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ORIGINAL RESEARCH

EAST syndrome: Refractory Epilepsy on Long term follow up

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Abstract

Epilepsy, **A**taxia, **S**ensorineural deafness, and **T**ubulopathy (EAST syndrome), is a rare autosomal recessive syndrome due to homozygous missense mutations of the KCNJ10 gene. We report two siblings from India, both presented with early-onset epilepsy, developmental delay, hearing impairment, ataxia, and electrolyte imbalances suggestive of tubulopathy. The firstborn boy presented at age 9yrs, with onset of epilepsy at 12 months. The younger sibling, a girl, presented at $2_{1/2}$ years with infrequent febrile and afebrile generalized seizures. Both demonstrated delayed milestones and had mild sensorineural hearing loss. They had multiple brain magnetic resonance imaging studies with a similar distribution of abnormalities involving the dentate nuclei, brainstem, thalami, basal ganglia, and cerebral white matter, with mild progression of the neuroimaging findings over time. Epilepsy was refractory in both of them at the last follow-up. The constellation of multiorgan involvement was characteristic of EAST syndrome, and mutation analysis of the KCNJ10 gene confirmed the diagnosis. Neuroimaging showed characteristic features that supported the diagnoses. Compared with other available reports, these children had refractory epilepsy uncontrolled on multiple medications. The significant intellectual delay forced them to be taken out of school.

Keywords: EAST syndrome, SeSAME syndrome, KCNJ10, Topiramate, and Zonisamide.

Introduction

Epilepsy, Ataxia, Sensorineural deafness, and Tubulopathy (EAST) syndrome, also known as Seizures, Sensorineural deafness, Ataxia, Mental retardation, and Electrolyte imbalance (SeSAME syndrome), is a rare autosomal recessive disorder among children, resulting from mutations in *KCNJ10* gene encoding for Kir4.1 protein [1]. As KCNJ10 is expressed in the brain, inner ear, eye, and kidney, mutations can result in complex manifestations, seizures, and hearing impairment. Renal salt-wasting tubulopathy resembles those of Gitelman and Bartter syndromes [2, 3]. Onset in infancy, generalised tonic-clonic seizures, shorter duration, nonspecific EEG changes less often with background slowing are the characteristic features of epilepsy in EAST syndrome. Hyperintensity in the dentate nucleus on brain magnetic resonance imaging (MRI) and volume loss, particularly in the cerebellum in the quantitative volumetric analysis, have been reported [4]. This syndrome seems to have both static and progressive qualities [5].

We describe two siblings from India with early onset epilepsy and other clinical features compatible with EAST syndrome, with progressive worsening of clinical and neuroimaging findings and proven homozygous mutations in the KCNJ10 gene with a detailed neurological and neuroradiological assessment and long-term follow-up.

Case Presentation

Written informed consent for publication of the clinical details and clinical images was obtained from the parent. A copy of the consent form is available for review by the Editor of this journal.

Patient #1

The index child was the firstborn male to a non-consanguineous couple, with an uneventful perinatal history and unremarkable family history. At one year, he had generalized tonic-clonic seizures (GTCS) with a frequency of 1-2/month, each lasting for 1-10 minutes. Additionally, he had focal with impaired awareness seizures (acute-onset severe headache with brief confusion) lasting for 1-2 minutes starting at four years. He received Sodium Valproate with an initial response at two years. Carbamazepine and clobazam helped in seizure control from 5 to 7 years of age. At eight years, Levetriacetam and Zon-

isamide were tried with an increased frequency of Focal with impaired awareness with the latter medication. At five years of age, the child was hospitalized with polyuria, mild polydipsia, and neuromuscular paralysis. Renal abnormalities included hypokalemic metabolic alkalosis with hypomagnesemia, consistent with Gitelman syndrome. In view of tubulopathy, he was prescribed potassium chloride syrup, milk of magnesia, and ibuprofen. Mild sensorineural hearing loss of 60 dB in both ears was documented.

