International Journal of Contemporary Pediatrics
Myathari R et al. Int J Contemp Pediatr. 2022 Sep;9(9):855-859
http://www.ijpediatrics.com
pISSN 2349-3283 | eISSN 2349-3291

DOI: https://dx.doi.org/10.18203/2349-3291.ijcp20222127

Case Report

Novel mutation in DMN1L gene in child with Landau Kleffner syndrome: a rare association

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Received: 07 July 2022
Revised: 03 August 2022
Accepted: 05 August 2022

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ABSTRACT

Landau Kleffner syndrome (LKS), occurs in healthy children who develop progressive aphasia along with seizures usually polymorphic with associated paroxysmal Electroencephalography (EEG) changes. Described cases in literature were neurologically normal with normal development prior to onset of LKS. This syndrome has male preponderance (2:1) age group affected being 3-7 years. Majority of cases (70-80%) shows additional symptoms viz. aggressive behaviour, decreased attention span, intellectual deficits etc. Index case is 13 years old female, who had seizure as initial symptoms, followed by expressive aphasia after a latent period of 2 months. She was not able to walk/post onset of aphasia. She was neurologically normal prior to onset of seizure.

Keywords: LKS, Acquired aphasia, DMN1L gene mutation, Encephalopathy, Lethal due to defective mitochondrial peroxisomal fission-1, Epileptic aphasia

INTRODUCTION

Landau Kleffner syndrome (LKS) is rare entity. It occurs in children with normal development. It is characterized by epileptic seizures of various morphology, aphasia and characteristic EEG abnormalities.[1]

LKS is synonyms with other names, aphasia with convulsive disorder, infantile acquired aphasia, acquired epileptic aphasia, Worster drought syndrome.[2] Most common age group affected being 3-7 years with male pre-ponderance.[3,4]

Exact etiology of disorder is unknown, various theories have been postulated. Most accepted one being an autoimmune etiology. It finds support in form of steroid being used in treatment with some success. But the causative antigen, the antibody remains elusive till date. Another theory linked to gene has also been considered genetic mutation involving GRIN2A gene has been found causal in some cases.[1,5] Though pattern on inheritance is not yet defined, likely it is of sporadic occurrence.

Our case had uncommon clinical manifestation motor weakness despite having normal motor examination. As rare as it can be, it finds merit in reporting, because literature regarding LKS is sparse.

CASE REPORT

Index case was 13 years female come who symptomatic for 2 weeks. She had aphasia, was not able to walk and one episode of seizure (Generalized tonic-clonic type) at day of the admission. There was no other significant history viz. fever altered sensorium prior admission.

HAEMATOLOGY

	Results	Unit	Biological Reference Interval
CBC (Haemogram)			
HB (Haemoglobin)	***11.9***	g/dl	12.0 - 15.0
TLC	8.58	10^3uL	4.0 - 11.0
DLC			
Neutrophils	68.5	%	40 - 80
Lymphocytes	20.4	%	20 - 40
Eosinophil	4.8	%	
Monocytes	5.7	%	02 - 10
Basophils	***0.6***	%	1 - 2
HCT	***35.8***	%	36 - 46
RBC	4.48	10^6/ul	3.8 - 4.8
MCV	***79.9***	fL	83 - 101
MCH	***26.6***	pg	27 - 32
MCHC	33.2	g/dl	31.5 - 34.5
RDW-SD	40.6	fL	39.0 - 46.0
RDW-CV	***14.2***	%	11.6 - 14.0
Platelets	195	10^3/ul	150 - 400
Absolute Counts			
* Absolute Neutrophil Count	5.88	10^3/ul	2.00 - 7.00
* Absolute Lymphocyte Count	1.75	10^3/ul	1.00 - 3.00
Absolute Eosinophil Count	0.41	10^3/ul	0.02 - 0.50
* Absolute Monocyte Count	0.49	10^3/ul	0.20 - 1.00
* Absolute Basophil Count	0.05	10^3/ul	0.02 - 0.1

