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Type II Lissencephaly with chronic epilepsy and behavioral disturbances: A rare case report

Ajinkya Sureshrao Ghogare

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Authors' Affiliation:
Consultant Psychiatrist, Manoday Mansopchar Clinic, Akot, Akola, Maharashtra, India; Email: ajinkyaghogaremd@gmail.com

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ABSTRACT

Lissencephaly is a rare genetic disorder of brain malformation. It is characterized by the absence of normal folds or convolutions of the cerebral cortex. It is caused by abnormal neuronal migration during a period of embryonic development. It has various symptoms such as difficulty in swallowing, unusual facial appearance, abnormal muscular spasms, failure to thrive, extreme psychomotor retardation, deformities of fingers, toes, or hands, intellectual disability, and the seizure episodes. There are two variants of Lissencephaly namely type I and II. This case report has highlighted a rare case of type II Lissencephaly with chronic epilepsy and behavioral disturbances in a 12-year-old child managed effectively with a mood stabilizing antiepileptic drug named Divalproex sodium and a benzodiazepine named Clobazam.

Keywords: Epilepsy, Seizures, Behavioral disturbances, Lissencephaly, Divalproex sodium, Clobazam.

1. INTRODUCTION

Lissencephaly is one of the rarest brain disorders with a prevalence of only 1.2 per 100,000 births (Leventer, 2008; de Rijk-van Andel et al., 1991). It is caused by the deletion of a gene LIS1 [also known as Platelet Activating Factor Acetyl Hydrolase 1B1 or PAFAH1B1 gene] located on the chromosome 17p13.3 (Di Donato et al., 2017; Iefremova et al., 2017). Majority of the cases i.e., 40% of Lissencephaly are associated with deletion or mutation of the LIS1 gene, whereas 23% are associated with the mutation of Doublecortin [DCX] gene, 5% are associated with the mutation of Tubulin Alpha 1a [TUBA1A] gene, and 3% are associated with the mutation of dynein cytoplasmic 1 heavy chain 1 [DYNC1H1] gene (Di Donato et al., 2018). Among the non-genetic causes, Lissencephaly is caused by the viral infections of fetus or mother during the first trimester of pregnancy and inadequate supply of oxygenated blood to the brain of developing fetus (Leruez-Ville & Ville, 2017). Among the viral infections, infection with the cytomegalovirus [CMV] during first three months of pregnancy is associated with defective neuronal migration secondary to the CMV induced reduced blood flow to the brain of developing fetus resulting in the development of Lissencephaly (Joseph et al., 2008).

Lissencephaly is also known as "smooth brain" which is characterized by the malformation of cerebral cortex as a result of insufficient neuronal migration (Di Donato et al., 2017). It consists of range of severe malformations of the brain such as absent gyri [agyria], broad gyri [pachygyria], and sub-cortical band heterotopia [SBH] (Di Donato et al., 2017). Lissencephaly is the result of abnormal migration of the neurons during a gestational period of 12 to 24 weeks of embryonic development resulting in abnormal sulci and gyri formation in the brain (Tan et al., 2018). Brain magnetic resonance imaging [MRI] usually reveals the patterns of agyria, pachygyria, and SBH. Agyria refers to the cortical regions with the sulci more than 3 centimeters apart, while pachygyria refers to the abnormally wide gyri with sulci 1.5 to 3 centimeters apart (Di Donato et al., 2017).

SBH refers to the longitudinal bands of the gray matter that are located deep to the cerebral cortex and are separated from the cerebral cortex by the thin layer of white matter (Di Donato et al., 2017). In pachygyria and agyria, the cerebral cortex may be either very thick in a range of 10 to 20 mm [classic or thick Lissencephaly] or less likely mildly thick in a range of 5 to 10 mm [thin Lissencephaly] (Di Donato et al., 2017). Children suffering from Lissencephaly present with the intellectual disability and the developmental delays, which tend to vary from case to case based on the severity of intractable epilepsy as well as the brain malformation (Bershteyn et al., 2017). The symptoms of Lissencephaly include seizure episodes, muscle spasms, psychomotor impairment, feeding difficulty, developmental delay, failure to thrive, and anomalies of toes or fingers in some of the cases (Chang et al., 2015). Type I or classic Lissencephaly is characterized by the presence of four layers of cerebral cortex instead of normal six layers (Leventer, 2008). Type II or cobblestone Lissencephaly is usually recognized by the presence of disorganized cerebral cortex with nodular or pebbled appearance secondary to the complete displacement of cerebral cortex with the clusters of cortical neurons separated by the glio-mesenchymal tissues (Leventer, 2008).

