Seizure: European Journal of Epilepsy 69 (2019) 228–234

Contents lists available at ScienceDirect

Seizure: European Journal of Epilepsy

journal homepage: www.elsevier.com/locate/seizure

Infantile epilepsy with multifocal myoclonus caused by *TBC1D24* mutations

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ARTICLE INFO

Keywords:
TBC1D24
Epilepsy
Epilepsia partialis continua
Brain atrophy
Hearing loss

ABSTRACT

Purpose: To summarize the clinical features and neuroimaging changes of epilepsy associated with *TBC1D24* mutations.

Methods: Genetic testing was conducted in all epilepsy patients without acquired risk factors for epilepsy. Epilepsy patients identified with *TBC1D24* compound heterozygous mutations by next-generation sequencing (NGS) epilepsy panel or whole exome sequencing (WES) were enrolled. The enrolled patients were followed up to summarize the clinical features.

Results: Nineteen patients were identified with *TBC1D24* compound heterozygous mutations. Nine patients carried the same pathogenic variant c.241_252del. The seizure onset age ranged from 1 day to 8 months of age (median age 75 days). The most prominent features were multifocal myoclonus and epilepsia partialis continua (EPC). Myoclonus could be triggered by fever or infection in 15 patients, and could be terminated by sleep or sedation drugs. Psychomotor developmental delay was presented in 11 patients. Six patients exhibited hearing loss. Brain MRIs were abnormal in eight patients. Twelve patients were diagnosed with epilepsy syndromes including one patient who was diagnosed with Dravet syndrome. Two patients died due to status epilepticus at 4 months and 19 months of age, respectively.

Conclusion: *TBC1D24* mutation related epilepsy was drug-resistant. Multifocal myoclonus, EPC, and fever-induced seizures were common clinical features. Most patients presented psychomotor developmental delay. The neuroimaging abnormality and hearing loss could exacerbate during follow-up.

1. Introduction

The gene *TBC1D24*, TBC1 domain family member 24 (OMIM 613577), encodes a protein with an N-terminal Tre2–Bub2–Cdc16 (TBC) domain linked to a TBC–LysM (TLDc) domain [1]. The TBC domain is involved in vesicle trafficking in brain and somatic development, whereas the function of the TLDc domain is largely unknown [1,2]. In 2010, Falace et al. first mapped the familial infantile myoclonic epilepsy (FIME) locus on chromosome 16p13.3 by linkage analysis. Systematic mutational screening of 34 genes in two affected family members by Sanger sequencing identified two compound heterozygous missense mutations in *TBC1D24* [3]. In 2014, Rehman reported that *TBC1D24* mutations caused non-syndromic deafness [4]. With the broad application of next generation sequencing (NGS), more diseases associated with *TBC1D24* mutations were reported. These diseases included FIME [3], DOORS (deafness, onychodystrophy, osteodystrophy, mental retardation, and seizures) syndrome [5,6], progressive myoclonic epilepsy (PME) [7], epilepsy of infancy with migrating focal seizures (EIMFS) [8,9], early-infantile epileptic encephalopathy-16 (EIEE16) [10–12], and autosomal dominant or autosomal recessive non-syndromic hearing loss [13–16]. Epilepsia partialis continua (EPC) is clinically defined as a syndrome of continuous focal jerking of a body part, and these symptoms are usually localized to limbs and occur over hours, days or even years [17]. Ragona et al reported that a patient with *TBC1D24* compound heterozygous mutations presented with alternating hemiplegia and recurrent episodes of EPC [18]. EPC appears to be common in TBC1D24-related seizure disorders, and all *TBC1D24*-related types of epilepsies are likely part of the same spectrum. Here, we report 19 epilepsy patients with *TBC1D24* mutations and summarize the clinical features.

2. Materials and methods

Genetic testing was conducted in all children diagnosed with epilepsy without acquired factors at the Pediatric Neurology Clinic of Peking University First Hospital from March 2015 to July 2018.

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https://doi.org/10.1016/j.seizure.2019.05.010
Received 1 November 2018; Received in revised form 9 May 2019; Accepted 11 May 2019

Table 1
The clinical features and genotypes of 19 patients with *TBC1D24* mutations.