CLINICAL BIO CHEMISTRY

	Results	Unit	Biological Reference Interval
RFT- II			
Urea	***13***	mg/dl	17 - 43
Creatinine	***0.29***	mg/dL	0.51 - 0.95
Sodium (Na+)	137.8	mmol/L	136.0 - 146.0
Potassium (K+)	3.71	mmol/L	3.5 - 5.1
Chloride (Cl)	101.9	mmol/L	101.0 - 109.0
Calcium (Total)			
Calcium	***8.73***	mg/dL	8.8 - 10.6
LFT- II			
S. BILIRUBIN			
Total Bilirubin	0.36	mg/dl	0.3 - 1.2
Direct Bilirubin	0.07	mg/dl	0.0 - 0.2
Indirect Bilirubin	0.29	mg/dl	0 - 0.6
SGPT	***39***	U/L	0.0 - 35.0
SGOT	***38***	U/L	0.0 - 35.0
Alkaline Phosphate	***210***	U/L	30.0 - 120.0
Total Protein	7.07	gm/dl	6.6 - 8.3
Albumin	3.92	gm/dl	3.5 - 5.2
Globulin	3.15	gm/dl	2.0 - 3.5
A/G Ratio	1.24		

CLINICAL PATHOLOGY

	Results	Unit	Biological Reference Interval
Urine R & M			
PHYSICAL EXAMINATION			
Colour	PALE YELLOW		
Transparancy	CLEAR		
CHEMICAL EXAMINATION			
pH	6.0		5.5 - 7.0
Specific gravity	1.020		1.015 - 1.025
Urine Albumin	NIL		NIL
Urine Sugar	NIL		NIL
Ketone Bodies	NIL		NIL
Urine Bilirubin	NIL		NIL
Urobilinogen	NORMAL		NORMAL
MICROSCOPIC EXAMINATION			
Pus Cells	4-5	/hpf	0 - 5
RBCS	4-5	/hpf	NIL
Casts	NIL	/hpf	NIL
Crystals	NIL	/hpf	NIL
Epithelial Cells	10-15	/hpf	0 - 5
OTHERS			
Bacteria	NIL		NIL
Yeast Cells	NIL		NIL

Measured (37.0C)

pH	7.39	
pCO2	35	mmHg
pO2	54	mmHg
Na+	159	mmol/L
K+	2.6	mmol/L
Ca++	0.30	mmol/L
Glu	66	mg/dL
Lac	0.8	mmol/L
Hct	32	%

Derived Parameters

Ca++(7.4)	0.30	mmol/L
HCO3-	21.2	mmol/L
HCO3std	22.2	mmol/L
TCO2	22.3	mmol/L
BEecf	-3.8	mmol/L
BE(B)	-3.3	mmol/L
SO2c	87	%
THbc	9.9	g/dL

Figure 1: Reports of basic investigation.

MRI BRAIN PLAIN AND CONTRAST

OBSERVATION:
MR imaging of the brain was done on 1.5 T MR scanner using head coil. T2 FLAIR, SE T1, FSE T2-Axial, SE T1- sagittal and GRE T2*- coronal images were acquired. The study was supplemented with diffusion weighted images using EPI sequence. Post contrast SET1 images were also obtained in sagittal, axial and coronal planes.

Findings:

The cerebral parenchyma shows normal signal characteristics of grey and white matter.
No focal lesion noted.

No evidence of any abnormal leptomeningeal or parenchymal enhancing pathology.

The bilateral basal ganglia, thalami and internal capsules appear normal.

The corpus callosum appears normal. No evidence of restricted diffusion noted.

The ventricular system appears normal. The septum is in mid line.

The fissures, sulci & basal cisterns appear normal.

The mid-brain, pons and medulla appear normal. The cerebellum appears normal.

Note is made of cavum septum pellucidum.

IMPRESSION:
CEMRI Brain imaging findings reveal:- No obvious intracranial abnormality.