He presented to us at nine years with right focal status epilepticus (FSE), which continued for an hour with an altered sensorium requiring ventilation for a week. Electroencephalogram (EEG) demonstrated left-hemispheric seizure discharges. Fosphenytoin, phenobarbitone, and levetiracetam with midazolam infusion were given to control status epilepticus (SE). He was discharged on levetiracetam, clonazepam, and phenobarbitone. He had mild gait ataxia but was walking unaided until another episode of status epilepticus at the age of 13 years. At 13 years of age, he had significant right FSE that required general anaesthesia, including ketamine infusion. Botox-A injection was administered twice for spasticity with partial response. Residual severe right hemiparesis required intensive rehabilitation and took three years to walk again.

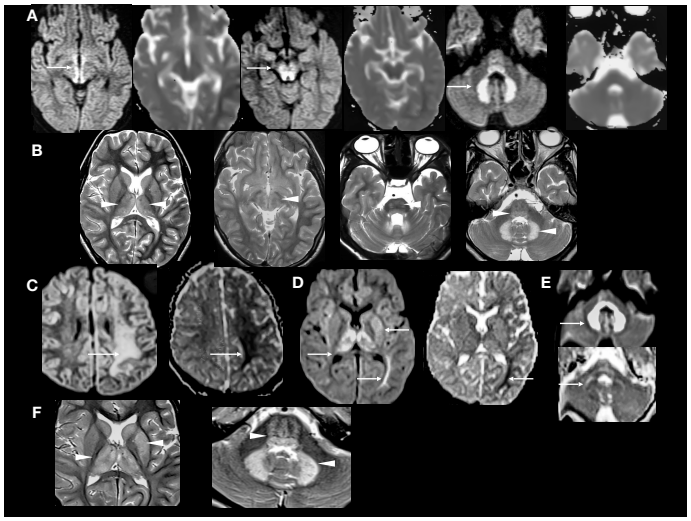
Two magnetic resonance imaging (MRI) scans were done at 13 years (a month apart). The first scan showed symmetrical hyperintensities on T2 weighted and diffusion-weighted images (DWI) in thalami (medial, central, and pulvinar nuclei), hypothalami, periaqueductal grey matter, brainstem, and dentate nuclei, with no restricted diffusion on Apparent diffusion coefficient (ADC) images, indicative of T2-shine through (Fig.1). The subsequent scan, post status epilepticus, had extensive areas of restricted diffusion in the left cerebral white matter, and in the right frontal & insular cortex, indicative of status epilepticus induced excitotoxic injury [6]. T2 hyperintensities with no restricted diffusion in the bilateral thalami and left basal ganglia and a mixed pattern of restricted and normal diffusivity with T2 hyperintensities in the brainstem and dentate nuclei were seen (Fig.1).

A follow-up MRI at 15 years of age showed T2 hyperintense changes in the dentate nuclei and brainstem without restricted diffusion. Atrophy of the left cerebral hemisphere, along with cerebellar atrophy, was noted (Fig.1). His renal problems did not require further admission, but he had low potassium levels and, along with borderline low magnesium levels, requiring regular supplements and was on three monthly testing for electrolyte abnormalities. His growth faltered around ten years of age and is currently less than 3rd centile for height and weight.

He was last evaluated at 21 years, with clinical improvement, characterized by short sentences of < five words and motor more than sensory aphasia. Right hemiparesis was slowly improving but required support for fine motor activities like dressing. Ataxia in him is currently not appreciable because of significant spasticity. He dropped out of school, unable to cope with academics.

Current antiepileptic drugs (AEDs) include perampanel 4 mg at night, levetiracetam 2 gm/day, clobazam 10 mg/day, and potassium supplements. He continues to have brief focal seizures with impaired awareness daily and has failed a ketogenic diet.

