Neuro-Anatomical Study of a Rare Brain Malformation: Lissencephaly, A Report of Eleven Patients

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Abstract

Background and Objectives: Clinical data and magnetic resonance imaging (MRI) / Computerised Tomography (CT) scans of patients with lissencephaly were reviewed. The clinico-anatomic profile and type of lissencephaly in patients attending the Paediatric Neurology Clinic in Western Rajasthan was determined. The major comorbid conditions, maternal and fetal factors associated with lissencephaly were also studied.

Methods: Patients with radiologically proven lissencephaly were included in the study. A detailed epidemiologic profile, clinical history, neurologic examination and neuro-imaging details (CT/MRI) were recorded. The data collected was analyzed.

Results and Interpretation: The prevalence of lissencephaly amongst the patients attending the clinic was 0.49%. All patients had anatomical features compatible with impaired neuronal migration. Seizure was the most common comorbid (90.9%) condition associated with lissencephaly.

Conclusion: MRI and appropriate genetic studies as feasible should be done to aid in accurate clinco-anatomic and genetic diagnosis in all patients suspected of having a congenital Central Nervous System (CNS) malformation such as lissencephaly.

Key words: CNS Malformations, Heterotopias, Lissencephaly, Neuronal Migration, Seizures.

Introduction

Lissencephaly, which literally means smooth brain, is a rare brain malformation caused by impaired neuronal migration of post-mitotic neurons from the ventricular zone to the cortical plate during 12th to 24th weeks of gestation. Lissencephaly is manifested as a smooth cerebral surface due to absence of cerebral convolutions / gyri, abnormally thick cortex with four abnormal layers that includes a deep zone of diffuse neuronal heterotopia and enlarged dysplastic ventricles[1]. It encompasses the pathologic terms agyria (absent gyri), pachygyria (broad gyri) and subcortical band heterotopia.

There are around 20 different types of lissencephaly and different systems for classifying lissencephaly exist. Based on the associated malforma-tions and underlying etiology two large groups can be distinguished: classical lissencep-haly (and its variants) and cobblestone lissenceph-aly. In classical lissencep-haly (or type I), the cortex appears thickened, with four more or less disorganised layers rather than six normal layers. In the variants of classical lissencephaly, extra-cortical anomalies are also present (total or subtotal agenesis of the corpus callosum and/or cerebellar hypoplasia).

The classical lissencephalies and the variant forms on the basis of their genetic etiology can be further divided into four groups: Anomalies in the LIS1 gene (isolated lissencephaly and Miller-Dieker syndrome), anomalies in the TUBA3 and DCX genes, and lissence-phalies caused by mutations in the ARX gene (XLAG syndrome, X-linked lissencephaly with agenesis of the corpus callosum). In addition to these four entities, isolated lissencephalies without a known genetic defect, lissencephalies with severe microcephaly (microlissencephaly) and lissencep-halies associated with polymalformative syndro-mes are also included in the group of classical lissencephalies.[2]

Cobblestone lissencephaly is a severe brain malformation observed in three overlapping

syndromes, all genetic with autosomal-recessive inheritance: the Walker-Warburg, Fukuyama and MEB (Muscle-Eye-Brain) syndromes. It is characterised by global disorganisation of cerebral organogenesis with an uneven cortical surface (with a pebbled or cobblestone appearance). The brain malformation consists of cobblestone cortex, abnormal white matter, enlarged ventricles, often with hydrocephalus, small brainstem and small dysplastic cerebellum[3]. The abnormal cortex is severely disorganized with no recognizable layers and with disruption by abnormal vascular channels and fibroglial bands that extend into and often obstruct the subarachnoid space. The changes are widespread in the most severe syndrome (Walker-Warburg syndrome) but are less extensive in the other syndromes.[3]

Children with lissencephaly have feeding and swallowing problems, muscle tone anomalies (early hypotonia and subsequently limb hypertonia), seizures (in particular, infantile spasms) and severe psychomotor retardation. The epilepsy is often resistant to treatment. The encephalopathy associated with lissencephaly is often very severe and affected children are completely dependent on the carer.[4]

All forms of lissencephaly and subcortical band heterotopias are genetic, and genetic testing is currently available for at least 80% of patients with lissencephaly or subcortical band heterotopias. The most productive order of testing is chromosome analysis and fluorescence in situ hybridization searching for deletions of chromosome 17p13.3 that include the *LIS1* gene, followed by sequencing of *LIS1*, then *DCX*, and finally *ARX*. Patients with Walker-Warburg syndrome or muscle-eye-brain disease have greatly enlarged lateral ventricles and many have frank hydrocephalus. Thus can be detected on prenatal ultrasound examination in the mid- to late second trimester.

