

Lissencephaly

MARGARET G. NORMAN, MAUREEN ROBERTS, J. SIROIS, L. J. M. TREMBLAY

SUMMARY: *The first reported case of lissencephaly resulting from a consanguinous union strengthens the supposition that in some cases, it is transmitted as an autosomal recessive trait. Comparison of this case with a sporadically occurring case of lissencephaly, with different cortical morphology, suggests that lissencephaly may be an example of either varying gene expressivity or gene-*

tic heterogeneity. Lissencephaly and pachygyria may eventually be shown to be due to different causes, some inherited, some acquired. The classical examples of lissencephaly are different morphologically from a case in which antenatal cytomegalovirus infection had produced a small smooth brain. This suggests that antenatal viral infections are destructive rather than teratogenic.

RÉSUMÉ: *Le premier cas de lissencéphalie résultant d'une union consanguine renforce l'hypothèse qu'au moins dans certains cas la lissencéphalie est transmise par un trait autosomal récessif. La comparaison de ce cas avec un autre cas d'occurrence sporadique présentant des différences morphologiques au niveau cortical, suggère que la lissencéphalie pourrait être un exemple soit d'expressivité génétique variable soit de gènes hétérogènes. Eventuelle-*

ment, il sera peut-être démontré que la lissencéphalie et la pachygyrie sont dues à des causes différentes, certaines étant héréditaires, d'autres étant acquises. Les exemples classiques de lissencéphalie sont différents morphologiquement d'un cas d'infection à cytomégalovirus du prépartum aboutissant à la formation d'un petit cerveau à surface lisse, suggérant que les infections in utero sont destructrices plutôt que tératogéniques.

INTRODUCTION

Lissencephaly (agyria) is characterized by a smooth brain, without sulci or gyri. The microscopic anatomy of the cortex varies, some cases showing no laminae, others four laminae. Associated abnormalities are masses of heterotopic grey matter around the ventricles. Heterotopias of the inferior olivary nuclei and cerebellar roof nuclei are frequently present. Pachygyria is a morphologically similar anomaly in which the brain has wide simple gyri. Some have regarded lissencephaly and pachygyria as similar disorders, a difference of degree rather than kind (Crome, 1956; Hanaway et al, 1968). Daube and Chou (1966) proposed pathologic and clinical criteria for separating lissencephaly from pachygyria. They thought that lissencephaly could be recognized clinically.

Features of the "lissencephaly syndrome" include a distinctive facies, with high forehead, slight ante-version of nostrils, slight upward palpebral slant, widely spaced eyes, micrognathia, and abnormal lowset ears (Dieker et al., 1969). Other abnormalities are microcephaly, decerebrate posture, severe motor retardation, seizures before one year of age, lack of response to the environment, failure to thrive, recurrent infection and death before two years of life. Other visceral anomalies may be present. Pneumoencephalograms show enlarged ventricles (colpocephaly, persistence of a fetal situation rather than true hydrocephalus) and absence of air over the cerebral convexities (Daube and Chou, 1966). Electroencephalogram (EEG) shows hypersarrhythmia (Harper, 1967).

The cause of lissencephaly has been regarded as a failure of

From the Divisions of Pathology and Genetics, Eleanor M. Paterson Laboratory, Children's Hospital of Eastern Ontario, Ottawa, and Departments of Pathology and Pediatrics, University of Ottawa, Ontario; and Departments of Pathology, Sacre Coeur Hospital, Hull, Quebec and St. Andrews Hospital, Midland, Ontario.

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Reprint requests to Dr. M. G. Norman, Children's Hospital of Eastern Ontario, 401 Smyth Rd. Ottawa, Ont. K1H 8L1 Canada.

