Computed tomographic appearance of lissencephaly syndromes.

W B Dobyns and C W McCluggage

AJNR Am J Neuroradiol 1985, 6 (4) 545-550
http://www.ajnr.org/content/6/4/545

Computed Tomographic Appearance of Lissencephaly Syndromes

William B. Dobyns[1]
Charles W. McCluggage[2]

Lissencephaly is a rare malformation of the human brain manifest by a smooth cerebral surface. It is usually associated with other brain anomalies. The computed tomographic appearance in nine patients with lissencephaly, representing several separate types and syndromes, is reported. Common manifestations include a smooth cerebral surface and absent opercula that may lend a figure-eight appearance to the brain and smooth subsurface lines that represent abnormal cortical layers or an abnormal white-gray interface.

Lissencephaly is a rare developmental defect of the brain manifest by widespread, though not necessarily complete, agyria. When incomplete, the rest of the brain usually is pachygyric. It is the major anomaly of several familial syndromes, but also occurs as an isolated malformation. Several distinct clinicopathologic types have been recognized. The most frequently described form is characterized by microcephaly and a thickened cortex with four or fewer layers rather than the normal six. All patients with Miller-Dieker syndrome (MDS) and most patients without a recognized syndrome have had this type of lissencephaly, which we have designated classical or type I lissencephaly [1]. A rarer form of lissencephaly is manifest by agyria, hydrocephalus, and other severe brain malformations, especially of the cerebellum, and has been designated type II lissencephaly [2]. Other types of lissencephaly, usually manifest by extremely low brain weights, have also been observed, but pathologic descriptions are few and incomplete [3]. Few reports of the computed tomographic (CT) appearance of lissencephaly are available in the literature [4–9]. Our purpose is to describe and demonstrate the CT findings in patients with several different types of lissencephaly.

Materials and Methods

We have studied nine patients with different types of lissencephaly. Specific diagnoses included MDS in three, isolated lissencephaly sequence (ILS) in two, and Walker-Warburg syndrome (WWS) in two. The other two patients did not meet the criteria of any previously described syndrome. Complete general and neurologic examinations, CT scans, and chromosome analyses (normal unless otherwise specified) were available for all.

We evaluated six separate features of brain development by review of CT scans and scored them on a 0–3 scale based on increasing severity of the abnormalities. Zero was always used for normal findings while 2 or 3 was used for the most severe abnormalities. Details of the scoring system are listed in table 1 and the results are presented in table 2. Though the features have been listed separately, all are interrelated and may be grouped into abnormalities of cerebral cortical formation, supratentorial midline structures, and infratentorial structures.

Results and Discussion

Radiologically, lissencephaly may be recognized by two primary and related

Received October 24, 1984; accepted after revision February 6, 1985.

[1] Departments of Neurology and Pediatrics, Baylor College of Medicine, Houston, TX 77030. Present address: Department of Neurology, Medical College of Wisconsin, Milwaukee Children's Hospital, Milwaukee, WI 53201.

[2] Department of Radiology, Baylor College of Medicine, St. Luke's Episcopal Hospital, and Texas Children's Hospital, 6720 Bertner, Houston, TX 77030. Address reprint requests to C. W. McCluggage.