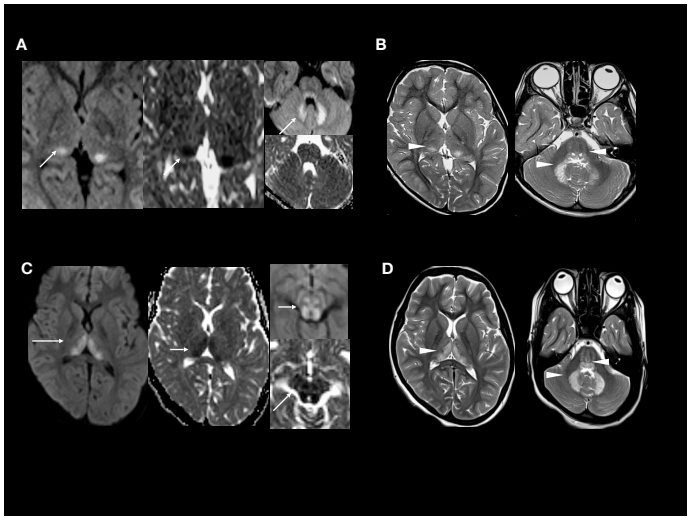
Figure 1. 1 Brain MRI of Patient 1 at 13 years (A,B) and follow up after a month (C,D,E,F). **A.** Symmetrical areas of high signal on Diffusion-Weighted Images(DWI)(arrows) with lack of true restricted diffusion and normal Apparent Diffusion Coefficient (ADC) in the medial thalami, periaqueductal grey matter, brainstem and dentate nuclei. **B.** T2 hyperintensities (arrowheads) in the medial thalami, periaqueductal grey matter, brainstem and dentate nuclei. Follow up MRI after a month, post status epilepticus (SE) **C.** DWI/ADC images demonstrates new areas of restricted diffusion on(arrows) in the left cerebral white matter. Similarly in the right frontal & insular cortex (not in the image). **D.** DWI/ADC images demonstrate symmetrical areas of high signals on DWI and lack of true restricted diffusion in the thalami. **E.** DWI/ADC images demonstrate inhomogeneous mixed pattern of restricted and normal diffusivity in the brainstem and dentate nuclei. **F.** T2 hyperintense changes (arrowheads) in the bilateral thalami, left basal ganglia, brainstem and dentate nuclei.



Patient 2

She is the younger sibling of Patient 1. She had generalized febrile seizures at ten and fourteen months; the first afebrile seizure developed at eighteen months. EEG demonstrated occasional generalized spike-wave discharges and was started on levetiracetam. Further investigation in view of the elder sibling's history revealed hypokalaemia with metabolic alkalosis; she was started on potassium chloride along with ibuprofen from the age of $2_{1/2}$ years. MRI at $2_{1/2}$ years showed symmetrical T2 hyperintensities in the dentate nuclei and brainstem (Fig.2). Seizures were initially well controlled with levetiracetam until eight years of age. Later, the patient had brief GTCS and occasional episodes of focal seizures with impaired awareness lasting < 1 minute. Seizures were controlled with sodium valproate, clobazam, and phenobarbitone. Brainstem-evoked response audiometry revealed 50dB bilateral sensorineural hearing loss.

Figure 2. Brain MRI of Patient 2 at 8 years (A,B) and 14 years (C,D). **A.** Symmetrical areas of high signal on Diffusion-Weighted Images(DWI)(arrows) in the bilateral thalami (pulvinar nuclei), dorsal brainstem and dentate nuclei with restricted diffusion on Apparent Diffusion Coefficient (ADC) in the thalami. There is lack of restricted diffusion with normal ADC signals in the dorsal brainstem and dentate nuclei. **B.** Symmetrical areas of T2 hyperintensities (arrowheads) in the posterior limb of internal capsule (plic), thalami (pulvinar nuclei), dorsal brainstem and dentate nuclei. Follow up MRI at 14 years of age. **C.** DWI/ADC images demonstrates progression of the lesions with restricted diffusion (arrows) involving the plic, thalami (ventrolateral and medial nuclei), brainstem (quadrigeminal plate, substantia nigra and red nuclei) and dentate nuclei. T2 hyperintensities (arrowheads) in the plic, thalami (ventrolateral and medial nuclei), brainstem and dentate nuclei.



MRI brain done during this period showed progression on imaging, with symmetrical T2 hyperintensities and restricted diffusion in the thalamus (pulvinar nuclei); no restricted diffusion and T2 hyperintensities were seen in the brainstem and dentate nuclei (Fig.2).

