure or mental retardation, stillbirth	10/36(27.8%)
Combined diseases	1/36(2.8%)
Congenital disorder of glycosylation, type Ik	1/36(2.8%)
Menkes disease	3/36(8.3%)
Intracranial infection	1/36(2.8%)
Inguinal hernia	1/36(2.8%)
Intracranial hemorrhage	1/36(2.8%)
Premature	10/36(27.8%)
Congenital heart disease (open foramen ovale, patent ductus arteriosus)	8/36(22.2%)
Perinatal history (pneumonia, HIE, intrauterine distress)	2/36(5.6%)
Other (visual disturbance, pachygyria)	
Seizure type	
Migrating focal	36/36(100.0%)
Tonic	21/36(58.3%)
Spasms	8/36(22.2%)
Clonic	5/36(13.9%)
Others(tonic-clonic, autonomic nerve, etc)	8/36(22.2%)
EEG findings	36/36(100.0%)
Seizure migration	
Hypsarrhythmia	13/36(36.1%)
Burst suppression	7/36(19.4%)
Neuroimaging abnormal	
Cerebral atrophy	3/36(8.3%)
Forehead dysplasia / Widened brain space	4/36(11.1%)
Hippocampal sclerosis	3/36(8.3%)
Encephalomalacia foci	3/36(8.3%)
Subependymal cyst	5 /36(13.9%)
Dysplasia of the corpus callosum	1/36(2.8%)
Pachygyria	1/36(2.8%)
Genetic tests	
Chromosome karyotype analysis	1/36(2.8%)
Copy number variant analysis	1/36(2.8%)
Mitochondrial genome sequencing	3/36(8.3%)
Epilepsy genes panel	11/36(30.6%)
Whole exome sequencing	15/36(41.7%)
No genetic tests	10/36 (27.8%)
Seizure control	

Abbreviations: HIE= Hypoxic-ischemic encephalopathy; MMPSI=Malignant migrating partial seizures of infancy

Feature	Incidence
Seizure free	14/36(38.9%)
Reduced > 50%	9/36(25.0%)
Ineffective	13/36(36.1%)
Outcomes	
Severe retardation	14/36(38.9%)
Mild-moderate retardation	13/36(36.1%)
Normal	3/36(8.3%)
Death	6/36(16.7%)
Abbreviations: HIE= Hypoxic-ischemic encephalopathy; MMPSI=Malignant migrating partial seizures of infancy	

Seizure type at onset included migrating focal seizure (36/36, 100%); tonic seizure (21/36, 58.3%); spasms (8/36, 22.2%); clonic seizure (5/36, 13.9%) and tonic-clonic, autonomic seizures and others (8/36, 22.2%). Hypsarrhythmia (classic or modified) was seen in 13 (13/36, 36.1%) patients, and a burst-suppression pattern was observed in 7 (7/36, 19.4%) patients. All patients underwent brain MRI and/or CT examinations, 17 of whom had abnormal brain imaging findings. Diffuse cerebral atrophy (with an increase in extra axial fluid) was observed in 3 children. Four cases demonstrated forehead dysplasia or widened brain space, 3 presented with hippocampal sclerosis, 3 presented with encephalomalacia foci, 1 presented with dysplasia of the corpus callosum, 5 presented with subependymal cyst, 1 presented with pachygyria and 1 presented with meningeal reinforcement. Specifically, one of the 3 children with cerebral atrophy was accompanied with hippocampal sclerosis. One child had encephalomalacia foci, hippocampal sclerosis, subependymal cyst and widened brain space.

The etiological composition of the 36 patients in this cohort was determined by the International League Against Epilepsy (ILAE) 2017 etiological classification criteria. Accordingly, there were 17 (17/36, 47.2%) cases of inheritance, of which 6 (6/17, 35.3%) had severe retardation, 3 (3/17, 17.6%) died and 2 (2/17, 11.8%) was normal. There were 17 (17/36, 47.2%) cases of structure (8 cases were inherited), of which 7 (7/17, 41.2%) had severe retardation, 4 (4/17, 23.5%) died and 1 (1/17, 5.9%) was normal. Three patient (3/36, 8.3%) had infectivity indications, and 1 died. There were two (2/36, 5.6%) cases of metabolic syndrome (both cases were inherited), of which 1 had severe retardation and 1 died. There was no immunity and 10 (10/36, 27.8%) cases for unknown reasons, of which 5 (5/10, 50.0%) had severe retardation and 1 (1/10, 10.0%) were normal.

Genotypic Spectrum

There were 26 (26/36, 72.2%) patients who underwent genetic testing, including 15 (15/26, 57.7%) with whole exome sequencing (WES), 11 (11/26, 42.3%) with an epilepsy gene panel, 3 (3/26, 11.5%) with mitochondrial genome sequencing, 1 (1/26, 3.8%) with chromosome karyotype analysis and 1 (1/26, 3.8%) with copy number variant (CNV). Specifically, one of the 2 patients with mitochondrial genome sequencing and WES, one of the 1 patient with mitochondrial genome sequencing, WES, chromosome karyotype analysis and CNV. Seventeen (17/36, 47.2%) cases had causative variants across 11 genes (Table 2), including 6 novel EIMFS genes: de novol *PCDH19*; paternal *ALDH7A1*, *DOCK6*, *PRRT2* and *ALG1*; maternal *ALDH7A1*, *ATP7A*, *DOCK6* and *ALG1*. Five genes have been reported in previous literature, including de novo *KCNT1*, *SCN2A*, *SCN1A*, paternal *PNPO*, *WWOX*, maternal *PNPO* and *WWOX*. The most frequently implicated genes were *KCNT1* (3/36, 8.3%) and *SCN2A*(6/36, 16.7%).

