Lissencephaly

G.L. Gupte
A.S. Kher
S.M. Joshi
B.A. Bharucha
S.P. Kanade

Lissencephaly means smooth brain, *i.e.,* brain without convolutions or gyri. Miller in (1963) and later Dieker in 1969 described a specific pattern of malfor mations, one feature of which was lissencephaly(l,2). They emphasized that this should be called lissencephaly syndrome because of the association of polydactyly, unusual facial appearanc es, malformation of the heart, kidneys and other organs(2). Jones *et al.* expand ed the clinical phenotype and intro-duced the term Miller-Dieker syndrome to distinguish this disorder from other conditions associated with lissencephaly(l-3). This is the first case series to be reported from India.

Case Reports

Three cases were referred to our Genetic Clinic for non-achievement of milestones. None of these cases had antenatal history of decreased fetal activity or prenatal and postnatal complication. All of these cases were born of non-consanguineous marriage and had normal sibs. The clinical details of these cases are summarized in *Table I.*

From the Genetic Clinic, Department of Pediatrics, Seth C.S. Medical College and K.E.M. Hospital, Parel, Bombay 400 012.

Reprint requests: Dr. Burjor A. Bharucha, Professor, Department of Pediatrics, Seth C.S. Medical College and K.E.M. Hospital, Parel, Bombay 400 012.

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Discussion

Lissencephaly results from a defect in neuronal migration with four rather than six layers in cortex(2). The thick-ened cortex in parieto-occipital region represents the cell sparse layer. The on-set of this disorder is presumed to be before 9 weeks of gestation. The pattern of brain involvement seen in lissencephaly would seem to support **a** vascular etiology(4). Two types of lissencephaly syndromes are known. Type 1 is associated with minimal hydrocephalus, but without any brain malformation. Type II lissencephaly is associated with hydrocephalus, cerebel-lar malformations and congenital mus-cular dystrophy, *i.e.,* Walker Warburg syndrorne (HARD ± E syndrome). Lissehcephaly is also found in a number of genetically determined disorders, as well as a result of metabolic, anoxic and other teratogenic insults. It is found in Zellweger syndrome, Pena Shokeir syn-drome, Neu Laxova syndrome, fetal alcohol syndrome, Cerebral perfusion failure and anoxia. Dobyns *et al.* has reported 8 patients and carried out an extensive review of the literature. He proposed a four way classification of lissencephaly syndromes(l,2,3,6): *(a)* Miller-Dieker syndrome with abnormal-ity of chromosome 17; *(b)* Miller-Dieker syndrome without evident abnormality of chromosome 17; (c) A disorder with sloping forehead and other facial fea-tures with manifestations unlike those

TABLE I—*Summary of Cases*

	Features	Case 1	Case 2	Case 3
1.	*Age*	7 yr	1 yr 3 mo	7 yr
2.	*Craniofacial features*			
	Microcephaly	+	+	+
	Broad nasal bridge with epicanthal folds	+	+	+
	Short nose with upturned nares	-	+	-
	Ptosis	-	-	-
	Vertical ridges in suprametopic soft tissue	+	+	-
	Micrognathia	-	+	-
	Malformed ears	-	+	-
3.	*General*			
	Postnatal growth deficiency	+	+	+
	CVS/renal abnormalities	-	-	-
	Hernias & musculoskeletal abnormalities	-	-	-
4.	*Central nervous system*			
	Severe psychomotor retardation	+	+	+
	Roving eye movements	-	+	-
	Initial muscular hypotonia	+	+	+
	Subsequent hypertonia	+	+	-
	Seizures	+	+	+
5.	*Karyotype of peripheral blood leukocytes*	Monosomy 17p	Normal	Normal
6.	*CT Scan of brain (Fig. 1)*			
	Agyria	+	+	+
	Colpocephaly	+	+	+
7.	*Developmental quotient*	<1%	<1%	10%
8.	*Diagnosis*	Miller-Dieker syndrome with monosomy 17p	Miller-Dieker syndrome with normal chromosomes	Variant without facial dysmorphism and without familial occurences

of Miller-Dieker syndrome, but with familial occurence and normal chromosomes (Norman-Roberts syndrome); and (*d*) A form without characteristic facial dysmorphism and without familial occurences.