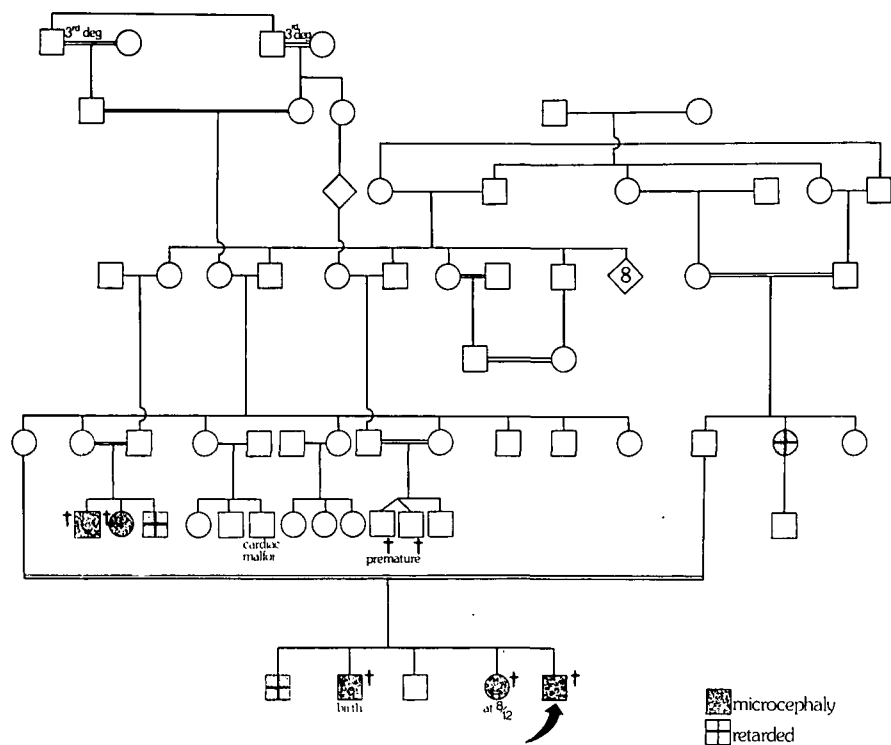


Figure 1—Case 1. Pedigree. Proband (arrow) is only case with necropsy diagnosis of lissencephaly. The other affected infants are said to have been “just the same”.

neuronal migration, with production of a four-layered cortex similar to that of a 50-100 mm. foetus (Hanaway et al., 1968). It has been suggested that factors intrinsic or extrinsic to the neurons could cause such a failure of migration (see Hanaway et al., 1968 and Stewart et al., 1975 for an historical account of these suggestions).

Our paper reports two cases of lissencephaly, one occurring in a consanguineous union, strengthening the evidence for autosomal recessive transmission. These two cases are compared with a third, in which a small smooth brain resulted from antenatal cytomegalovirus (CMV) infection. This brain is quite different from lissencephaly.

Case No. 1

This male infant was the fifth born to a 31-year-old mother. Gestation lasted 36 weeks; the Apgar at birth was unrecorded; the infant cried spontaneously before a minute and required no resuscitation. Birth weight was 2460 grams. The infant was transferred at birth for investigation of microcephaly and convulsions. Crown-heel length was 51

cm., head circumference was 26.5 cm. On admission he was obviously microcephalic with a small forehead, and almost closed anterior fontanelle. His eyes were wideset, his jaw small and receding. There was questionable pallor of the optic nerves. Chorioretinitis was absent. His pupils were small and fixed. The bridge of the nose was flattened and the right side of the mouth was twitching. Moro and grasp reflexes were absent, the sucking reflex weak. A short chordee was present. The little fingers were in-curved. Investigations for cytomegalic inclusion disease and rubella were negative. Chromosomes were normal 46XY. Dermatoglyphics showed whorls on nine fingertips and a bilateral atd angle of 60°.

While in hospital the infant had continual twitching of the extremities and occasional convulsions. He was placed on diphenylhydantoin and phenobarbital which failed to control these seizures. He fed poorly and required gavaging. He was discharged and died at home at two months of age.

The parents are first cousins. The proband was the fifth child. An older

brother and sister who died in infancy were said to be exactly like this infant. Two first degree cousins who were also related through both parents were also said to “be the same”. They were children of a consanguineous mating and all four parents had one common ancestor (Fig. 1). Unfortunately, necropsies were not performed so a diagnosis of

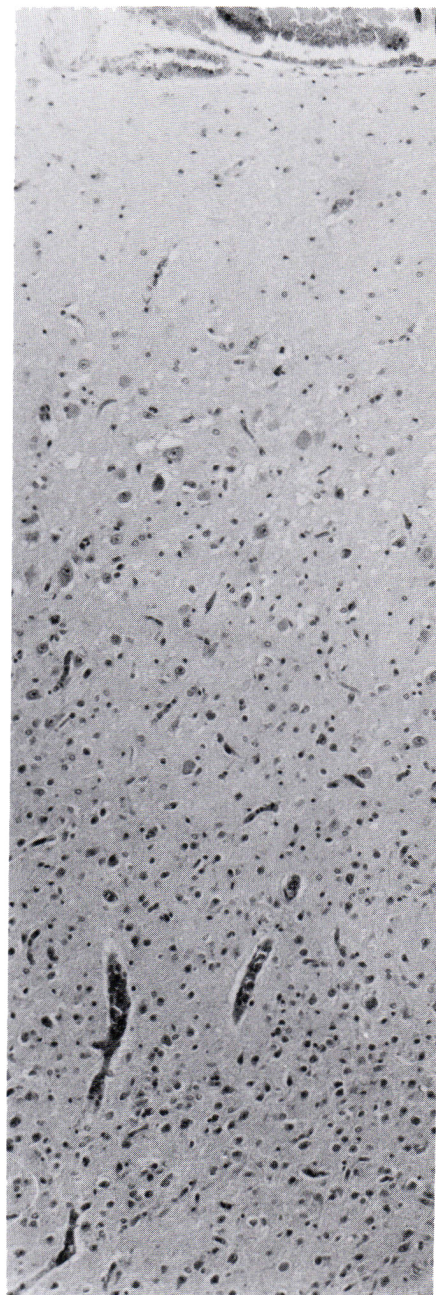


Figure 3—Case 1. Frontal cortex showing molecular layer. (Haematoxylin and eosin x 150.).

