Asian Journal of Clinical Pediatrics and Neonatology Case Report

# Classical Lissencephaly: A Case Report

**Rahul V. Bharad[1], Tasso Byai[2], M. Amita Devi[3], Prof. L. Ranbir Singh[4]**

[1,2]Junior resident, 3Senior resident, [4]Professor and Head, Department of Pediatrics,Regional Institute of Medical Sciences, Imphal, Manipur.

## Abstract

Classical lissencephaly is a rare cause of intractable seizures in infancy. Here, we report a 2 months old male baby with failure to thrive, refractory seizures, spasticity and characteristic facies including prominent forehead, bitemporal hollowing, anteverted nostril, prominent upper lip and micrognathia. CT brain showed typical agyria.

Key words:Lissencephaly, Agyria, Miller-Dieker syndrome, Neuronal migration, Micrognathia, Intractable seizures.

## INTRODUCTION

Lissencephaly is a developmental brain disorder characterized by a smooth cerebral surface, thickened cortex and misplaced neurons.[1] The word "Lissencephaly" is a greek word meaning "smooth brain" (the absence of normal circumvolutions of the cerebral cortex or agyria).[2] Five major groups of lissencephalies can be recognized of which type 1 (classical) is most common. Classical lissencephaly is caused by sporadic mutations in LIS1, which encodes a WD-repeat protein involved in cytoplasmic dynein regulation, mitosis and nuclear migration.[1] Approximately 60% of patients with classical lissencephaly have been found to have deletions or mutations of the LIS1 gene, located on 17p13.3[3] ]lt is characterized histologically by arrested neuronal migration such that the brain resembles that of a fetus before 23–24 weeks gestation.[4] Migration of post-mitotic neurons from the ventricular zone to the cortical plate during embryogenesis comprises one of the most critical stages in brain development. Deficiency of this process often results in major brain malformations, including lissencephaly.[5]

## CASE REPORT

A 2 months old male baby admitted with the complaints of difficulty in feeding since birth, seizures (Generalised tonic clonic type) since birth with stiffness, abnormal posturing of all the four limbs and failure to gain weight. Baby was born out of non-consanguinous marriage at full-term delivered at home with history of delayed crying. On examination, forehead was prominent with bitemporal hollowing and nose was anteverted. Upper lip was prominent with micrognathia. Generalised muscle wasting was present [Figure 1].

Physical examination revealed weight - 3.8 kg (expected- 5.6 kg, Z score -3), Head circumference was 36 cm (microcephaly, expected- 39.1 cm, Z score -2.68) and length was 53 cm (expected- 58.4 cm, Z score -2.69). Upper segment: lower segment ratio was 1.65. On CNS examination, there were intractable seizures, generalized tonic clonic type and spasticity of all the limbs. Examination of the cranial nerves and spine were normal. There was global delay in milestones. Other systemic examinations were within normal limits.

Routine investigations were normal. On CT brain, cerebrum showed shallow sylvian fissures and figure of eight appearance with smooth grey-white interface. The cortex was thickened with virtual absence of sulcation suggestive of lissencephaly and associated colpocephaly (dilatation of posterior horns of lateral ventricles) [Figure 2]. Baby was managed with conventional anti-epileptic drugs including phenobarbitone, phenytoin, lorazepam. As seizures were not controlled, midazolam IV infusion was started but there were breakthrough seizures off and on. The parent took the baby home on 4th day of hospitalization against medical advice and was lost to follow up.

## DISCUSSION

Congenital structural defects of the central nervous system (CNS) constitute part of the 3% of severe malformations encountered in newborns. Whereas some may be due to hereditary abnormal development; others may arise from iatrogenic factors such as infections and teratogens. A prototype of the disorders of neuronal migration is lissencephaly or agyria. Currently, it is defined as a brain malformation manifested by a smooth cerebral surface, thickened cortical mantle with microscopic evidence of incomplete neuronal migration.[2]

The incidence of classical lissencephalies has been estimated to 1.2 in 100,000 births. Five major groups of lissencephalies can be recognized: i) Classic lissencephalies (previously known as type 1 lissencephalies), which include: lissencephaly due to LIS1 gene mutation (type 1 isolated lissencephaly and Miller-Dieker syndrome), lissencephaly due to double cortin (DCX) gene mutation, lissencephaly type 1, isolated, without known genetic defects, ii) Lissencephaly X-linked with agenesis of the corpus callosum (ARX gene), iii) Lissencephaly with cerebellar hypoplasia, iv) Microlissencephaly, v) Cobblestone lissencephaly or cobblestone dysplasia (also known as type 2 lissencephaly), which includes Walker-Warburg syndrome or HARD(E) syndrome, Fukuyama syndrome and Muscle-Eye-Brain (MEB) disease.[6]