AJNR 6:545–550, July/August 1985
0195–6108/85/0604–0545

TABLE 1: **Key to interpretation of CT Manifestations of Lissencephaly**

Cerebral surface:	
0	Normal gyration with well formed opercula
1	Partial figure-eight shape due to subtotal agyria with areas of pachygyria and incomplete opercular development
2	Classical figure-eight shape due to widespread agyria and absent opercula
3	Complete agyria without figure-eight shape, associated with hydrocephalus
Lamination:	
0	Normal
1	Areas of broad white-gray interdigitation mixed with areas with smooth subsurface laminations
2	Homogeneous cerebral mantle with smooth subsurface laminations, especially just below surface and just above ventricles
3	Inhomogeneous cerebral mantle with strikingly demarcated smooth subsurface lamination
Ventricles:	
0	Normal configuration
1	Mild dilatation of lateral ventricles, especially posteriorly (colpocephaly)
2	Moderate dilatation of entire lateral ventricles and third ventricle in nonobstructive pattern
3	Obstructive hydrocephalus which may be untreated (3a) or shunted (3b)
Calcifications:	
0	None observed
1	Small midline calcification anterior to third ventricle
2	Bilateral thalamic calcifications
Supratentorial midline:	
0	Normal
1	Abnormal relation of lateral and third ventricles and interhemispheric fissure due to regional hypoplasia of the corpus callosum (see text)
2	Extensive abnormalities of midline structures including absence of the septum pellucidum and absence or severe hypoplasia of the corpus callosum
Posterior fossa:	
0	Normal
1	Hypoplasia of the posterior vermis with mild enlargement of fourth ventricle
2	Absence of most of the vermis including entire posterior vermis; cystic dilatation of fourth ventricle (Dandy-Walker malformation), which may be confined to posterior fossa (2a) or associated with posterior cephalocele (2b)
3	Severe hypoplasia of cerebellar hemispheres with absent midline structures; hemispheres represented by small masses on either side of brainstem. No evidence of cystic structure

manifestations: a smooth cerebral surface (with poor or absent opercular development) and absent or severely attenuated white-gray interdigitations. In many patients, the smooth surface and absent opercula result in a striking and characteristic figure-eight appearance that is readily apparent on CT scans (particularly figs. 1–3). The cerebral surface in these patients is best seen in the sylvian region and anterior interhemispheric fissure. In other patients, especially those with hydrocephalus, the surface contour is obscured by close apposition to the inner table of the skull.

In normal brains, the cortex and white matter interdigitate in direct relation to the overlying surface convolutions. In lissencephalic brains, the interdigitations are either absent (agyria) or severely attenuated (pachygyria) and are replaced by a smooth line marking the abnormal white-gray interface. Additional subsurface lines that probably represent abnormal cortical layers may also be observed. This interpretation was supported by pathologic observations in cases 6 and 7 and in other reported patients. In the rest of the article, the CT manifestations of several different types of lissencephaly are described.

Type I Lissencephaly

Cases 1–3 have MDS, which consists of type I lissencephaly and the lissencephaly sequence, characteristic facial changes, and postnatal growth deficiency [1]. Small deletions of the chromosome 17 short arm (band 17p13.3) were detected in two of the three. Before this discovery, the cause of MDS was thought to be an autosomal-recessive genetic defect [1, 6]. However, most patients are now known to have a chromosome abnormality resulting in deletion of the above band [10, 11]. In patients with MDS and apparently normal chromosomes, familial recurrence has not been observed [3].

On CT (figs. 1–3), agyria is indicated by the smooth cerebral surface, figure-eight shape, and absent white-gray interdigitations. The latter are replaced by smooth subsurface lines just beneath the surface (representing an abnormal cortical layer, best seen in fig. 1) and just above the ventricles (representing the abnormal white-gray interface, best seen in figs. 2 and 3). The ventricles are more enlarged posteriorly, similar to the fetal configuration (colpocephaly). Ventricular size varies considerably among patients, though none have hydrocephalus.

