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Case Report

Lissencephaly with subcortical band heterotopia in an East African child: A case report ☆

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ABSTRACT

Lissencephaly is a rare neuronal migration defect that results in a smooth cerebral surface, mental retardation, and seizures. It is diagnosed primarily by correlating clinical manifestations with MRI findings. We present a case of a 3-year-old girl with developmental delay and seizures. Her first seizure was at 14 months and MRI showed features of lissencephaly and subcortical band heterotopia. Lissencephaly is associated with gene mutations. Treatment focuses on antiseizure meds and physiotherapy to reduce seizures and improve motor skills. This case report highlights the importance of promptly diagnosing the LIS/SBH spectrum to enhance patient outcomes. Timely identification and treatment, such as physiotherapy, can significantly improve the quality of life, especially in resource-limited settings.

Introduction

Lissencephaly (LIS) is a condition characterized by a smooth cerebral surface, resulting in a severe lack of gyrus and sulcus formation. It is often associated with mental retardation and seizures. Subcortical band heterotopia (SBH) refers to a disorder of cortical migration, marked by a distinct layer of gray matter within the white matter between the cerebral cortex and lateral ventricles. SBH is frequently seen as a concurrent malformation with Lissencephaly, together referred to as Lissencephaly/Subcortical band heterotopia (LIS/SBH) spectrum [1,2].

The prevalence of lissencephaly is largely unknown due to its rarity. Advances in imaging technology are expected to improve its diagnosis. On MRI imaging, it is characterized by a

Abbreviations: LIS, Lissencephaly; SBH, Subcortical Band Heterotopia; LIS/SBH, Lissencephaly—Subcortical Band Heterotopia; MRI, Magnetic Resonance Imaging; DCX, Double Cortin Gene.

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thicker cortex with reduced or absent gyration, whereas SBH presents as abnormal bands of subcortical neurons beneath the cerebral cortex [1,3].

Lissencephaly (LIS) is divided into 2 main groups: classical lissencephaly (type 1) and cobblestone lissencephaly (type 2). Type 1 presents with facial dysmorphisms such as bitemporal hollowing, midfacial hypoplasia, micrognathia, and a short nose with upturned nares. Miller-Dieker syndrome is also classified under type 1 lissencephaly. Type 2 presents with abnormalities of the eyes and muscles, as well as hydrocephalus and cerebellar dysgenesis [4].

The LIS1 gene was the first neuronal migration gene to be discovered and cloned in any organism. Defective neuronal migration results in the brain becoming smoother in lissencephaly due to an insufficient population of the cortical plate of the cerebral cortex. This leads to abnormal thickening and reduced or even absent gyri and sulci [5].

We present a case of lissencephaly/subcortical band heterotopia spectrum which was diagnosed in a low-resource country. The objective of this case report is to emphasize the presence of such a rare condition and offer insights to healthcare providers regarding the extensive range of neurological differentials to consider when managing patients presenting with seizures.

Case presentation

A 3-year-old female presented with a history of developmental delay and recurrent seizures. The child's developmental delay was first noticed at 7 months of age when she had not achieved neck control, prompting the start of physiotherapy. She experienced her first intractable seizures at 14 months, characterized by right-sided focal seizures associated with loss of consciousness. Although initially not associated with fevers, the seizures later became triggered by mild febrile illnesses such as viral upper respiratory tract infections, pneumonia, or acute gastroenteritis. Antenatal ultrasound had revealed features of fetal hydrocephalus which were not present after birth. The child was delivered by elective cesarean section due to 2 previous scars and cried immediately after delivery with no reported postnatal complications. Born to East African native parents with no history of consanguinity, she is the 3rd born in the family, her siblings are alive and well with no similar manifestations.

The child weighed 16 kilograms and had a height of 95 centimeters at 3 years of age, above the 90th percentile. On examination, she was floppy with normal muscle bulk, and no facial and skeletal dysmorphisms. The cranial nerves examination was unremarkable.

Laboratory investigations done were unremarkable for any cause for the seizures. Electroencephalogram showed left cerebral slowing. Initial MRI was done at 14 months of age when the child presented with unprovoked seizures which showed features of ventricular dilation with an Evans index of 49%, shallow cortical sulci, and a subtle continuous thick band of grey matter just deep to the cortex separated from it by a thin layer of white matter as seen on Figure 1.

The child was kept on daily Carbamazepine and folic acid to control the focal seizures. Due to recurrent seizures mostly aggravated by simple febrile illnesses, a subsequent MRI done at 3 years of age showed features of mild ventriculomegaly and a continuous ribbon of grey matter deep to the cortex, signifying lissencephaly with subcortical band heterotopia as seen on Figure 2.