Table 2
Variants in novel MMPSI genes and in silico analysis of pathogenicity

Patient	Gene	Inheritance	gDNA(GRCh37/hg19)	Amino acid	rs ID	ExAc and gnomAD	Poly-phen2	SIFT	How identi
1	*KCNT1*	*De Novo*	Chr9:138651532G>A	p.G288S	rs587777264	0;0	PD	T	WES
2	*KCNT1*	*De Novo*	Chr9:138660694G>A	p.R474H	rs397515404	0;0	PD	D	WES
3	*KCNT1*	*De Novo*	Chr9:138670635C>T	p.A899V	-	0;0	PD	D	panel
4	*SCN2A*	Maternal	Chr2:166246069G>A	p.R1918H	rs201718767	0.00004957203;0.000129241	B	T	WES
5	*SCN2A*	*De Novo*	Chr2:166237654G>A	p.A1500T	-	0;0	PD	D	WES
6	*SCN2A*	*De Novo*	Chr2:166237657A>G	p.M1501V	-	0;0	PD	D	panel
7	*ALDH7A1#*	Paternal	Chr5:125889987G>T	p.G398W	rs1347421419	0;0	PD	D	WES
		Maternal	Chr5:125918644dupA	p.I139fs	-	0;0	NA	NA	
8	*PNPO*	Paternal	Chr17:46022062G>A	p.S115N	-	0;0	PD	D	panel
		Maternal	Chr17:46023290C>T	p.R161C	rs146027425	0;0.00002473207	PD	D	
9	*SCN1A*	*De Novo*	Chr2:166909430T>C	p.L209P	NA	0;0	PD	D	panel
10	*WWOX*	Maternal	Chr16:78133677T>C	p.M1?	rs758588684	0;0.0000323039	PD	D	WES
	WWOX	Paternal	Chr16:78148874C>T	p.H78Y	-	0;0	PD	D	
	ATP7A#	Maternal	ChrX:77271345DelG	p.G865Dfs*5	-	0;0	PD	D	
11	*DOCK6#*	Maternal	Chr19:11324989T>C	p.Q1434X	rs1194206302 rs868514448	0;0	NA	NA	WES
	DOCK6#	Paternal	Chr19:11354308G>A	p.A395T		0;0.00000822145	PD	D	
12	*PRRT2#*	Paternal	Chr16:29825016DupC	p.R217Pfs*8	rs772994486	0;0	NA	NA	WES
13	*PCDH19#*	*De Novo*	ChrX:99662806G>C	p.D264H	-	0;0	PD	D	panel
14	*ALG1*	Maternal	Chr16:5123195C>A	p.Q110K	rs774489344	0;0	PD	D	WES
		Paternal	Chr16:5129065A>G	NA	rs768733117	0.000017;0	NA	NA	
15	*SCN2A*	*De Novo*	Chr2:166164381	p.C137Y	-	0;0	PD	D	WES
16	*SCN2A*	*De Novo*	Chr2:166170520	p.G429L	rs1553568987	-	PD	D	WES
17	*SCN2A*	*De Novo*	Chr2:166165304	p.A202V	-	-	PD	D	WES

Abbreviations: ACMG= American College of Medical Genetics; B = Benign; CMA = clinical microarray; CNV=Copy Number Variant; D = Deleterious; ExAC = Exo Consortium; gnomAD = Genome Aggregation Database; LP = likely pathogenic; MMPSI=Malignant migrating partial seizures of infancy; NA = Not applicable: mutation is nonsense or frameshift mutation, the software can not predict the pathogenicity of the mutation; P = pathogenic; PD = Possibly Damaging; SIFT from Tolerant; T = Tolerated; VUS = variant of unknown significance; WES = Whole Exome Sequencing; #: novel gene

Eimfs Phenotype-genotype Correlation

Phenotypic data are summarized according to each gene in Table 3. We highlight the phenotypes of the five most frequently implicated genes for EIMFS here.