EEG

OBSERVATION:

EEG REPORT

(This EEG was done by using 10-20 system of electrode placement .)
Activation:Photic .
EEG Summary: 21 channel awake EEG record with 10-20 international system of electrode .
Background rhythm consist of 5-6 Hz bilaterally symmetrical theta activity.
Generalized sharp wave discharges seen.
No focal or generalized slowing seen .
No abnormality seen during photic stimulation.
Impression - Abnormal awake EEG record shows slow background with generalized sharp wave discharges.Kindly corelate clinically .

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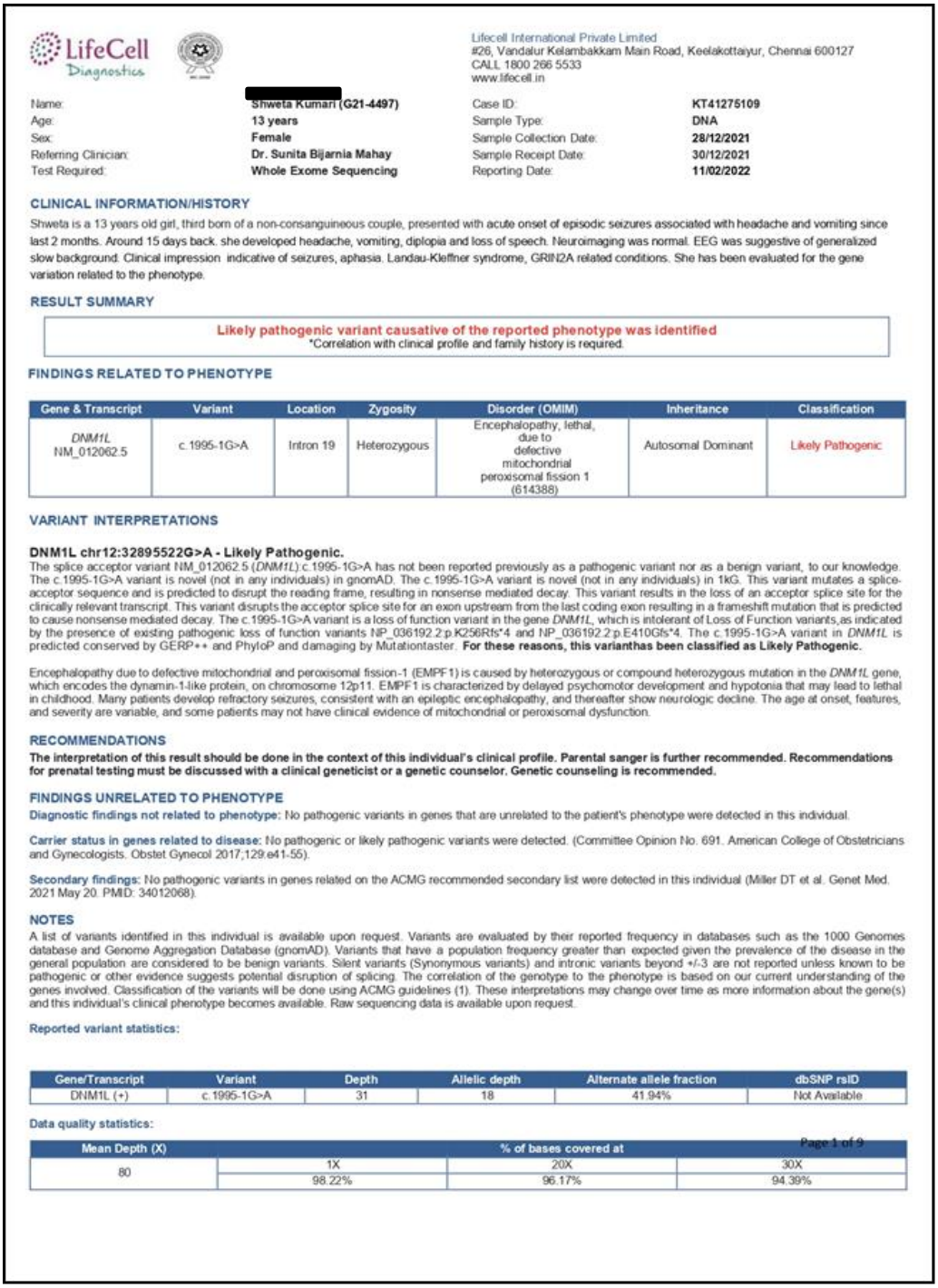
Figure 2: Reports of MRI brain and EEG.