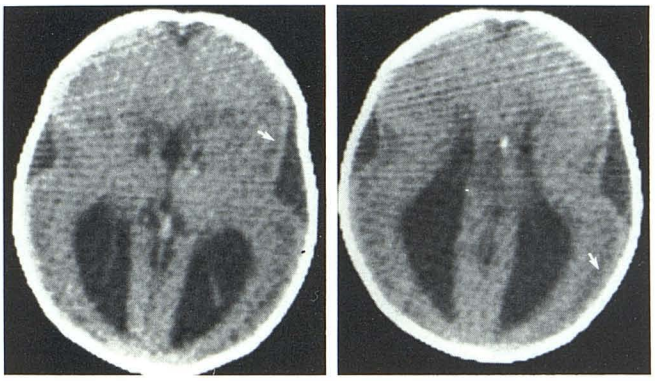
Other abnormalities include abnormal rostral extension of the third ventricle, abnormal separation of the frontal horns of the lateral ventricles, and decreased distance between the third ventricle and the anterior interhemispheric fissure; these are indicative of agenesis or hypoplasia of the corpus callosum. Small midline calcifications in the septum pellucidum or genu of the corpus callosum were present in the two patients with deletion of band 17p13.3 (figs. 1B and 3). The significance of this observation is not known. Infratentorial structures are grossly normal except for hypoplasia of the cerebral peduncles and slightly small cerebellar hemispheres.

Cases 4 and 5 had ILS, which consists of type I lissencephaly and the lissencephaly sequence (the direct craniofa-

TABLE 2: **CT Manifestations of Lissencephaly**

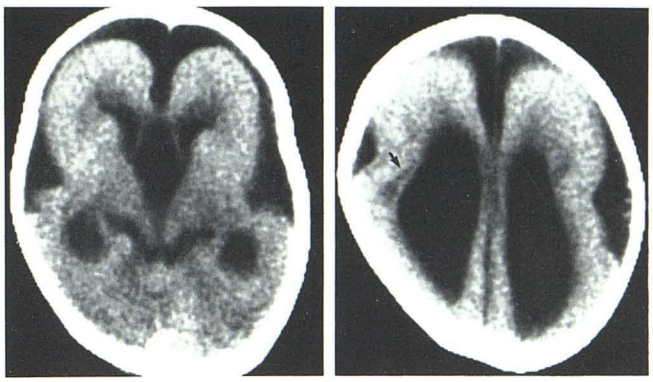
Type of Lissencephaly: Reference: Case No., Syndrome	Cerebral Surface	Lamination	Ventricles	Calcifications	Supratentorial Midlines	Posterior Fossa
Type I:						
[1 and 10]:						
3, MDS	2	2	1	1	1	0
This series:						
1, MDS	2	2	1	1	1	0
2, MDS	2	2	1	0	1	0
3, MDS	2	2	2	1	1	0
4, ILS	1	1	0	2	0	0
5, ILS	1	1	2	0	0	0
Type II:						
[9]:						
3, COMS	3	3	3a	0	2	2b
This series:						
6, WWS	3	3	3b	0	2	2a
7, WWS	3	?3	3a	0	2	?
8, ?	2	3	2	0	2	2b
Cerebrocerebellar:						
This series:						
9, ?	2	?2	1	0	1	3

Note.—Key to CT manifestations is in table 1. MDS = Miller-Dieker syndrome; ILS = isolated lissencephaly sequence; COMS = cerebrooculomuscular syndrome; WWS = Walker-Warburg syndrome.



A B

Fig. 1.—Case 1 (case 1 in [10]). Type I lissencephaly in MDS. **A**, CT scan at 1 month. **B**, Higher cut. Typical manifestations of type I lissencephaly and midline calcification. Chromosome analysis demonstrated ring (17) with deletion of part of band 17p13.3. Smooth subsurface line (*arrows*).

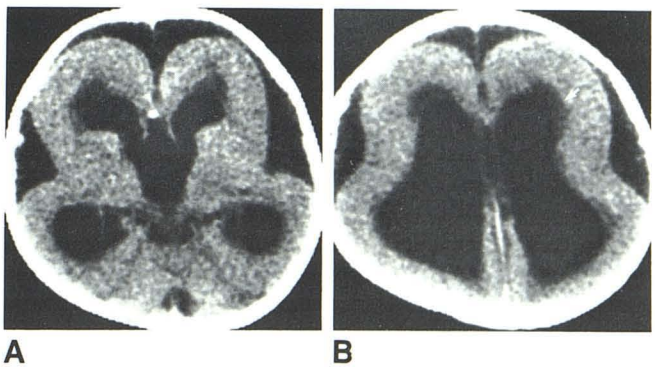


A B

Fig. 2.—Case 2 (case 2 in [10]). Type I lissencephaly in MDS. **A**, CT scans at 3 years (**A** and, higher cut, **B**) are similar to fig. 1 except that no midline calcification is observed. Chromosome analysis was apparently normal. Smooth subsurface line (*arrow*).

