Case Report

Cobblestone Lissencephaly with Polydactyly, Anterior Uveitis and Single Palmar Crease in two brothers — A case report

Jasodhara Chaudhuri[1], Tarun Kumar Samanta[2], Moumita Ghosh[3], Swapna Chakraborty[4]

The term "lissencephaly" refers to smooth brain points to a group of rare malformations that share the absence of normal cerebral convolutions. It leads to severely disabling conditions and seizures. There are several types of lissencephaly and on the basis of a classification based on etiologies and morphology five major groups of lissencephalies are identified of which cobblestone lissencephaly also known as type 2 lissencephaly is atypical. This group includes Walker-Warburg syndrome, Fukuyama Congenital Muscular Dystrophy and Muscle-Eye-Brain disease. We present an unreported form of syndromic type 2 lissencephaly with global developmental delay, generalized tonic clonic seizures, polydactyly, single palmer crease, anterior uveitis but with no features of muscle dystrophy in two brothers born of parents with non-consanguineous marriage.

[*J Indian Med Assoc* 2019; **117(11):** 39-40]

Key words **: Lissencephaly, Cobblestone Lissencephaly, Walker-Warburg Syndrome, Fukuyama Congenital Muscular Dystrophy, Muscle-Eye-Brain disease.**

Cobblestone lissencephaly results from abnormal organogenesis of the brain and particularly of the glia limitans, which leads to complex neuronal migration disorders[1,2]. Cobblestone lissencephalies are characterized by a granular surface of the brain aspect associated with shallow sulci, abnormal myelination of the white matter, enlarged ventricles, brainstem and cerebellar hypoplasia. In contrast with classic lissencephalies brain is typically lined by a neuroglial layer. The most common form is associated with hydrocephaly(H), agyria(A), retinal dysplasia (RD) with or without encephalocoele(E). All these features are part of Walker-Warburg syndrome also known as HARD(E) which is usually lethal within first few months of life. Type 2 lissencephalies also include Fykuyama Congenital Muscular Dystrophy marked by a mutation in fukutin on 9q31 and Muscle-Eye-Brain disease caused by mutation in POMGNT 1 gene on 1p34-p33. These diseases are very rare and reliable population data to estimate incidence at birth is not available[3] (Fig 1).

Fig 1 — Patients with Parents

Case Report

Case 1 :

An eleven year old male presented with global developmental delay, seizure disorder, polydactyly (one digit extra in all four limbs), single palmer crease, crowding of teeth, left sided anterior uveitis. Born with an uneventful perinatal history, he was apparently well till 7 months of age when one day the parents noticed that he was having "fits" which was like generalized tonic clonic seizures. He was prescribed antiepileptics which he is continuing. He had 2 episodes of breakthrough seizures. He attained head control at 8 months of age, learnt to sit at 6 years of age, learnt to stand at 9 years of age and learnt to walk at 10 years of age. He can only shout "ma", "ba" and nothing else. He recognizes his parents but cannot see properly and goes on picking aimlessly (Figs 2&3).

Examinations — On clinical examination he had microcephaly (HC 47 cm), flat facies, haziness in the media of left eye, polydactyly, single palmar crease. Slow writhing movements of the hands were present. The child had generalized wasting falling under Grade 4 Protein Energy Malnutrition (PEM).

Fig 2 — Polydectyly with single Palmar Crease

On neurological examination, Grade 4 power in all four limbs, athetotic movement of both the hands, nystagmus and diminished tendon reflexes. IQ evaluation showed profound mental retardation. Opthalmological examination showed left sided anterior uveitis, high myopia and normal optic disc and macula. Serum CPK was normal. MRI of the brain showed diffuse symmetrical T2 and Fluid Attenuated Inversion Recovery (FLAIR) hyperintensities involving periventricular deep white matter

Department of Paediatric Medicine, Medical College and Hospitals, Kolkata 700073

[1]MBBS, MD, Postgraduate Trainee of Paediatric Medicine

[2]MBBS, DGO, DCH, MD (Paediatric Medicine), RMO *cum* Clinical Tutor and Corresponding Author

[3]MBBS, MD (Paediatric Medicine), previously Senior Resident. At present : RMO *cum* Clinical Tutor

[4]MBBS, DCH, MD (Paediatric Medicine), Professor & Head

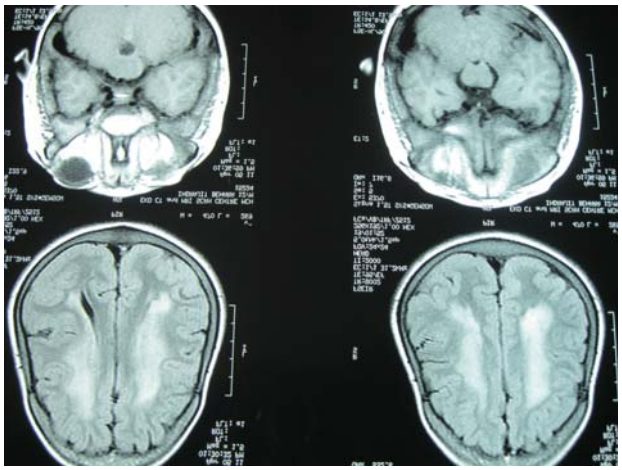

Fig 3 — MRI Brain of the older brother

of the frontoparietal lobes and pachygyria bilaterally with relative sparing of subcortical U-fibres and parieto-occipital and temporal lobes. There were tiny bilateral cerebellar cysts with hypoplasia of vermis, all suggestive of type II lissencephaly with level of confidence 10/10 (Fig 3). Muscle biopsy was normal. Brainstem Evoked Response Audiometry (BERA) was done and found to be normal and no metabolic abnormality was present.

