Nepal Med J 2020;03(05):60-63 OPEN ACCESS Crossref DOI: 10.37080/nmj

A Case of Agyria-Pachygyria Presentingas Seizure Disorder in a Young Girl

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ARTICLE HISTORY
Received : 09 Jan 2020
Accepted: 25 Jan 2020

ACCESS THE ARTICLE ONLINE

DOI: https://doi.org/10.37080/nmj.133

ISSN : 2645-8438

KEYWORDS
Agyria; Cortical dysplasia; Seizure; Miller-Dieker Syndrome (MDS)Pachygyria, Polygyria

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CONFILICT OF INTEREST : None

ABSTRACT

"Lissencephaly", a raregenelinked defective neuroblastmigration disorder resulting in defective cortical lamination, abnormal gyral development and subcortical heterotropia.Advances in molecular genetics have led to the identification of lissencephaly gene onchromosome 17p13.3and causing Type-1 Lissencephaly or miller Diecker syndrome where lissencephaly is severe in posterior brain region. Another X-linked gene Doublecortin (DCX) gene where the lissencephalyis more severe in anterior region of thebrain. Usually this defect manifests in early infancy or childhood as seizure disorder. A case of lissencephaly with features of Miller Diekersyndrome in a young girl is reported and literature is reviewed. The important feature of the case was its late presentation in a 17 years old girl.

INTRODUCTION

Lissencephaly(LIS), a combination of two Greek words (Lissos= smooth: Encephalin=brain),is a developmental anomaly of brain resulting from abnormalities of neuronal migration[1] and is characterized by absent (agyria) or broad, flat and thick gyri (pachygyria).It is a rare disease with a prevalence rate of 12 per million births[2]. The affected children have varied neurological manifestations depending upon the severity of conditions and associated abnormalities. Rarity of condition led to this case report.

CASE SUMMARY

Ms. SC,a 17 years old girl was admitted in Neurology centreof Collage of Medical Sciences (COMS),Bharatpur, (Chitwan-District), Nepal on 16 January 2016 following a seizure episode. As per informant (i.e. her father) her illness started 03 years back when she started having recurrent seizures with a frequency of 3-4 seizures per month. Her old documents were not available but according to history after initial episode she was put on carbamazepine 200mg twice a day. As her seizures were uncontrolled the dose of carbamazepine was increased in astepwise manner to 400 mg twice aday. Inspite of increasing dose of carbamazepine her seizures were uncontrolled and

How to cite (Vancouver Style)
Pandey S, Bhusal M, Rana P. A Case of Agyria-Pachygyria Presenting as Seizure Disorder in A Young Girl. Nepal Med Jor [Internet]. 2020Dec.31;3(2):60-3. Available from: https://nmj.com.np/nmj/index.php/nmj/article/view/133

were occurring at irregular intervals. When reported she was not taking carbamazepine for the last 3-4 weeks.

(Pandey S, BhusalM, Rana PVS)

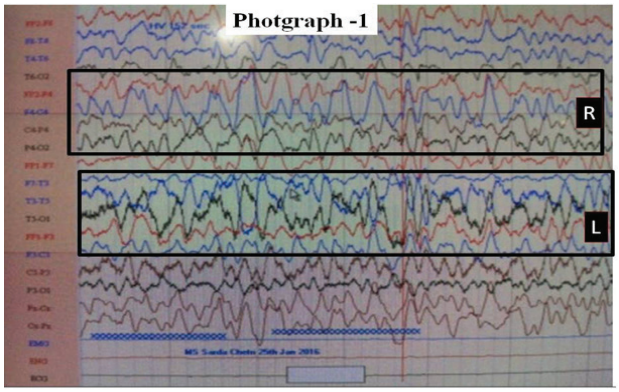

Figure – 1 EEG showing markedly disorganized background activity with seizure activity

The seizure semiology suggested complex partial seizure with loss of consciousness. Her seizure started with staring look followed by turning of face to left side, stiffening of the left half of the body and loss of consciousness. She denied history of inter-ictal tongue bite,sphincterincontinence, post-ictal paralysis or automatism. There was no history of birth trauma or major systemic illness in the past. Family history for similar illness was negative. Her milestones were normal but her scholastic performance was poor and she dropped out after 7th class. Neurological examination revealed facial paresis of upper motor neuron type and hemiparesis (power grade 4/5) on right side. Deep tendon reflexes were brisk on right side with plantar response mute on bothsides.