At 10 1/2 years, was hospitalized with acute gastroenteritis and loss of ambulation secondary to hypomagnesemia (1mg/dL) and hypokalaemia (3.2mMol/L), discharged on oral (syrup) potassium chloride along with oral etoricoxib (90 mg, 1/2 tab once a day). The renal tubular acidosis never required further acute management as long as she was on regular medications, as noted. She made slow progress in her speech, could speak in 2-3-word sentences, was walking independently with mild gait ataxia, and retained hearing without hearing aids. By the age of 14 years, frequent brief focal seizures with impaired awareness lasting <1 minute, 3-5 episodes/day noted. Her medications were changed (levetiracetam 1.5 gm/day, phenobarbitone 90 mg/day, and lamotrigine 50mg/day) and she was started on the ketogenic diet, later controlled with phenytoin. Progressively increasing seizures in both children were suggestive of the slow progression of the disease process.

Follow-up MRI at 14 years showed restricted diffusion and T2 hyperintense signal changes in the posterior limb of the internal capsule (PLIC), thalami (ventrolateral and medial nuclei), brainstem (quadrigeminal plate, substantia nigra and red nuclei) and dentate nuclei along with mild cerebral and cerebellar atrophy. Magnetic resonance spectroscopy (MRS) of the thalamus showed normal peaks (Fig.2).

Genetic study

The samples were sent to Royal Free Hospital Medical school, United Kingdom, for genetic testing. The genetic defect of KCNJ10 mutation was demonstrated, and its pathogenicity was proved in oocytes. There was no residual activity in the oocytes with p.V259fs259X mutation in the intracellular carboxy terminus region with the generation of a premature stop codon [7]. It is postulated that multimerization and a cytoplasmic extension of the ion pathway are brought about by the placement of V259 within the carboxy-terminal region. The formation of significantly truncated protein is the result of mutation V259X. Two affected siblings were homozygous for the mutation, and their parents were both heterozygous carriers.

She had short stature along with normal weight for age by 14 years of age. At the age of 16 years, she was hospitalised in an adult facility with acute encephalopathy and hypernatremia in the setting of acute gastroenteritis, which was managed with rehydration and correction of sodium, ventilation (exact details are not available for review) and died due to encephalopathy with hypernatremia (sodium–190 mmol/dL) with encephalopathy requiring ventilation. Details of clinical and radiological findings and laboratory investigations are provided in tables 1 & 2.

Discussion

EAST syndrome is a multiorgan disorder caused by homozygous or compound heterozygous mutations in the *KCNJ10* gene localized on chromosome 1q23.2.1 [2, 3]. Considerable clinical variability has been described, even within the family members with the same mutations. Though there was no history of consanguinity, the parent belonged to the same close community. Non-consanguinity is reported in patients with EAST syndrome [5]. Initially reported in children of Pakistani origin and named EAST syndrome, cases with different nativity have been reported.

KCNJ10 encodes potassium channels and maintains healthy homeostasis of potassium in the body. *KCNJ10* polymorphism and mutations are related to the development of epilepsy in children. Celima et al. [5] have compiled known mutations of the *KCNJ10* causing EAST/SeSAME syndrome, wherein both homozygosity and compound heterozygosity is noted. Mislocalization of K+ channels is considered to cause the electrolyte imbalance seen in EAST syndrome. Mutations involving *KCNJ10* have been described in 16 cases [5]. Our patients had deletions of a single nucleotide c.775delG, resulting in frame-shift mutation and premature stop codon. V259 at the carboxy-terminal region is crucial for multimerization, a cytoplasmic extension of the ion pathway, and a mutation of V259X caused a significantly truncated protein in our patients [7].