Lissencephaly typically manifests with the drug resistant or intractable epilepsy. Seizures tend to occur in > 90% cases of Lissencephaly (Ikemoto et al., 2019). Majority of the cases with daily seizures are burden for the children and their caretakers as most of the children with Lissencephaly fail to achieve seizure control despite of using various antiepileptic medicines (Ikemoto et al., 2019; Herbst et al., 2016). This case report sheds a light on a rare case of type II Lissencephaly with chronic epilepsy with behavioral disturbances and its management.

2. CASE PRESENTATION

A 12-year-old girl, living with her family in a village, presented to the psychiatric outpatient clinic along with her mother with the primary presentation of repetitive episodes of generalized tonic clonic seizures [GTCS] since last 11 years and frequent episodes of irritable behavior since last six years. On detailed history it was revealed that the child was having about two to four episodes of GTCS every month and the frequency of seizure episodes was increased to about four episodes per day over a period of last five days. She tend to have symptoms like up rolling of eyes, clenching of teeth, frothing from mouth, deviation of mouth, abnormal jerky movements of all the four limbs, sudden fall on the ground, soiling of cloths with urine, and loss of consciousness over a period of about 10 to 15 minutes on every occasion.

The seizure episodes used to occur during both the awake and the sleeping states. Since last six years, the child was exhibiting irritable behavior like episodes of crying and shouting loudly without any apparent reasons. Further history revealed that the child was born of institutional full-term normal delivery and her birth weight was apparently normal as per her mother. Antenatal history was apparently uneventful. Her developmental milestone achievement showed significant delay. She started sitting after an age of one year and started walking after an age of two years. At the present age of 12 years, she was not able to talk fluently by forming simple and complete sentences. She was not even capable of dressing and undressing herself. She was totally dependent on her mother for her personal hygiene. She attended school up to primary level of education, but she was not even able to read and write in her vernacular language.

On neurological examination, child had bilateral extensor plantar responses and the brisk deep tendon reflexes indicative of underlying brain pathology. On mental status examination [MSE], child had psychomotor retardation, withdrawn behavior, increased reaction time while responding to the examining psychiatrist, poor eye contact, and impairment of intelligence. Her basic blood investigations were normal. Figure 1 shows shallow sylvian fissures and the sulci with thick nodular or cobblestone shaped cerebral cortex. Figure1 also shows the small focal hyperintensity in the right posterior putamen suggestive of focal demyelination. Figure 2 shows that the thickness of the cerebral cortex was most marked in frontal and temporal lobes than the occipital lobes. No obvious SBH were seen on MRI brain. Septum was in midline and cerebrospinal fluid spaces were unremarkable.

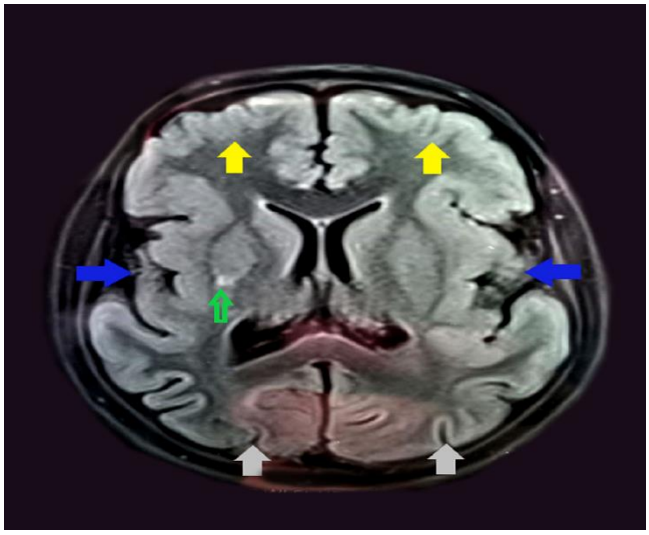

Figure 1 MRI Brain showing shallow sulci (denoted by light gray colored arrows), shallow sylvian fissures (denoted by indigo colored arrows), nodular or cobblestone shaped cerebral cortex (denoted by yellow colored arrows), and a small focal hyperintensity in the right posterior putamen suggestive of focal demyelination (denoted by green colored arrow).