Case ID, Age at last follow-up, Gender	Age at seizure onset	EPC	Developmental delay	Nails of hands/feet	Hearing Screen (age)	MRI (age)	Syndrome classification	*TBC1D24* mutations	Transmission
1, 4 m, M	2 d	+	+	NA	profound sensorineural deafness (at birth)	normal (3 m)	EIMFS	c.619C > T (p.Gln207Ter) [20]	NA
								c.866C > T (p.Ala289Val) [9]	maternal
2, 3y4 m, M	2.5 m	+	+	normal/ normal	normal (2y)	normal (2y)	EIMFS	c.116C > T (p.Ala39Val) [21]	paternal
								c.1499C > T (p.Ala500Val) [2]	maternal
3, 5y, M	1.5 m	+	+	NA	ND, hearing normal	normal (2y)	EIMFS	c.116C > T (p.Ala39Val) [21]	maternal
								c.1499C > T (p.Ala500Val) [2]	paternal
4, 2y1m, F	1 m	+	+	normal/ normal	normal (2y)	normal (2y)	EIMFS	c.1153C > T (p.Gln385Ter)	paternal
								c.1499C > T (p.Ala500Val) [2]	maternal
5, 2y3 m, F	1 d	+	+	normal/ normal	normal (2y)	normal (1y)	EIEE	c.1499C > T (p.Ala500Val) [2]	maternal
								c.725 G > A (p.Arg242His)	paternal
6, 1y7m, M	1.5 m	+	+	NA	profound sensorineural deafness (at birth)	cerebral atrophy (1y)	EIEE	c.1523_1525delTCG (p.Val508del)	paternal
								c.116C > T (p.Ala39Val) [21]	maternal
7, 5y10 m, M	8 m	+	+	normal/ normal	ND, hearing normal	cerebellar atrophy with hyperintense T2 signals in cerebellar (5y)	Epileptic encephalopathy	c.116C > T (p.Ala39Val) [21]	maternal
								c.241_252del (p.Ile81_Lys84del) [21]	paternal
8, 2y4 m, F	2 m	+	+	NA	profound sensorineural deafness (at birth)	NA	EIEE	c.404C > T (p.Pro135Leu) [20]	maternal
								c.457 G > T (p.Glu153Ter) [22]	paternal
9, 4y7m, M	2 d	+	+	normal/the nails of bilateral fifth toes were hypoplasia	profound sensorineural deafness (at birth)	cerebral atrophy (1y3 m)	EIEE	c.442 G > A (p.Glu148Lys)	paternal
								c.431A > G (p.Tyr144Cys)	maternal
10, 10y3 m, F	7 m	+	+	normal/ normal	profound sensorineural deafness (9y) †	cerebral and cerebellar atrophy with hyperintense T2 signals in cerebellar (9y)	PME	c.241_252del (p.Ile81_Lys84del) [21]	paternal
								c.1153C > T (p.Gln385Ter)	maternal
11, 5y, M	3 m	+	+	normal/ normal	ND, hearing normal	cerebellar atrophy with hyperintense T2 signals in cerebellar (3y)	PME	c.241_252del (p.Ile81_Lys84del) [21]	maternal
								c.139A > G (p.Ser47Gly)	de novo
12, 6y2m, F	3 m	+	+	NA	ND, hearing normal	normal (5y)	Dravet syndrome	c.1544C > T (p.Ala515Val) [2]	NA
								c.1499C > T (p.Ala500Val) [2]	maternal
13, 7y1m, F	4 m	+	-	NA	profound sensorineural deafness (6y) ‡	normal (6y)	Unclassified	c.119 G > A (p.Arg40His) [6]	paternal
								c.241_252del (p.Ile81_Lys84del) [21]	maternal
14, 4y5m, M	7 m	+	-	normal/ normal	ND, hearing normal	cerebellar atrophy with hyperintense T2 signals in cerebellar (4y)	Unclassified	c.241_252del (p.Ile81_Lys84del) [21]	maternal
								c.1526-2A > C	paternal

(*continued on next page*)

Table 1 (*continued*)