Table 3
Phenotype-genotype data of 36 patients with MMPSI

	n	Age (M)	Age seizure onset (M)	Age at death (M)	Seizure types (n)	MRI findings: Normal (n) Abnormal (n)	EEG fingdings: Hypsarrhythmia (n); Burst suppression (n)	Effective drugs (n)	Seizure control: Seizure free (n) Reduced > 50% (n) Ineffective (n)	Outcomes: Severe retardation (n); Mild-moderate retardation (n); Normal (n); Death (n)
Cohort	36	1y8m	2m	8m	F(36); T(20); C(5); S(8); O(8)	19; 17	13; 6	9 (OXC, VGB, CBZ, Vitamin B6, ACTH, LEV, VPA, CLP, TPM)	14; 9; 13	14; 13; 3; 6
Patients without genetic diagnosis										
*Gene negative	19	1y8m	2m	6m	F(19); T(12); C3); S(1); O(3)	10; 9	6; 2	3(LEV, TPM, VPA)	6; 6; 7	8; 7; 1; 3
Patients with genetic diagnosis										
Gene positive	17	1y4m	2m	2y	F(17); T(8); C(2); S(7); O(5)	9; 8	7; 4	9 (OXC, VGB, CBZ, Vitamin B6, ACTH, VPA, CLP, TPM, LEV)	9; 2; 6	6; 6; 2; 3
Dominant Genes (11/36, 30.6%, 3 female)										
KCNT1	3	1y4m	1m	2y	F(3); T(1); S(2); O(2)	3; 0	2; 1	-	0; 0; 3	2; 0; 0; 1
SCN2A	6	1y5m	2d	-	F(6); T(4); S(2); O(1)	2; 4	3; 2	4(OXC, CBZ, VGB, LEV)	4; 1; 1	3; 3; 0; 0
SCN1A	1	6m	2m	6m	F(1); T(1); S(1); O(1)	1; 0	0; 0	-	1; 0; 0	0; 0; 0; 1
PRRT2	1	10.5m	3m	-	F(1)	1; 0	0; 0	1(OXC)	1; 0; 0	0; 0; 1; 0
Recessive Genes (5/36, 13.9%, 1 female)										
ALDH7A1	1	3y10m	1m	-	F(1) C(1)	1; 0	0; 0	1(Vitamin B6)	1; 0; 0	0; 1; 0;0
PNPO#	1	4y4m	2d	-	F(1)	0; 1	0; 0	1(Vitamin B6)	1; 0; 0	0; 0; 1; 0
*WWOX***	1	6m	3.5m	-	F(1)	0; 1	0; 0	1(OXC)	0; 0; 1	1; 0; 0; 0

Abbreviations: ACTH=Adrenocorticotropic Hormone; C=clonic; CLP=Clonazepam; CBZ=Carbamazepine; F=focal; m=months; M=median; MMPSI=Malignant migrating partial seizures of infancyn=number; LEV=Levetiracetam; O=other (includes tonic-clonic, spasms and others); OXC=Oxcarbazepine; S=spasms; T=tonic; TPM=Topiramate; VGB=Vigabatrin; VPA=Valproic Acid; y=year; *: Gene negative patients include those who have had a genetic test and the result was negative and those who have not been tested; **: one patient has two genetic mutations.; #: The mutant was female.

	n	Age (M)	Age seizure onset (M)	Age at death (M)	Seizure types (n)	MRI findings: Normal (n) Abnormal (n)	EEG fingdings: Hypsarrhythmia (n); Burst suppression (n)	Effective drugs (n)	Seizure control: Seizure free (n) Reduced > 50% (n) Ineffective (n)	Outcomes: Severe retardation (n); Mild-moderate retardation (n); Normal (n); Death (n)
DOCK6	1	2y7m	6m	-	F(1) S(1)	0; 1	1; 0	2(ACTH, VGB)	1; 0; 0	1; 0; 0; 0
ALG1	1	1y	4m	1y	F(1) C(1)	0; 1	0; 0	-	0; 0; 1	0; 0; 0; 1
X-linked Genes (2/36, 5.6%, 1 female)										
*ATP7A***	1	6m	3.5m	-	F(1)	0; 1	0; 0	1(OXC)	0; 0; 1	1; 0; 0; 0
PCDH19#	1	2y11m	9m	-	F(1); T(1); S(1)	1; 0	1; 0	3(TPM, VPA, CLB)	0; 1; 0	0; 1; 0; 0

Abbreviations: ACTH=Adrenocorticotropic Hormone; C=clonic; CLP=Clonazepam; CBZ=Carbamazepine; F=focal; m=months; M=median; MMPSI=Malignant migrating partial seizures of infancyn=number; LEV=Levetiracetam; O=other (includes tonic-clonic, spasms and others); OXC=Oxcarbazepine; S=spasms; T=tonic; TPM=Topiramate; VGB=Vigabatrin; VPA=Valproic Acid; y=year; *: Gene negative patients include those who have had a genetic test and the result was negative and those who have not been tested; **: one patient has two genetic mutations.; #: The mutant was female.

KCNT1 EIMFS patients (n=3)

Three patients (3 males) with *KCNT1* variants aged 1 year and 4 months to 2 years were studied (median 1 year 4months). The median seizure onset was 1 months (range 15 days to 4 months). All had focal seizures, 1 had tonic seizures, 2 had spasms seizures, and 2 had autonomic seizures. All had normal brain imaging findings. EEG showed seizure migration in all patients, hypsarrhythmia in 2/3, and burst suppression in 1/3. Two patients had severe developmental retardation, and one died. The age of death was 2 years.

SCN2A EIMFS (n=6)

There were 6 patients with *SCN2A* EIMFS studied at 1 month to 6 years of age (median 1 years 5 months) with median seizure onset at 2 days (range 1 day to 9 months). All had focal seizures, 4 had tonic seizures,2 had spasms seizures, and 1 had an autonomic seizure. A total of 2/6 had normal brain imaging findings, and 4/6 had abnormal imaging findings. EEG data showed seizure migration in all patients, hypsarrhythmia in 3/6, and burst suppression in 2/6. The effective drugs for 6 patients with seizure control were oxcarbazepine, carbamazepine, vigabatrin and levetiracetam. Three patients had severe developmental retardation, three patients had mild-moderate development retardation, and no patients died.

PNPO and *ALDH7A1* EIMFS (n=2)

One patient (female) with *PNPO* variants was studied at 4 years and 4 months of age. Seizure onset was 2 days after birth. She had focal seizures and abnormal brain imaging findings. One patient (male) with *ALDH7A1* variants was studied at 3 years and 10 months of age. Seizure onset was 1 month. He had focal and clonic seizures and normal brain imaging. There was no hypsarrhythmia or burst suppression in the EEG of these two patients. Vitamin B6 was effective in both patients. One patient had only mild development retardation, and one patient had normal development.