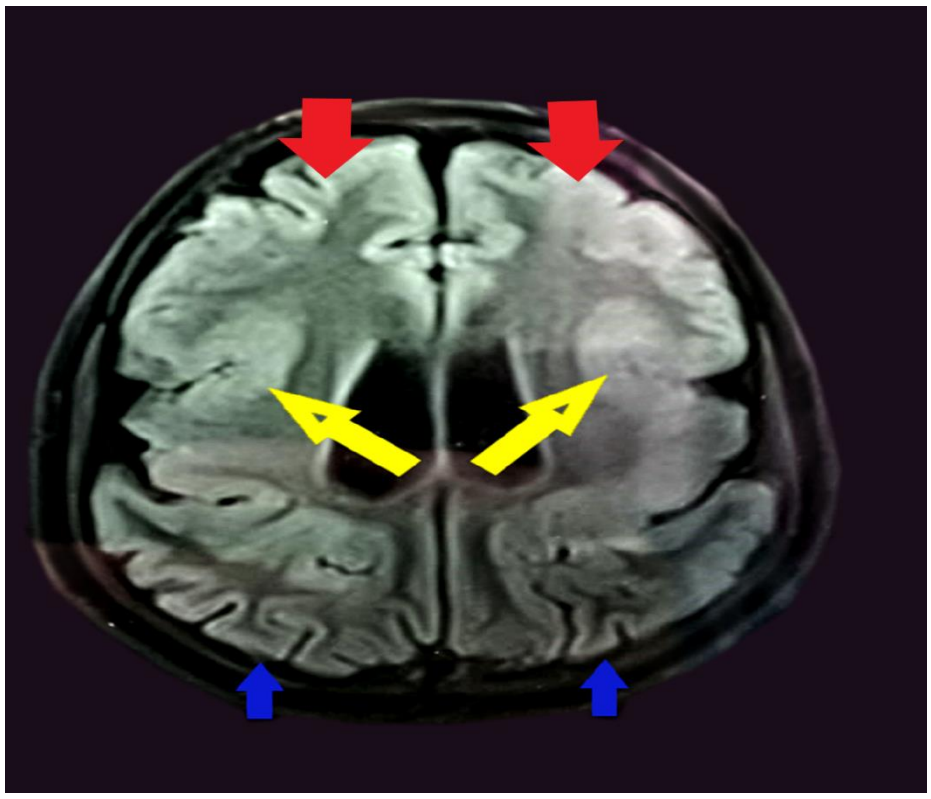

Figure 2 MRI Brain showing abnormally thick cerebral cortex with more pronounced thickness of frontal lobes (denoted by red colored arrows) and temporal lobes (denoted by yellow colored arrows) than the occipital lobes (denoted by the indigo colored arrows).

Her drowsy state electroencephalogram [EEG] showed background attenuation with an increased medium to high amplitude fronto-centrally prominent delta and theta activities. Her sleeping state EEG revealed that there were symmetrical mixtures of anterior low amplitude beta, central medium amplitude theta, and predominantly posterior polymorphic delta. EEG also revealed frequent bursts of generalized spike and wave discharges of moderate amplitude suggestive of the generalized epileptiform activity. EEG also revealed generalized epileptiform discharges predominantly from the right cerebral hemisphere. Unfortunately,

index child's mother had only the photocopy of the reporting page of the EEG with her and she lost the other pages of the report. Based on the detailed clinical history of the developmental delays, epilepsy, intellectual disability, and MRI brain as well as EEG findings, a diagnosis of type II Lissencephaly was made.

