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Genetic and clinical variations of developmental epileptic encephalopathies

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ABSTRACT

Objective: The concept of 'developmental and epileptic encephalopathy (DEE)' recognises that in infants presenting with severe early-onset epilepsy, neurodevelopmental comorbidity may be attributable to both the underlying cause and to adverse effects of uncontrolled epileptic activity. There is no direct genotype – phenotype correlation in DEEs. This study aimed to report the genetic and phenotypic differences in patients with DEE.

Methods: Genetic evaluations of the patients were performed due to epilepsy combined with developmental delay, epileptic encephalopathy, motor deficits, autistic features, or cognitive impairment. Patients were assessed for demographic characteristics, medical history, family history, psychomotor development, seizure control interventions, electroencephalogram (EEG) and magnetic resonance imaging (MRI) findings.

Results: This study included 20 children aged 0–16 years who were diagnosed as having DEE. The types of DEE detected in our study were DEE 2, 4, 6B, 7, 11, 26, 30, 33, 35, 42, 58, 62, and 67. Status epilepticus was recorded in only DEE7. The most common EEG abnormality was multifocal epileptic discharges (35%,) followed by burst-suppression patterns in patients with neonatal-onset seizures. Thirteen of the children were aged over 2 years, two (15%) were non-ambulatory and six (46%) were non-verbal. MRI scans were normal in 80% of the patients. Refractory epilepsy seen in 33% of cases.De-novo mutation, microcephaly and dysmorphic findings accompany resistant seizures and are associated with poor prognosis

Discussion: For patients with movement disorders, developmental delay, autism, and ID with or without epilepsy in any period of their life, next-generation sequencing is the only diagnostic technique available, with genetic analysis often being the only diagnostic method.

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Developmental delay; epilepsy; encephalopathy; epıleptıc encephalopathy; mental retardatıon

The incidence of epilepsy under the age of 5 years is > 60 per 100,000. Greater drug resistance and morbidity-mortality are seen in epilepsies that begin in very early life. Early infantile epilepsies are classified as self-limited and developmental epileptic encephalopathies. Developmental and epileptic encephalopathies (DEEs) are a type of complex epilepsy. The concept of 'developmental and epileptic encephalopathy (DEE)' recognises that in infants presenting with severe early-onset epilepsy, neurodevelopmental comorbidity may be attributable to both the underlying cause and to adverse effects of uncontrolled epileptic activity. Most DEEs are currently known to have an identifiable molecular genetic basis. Therefore, the concept of DEEs has been further clarified to describe conditions in which epilepsy and developmental impairments are secondary symptoms of the underlying cause developmental impairments are not considered to be caused by seizures or interictal epileptic activities. In DEEs, a single electroclinical syndrome may be caused by a combination of genes; alternatively, a single gene may be associated with various clinical manifestations. There is no direct genotype – phenotype correlation in DEEs. Hence, the clinical diagnosis of DEEs is difficult due to genetic and phenotypic heterogeneity. Traditionally, epileptic syndromes are classified according to electrophysiologic findings, despite efforts to classify epilepsies according to clinical and electroencephalographic in the last two decades. Gene discovery in epilepsies has enabled us to see cohorts of cases with a common genetic etiology. Next-generation sequencing-based methods have been proven to be highly effective in establishing the diagnosis of DEEs [1–6].

Recent advances in whole-exome sequencing (WES) and targeted gene panel sequencing have improved the understanding of the pathophysiology of DEEs, allowing us to describe novel phenotypic subgroups and visualise the complex relationships between genotype and phenotype that distinguish this group of paediatric epilepsy [7]. However, non-specific and negative genetic studies are often challenging to conduct. This study aimed to report the genetic and phenotypic differences in patients with DEE in Turkey and the efficacy and necessity of WES in the diagnostic approach. Defining epilepsy etiologies will increase targeted therapies.

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Materials and methods

This study included 20 children aged 0–16 years who were diagnosed as having DEE between 2020 and 2022. The term DEE is appropriate to use when both developmental impairment and epileptic activity have impact on the cognitive and behavioral state of the affected person. Most patients with DEE have a genetic etiology, whereby the genetic variant is responsible for both cognitive impairment and severe epilepsy: in such cases, even with control of seizures [8]. Genetic evaluations of the patients were performed due to epilepsy combined with developmental delay, epileptic encephalopathy, motor deficits, autistic features, or cognitive impairment.