PRRT2 EIMFS (n=1)

One patient (female) with *PRRT2* variants was studied at 10.5 months of age. Seizure onset was 3 months. She had migarating focal seizures and normal brain imaging findings. Migarating focal seizures and no hypsarrhythmia or burst suppression was evident in the EEG data of the patient (Figure 1).

Oxcarbazepine was effective in controlling seizures in this patient, who had normal development.

Treatment

Antiepileptic treatment effects on seizures were analyzed in 36 patients with EIMFS (Table 3). In addition to classical antiepileptic drugs (AEDs), vitamin B6 and adrenocorticotropic hormones (ACTH) were used to treat EIMFS patients. Vitamin B6 allowed patients with *ALDH7A1* and *PNPO* mutations to achieve seizure-free status, oxcarbazepine was effective for patients with *SCN2A*, *ATP7A*, *WWOX*, and *PRRT2* mutations, and ACTH was partly effective for *DOCK6* mutation patients with spasms and hypsarrhythmia.

Outcome

We obtained data regarding seizure control and motor development for 36 patients: 14/36 (38.9%) patients were seizure free, and 9/36 (25.0%) patients had seizures reduced > 50%. However, 13/36 (36.1%) patients had ineffective seizure control. 14/36 (38.9%) patients had severe retardation, 13/36 (36.1%) patients had mild-moderate retardation, and 3/36 (8.3%) patients had normal development (Table 3). Our cohort had a high mortality rate: 6/36 (16.7%) patients died at a median age of 8 months (range 3 months to 2 years). In 3/6 patients who died, pathogenic variants were identified in the following genes: *KCNT1* (1), *SCN1A* (1) and *ALG1* (1), with 3 cases remaining unsolved. The genes for ineffective seizure control and severe retardation include *KCNT1* (2), *SCN2A* (1), *ATP7A* (1) and *WWOX* (1). Genes associated with seizure-free, mild-moderate retardation or normal of mental and motor development included *PRRT2* (1), *SCN2A* (3), *ALDH7A1* (1) and *PNPO* (1).

Of the 36 patients with EIMFS, 19 had normal MRI findings, of which 9 (9/19, 47.4%) were seizure free, 9 (9/19, 47.4%) had ineffective seizure control, 7 (7/19, 36.8%) had severe retardation and 2 (2/19, 10.5%) died. Also, 17 had abnormal MRI, of which 5 (5/17, 29.4%) were seizure free, 8 (8/17, 47.1%) had ineffective seizure control, 7 (7/17, 41.2%) had severe retardation and 4 (4/17, 23.5%) died. The details are shown in Table 4.

Table 4
The table of MRI and prognosis

MRI	Seizure control: Seizure free (%); Reduced > 50% (%); Ineffective (%)	Outcomes: Normal (%); Mild-moderate retardation (%); Severe retardation (%); Death (%)
Normal	9/19(47.4%)	2/19(10.5%)
	1/19(5.3%)	8/19(42.1%)
	9/19(47.4%)	7/19(36.8%)
		2/19(10.5%)
Abnormal	5/17(29.4%)	1/17(5.9%)
	4/17(23.5%)	5/17(29.4%)
	8/17(47.1%)	7/17(41.2%)
		4/17(23.5%)
Abbreviations: MRI=Magnetic resonance imaging		

Of the 36 patients with EIMFS, 13 had hypsarrhythmia, of which 5 (5/13, 38.5%) were seizure free, 6 (6/13, 46.1%) had ineffective seizure control, 6 (6/13, 46.1%) had severe retardation, 2 (2/13, 15.4%) died and 0 (0/13, 0%) were normal; also, 7 had burst suppression, of which 1 (1/7, 14.3%) were seizure free, 1 (1/7, 14.3%) had ineffective seizure control, 3 (3/7, 42.9%) had severe retardation, 3 (3/7, 42.9%) died and 0 (0/3, 0%) were normal. 3 patients had hypsarrhythmia and burst suppression, of which 1 (1/3, 33.3%) were seizure free, 1 (1/3, 33.3%) had ineffective seizure control, 2 (2/3, 66.7%) had severe retardation, 0 (0/3, 0%) died and 0 (0/3, 0%) were normal, and 19 had no hypsarrhythmia or burst suppression, of which 8 (8/19, 42.1%) were seizure free, 7 (7/19, 36.8%) had ineffective seizure control, 5 (5/19, 26.3%) had severe retardation, 2 (2/19, 10.5%) died and 3 (3/19, 15.8%) were normal. The details are shown in Table 5.

Table 5
The table of EEG and prognosis

EEG	Seizure control: Seizure free (%); Reduced > 50% (%); Ineffective (%)	Outcomes: Normal (%); Mild-moderate retardation (%); Severe retardation (%); Death (%)
Hypsarrhythmia	5/13 (38.5%); 2/13(15.4%); 6/13(46.1%)	0/13(0); 5/13(38.5%); 6/13(46.1%); 2/13(15.4%)
Burst suppression	1/7(14.3%); 5/7(71.4%); 1/7(14.3%)	0/7(0); 1/7(14.3%); 3/7(42.9%); 3/7(42.9%)
Hypsarrhythmia and burst suppression	1/3(33.3%); 1/3(33.3%); 1/3(33.3%)	0/3(0); 1/3(33.3%); 2/3(66.7%); 0/3(0)
No hypsarrhythmia and burst suppression	8/19(42.1%); 4/19(21.1%); 7/19(36.8%)	3/19(15.8%); 9/19(47.4%); 5/19(26.3%); 2/19(10.5%)

