Cystic degeneration of the telencephalic subependymal germinal layer in newborn infants

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SYNOPSIS Cystic lesions were found in the telencephalic germinal layer of 12 newborn babies. According to their location, the cysts could be divided into three groups: anterior, middle or thalamostriate, and posterior. The histological appearance of all cysts was essentially the same, but in three cases the germinal layer had a peculiar alveolar type of microcystic degeneration. A constant feature was the presence in the cyst wall of small white granulations composed of germinal cells and/or glial tissue. Cystic degeneration of the germinal layer was usually bilateral and sometimes quite extensive. After the involution of the germinal layer, these lesions are likely to persist as subependymal cysts, characterized by their specific location and the presence of glial granulations.

It is the purpose of this paper to describe cystic lesions of the telencephalic subependymal germinal layer in newborn infants. Brief reference to subependymal or germinal layer cysts has been made by a number of authors but some of the histological characteristics of such lesions are yet to be defined. The telencephalic germinal layer plays an important role in neonatal neuropathology. Bleeding into this structure is probably the single most common abnormality found in brains of premature babies. However, our knowledge about the anatomy, physiology, and pathology of this layer is very limited. Therefore, it seems desirable to bring up for discussion one of the few recognizable morbid changes other than haemorrhage affecting this structure.

During the second half of gestation, the telencephalic subependymal germinal layer is a periventricular, densely cellular, multistratified layer of undifferentiated cells, which is separated from the ventricle only by the unicellular lamina of the definitive ependyma. The thickness of the germinal layer is characteristically greater over the ventricular aspects of the striatum. Due to migration of its cells, the layer gradually disappears with advancing fetal age.

METHODS

Included in this investigation were 10 newborn babies in whom cystic lesions were found macroscopically in the telencephalic germinal layer. In two additional cases, the diagnosis of germinal layer cysts was made histologically. The brains were fixed in 10% formalin/saline solution. Blocks were taken from all cysts as well as from associated lesions and other representative areas of the central nervous system, and embedded in paraffin, sectioned and stained with the usual neuropathological techniques. The pertinent clinical data of all cases are included in Table 1.

RESULTS

MACROSCOPIC FINDINGS For convenience of description, the cysts can be divided into three groups according to their location in the germinal layer: anterior, middle or thalamostriate, and posterior cysts. The distribution of cysts in the different cases as well as the associated pathological findings are summarized in Table 2.

Anterior germinal layer cysts were present in
eight babies (cases 1–6, 8, 9), being bilateral in six cases. The cysts were located immediately in front of and/or above the anterior pole of the head of the caudate nucleus. In coronal sections they varied in size from a small horizontal slit, about 1.5 mm in length, to large cavities measuring up to about 10 mm in diameter. Some cysts were loculated by septa. In most cases, variable numbers of tiny white granulations were present in the cyst wall. In two cases with neighbouring haemorrhages (cases 2 and 6), there was evidence of bleeding into the cysts. In one case with bilateral cysts (case 9), the ependyma overlying the cysts was torn and there was wide communication between the cysts and the ventricle.

Middle or thalamostriate cysts were found in five babies (cases 7, 9–12), and were bilateral in four of them. Two types of cyst were found at this level: (1) in cases 11 and 12, the germinal layer, bilaterally, was dark and had a peculiar spongy appearance. Small clusters of tiny cysts could be recognized macroscopically in some areas in case 11. The diagnosis of cystic lesion could not be made macroscopically in case 12, and was not even suspected in case 10, in which the micro-cysts were overshadowed by local
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germinal layer haemorrhages. (2) In the remaining two infants (cases 7, 9), the cystic nature of the lesions was obvious macroscopically. They looked like collapsed tents at the level of the anterior part of the thalamostriate sulcus. The ventricular walls of the cysts were usually redundant, suggesting that when distended they would protrude into the ventricle. The cysts extended to a variable distance along the thalamostriate sulcus, and also had prolongations over the ventricular aspect of the head of the caudate nucleus, anterior to the foramen of Monro. The larger cysts measured up to 2 cm in length. White granulations were rarely seen macroscopically in the walls of the thalamostriate cysts. In case 7, there was unilateral hydrocephalus on the side of the larger thalamostriate cyst. The foramen of Monro was not sealed with adhesions but the cyst had possibly been acting as a valve.