cial and neurologic sequela of lissencephaly [1]) with few or no other manifestations. Familial recurrence has been observed only rarely in this disorder [3]. The CT scans of both patients (figs. 4 and 5) showed less severe lissencephaly and fewer associated malformations than the scans in cases 1–3. Areas of agyria (smooth subsurface lines best seen in fig. 5B) alternate with areas of pachygyria, which are manifest by broad gyri with only limited white-gray interdigitations (best seen in fig. 4A). The ventricles are moderately enlarged throughout in case 5, which differs from the colpocephaly observed in cases 1 and 2. Other differences include normal supratentorial midline structures in both cases and unusual bithalamic calcifications in case 4 (fig. 4A). The significance of the calcifications is not known.

The pathologic manifestations of type I lissencephaly include a smooth cerebral surface, sometimes with areas of



A B

Fig. 3.—Case 3 (case 5 in [11]). Type I lissencephaly in MDS. **A**, CT scan at 3½ years. **B**, Higher cut. Larger ventricles than in figs. 1 and 2 and midline calcification. Chromosome analysis demonstrated terminal deletion of chromosome 17 with breakpoint in band 17p13.1. Smooth subsurface line (*arrow*).

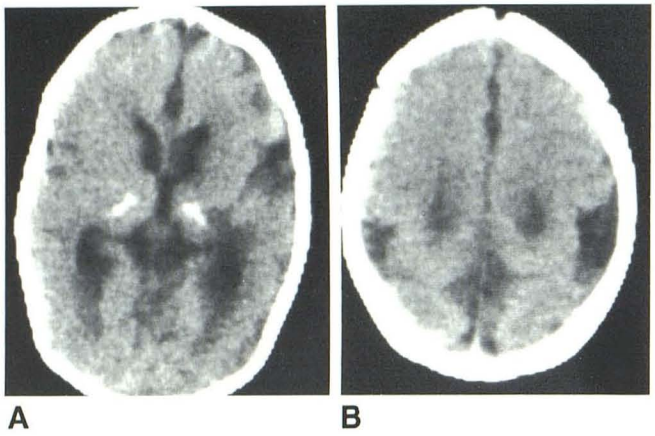


Fig. 4.—Case 4 (case 7 in [1]). Type I lissencephaly in ILS. **A**, CT scan at 1 month. **B**, Higher cut. Areas of pachygyria (e.g., right frontal convexity) and agyria (medial frontal lobes, insulas, probably parietal lobes) with unusual posterior displacement of sylvian region. Bilateral thalamic calcifications have not been observed in patients with MDS. (**A** reprinted from [1].)

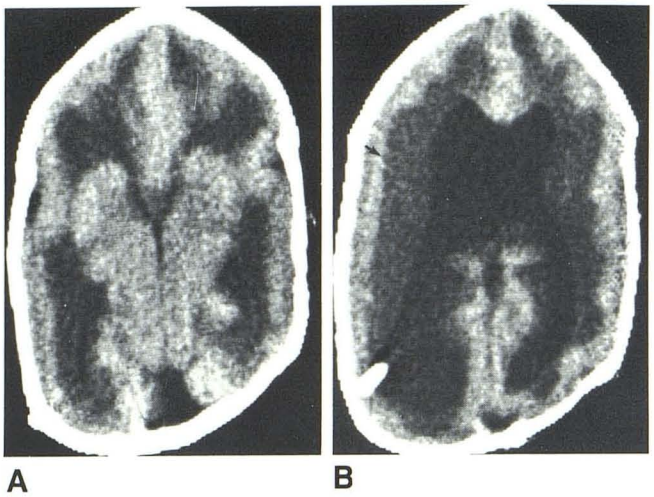


Fig. 6.—Case 6 (case 1 in [2]). Type II lissencephaly in WWS. **A**, CT scan at 5 months. **B**, Higher cut. Typical manifestations of type II lissencephaly. This patient had congenital noncommunicating hydrocephalus and was shunt-dependent. Smooth subsurface line (*arrow*).

