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Research Article

Uncommon Presentation Of Lissencephaly

Dr. Sukriti Amraik[1], Dr. Ranjit Ghuliani[2], Dr,Rajeev Kumar Thapar[3], Dr.Bindu T Nair[4], Dr. Praneta Swarup[5*]

[1]Resident, Department of Pediatrics, SMS&R, Sharda University.
[2,3,4]Professor, Department of Pediatrics, SMS&R, Sharda University.
[5*]Assistant Professor, Department of Pediatrics, SMS&R, Sharda University.

***Corresponding Author:** Dr. Praneta Swarup
*Email: praneta.swarup@sharda.ac.in, ORCID ID: 0009-0000-7402-5161

Abstract
Introduction: Neuronal migration is a critical step for cortical development, and disruptions in this process can lead to disorders like lissencephaly, heterotopia, polymicrogyria, schizencephaly, and focal cortical dysgenesis, which cause developmental delays, intellectual disabilities, or epilepsy. Lissencephaly is the most common neuronal migration disorder in communities with parental consanguinity.
Case report: A 5-month-old female, born to a four degree consanguineous marriage, presented with developmental delay and limb stiffness. Examination revealed cortical visual blindness and hearing impairment, increased muscle tone, especially in the lower limbs, head lag, and a rag-doll appearance on ventral suspension, indicating significant motor and developmental delays.
Diagnosis: MRI of the brain showed bilateral ex-vacuo ventriculomegaly, including fourth ventricle and temporal horn dilatation with irregular margins. Findings included reduced white matter, delayed myelination, and pachygyria with limited sulci and gyri in the frontal region. Agenesis of the corpus callosum was also observed.

***Authors for correspondence: E-mail Id:** praneta.swarup@sharda.ac.in*

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Introduction

The development of the central nervous system (CNS) is a complex, stepwise process that involves primary neurulation, prosencephalic development, neuronal proliferation, neuronal migration, organisation, and myelination.

Neuronal proliferation in the developing human brain primarily occurs between 8 and 15 weeks of gestation. Neural progenitor and radial glial cells, which generate both neurons and glial cells, proliferate in the ventricular and subventricular zones. Radial glial cells are crucial for controlling neuronal migration, forming the radial glial fibre system that guides cortical projection neurons to their correct locations. By 28 weeks of gestation, migrating neurons attach to these fibres and settle in predetermined sites, forming the six-layered cerebral cortex.

Neuronal migration is highly coordinated, and recent research focuses on understanding the signalling mechanisms that regulate this process. These mechanisms can be disrupted by genetic errors or external factors, affecting normal CNS development.

Neurons originating from the cortical ventricular zone (VZ) migrate radially to form the cortical plate (CP) and primarily become projection neurons. Neuronal migration in the neocortex mainly occurs between the

12th and 24th weeks of gestation. The first post-mitotic neurons produced in the VZ migrate to create a subpial preplate or primitive plexiform zone.[1]
Neuronal migration disorders include: 1. Lissencephaly 2. Heterotopia 3. Polymicrogyria 4. Schizencephaly 5. Focal cortical dysgenesis [2] These may have overt clinical presentations mentioned above; less severe cases may be detected incidentally on brain MRI. [3]
Prenatal diagnosis of neurodevelopmental disorders is typically possible after 27 weeks of gestation using fetal MRI or ultrasound. Postnatally, MRI is a reliable diagnostic tool. With 31 genes identified that account for nearly 90% of lissencephaly diagnoses, genetic testing is highly recommended. Genetic testing provides valuable information for prenatal diagnosis, prognosis, recurrence risk in families, avoiding unnecessary testing, and guiding personalized medicine.[4]

Case Report

A 5-month old, female child born out of four degree consanguineous marriage presented with complaints of developmental delay and stiffness of bilateral upper and lower limbs. Antenatal period was uneventful, there was history of delayed cry, significant family history of consanguinity (Fig 1, Fig 2), along with developmental delay in elder sibling. There was no history of feeding difficulties, nasal regurgitation, abnormal fisting, seizures.
On examination, the child is underweight with normal facies, normocephalic, pupils were bilaterally symmetrical and non-reactive, but there was no visual fixation. Fundus examination revealed cortical visual blindness. Clinically patient appeared to be having hearing disability too as there was no response to sound. There was increased tone bilaterally in upper and lower limbs, noted more in the lower limbs, however, head lag was noted on pull to sit, rag doll appearance on ventral suspension suggesting that the child was in evolving stage of neurological deficit.
MRI Brain revealed bilateral ex-vacuo ventriculomegaly (Rt>Lt), with involvement of fourth ventricle including temporal horn dilatation with irregular margins, paucity of white matter and myelination with limitation of sulci and gyri in the frontal region suggestive of pachygyria. Agenesis of corpus callosum is also noted.(Fig 3, Fig 4) The above mentioned findings suggest either a disorder of neuronal migration or an intra uterine CMV infection. Work up for CMV infection was done which came out to be negative.