Case ID, Age at last follow-up, Gender	Age at seizure onset	EPC	Developmental delay	Nails of hands/feet	Hearing Screen (age)	MRI (age)	Syndrome classification	*TBC1D24* mutations	Transmission
15, 3y1m, F	3 m	+	-	normal/ normal	normal (2y)	cerebellar atrophy (2y)	Unclassified	c.404C > T (p.Pro135Leu) [20] c.679C > T (p.Arg227Trp) [2]	maternal paternal
16, 4y, F	5 m	+	-	NA	normal (4y)	cerebellar atrophy with hyperintense T2 signals in cerebellar (4y)	Unclassified	c.116C > T (p.Ala39Val) [21] c.241_252del (p.Ile81_Lys84del) [21]	paternal maternal
17, 4y1m, F	6 m	+	-	normal/ normal	ND, hearing normal	normal (2y)	Unclassified	c.241_252del (p.Ile81_Lys84del) [21] c.1499C > T (p.Ala500Val) [2]	paternal maternal
18, 8y9m, M	8 m	+	-	NA	ND, hearing normal	normal (3y)	Unclassified	c.116C > T (p.Ala39Val) [21] c.241_252del (p.Ile81_Lys84del) [21]	maternal paternal
19, 2y4 m, M	4 m	+	-	normal/ normal	normal (2y4 m)	normal (1y)	Unclassified	c.151C > T (p.Arg51Trp) c.241_252del (p.Ile81_Lys84del) [21]	paternal maternal

Abbreviations: NA, not assessed; y, years; m, months; d, days; F, female; M, man; EPC, epilepsia partialis continua; EIMFS, epilepsy of infancy with migrating focal seizures; EIEE, early-infantile epileptic encephalopathy; PME, progressive myoclonic epilepsies; ND, Not done. †, hearing normal before the age of 9 years, then she had bilateral profound sensorineural deafness at 9 years old; ‡, hearing normal after birth, she was found with hearing difficulties after 3 years old, and she was identified with sensorineural deafness at the age of 6 years.

TBC1D24 mutations were identified using epilepsy NGS panels from March 2015 to June 2017. The test was conducted as singleton for proband. Segregation analysis was performed by Sanger sequencing with parental DNA samples for all *TBC1D24* variants to determine whether the variants were inherited from father/mother or arose de novo. The mutations were identified using trio-based whole exome sequencing (WES) from July 2017 to July 2018 due to the reduction of WES's cost. A customized panel capturing the coding exons of 153 genes associated with epilepsy (Supplementary Table 3) was synthesized by Agilent Technologies on a chip (MyGenostics, Baltimore, MD, USA). Targeted gene capture, massive parallel-sequencing, and sequence alignment were performed. For the WES, exon-enriched DNA was sequenced by the Illumina Hiseq2500 platform following the manufacturer's instructions. Synonymous variants and single nucleotide polymorphisms with minor allele frequency (MAF) higher than 5% were removed (http://gnomad.broadinstitute.org/). The longest *TBC1D24* isoform was referenced (NM_001199107.1, GRCh37/hg19). Human Splicing Finder (http://www.umd.be/HSF3/HSF.shtml) was used to determine whether variants affected mRNA splicing. Functional consequences were predicted by MutationTaster (http://www.mutationtaster.org/), Polyphen-2 (http://genetics.bwh.harvard.edu/pph2/), and SIFT (http://sift.jcvi.org/). Pathogenicity of variants was evaluated according to the American College of Medical Genetics and Genomics (ACMG) guidelines [19]. Identified variants were further validated by Sanger sequencing.

All epilepsy patients identified with *TBC1D24* mutations were followed in outpatient or by telephone. This study was approved by the Ethics Committee of Peking University First Hospital. Parental written informed consent was obtained for all children included in this study.

3. Results

A total of 2174 children diagnosed with epilepsy without acquired factors underwent genetic testing using NGS panels of epilepsy or WES, and 19 children were identified with *TBC1D24* compound heterozygous mutations. There were 10 males and 9 females, and they were all from nonconsanguineous parents. The clinical features and genotypes of 19 patients with *TBC1D24* mutations are summarized in Table 1. The seizure onset age ranged from 1 day to 8 months of age (median age 75 days). Three patients had family history of epilepsy or febrile seizures. The elder sister of patient 1 had seizure onset at 30 days old and died from status epilepticus at 84 days, but her DNA was not available. The father of patient 12 and the elder brother of patient 15 had febrile seizures in childhood.

