Brain & Development 41 (2019) 706–715

BRAIN & DEVELOPMENT
Official Journal of the Japanese Society of Child Neurology

www.elsevier.com/locate/braindev

Original article

Epilepsy in patients with EAST syndrome caused by mutation in the *KCNJ10*

Ali Mir [a,*], Mohammed Chaudhary [a], Hani Alkhaldi [a], Rami Alhazmi [b], Raidah Albaradie [a], Yousef Housawi [c]

[a] *Pediatric Neurology Department, King Fahad Specialist Hospital, Dammam, Saudi Arabia*
[b] *Medical Imaging Department, King Fahad Specialist Hospital, Dammam, Saudi Arabia*
[c] *Genetic and Metabolic Department, King Fahad Specialist Hospital, Dammam, Saudi Arabia*

Received 5 April 2018; received in revised form 3 March 2019; accepted 19 March 2019

Abstract

Objective: EAST syndrome comprises of **e**pilepsy, **a**taxia, **s**ensorineural deafness, and **t**ubulopathy. It is caused by a mutation in *KCNJ10* gene. Less than thirty cases have been reported in the literature with emphasis on genetic mutation and renal tubulopathy. In this article, our goal is to present a comprehensive description of epilepsy and its management. A literature review is also presented to consolidate and compare our findings with the previously reported cases.

Methods: Retrospective chart review was done to collect patient data. Research clinic was organized to obtain missing data. Molecular genetic testing was done at the *CGC Genetics Laboratory*. Electroencephalogram (EEG) was done for all patients and interpreted by a pediatric epileptologist and brain MRI was reviewed by a pediatric neuroradiologist. Developmental assessment was done by a developmental pediatrician using Griffiths Mental Developmental Scale.

Results: In patients with EAST syndrome, seizure is the first symptom occurring around 3–4 months of age. Most common seizure type was generalized tonic clonic (GTC). Usually, the seizures were brief lasting <3 min but few patients also presented with status epilepticus especially when the medication was weaned. Carbamazepine (CBZ) was found to be effective in most cases. Lamotrigine (LTG), valproic acid (VPA), and topiramate (TPM) were also found to be helpful. Routine EEGs were usually normal or showed non-specific findings. In few patients, EEG showed background slowing. Brain MRI revealed hyperintensity in the dentate nuclei in some patients, and quantitative volumetric analysis studies showed volume loss in different regions of the brain especially the cerebellum. All our five patients have the same homozygous c.170C>T (p.Thr57Ile) missense mutation in *KCNJ10* gene.

Conclusion: This article provides the readers with an understanding of the natural history of epilepsy in this syndrome to help in early recognition, avoid unnecessary investigations, and provide the best treatment for seizures. It also helps the physicians to share the prognosis of this rare syndrome with the parents.

Keywords: EAST syndrome; SESAME syndrome; *KCNJ10*; Epilepsy; Precision medicine

1. Introduction

EAST syndrome is an autosomal recessive disorder. It comprises of **e**pilepsy, **a**taxia, **s**ensorineural deafness, and **t**ubulopathy [1]. Another acronym used for this

* Corresponding author at: King Fahad Specialist Hospital, Neuroscience Center, Ammar Bin Thabit Street, Dammam 31444, Saudi Arabia.
E-mail address: ali.mir@kfsh.med.sa (A. Mir).

https://doi.org/10.1016/j.braindev.2019.03.009

syndrome is SeSAME (**Se**izures, **s**ensorineural deafness, **a**taxia, **m**ental retardation and **e**lectrolyte abnormalities) syndrome [2]. It is caused by a mutation in the *KCNJ10* gene located on chromosome 1q23.2. In this article, we describe five genetically diagnosed patients with this syndrome. The patients were from two families in the eastern province region of Saudi Arabia. The first symptom of this syndrome was a seizure occurring around the age of 3 months, and later other clinical features became apparent. <30 cases have been reported in the literature with more emphasis on genetic mutation and renal tubulopathy. Cross et al. provided more detail about neurological problems including epilepsy [3]. In this article, our goal is to present a comprehensive description of epilepsy and its management along with some findings of genetic testing and brain MRI. A literature review is also presented to consolidate and compare our findings with the previously reported cases. This article provides the readers with an understanding of the natural history of epilepsy in this syndrome to help in early recognition, avoid unnecessary investigations, and provide the best treatment for seizures. It also helps the physicians to share the prognosis of this rare syndrome with the parents.

2. Methods

Informed consent was obtained from parents of all the patients. A new research protocol was submitted to the institutional review board (IRB). After the IRB approval, the data was collected from a retrospective chart review. A research clinic was organized and all the patients were seen to obtain any missing data. Electroencephalogram (EEG) was performed for all the patients, and the EEGs were read by a pediatric epileptologist. MRI of all the patients was reviewed by a pediatric neuro-radiologist. Molecular genetic testing was done at the CGC lab, and all patients had a homozygous mutation in *KCNJ10* gene. The test was done by PCR amplification and sequencing analysis of the entire coding region and all exon-intron splice junctions of the *KCNJ10* gene. Normal variants (polymorphisms) previously reported in the literature and/or listed on dbSNP and found on this test were not reported. Reference Sequence: NM_002241, with the A of the ATG start codon at position 1. Analysis on prediction software programs (Polyphen-2 and Mutation Taster) was done for novel variants. Developmental assessment was done by a developmental pediatrician using Griffiths Mental Developmental Scale.