A posterior cyst was found in one case only (case 9), and in this brain there were also bilateral anterior cysts, as well as one thalamostriate cyst on the right side. The posterior cyst

FIG. 3 Case 9. Coronal section of right cerebral hemisphere, rostral to the anterior pole of the head of the caudate nucleus. Lined by ependyma, the lateral ventricle is seen medial (left) to the cyst, which has apparently expanded into the periventricular white matter, beyond the limits of the gliosed germinal layer. There are a few glial granulations on the cyst wall. At a more posterior level this cyst was in communication with the ventricle (not shown). H and E, ×9.

FIG. 4 Case 12. Alveolar type of cystic degeneration. Germinal cell granulations of variable size are present on the walls of every microcyst. Germinal cells, glial tissue, and blood vessels have grown into the lateral ventricle (left) through the extensively disrupted ependyma, which is seen forming multiple rosettes. Blood vessels are normally cufféd by germinal cells. Nissl, ×45.
### TABLE 1

**SUMMARY OF CLINICAL DATA IN PRESENT SERIES OF CASES**

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<th>Case no.</th>
<th>Sex</th>
<th>Age (h)</th>
<th>Gestation (wk)</th>
<th>Birth weight (g)</th>
<th>Complications of Pregnancy</th>
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<th>Respiratory distress syndrome</th>
<th>Apnoeic attacks</th>
<th>Other complications</th>
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### TABLE 2

**GERMINAL LAYER CYSTS AND ASSOCIATED PATHOLOGICAL FINDINGS IN PRESENT SERIES OF CASES**

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<th>Case no.</th>
<th>Maudsley no.</th>
<th>Brain weight, fresh (g)</th>
<th>Germinal layer cysts (R = right, L = left)</th>
<th>GLH*</th>
<th>IVH†</th>
<th>Multiple CNS haemorrhages‡</th>
<th>Periventricular leucomalacia§</th>
<th>Kernicterus</th>
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* Germinalt layer haemorrhage. † Intraventricular haemorrhage. ‡ Multiple intracerebellar, leptomeningeal, and intracerebral haemorrhages, often associated with disseminated intravascular coagulation (Chessells and Wigglesworth, 1970). § Coagulation infarcts, usually multiple and more common in the periventricular region (Banker and Larroche, 1962). ¶ Hyaline membrane disease.
was larger at the level of the ventricular confluence, behind the descending portion of the tail of the caudate nucleus. It extended forward for about 0.5 cm above the caudate nucleus and along the lateral angle of the body of the lateral ventricle. There was a tiny perforation on its ventricular wall.

**MICROSCOPIC FINDINGS** Germinal layer cysts were histologically characterized by the following features: (1) They were within the germinal layer and sometimes spread extensively through this structure. The smaller cysts were contained within the normal boundaries of the germinal layer, but the larger cysts tended to bulge into the ventricle (Fig. 1); some had expanded into the neighbouring white matter. (2) In cases where the germinal layer was relatively well preserved, the walls of the cyst were formed by the parenchyma of the germinal layer. In cases in which this was gliosed or depopulated, the walls were formed by glial tissue. (3) A feature of all germinal layer cysts was the presence of small polypoid structures corresponding to the white granulations described macroscopically. In some cysts these granulations were very numerous, but in others, particularly in the large gliosed lesions, they were rather sparse. Most granulations consisted of dense, rounded aggregations of small, dark germinal cells (germinal cell granulations) (Fig. 2). In the gliosed, probably older cysts, some germinal cell granulations were partially gliosed, while other granulations were coniform and consisted of proliferated astrocytes and glial fibres (glial granulations) (Fig. 3). Some of these contained small nests of germinal cells. Some germinal cell granulations had a rim or core formed by pale eosinophilic matrix. Small PAS-positive areas were seen near the base of some granulations.