Eighteen *TBC1D24* pathogenic variants were identified in 19 patients, and eight were novel variants. The detailed genotypes of 19 patients with *TBC1D24* mutations are shown in Table 1. All variants were assessed by MutationTaster, PolyPhen-2, and SIFT and evaluated according to the ACMG guidelines. All of these variants are pathogenic or likely pathogenic. These data and gnomAD variant frequencies are shown in Supplemental Table 2. Patient 11 had one variant inherited from his mother, and another variant was de novo. This de novo variant was confirmed to be of paternal origin by allele-specific PCR. The result was shown in Supplementary Fig. 1. Among the 16 patients, the two variants were inherited from his/her father and mother. Paternal DNA for patients 1 and 12 was not available due to loss of follow-up, and the DNA of other relatives was not available. We only know that one of the two variants was inherited maternally. The pathogenic variant c.241_252del was found in nine patients, with c.1499C > T found in six patients and c.116C > T found in six patients. These recurrent variants have been reported in ClinVar (https://www.ncbi.nlm.nih.gov/clinvar/). The variants c.241_252del, c.1499C > T and c.116C > T were reported in ClinVar as conflicting interpretations of pathogenicity, likely pathogenic, and uncertain significance, respectively.

All of the 19 patients had focal seizures, manifesting as eyes staring to one side, unilateral limbs clonus or body deflecting to one side. Three

patients had generalized tonic-clonic seizures (GTCS). Only patient 9 had epileptic spasms. All 19 patients exhibited multifocal myoclonus with retained awareness, which could last for a few hours to two weeks. The multifocal myoclonus could be triggered by fever or infections in 15 patients. All patients had EPC, which could be terminated by sleep or sedation drugs. The EPC could be terminated by chloral hydrate in 11 patients. Two patients developed EPC with unawareness during infection and high fever, and intravenous valproate, midazolam, or propofol were ineffective. Chloral hydrate could terminate the EPC, but EPC reappeared repeatedly during the infection period. The detailed seizure manifestations of 19 patients with *TBC1D24* mutations are shown in Supplementary Table 1.

Eleven patients presented psychomotor developmental delay. Four patients (patients 2, 6, 8 and 9) exhibited severe developmental delay. They could not hold up their heads before 18 months, and they could only form simple sounds at last follow-up (19 months to 4 years and 7 months). Six patients (patients 3, 4, 5, 7, 11 and 12) showed mild developmental delay. They could say simple words or sentences at 5–6 years old. Patient 10 developed cerebellar ataxia and walked unsteadily after severe EPC during infection at 9 years old. Seven patients showed normal psychomotor development at the last follow-up. Patient 1 could not hold up his head before the death due to status epilepticus at 4 months old.

Six patients exhibited hearing loss. Four patients were found with sensorineural deafness in the neonatal period. The hearing of patients 10 and 13 was normal after birth, but they were found to have sensorineural deafness at 9 years old and 6 years old, respectively. Thirteen patients had normal hearing. The hearing screen results of 19 patients with *TBC1D24* mutations are shown in Table 1.

Eighteen patients underwent video electroencephalogram (EEG) monitoring for 4 h at least once. The EEG results of 19 patients are shown in Supplementary Table 1. Interictal epileptiform discharges were captured in 13 patients. The interictal EEG of five patients were normal in several records. Focal myoclonic jerks were captured in 11 patients. However, only in patient 6, the corresponding scalp EEG was correlated to generalized polyspike-slow waves. The epileptiform discharges of the remaining 10 patients were not correlated to the myoclonus. The ictal EEG of patient 16 is shown in Fig. 1, and the epileptiform discharges were not correlated to myoclonic jerks.

A: In awake and quiet state, 3 Hz δ rhythm distributed nearly continuously at the bilateral occipital regions, mixed with fragments of 5–6 Hz low-medium amplitude θ activity and low amplitude fast waves. B–D: The face and limb are jerking continuously, and the jerks reduced and stopped when the patient was asleep. The corresponding EEG showed no correlated epileptiform discharges (EMG electrodes: left and right deltoids, thenar, mouth angle).