On further probing, child had history of seizure two months prior to the onset of current symptoms. She was treated elsewhere, available documents showed that, it was status epilepticus morphology being left focal, it was controlled on phenytoin, NCCT head done suggesting ICSOL (Intra cranial space occupying lesion) in right temporal region. Birth history was uneventful, she had normal development, no family history of seizures.

On examination higher mental functions showed expressive aphasia, normal sensorium, normal cranial nerve examination, motor and sensory examination was unremarkable as tone, power, reflexes were well preserved. Rest of neurological examination was within normal limits, there were no meningeal signs, no signs of raised intra cranial pressure.

Investigations showed normal haemogram/ liver/renal function tests/ electrolytes/ sugar/ lactate/ urine R and M/ inflammatory markers were normal (Figure 1). MRI brain normal and EEG showed slow background activity with generalized sharp wave discharges (Figure 2).



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Name:	[redacted] Shweta Kumari (G21-4497)	Case ID:	KT41275109
Age:	13 years	Sample Type:	DNA
Sex:	Female	Sample Collection Date:	28/12/2021
Referring Clinician:	Dr. Sunita Bijarnia Mahay	Sample Receipt Date:	30/12/2021
Test Required:	Whole Exome Sequencing	Reporting Date:	11/02/2022

CLINICAL INFORMATION/HISTORY

Shweta is a 13 years old girl, third born of a non-consanguineous couple, presented with acute onset of episodic seizures associated with headache and vomiting since last 2 months. Around 15 days back, she developed headache, vomiting, diplopia and loss of speech. Neuroimaging was normal. EEG was suggestive of generalized slow background. Clinical impression indicative of seizures, aphasia. Landau-Kleffner syndrome, GRIN2A related conditions. She has been evaluated for the gene variation related to the phenotype.

RESULT SUMMARY

Likely pathogenic variant causative of the reported phenotype was identified
*Correlation with clinical profile and family history is required.

FINDINGS RELATED TO PHENOTYPE

Gene & Transcript	Variant	Location	Zygosity	Disorder (OMIM)	Inheritance	Classification
DNM1L NM_012062.5	c.1995-1G>A	Intron 19	Heterozygous	Encephalopathy, lethal, due to defective mitochondrial peroxisomal fission 1 (614388)	Autosomal Dominant	Likely Pathogenic

VARIANT INTERPRETATIONS

DNM1L chr12:32895522G>A - Likely Pathogenic.
The splice acceptor variant NM_012062.5 (*DNM1L*):c.1995-1G>A has not been reported previously as a pathogenic variant nor as a benign variant, to our knowledge. The c.1995-1G>A variant is novel (not in any individuals) in gnomAD. The c.1995-1G>A variant is novel (not in any individuals) in 1kG. This variant mutates a splice-acceptor sequence and is predicted to disrupt the reading frame, resulting in nonsense mediated decay. This variant results in the loss of an acceptor splice site for the clinically relevant transcript. This variant disrupts the acceptor splice site for an exon upstream from the last coding exon resulting in a frameshift mutation that is predicted to cause nonsense mediated decay. The c.1995-1G>A variant is a loss of function variant in the gene *DNM1L*, which is intolerant of Loss of Function variants,as indicated by the presence of existing pathogenic loss of function variants NP_036192.2:p.K256Rfs*4 and NP_036192.2:p.E410Gfs*4. The c.1995-1G>A variant in *DNM1L* is predicted conserved by GERP++ and PhyloP and damaging by Mutationtaster. **For these reasons, this varianthas been classified as Likely Pathogenic.**