Patients were assessed for demographic characteristics, medical history, family history, psychomotor development, seizure control interventions, electroencephalogram (EEG) and magnetic resonance imaging (MRI) findings. Seizures and epilepsy syndromes were classified according to the International League Against Epilepsy (ILAE) classification system [8]. EEGs were performed during the sleep-wake cycle using 21 electrodes (including Fp1, Fp2, F3, F4, F7, F8, T3, T4, T5, T6, C3, C4, P3, P4, O1, O2, Fz, Cz, Pz, a ground electrode and a reference electrode). These electrodes were placed according to the international 10–20 system using a Nihon Kohden EEG device for recording. The neonatal EEG montage included Fp1, Fp2, C3, C4, Cz, T3, T4, O1, and O2 electrodes. As a part of the routine cranial MRI protocol, 3-D MP-RAGE T1-weighted imaging, coronal and axial T2-weighted imaging, and axial fluid-attenuated inversion recovery (FLAIR) examinations were conducted.ID diagnosed according to the International Classification of Diseases, 10th revision (ICD-10) and the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5) with IQ/DQ < 70 assessed by the Gesell Development Scale, the Wechsler Preschool and Primary Scale Intelligence, or the Wechsler Intelligence Scale for Children ID severity: mild (IQ level 55–70), moderate (IQ level 40–55), severe (IQ level 25–40), profound (IQ level<25)) [9].

Preparation for genetic analysis

Genomic DNA extraction was performed according to the manufacturer's instructions (Maxwell RSC Blood DNA kit, Promega, U.S.A) using a Maxwell RSC Instrument (Promega, U.S.A). Proteinase K (PK) solution (30 µL) was added to 200 µL blood samples. Lysis buffer (300 µL) was added to blood and PK mix and incubated at 56°C for 20 minutes. After this step, each blood lysate sample was transferred to the cartridges. At the end of the assay in the instrument, 50 µL DNA was eluted. The concentration of DNA was determined spectrophotometrically by measurement of the absorbance at 260/280 nm using Nanodrop 1000 apparatus (Thermo Fisher Scientific). The concentration of DNA samples for libraries was determined using Qubit 3.0 (Thermo Fisher Scientific). The sequencing libraries for exome sequencing were prepared according to the Twist Human Core Exome Kit protocol (Twist Bioscience, U.S.A). Paired-end 150 bp read sequencing was performed on a NovaSeq system (Illumina, U.S.A).

Ethics approval

This study was approved by the Institutional Ethics Committee of Hasan Kalyoncu University, Gaziantep. Signed informed consent was provided by the legal representatives of all study participants. All clinical investigations were conducted in accordance with the 1964 Helsinki Declaration and its later amendments.

Results

Of the 20 study participants, 10 were girls and 10 were boys. The median age of the participants was 4 ± 3.93 years (range of 3 months to 16 years). The types of DEE detected in our study were DEE 2, 4, 6B, 7, 11, 26, 30, 33, 35, 42, 58, 62 and 67. DEE type 7 was the most common type (20%, $n = 4$), followed by DEE types 2, 4, 11 and 26 (10%, $n = 2$ per type).

The genetic analyses of the patients were found pathogenic and possibly pathogenic results compatible with a variant of uncertain significance (VUS) in three patients with DEE types 11, 30 and/or 62. There were nine (45%) cases of second-degree consanguineous marriage, and ten children (50%) had a family history of epilepsy or seizures, as shown Tables 1–2. However, the prenatal and natal histories of all the patients were unremarkable.

In total, 19 of the 20 patients (95%) experienced seizures; and the only participant with no clinical seizures had DEE type 35 (5%, $n = 1$) was the only participant with no clinical seizures. The age at onset of seizures was 14.1 ± 31.4 months (range of 1 day to 9 years). The most common seizure type was tonic-clonic (75%) followed by infantile spasm (25%), absence seizures (15%), generalised tonic-clonic seizures (10%), apneic seizures (10%) and hypomotor seizures (5%). Myoclonic seizures were not recorded in any of the patients, and status epilepticus was recorded in two patients (10%, $n = 2$) with DEE type 7. While DEE type 6B (5%, $n = 1$) experienced seizures after vaccine administration, there were no factors precipitating seizures in the remainder. All patients recorded abnormal EEG findings; the most common EEG abnormalities were multifocal epileptic discharges (35%) followed by burst-suppression patterns in patients with neonatal-onset seizures. Generalised

Table 1. Demographic, clinical and radiological features.