Some features of the spongy thalamostriate lesions in cases 10, 11, and 12, were significantly different. There was no large cavitation as in the other cases, but the area was disrupted by a conglomeration of numerous tiny cysts which gave the germinal layer an alveolar appearance. The alveoli varied in size and some of the larger ones were apparently the result of coalescence of smaller cysts. In case 12, the germinal cell granulations were quite numerous but there were only one or two in the smaller microcysts. Some of these cavities were almost filled by the granulation(s). The germinal layer was moderately gliosed and occasional cells were distended by PAS-positive material. The overlying ependyma was extensively disrupted. Germinal cells, glial tissue, and blood vessels had grown through the breaks of continuity and proliferated over the ventricular wall. The margins of buried fragments of ependyma curled up and formed rosettes (Fig. 4). Occasional glial nodules were present in the neighbouring caudate nuclei and other areas. Scattered perivascular calcification was seen involving the striatal vessels. No micro-organisms or inclusion bodies were found.

Although germinal layer haemorrhages were present in eight babies, the cysts were involved by fresh bleeding in only three (cases 2, 6, 10). In case 6, only a small, loculated, caudal part of the cyst had been involved by an adjacent germinal layer haemorrhage. In case 2, the bleeding into the anterior germinal layer and the cyst was a small part of an enormous haemorrhage which extended from the thalamostriate region to the white matter of the anterior frontal lobe.

**DISCUSSION**

The cystic degeneration of the subependymal germinal layer described here is frequently bilateral (10 out of 12 cases) and may be quite extensive. In case 9, most of the germinal layer had been replaced on one side by large anterior, middle, and posterior cysts. It seems that once formed, the cysts tend to increase in size and spread through the germinal layer, which apparently offers little resistance to expanding lesions. In contrast, the cysts seem incapable of eroding the immediately adjacent basal ganglia. The ganglionic wall of the cysts is characteristically convex and outlines the normal contour of the caudatum and thalamus which remain intact even when the cysts have bulged inside the ventricle (thalamostriate cysts) or expanded into the neighbouring white matter (anterior and posterior cysts).

In general, except for the alveolar type of cystic degeneration (cases 10, 11, 12), the diagnosis of germinal layer cysts is straightforward macroscopically. However, the more common variety of germinal layer cyst in this series, the anterior, may be missed unless a slice...
is made at about the level of the anterior pole of the head of the caudate nucleus. Cysts were not diagnosed macroscopically in two of the cases with alveolar microcystic degeneration (cases 10, 12), but, in case 12, the germinal layer had a peculiar spongy appearance and so it might be possible to recognize similar future cases on naked eye examination.

The incidence of germinal layer cysts cannot be stated at this time. During 1969, germinal layer cysts were found in seven cases (7.7%) out of a total of 90 examined newborn brains. It is possible that a higher incidence would be found by systematic histological examination of the germinal layer.

Germinal cell and/or glial granulations were present in all the germinal layer cysts of this series and probably can be considered to be a distinctive characteristic of these lesions. The coexistence of germinal cell and glial granulations in the same cyst, as well as the finding of mixed forms (partially gliosed germinal cell granulations or glial granulations with nests of germinal cells), strongly suggest that one is the product of maturation of the other. From their general appearance, it seems that the germinal cell granulations are not surviving islands of a disrupted germinal layer but the result of proliferation of germinal cells in contact with the cyst cavity. Whether this proliferation is induced by the chemical composition of the cyst fluid, by the physical properties of the surface, or by other factors is unknown, but similar growths may occur in other parts of the infantile central nervous system in contact with a fluid-filled cavity. Perhaps the more common example of this is the supraependymal proliferation of germinal cells in areas where there has been a disruption of the ependymal lining.