Encephalopathy due to defective mitochondrial and peroxisomal fission-1 (EMPF1) is caused by heterozygous or compound heterozygous mutation in the *DNM1L* gene, which encodes the dynamin-1-like protein, on chromosome 12p11. EMPF1 is characterized by delayed psychomotor development and hypotonia that may lead to lethal in childhood. Many patients develop refractory seizures, consistent with an epileptic encephalopathy, and thereafter show neurologic decline. The age at onset, features, and severity are variable, and some patients may not have clinical evidence of mitochondrial or peroxisomal dysfunction.

RECOMMENDATIONS

The interpretation of this result should be done in the context of this individual's clinical profile. Parental sanger is further recommended. Recommendations for prenatal testing must be discussed with a clinical geneticist or a genetic counselor. Genetic counseling is recommended.

FINDINGS UNRELATED TO PHENOTYPE

Diagnostic findings not related to phenotype: No pathogenic variants in genes that are unrelated to the patient's phenotype were detected in this individual.

Carrier status in genes related to disease: No pathogenic or likely pathogenic variants were detected. (Committee Opinion No. 691. American College of Obstetricians and Gynecologists. Obstet Gynecol 2017;129:e41-55).

Secondary findings: No pathogenic variants in genes related on the ACMG recommended secondary list were detected in this individual (Miller DT et al. Genet Med. 2021 May 20. PMID: 34012068).

NOTES

A list of variants identified in this individual is available upon request. Variants are evaluated by their reported frequency in databases such as the 1000 Genomes database and Genome Aggregation Database (gnomAD). Variants that have a population frequency greater than expected given the prevalence of the disease in the general population are considered to be benign variants. Silent variants (Synonymous variants) and intronic variants beyond +/-3 are not reported unless known to be pathogenic or other evidence suggests potential disruption of splicing. The correlation of the genotype to the phenotype is based on our current understanding of the genes involved. Classification of the variants will be done using ACMG guidelines (1). These interpretations may change over time as more information about the gene(s) and this individual's clinical phenotype becomes available. Raw sequencing data is available upon request.

Reported variant statistics:

Gene/Transcript	Variant	Depth	Allelic depth	Alternate allele fraction	dbSNP rsID
DNM1L (+)	c.1995-1G>A	31	18	41.94%	Not Available

Data quality statistics:

Mean Depth (X)	% of bases covered at		
	1X	20X	30X
80	98.22%	96.17%	94.39%

Page 1 of 9

Figure 3: Whole exome sequencing report.

Diagnosis of LKS considered and child was treated with prednisolone at 2 mg/kg, oral diazepam at 0.2 mg/kg, seizure control done with levetiracetam at the 20 mg/kg/day.

Child showed remarkable improvement with above treatment. Speech gradually normalized, she remained seizure free, regained the ability to walk. Clinical improvement strengthened the diagnosis of LKS. Whole exome sequencing showed normal GRIN2A gene normal, heterozygous mutation in DNM1L gene was identified (Figure 3).

DISCUSSION

LKS is an age-related epileptic syndrome of childhood. Main manifestation being loss of speech, language skills, and seizures.[6] Seizure were varied type ranging from focal, tonic-clonic to absence seizures. It is characterized by acquired aphasia, convulsions and sleep activated EEG paroxysms predominating over the temporal and/or

parieto-occipital regions. Other symptoms include behavioral and/or psychomotor disturbances. Epilepsy is associated with favorable outcome in terms of seizures control. Being a rare disorder prevalence is not clear, to the best of our knowledge only 200 cases have been reported so far.