Abbreviations: EEG=Electroencephalogram

Discussion

EIMFS is characterized by nearly continuous seizures involving multiple independent areas of both hemispheres with arrested psychomotor development. It is an age-dependent, often overlooked syndrome among the epileptic encephalopathies that can occur within the first 6 months of life [7]. It may therefore be included among epileptic encephalopathies, together with others beginning in the same period, such as early infantile epileptic encephalopathy, early myoclonic encephalopathy, and infantile spasms [8]. The clinical manifestations of children with EIMFS are characterized by migrating and focal seizures, with an onset peak from 40 days to 3 months. Symptoms can manifest on EEG readings as diffuse slow waves in the background, multifocal discharge with or without spastic between episodes, typical or atypical hypsarrhythmia and never a suppression burst pattern [3]. EIMFS has no specific neuroimaging changes, and the neuroimaging abnormalities reported in the current literature include delayed myelination, abnormal signals in the basal ganglia, dysplasia in the corpus callosum, diffuse brain atrophy, microcephaly, multiple cortical developmental malformations with multiple cerebellar gyri, focal cortical dysplasia, and hippocampal sclerosis [2, 8, 9]. We described the phenotype spectrum of 36 patients with EIMFS in this study. All patients had clinical seizure migration associated with a significant impact on development. We identified several key phenotypic features that have only been rarely reported in the EIMFS phenotypic spectrum: 11 (11/36, 30.6%) patients had suspected in utero seizures with postnatal seizures described between 4 hours and 3 days, 8 (8/36, 22.2%) patients had epileptic spasms, 7 (7/36, 19.4%) had a burst-suppression pattern in EEG activity, 1 patient had congenital disorder of glycosylation—type Ik, 1 patient had Menkes disease, 3 patients had intracranial infection, 1 patient had inguinal hernia, 1 patient had intracranial hemorrhage, 1 patient had premature disease, 10 patients had congenital heart disease (open foramen ovale, patient ductus arteriosus), and 8 patients had a perinatal history (pneumonia, HIE, intrauterine distress). Furthermore, it is mostly believed that the etiology of EIMFS is caused by genetic mutations [7]. According to our etiological analysis, the genetic etiology accounted for 17/36 cases, and brain injury accounted for 17/36 cases, including 1 case of EIMFS caused by hypoxic-ischemic encephalopathy (HIE); hence, HIE sequelae can also lead to EIMFS. Analysis of etiology and prognosis results suggests that structural causes may be related to poor prognosis. Our data expand the clinical phenotype of EIMFS.

We describe the genotypic spectrum of 17 patients with EIMFS. We highlight the extensive genetic heterogeneity of EIMFS, which is similar to that in other epilepsy syndromes, such as infantile spasms (West syndrome) and Lennox-Gastaut syndrome, but with a considerably higher yield on current testing. We identified the etiology in 47.2% of our cohort, including 6 novel EIMFS genes. The most commonly involved genes were *KCNT1* (8.3%) and *SCN2A* (16.7%), together explaining 25.0% of EIMFS cases. Among the 3 patients with *KCNT1* gene mutations, the mutation sites of 1 patients were classified as a variant of unknown significance (VUS) by the American College of Medical Genetics (ACMG), and among the 6 patients with *SCN2A* gene mutations, the mutation site of 1 patient was classified as a VUS by the ACMG. However, according to the analysis of the clinical phenotypes and responses to drug therapy of the patients, we still believed that *KCNT1* and *SCN2A* were the pathogenic genes of patients. This pattern differs from that reported in patients with neonatal-onset developmental and epileptic encephalopathy [10], including Ohtahara syndrome [11], for which *KCNQ2* and *SCN2A* are most common. These studies highlight

the importance of classifying a patient's epilepsy syndrome, which influences genetic testing and interpretation [12]. Epileptic spasms have only been rarely reported in EIMFS patients [2]. In this series, 8/36 patients (22.2%) had epileptic spasms, including those with *KCNT1*, *SCN2A*, *SCN1A*, *DOCK6* and *PCDH19* variants. Epileptic spasms are a hallmark of *CDKL5* encephalopathy, but EIMFS had not been previously described in this disease. Whether other genes predispose patients with EIMFS to epileptic spasms will require studies with large cohorts to enable phenotype-genotype correlation.

The *PNPO* gene encodes pyridoxine 5-prime-phosphate oxidase, and the maintenance of optimal pyridoxal 5-prime-phosphate levels in the brain is important in many neurologic disorders in which neurotransmitter metabolism is disturbed, which is associated with autosomal recessive pyridoxamine 5'-phosphate oxidase deficiency [13]. The *PNPO* gene was EIMFS-related genes reported in previous literature. In our study cohort, although the mutation sites of the gene were classified as VUS by the ACMG, taking into account the analysis of the clinical phenotypes and responses to drug therapy of the patient, we still believed that *PNPO* was the pathogenic genes of patients.

We discovered 6 novel EIMFS genes in our cohort - de novo *PCDH19*; paternal *ALDH7A1*, *DOCK6*, *PRRT2* and *ALG1*; and maternal *ALDH7A1*, *ATP7A*, *DOCK6* and *ALG1* - encoding a wide range of proteins. These genes have not been described in patients with EIMFS, but they have been associated with other neurological diseases.