	Type	Gene anomaly	Gender	Age at diagnosis	Seizure type	Seizure onset	EEG features	Brain Imaging	Treatment	Development	Seizure control
1	DEE 2	CDKL5 Exon11 c.1247_1248 del hemizygous frameshift	M	6 mo	IS, TCS	25 day	BS, MFED, Abnormal bg	Normal	VGB, CBZ,CZP	Hypotonic,DD moderate	Refractory
2	DEE 2	CDKL5 Exon 11 c.1675C>T heterozygous nonsense	F	1,3 y	TCS	23 day	MFED	Cerebral atrophy	VGB,CZP,TP	NA, NV, DD severe, hypotonic	Refractory
3	DEE 4	STXBP1 Exon 18 c.1624C>T heterozygous missense	M	7 y	TCS	1 day	MFED, Abnormal Bg	Cerebral and cerebellar atrophy	LVT	Limited walk-speech, ID moderate,ASD	Sz-free 3 y
4	DEE 4	STXBP1 Exon 17 c.1462 G>C heterozygous missense	M	8 y	TCS	8 y	GSW	Normal	VPA,TP	A, Limited speech,ID mild	Controlled AEDs
5	DEE 6B	SCN1A 17–26 Exon heterozygous deletion	F	16 y	TCS,GTCS	3 mo	SSW	Normal	VPA,LCT,CBZ	Limited walk, NV,ID moderate, ASD	Controlled AEDs
6	DEE 7	KCNQ 2 Exon 3 c.419A>C heterozygous missense	F	1,2 y	IS,TCS,ApS	1 mo	BS,MFED	Mild cerebral atrophy	TP, LVT,VGB, CZP	NA, NV,DD severe	Refractory Exitus 21 mo
7	DEE 7	KCNQ2 Exon 4 c.637C >T heterozygous missense	F	4 y	TCS	7 day	MFED, Abnormal Bg	Normal	VPA,LVT,CBZ	NA,V,DD severe	Refractory
8	DEE 7	KCNQ2 Exon 5 5 c.758C>G heterozygous missense	M	1,2 y	IS,TCS	7 day	BS, Abnormal Bg	Normal	LVT	A,NV,DD mild	Controlled AEDs
9	DEE 7	KCNQ2 Exon 4 c.6386>A heterozygous missense	M	3 mo	IS,TCS	1 day	BS	Normal	VGB,LVT,TP, CZP	Hypotonic,DD severe	Refractory Exitus 3mo
10	DEE 11	SCN2A Exon 22 c.415GT> heterozygous missense	M	6y	TCS	1 y	MFED, Abnormal Bg	Normal	VPA,CBZ	Limited walk- speech, ID moderate, ASD	Controlled AEDs
11	DEE 11	SCN2A Exon 11 c.14576>C heterozygous missense	F	8 y	GTCS	1,5 y	GSW	Normal	VPA	A,V,ID mild	Controlled AEDs
12	DEE 26	KCNB1 Exon 2 c.1464 G>A heterozygous nonsense	F	4 y	TCS,AS	6 mo	Abnormal Bg	Normal	TP	Limited walk,NV,DD severe,	Sz-free for 1 y
13	DEE26	KCNB1 Exon 2 c.629C>T heterozygous missense	M	2,6 y	TCS	4 m	SSW, Abnormal Bg	Normal	VPA,LVT	Limited Walk,NV, DD severe,ASD	Controlled AEDs
14	DEE 30	SIK 1 Exon 14 c.1994A>G heterozygous missense	F	3 y	TCS,HypS	10 mo	Abnormal Bg	Normal	-	Ataxic gait-Limited speech,DD mild	Sz-free for 1 y
15	DEE 33	EEF 1 A2 Exon 7 c.1142 G>A heterozygous missense	M	3 y	AS	1 y	GSW	Normal	VPA,CBZ	A,NV,ASD, DD moderate	Controlled AEDs
16	DEE 35	ITPA Exon 6 c.359_366 duplıication homozygous frameshıft	F	7 mo	-	-	Abnormal Bg	Cerebral and cerebellar atrophy, hypomyelination	-	Hypotonic, DD severe	Exitus 12 mo
17	DEE 42	CACNA1A Heterozygous	M	2 y	IS,TCS	1 mo	BS,MFED,GSW	Normal	VGB, CZP, TP	NA,NV,DD severe,Axial hypotonic	Refractory
18	DEE 58	NTRK2 Exon 15 c.1937C >T heterozygous missense	F	2,2 y	TCS	1 mo	Abnormal Bg	Normal	-	A,V,DD mild	Sz-free for 2y
19	DEE62	SCN3A Exon 13 c.1970T>C heterozygous missense	M	1 y	ApS	15 day	Abnormal Bg	Normal	LVT	NA, DD mild,	Sz-free for 11mo
20	DEE 67	CUX2 Exon 17 c.2042_2059 duplication heterozygous inframe 18	F	9 y	AS	9 y	GSW	Normal	VPA	A,V,ID mild	Sz-free for1 y