The genetic and congenital disorder is the second most common cause of infant and childhood mortality and occurs with a prevalence of 25-60 per 1000 births.[5] The incidence of all forms of type I lissencephaly is around 1 in 100,000 births.[6] Malformations represent an important contribution to the total disease burden seen in pediatric neurology. An extensive review of the literature has revealed that there is a paucity of literature from India and especially Western Rajasthan regarding the prevalence of lissencephaly. This study made a fresh attempt to evaluate both the anatomic and the clinical profile of these patients presenting exclusively in a Pediatric Neurology clinic of tertiary care centre in Western Rajasthan, India.

Material and Method

The study was conducted in the Department of Anatomy and the Pediatric Neurology Clinic at the Department of Pediatrics, Umaid Hospital for Women and Children attached to Dr. S. N. Medical College, Jodhpur, Rajasthan. Over the study period 2255 patients attended the Pediatric Neurology clinic. MRI/CT Scans and clinical records of patients with lissencephaly were reviewed. A detailed epidemiologic profile, clinical history, neurologic examination and results of electrophysiology were recorded. Major Comorbid conditions such as seizures, global developmental delay (GDD), gross motor delay (GMD), speech and language delay (SLD), autism, microcephaly and hydrocephalus associated with this anomaly was evaluated.

Results and Discussion

Out of the two thousand two hundred and fifty five patients that attended the clinic during the study period thirty three patients had different congenital CNS malformations. Lissencephaly was the most predominant anomaly and was detected in eleven patients (33.3%). The prevalence of lissencephaly among the patient attending the clinic was 0.49%. Sanghvi et al[7] identified seventy six cases with epileptogenic brain malformations based on neuro imaging. Lissencephaly was reported in nine cases. Barkovich et al[6] reported incidence of various CNS anomalies. Incidence of lissencephaly was 1 to 4 per 100,000 births.

Table 1 presents the spectrum of lissencephaly with relevant clinical features and radiologic findings. 58.3% cases with lissencephaly had other associated CNS abnormalities, which included Dandy-Walker variants, heterotopia, agyria, pachygyria, agenesis of corpus callosum and closed lip schizencephaly. Similar to our findings Sanghvi et al[7] also reported that 55.5% cases with lissencephaly had other associated CNS abnormalities, which included colpocephaly, Dandy-Walker variants, cysts, heterotopia, FCD, polymicrog-yria and pachygyria.

Of the total patients with lissencephaly and its variants 36.4% were males where as 63.6% were females. The female to male ratio was 1.75: 1 showing female preponderance. The mean age of presentation was 4.72 years with the age range of 2.5 month to 11 years. Similar to our results Parmar et al[8] reported that incidence of congenital malformation were slightly more in female with F: M ratio of 1.6:1. In contradiction to our study Sanghvi et al[7] reported a male preponderance (60.5%) in their study, mainly in pachygyria and heterotopias (100%). Verma et al[9] and Swain et al[10] could not observe any sex predilection of malformation.

On studying the antenatal, perinatal, postnatal association and family history in patients with lissencephaly pregnancy induced hypertension (PIH) was observed in 9.0%, intra uterine growth retardation (IUGR) was observed 18.2% and oligohydraminos was observed in 9.0% of eleven cases. Datta et al[11] reported a history of oligohydramnios in 3/37 (8.1%) and polyhydramnios in 2/37 (5.4%) cases. Percentage of anomalous babies in mothers with PIH, oligohydromnious and polyhydromnious, was 3.9, 5.12 and 11.7% respectively.[12]

Nine percent of the patients had low birth weight, 18. 2 % were born by LSCS, 63.6 % were born at home by normal delivery and 9.0 % of subjects were born preterm. Only 27.2 % of mothers attended the antenatal clinic regularly. The rate of malformations in preterms was twofold of that in term babies[9]. In a study from rural Maharashtra twenty two of the thirty seven malformed babies (59.4%) were full term whereas 40.5% (15/37) were pre terms. Thirteen of the thirty seven congenitally malformed babies (35.1%) were very low birth weight (mean ± SD; 1314.2 ± 175 g); 13/37 (35.1%) were low birth weight (mean ± SD; 1938.4 ± 268.8 g)[11].

Of the total patients with congenital CNS malformation 9.0 % of subjects had icterus, 18.2 % had episodes of excessive cry during their neonatal period, 9.0 % of subjects had delayed feeding. Parakh et al[13] also reported that 5.50% patients had history of inconsolable crying during infancy. Family history of consanguinity (18.2%), seizure (45.5%) and speech language delay (9.0%) was also present in these patients. Sanghvi et al[7] reported that six patients were born of a consanguineous marriage, including two siblings with lissencephaly and six had a family history of epilepsy.