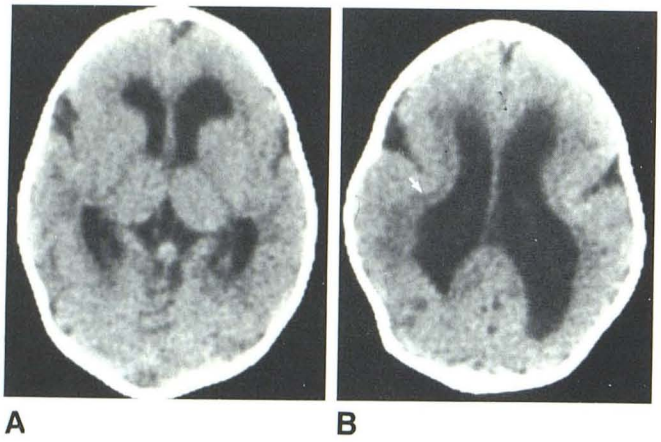


Fig. 5.—Case 5 (case 8 in [1]). Type I lissencephaly in ILS. **A**, CT scan at 11 days. **B**, Higher cut. Areas of pachygyria (e.g., immediately posterior to right sylvian fossa in **B**) and agyria. Ventricles are large and malformed but hydrocephalus was not present. Smooth subsurface line (*arrow*). (**B** reprinted from [1].)

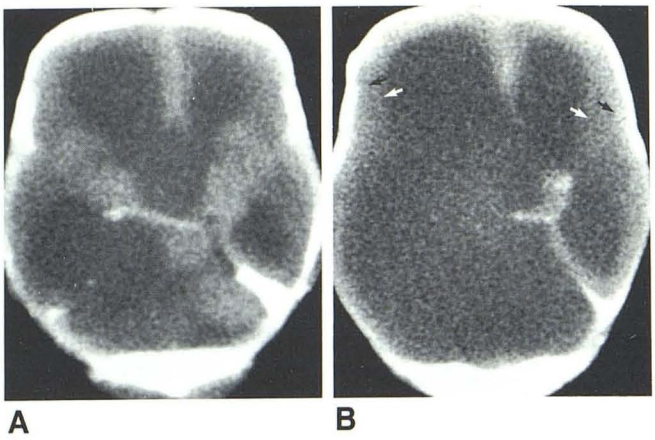


Fig. 7.—Case 7 (case 3 in [2]). Type II lissencephaly in WWS. **A**, CT scan at 1 day. **B**, Higher cut. Severe hydrocephalus but no posterior fossa cyst. Faint smooth subsurface line may be seen in places despite hydrocephalus. Ventricular wall (*white arrows*). Subsurface line (black *arrows*). Dense band of tissue has obliterated anterior interhemispheric fissure; this observation should suggest WWS even if other details are obscured. Dense septum passing obliquely across both cuts most likely represents displaced dural structure surrounded by thick fibroglial rind (it was not specifically described in pathologic report).

pachygyria, absent opercular development, colpocephaly, and variable hypoplasia of the corpus callosum on external examination [1, 12, 13]. On coronal section, a reversal of the usual white- to gray-matter ratio is observed, bringing the white-gray interface much closer to the ventricular surface. The width of the subcortical zone (white matter) appears to vary between adjacent brain areas (e.g., figs. 1B and 1C in [13]); this may account for some of the variability of the deeper of the smooth subsurface lines on CT. Increased permeability of the ependyma (as in hydrocephalus) has not been observed.