3. Results

Patients 1.1–1.4 belong to Family #1 (Fig. 1A) and the patient 2.1 belong to Family #2 (Fig. 1B). Patient 1.1 and 1.3 are siblings, and are maternal cousins of patient 1.2. Patients # 1.1, 1.2, 1.3 are maternal cousins of the mother of patient # 1.4.

3.1. Patient 1.1

This is a 12-year-old boy who was born at term after uneventful pregnancy and delivery to first-degree consanguineous Saudi Arabian parents from the Eastern Province with uneventful post-neonatal period. Father has familial spastic paraplegia type 4 diagnosed by molecular genetic testing.

The first symptom was a generalized tonic-clonic seizure at 4 months of age which was controlled with VPA. His seizures usually lasted <5 min. At 2½ years of age, he developed dyselectrolytemia in the form of hypokalemia, hypomagnesemia and metabolic alkalosis with normal blood pressure which needed replacement of potassium and magnesium. Despite these supplementations, he had several hospitalizations due to dyselectrolytemia, and amiloride with indomethacin was

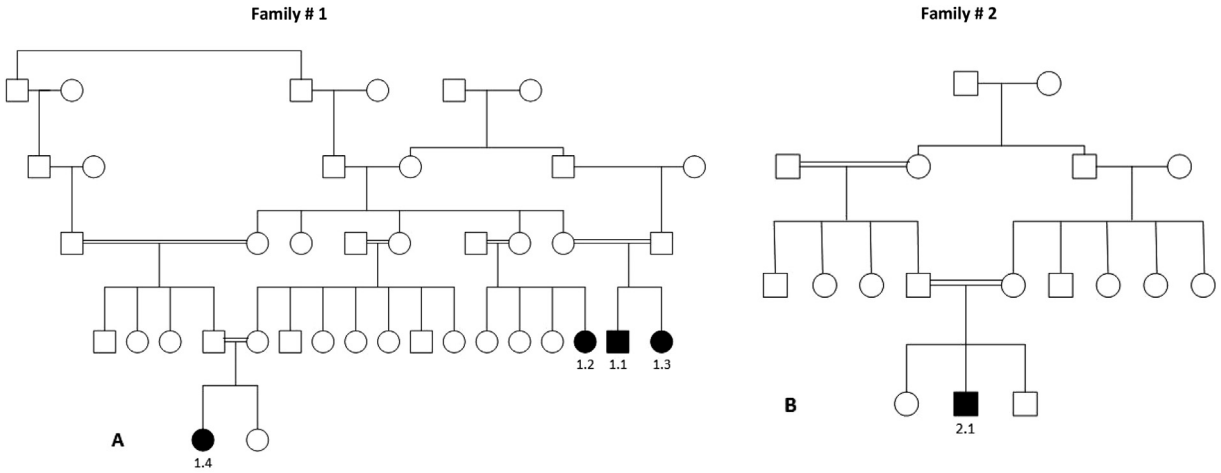

Fig. 1. A: Pedigree of family # 1 with four affected members 1.1–1.4. B: Pedigree of family # 2 with one affected member 2.1.

added to treatment resulting in less frequent episodes of electrolyte abnormalities. For his seizures, during the second year of life, VPA was electively changed to CBZ which was tapered and discontinued after two years of seizure freedom, but seizures recurred needing re-introduction of the same. He was referred to us at the age of 7 years with tremulousness of limbs for few months with frequent falls, and speech problems. He was attending regular school with good scholastic performance. He was found to have normal tone, generalized hyperreflexia with ankle clonus, up-going planters and ataxic gait. Rest of his neurological examination and other systemic examination was unremarkable. At eight years of age, he developed nystagmus and poor co-ordination. Lately, he gets admitted to the hospital due to dyselectrolytemia 1–2 times every year.

On the last outpatient follow up at the age of 12 years he was reasonably well in school but has ataxic speech, moderate to severe sensorineural hearing loss (SNHL), end-of-gaze nystagmus, dysmetria and ataxic gait. His EEG during wakefulness was normal. He was on 12 mg/kg/day of CBZ and was seizure free for past four years. We decided to wean his medication off. Two days after completely stopping the CBZ he had a 20-minute-long generalized tonic-clonic status epilepticus which required two doses of IV diazepam in the ER. CBZ was resumed, but father preferred to continue on the previous low dose.

3.2. Patient 1.2

This is a six-year-old girl who was born at term via normal spontaneous vaginal delivery (NSVD). The mother reported subjective increased fetal movements and borderline polyhydramnios. Early infancy was unremarkable with the social smile at two months.