Note: Abbreviations: M: male,F:female, mo:month, y:years, IS:infantile spasms, TCS:tonic-clonic seizures, GTCS:generalized tonic-clonic seizures, ApS:apneic seizures, AS:absance seizures, HypS:hypomotor seizures, BS:burst supression, MFED:multifocal epileptiform discharges, bg:background, GSW:generalised spike-wave or polyspike wave discharges,SSW:slow spike-wave discharges, VGB:vigabatrin, CBZ:carbamazepine, CZP:clonazepam, TP:topiramate, LVT:levetiracetam, VPA:sodium valproate, LCT:lamictal, DD:developmental delay, NA:non-ambulatory, NV:non-verbal,A:ambulatory,V:verbal, ID:ıntellectuel disability, ASD:autistic spectrum disease, Sz :seizure, Controlled AEDs: seizures controlled by antiepileptic drugs

Table 2. Other clinical features and family characteristics of patients.

		Dysmorphology	Movement Disorder	Mıcrocephaly	Family gene	Epilepsy in family	Consanguinity
1	DEE2	+	None	+	Negatif	None	None
2	DEE2	+	None	+	Negatif	Cousin	None
3	DEE4	None	None	None	Negatif	Cousin	Cousins
4	DEE4	None	None	None	Father,brother	Grandfather	Cousins
5	DEE 6B	None	None	None	Negatif	None	None
6	DEE 7	+	None	+	Negatif	None	None
7	DEE 7	None	None	+	Negatif	None	None
8	DEE 7	None	None	None	Mother	Mother, Cousin	Cousins
9	DEE 7	+	None	None	None	Cousin	Cousins
10	DEE 11	None	Sterotype hand movements	+	Negatif	None	Cousıns
11	DEE 11	None	none	None	Father	Father Uncle	None
12	DEE 26	None	Sterotyped hand movements	+	None	None	None
13	DEE 26	None	Sterotyped hand movements	None	Negatif	None	None
14	DEE 30	+	None	None	Father	None	None
15	DEE 33	None	Sterotyped movements	None	Father	Father	None
16	DEE 35	+	None	+	None	None	Cousins
17	DEE 42	+	None	+	None	Sibling	None
18	DEE 58	None	None	None	Father,brother	None	Cousins
19	DEE62	None	None	None	None	Sibling	Cousins
20	DEE 67	None	None	None	Father	Uncle	Cousins

sharp wave activity was noted in 20% of the children, and sporadic sharp wave activity detected in 10%. The EEGs of DEE types 26, 30, 35, 58 and 62 (25%, $n = 5$) demonstrated no epileptic activity but did show abnormal ground activity. Continuous spikes and waves during slow-wave sleep (CSWS) or focal epileptic discharges were not detected in the EEG findings of any patients.

During the follow-up, seizures were controlled by anti-epileptic drugs (AEDs) in DEE types 4, 26, 30, 58, 62 and 67 (30%, $n = 6$), the seizure-free duration in these patients was≥11 months. Seizures in DEE types 2, 7 and 42 (30%, $n = 6$) were resistant to treatment and were receiving multiple AEDs. Seizures associated with DEE types 4, 6B, 7, 11, 26, and 33 (35%, $n = 7$) were controlled by AEDs with intermittent recurrent seizures recorded. The most commonly used AED was sodium valproate (40%, $n = 8$) followed by levetiracetam (40%, $n = 8$), vigabatrin (25%, $n = 5$), clobazam (25%, $n = 5$), clonazepam (20%, $n = 4$), topiramate (20%, $n = 4$) and lamotrigine (5%, $n = 1$). Two children were not receiving any AED treatment (DEE types 35 and 58); DEE type 35 had no seizures, died infantil period and DEE 58 discontinued the antiepileptic treatment voluntarily. In all cases of infantile spasm, vigabatrin was sufficient to control seizures.