The normal duration of gestation, absence of grotesque dysmorphic features and development of microcephaly in the first year of life, are suggestive of Lissencephaly type 1. As with the case being presented, a large majority of patients with

## Address for correspondence*

**Prof. L. Ranbir Singh,**
Professor and Head, Department of Pediatrics,
Regional Institute of Medical Sciences,
Imphal - 795 004,Manipur.
Mobile- 9436026792
Email: drranbirlai@yahoo.co.in

**Fig 1:- Characteristic facies (prominent forehead, bitemporal hollowing, anteverted nostril, micrognatia and prominent upper lip).**

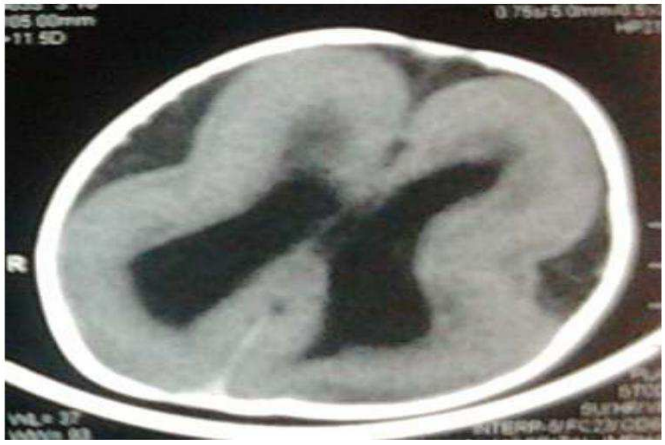

**Fig 2: CT brain:- Cerebrum shows shallow sylvian fissures and giving figure of eight appearance with smooth grey-white interface and thickened cortex with virtual absence of sulcation**

lissencephaly have seizures during the first year of life and more than half of these present with infantile spasms. Other neurological manifestations include profound mental retardation and hypotonia that evolves to spasticity with time.[2]

Radiologically, the CT scan and MRI features can be divided into primary or secondary findings. The primary finding is usually indicative of a neuronal migration defect which consists of a completely smooth brain that is agyric or areas of pachygyria. The sylvian grooves may be shallow and the distribution of white matter throughout the brain may be scanty. Secondary features include hydrocephalus, colpocephalus (dilatation of posterior horns of lateral ventricles), absent corpus callosum and Dandy-Walker malformation.[7]

Treatment of children with lissencephaly is essentially symptomatic. This may consist of physiotherapy, use of appropriate antiepileptic drugs and introduction of affected children to appropriate rehabilitative programs. Genetic evaluation and counseling are indicated for families of children with lissencephaly.[2] Lissencephaly associated with abnormalities of the LIS1 gene usually results in severe clinical sequelae. These include severe or profound mental retardation, early-onset intractable epilepsy, early and persistent hypotonia that may progress to mild spastic quadriparesis, and major feeding problems. Early data suggested that lifespan is usually shortened with few patients surviving beyond the first decade, the major causes of death being aspiration pneumonia and sepsis.[3] Lissencephaly is a neurological disorder, which carries a bad prognosis because of poorly controlled seizures and mental retardation.[8]

## REFERENCES


1. Pedersen LB, Rompolas P, Christensen ST, Rosenbaum JL, King SM: The lissencephaly protein Lis1 is present in motile mammalian cilia and requires outer arm dynein for targeting to Chlamydomonas flagella. J Cell Science. 2006;120:858-67.
2. Jouini S, Al-Awashiz AS, Izuora GI: An infant with isolated lissencephaly. Neurosciences. 2001;6(4):250-52.
3. Cardoso C, Leventer RJ, Dowling JJ, Ward HL, Chung J, Petras KS, et al: Clinical and Molecular Basis of Classical Lissencephaly: Mutations in the LIS1 Gene (PAFAH1B1). Human mutation. 2002;19:4-15.
4. Rollins N, Reyes T, Chia J: Diffusion tensor imaging in lissencephaly. Am J Neuroradiol. 2005;26:1583–6.
5. Kato M, Dobyns WB: Lissencephaly and the molecular basis of neuronal migration. Human Mol Genetics. 2003;12(1):89–96.
6. Verloes A. Lissencephaly, generic term. Orphanet Encyclopedia. March 2004. http://www.orpha.net/data/patho/GB/uk-lissencephaly.pdf, accessed on 18th Oct. 2013.
7. Thong MK, Lim CT, Koh MT, Kumar GG: The lissencephalic syndromes. Med J Malaysia. 1996;51(3):353-7.
8. Gupta BV, Verma S, Raina VP, Iravathy GK: Lissencephaly child showing FISH negative and mutation in DCX gene with normal parental genetic makeup. Indian J Hum Genetics. 2006;12(2):93-5.