Table 1. Clinical and Imaging findings

Parameters	Patient 1	Patient 2
Age at presentation	10 months	1 Year
Age at last follow up	19 Years	14 Years
Sex	Male	female
Developmental delay	Present	present
First Seizure	10 months	1 year
Current seizure	Focal with impaired awareness	Focal with impaired awareness
Seizure recurrence	Daily for last 3 years	Daily for past 2 months
Antiepileptics (mg/kg/dl)	Levetriacetam 32 mg/kg/day Perampenel 6 mg/day Phenobarbitone 2.5mg/kg/day	Levetriacetam 20mg/kg/day Perampenal 4 mg/day Lamotrigine 1mg/kg/day(plan to increase) Phenobarbitone 2.8mg/kg/d
Clinical findings		
Ataxia	Present,	Present
Gait	Right Hemiparetic walks with minimal support	walks independently
Nystagmus	none	none
Muscle tone	Spasticity right>left, Upper limb>lower limb	Mild lower limb spasticity at achilles
Deep Tendon Reflexes	Brisk right >left	Lower limb brisk reflexes
Plantar	Extensor bilateral	flexor
Audiometry	60dB SNHL at 12 years	50dB SNHL at 8 years
Speech	Joins two words, spastic dysarthria	3-4 word sentences, cerebellar dysarthria
Hyperactivity	mild	none
Epilepsy (Clinical) - static or progression	Epilepsy progressive worsening -15 years of age	Epilepsy worsening from 14 year of age
Mutations in KCNJ10	p.V259fs259X, complete loss of function in oocytes	p.V259fs259X, complete loss of function in oocytes
EEG	Left hemispheric discharges during status epilepticus	Interictal occasional generalized spike wave discharges
Radiological findings		
MRI	Symmetrical involvement of thalami, brainstem, and dentate nuclei.	Symmetrical involvement of dentate nuclei, brainstem, hypothalami, thalami and posterior limb of internal capsule.
Neuroimaging follow up - Static or Progression	Progression with Mild cerebral and cerebellar atrophy	Progression with Mild cerebral and cerebellar atrophy

Table 2. Laboratory Investigations

Laboratory parameters	Patient 1	Remark	Patient 2	Remark
Potassium	2.6 mmol/l	Hypokalemia	2.8 mmol/L	On regular K+ supplements
Magnesium	1.3 mg/dl	Hypomagnesimea	0.9 mg/dl	
Sodium	142	Normal	139 mg/dl	
Chloride	88	Hypochloremia	90	
Lactate	1.6	Normal	1.2	Normal
Ammonia	35	Normal	24	Normal
Tandem mass spectroscopy	Normal	-	Normal	-
Urine organic acid analysis	Normal	-	Not done.	-

Tubulopathy-related symptoms in our patients were present before presenting to us. Both patients presented with developmental delays in the form of delayed motor milestones and learning difficulties. Early-onset epilepsy manifested as GTCS and focal seizures, similar to previous reports [5]; they did not have severe failure to thrive.

It is suggested that extracellular accumulation of potassium and myelination defects are due to a mutation of the *KCNJ10* gene [8]. Celima et al. report the early onset of seizures as early as four months (range four months to 7 months). First seizures ranged from upward gaze, lip smacking, head turn, dystonic hand posture, clonic jerking, and shallow breathing. Developmental delay was remarkable. The first seizures were noticed in our patients at one year in patient one and ten months in patient 2.

In both patients, there was a significant increase in the frequency and severity of seizures around adolescence. There was an increasing severity of seizures and poor cognitive improvement along with worsened motor deficits in the elder sibling due to zero residual activity, unlike the data available in the literature. These children had zero residual activity; whether this in some way predisposes to exaggeration of epilepsies is not clearly known. The genotype has not been reported in other patients. Also, zero activity in oocytes has not been reported [9]; Seizures are generally controlled with sodium valproate and lamotrigine in combination or alone. Other medications used included phenobarbitone, phenytoin, and carbamazepine [5].

Index child continued to have seizures daily, uncontrolled by more than 5 anti seizure medications. Increased frequency of seizures was noted around 13-14 years of age, a unique unreported phenomenon. This could be attributable to the zero residual activity of the gene in the oocyte transfer studies in our cases, whereas others had some residual activity [7]. The second child had two episodes of febrile seizures initially and managed accordingly. Anti-seizure medications(ASM) were started when afebrile seizures were noted, i.e., at 18 months.

There is an impression of increasing tone with age, with dystonic posturing seen in older children. Thus, EAST syndrome appears to have static and progressive features, in contrast to the episodic or self-limiting disease seen in other potassium channelopathies with neurological features [10]. Our patients had significant worsening of epilepsy. The later re-emergence of seizures has been documented in other cases, controlled well in most, but few have uncontrolled epilepsy. In all but the youngest two patients (6y 4.8mo and 4y), focal seizures later re-emerged (with or without progression to bilaterally convulsive seizures) but were readily controlled with ASMs in four [11]. There is a pattern of re-emergence of seizures later in EAST syndrome and may or may not be controlled; reemergent seizures were uncontrolled in our cases. The exact reason or mechanism for the same is not documented or established.