The principal features of our 3 cases are listed in *Table I.* The typical facial characteristics of Miller-Dieker syndrome like microcephaly, bitemporal hollowing, anteverted nares, broad nasal bridge with epicanthal folds, abnormal ears and anteverted nares were present in only one of the two cases of Miller-Dieker Syndrome. Dobyns *et al.* had observed these typical facial characteristics in all cases(6). However, others failed to document the typical facial characteristics in their case reports(6). Dobyns *et al.* and Jones *et al.* had documented non-craniofacial abnormalities in more than half of their patients(6,7). None of our patients had any non-craniofacial abnormalities. Typical CNS manifestations of a striking degree of initial hypotonia with subsequent hypertonia was noted in all our patients. All the three patients had severe developmental delay. Most patients die by the age of 5 years; however, two of our cases were seen at the age of 7 years. Other features reported in the literature, but not observed in our patients were prominent occiput, downslanting palpebral fissures, divergent squint, cloudy cornea, late eruption of primary teeth, arachnodactyly, low set thumbs, polydactyly, abnormal palmar creases, clinodactyly, inguinal hernia, sacral dimple, congenital heart defect and renal abnormality(1,2,5,8,9).

Neuroimaging of the brain reveals thick cortical mantle, decreased white matter, smooth cortex, shallow vertical sylvian fissures that are open superficially, colpocephaly (posterior enlargement of the lateral ventircles with a figure of 8 appearance), heterotopias of gray matter, absence of white-gray interdigitations, close approximation of the middle cerebral arteries and veins to the inner table of skull and cavum septum pellucidum(10,11). All our three patients had typical CT scan picture resembling lissencephaly *(Fig.* 7). In addition, small midline calcifications in the area of the genu of the corpus callosum reported by others were not present in any of our cases. MRI reveals a reversal of gray to white matter ratio and thickened cortex seen as a circumferential band of high intensity on T2 weighted images; prominent in the parieto-occipital region and less of the frontal area(4).

Most patients who have been adequately studied have monosomy of the distal short arm of chromosome 17. These chromosome deletions arise as *de novo* terminal deletion, inherited, or *de novo* unbalanced translocations involving 17p or unbalanced inversion of chromosome 17(2). The critical region for .this syndrome is the sub band 13.3(5). However, there are some patients who have normal prophase chromosome studies. Whether these cases represent submicroscopic deletions of 17p or phenocopy is currently unknown(2). Prenatal diagnosis by ultrasonography is possible in the third trimester, but has not been recorded to date(12). Failure to visualize the thalamic structures should raise an high index of suspicion(12).

Parental chromosomes should be studied whenever the child is found to have interstitial deletion of 17 pl2-13. Lissencephaly can be diagnosed antenatally by amniocentesis or chorionic villus sampling, when parents are found to have a balanced translocation. The risk of recurrence is extremely low in cases of *de novo* deletion.

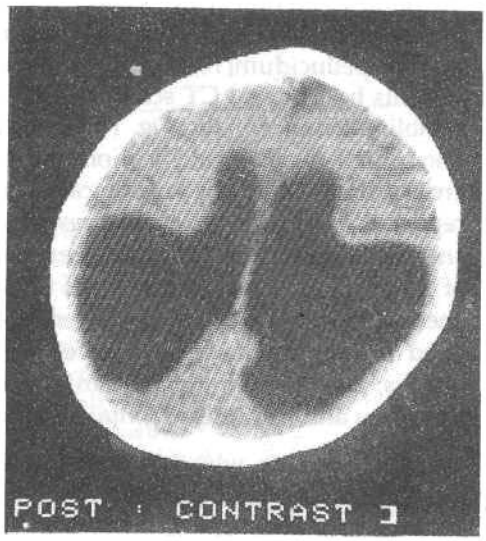

Fig. 1. CT scan shows presence of colpocephaly and agyria

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