She had her first symptom at four months of age with seizures in the form of generalized clonic activity with staring starting during sleep once daily lasting for less than a minute initially for first two weeks. The duration of seizures gradually increased up to 5–7 min over next four weeks. She was first seen by us at 5½ months of age and had no dysmorphic features or neurocutaneous stigmata. She had axial and appendicular hypotonia at presentation with otherwise unremarkable neurological examination. She had partial response to levetiracetam (LEV) and was changed to CBZ at eight months given good response in elder cousin after which she became seizure free within one month. She sat without support at 12 months, crawled at 14 months, cruised around furniture at 20 months and never achieved independent walking. Pincer grasp was achieved at 14 months, and she spoke her 1st word at 14 months, started putting two words together at two years and has good receptive and expressive language. Her hypotonia improved by one year to normal tone followed by hypertonia in both lower extremities by five years. She had mild incoordination by 2½ years with ataxia appearing at three years, and intention tremors and past pointing by five years. She did not have nystagmus or ataxic speech. On the last visit at five years, she had global hyperreflexia with bilateral ill-sustained ankle clonus. Her seizures are fairly well controlled from 9 months of age except breakthrough generalized tonic seizures lasting up to 2 min with febrile illnesses at 1½, 2½, 3 and 4½ years of age and she is currently on carbamazepine at the dose of 18 mg/kg/day.

3.3. Patient 1.3

This is a five-year-old girl who is the younger sister of patient # 1.1. She was born at term after uneventful pregnancy and delivery to first-degree consanguineous Saudi Arabian parents from the Eastern Province with uneventful post-neonatal period.

There were no concerns till the onset of seizures at three months of life with staring episodes and unresponsiveness lasting for 1–2 min, 2–3 episodes daily. LEV was initiated and the dose was subsequently increased reaching up to 60 mg/kg/day without any response. The seizures were controlled by switching to TPM at the dose of 5 mg/kg/day.

The patient was referred to us at 6 months of age because of diagnosis of EAST syndrome on the maternal side of family. She had no dysmorphic features or neurocutaneous stigmata. She had axial and appendicular hypotonia at presentation but otherwise unremarkable neurological examination. She sat without support, had pincer grasp and said her first word, all at the age of 1 year. She pulled to stand at 20 months and cruised around furniture at two years and had two words vocabulary. Mild tremors and ataxia were noticed at 2 years. She never walked independently except few steps. Her hypotonia improved by four years of age and her reflexes were not exaggerated. She developed hypokalemia around 2½ years of age and hypomagnesemia around 4½ years of age. Hearing assessment at 4½ years showed moderate bilateral SNHL on auditory brain-stem evoked response (ABER), and she is waiting for bilateral cochlear transplant.

Though she was seizure-free from 7 months of age, her topiramate was electively changed to CBZ at the age of 3 years, and she is currently seizure-free on a dose of 21 mg/kg/day.

3.4. Patient 1.4

This is a seven-year-old girl who was born at term after unremarkable pregnancy and delivery to 1st degree consanguineous Saudi Arabian parents from the Eastern Province.

She was referred to us at the age of 4 years and three months with history of difficulty walking, speech delay, fearfulness, tendency to fall frequently and epilepsy. The seizures started at the age of 3 months. Parents described two types of seizures. The first one in the form of clonic upper extremities and head movements lasting for one minute each, and the second type as generalized hypotonia which usually lasted for 3 min. She was started on sodium valproate but with poor control. Her antiepileptic medication was changed to CBZ with no more seizures for past 2½ years when we first saw her. Her milestones were delayed from the beginning with rolling over at 15 months, sitting alone at 18 months and taking the first steps independently at three years. She transferred objects at seven months and had a pincer grasp at 12 months.

On examination, she was attentive with poor receptive language and alternating exotropia with horizontal nystagmus. The tone was borderline low overall with global hyperreflexia and ataxic gait on first visit. At 5½ years she had deterioration in her balance and coordination, could not hold a cup or walk without support with increased tone and reflexes in lower extremities with bilateral ill-sustained ankle clonus. She worsened further after a febrile illness with head nodding, tremors in both upper extremities increasing with activity and needing to be held by both arms for ambulation. On the last outpatient follow up at age seven years, she had severe ataxia, dysarthria. Her seizures were well controlled on CBZ 20 mg/kg/day.

3.5. Patient 2.1

This is a five-year-old boy who was born at term after unremarkable pregnancy and delivery to 1st degree consanguineous Saudi Arabian parents from the Eastern Province. His birth weight was 3 kg.

His first symptom was generalized tonic-clonic seizures at three months of age. Each seizure lasting for 30 s to one minute, last such was at the age of 16 months. He also had myoclonus during sleep occurring up to 2–3 per day from the neonatal period and is persisting.

He was developmentally delayed from the beginning with head control at 12 months, sitting without support at 14 months and cruising around furniture by 2 years of age but never achieved independent ambulation. At three years of age he was saying only two words. There is strong family history of neurological disorders in both sides of the parents. He was dysmorphic with high-arched palate with right-side simian palmar crease with two small café-au-lait spots over trunk and nevus flammeus over the forehead. He had hypotonia with normal deep tendon reflexes. LEV used initially failed to control his seizures but responded well to TPM at the dose of 5 mg/kg/day. Ataxia was noticed at 3½ years starting in lower extremities with tremors and nystagmus at the last visit. He had started taking few steps independently after intensive physiotherapy and occupational therapy. Currently, his vocabulary is limited to 50 words. He is on potassium supplementations.

The clinical details other than epilepsy for all the patients are described in table 2.