Brain MRI was abnormal in eight patients, including cerebellar atrophy with abnormal signals in four patients, cerebral atrophy in two patients, cerebellar atrophy in one patient, and cerebral and cerebellar atrophy with cerebellar abnormal signals in one patient. The MRIs of 10 patients were normal at the last follow-up. The brain MRI results of 19 patients with *TBC1D24* mutations are shown in Table 1. The progressive brain atrophy and cerebellar abnormal signals of patient 10 is shown in Fig. 2.

(a, b, c): Normal brain MRI at age of 8 years and 2 months (before myoclonic status epilepticus). (d, e, f): Ten days after the myoclonic status epilepticus at age of 8 years and 11 months. MRI showed cerebellar atrophy with hyperintense T2 signal. (g, h, i): Thirty days after the myoclonic status epilepticus. Cerebral atrophy aggravated compared to (d, e, f), and bilateral hippocampus atrophy was observed. (j, k, l): Seven months after the myoclonic status epilepticus, both cerebral and cerebellar atrophy aggravated, as well as bilateral hippocampus atrophy.

Among the 19 patients in this study, 12 patients were diagnosed with epilepsy syndromes. Four patients were diagnosed with epilepsy of EIMFS. The electroclinical features included migrating focal seizures, developmental delay. The ictal EEG showed multifocal discharges that migrated within one hemisphere or between both hemispheres. Patients 10 and 11 were diagnosed with PME. The clinical manifestations included prominent myoclonus, cerebellar ataxia and developmental delay. They both had polyspike-slow wave discharges in EEG and brain atrophy. Patient 12 was diagnosed with Dravet syndrome. The clinical features included GTCS, focal seizures, and myoclonus with fever-sensitive, developmental delay, and common status epilepticus. Five patients were diagnosed with unclassified epileptic encephalopathy, they all manifested refractory epilepsy and significant developmental delay.

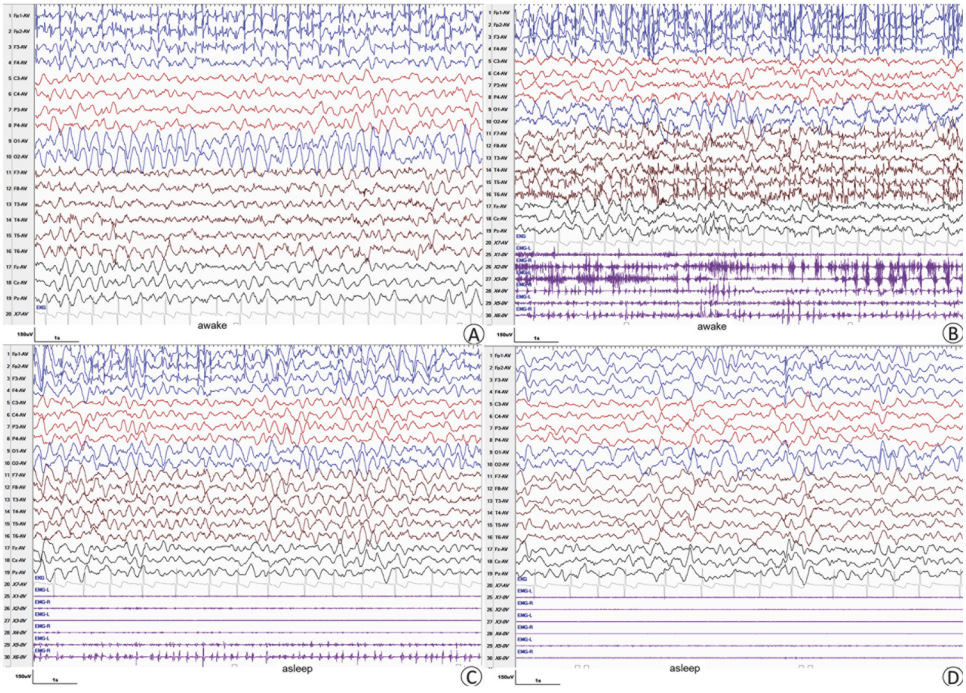

Fig. 1. The ictal scalp electroencephalogram of patient 16 with *TBC1D24* mutations.