DEE types 2, 7, 26, 35 and 42 had microcephaly (40%, $n = 8$) and mild dysmorphic findings were present in DEE types 2, 7, 30, 35 and 42 (35%, $n = 7$), but neither of these findings were specific to the diagnosis. In type 2 exhibited DEE type 2, broad foreheads, large and deep-set eyes, anteverted nares and full lips. One DEE type 7 had sunken nipples and fat pads on the hands and feet, while another had a prominent broad forehead and deep small eyes. DEE type 30 had deeply located slanting almond eyes and split nipples. DEE type 35 had retromicrognatia, a high arched palate and low- set ears, while DEE type 42 had deep, broad-set eyes. DEE types 11, 26, and 33 (20%, $n = 4$) had an accompanying movement disorder, including stereotyped movements.

Autistic traits were seen in DEE types 4, 6B, 11, 26 and 33 (25%, $n = 5$), and ID was seen ın DEE types 4, 6B, 11 and 67 (30%, $n = 6$).

Thirteen of the children were aged over 2 years, two children (15%) were non-ambulatory (DEE types 7 and 42) and six (46%) were non-verbal (DEE types 6B, 7, 26, 33 and 42). There was limited ambulation in seven (54%) children (DEE types 4, 6B, 11, 26, 30 and 33), and four (31%) had free unaided ambulation (DEE types 4, 11, 58 and 67). Axial hypotonia was seen in DEE types 2, 7, 35 and 42 (25%, $n = 5$) and ataxic gait was seen in DEE type 30 (5%, $n = 1$).

Magnetic resonance images (MRI) were normal in 80% of the patients ($n = 16$) and abnormal in DEE types 2, 4, 7 and 35. Cerebral and/or cerebellar atrophy was detected in three of these patients, and pontocerebellar atrophy and hypomyelination were reported in DEE type 35.

Three patients (DEE types 7 and 35) died during their follow-up; one DEE type 7 (p. 6) died aged 21 months and another at age 3 months, and DEE type 35 died aged 12 months.

De-novo mutations were detected in eight (40%) patients (DEE type 2, 4, 6B, 7, 11 and 26) the parents of seven (35%) patients, were heterozygous for the same mutation (DEE types 4, 7, 11, 30, 33, 58 and 67) and the parents of five patients refused genetic testing.

STXBP1, KCNQ 2, SIK 1, EEF 1,CACNA1A, NTRK2, SCN3A, KCNB1 heterozygous missense; CDKL5, KCNB1 heterozygous nonsense; CDKL5 hemizygous frameshift; ITPA homozygous frameshift and CUX 2 heterozygous inframe mutation were detected.

The demographic, clinical and radiologic findings of the patients are summarised in Tables 1 and 2.

Discussion

Our study included 20 patients with DEE, representing 13 different DEE groups and a broad phenotypic and genotypic spectrum. The phenotype of DEE is typically characterised by refractory epilepsy with onset in the infantile period and intellectual disability independent of seizure activity [1–6].

One of the most prominent features of developmental and epileptic encephalopathies is the onset of seizures in the neonatal or infantile period. In our study, seizures started in the infantile period in all but two patients (DEE types 4 (p.4) and 67); we propose that DEE 4 is better defined as a neurodevelopmental disease rather than epileptic encephalopathy. Overall, 95% of the patients in this study have epilepsy, 100% have an intellectual disability (ID) and 20% have autistic traits or autism, axial hypotonia, atactic gait and movement disorders. Additionally, seizure freedom is observed in 33.33% of these patients. Late childhood-onset cases have been reported in moderate cases [10–12]. For DEE type 4 patients, seizures were controlled by AEDs and patient 3 has been seizure free for three years; and ID was more prominent than epilepsy in these patients. Although missense mutations have been associated with severe-to-profound ID, patient 3 had moderate ID associated with ASD and patient 4 had mild ID. Patient 3 had more severe phenotypic features than patient 4 due to de-novo mutation and infantile onset seizures.