3.6. Epilepsy

Patients with EAST syndrome are usually born normally with an uneventful neonatal period. Both male and female are affected. The first symptom in almost all the patients is a seizure. The age of seizure onset is around 3–4 months. Less frequently earlier seizure onset possibly in the neonatal period, and at the age of two months in one each [3], and later onset at the age of 8.5 months in other patient [4] have been described in the literature

The most common seizure type is an apparent generalized tonic-clonic seizure. In our cohort, two patients had generalized clonic seizures. One patient had non-motor seizures characterized by staring and unresponsiveness. This same patient also had generalized tonic-clonic seizures which raises a possibility of focal onset seizure evolving into bilateral tonic-clonic seizure. In the cohort of Cross et al., three patients who initially had generalized tonic-clonic seizures and became seizure free for years had subsequent recurrence of seizures which were thought to be of focal in nature, one characterized as having staring episodes and other with episodes of behavioral arrest, lip-smacking and loss of awareness [3]. One of our patients (# 2.1) has generalized body jerks only during sleep, especially when the parents touch him or try to change his position. These events could be non-epileptic sleep myoclonus but an EEG is needed to better characterize them.

Seizures are usually brief, lasting for 30 s to 3 min. Some patients develop status epilepticus. In the cohort of Cross et al., one patient had tonic-clonic seizure in sleep with left-sided facial twitching lasting 20 min, and another patient had non-convulsive status epilepticus on an attempted wean of VPA [3]. Scholl et al. reported four cases of SeSAME syndrome in four siblings of Somali origin, one of whom had a history of status epilepticus with right hemiparesis [4].

In our cohort, seizures were well controlled with low dose (12–21 mg/kg/day) CBZ (see Table 1). TPM was also effective in two patients. LEV was not as effective. Papavasiliou et al. reported one case whose seizures were fully controlled with TPM and CBZ [5]. Cross et al. described one patient whose seizures were well controlled on CBZ, but other patients responded well to VPA and lamotrigine (LTG) [3]. In the cohort of Scholl et al., one patient was maintained on Oxcarbazepine, another one on Phenobarbital (PHB) and VPA and

Table 1
Summary of epilepsy.

Patient	Age (y:m)	Sex	First symptom	Seizure onset	Seizure types	Seizure duration	Age at last seizure	Effective anticonvulsants	Ineffective anticonvulsants	EEG findings
1.1	12:0	M	Seizure	4 months	1. GTC	Usually <5 min. SE up to 20 min	12 years	Valproic acid Carbamazepine (12 mg/kg/day)	None	Normal awake at age 11 years
1.2	6:0	F	Seizure	3 months	1. Generalized clonic with staring and eye blinking starting during sleep	Usually up to 3 min. Once SE lasting for 15 min	Fairly controlled since 9 months of age but four episodes of exacerbation with fever. Last one 4½ years of age	Carbamazepine (18 mg/kg/day)	Partial response to levetiracetam	Normal awake and sleep at 5 and 10 months Awake and sleep at 5 years of age – BG slightly slow for age. Intermittent independent left and right P-O sharply contoured slowly
1.3	5:5	F	Seizure	3 months	1. Started with Staring episodes and unresponsiveness 2. GTC	1. 1–2 min 2. 1–2 min	7 months	Topiramate – good control but later changed to Carbamazepine (21 mg/kg/day)	Levetiracetam (up to 60 mg/kg/day)	Normal awake and sleep at 6 months of age Normal awake at 5 years of age
1.4	7:6	F	Seizure	3 months	1. Clonic upper extremities and head movements 2. Generalized hypotonia	1. 1 min 2. 3 min	21 months	Carbamazepine (20 mg/kg/day)	Valproic acid	Generalized slow with myoclonic jerks upon arousal associated with gen irregular epileptic discharges (3 years) Normal awake at 7 years of age
2.1	5:6	M	Seizure	3 months	1. GTC 2. Myoclonic jerks in sleep	1. 30 s to 1 min	16 months	Topiramate (5 mg/kg/day)	Levetiracetam	Awake EEG at 5 years of age showed focus of spike activity in left central region. Normal BG

Abbreviations: GTC, generalized tonic-clonic; M, male; F, female; y, years; m, months; SE, status epilepticus; EEG, electroencephalogram; BG, background

Table 2
Clinical details other than epilepsy.