About three years back she was started on antiepileptic treatment by the pediatrician, but her mother gave her treatment only for a single day and then stopped treatment by herself due to perceived over-sedation of the child on treatment. Her mother also stopped antiepileptic treatment secondary to the lack of knowledge and misconception about the antiepileptic medications that the medicines tend to cause dependence and child will be required to take the medicines for rest of the life. Her mother even took her to faith-healers for the treatment of seizure episodes, but there was no improvement. Her mother did not preserve previous treatment document. Because of the persistent irritability and increased frequency of seizure episodes over a period of five days, mother brought the child to psychiatric clinic where the child was started on oral Clobazam 5mg in a dose of half tablet in the morning and one tablet in the evening. Along with it, the child was started on oral Divalproex sodium solution in a dose of 5ml (250mg/5ml) twice a day.

On subsequent follow up after a month, the child showed clinical improvement. She was seizure free on regular treatment and her irritability was reduced significantly. Child had only a mild daytime sedation and because of it the morning dose of Clobazam was shifted to evening. On subsequent follow up after two months period, patient was seizure free and did not have a daytime sedation. By that time, her irritability was stopped completely according to the history from her mother. Informed consent was taken from the mother regarding the publication of this rare case. Mother was counseled in detail in her vernacular language about the nature and prognosis of Lissencephaly of her child, precautions to be taken while the child is having episodes of seizures, and need of regular treatment as well as follow-up visits. But despite of the detailed counseling of the mother, she did not bring the child for regular follow-up visits and eventually the child lost to follow-up.

3. DISCUSSION

This case has highlighted a rare presentation of type II Lissencephaly with chronic epilepsy. Index child was 12 years old and had history of epilepsy since 11 years i.e., she had onset of epilepsy by the age of one year. Available literature also shows that 9 out 10 cases of Lissencephaly develop epilepsy during first year of the life (Stat pearls, 2021). Index child had abnormalities on neurological examination like bilateral extensor plantar responses and the brisk deep tendon reflexes. Sharma et al., (2014) found similar neurological findings like an extensor plantar reflex and the brisk deep tendon reflex in an infant suffering from Lissencephaly. These abnormal findings on neurological examination might hint towards the underlying brain pathology like Lissencephaly in the index child. Index child had developmental delay and psychomotor retardation. Sharma et al. (2014) also found that the infant with Lissencephaly had developmental delay. Bershteyn et al., (2017) also observed that the children with Lissencephaly tend to have significant intellectual or mental disability and the developmental delays. These findings were consistent with the clinical diagnosis of Lissencephaly.

MRI brain of the index child showed shallow sylvian fissures and sulci, and nodular or cobblestone shaped thickened cerebral cortex. Those abnormalities were more pronounced in the frontal and temporal lobes than the occipital lobes which mean that the changes were predominantly seen in anterior parts of the cerebral cortex. Such findings were consistent with the available literature which showed that on MRI the brain exhibits reduction of the normal sulcation or the shallow sulci, shallow sylvian fissures, and cobblestone or multi-nodular cortical surface which tends to be more prominent in anterior parts of cerebral cortex (Radiopedia, 2019). These findings were consistent with the radiological diagnosis of type II Lissencephaly. Menascu et al., (2013) observed that EEG can help in establishing a diagnosis of Lissencephaly. Three classical EEG findings are generally observed among the children suffering from Lissencephaly (Sharma et al., 2014; Hakamada et al., 1979). Type 1 EEG pattern in Lissencephaly is generally characterized by the high amplitude (>100 mV) beta and alpha activities over all the cortical areas (Sharma et al., 2014; Hakamada et al., 1979).

Type 2 EEG pattern in Lissencephaly is associated with alternating high amplitude (up to 300 mV) bursts of slow and sharp waves followed by shorter periods of attenuated cortical activities which last for only 3 seconds (Sharma et al., 2014; Hakamada et al., 1979). Type 3 EEG pattern in Lissencephaly shows high amplitude sharp or spike wave activities without attenuation of the cortical activity and beta or alpha frequencies (Sharma et al., 2014; Hakamada et al., 1979). Index child had medium to high amplitude fronto-centrally prominent theta and delta activities along with the symmetrical mixtures of predominantly posterior polymorphic delta waves, central medium amplitude theta waves, and anterior low amplitude beta waves. She also had frequent moderate amplitude generalized spike-and-wave discharges with burst suppression pattern and the generalized epileptiform discharges were more prominent from the right cerebral hemisphere. Index child had some overlapping features of type 1 and type

3 EEG patterns consistent with the Lissencephaly diagnosis. Sharma et al., (2014) found that infant with Lissencephaly had diffused high voltage theta wave activities on the EEG. So, these EEG findings were consistent with the electroencephalographic diagnosis of the Lissencephaly.