Considering the *PCDH19* gene first, most of the *PCDH19* gene variants resulted in protein termination and nonsense-mediated decay and affected *PCDH19* through impaired calcium binding, which is associated with X-linked early infantile epileptic encephalopathy-9 (EIEE-9) in females [14]. Considering that one of our patients was a female and had a de novo mutation of the *PCDH19* gene, which is consistent with the X-linked genetic classification and the common clinical phenotype of spasms seizure and delayed motor development, the software predicted the likely pathogenicity of the mutation; thus, these findings suggest that the *PCDH19* gene could be associated with EIMFS.

The *ALDH7A1* gene encodes an aldehyde dehydrogenase that is an alpha-aminoadipic semialdehyde dehydrogenase in the pipecolic acid pathway of lysine catabolism, which is associated with autosomal recessive pyridoxine-dependent epilepsy [15]. Considering that some of our patients had paternal and maternal mutations of the *ALDH7A1* gene, which is consistent with the autosomal recessive genetic classification and the common clinical phenotype of seizures, delayed motor development and effective treatment with vitamin B6, the software predicted the likely pathogenicity of the mutation; thus, these findings suggest that the *ALDH7A1* gene could be associated with EIMFS.

DOCK6 belongs to subfamily C of the *DOCK* family and has a role in remodeling the actin cytoskeleton by functioning as a GEF for both CDC42 and RAC1 [16], which is associated with autosomal recessive Adams-Oliver syndrome-2. Adams-Oliver syndrome is a multiple congenital anomaly syndrome that is characterized by aplasia cutis congenita (ACC) as well as terminal transverse limb defects (TTLD) in addition to variable involvement of the brain, eyes, and cardiovascular system [17]. Although one of our patients had maternal and paternal mutations of the *DOCK6* gene, which is consistent with the autosomal recessive genetic classification, and the software predicted the likely pathogenicity of the mutation, the patient lacked the typical clinical phenotype of Adams-Oliver syndrome-2. Therefore, we could not determine whether the *DOCK6* gene was the causative gene of EIMFS, and further data are needed for verification.

The *PRRT2* gene encodes proline transmembrane protein 2 and is involved in signal transduction between neurons. *PRRT2*-associated paroxysmal movement disorders (*PRRT2*-PxMD) include autosomal dominant genetic paroxysmal kinesigenic dyskinesia (PKD), benign familial infantile epilepsy (BFIE), paroxysmal kinesigenic dyskinesia with infantile convulsions (PKD/IC), and hemiplegic migraine (HM). The characteristics of BFIE include early onset, cluster seizures that could be self-healing or that respond well to the treatment of sodium channel blockers, and normal development. In addition, *PRRT2* pathogenic variants have been identified in other childhood-onset movement disorders and different types of seizures, suggesting that the understanding of the spectrum of *PRRT2*-PxMD is still evolving [18]. The patient with this mutation in our cohort was very interesting. He presented with very frequent cluster seizures when he was 3 months old, video-EEG demonstrated migrating focal seizures and typical background characteristics of EIMFS, and he experienced obvious cognitive retardation after the onset of epilepsy. He achieved seizure-free status after the administration of oxcarbazepine, and follow-up showed normal cognitive development. The patient had a paternal mutation of the *PRRT2* gene—his father had symptoms of dystonia in his youth—and the software predicted the likely pathogenicity of the mutation. We considered that the *PRRT2* gene was the causative gene of EIMFS, and further data were needed for verification.

In the 10th patient, two pathogenic genes were detected simultaneously, namely, *WWOX* and *ATP7A*. The clinical phenotypes reported in the literature were X-linked Menkes disease, occipital horn syndrome, distal spinal muscular atrophy 3, epileptic encephalopathy, early infantile 28, esophageal squamous cell carcinoma, somatic and spinocerebellar ataxia, and autosomal recessive 12, which theoretically can cause epileptic encephalopathy [19–23]. This patient also had a significant decrease in blue copper protein, had hair and skin color changes and could have been diagnosed with Menkes disease. *WWOX* conformed to the genetic classification. One of the two mutation sites was a pathogenic mutation, and the other was a VUS. We could not confirm whether it was a copathogenic gene.

The *ALG1* gene encodes mannosyltransferase I (MT I). The biosynthesis of lipid-linked oligosaccharides is highly conserved among eukaryotes and is catalyzed by 14 glycosyltransferases in an ordered stepwise manner. MT I catalyzes the first mannosylation step in this process [24]. The gene variants can result in autosomal recessive congenital disorder of glycosylation type Ik [25, 26]. The characteristics of congenital disorder of glycosylation type Ik includes feeding problems and diarrhea, profound hypoproteinemia with massive ascites, muscular hypertonia, seizures refractory to treatment, recurrent episodes of apnea, cardiac and hepatic involvement and coagulation anomalies [27]. The clinical characteristics of this patient were consistent with the above core symptoms, the genetic results were consistent with the law of autosomal recessive inheritance, and the software predicted the likely pathogenicity of the mutation. We considered the *ALG1* gene to be a newly pathogenic gene of EIMFS.