Characteristics	Patient 1.1	Patient 1.2	Patient 1.3	Patient 1.4	Patient 2.1
Age (years)	12	6	5	7	5
Gender	M	F	F	F	M
First symptom	Seizures	Seizures	Seizures	Seizures	Seizures
Ataxia (age of onset)	+ (7½ years)	+ (3 years)	+ (3 years)	+ (6 months)	+ (3½ years)
Sensorineural Hearing loss	Moderate to severe	Moderate	Moderate to severe	Mild	Severe
Tremors	+	+	+	+	+
Development	Severe delay in gross motor skills but moderate delay in other domains	Moderate delay in gross and fine motor skills but normal in speech and cognition	Moderate global developmental delay including cognition	Severe delay in gross and fine motor skills but moderate delay in other domains	Severe global developmental delay particularly more in gross and fine motor skills
Head circumference in centimeter (percentile)	51 (10–25)	48 (10–25)	50 (50)	49 (10–25)	49 (10–25)
Dysmorphic features	None	None	None	None	Right-side simian crease, high-arched palate
Skin findings	None	None	One hypopigmented macule	None	2 small café-au-lait spots, naevus flammeus over forehead
UMN signs	Hyperreflexia	Hyperreflexia	Hyperreflexia	Hyperreflexia	Normal reflexes
Tone	Hypertonia	Hypertonia	Hypertonia	Hypertonia	Hypotonia
Other cerebellar signs	Past-pointing, scanning speech, nystagmus	Scanning speech	Scanning speech	Nystagmus, scanning speech	Nystagmus
Serum electrolyte abnormalities (age of onset)	Hypomagnesemia, Hypokalemia, Metabolic Alkalosis (1 year)	Hypomagnesemia-(2½ years) Hypokalemia -(4½ years)	Hypomagnesemia & hypokalemia -(2½ years)	Normal magnesium, Hypokalemia -(3 ¾ years)	Hypomagnesemia, Hypokalemia, Normal bicarbonate
Salt Craving	+	+	–	+	–
Polyuria	+	–	–	–	–
Polydipsia	+	–	+	–	–
Ophthalmology exam (seen at age)	Refractive error (10½ years)	Refractive error (4¼ years)	Refractive error (4½ years)	Alternating exotropia	Refractive error (4½ years)
Brain MRI	Normal	Normal	Not available	Bilateral symmetric T2/ FLAIR hyperintensity in the dentate nuclei	Bilateral symmetric T2/ FLAIR hyperintensity in the dentate nuclei

Abbreviations: UMN, upper motor neuron; MRI, magnetic resonance imaging; FLAIR, fluid-attenuated inversion recovery.

other two on PHB alone. It is not clear how well controlled the seizures were in those patients [4].

Recurrence of seizures occurs in some patients after weaning the anti-seizure medications even though they were seizure free for a long time. In one of our patients, CBZ wean was tried two times after being seizure free for more than two years and both the times seizures recurred, and CBZ was restarted. Two patients had seizure recurrence on weaning VPA, and one patient remained seizure free after weaning the VPA from the age of 4 until 12 when seizures recurred [3].

Routine EEGs are usually normal or show non-specific findings. In a few patients, EEG showed background slowing. Cross et al. reported one case in which EEG showed spikes and sharps localizing to vertex [3]. In the patient reported by Scholl et al. who had status epilepticus with right hemiparesis, EEG showed slow and disorganized background with focal slowing and occasional sharp activity arising from left hemisphere [4]. EEG of one of our patients (#1.4) done at the age of 3 years showed myoclonic jerks upon arousal associated with generalized irregular epileptic discharges but a repeat EEG at the age of 7 years was normal.

3.7. Genetics

The first case of EAST syndrome was reported in 2009 by Bockenhauer et al. when they found the causative gene by linkage analysis [1]. It is caused by a mutation in the *KCNJ10* gene located on 1q23.2. The

approved name of the gene is potassium inward-rectifying channel, subfamily J, member 10. It is a heterogeneous disease with interfamilial variability with autosomal recessive inheritance pattern. About 16 different mutations have been discovered in this gene to date. The first and the most common mutation reported in *KCNJ10* is p.R65P (c.194G>C). This mutation leads to loss of function in related potassium channels. This pathology with the involvement of the central nervous system, inner ear, and renal tubules mimics the ciliopathies. We report 5 cases, four from one consanguineous family, and one from another consanguineous family (Fig. 1). This is the first case series reported on EAST syndrome from Saudi Arabia. All five patients have the same homozygous c.170C>T (p.Thr57Ile) missense mutation in *KCNJ10* gene. This mutation was only reported previously in three patients of Somali origin by Scholl et al. [4]. The symptoms were variable even within the family and there was no evidence of genotype phenotype correlation in these patients.

The genetic mutations of the cases reported in the literature are presented in table 3.

3.8. Neuroimaging

Brain MRI studies were available for all patients except patient # 1.3. MRI showed bilateral symmetric T2/FLAIR hyperintensity in the dentate nuclei in two patients (patient # 1.4 and 2.1) (See Fig. 2 and Fig. 3). There is no associated mass effect, diffusion restriction or abnormal enhancement. The brain MRI of the other two cases was unremarkable. These findings are very characteristic and described in only two studies [3,6]. There are few entities affecting the dentate nuclei and the neuroradiological differential diagnosis is limited if there are no associated findings. Possible differential diagnosis includes metronidazole toxicity but usually, there is associated diffusion restriction, and it is reversible after metronidazole discontinuation. Other diseases affecting the dentate include Canavan disease, Leigh syndrome, Glutaric aciduria type I, Maple syrup urine disease, but usually, there are associated characteristic white matter, basal ganglia, Sylvian fissure, brain stem and medial cerebellar abnormalities respectively.

Quantitative volumetric analysis studies were performed in two studies and showed volume loss in different regions of the brain, especially the cerebellum [3,6]. In our case series, there was one case with mild diffuse volume loss (patient # 1.2) based on visual assessment only. More reports and longer follow up are needed to validate the sensitivity and persistence of this characteristic dentate nuclei abnormality.