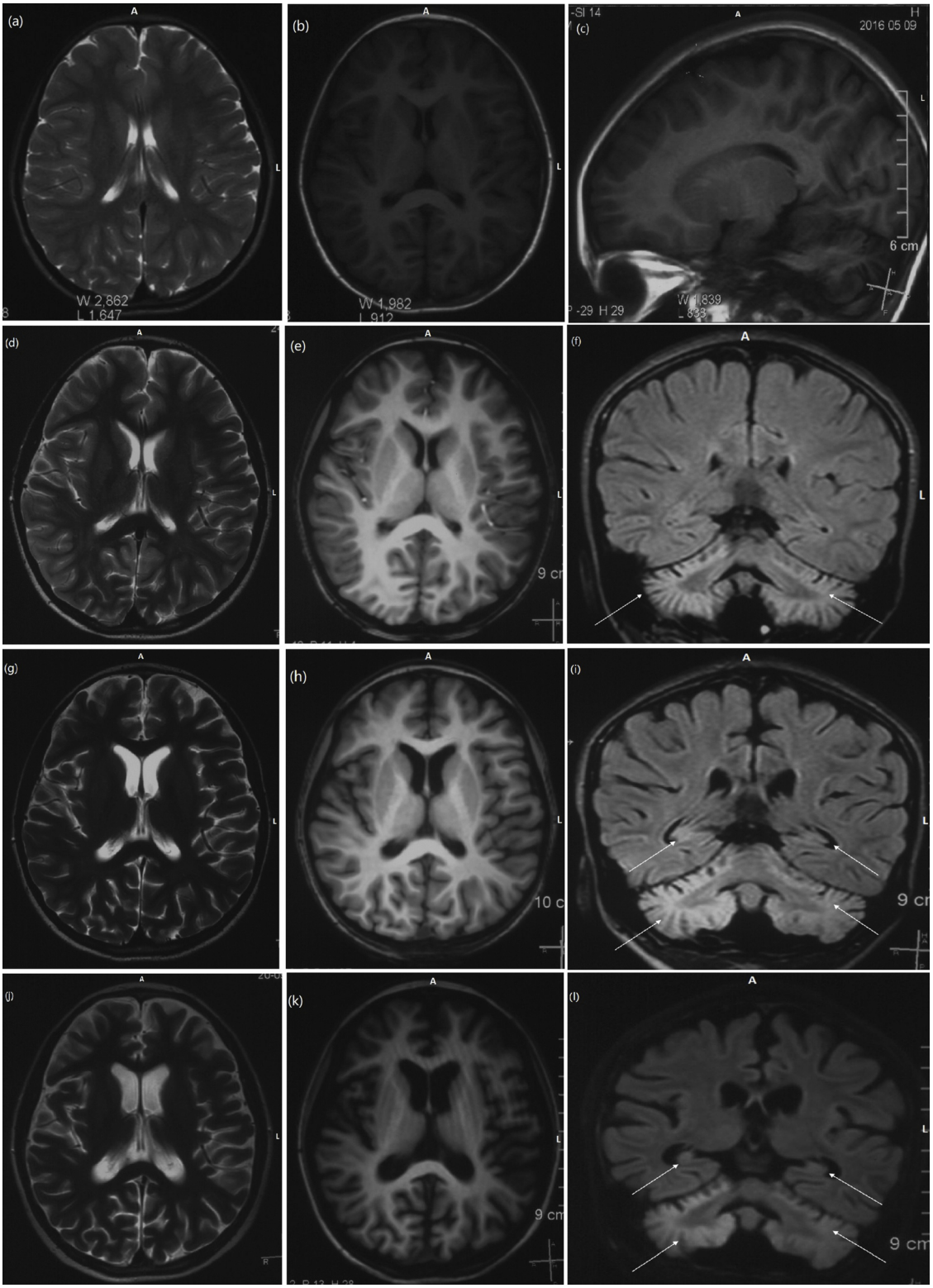

Fig. 2. Brain imaging manifestations of patient 10 with *TBC1D24* mutations.