Most patients with EIMFS are refractory to AEDs, but some have shown good progression or a near satisfactory response to treatment. The AEDs used alone or in combination with one another that may achieve seizure control or reduction are potassium bromide, levetiracetam, ACTH, stiripentol, clonazepam, and rufinamide [28]. Mikati et al. reported that quinidine is effective in the treatment of patients with *KCNT1* gene mutations in EIMFS [29]. At present, there are few

literature reports on the use of corresponding effective drug treatments for patients with different EIMFS gene mutations. In our cohort, we determined that vitamin B6 could allow patients with *ALDH7A1* and *PNPO* mutations to achieve seizure-free status. Oxcarbazepine was effective for patients with *SCN2A*, *ATP7A*+*WWOX*, and *PRRT2* mutations. One of the patients with a maternal *SCN2A* heterozygous mutation was treated with oxcarbazepine; subsequently, the patient's convulsions were controlled. The patient's mother had a normal heterozygote phenotype, which was consistent with the pathogenesis of autosomal dominant inheritance (incomplete penetrance). ACTH was partly effective for patients with *DOCK6* mutations who had spasms and hypsarrhythmia.

While seizure outcomes and developmental prognoses are generally poor in EIMFS, there are rare reports of mildly affected patients [30]. In our study cohort, the incidence of poor prognosis was also relatively high; 6/36 (16.7%) patients died, and the related pathogenic genes were *KCNT1*, *SCN1A*, *ALG1*. 14/36 (38.9%) patients had severe retardation, and the genes for ineffective seizure control and severe retardation included *KCNT1*, *SCN2A*, *WWOX* and *ATP7A*. The results indicated that the related pathogenic genes *KCNT1*, *SCN1A*, *ALG1*, *SCN2A*, *WWOX* and *ATP7A* may be associated with ineffective seizure control and poor prognoses. While all patients experienced refractory epilepsy early in the course of the disease, 3/36 (8.3%) patients had normal mental and motor development. Genes associated with seizure-free, mild-moderate retardation or normal of mental and motor development included *PRRT2*, *SCN2A*, *ALDH7A1*, *PCDH19* and *PNPO*.

In addition, we compared the association of MRI abnormalities, hypsarrhythmia and burst suppression in EEG with poor prognosis. The results found that patients with EIMFS characterized by abnormal MRI, hypsarrhythmia and burst suppression in EEG have a higher incidence of ineffective seizure control, severe retardation and a higher mortality rate. The results suggest that EIMFS patients who present with abnormal MRI, hypsarrhythmia and burst suppression in EEG may be associated with ineffective seizure control and poor prognosis. We need to further expand the sample to analyze and confirm these correlations.

Conclusions

In conclusion, our study expands the EIMFS clinical phenotype and genotype spectra. EIMFS patients who present with abnormal MRI findings, hypsarrhythmia and burst suppression in EEG may be associated with ineffective seizure control and poor prognosis. Etiological analysis showed that in addition to genetic mutations, structural brain injury such as HIE could also be secondary to EIMFS, and structural and infectious etiology may be associated with poor prognosis. This study is the first to report that *ALDH7A1*, *ATP7A*, *DOCK6*, *PRRT2*, *ALG1*, and *PCDH19* mutations cause the phenotypic spectrum of EIMFS. The genes *KCNT1*, *SCN1A*, *ALG1*, *SCN2A*, *WWOX* and *ATP7A* may be associated with ineffective seizure control and poor prognosis. Through early diagnosis with genetic tests and the administration of the corresponding precise treatment, the outcomes of EIMFS can be notably improved.

Methods

Participants and phenotyping

Our EIMFS cohort comprised 36 patients from Hunan Children's Hospital and Qilu Hospital of Shandong University. A multicenter retrospective case study was performed over a 10-year period (January 2010 to January 2020). The parents of the patients provided written, informed consent. This study was approved by the Medical Ethics Committee of Hunan Children's Hospital and Qilu Hospital of Shangdong University.

According to the clinical characteristics of EIMFS described by Coppola [1], the inclusion criteria are as follows: (1) onset within 6 months after birth; (2) migrating focal seizures at onset; (3) multifocal seizures intractable to conventional antiepileptic drugs; (4) the EEG during the onset period is characterized by multifocal discharges, migrating in one hemisphere or between the two hemispheres, involving multiple parts, and the clinical onset is closely related to the time and location of the EEG discharge; and (5) delayed developmental progress or signs of psychomotor regression associated with seizure onset. The phenotypic information of all patients was collated on clinical presentation, disease course, EEG, neuroimaging, treatment strategies and the results of neurometabolic and diagnostic genetic investigations. All patients were followed up every 1-6 months by telephone or outpatient department.

It should be noted in particular that one of our patients met the inclusion criteria except for the onset age of 9 months. Considering that EIMFS with onset age of 9 months has been reported in literatures, we still included this patient in our study cohort.

Genetic Tests

Genetic testing was carried out using chromosome karyotype analysis, CNV analysis, mitochondrial genome sequencing, epilepsy gene panels and WES. CNV analysis was performed with the Illumina HumanOmniZhonghua-8 Bead Chip; Mitochondrial genome sequencing was subsequently performed on an Illumina HiSeq 2000 platform (Illumina, San Diego, CA, USA); details were provided by our team previously[31]. The epilepsy gene panel contained 265 epilepsy-associated genes was performed on methods previously reported by Lemke et al [32]. WES was also performed based on methods previously reported by our team [31] by using Illumina HiSeq X Ten (Illumina, San Diego, CA, USA) with 150-bp paired-end reads.