Celima et al. [5] have described EEG changes as nonspecific; some background slowing and bilateral asymmetric temporal, central or frontal spikes or spike waves and some regional slow waves were noted in their patients. Our patients showed occasional generalized spike-wave discharges (patient 1) and occasional episodes of focal and generalized spike and slow-wave discharges (patient 2).

Neuroimaging changes in our patients were consistent with previous reports showing symmetrical areas of abnormal signal changes in the dentate nuclei, brainstem, hypothalamus, and thalamus [12]. There was a mixed pattern of cytotoxic and vasogenic oedema in both patients, which to our knowledge, has not been described before and is likely related to the timeframe of imaging. Restricted diffusion seen in patient two can be suggestive of intramyelinic oedema, supporting the role of Kir4.1 in leading to action potential induced cellular swelling with changes of spongiform vacuolization and axonal degeneration [12]. Progressive generalized volume has been described previously [5]. The radiological differential includes mitochondrial disorders. Restricted diffusion seen in MRI is attributable to secondary to prolonged status epilepticus. Celima et al. [5] have described no MRI changes in one child; of the other three, slightly wider lateral ventricles in all, of whom changes in the posterior horn were remarkable in two. Slight periventricular demyelination and slightly wider temporal and frontal lobe subarachnoid space in one patient each were seen.

Celmina et al. [5] state that intellectual disability is not generally part of the disease manifestation; as the data is limited on the developmental trajectory in EAST syndrome, it is often referred to as "delay". Impaired communication, ataxia, and hearing impairment make it difficult to assess the intellectual disability in these children. They are trained in special schools because they cannot cope with the regular school curriculum [11]. Patient 1, in our case report, too, could not continue in regular school, hence dropped out of school. The intellectual profile of EAST syndrome and its progression in adults is not well researched, and there is a need for further studies.

There is limited data on drugs precipitating the seizures (complex focal seizures)/symptoms. Our patients showed exacerbation of focal with impaired awareness seizures with Zonisamide and Topiramate. In contrast, Mir et al. [4] have reported that topiramate is helpful in epilepsy in those with EAST syndrome due to the *KCNJ10* mutation. We do not have a clear electrophysiological explanation for the difference. There is no early death reported in children with EAST Syndrome except in this family, which is likely multifactorial with the genetic defect contributing.

The similarities between the renal features of EAST syndrome and Gitelman syndrome calls for detailed evaluation; the former is due to mutations in the *KCNJ10* gene that is expressed in other regions apart from the kidney, while the latter is renal specific, due to mutations in CLCNKB, a chloride channel, resulting in solute carrier family 12, member three gene, SLC12A3, which encodes the thiazide-sensitive NaCl cotransporter (NCC), and in few patients mutations in CLCNKB gene, both specific for distal convoluted tubule (DCT) [13, 14]. Serum electrolyte profiles appear to be similar as both have features of salt-wasting conditions, i.e., hypokalemia, hyponatremia, metabolic alkalosis, hypomagnesemia, and hypocalciuria. Renal tubulopathy features

are similar to Gitelman syndrome, but extrarenal manifestations, neurological features in particular, in EAST syndrome are characteristic differentiating features [11].

At the time of submission, there were a total of $\sim$ 39 cases, most of the reported cases with South Asian roots [5, 15, 16, 17]. The index children had a more severe and progressive epilepsy phenotype, although the renal tubulopathy remained well-controlled with supplements.

This case report will help identify the appropriate phenotypes and neuroradiological characteristics to diagnose EAST syndrome and analyse the genetics of Indian patients with this condition. These children require multidisciplinary monitoring from Neurology, Nephrology, Rehabilitation, Genetics, and ENT. As there is limited data, international collaboration is required to correlate intellectual delay to identify beneficial antiseizure medication and optimal management of tubulopathy.

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Competing interests

None.

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