This syndrome as a male preponderance, approximately being 2:1, it usually affects children aged three to nine years.[7]

The etiology remains elusive, many theories have been postulated. Autoimmune etiology has been suggested. Use of steroids and improvement in outcome support the same. Genetic etiology has also been considered, though largely cases remain sporadic, mutation in GRIN2A gene have been found casual in some cases.[8-10]

LKS is diagnosed based on excluding other neurological disorders viz. Encephalitis, toxoplasmosis, Neurocysticercosis, Space occupying lesions, meningitis, subacute sclerosing panencephalitis (SSPE), inflammatory demyelinating diseases.[11-19] It should also be differentiated from autism, especially when it is related with isolated EEG anomaly.

This syndrome has relapsing remitting course with unpredictable outcome. It ranges from complete recovery to severe permanent aphasia, majority of reported children experienced seizure free outcome with moderate language deficitis.[20]

Treatment of this disorder is entirely symptomatic, seizure control is achieved using valproic acid / levetiracetam / clobazam, nocturnal diazepam is used for aphasia, oral prednisolone is used over long period of time (2-3 months). If even after, above therapy patient does not respond then course of intravenous immunoglobulin (IVIG) can be given as some patient respond to IVIG. Speech therapy should be continued for a long period of time as improvement in language occurs over prolonged period.

Our case was started on oral prednisolone, night time diazepam, speech therapy and levetiracetam for seizures. Child showed improvement in language and motor sector with no seizure recurrence.

Current case highlights the importance of having high clinical index of suspicion, as our case was not very typical of what is described in literature, in terms of age of onset, no behavioral disturbance, loss of ability to walk. Therefore, a vigil eye with high index of suspicious is required in diagnosing and managing such rare disorders.

Analysis of whole exome sequencing showed heterozygous mutation in DNM1L Gene which is located on chromosome (12P11) and encodes for Dymanin-1 like protein. Its mutation is known to cause EMPF-1 (Encephalopathy, lethal, due to defective mitochondrial peroxisomal fission-1 (614388). This disease is lethal in Early childhood, clinical features being encephalopathy, delayed psychomotor development and hypotonia with laboratory finding showing metabolic acidosis, lactic acidosis, MRI brain showing nonspecific white matter changes.[21-25]

As the literature is still evolving, we believe that mutation in DNM1L gene is related in pathogenesis of LKS. Further studies are required to establish association between LKS and mutation in the above-mentioned gene.

To the best of our knowledge only one case with mitochondrial respiratory chain-1 deficiency has been reported in association with LKS. Though this causal association between two still remains elusive.

CONCLUSION

Being a rare disorder, such research is needed to pen diverse clinical features of this enigmatic entity. More so, myriad clinical features associated with LKS after remains unrecognized citing paucity of literature. As in our case inability to walk despite having normal motor/sensory examination suggests the same.

Moreover, mutation in DNM1L gene which has not been reported previously, suggests that LKS may have more of genetic involvement as previously thought.

Timely detection and management offer a favorable outcome in terms of speech and seizure control. Further research is needed in elucidating the cause there by hoping for better treatment and outcome.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

REFERENCES

1. Landau WM, Kleffner FR. Syndrome of acquired aphasia with convulsive disorder in children. Neurology 1957;7:523-30.
2. Raybarman C. Landau Kleffner Syndrome: a case report. Neurol Ind. 2002;50:212-3.
3. Pearl PL, Carrazana EJ, Holmes GL. The Landau-Kleffner syndrome. Epilepsy Curr. 2001;1:39-45.
4. Landau WM, Kleffner FR- Syndrome of acquired aphasia with convulsive disorder. Neurology. 1957;7:523-30.
5. Feekery CJ, Parry-Fielder B, Hopkins JJ. Landau-Kleffner syndrome: six patients including discordant monozygotic twins. Pediatr Neurol. 1993;9:49-53.
6. Bishop DVM. Age of onset and outcome in “acquired apha-sia with convulsive disorder” (Landau Kleffner syn drome). Dev Med Child Neurol. 1985;27:705-12.