Only patient 9 was diagnosed with DOORS. He exhibited neonatal deafness and a severe developmental delay, as well as hypoplasia of the nails on the bilateral fifth toes. The pictures of his hands and feet nails are shown in Supplementary Fig. 2. We examined 11 patients' nails on their hands and feet, and the data was shown in Table 1. Except for patient 9, the other 10 patients' nails were normal.

Patients 1 and 6 died due to status epilepticus at the ages of 4 months and 19 months, respectively. The surviving 17 patients were followed up for 1 year to 3 years and 5 months, and the final follow-up age ranged from 2 years and 1 month to 10 years and 3 months. In our 19 patients, 18 patients had tried two or more antiepileptic drugs (AEDs), and the epilepsy was drug-resistant. Sodium valproate (VPA) was most commonly used in 15 cases, with seizures significantly reducing in four patients. Patient 2 continued ketogenic diet therapy for

1.5 years with seizures decreased and cognition improved. The seizures of 14 patients decreased in the 17 surviving patients. The details of epilepsy treatment for all patients is shown in Supplementary Table 1.

4. Discussion

TBC1D24 compound heterozygous mutations (c.439 G > C and c.1526C > T) were initially reported in a FIME family with seven affected individuals [3]. A wide spectrum of epilepsies, non-syndromic deafness, alternating hemiplegia, and recurrent episodes of EPC caused by *TBC1D24* mutations have been reported recently [2,8,9,13]. In this study, we expanded the phenotypic spectrum, and found that Dravet syndrome was also associated with *TBC1D24* mutations. The patient was initially diagnosed with Dravet syndrome, but the *SCN1A* mutation screening was negative. She was identified with *TBC1D24* mutations by epilepsy gene panel. Her seizure onset age was 3 months, and her epilepsy was refractory. The seizures included GTCS, focal motor seizures, multifocal myoclonus, and EPC. The prolonged focal or myoclonic seizures were often triggered by fever. She had psychomotor development delay and normal brain MRI.

In our cohort, only patient 9 was diagnosed with DOORS. Patients 1,6 and 8 also exhibited neonatal deafness, developmental delay and frequent seizures. Patients 1 and 6 died due to status epilepticus at 4 months and 19 months of age, respectively. However, these patients did not have their limbs assessed for nail or digit hypoplasia. We suspect that patients 1,6 and 8 may still represent DOORS syndrome.

Although different epilepsy syndromes were related to *TBC1D24* mutation, we found that there were some common features of *TBC1D24*-related epilepsy. In our patient cohorts, the most prominent clinical feature among epilepsy types was multifocal myoclonus. All patients had recurrent EPC, which could be terminated after taking sedative drugs or falling asleep. Ngoh et al found that the seizures of two patients with *TBC1D24* mutation could be abolished after asleep and suggested that the best therapeutic strategy was to use chloral hydrate to induce sleep during prolonged myoclonus [22]. Another common clinical feature of *TBC1D24*-related epilepsy was fever-induced seizures. Balestrini et al found that seizures were easily exacerbated by fatigue in *TBC1D24* mutation-related epilepsy [2]. However, in our study, we found that seizures were exacerbated during fever or infection in 16 patients. In summary, EPC and fever-induced seizures were significant clinical features of *TBC1D24*-related epilepsy. It is critical to control the infection and temperature to terminate EPC.

No clear correlation between seizure attacks and ictal scalp EEG was another important feature in patients with *TBC1D24* mutations [8,23,24]. In this study, epileptic discharges were not correlated to focal myoclonus in 10 cases. However, jerk-locked back averaging confirmed that the myoclonus were cortical origin [18,25]. Several studies have found cerebellar atrophy or cerebellar atrophy with abnormal MRI signals in patients with *TBC1D24* mutations [20,22,25–27]. In our study, abnormal brain MRI was found in eight patients, including cerebellar atrophy, cerebral atrophy and abnormal signals in cerebella. Two patients were found to be cerebellar atrophy with abnormal signals after a prolonged myoclonus induced by infection and fever. Hearing loss was common in *TBC1D24* mutation-related epilepsy, and it could occur and exacerbate during follow up.