The child is currently on an adjusted dose of Carbamazepine equivalent to 20mg/kg/day daily dose and folic acid

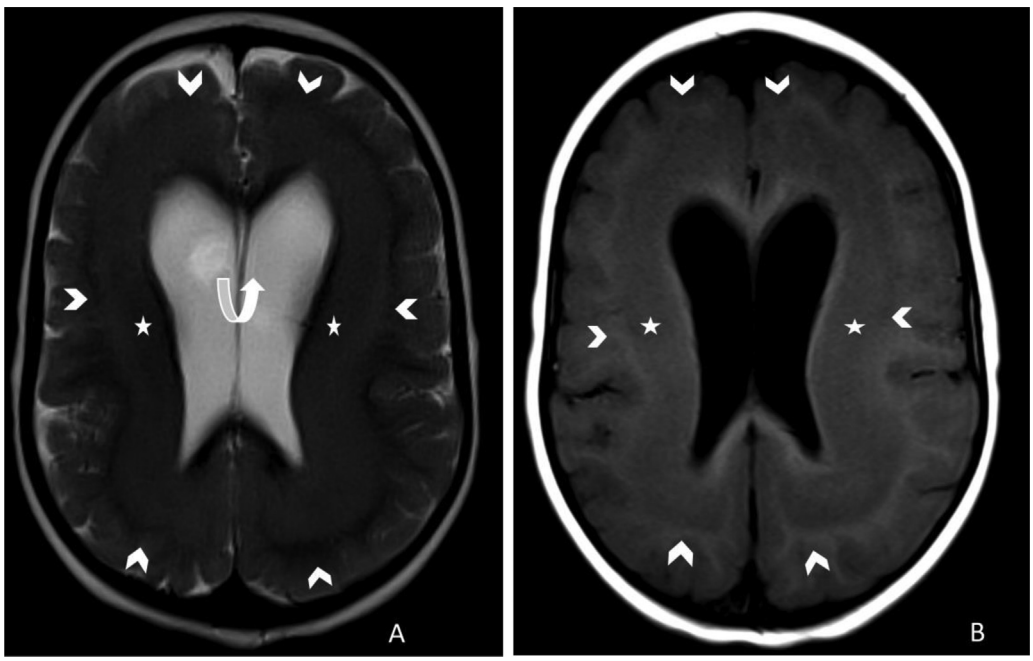

Fig. 1 – T2W (A) and T1W (B) axial images through the level of the body of lateral ventricles showing mild dilatation of lateral ventricles (curved white arrow), shallow cortical sulci (white arrows), and continuous band of grey matter (white stars) just deep to the cortex left posteriorly separated from the cortex with a thin layer of white matter (white chevron).

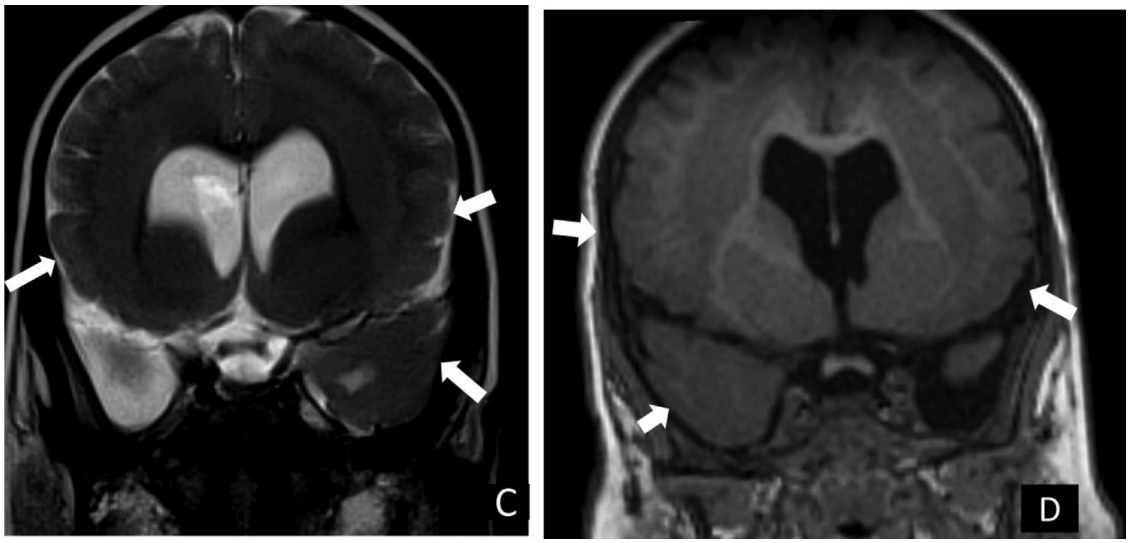

Fig. 2 – T2W (C) and T1W (D) coronal MRI images at the level of the pituitary fossa show diminished shallow sulcation (white arrows). Many of the cortical sulci are shallow. Re-demonstration of a continuous ribbon of grey matter just deep to the cortex, separated from it with a thin layer of white matter and mild enlargement of lateral ventricles was noted.