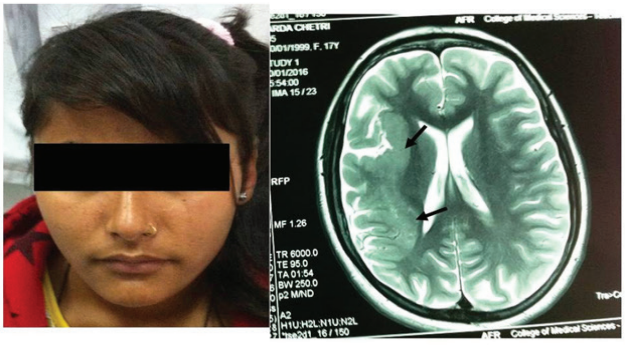

Figure -2 MRI Showingthickened gyrus in right posterior frontal and anterior parietal region

Fundus examination was normal. No phakomadetected. Other systems werenormal.Investigations done i.e. completehaemogram, urinalysis, metabolic parametersandX-raychestwerenormal.EEG (Figure-1) showed dysrhythmia withfrequent seizure discharges arising from both sides.No phenomenon of phase reversal, periodic discharges or suppression burst noted.MRI (Figure-2) revealed abnormally thickened gyrus (Pachygyria)involving insular, temporal and parietal region. She was put on sodium valproate (a drug of choice for her seizure type as carbamazepine was ineffective). Her seizures were satisfactorily controlled bysodium valproate 400 mg/twice daily.

DISCUSSION

Lissencephaly is a cortical dysplasia resulting from defective migration of neuronal precursor (neuroblast) from germinal matrix (lining the lateral and 3rd ventricles) along radial glial fibers (extending from ventricles to brain surface)to form cortex between 12 &24th week of gestation.1,2A completely smooth brain, devoid of sulci and gyri (complete lissencephaly)is rarely seen. Most of the patientshave incomplete lissencephalywithagyria and pachygyriain varied combination. Present classification of lissencephaly is based on MRI findings and on associated developmental anomalies.[3, 4]

Damaska(1983)3classifiedLissencephalyinto Type-1(classical) lissencephaly havingagyria –pachygyria in varied combination with Miller-Diekersyndrome as its prototypeand Type-II (Cobblestone) lissencephaly with polymicrogyria (excessive number of abnormal small gyri). Dietrich et al.,(1992)4classified lissencephalyintoi.e. Type-I lissencephaly showing colpocephaly, thickened cortex with broad flatten gyri, smooth grey white matter intersurface and straight, oblique or shallow sylvian fissure giving a figure of eight appearance; Type-II lisssencephaly with polymicrogyria and Type-III lissencephaly with microcephaly, moderately thick cortex and hypoplasia of cerebellum and brainstem.

Additional developmental anomalies reported include Miller-Dieker syndrome* with Type-1, Walker-lissencephaly respectively. For above classifications, pachygyria needs to be distinguished from polymicrogyria which at time is difficult to distinguish by MRI, hence it was suggested to reclassify Type-1 lissencephaly, having only agyria-pachygyriaas non lissencephaly cortical dysplasia[5]

Many genetic mutations have been reported in lissencephaly cases.[6,7,8] Two major genes implicated in classical lissencephalyare LISI on Chromosome 17 and Doublecortin (DBX) or XLIS gene on chromosome X.While larger deletion of LISI gene toward telomere 17pcauses Miller-Dieker syndrome, smaller deletion or point mutation of LISI and mutation of XLIS in affected males leads to lissencephaly-17 and lissencephaly-X respectively. Thesecaseshave normal facial appearance or may have subtle abnormalities which are different than reported in Miller-Dieker Syndrome. Other genetic abnormalitiesencountered are (a) mutation of TUBA1A gene with posteriorly dominant gyral pattern[8]; (b) RELIN gene mutation which is associated with autosomal recessive lissencephaly and cerebellar hypoplasia[9] and(c) ARX gene mutations which areassociated with X-linked lissencephaly, abnormal genitalia andcorpus callosum agenesis.

Children with classical lissencephaly (Miller Dieker Syndrome) have typical dysmorphic features (microcephaly, mid face hypoplasia, small upturned nose, low set small ears, small jaw, thick upper lips and anomalies affecting other organs) and presents with severe mental retardation, motor disabilities varying from severe hypotonic to severe spastic paraplegia, feeding problems and failure to thrive. The case under discussion has MRI findings of classical Lissencephalybut she had no dysmorphic feature Miller-Dieker syndrome.

In Miller-Dieker syndrome seizures occurs in over 90% of cases with onset before 06 months in about 75% of cases.[7] Typically seizures begin in first month of life as massive bilateral myoclonus or infantile spasms in 80% cases butwithout typical hypsarrhythmiaon EEG.[7,10] The EEG is in these patients show characteristic high amplitude fast activity, predominantly in alpha and beta range persisting on eye opening and during sleep phase. The sleep phase lack vortex wave, spindling formation and theta slowing. A 14 CPS activity may be seen. With age the faster activity increases to 25-30 HZ over posterior region with alfa activity is noted in rolandic and parietal region .[10]

Though developmental anomaly was present since birth,in present case it presented with multiple seizure typeswhen patient was 13 years old. Similar multiple type seizures are recorded in older children. The EEG showed disorganized background activity consisting of high voltage activity of 5-6 HZ and seizure activity. Earlier these cases remained undiagnosed and such patients were considered having seizure disorder of idiopathic etiology.

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