TBC1D24 mutation-causing epilepsy was mostly drug-resistant [2,22,25]. Balestrini [2] has summarized the treatment of 48 patients (11 previously unreported and 37 published) with *TBC1D24* mutations. The seizures were controlled in only 18 patients. The most effective antiepileptic drugs were VPA combined with phenobarbital [2]. None of our 19 patients were seizure free. Seizure frequency was reduced in 14 patients, and the most effective drugs were VPA and clobazam. One patient under a ketogenic diet for 1.5 years showed reduced seizures. According to the literature, 19% of patients with *TBC1D24* gene mutations were deceased before the age of 8 years [2,27]. The percentage could reach to 32% in DOORS syndrome, and most of them died before the age of 2 years [28]. The cause of death was mainly due to status epilepticus, respiratory distress, and sudden unexpected death (SUDEP) [27,28]. Two patients in our cohort died from status epilepticus. Most of the patients in our study were still young, and further follow-ups are needed to determine the final outcome.

Eighteen *TBC1D24* variants were identified in our 19 patients, of which eight were novel. Nine patients carried the same pathogenic variant c.241_252del, and this variant has been previously reported in one Chinese epilepsy patient [21]. The allele frequency of this variant in the general population is 0.0001121 according to the gnomAD database. There are 31 heterozygous allele counts, and 22 heterozygotes are of East Asian descent. This suggests that the variant c.241_252del might be a common ancestral mutation in East Asian populations, particularly founder mutation in Chinese populations. Six patients in our cohort carried the variant c.116C > T, and this variant was reported as uncertain significance. However, according to the PS4 evidence of ACMG guidelines, the prevalence of the variant in affected individuals (6/19 in our study) is significantly increased compared to the prevalence in controls (1.22E-05 according to http://gnomad.broadinstitute.org/). Therefore, the variant c.116C > T was reclassified as likely pathogenic.

There were no significant correlations between genotypes and phenotypes of *TBC1D24* mutations. Three patients were detected with identical c.116C > T and c.241_252del compound heterozygous mutations of *TBC1D24*. However, their phenotypes were different. The brain MRI varied from normal to abnormal, and psychomotor development could be normal or delayed. Two patients were diagnosed with EIMFS, and they both had c.116C > T and c.1499C > T compound heterozygous mutations of *TBC1D24*.

TBC1D24 mutation-related epilepsy was autosomal recessively inherited. Banuelos et al reported a family with *TBC1D24* mutations. The proband with c.1078C > T and c.404C > T compound heterozygous mutations manifested epilepsy, Parkinsonian tremor, intellectual disability, and psychosis [20]. The mother and sibling carried the c.404C > T variant, and both of them had tonic-clonic seizures and myoclonic seizures. The authors suspected that the *TBC1D24* variant c.404C > T might lead to dominant inherited epilepsy [20]. In our study, patient 8 had c.404C > T and c.457 G > T compound heterozygous mutations, and patient 15 had c.404C > T and c.679C > T compound heterozygous mutations of *TBC1D24*. Both patients inherited variant c.404C > T from their mothers, but the phenotype of their mothers was normal. The result of our study was inconsistent with the autosomal dominant inheritance of *TBC1D24* variant c.404C > T reported by Banuelos et al.

5. Conclusion

In summary, multifocal myoclonus, EPC, and fever-induced seizures were the most prominent features of epilepsy patients with *TBC1D24* mutations. The best therapeutic strategy to terminate EPC might be using chloral hydrate to induce sleep and control the infection and temperature. Hearing loss and abnormal brain MRIs might exacerbate the condition during follow-up. Most focal myoclonus and ictal scalp EEG data lacked clear correlation. Seizures were refractory to antiepileptic drugs, and developmental delay was common. Mortality was high in *TBC1D24*-related epilepsy patients.

Funding

This work was supported by Key Research Project of the Ministry of Science and Technology of China (grant numbers 2016YFC0904400 and 2016YFC0904401); The capital health research and development of special (grant number 2016-1-2011).

Declarations of interest

Authors have no competing interests.

Acknowledgments

We would like to extend our deepest appreciation to the patients and their families participating in this study. We would also like to thank team staff who assisted in the data collection as well as Dr. Xiaodong Wang from Cipher Gene, LLC for her assistance in editing the manuscript.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.seizure.2019.05.010.

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