4. Discussion

We report five genetically diagnosed patients with EAST syndrome from two families in the eastern province region of Saudi Arabia. Only few case series and case reports have been published regarding this syndrome with emphasis on genetic mutation and renal tubulopathy. Cross et al. presented neurological features of this syndrome in more detail [3]. We present a comprehensive description of epilepsy in our patients and

Table 3
Genetic mutations of the cases reported in the literature.

No.	Mutation	Homozygosity/ Heterozygosity	Type of Mutation	Experimental Residual Activity	References
1	p.T57I (c.170C>T)	Yes/No	Missense	Loss of function	[4,6]
2	p.R65C (c.193C>T)	Yes/Yes	Missense	<20%	[16,20]
3	p.R65P (c.194G>C)	Yes/Yes	Missense	<20	[1,2,12,13,15,17–19]
4	p.F75C (c.224 T>G)	Yes/No	Missense	Loss of function	[6,14]
5	p.F75L (c.225 T>G)	Yes/No	Missense	<10%	[16]
6	p.G77R (c.229G>C)	Yes/No	Missense	<5%	[1,12,13,16,18]
7	p.C140R (c.418 T>C)	Yes/No	Missense	Loss of function	[2,12,18,19]
8	p.T164I (c.491C>T)	Yes/No	Missense	Loss of function	[2,12,16,18,19]
9	p.A167V (c.500C>T)	Yes/Yes	Missense	60%	[2,12,14,16,18,19]
10	p.R175Q (c.524G>A)	Yes/No	Missense	<5%	[13]
11	p.R199Ter (c.595C>T)	No/Yes	Nonsense	Loss of function	[2,12,16,18,19]
12	p.R240H (N/A)	Yes/No	Missense	N/A	[11]
13	p.V259Ter (c.775delG)	Yes/No	Frame-shift/ nonsense	Loss of function	[16]
14	p.R297C (c.889C>T)	Yes/Yes	Missense	<10%	[2,3,12,16,17–19]
15	p.V91fs197Ter (c.272delT)	Yes/No	Frame-shift	Loss of function or < % residual activity	[14]
16	p.F119GfsTer25 (c.297_354dup)	No/Yes	Frame-shift	N/A	[5]

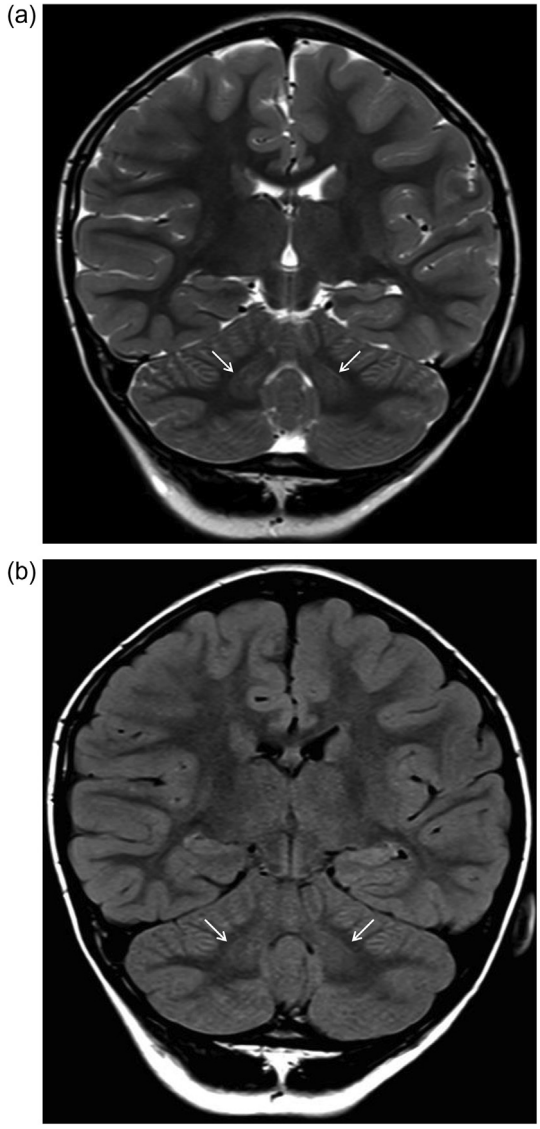

Fig. 2. Brain MRI of Patient 1.4: Coronal T2 (A) and FLAIR (B) show bilateral symmetric hyperintensity of the dentate nuclei (arrows).

