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Early infantile epileptic encephalopathy 3 - A rare disorder: Case report

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CASE REPORT

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ABSTRACT

Early infantile epileptic encephalopathy is a severe form of epileptic encephalopathies which is characterized by the onset of generalized or lateralized tonic spasms within 3 months of life. These spasms are not dependent on sleep cycle and can occur hundreds of times per day, which may lead to psychomotor impairment and death. EIEE may be caused by different etiologies. Structural brain abnormalities, metabolic disorders or genetic abnormalities in certain genes can lead to EIEE. Interictal 'Suppresion Burst' EEG pattern is characteristic of EIEE. We are reporting this infant who showed neurodevelopmental delay and severe psychomotor impairment. He received inj. ACTH therapy and oral steroids along with multiple anticonvulsants, which showed only marginal improvement. He was diagnosed as having Early Epileptic Encephalopathy-3, due to SLC25A22 gene, (also named 'GC1', MIM #609302, NM_024698), which encodes a mitochondrial glutamate carrier, responsible for an autosomal recessive form of neonatal epileptic encephalopathy, hence parents were studied for the gene defect, although they were asymptomatic. In both the parents, SLC25A22 gene was detected on exon 2 on chromosome11 in heterozygous form. Parents were counselled regarding poor prognosis of baby. At the age of 15 months of life, baby succumbed to death.

Abbreviations

EIEE: early Infantile Epileptic Encephalopathy

SB EEG: Suppression burst (SB) Electroencephalogram

EEG: Electroencephalogram

Key Words

Early infantile epileptic encephalopathy, Brain abnormalities, Metabolic disorders

Introduction

Early infantile epileptic encephalopathy is an uncommon epilepsy syndrome that causes therapy resistant seizures with multiple seizure types and manifests in the initial months of life. The prevalence of EIEE is unclear (about 1.2 of 100000 live births)[1]. EIEE patients typically have profound intellectual impairment, developmental delay, early progress to severe psychomotor impairment and early death[2,3]. The characteristics of EIEE syndrome are: Onset in early infancy, tonic spasms as the predominant seizure type, SB EEG pattern, intractable seizures, severe psychomotor retardation, poor prognosis and sequential evolution to West syndrome and Lennox-Gastaut syndrome[4]. Neonatal epileptic encephalopathy with suppression burst pattern (NEESBs) is a rare condition characterized by early onset of seizures and interictal 'suppression burst (SB) EEG pattern. This pattern is described as high-voltage, generalized and multifocal, spikes and sharp wave complexes alternating with periods of suppression of the electrical activity, which is specific for early infantile epileptic encephalopathy[5,6].

EIEE is associated with significant morbidity and mortality. Around 50 per cent of the affected patients die in infancy. Those who survive develop significant developmental delays and therapy resistant epilepsy[7]. Inborn errors of metabolism, structural brain malformations and birth injury can cause EIEE, but once these causes are accounted for, most remaining cases of EIEE are presumed to have a genetic basis[8,9]. Mutations in more than 50 different genes are known to cause EIEE[10]. Recently, a homozygous

mutation in the SLC25A22 gene (also named 'GC1'. MIM #609302, NM_024698) which encodes a mitochondrial glutamate carrier is identified. It causes an autosomal recessive form of neonatal epileptic encephalopathy[11]. SLC25A22 is more abundant in astrocytes than in neurons, whereas expression of both SLC25A12/AGC1 and SLC25A13/AGC2 carriers is restricted to neurons. So, glutamate uptake in astrocytes is assumed only by SLC25A22, hence a defect in this protein leads to accumulation of glutamate in the astrocytes cytosol and then to glutamate liberation in the synaptic cleft resulting in neuronal synchronicity which leads to the generation of epileptiform discharges in the brain[11].