Index child with type II Lissencephaly had chronic epilepsy which was not adequately treated because of an issue of perceived sedation secondary to the treatment with antiepileptic medicines as well as because of the lack of knowledge and misconception about the antiepileptic treatment. Santosh et al., (2014) also found the same finding that the factors like lack of knowledge about epilepsy and antiepileptic medicines, stigma, poverty, cultural or superstitious beliefs, poor health facilities, and paucity of trained professionals contribute to treatment gaps while managing the cases of epilepsy. Index child was a resident of a small village. The level of epilepsy management gap in Indian population spans from 22% in urban Indians to 90% among rural Indians (Meyer et al., 2010).

During the visits at psychiatric clinic, patient's mother was counseled in detail about her child's illness and about the need for regular treatment as well as follow-up visits. Child's epilepsy and irritable behavior showed significant improvement on treatment with mood stabilizing antiepileptic medicine named Divalproex sodium and a benzodiazepine named Clobazam as discussed above. On these medicines, index child was seizure free over a period of last two months and she was also free of behavioral disturbances over a period of last one month. Divalproex sodium consists of a stable coordination of valproic acid and sodium valproate (Rxlist, 2021). As Divalproex sodium is having broad spectrum antiepileptic property, it is indicated for the management of a wide range of epilepsy such as absence seizures, partial seizures, generalized seizures, status epilepticus, and myoclonic seizures (Rahman & Nguyen, 2021; Olsen et al., 2007; Willmore, 2003).

Valproic acid is indicated for the treatment of various types of epilepsy including tonic-clonic seizure (Longo et al., 2013). Sodium valproate is an antiepileptic indicated for the treatment of focal as well as generalized seizure episodes (Zawab & Carmody, 2014). In children, Valproic acid is also indicated for the symptoms of irritability, impulsivity, and aggression (Rana et al., 2005). Index child was continued on oral Divalproex sodium and oral Clobazam on which she showed remarkable improvement. Perampanel is a selective non-competitive alpha-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid [AMPA] receptor antagonist which has shown improvement with more than 50% decrease in the episodes of seizures among the individuals with Lissencephaly associated epilepsy (Ikemoto et al., 2019).

Index child was also referred for speech therapy sessions to improve her communication skills. Lissencephaly is not curable. Lissencephaly can be associated with various complications that include seizures, breathing difficulties, and feeding difficulties (Okumura et al., 2013). Management of Lissencephaly is largely symptomatic and supportive. Treatment of Lissencephaly should aim at improvement of nutritional intake and use of anticonvulsants for controlling or preventing the recurrent seizure episodes (Stat pearls, 2021). Speech therapy can be advised for the children with language deficits to improve their communication skills (Child neurology foundation, 2021). Swallowing therapy can be advised for safer eating practices in children with difficulty in swallowing due to Lissencephaly (Child neurology foundation, 2021). Physical and occupational therapy can be advised for promoting motor development, improving motor skills, facilitating muscle flexibility, and reducing the muscle stiffness (Child neurology foundation, 2021).

Prognosis in case of Lissencephaly is poor with shorter life expectancy as many children with the disorder tend to die before an age of 10 years (Statpearls, 2021). Most common causes of death among the sufferers with Lissencephaly are respiratory diseases and aspiration (Statpearls, 2021). This case report has highlighted an importance of neuroimaging in a case of neuropsychiatric manifestations in the context of underlying pathological changes of the brain parenchyma (Ghogare et al., 2020; Ghogare & Nemade, 2021).

4. CONCLUSIONS

Although rare, Lissencephaly is commonly associated with the chronic and intractable epilepsy. Timely first and/or second trimester antenatal diagnosis of Lissencephaly by using ultrasonography is of crucial importance to prevent the disease burden over the parents and the families. Genetic counseling must be offered to the parents and other family members of children suffering from Lissencephaly. Psychological support and parental counseling should be done regularly for the better outcome.

Informed consent

Oral and written informed consent was obtained from the patient's mother.

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Conflicts of interest

The authors declare that there are no conflicts of interests.

Data and materials availability

All data associated with this study are present in the paper.

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