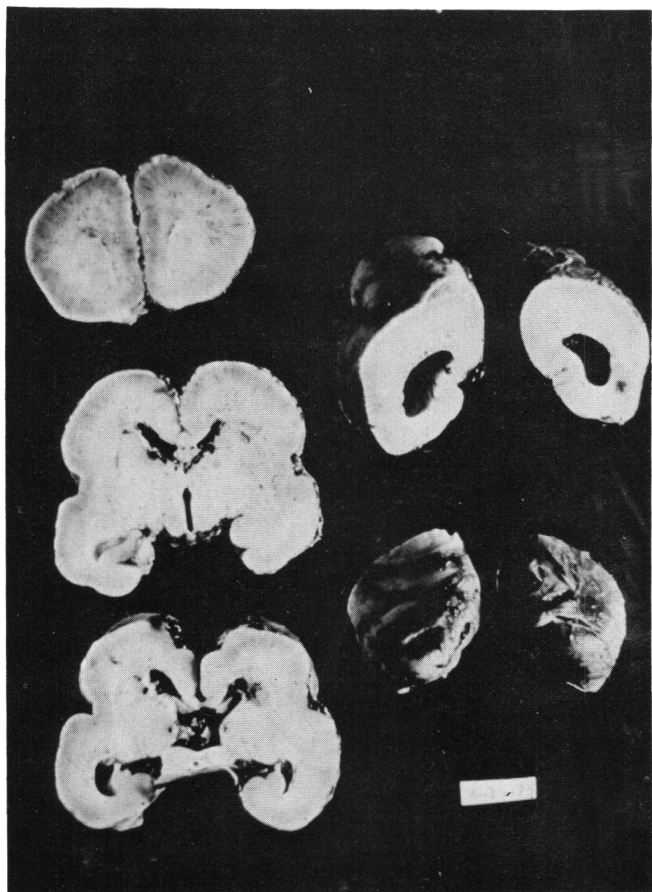


Figure 2—Case 1. Coronal sections of cerebral hemispheres.

Figure 5—Case 2. Hemisphere section. Note paucity of myelin in centrum semiovale (Luxol fast blue — cresyl violet).



lissencephaly could not be made in these four other children. The living retarded cousin's dermatoglyphics also showed ten whorls.

Necropsy showed the immediate cause of death was bronchopneumonia. There was an increased number of obsolescent glomeruli in the kidney. The brain weighed 98 grams (normal for age 516 grams). The thickened leptomeninges contained tortuous, congested vessels. It was difficult to strip the leptomeninges from the underlying brain. The underlying hemisphere was smooth without gyri or sulci. There was a smooth depression in the region of the insula. Coronal sections of the cerebral hemispheres again showed the smooth outer surface of the brain (Fig. 2). The cortex

could not be differentiated from the as yet unmyelinated centrum semiovale and it was impossible to discern the internal architecture of the central nuclei. The ventricles were slightly enlarged. Horizontal sections of the brainstem and cerebellum showed poor myelination.

Microscopic examination showed abnormal cortex. It had four layers. The first corresponded to a normal molecular layer. Next there was a superficial broad cellular band which was two to three times the width of the molecular layer. In this layer most of the neurons were small, but large pyramidal neurons were scattered through it at all levels, including superficially (Fig. 3). Most of the large pyramidal neurons were in this layer. The third layer was cell poor.

The fourth was cellular. The third and fourth layers together were about as thick as the molecular layer. Occasional large pyramidal neurons were present in the third and fourth layers. There was neuronal loss and gliosis in the hippocampal end plate and Somer's sector, attributed to seizures.

The unmyelinated white matter under the cortex contained many myelination glia and occasional large heterotopic neurons. A Luxol fast blue (LFB) stain showed slight myelination of the centrum semiovale with more myelin in the region of the internal capsule. Myelination in the hemisphere was consistent with age.

The basal ganglia and thalamus were normal. Large round masses of

heterotopic grey matter lay under the ventricular surface.