Clinical diagnosis of EIEE is not yet standardized and includes metabolic testing, radiological imaging and genetic testing ranging from single gene tests to panel testing or whole-exome sequencing[12]. The characteristic findings in EEG show suppression burst pattern. SBP consists of bursts of high amplitude spikes and polyspikes alternating with periods of low voltage basic rhythm. This EEG pattern remains unchanged during both waking and sleeping states of subjects[13]. Many subjects remain undiagnosed because of non-standardized diagnostic tests, leading to prolonged and expensive diagnostic assay. But the increasing availability of DNA sequencing has led to an increased number of diagnosed EIEE patients with the help of genetic testing. In a recent study of infants with epileptic encephalopathies, a definitive genetic diagnosis was reached in approximately 60 per cent infants using combination of epilepsy gene panels and whole-exome sequencing[14].

Case

This is 1 month old male baby, born of non-consanguineous marriage (mothers age - 25 years, fathers age - 34 years, developed seizures in the form of tonic spasms for which he was shown to paediatrician and was started on anticonvulsant medication. On anticonvulsant therapy, baby continued to have recurrent seizures and also started showing signs of delayed development for which additional anticonvulsant medications were started. Baby underwent EEG testing as advised by paediatric neurologist, which was showing abnormal EEG record showing parietotemporo-occipital and generalized epileptiform abnormality with burst attenuation pattern. In the meantime, baby developed flexor spasms. His MRI brain was suggestive of diffuse cortical atrophy. Baby was given oral steroid (prednisolone – 1 mg/kg/day) trial which showed only marginal improvement. At 8 months of age, baby was also given Inj. ACTH once a day for 15 days f/b every alternate day for 15 days. But there was only marginal improvement. In view of clinical diffuse cortical atrophy, he is diagnosed as having refractory west epileptic encephalopathy and had been advised "Epileptic encephalopathy panel genes." In that report, SLC25A22 gene was detected on Exon-2 and disease was labelled as early infantile epileptic encephalopathy-3. (Figure 1-3)

As early infantile epileptic encephalopathy-3 is inherited in autosomal recessive pattern, parents were studied for the gene defect, though they were asymptomatic.

In both the parents, SLC25A22 gene was detected on exon 2 on chromosome11in heterozygous form. Parents were counselled about the disease and its outcome. Over the period of time, child developed severe neurological morbidity and succumbed to death at the age of 15 months.

Conclusion

In presence of recurrent seizures, developmental delay and abnormal EEG in the form of suppression burst pattern, early infantile epileptic encephalopathy should be considered as one of the possible diagnosis and genetic tests should be advised accordingly to establish the recurrent risk for future pregnancies.

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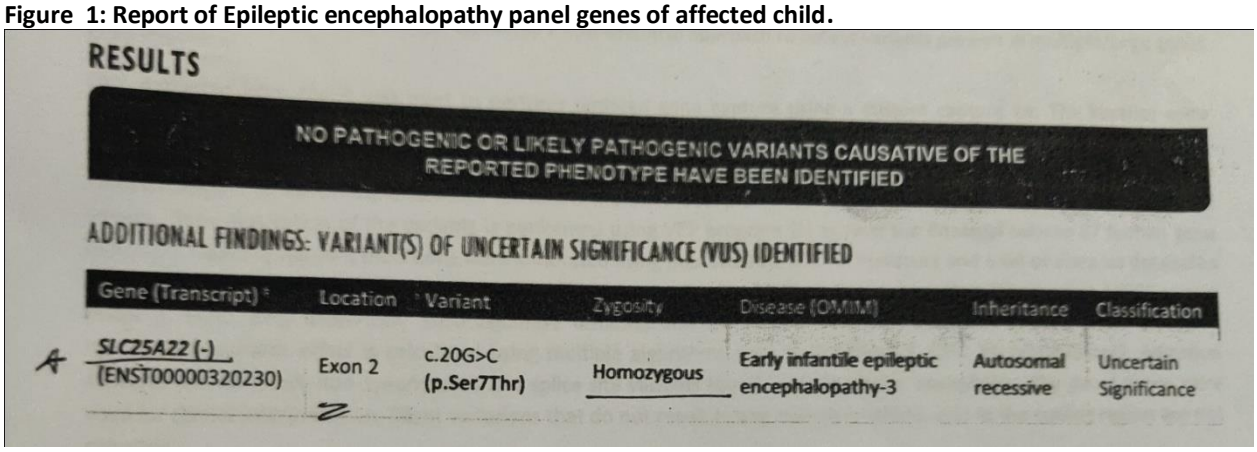
Figures

Figure 1: Report of Epileptic encephalopathy panel genes of affected child.