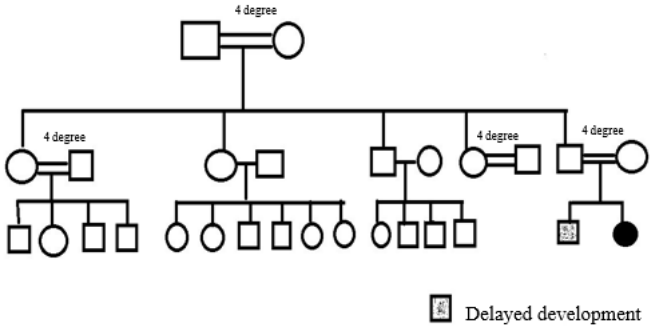

Fig 1. Pedigree chart showing consanguinity between paternal grandparents and parents.

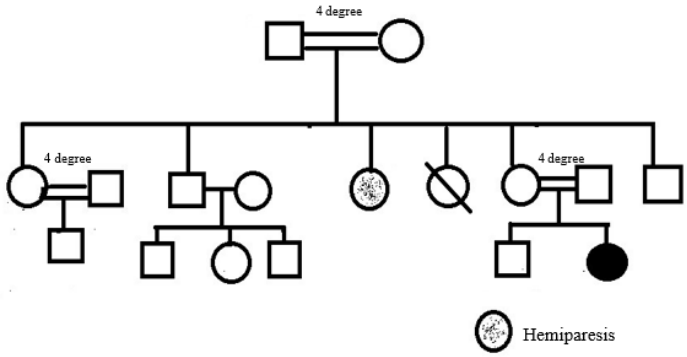

Fig 2. Pedigree chart showing consanguinity between maternal grandparents and parents

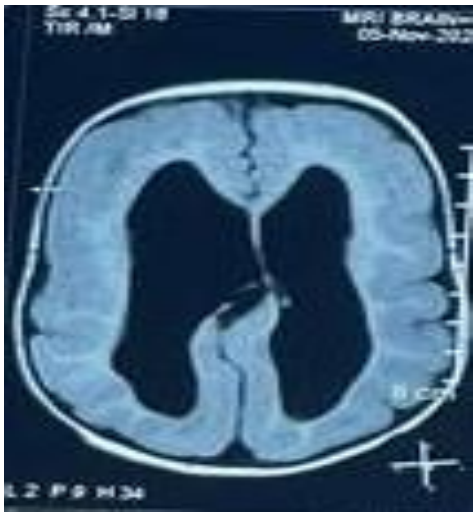

Fig. 3 MRI Brain showing ex- vacuo ventriculomegaly with paucity of white matter and myelination. Limitation of sulci and gyri.

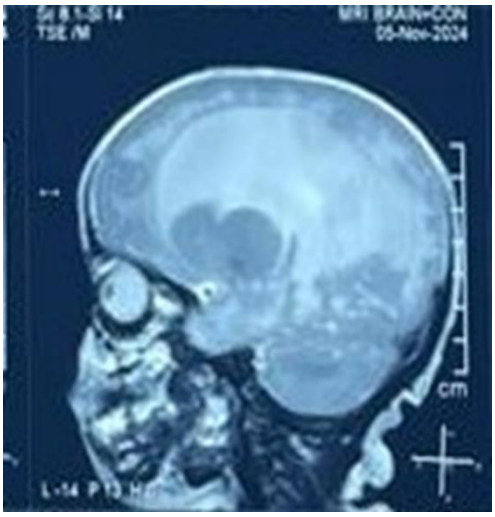

Fig. 4 showing agenesis of corpus callosum.

Discussion

Neuronal migration disorders are caused by abnormalities in neural migration during the 3-5 months post-conception period. The exact cause is not fully understood, but factors that disrupt migration include hypoxic-ischemic encephalopathies (HIE), inborn metabolic errors, congenital infections, chromosomal abnormalities, genetic defects, and prenatal exposure to substances like cocaine and other street drugs.[5]

In our case, there was history of birth asphyxia, along with history of consanguinity in parents and both maternal and paternal grandparents. The differential diagnosis ascertained were neuronal migration disorder, intrauterine CMV infection which can explain both ventricular dilatation and agenesis of corpus callosum. Further, mitochondrial cytopathy, neurometabolic disorder were also considered as differentials.

There have been cases reported of lissencephaly resulting from consanguineous union strengthening the suspicion of it being transmitted as an autosomal recessive trait.[6]

Conclusion

Lissencephaly is a rare congenital condition, with varied severity of symptoms. Lissencephaly is probably the commonest neuronal migrational disorder in communities with a high rate of parental consanguinity, adding significant support to the literature on the genetic aetiology of lissencephaly. Although the child had normal facies, and was normocephalic, with no seizures, was diagnosed as a case of lissencephaly on the basis of MRI findings. Hence, a high index of suspicion for lissencephaly should be kept in children with developmental delay and consanguinity in family.

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