Sections of the brainstem were normal. Heterotopia of the inferior olives was not present. Brainstem structures were poorly myelinated. The posterior columns in cervical cord were not as well myelinated as they should have been for age, though nerve roots were normally myelinated.

The external granular layer of the cerebellum was absent except in a few foci deep in the hemispheres. Cigar shaped masses, interpreted as abnormal dendrites, were present in the molecular layer. Purkinje cells were normal. There was a striking loss of cells of the internal granular layer (Fig. 4B). There was a paucity of neurons in the dentate nucleus. A few huge neurons about twice the size of dentate neurons, lay between the dentate nucleus and ependyma. The cerebellum, cerebellar pedun-

cles and olivary fleece were poorly myelinated.

Case No. 2.

This infant was the first born to a healthy woman. Pregnancy and delivery were normal. There was an undocumented history of placental insufficiency, but the normal birth weight of 3.4 Kg. was against this. Neurological problems were suspected almost from birth because of poor feeding and slow development.

At four months of age he was investigated at the Montreal Children's Hospital. He had a small face and deformed, lowset ears. Pneumoencephalogram showed moderate enlargement of the entire ventricular system and a cyst of the septum pellucidum. EEG during light sleep showed minor asymmetry with slightly higher voltage on the right and better-developed spindles over the right as compared to the

left. During deep sleep, bilateral symmetrical slow high voltage activity was present. During the waking state there was no alpha activity.

He was first admitted to the Hospital for Sick Children, Toronto at ten months of age because of dyspnea and difficulty in feeding. At six months of age he had developed seizures which were treated with phenobarbitol, diphenylhydantoin and primidone. At ten months he could not sit or control his head, could not pick up objects or focus his eyes. Admission examination showed the head circumference was 42 cm., and crown-heel length was 71 cm. The skull was asymmetric, with right frontal bossing and an open fontanelle. The pupils were round, equal, symmetrical and reacted to light and accommodation. The fundi were normal. He had a slight strabismus of the right eye. Cranial nerves were otherwise nor-



Figure 4a

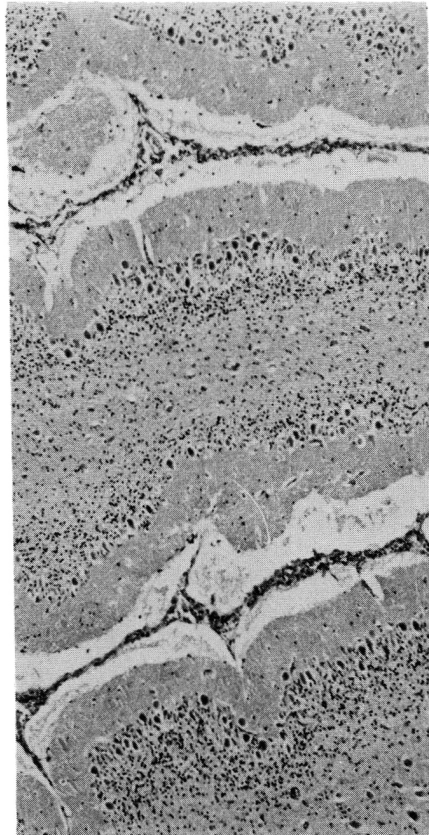


Figure 4b

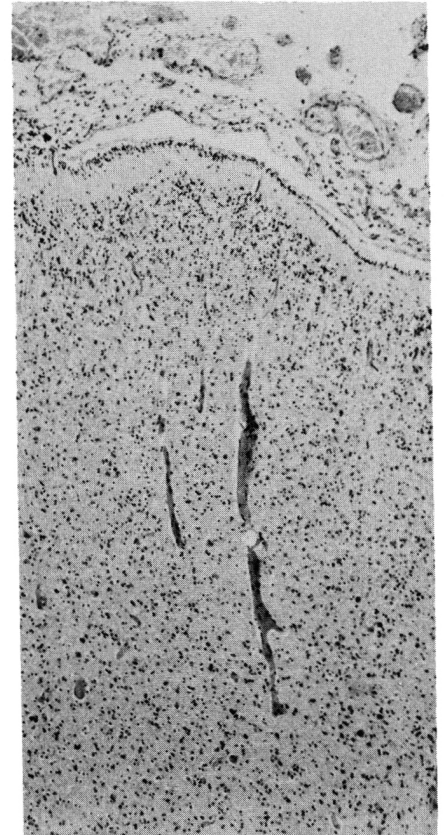


Figure 4c

Cerebellum (a) Normal 2 month infant "crib death". (b) Case 1. Note paucity of internal and external granular layer. (c) Case 3. Note abnormal surface, cell loss. (All microphotographs haematoxylin and cosin x 60.)

mal. He responded only to manipulation and painful stimuli. He had an abnormal cry. Sucking was poor. He had little spontaneous movement. He was hypotonic with bilaterally sluggish reflexes. The feet were held in dorsiflexion. Chromosome analysis showed a normal male 46XY pattern. He died at seventeen months of age in a chronic care institution after multiple chest infections.