Patients with DEE type 67 presented with a severe form of infantile myoclonic epilepsy but with seizures controlled by AEDs, and this was accompanied by severe static developmental epileptic encephalopathy. Affected individuals have overall developmental delay, poor or absent speech, ID, movement disorders and stereotypic or ASD behaviour. Those with later onset may show mild phenotypic features, and the frequency of seizures in these patients decreases with age [13–15]. In this study, DEE type 67 showed a moderate phenotype with late onset and clinical findings. She had a static developmental delay, her seizures were controlled by AEDs and her father was heterozygous for same the mutation. The patients with late-onset epilepsy (DEE types 4 (p.4) and 67) showed a moderate phenotype, seizures were controlled by AEDs, had no de-novo mutations, but did have familial mutations

Refractory seizures were observed in DEE type 2 (p.1 and 2), DEE 7 (p. 6, 7 and 9) and DEE 42 (p.17). DEE2 is characterised by polytherapy-resistant seizures that mostly occur in the first two months of life. Females are most often affected while males are rarely but severely affected. Dysmorphic facial features are subtle; we observed that our patients with DEE type 2 exhibited deep-set eyes, anteverted nares, broad forehead and dysmorphic features such as microcephaly and hypotony. It has been reported that nonsense mutations may have milder phenotypic features. In our study, patient 2 had the nonsense mutation and a more severe phenotype, and a decrease in seizures was observed in patient 1 after the fifth month. Patients 1 and 2 showed phenotypic features consistent with the literature [16–18] and both had de-novo mutations, refractory seizures, microcephaly and hypotonia. In our study, DEE type 2 had severe phenotypic features.

Developmental and epileptic encephalopathy type 7 (DEE 7) was the most common type in our study group. DEE 7 is frequently characterised by neonatal-onset refractory seizures, delayed neurodevelopment and persistent neurologic deficits. Seizures resolve by 3–4 years of age with improvement in EEG abnormalities. The severity of the disease may vary within the family. In our study, all patients with DEE 7 had neonatal seizures. The initial EEGs of patients 6 and 9 revealed a burst-suppression pattern that could subsequently progress to multifocal epileptiform activity (MFED), and were consistent with a clinical diagnosis of Ohtahara syndrome. Patients 6 and 9 were exitus, patient 7 was followed because of refractory epilepsy and patient 8 was developing close to normal. Dysmorphology was also present in patients 6 and 9. The authors note that the phenotypic variability could be due to the interplay of pathogenic mutations, modifying genes and more subtle environmental factors. In children with self-limiting neonatal epilepsy due to a pathogenic KCNQ2 variant, the flow of brain potassium ions is disturbed but to a lesser extent than in children with KCNQ2 developmental and epileptic encephalopathy. This difference possibly explains why these children have less severe disease than children with KCNQ2 developmental and epileptic encephalopathy [19–22]. In our study, the form with the most severe phenotype and the most resistant seizures was seen in DEE 7 and half of these patients died. Patients 6, 7 and 9 had de-novo mutations and patient 8 had a familial mutation and mild phenotypic features.

DEE 42 is similar to other epileptic encephalopathies; it is characterised by seizures that start early in childhood (even in the first hours or days of life) and substantial overall developmental delay in affected individuals. Axial hypotonia, peripheral hypertonia, hyperreflexia, tremor, ataxia and abnormal eye movements are possible additional characteristics seen in such patients. The patient in this study with DEE 42 had microcephalic and dysmorphic findings in accordance with the literature, and had axial hypotonia with peripheral hypertonia, a severe phenotype and refractory epilepsy [23–25]. Microcephaly and dysmorphic findings were seen in DEE types 2, 7 and 42 who had refractory seizures and poor prognosis.

We had three cases with exitus; two of whom were DEE 7 (patients 6 and 9) and one patient was DEE type 35. DEE type 35 is characterised by early-onset seizures, encephalopathy, developmental delay and specific findings on MRI scans. Death in early childhood may also occur. DEE type 35 had microcephalic and dysmorphic findings consistent with the literature; however, contra to the literature she had no clinical seizures but may have subtle seizures that her family is unaware of. She was diagnosed with DEE by genetic analysis, and the EEG findings revealed irregular and slow background activity with no epileptic activity [25–27].