Case 2 :

The six year old brother of the previous patient presented with exactly same findings and uneventful perinatal history. He was apparently well till 1 year of age when he started having convulsions in same manner. This child however has not achieved head holding as yet, cannot sit or do anything. He cannot speak and always stares vacantly. His investigation reports were similar to his brothers' from all aspects (Fig 4).

Examinations — Based on the history, clinical examination and investigations, the clinical features of the two brothers cannot be attributed to any of the three syndromes associated with lissencephaly type 2. The family was advised that the brothers should undergo further genetic analysis but that was not possible due to financial reasons. The parents apart from these two brothers have another child who is 8 year old male and is apparently normal till now with normal mental ability as he goes to a normal school and studies in a class appropriate for his age.

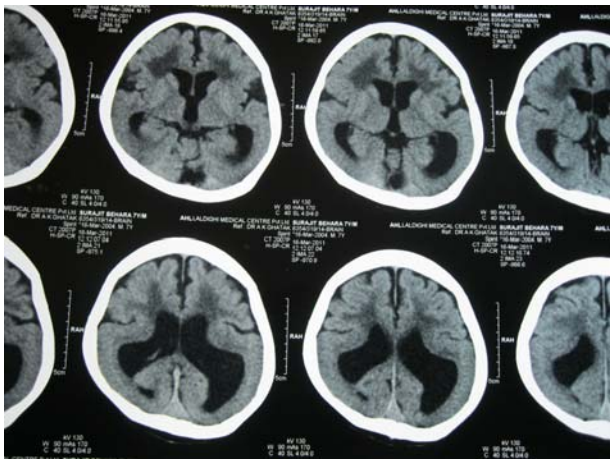

Fig 4 — CT Scan of the younger brother

Discussion

The lissencephaly syndromes associated with abnormal cortical lamination and are medically categorized as neuronal migration defects. Type 2 lissencephaly or cobblestone lissencephaly the cortex is unlayered. Type 2 lissencephaly is associated with 3 syndromes- Walker Warburg syndrome, Fukuyama congenital muscular dystrophy and Muscle-eye-brain disease[4]. The features of the three are the following (Table 1).

Table 1 — *differentiating features of the 3 congenital muscular dystrophies under lissencephaly type 2*

Features	WWS*	MEB**	FCMD***
Distribution	Worldwide	Finland	Japan
Severity	Most severe	Moderate	Less severe
Ocular feature	Anterior chamber malformation, retinal dysplasia	High myopia, cataract	cataract
Hydrocephalous	Common	Uncommon	Uncommon
Brainstem involvement	Common	Uncommon	Uncommon
Cerebral cortex	Type 2 lissencephaly	Type 2 lissencephaly	Type 2 lissencephaly
Hypotonia	Generalised	Generalised	Generalised
Cerebellar involvement	Cysts	Vermis hypoplasia[5]	Uncommon
Dandy Walker malformation	Common	Uncommon	Uncommon

*WWS =Walker-Warburg Syndrome
**MEB=Muscle-Eye-Brain disease
***FCMD=Fukuyama Congenital Muscular Dystrophy

Since the clinical spectrum of the two brothers do not match with any of the three syndromes associated with lissencephaly type 2, it may be a new syndrome associated with lissencephaly type 2 that is yet to be explored. No previous case report of such a syndrome is available anywhere.

Treatment options : Primarily supportive, including physical exercise and stretching activities. Genetic counseling should be offered to the parents.

Source of support : Nil

Conflict of interest : Nil

References

1 Dobyns WB, Leventer RJ — Lissencephaly: the clinical and molecular genetic basis of diffuse malformations of neuronal migration, PG Barth, ed. Mac Keith press, London. *International Review of Child Neurology series* 2003; 24-57.

2 Kato M, Dobyns WB — Lissencephaly and the molecular basis of neuronal migration. *Hum Mol Genet* 2003, **1:** R89-96.

3 Torres FR, Montenegro MA, Marques-De-Faria AP, Guerreiro MM, Cendes F, Lopes-Cendes I — Mutation screening in a cohort of patients with lissencephaly and band heterotopia. *Neurology* 2004; **62:** 799-802.

4 Taniguchi K, Kobayashi K, Saito K, Yamanouchi H, Ohnuma A, Hayashi YK, *et al* — Worldwide distribution and broader clinical spectrum of muscle-eye-brain disease. *Hum Mol Genet* 2003; **12(5):** 527-34.

5 Jissendi –Tchofo P, Kara S, Barkovich AJ — Midbrain-hindbrain involvement in lissencephalies. *Neurology* 2009; **72(5):** 410-8. doi: 10.1212/01.wnl.0000333256.74903.94. Epub 2008 Nov 19.