The parents were unrelated. Two subsequent pregnancies resulted in the birth of two normal boys.

Gross examination at necropsy showed a child with peculiar facies and lowset ears. The immediate cause of death was a suppurative bronchopneumonia. Bilateral infarcts of the kidneys and stenosis of the left ureterovesical junction were present.

The brain weighed 758.3 grams (normal for age, 1010 grams). The leptomeninges were thickened, grey and hard to strip from the fixed brain. The brain was firmer and harder than normal. No sulci or gyri were present, except in the temporal lobes where a few shallow grooves were present (Fig. 5). Sections showed no normal cortex; the whole cortical area appeared wider and whiter than normal. In the white matter there were abnormal opaque white masses and whorls which stood out against a more translucent

background. The basal ganglia, thalamus and internal capsule appeared normal. The ventricles were large, the aqueduct dilated. The pyramids were present, the inferior olives were poorly-formed.

Microscopic examination of the cortex showed a thin molecular layer, beneath which there was a continuous mass of neurons, without lamination. Neurons were pyramidal, of moderate size and mixed randomly with a population of smaller neurons. This sheet of neurons extended towards the ventricles. Tapering bands of myelin radiated into this grey matter from around the ventricles, and surrounded periventricular nodules of heterotopic grey matter (Fig. 6). In the occipital lobes there were foci of ill-defined lamination where a thin outer cellular layer was separated by a narrow acellular band from the deeper cortex which extended down to a narrow band of myelin surrounding the ventricles. This occipital cortex contained the same random mixture of moderate-sized pyramidal and smaller neurons. The hippocampus was normal. The basal ganglia and thalamus were normal. Claustrum and external capsule were absent. Sections of the brainstem were normal except for heterotopia of the inferior olive (Fig. 7). The pyramids were normal. Sections of the cerebellum showed almost complete loss

of the Purkinje cells, increased numbers of Bergmann astrocytes and decreased internal granule cells.

Urine recovered at necropsy showed a normal amino-acid chromatogram.

Case No. 3

This female infant was born to a 35-year-old Gravida iv, Para i woman whose first two pregnancies had ended with spontaneous abortions. The third pregnancy produced a 6 lb. 2 oz. child after 35 weeks gestation. Our case, the result of the fourth pregnancy which was apparently uncomplicated and lasted 35 weeks, was a female infant delivered spontaneously. The baby required intubation and resuscitation. Her condition remained poor; she died at several hours of age.

Necropsy showed a "small for dates" infant. The head circumference was 26.5 cm., crown-heel length, 38.8 cm. and weight, 1465 grams. Facies was normal. Inclusions characteristic of CMV were widespread in lung, liver, pancreas, kidneys and adrenals. There was hepatosplenomegaly with mild periportal fibrosis in the liver, excessive extramedullary hematopoiesis in liver and pancreas and interlobular pancreatic fibrosis. The hypoplastic adrenal glands showed loss of fetal cortex.

The brain was smaller than the cranial cavity and weighed 45.5

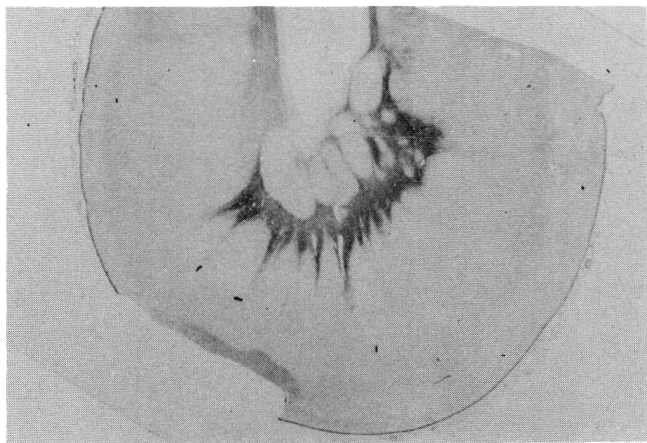


Figure 6—Case 2. Section around occipital horn of lateral ventricle. Note masses of heterotopic grey and radiating dividing bands of myelin which gave the brain an appearance of whorling. (Luxol fast blue — cresyl violet x 5.4).