5mg daily. Seizure frequencies have reduced greatly. There are improved milestones after the initiation of regular physiotherapy as the child can now make a few steps and stand with support.

Discussion

Lissencephaly, also referred to as "smooth brain" is a genetic brain malformation with characteristic reduction of normal cerebral cortical sulci and gyri. It is a neuronal migration disorder implicated with genes like LIS1, DCX, RELN, ARX, TUBA1A, and DYNC1H1 [6]. Cases of LIS/SBH show a predominance for the X-linked chromosome, as well as a predominance in the frontal and temporal lobes [7]. Genetic studies were not performed on our patient to identify the specific mutated gene due to the cost implications. However, the clinical and radiological features strongly indicate features of LIS/SBH.

While there is no specific environmental association, some studies have suggested a potential link with cytomegalovirus infection, although these cases were primarily associated with polymicrogyria rather than lissencephaly [8]. In our patient, there was no history of perinatal or postnatal cytomegalovirus infection, and no reported history of hepatitis during childhood.

The prevalence of Lissencephaly is largely unknown, but the diagnosis and incidence have increased in recent years due to improved imaging technology as well as awareness of the condition among healthcare professionals [6]. There are no published studies on the incidence in East Africa. However, a study by Stelzle et al., published in 2022, showed the presence of features of Lissencephaly in patients with epileptic syndromes in this region [9].

Clinical manifestations of children with LIS mostly begin during the first year of life with children not achieving motor milestones and unprovoked seizures. The major medical concerns are feeding difficulties and gastroesophageal reflux with recurrent aspiration pneumonias and epilepsy of different types [10]. Our patient presented with delayed motor milestones as she could not control neck or sit at 1 year of age which is in line with the clinical features described in the studies above. Almost all children will have seizures and infantile spasms. Mixed seizure types are more common rather than specific types of seizures [11]. Our patient presented with unprovoked focal seizures initially and subsequent seizures triggered by simple febrile illnesses.

LIS can be classified into 6 grades as proposed by Dobyns et al., in 1995, with Subcortical Band Heterotopia (Double Cortex Syndrome) being grade 6. SBH is characterized by symmetric and circumferential bands of grey matter beneath the cortex, with only a thin band of white matter separating it. The inner and outer margins are smooth, and the overlying cortical surface appears normal [12].

In subcortical band heterotopia, most patients are females according to studies published. The characteristic MRI features are isointensity of the heterotopic band with the cortex in all imaging sequences. The cortex's thickness and the band's extent may vary among patients. The genes demonstrated are located on chromosome Xq22.3-q23. Most are sporadic cases, but some studies have described a relation with X-linked inheritance with most being female carriers [11]. MRI recognizes different patterns of lissencephaly; hence a grading system was developed. Most patients show a posterior-to-anterior gradient where the gyral malformation is more severe posteriorly than anteriorly, but other patients manifest a reverse anterior-to-posterior gradient. MRI most typically shows agyria or pachygyria and thickened cortex [6]. Our patient had typical features on MRI with diminished gyral sulcation, shallow cortical sulci as seen in Lissencephaly type 1, as well as a continuous ribbon of grey matter deep to the cortex separated by a thin layer of white matter, all in keeping with Subcortical band heterotopia.

There is no curative management for this condition and no consensus management recommendations published [3]. The goal of treatment currently is to improve quality of life

and minimize complications from seizures. Antiseizure medications and physiotherapy have been utilized in the management of this condition. Some patients may be refractory to antiseizure medications even with multiple regimens. Surgical management has been tried in some cases but has not shown a sustained reduction in the severity of seizures in many patients, postsurgical management [11]. Our patient was initiated on antiseizure medication and frequent physiotherapy which have shown to improve the motor abilities as well as reduced significantly the frequency of seizures.

Conclusion

This case report highlights a typical presentation of the LIS/SBH spectrum. Having a high index of suspicion is important for early diagnosis of such rare genetic conditions. Early diagnosis allows for prompt initiation of conservative care which improves quality of life and prognosis of the condition. Early physiotherapy can improve milestones in these children as seen in our patient. Physicians in low-resource settings ought to consider LIS/SBH as a possible cause of morbidity in patients with such symptoms, given the rarity of this disease in this geographical location.

Patient consent

I, the corresponding author, declare that informed consent was obtained from the patient's legal guardian who is the biological mother for publication of this case report. In case it may be required, I will provide evidence of the copies of the consent form.

Ethical approval

Not required for case reports at our hospital for single case reports.

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No funds were needed to publish this case.

Authors' contributions

All authors read and approved the final manuscript.

Data availability

The datasets of the present study are available from the corresponding author upon request.

Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work, the author(s) used Grammarly to correct sentence grammar and spelling. After using this tool/service, the author(s) reviewed and edited the content as needed and take(s) full responsibility for the content of the publication.

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