Abbreviations

AEDs: antiepileptic drugs; ACTH: adrenocorticotropic hormones; ACC: aplasia cutis congenita; BFIE: benign familial infantile epilepsy; CNV: copy number variant; EEG: electroencephalography; EIEE-9: early infantile epileptic encephalopathy-9; HM: hemiplegic migraine; EIMFS: Epilepsy of Infancy with Migrating Focal Seizures; HIE: hypoxic-ischemic encephalopathy; ILAE: International League Against Epilepsy; IC: infantile convulsions; MT I: mannosyltransferase I; PRRT2-PxMD: PRRT2-associated paroxysmal movement disorders; PKD: paroxysmal kinesigenic dyskinesia; TTLD: terminal transverse limb defects; VUS: variant of unknown significance; WES: whole exome sequencing

Declarations

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Authors' contributions

LW conducted the literature review and drafted the manuscript. FC, SG and SY made substantial contributions to the conception and interpretation of data. XY and HY were responsible for revising the manuscript critically and gave final approval of the version to be published.

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Data Availability Statement

The datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

The study was performed in accordance with the Declaration of Helsinki, with the approval of the study protocol by an independent ethics committee or institutional review board at each site. All patients provided written informed consent before participation.

Consent for publication

All authors have approved the final article and its publication.

Conflict of interest

The authors declare that they have no competing interests.

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Figures

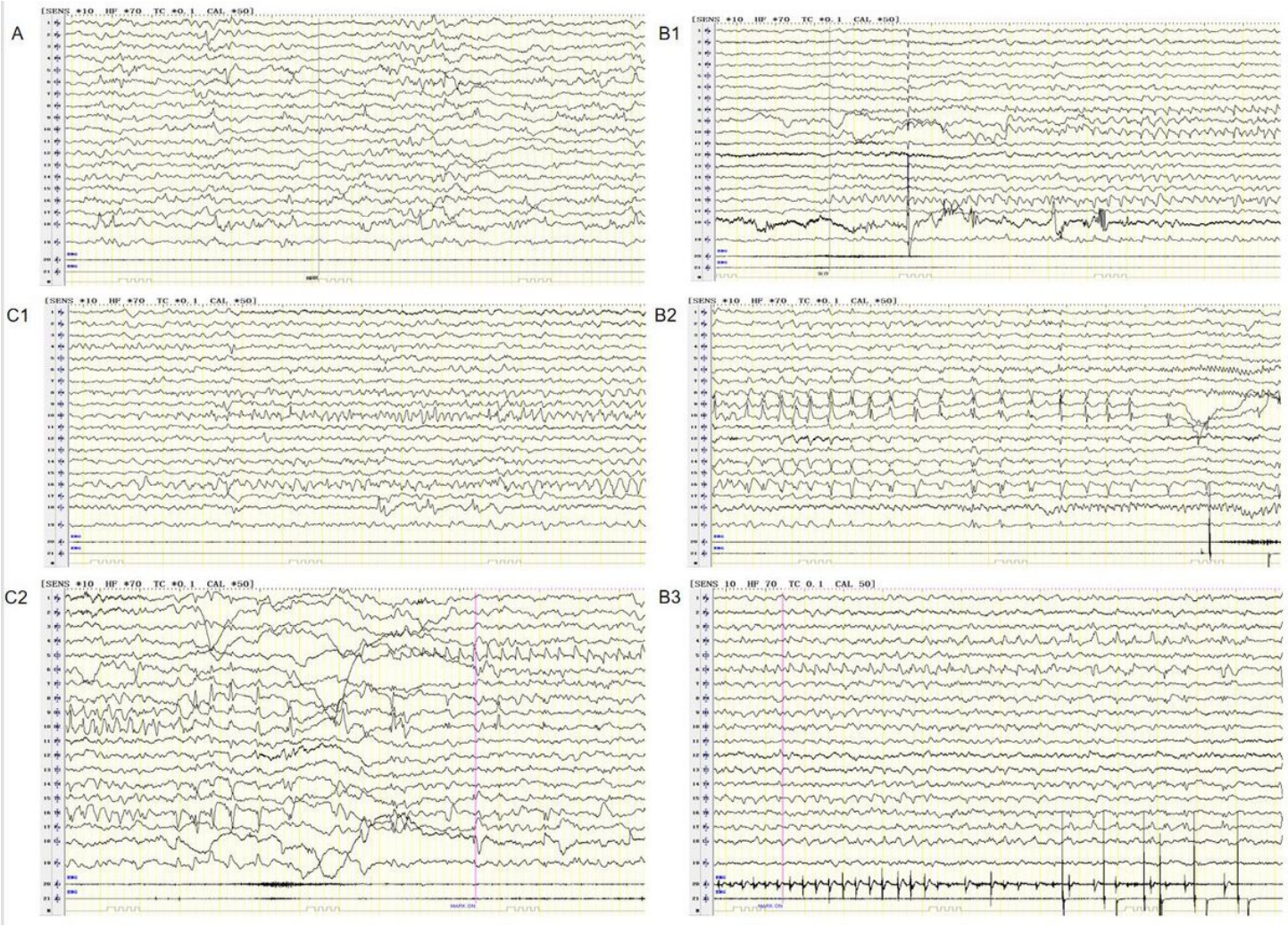

Figure 1

Migrating focal seizures was evident in the EEG data of the patient with PRRT2 gene mutation. A: Interictal period showed multifocal discharge; B1: Focal seizures originating in the right occipital and posterior temporal regions; B2: More than 10 seconds later, the epileptiform electrical seizure in the right posterior occipital temporal region relieved, and electrical rhythm changes appeared in the right central region. B3: Convulsions of the left upper limb, simultaneous electrical seizures in the right central region; C1: Focal seizures originating in the right occipital and posterior temporal regions; C2: Focal seizures migrate to the left central region.