Histologically, the thickened cortex is divided into four layers [1, 12, 13]. The third, or cell-sparse layer, which is present in some areas and not in others (e.g., fig. 2 in [12]), is less dense than the surrounding superficial and deep cellular layers and most likely correlates with the more superficial of the smooth subsurface lines seen on CT.

Type II Lissencephaly

Cases 6 and 7 had WWS, which consists of hydrocephalus, type II lissencephaly, hypoplasia of the vermis with or without Dandy-Walker malformation, retinal dysplasia, and anterior chamber mesenchymal dysgenesis. The same manifestations plus congenital muscular dystrophy constitute a closely related disorder, cerebrooculomuscular syndrome (COMS). Additional manifestations in both disorders include minor facial changes and profound hypotonia and mental retardation. Both are caused by an autosomal-recessive genetic defect [2]. Case 8 also had type II lissencephaly, but without obstructive hydrocephalus. The facial appearance of this patient was much more abnormal than that of the two previous patients

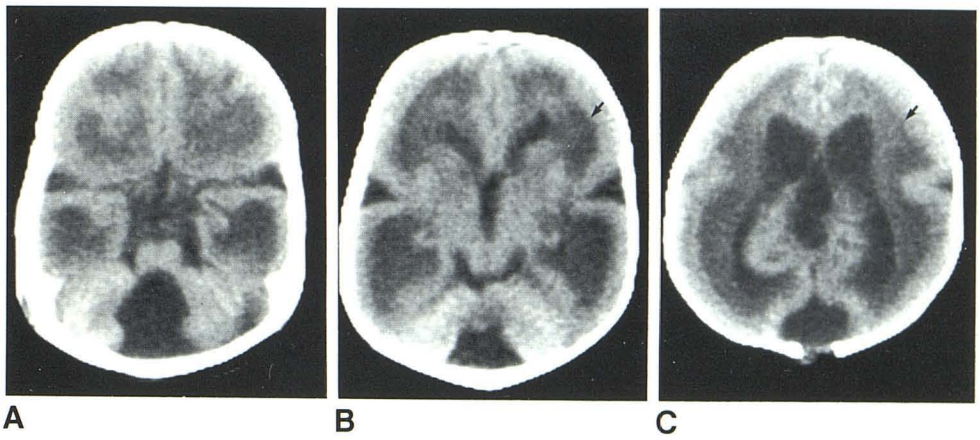


Fig. 8.—Case 8 (case 4 in [2]). Type II lissencephaly in previously undescribed disorder. **A**, CT scan. **B** and **C**, Higher cuts. Only moderate ventricular dilatation without hydrocephalus. Bony defect overlies posterior fossa cyst. Smooth subsurface line (*arrows*). On physical examination, small cephalocele was at this site, though it was not demonstrated on CT.

and anterior eye structure was normal, suggesting a separate but related disorder. Mild retinal dysplasia was observed. A shunt was never inserted [2].

The CT appearance of type II lissencephaly (figs. 6–8) is strikingly different from that of type I lissencephaly. The lateral and third ventricles are always enlarged, usually with obstructive hydrocephalus (probably always in WWS and COMS). In patients with hydrocephalus, the appearance of the cerebral surface and opercula is obscured by close apposition to the inner table of the skull (figs. 6 and 7). In case 8 (fig. 8), the ventricles were less severely enlarged and the smooth surface and a figure-eight appearance could be appreciated. In patients without severe hydrocephalus or with treated hydrocephalus (figs. 6 and 8), a well demarcated smooth line is seen midway between the ventricular and cerebral surfaces. The zone superficial to the line (the cortex) is a homogeneous region of unremarkable density. A fainter smooth line is sometimes seen just under the surface (fig. 6B). Deep to the demarcation (white matter) is a region of remarkable radiolucency completely surrounding the lateral ventricles. Thus, the line separates the mantle into two distinct layers with a striking lack of interdigitation. In case 7, the degree of cortical thinning secondary to hydrocephalus was so severe that this line was seen only faintly in some places (fig. 7).