7. Landau WM, Kleffner FR. Syndrome of acquired aphasia with convulsive disorder in children. Neurology. 1957;7:523-30.
8. Nakano S, Okuno T, Mikawa H. Landau-Kleffner syndrome: EEG topographic studies. Brain Dev. 1989;11:43-50.
9. Feekery CJ, Parry-Fielder B, Hopkins JJ. Landau-Kleffner syndrome: six patients including discordant monozygotic twins. Pediatr Neurol. 1993;9:49-53.
10. Lou HC, Brandt S, Bruhn P. Progressive aphasia and epilepsy with a self-limited course. In: Perry JK. Epilepsy: the VIII In-ternational Symposium. Raven Press. 1977;295-303.
11. Maichalowicz R, Jozwiak S, Szwabowska-Orzeszko E, Igna-towicz L, Ignatowicz R. The Landau-Kleffner syn-drome. Zespol Laudau-Kleffnera WiadLek. 1989;42:256-9.
12. Otero E, Cordova S, Diaz F, Garcia-Terul I, Del Brutto OH. Acquired epileptic aphasia due to neurocysticerco-sis. Epilepsia. 1989;30:569-72.
13. Solomon GE, Parson D, Pavlakis S, Fraser R, Labar D. In-tracranial EEG monitoring in Landau-Kleffner syndrome as-sociated with a left temporal lobe astrocytoma. Epilepsia. 1993;34:557-60.
14. Nass R, Heier L, Walker R. Landau-Kleffner syndrome: temporal lobe tumor resection results in good out-come. Pediatr Neurol. 1993;9:303-5.
15. Ansink BJ, Sarphatie H, VanDongen HR. The Landau-Kleffner syndrome: case report and theoretical considera-tions. Neuropediatrics. 1989;20:132-8..
16. Bicknese AR, Preston J, Ettinger AB, Brook S. Epileptic Aphasia (Landau-Kleffner syndrome) secondary to progres-sive encephalitis. Ann Neurol. 1996;40:306-7.
17. Perniola T, Margari L, Buttiglione M, Andreula C, Simone IL, Santostasi R. A case of Landau-Kleffner syndrome sec-ondary to inflammatory demyelinating disease. Epilepsia. 1993;34:551-6.
18. Fayad M, Choveiri R, Mikati M. Landau-Kleffner syn-drome: consistent response to repeated intravenous gamma-globulin doses: a case report. Epilepsia. 1997;38:489-94.
19. Mouridsen SE. The Landau-Kleffner syndrome: a re-view. Eur Adolesc Psychiatry. 1995;4:223-8.
20. Waterham HR, Koster J, Van Roermund CWT, Mooyer PAW, Wanders RJA, Leonard JV. A lethal defect of mitochondrial and peroxisomal fission. New Eng J Med. 2007;356:1736-41.
21. Sheffer R, Douiev L, Edvardson S, Shaag A, Tamimi K, Soiferman D et al. Postnatal microcephaly and pain insensitivity due to a de novo heterozygous DNM1L mutation causing impaired mitochondrial fission and function. Am J Med Genet. 2016;170A:1603-7.
22. Fahrner JA, Liu R, Perry MS, Klein J, Chan DC. A novel de novo dominant negative mutation in DNM1L impairs mitochondrial fission and presents as childhood epileptic encephalopathy. Am J Med Genet. 2016;170A:2002-11.
23. Chao YH, Robak LA, Xia F, Koenig MK, Adesina A, Bacino CA et al. Missense variants in the middle domain of DNM1L in cases of infantile encephalopathy alter peroxisomes and mitochondria when assayed in Drosophila. Hum Molec Genet. 2016;25:1846-56.
24. Vandeleur D, Chen CV, Huang EJ, Connolly AJ, Sanchez H, Moon-Grady AJ. Novel and lethal case of cardiac involvement in DNM1L mitochondrial encephalopathy. Am J Med Genet. 2016;179A:2486-9.

Cite this article as: Myathari R, Gupta A, Bijarnia-Mahay S. Novel mutation in DMN1L gene in child with Landau Kleffner syndrome-a rare association. Int J Contemp Pediatr 2022;9:855-9.