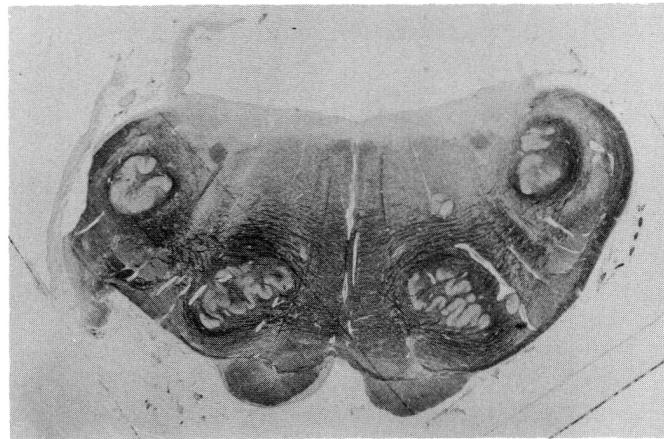


Figure 7—Case 2. Heterotopias of inferior olivary nuclei in medulla (Luxol fast blue — cresyl violet x 6).

grams, one-sixth of the normal weight expected at 35 weeks gestation. The cerebral hemispheres were symmetrical, small and smooth without sulcation. The leptomeninges were thickened, brown and wrinkled with prominent, congested, tortuous vessels. The basilar artery appeared disproportionately large and tortuous for the size of the brain. Coronal sections of the cerebral hemisphere showed dilated ventricles. The ventricles were 1 cm. in diameter, cerebral mantle 0.5 cm. in thickness. The inner surface of the ventricles was rough and granular. There was a chalky, yellow, calcific change in the cerebral parenchyma around the ventricles for a depth of 2-3 mm. This area had a sharply-defined irregular edge with a tendency for the calcific deposits to extend as small rays into the cerebral parenchyma (Fig. 8). Basal ganglia and thalamus were free of these deposits. There was no differentiation between cortex, unmyelinated parenchyma and central nuclei. In the brainstem the same chalky, calcific, yellow deposits were present around the aqueduct, in the colliculi, in the tegmentum of the pons under the ventricular lining and in the medulla at about the site of the Xth and XIIth cranial nerve nuclei. The remaining cerebral tissue was discolored and the normal architectural markings of the brain were obscured.

Microscopic examination showed the large leptomeningeal vessels were more prominent than expected for the size of the brain. There was a thick layer of astroglial scar on the surface of the brain (Fig. 9). This scar was laid on the brain like icing on a cake and contained an excessive number of dilated vessels which progressed radially down through the cortex. Occasional plasma cells were present near vessels. The vessels tended to break up the cortical lamina into clumps of neurons disposed vertically to the surface of the brain. Six layers of cortex were not identifiable. There was extensive, patchy neuronal loss. In some places large neurons corresponding to those in layer five were in a relatively normal position, while in other places neurons of similar size were present much more superficially. Small calcific masses were present in the remains of cortex. Beneath the cortex there was a band of unmyelinated white matter in which occasional hypertrophied astrocytes and small unidentifiable dark nuclei were present. Surrounding the ventricle there was a broad band of calcification extending up to a third of the width of the cerebral mantle. The calcifications varied from fine and dust-like to large masses up to 100 μ in diameter. The ependymal lining was lost except over the basal ganglia where a few buried subependymal rosettes were seen. The

ependymal lining over thalamus had been buried by a broad strip of astroglial scar. There were small scattered foci of neuronal loss, gliosis and calcification in the basal ganglia and thalamus. Sections of the brainstem showed such severe neuronal loss, gliosis and calcification that the normal structures were unidentifiable. There was almost total neuronal loss in the inferior olivary nuclei. The corticospinal tracts were small. There was loss of fibers forming the middle cerebral peduncles. One dentate nucleus was extensively calcified, the other relatively spared. The cerebellar folia were abnormal, the surface of the cerebellum was knobby. External granule cells were reduced in some folia with variable loss of Purkinje cells and marked loss of the internal granular layer (Fig. 4C). In the medulla there were many macrophages around vessels, producing a granulomatous appearance. Inclusions at the light microscopic level and viral particles at the ultrastructural level could not be identified in the brain, though found easily in other viscera.