Other abnormalities of supratentorial structures evident on CT include absence or severe hypoplasia of the septum pellucidum and corpus callosum with a large communication between the lateral ventricles, asymmetric eye size in some patients, and increased radiodensity of the medial frontal region that obscures or obliterates the anterior interhemispheric fissure. The latter is observed only in type II lissencephaly and a related disorder, Fukuyama congenital muscular dystrophy [14], and may allow recognition of the condition even in the presence of severe hydrocephalus (fig. 7).

Abnormalities of cerebellar midline structures are always observed on CT. In case 7 (fig. 7A), moderate hypoplasia of the vermis was observed pathologically but could not be distinguished on CT because of hydrocephalus. In case 6 (fig. 6A), the fourth ventricle was significantly enlarged and communicated in the midline with a large posterior fossa cyst consistent with a Dandy-Walker malformation. A small remnant of the anterior part of the superior vermis was observed pathologically but could not be seen on CT. Neither patient had a posterior cephalocele, though these have been observed in just under half of all patients with WWS or COMS [2]. Case 8 also had a Dandy-Walker malformation (fig. 8); the associated cyst appeared to protrude superiorly between the cerebral hemispheres. A defect in the occipital bone overlay the cyst and the patient had a small cephalocele at that site on physical examination, though it was not demonstrated on CT (the size varied considerably on different examinations).

The pathologic manifestations of type II lissencephaly include global agyria in most patients (small areas of a variant type of pachygyria in a few), hydrocephalus, variable hypoplasia of the vermis with or without Dandy-Walker malformation, and glial proliferation and scarring associated with marked vascular proliferation within the mantle and subarachnoid space [2]. The latter results in gliotic fusion of the cerebral hemispheres, especially frontally, which correlates with the CT radiodensity. On coronal section, the cortex constitutes about half the width of the mantle regardless of its overall thickness. The marginal layer is much thicker than normal and may correspond to the faint line just beneath the surface seen in some scans. As on CT, the white matter and cortex are clearly demarcated with no interdigitations. The septum pellucidum and corpus callosum are very small or absent.

Histologically, the cortex is severely disorganized with no horizontal lamination. The white matter is more cellular than normal but is still much less cellular than the cortex. It is also poorly myelinated and edematous with areas of cystic degeneration, especially near the ventricles (observed in case 6 despite a functioning shunt). It is possible, though not proven, that there is excessive passage of cerebrospinal fluid into the paraventricular white matter despite apparently normal intraventricular pressure.

Lissencephaly with Severe Cerebellar Hypoplasia

Case 9 had manifestations different from any of the other patients. Her facial appearance was dominated by severe microcephaly. The CT appearance (fig. 9) differed from the others because of severe cerebellar hypoplasia involving the vermis and hemispheres. Few patients with similar malformations have been reported. On the basis of these reports, etiologic heterogeneity is likely, though two children from one

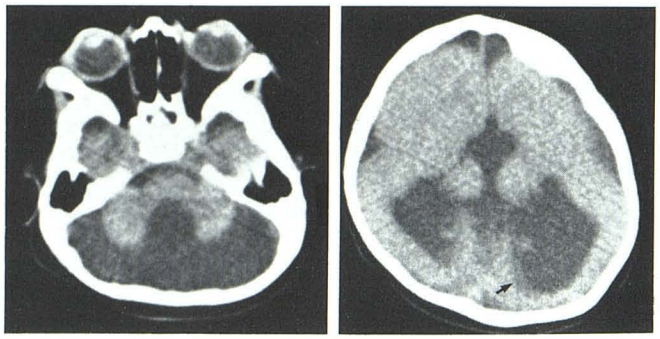


Fig. 9.—Case 9 (case 2 in [3]). Cerebrocerebellar lissencephaly variant. **A**, CT scan. **B**, Higher cut. Typical figure-eight appearance of cerebrum and striking hypoplasia of cerebellar hemispheres with apparently absent vermis. Smooth subsurface line (*arrow*).

