PHENOTYPIC LANDSCAPE OF OMANI CHILDREN WITH KCNJ10 MUTATED EAST/SESAME SYNDROME : A SINGLE CENTER EXPERIENCE

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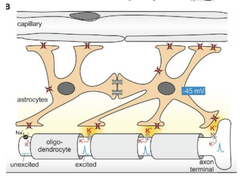
BACKGROUND

- EAST syndrome is an autosomal recessive disorder comprising of **e**pilepsy, **a**taxia, **s**ensorineural deafness and **t**ubulopathy. Another acronym used for this syndrome is SeSAME (**Se**izures, **s**ensorineural deafness, **a**taxia, **m**ental retardation and **e**lectrolyte abnormalities) syndrome.
- It is caused by mutation in the KCNJ10 gene located on chromosome 1q23.2 which encodes the inward-rectifying potassium channel Kir4.1. expressed in the brain, eye, ear and kidneys.
- To date, <30 cases have been reported in the literature with more emphasis on genetic mutation and renal tubulopathy. Cross et al and Mir et al presented a comprehensive report of epilepsy patterns and management response in EAST/SeSAME syndrome.[1,2]
- In this case series , we attempted to provide a comprehensive view of phenotypic variabilities of patients harboring KCNJ10 mutation; side by side evaluating the neurological and systemic manifestations as expected from expression of KCNJ10
- The rationale for this consolidated report from a single center was to aid patient management with respect to diagnosis, systemic surveillance, prognostic as well as genetic counselling and identification of best treatment modalities.

OBJECTIVES

- To evaluate the neurological manifestations of genetically confirmed KCNJ10 mutated patients; and identifying their mutation type and variants.
- To describe the phenotypic variability in terms of age and varied neurological and systemic manifestations corelating with electrophysiological, neuroimaging data and lab data.



Astrocyte K+ buffering in defective Kir 4.1 channels

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MATERIAL & METHODS

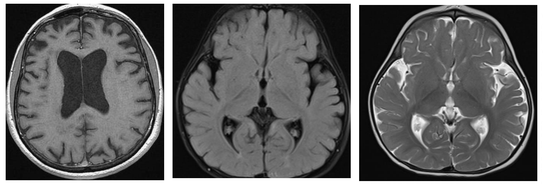
It was a retrospective review of genetically confirmed cases of KCNJ10 mutation; Trackcare data after getting informed consent from the families was retrieved comprising of ethnicity, consanguinity, clinical details including neurological and systemic evaluation; Research clinic was organized to obtain missing data. Electroencephalogram (EEG) was done for all patients and interpreted by a pediatric neurologist and MRI was reviewed by a pediatric neuroradiologist. Developmental assessment was done by a developmental pediatrician using Griffiths Mental Developmental Scale.

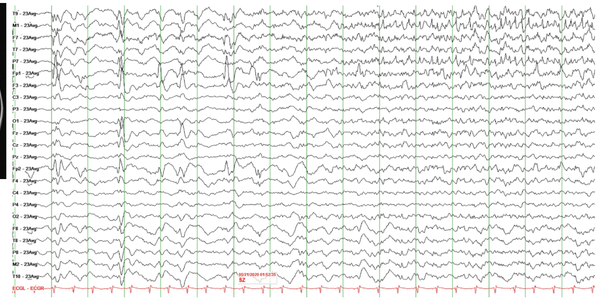
RESULTS

- Three Omani families comprising of 9 affected members had genetically confirmed EAST syndrome (KCNJ10 mutation). Family 1 has 4 siblings; 1.1 and 1.2 are following with us and two of the affected siblings in age range 20-24 y are also genetically confirmed with ataxia and tubulopathy are in service of adult neurology. Family 2 has two affected cases 2.1 and 2.2 ; family 3 has 3 affected sibs (3.1, 3.2 and 3.3).
- Seizure was the initial manifestation in all the patients and ataxia became evident by almost one decade with variation in cerebellar signs , seizure semiology and response to ASM as depicted in table 1.
- All the patients were screened for tubulopathy (urine and serum electrolytes, blood gas, USG KUB), eye abnormalities and audiometry.
- To report, two elder children of family 1 had no seizures in early life, developed late onset ataxia with polyuria and salt craving, they were found to have hypokalemic metabolic alkalosis, later confirmed to have SeSAME syndrome. However, none of our 7 affected patients demonstrated tubulopathy or SNHL till date and they are on regular follow up with nephrologist for biennial surveillance
- Electroretinogram was abnormal in patient 2.1 without noticeable visual complaints.
- Genetic result was consistent in all our patients:

Gene mutation	Variant	Type of mutation	Zygosity
KCNJ10	c.179T>C	Missense	Homozygous

- Three of the patients from our cohort underwent extensive metabolic and mitochondrial investigations before their confirmed diagnosis. All the patients are on regular follow up with neurology, nephrology





A. MRI T1W axial of patient 2.1 showes prominent ventricles and B/L frontal atrophy
B. MRI T2W and FLAIR sequence of patient 3.1 exhibiting B/L temporal atrophy with prominent extra axial spaces (B & C)
C. EEG of patient 3.1 shows left fronto-tempral discharges evolving left into frontotemporal electrographic seizures

Table 1 : Neurological Characteristics in Omani Children with EAST Syndrome

Characteristic	Patient 1.1	Patient 1.2	Patient 2.1	Patient 2.2	Patient 3.1	Patient 3.2	Patient 3.3
Age (years)	7	17	10	9	11	2.5	9
Gender	M	M	M	F	F	M	F
First symptom	Seizure	Seizure	Seizure	Seizure	Seizure	Seizure	Seizure
Age of seizure onset (months)	5	18	7	5	9	7	11
Predominant Seizure type	GTC	GTC	GTC, evolved to autonomic seizures	GTC, evolved to autonomic seizures	GTC, later Nocturnal with dystonic limb posturing	Focal to BTC	Focal to BTC
Age of last seizure(years)	2	3.5 Recurred at 5	7	7	1.5, Recurred at 8	2	1
Antiseizure medications	PHB	PHY VPA	VPA	LEV PDX **VPA**	LEV **CBZ**	LEV **CBZ**	-
EEG findings	Right occipital ED	Left centrotemporal ED	N	N	Focal; left fronto temporal discharges	Focal; Temporal spikes	-
Ataxia (age of onset)	6	9	9	8	8	-	8
Other cerebellar signs							
Hypotonia	+	-	-	+	-	-	-
Intention tremors	+	+	-	+	-	-	+
Dysmetria	+	+	-	+	+	-	-
Nystagmus	-	+(upward gaze)	-	-	-	-	-
Hyper/Hyporeflexia	+/-	-	-	-	-	-	+/-
Development and Intellect	Moderate global delay, cognition deficits	Normal; Arithmetic and writing difficulties	Gross motor delay ADHD ID (IQ-55)	Normal; Mild ID (IQ-71) Writing and arithemetic issues	Normal; ID (IQ 70)	Motor and speech delay	Motor and speech delay
Brain MRI	N	B/L frontal atrophy	B/L T2W hyperintensities in dentate nuclei	N	Bitemporal atrophy	N/A	N

CONCLUSION

- EAST syndrome has phenotypic with all the constellation of reported symptoms may not be present at outset requiring regular systemic surveillance.
- This variation can be explained through the growing literature on Kir4.1 and Kir5.1, discussing the complex disease mechanisms and the variable expression of disease symptoms from a molecular physiology perspective.

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