DISCUSSION

Our first two cases showed most of the features of "lissencephaly syndrome" (Daube and Chou, 1966). The head of Case 1 was small and the high forehead of the syndrome was lacking, but the slightly hollow temples and receding, small jaw

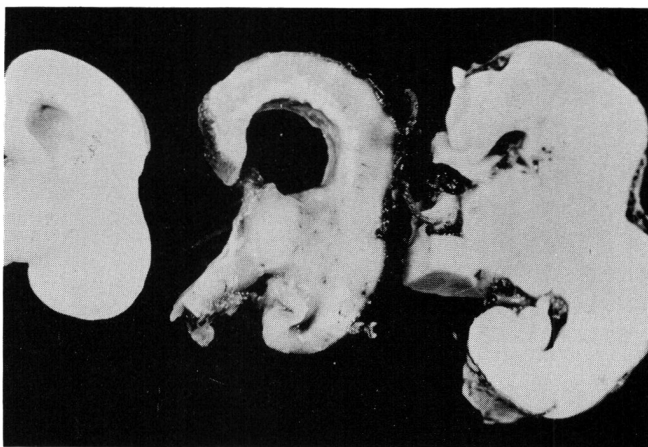


Figure 8—Hemisphere sections for comparison. Left: normal 16-18 week twin fetus dying of chorioamnionitis following amniocentesis. Middle: Case 3. Note smooth outer surface, calcium around ventricle. Right: Case 1.

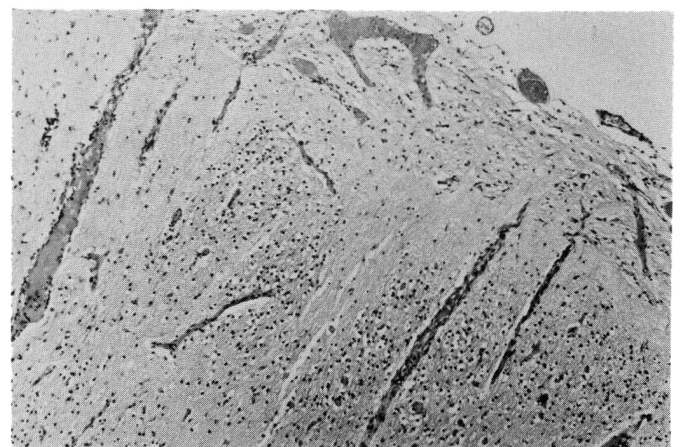


Figure 9—Case 3. Frontal cortex showing subpial layer of astroglial scar, large arteries radiating into cortex (Haematoxylin and eosin x 150).

were present. The facies of Case 2 was not described in detail. Case 1 showed the four-layered cortex usually described in lissencephaly, no olivary heterotopia, heterotopias of neurons in the cerebellar roof nuclei, and loss of many cerebellar neurons, an unusual finding. Case 2 showed no cortical lamination, just a broad band of cells and resembled Miller's cases (1963). The loss of cerebellar neurons was attributed to seizures in Case 2.

Lissencephaly has been regarded as a failure or arrest of neuronal migration. During embryogenesis, neurons arrive at the cortex by an "inside-out" migration. The deepest cortical layer migrates first; the superficial layers progressively migrate past the deeper layers to take their place beyond the first-migrating deep layers (Sidman and Rakic, 1973). Studies of lissencephaly with the Golgi technique by Williams et al (1975) showed that the polymorphic neurons of layer VI lay deep, while pyramids of layers III to V had arrived normally, though the most superficial pyramids in layer III tended to be upside-down. They found neurons of all classes, not segregated by class into laminae, in the heterotopic zone. Cortical and heterotopic neurons had well-differentiated dendritic arbors, and were rich in spines. They concluded that cell class was an inherent property of the post mitotic neuron, independent of cell position, but segregation of cells in lamina occurred only if cortical migration was complete.

The factor causing lissencephaly probably operates at 50-100 mm. fetal state (Hanaway et al., 1968) or between the second to fourth fetal month (Crome, 1956), or earlier (Brun, 1965). At the same time associated anomalies of the inferior olive and cerebellar nuclei occur, when cells are migrating from the rhombic lip at the tenth to fifteenth fetal week (Hanaway and Netsky, 1971). As Crome (1956) has pointed out, the arrest in pachygyria probably occurs at an earlier fetal stage than microgyria. Structures such as the pulvinar, formed at a later developmental stage (Sidman and

Rakic, 1973) are normal in lissencephaly.

The brain in lissencephaly is small, the surface smooth. Part of the smallness is due to lack of white matter in the centrum semiovale, but probably total numbers of neurons are also deficient. It is hard to believe that a normal complement of neurons remains in the deep heterotopic masses. Neuronal multiplication has been said to be complete by the fifth lunar month, though migration to the cortex probably continues after this (Sidman and Rakic, 1973). A factor operating before or at about the sixteenth to eighteenth fetal week might account for both the cortical abnormality and the small size of the brain. Since neurons of all classes remain in the deep heterotopic masses, (Williams et al., 1975) whatever happens is probably not just a simple loss or destruction of neurons destined for the most superficial cortical layers.