family were affected [3]. The CT scans (fig. 9) showed a figure-eight shape, a smooth cerebral surface, and a homogeneous mantle with only a few, faint subsurface lines (perhaps due to poor resolution on an earlier-generation CT scanner). The ventricles were colpocephalic and the corpus callosum was hypoplastic. The cerebellum was represented by two small masses on either side of the brainstem; no midline cerebellar structures could be seen. The lack of a clearly defined cyst, the lack of a visible vermis, and the absence of hydrocephalus suggested a difference between this malformation and a Dandy-Walker malformation, though pathologic confirmation was not available.

ACKNOWLEDGMENTS

We thank the many physicians involved in the care of these children, especially Julie T. Parke, Stephen H. Whitaker, Carmela Tardo, Marvin A. Fishman, Alan K. Percy, and Thomas E. Zion; and Nancy Broderick for manuscript preparation.

REFERENCES

1. Dobyns WB, Stratton RF, Greenberg F. Syndromes with lissencephaly. I: Miller-Dieker and Norman-Roberts syndromes and isolated lissencephaly. *Am J Med Genet* **1984**;18:509–526
2. Dobyns WB, Kirkpatrick JB, Hittner HM, Roberts RM, Kretzer FL. Syndromes with lissencephaly. II: Walker-Warburg and cerebro-oculo-muscular syndromes and a new syndrome with type II lissencephaly. *Am J Med Genet* (in press)
3. Dobyns WB, Gilbert EF, Opitz JM. Further comments on the lissencephaly syndromes. *Am J Med Genet* (in press)
4. Garcia CA, Dunn D, Trevor R. The lissencephaly (agyria) syndrome in siblings. *Arch Neurol* **1978**;35:608–611
5. Ohno K, Enomoto T, Imamoto J, Takeshita K, Arima M. Lissencephaly (agyria) on computed tomography. *J Comput Assist Tomogr* **1979**;3:92–95
6. Jones KL, Gilbert EF, Kaveggia EG, Opitz JM. The Miller-Dieker syndrome. *Pediatrics* **1980**;66:277–281
7. Aymé S, Mattei J-F. HARD (±E) syndrome: report of a sixth family with support for autosomal recessive inheritance. *Am J Med Genet* **1983**;14:759–766
8. Whitley CB, Thompson TR, Mastri AR, Gorlin RJ. Warburg syndrome: lethal neurodysplasia with autosomal recessive inheritance. *J Pediatr* **1983**;102:547–551
9. Korinthenberg R, Palm D, Schlake W, Klein J. Congenital muscular dystrophy, brain malformation and ocular problems (muscle, eye and brain disease) in two German families. *Eur J Pediatr* **1984**;142:62–68
10. Dobyns WB, Stratton RF, Parke JT, Greenberg F, Nussbaum RL, Ledbetter DH. Miller-Dieker syndrome: lissencephaly and monosomy 17p. *J Pediatr* **1983**;102:552–558
11. Stratton RF, Dobyns WB, Airhart SD, Ledbetter DH. New chromosomal syndrome: Miller-Dieker syndrome and monosomy 17p13. *Hum Genet* **1984**;67:193–200
12. Stewart RM, Richman DP, Caviness VS Jr. Lissencephaly and pachygyria—an architectonic and topographical analysis. *Acta Neuropathol* (Berl) 1975;31:1–12
13. Jellinger K, Rett A. Agyria-pachygyria (lissencephaly syndrome). *Neuropediatrics* **1976**;7:66–91
14. Fukuyama Y, Osawa M, Suzuki H. Congenital progressive muscular dystrophy of the Fukuyama-type—clinical, genetic and pathological considerations. *Brain Dev* **1981**;3:1–29