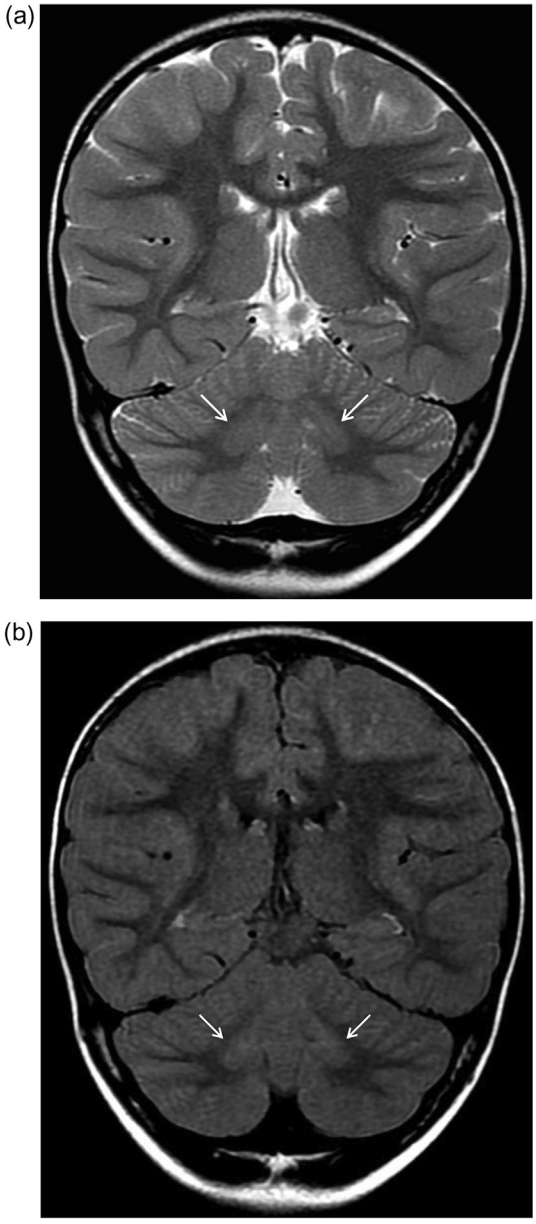

Fig. 3. Brain MRI of Patient 2.1: Coronal T2 (A) and FLAIR (B) show bilateral symmetric hyperintensity of the dentate nuclei (arrows).

also a review of the previously reported findings of epilepsy in this syndrome. We also discuss the treatment options for seizures.

Epilepsy is a core feature of this syndrome and seizure is the first manifestation. As the child grows sensorineural hearing loss, and ataxia becomes more apparent. Dyselectrolytemia in the form of hypokalemia, hypomagnesemia, and hypochloremia develops later in childhood. Often, patients presenting with seizures during the first year of life pose a challenge to the physicians, requiring a thorough work up to investigate the etiology, especially the treatable causes of epilepsy. Early recognition of this entity could help to avoid unnecessary testing and may help in providing information about natural history and prognosis of the disease to the family.

The age of seizure onset is strikingly around 3–4 months of age in most patients. The most common type is generalized tonic-clonic seizure. A few patients who previously were known to have generalized tonic-clonic seizures also had non-motor seizures in the form of staring and behavior arrest which raises a possibility of focal onset seizures evolving into bilateral tonic-clonic seizures. Seizures are usually brief lasting less than three minutes. Focal status epilepticus with or without Todd's paralysis, generalized and non-convulsive status epilepticus have been reported [3,4]. Cautious weaning of anti-seizure medications is warranted since status epilepticus could be precipitated even after a prolonged period of seizure freedom.

Selecting the right anti-epileptic medication could help in better seizure control and avoid unnecessary side effects. In our cohort, patients responded very well to 12–21 mg/kg/day of CBZ without any side-effects. It was effective in two other patients reported [3,5]. It is reported that CBZ is a novel corrector of KATP channels which were previously identified in congenital hyperinsulinism [7]. CBZ has also shown to be effective in episodic ataxia type 1 which is caused by missense mutations in *KCNA1* gene [8]. The effectiveness of CBZ at low doses in controlling the seizures in patients with EAST syndrome brings up a question about the potential for personalized genomics and therapeutics. Genomic research and modern translational medicine tools could help to validate this hypothesis. VPA and LTG were also reported to be effective in achieving good seizure control [3]. Hepatic fatalities can occur in patients receiving VPA, especially in children less than two years of age [9]. Since seizures begin very early in infancy, we recommend avoiding VPA as the first choice of anti-seizure medication early in the disease course. Tremors as a side effect of VPA which may worsen the tremors and unsteadiness in these patients. LTG, on the other hand, could be a good option with a better side effect profile although it needs to be titrated very slowly due to the risk of Steven Johnson syndrome. If the patient has frequent seizures, LTG could be bridged with either clonazepam or clobazam until target dose is reached. TPM was also efficacious in two patients. TPM is associated with a negative impact on cognition and verbal fluency [10], and hence we recommend avoiding this medication as the first line since patients with this condition have scanning or ataxic speech, and some patients have some cognitive issues as part of the syndrome complicated with associated SNHL. PHB has been used in some patients although it is not clear how effective it was except in three patients who had partial seizure control [2,3,6,11]. LEV was used in two of our patients and was not found to be as effective. Phenytoin (PHT) was used in one patient [2]. But it is usually avoided as a first line anti-epileptic medication in children due to non-linear kinetics of metabolism and availability of medicines with better side-effect profile. But PHT can be used in these patients in the setting of status epilepticus. Monotherapy is usually sufficient to manage seizures in this syndrome.

Seizure recurrence can occur in some patients after weaning the anti-epileptic medications even though they were seizure free for a long time, sometimes with status epilepticus. If weaning of anti-epileptic medication is considered, family has to be informed about recurrence of seizures and possibility of status epilepticus and it is advisable to prescribe a rescue medication like rectal diazepam or buccal midazolam. A long-term follow up is necessary to see if these patients eventually become seizure-free or continue to have seizures lifelong.