Lissencephaly could be caused by a defect intrinsic to neurons, perhaps inherited, or some extrinsic toxic, destructive or metabolic factor. Of the twenty cases referred to by Dieker et al (1969) and two subsequent cases (Harper, 1967; Damska and Schmidt-Sidor, 1971), there have been five cases in two kindred (Daube and Chou, 1966; Dieker et al., 1969; Miller, 1963). Our Case 1, occurring in a third kindred, is the result of a first cousin marriage and further strengthens the supposition that lissencephaly might be divided into a primary hereditary lissencephaly and a secondary lissencephaly-pachygyria which could be intrinsic and inherited or caused by some extrinsic factor acting on the developing cerebrum at the critical gestational time. It is probably significant that all three kindred show the severe infantile "lissencephaly syndrome", a term which should be reserved to this rarity. The hereditary pattern postulated would fit with causation by an autosomal recessive gene. The occurrence of sporadic cases does not rule out autosomal recessive transmission, for it must be remembered that the statistical chance of small families of two or three children

showing more than one case of a severe autosomal recessive disorder is low. More extensive family histories in so-called sporadic cases might produce more evidence in favor of a rare recessive gene if distant cousin relationships were established. On the other hand, the family reported by Reznick and Alberca-Serrano (1964) was clinically less severe and showed combined agyria and pachygyria. Since the mother had hypertelorism and epileptiform seizures, McKusick (1971) suggested the possibility of sex-linked recessive inheritance in that family. Holmes (1974) has suggested that cebocephaly may represent an example of genetic heterogeneity; similarly, the differences in lissencephaly and pachygyria might also represent an example of genetic heterogeneity or of variable gene expressivity. Even if lissencephaly is an autosomal recessive trait, the mechanism which results in neuronal migration failure has not been identified. Chromosomes, when examined in these patients have been normal (our Cases 1 and 2, Daube and Chou, 1966).

It could be postulated that lissencephaly could be caused by factors extrinsic to neurons such as viral infections, radiation, some toxic substance ingested by the mother, or a metabolic disturbance. Antenatal CMV infection has resulted in microgyria (Crome and France, 1959; Navin and Angevine, 1968), though the microscopic appearance is not entirely typical of the classic four-layered microgyric cortex (Crome and France, 1959). Our Case 3, however, appears to be unique. It is included to compare the morphology of a small, smooth brain where the lesion was due to antenatal infection, in this case by CMV, with the classical cases of lissencephaly. The final appearance of this brain was due to destruction of cells. Though the brain was one-sixth the size expected at 35 weeks gestation, it had been larger at some time, for it was smaller than the calvarium, the basilar artery was bigger than expected for the size of the brain and there had been extensive periventricular necrosis which had calcified. Cortical neurons were ar-

ranged in clumps divided by penetrating arteries. These clumps were reminiscent of the neuronal arrangement in ulegyria, a destructive lesion due to perinatal hypoxia-ischemia (Norman, 1966). The appearance of our case suggests that the infection occurred early, perhaps at 18-22 weeks. There had been random destruction of neural and glial elements with marked cell loss. If the infection occurred as early as postulated, there may have also been a disturbance of migration along the radial glial guides described by Rakic (1972) for neuronal migration may continue beyond midgestation (Sidman and Rakic, 1973). It is unlikely that antenatal viral infection is a cause of classical lissencephaly, for viral infections tend to be destructive with production of cysts and scars and stenosis as shown in experimental infections (Osburn et al., 1971; Johnson, 1972). Rubella, a known teratogen, does not produce structural malformations of the brain (Rorke, 1973).

Polymicrogyria is another condition with a four-layered cortex also ascribed to failure of neuronal migration. Recently, Levine et al (1974) suggested that the microgyria occurring with porencephaly might represent a form of laminar cortical necrosis occurring as a result of failure of arterial perfusion during gestation. Stewart et al (1975) made the same suggestion for the pathogenesis of a case of combined pachygyria and lissencephaly. They based this on the laminar character of the cell sparse region plus the topographic distribution of the most severely involved cortex posterior to the distal fields of perfusion of the major cerebral arteries. Our cases of lissencephaly do not show this topical distribution and Case 2 does not have a four-layered cortex, so it is hard to visualize perfusion failure as the cause in our cases.

Other possibilities are some toxic substance ingested by the mother, a metabolic disorder or radiation. There is little evidence to support any of these suggestions, though it has been reported that radiation has produced disturbed neuronal migration in rats (Cowen and Geller,

1960). Disorders of amino-acid metabolism have been suggested, however our Case 2 had normal urine amino-acid chromatogram.

In summary, there is some evidence to support the theory that severe infantile lissencephaly may be inherited as an autosomal recessive trait. If so, variations between different cases may represent an example of genetic heterogeneity or varying gene expressivity. In other cases, or those where a combination of lissencephaly and pachygyria occur, some acquired extrinsic factor may operate, but at present it is not known what it is.

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