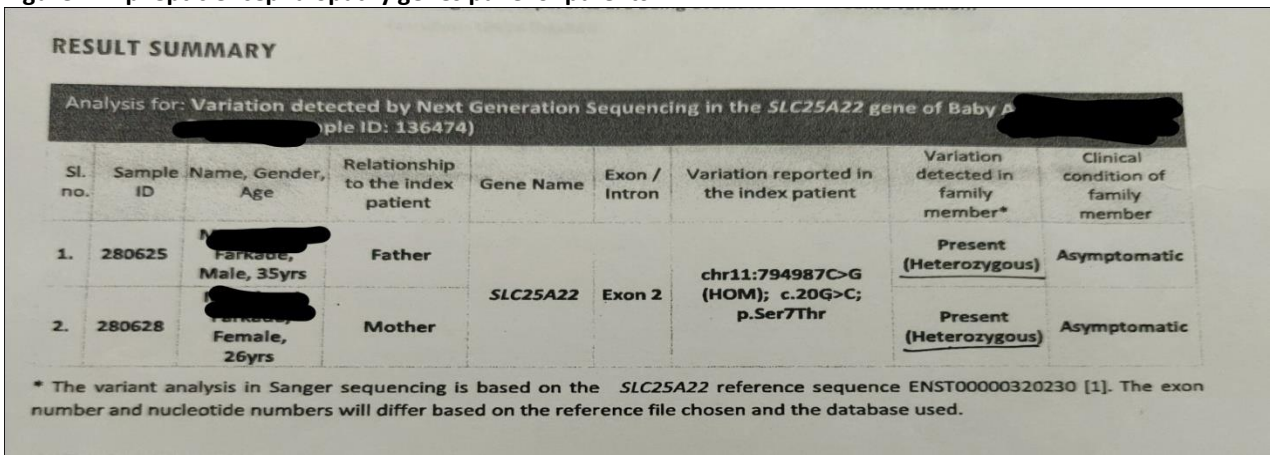
RESULTS

NO PATHOGENIC OR LIKELY PATHOGENIC VARIANTS CAUSATIVE OF THE REPORTED PHENOTYPE HAVE BEEN IDENTIFIED

ADDITIONAL FINDINGS: VARIANT(S) OF UNCERTAIN SIGNIFICANCE (VUS) IDENTIFIED

Gene (Transcript)	Location	Variant	Zygosity	Disease (OMIM)	Inheritance	Classification
SLC25A22 (-) (ENST00000320230)	Exon 2	c.20G>C (p.Ser7Thr)	Homozygous	Early infantile epileptic encephalopathy-3	Autosomal recessive	Uncertain Significance

Figure 2: Epileptic encephalopathy genes panel of parents.



RESULT SUMMARY

Analysis for: Variation detected by Next Generation Sequencing in the *SLC25A22* gene of Baby A [redacted] ple ID: 136474)

Sl. no.	Sample ID	Name, Gender, Age	Relationship to the index patient	Gene Name	Exon / Intron	Variation reported in the index patient	Variation detected in family member*	Clinical condition of family member
1.	280625	[redacted] Male, 35yrs	Father	*SLC25A22*	Exon 2	chr11:794987C>G (HOM); c.20G>C; p.Ser7Thr	Present (Heterozygous)	Asymptomatic
2.	280628	[redacted] Female, 26yrs	Mother				Present (Heterozygous)	Asymptomatic

* The variant analysis in Sanger sequencing is based on the *SLC25A22* reference sequence ENST00000320230 [1]. The exon number and nucleotide numbers will differ based on the reference file chosen and the database used.

Figure 3: Sequence Chromatogram and alignment to the reference sequence showing the variation in exon 2 of the SLC25A22 gene(chr 11:794987 C>G; c.20G>C; p.ser7Thr) detected in heterozygous condition in the parents of the index patient.