Seizure was the most common comorbid condition associated with lissencephaly. Ten out of eleven subjects (90.9 %) had seizures. 63.6 % had primary generalized seizures. 9.0 % had myoclonic, 27.2 % had tonic, 9.0 % had clonic and 18.2 % had tonic clonic seizures. 27.2% had complex partial seizures. (Table 3) At presentation 81.8 % of patients had global developmental delay, 18.2 % patients had gross motor delay and 45.5 % patients had speech and language delay. Sanghvi et al[7] reported that all cases of lissencephaly showed global developmental delay.

Table 1: Clinico–Radiologic Phenotype of patients studied.

S. No.	Clinico–Radiologic Phenotype	No. of patients
1.	Lissencephaly with double cortex heterotopia and bilateral closed lip schizencephaly	1
2.	Classic lissencephaly	2
3.	Lissencephaly- pachygyria	1
4.	Lissencephaly -agyria	1
5.	Lissencephaly agyria-pachygyria	2
6.	X–linked lissencephaly variant	1
7.	Autosomal lissencephaly variant with Dandy Walker variant	1
8.	Lissencephaly with agenesis of corpus callosum	1
9.	Nodular Heterotopia of left temporal region	1

Table 2: Comorbid conditions amongst patients with Lissencephaly

S. No.	Comorbid Condition	Number of patients (%)
1.	Global Developmental Delay	9 (81.8)
2.	Gross Motor Delay	2 (18.2)
3.	Speech Language Delay	5 (45.4)
4.	ADHD	1 (9.1)
5.	Seizures	10 (90.9)
6.	Microcephaly	2 (18.2)

Table 3: Type of seizures in patients with Lissencephaly

S. No.	Type of Seizures		Number of patients
1.	Primary Generalized Seizures	Myoclonic	1
		Tonic	3
		Clonic	1
		Tonic–Clonic	2
2.	Partial Seizures	Complex	3

Conclusion

As stated in the aforementioned discussion it is evident that Lissencephaly (congenital CNS malformations) constitute an important entity in patients presenting in a pediatric neurology clinic. They are also associated with significant morbidity including neuro developmental delay and epilepsy. Although not treatable many of these are manageable by supportive care and treatment.

Congenital malformations are a major cause of death of neonates in India where prenatal detection and treatment are not adequate in many hospitals and health centers. Congenital malformation will begin to emerge as one of the major childhood health problems. Treatment and rehabilitation of children with congenital malformations is costly and complete recovery is usually impossible, however prevention in future in largely based on accurate genetic diagnosis in the index case and performing a prenatal work up in future pregnancies.

Antenatal diagnosis, genetic counseling, better diagnostic and management facilities should be provided so that appropriate prophylactic measures can be taken in time, which will prevent handicaps resulting out of congenital anomalies

Conflict of Interest: None
Source of Support: Nil

References

1. Barkovich AJ, Koch TK, Carrol CL. The spectrum of lissencephaly: Report of ten patients analyzed by magnetic resonance imaging. Ann Neurol 1991;30:139.
2. Dobyns WB.The clinical patterns and molecular genetics of lissencephaly and subcortical band heterotopias. Epilepsia 2010; 51: 5-9
3. Dobyns WB, Kirkpatrick JB, Hittner HM, et al. Syndromes with lissencephaly. II: Walker-Warburg and cerebro-oculo-muscular syndromes and a new syndrome with type II lissencephaly. Am J Med Genet 1985;22:157.
4. Dobyns WB, Elias ER, Newlin AC, et al. Causal heterogeneity in isolated lissencephaly. Neurology 1992;42:1375.
5. World Health Organization: The global burden of disease: 2004 update. Geneva, 2008.
6. Barkovich AJ, Moore KR, Jones BV, et al. Diagnostic Imaging: Pediatric Neuroradiology. Salt Lake City: Amirsys Inc; 2007
7. Sanghvi JP, Rajadhyaksha SB and Ursekar M: Spectrum of Congenital CNS Malformations in Pediatric Epilepsy. Ind Paed. 2004; 41; 831
8. Parmar A, Rathod SP, Patel SV and Patel SM: A Study of Congenital Anomalies In Newborn.NJIRM;2010; Vol. 1(1); Jan-March;13-17.
9. Verma M, J. Chhatwai J and Singh D: Congenital Malformations-A Retrospective Study of 10,000 Cases. Indian J Pediatr 1991; 58 : 245-252

10. Swain S, Agarwal A and Bhatia BD: congenital Malformations at birth.Ind Paed 1994; 12; 1187
11. Datta V, Chaturvedi P. Congenital malformations in rural Maharashtra. Indian Pediatr. 2000;37; 998–1001
12. Gupta S, Gupta P and Soni JS: a study on incidence of various systemic congenital malformations and their association with maternal factors. Nat J Med Res 2012; 2 (1);19
13. Parakh M, Parakh P, Bhansali S: A clinico-epidemiologic study of neurologic associations and factors related to speech and language delay Nat J Community Medicine 2012; 3;518