The genetic analysis results were compatible with pathogenic, possibly pathogenic and variant of uncertain significance (VUS) in three patients (DEE types 11 (p. 11), 30 and 62). They were included in the study because they were clinically compatible with DEE and might contribute to the literature; however, the genes warrant validation in future studies.

In DEE 11, most individuals have significant mental retardation, encephalopathy and autism spectrum disorder, and 50% of these patients become seizure-free during their childhood [28–30]. In a large study by Wolf et al [30]. Patients were classified into two groups based on disease onset before and after 3 months of age. Burst-suppression patterns, generalised spike-wave discharges and multifocal spikes were observed in those with seizure onset before 3 months; with more absence and myoclonic seizures in the group with onset after 3 months. Other conditions described in their study, including microcephaly, hypotonia, abnormal movements, pyramidal findings and oculogyric crises, were not seen in our cases [28–30]. Some patients with onset of seizures before 3 months of age may respond to sodium channel blockers, especially phenytoin. Both of our DEE 11 cases showed mild phenotypic features and epilepsy that began after 3 months and was controlled by AEDs. Patient 10 had autism spectrum disorder and moderate ID, and patient 11 had moderate ID. In both cases, generalised tonic-clonic and/or tonic-clonic seizures were seen. Absence and myoclonic seizures were not seen.

Individuals with SIK 1 mutations observed in DEE type 30 have short survival in cases with neonatal epilepsy onset and autism plus developmental syndrome after infantile spasms in others [31]. In our case DEE type 30, seizures first years of life and were not resistant to treatment, and they had an ataxic gait, mild developmental delay and dysmorphic findings. The patient's father had the same mutation and, his school performance was poor and he had a history of seizures in childhood [31,32]. The father of two children (DEE types 11 (p. 11) and 30) had the same mutation and seizure history. The parents of patient 19 (DEE type 62) were negative in genetic analysis; however, one sibling died of epilepsy at the age of one and their genetic analysis was not performed. DEE type 62 is characterised by the onset of refractory seizures in the first weeks or months of life. Affected individuals have severe-to-profound developmental delay with hypotonia, impaired motor and cognitive development. Additional features may include spasticity, microcephaly, and brain imaging abnormalities. We did not observe these in our patient, although he had mild developmental delay.

In DEE types 4 (p. 3), 6B, 11 (p. 10), 26 (p. 13) and 33 had epilepsy and ID or DD accompanied by ASD; and ASD was observed more frequently in patients whose seizures were controlled by AEDs. The patient with DEE type 6B [33–37] experienced the first episode of seizures at the age of 9 months (after vaccination) and the patient continues to experience fever induced seizures during periods of infection. In DEE type 33, the patient had normal motor development, speech delay, mirror movements and stereotypic movements [38,39]. The father had the same mutation and was epileptic; however, he is currently not under medication.

In DEEs, the same mutation may show different phenotypic features even within the same family. The patient with DEE type 58 was autosomal dominant and presented with non- refractory neonatal seizures and mild central hypotonia. The patient showed a slight delay in gross and fine motor development but had normal social development. The father and brother were homozygous for the same mutation, and the father had a history of seizures in infancy and the brother had mental motor retardation [40].

In conclusion, dysmorphic features have rarely been reported in DEEs but are associated with poor prognosis if present. Microcephaly, dysmorphic features and de-novo mutations are associated a poor prognosis. The severity of the disease may vary within the family, and there is no direct genotype – phenotype correlation in DEEs. ID can be independent of seizure activity, and the onset of DEEs onset is mostly during the infantile period, with later onset cases rarely seen. In these cases seizures are controlled by AEDs.

Physicians must provide patients with customised care that meets their individual needs and also offer realistic expectations for each affected person; for example, those with developmental encephalopathy are unlikely to benefit from aggressive anti-epileptic medications, whereas those with epileptic encephalopathy can benefit. Patients with DEE might benefit from a precision medicine approach to reduce the overall burden of epilepsy. For patients with movement disorders, developmental delay, autism and ID with or without epilepsy in any period of their life, next-generation sequencing is the only diagnostic technique available, with genetic analysis often being the only diagnostic method.

Disclosure statement

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This article does not contain any studies with human participants or animals performed by any of the authors.This study was approved by the local medical ethical committee, and all data was processed anonymously, according to the privacy legislation.

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