Routine EEGs are usually normal or show non-specific findings. Only in a few patients, EEG shows background slowing which may suggest that some patients could have mild encephalopathy. Focal epileptiform discharges can also be seen on the EEG.

Acknowledgements

The authors would like to thank Dr. Shahid Bashir and Ms. Alhanoof Jowaiser for their administrative help. We would also like to thank Dr. Hafiz Habeebullah for doing developmental assessment for the patients.

References

[1] Bockenhauer D, Feather S, Stanescu HC, Bandulik S, Zdebik AA, Reichold M, et al. Epilepsy, ataxia, sensorineural deafness, tubulopathy, and KCNJ10 mutations. N Engl J Med 2009;360:1960–70.

[2] Scholl UI, Choi M, Liu T, Ramaekers VT, Häusler MG, Grimmer J, et al. Seizures, sensorineural deafness, ataxia, mental retardation, and electrolyte imbalance (SeSAME syndrome) caused by mutations in KCNJ10. Proc Natl Acad Sci U S A 2009;106:5842–7.

[3] Cross JH, Arora R, Heckemann RA, Gunny R, Chong K, Carr L, et al. Neurological features of epilepsy, ataxia, sensorineural deafness, tubulopathy syndrome. Dev Med Child Neurol 2013;55:846–56.

[4] Scholl UI, Dave HB, Lu M, Farhi A, Nelson-Williams C, Listman JA, et al. SeSAME/EAST syndrome–phenotypic variability and delayed activity of the distal convoluted tubule. Pediatr Nephrol 2012;27:2081–90.

[5] Papavasiliou A, Foska K, Loannou J, Nagel M. Epilepsy, ataxia, sensorineural deafness, tubulopathy syndrome in a European child with KCNJ10 mutations: A case report. SAGE Open Med Case Rep 2017:5.

[6] Abdelhadi O, Iancu D, Stanescu H, Kleta R, Bockenhauer D. EAST syndrome: Clinical, pathophysiological, and genetic aspects of mutations in KCNJ10. Rare Dis 2016;4 e1195043.

[7] Chen PC, Olson EM, Zhou Q, Kryukova Y, Sampson HM, Thomas DY, et al. Carbamazepine as a novel small molecule corrector of trafficking-impaired ATP-sensitive potassium channels identified in congenital hyperinsulinism. J Biol Chem 2013;288:20942–54.

[8] Eunson LH, Rea R, Zuberi SM, Youroukos S, Panayiotopoulos CP, Liguori R, et al. Clinical, genetic, and expression studies of mutations in the potassium channel gene KCNA1 reveal new phenotypic variability. Ann Neurol 2000;48:647–56.

[9] Dreifuss F, Santilli N, Langer DH, Sweeney KP, Moline KA, Menander KB, et al. Valproic acid hepatic fatalities: a retrospective review. Neurology 1987;37:379–85.

[10] Thompson PJ, Baxendale SA, Duncan JS, Sander JW. Effects of topiramate on cognitive function. J Neurol Neurosurg Psychiatry 2000;69:636–41.

[11] Kara B, Ekici B, Ipekçi B, Aslanger AK, Scholl U. KCNJ10 gene mutation in an 8-year-old boy with seizures. Acta Neurol Belg 2013;113:75–7.

[12] Williams DM, Lopes CM, Rosenhouse-Dantsker A. Molecular basis of decreased Kir4.1 function in SeSAME/EAST syndrome. J Am Soc Nephrol 2010;21:2117–29.

[13] Reichold M, Zdebik AA, Lieberer E. KCNJ10 gene mutations causing EAST syndrome (epilepsy, ataxia, sesnsorineural deafness, and tubulopathy) disrupt channel disfunction. PNAS 2010:14490–5.

[14] Parrock S, Hussain S, Issler N. KCNJ10 mutations display differential sensitivity to Heteromerisation with KCNJ16. Nephron Physiol 2013:7–14.
[15] Abdelhadi O, Iancu D, Tekman M, Stanescu H, Bockenhauer D, Kleta R. Founder mutation in KCNJ10 in Pakistani patients with EAST syndrome. Mol Genet and Genomic Med 2016;4:521–6.
[16] Freudenthal B, Kulaveerarsingam D, Lingappa L. KCNJ10 mutations disrupt function in patients with EAST syndrome. Nephron Physiol 2011:40–8.
[17] Thompson D, Sally F, Stanescu H. Altered electroretiongrams in patients with with KCNJ10 mutations and EAST syndrome. J Physiol 2011;589:1681–9.
[18] Sala-Rabanal M, Kucheryavykh LY, Skatchkov SN, Eaton MJ, Nichols CG. Molecular mechanisms of EAST/SeSAME syndrome mutations in Kir4.1 (KCNJ10). J Biol Chem 2010;285:36040–8.
[19] Tang X, Hang D, Sand A, Kofuji P. Variable loss of Kir4.1 channel function in SeSAME syndrome mutations. Biochem Biophys Res Commun 2010;399:537–41.
[20] Celmina M, Micule I. Inashkina I. EAST/SeSAME syndrome: Review of the literature and introduction of four new Latvian patients. Clin Genet 2019:63–78.