It is important to differentiate this form of cystic degeneration of the germinal layer from other varieties of cystic lesions that can be seen in the periventricular region. Subependymal cysts are seen in the brains of older infants in whom the germinal layer is no longer present; many are morphologically similar to germinal layer cysts and contain glial granulations. Some of these subependymal cysts are likely to be, in fact, gliosed germinal layer cysts in infants surviving the neonatal period. Ependymal cysts are characterized by their epithelial wall. Post-necrotic cavitation, the result of infarction and/or haemorrhage, is not rare in the periventricular region of older infants, but these lesions are not restricted to the germinal layer and usually contain collections of macrophages full of lipid, pigment or debris. Lesions similar to état criblé are seen in infantile brains but their appearance is quite different from that of germinal layer cysts. There should be no difficulty in differentiating germinal layer cysts from intraventricular and choroidal cysts that may be seen in cases of adhesive ependymitis (Merle, 1910). Periventricular diverticula may occur in older infants secondary to traumatic tears of the ventricular wall, including those after ventricular needle puncture, but these lesions could hardly be confused with germinal layer cysts.

From the present findings there is no obvious indication as to the pathogenesis of the germinal layer cysts. Schwartz (1961) briefly described subependymal cysts which he considered the sequela of local haemorrhage. In the present series, the apparent incidence of germinal layer haemorrhage (66%) is higher than in our general neonatal material (about 50%), but the number of cases involved is too small (Table 2). In only three cases was there evidence of bleeding inside the cysts, but in all the haemorrhage was recent and the cysts were already well-formed. In most cases there is no correlation between the site of the haemorrhage and the cysts. The majority of cysts were anterior, while most of the germinal layer haemorrhages originated in the thalamostriate region.

A number of other pathological abnormalities, like periventricular leucomalacia (Banker and Larroche, 1962), multiple haemorrhages associated with disseminated intravascular coagulation (Chessells and Wigglesworth, 1970), and malformations were present in several of our cases, but their incidence in this small series was not different from that in our general neonatal material. Subependymal or germinal layer cysts have been frequently found in cases of congenital rubella encephalopathy (Anzil, 1967; Gilles, 1967; Rorke and Spiro, 1967; Stadlan and Sung, 1967; Shaw, 1973), as well as in cytomegalovirus disease (Shaw, 1973; personally examined case, Maudsley No. 11-57). In the rubella cases, as well as in our own micropolygyric case of cytomegalovirus disease, the
cysts were located in the thalamostriate region and there was evidence of widespread vascular involvement. Though the possibility of direct viral invasion of the germinal layer inducing the cystic change should be considered in cases such as these, as suggested by Shaw (1973), it is also conceivable that some sort of circulatory disorder could be a common underlying factor in all cases. Similar cysts have also been seen in conditions such as leuencephalopathy associated with congenital lactic acidosis (Farkas-Bargeton et al., 1971), arrhinencephaly (Shaw, 1973; our case 9), pachygyria (Bargeton, 1959), and agyria (unpublished case, Maudsley No. 5446). It is possible that cystic degeneration of the germinal layer represents a non-specific type of reaction of this structure to a variety of pathological factors.

With the exception of blockage to Monro’s foramen by large thalamostriate cysts, such as apparently occurred in case 7, the possible clinical implications of lesions involving the germinal layer are uncertain. Little is known about the destiny of the cells originating in the telencephalic subependymal germinal layer during the second half of gestation. It is generally thought that such cells will mostly generate glial cells. Evidence has been presented by Rakic and Sidman (1969) suggesting that part of the pulvinar, a highly developed structure in the human brain, may originate from late migrating telencephalic germinal cells. The possibility of cerebral hypoplasia (defective myelination) resulting from devastation of the telencephalic germinal layer late in gestation was originally suggested by Patten and Alpers (1933) in cases of haemorrhage in that region. It is reasonable to think that destruction of the subependymal germinal layer may somehow impair the normal development of the brain. However, further cases should be investigated to find out whether or not cystic degeneration of the germinal layer may occur in the absence of other lesions, such as were present in our cases. Unless the damage is restricted to the germinal layer, the resulting clinical manifestations cannot be attributed to lesions of that structure.

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