MULTILOCULAR ENCEPHALOMALACIA*

BY

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The genesis of cavitation in the central nervous system presents an important problem. This holds true for porencephalia, syringomyelia, cystic tumours, Wilson's disease, and for cases of multilocular encephalomalacia. The last condition has been described under many different names which are summarized in Table 1. I have accepted the name multilocular encephalomalacia as it combines in two words the main characteristics, namely the multiple cavity formation and the softening. Some investigators have concerned themselves solely with the anatomy and physiology of this condition (Edinger and Fischer, 1913; Jakob, 1931; Verhaart, 1936), but most papers have dealt with the pathogenesis.

TABLE I

NOMENCLATURE

<table>
<thead>
<tr>
<th>Condition</th>
<th>Author</th>
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<tbody>
<tr>
<td>Porencephaly (Heschl, 1859).</td>
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<td>Encephalitis interstitalis congenita (Virchow, 1867).</td>
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<td>Hydrocephalic porencephaly (Pallau, 1901).</td>
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<td>Child without forebrain (Edinger and Fischer, 1913).</td>
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<td>Encephalodystrophia neonatorum (Segmund, 1923).</td>
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<td>Central porencephaly (Schwartz, 1926).</td>
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<td>Polyporencephaly (Brocher, 1932).</td>
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<td>Encephaloclastic porencephaly (Yakovlev and Wadsworth, 1946).</td>
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<td>Multiple cystic softening of the brain in newborn (Lumsden, 1950).</td>
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<td>Cystic degeneration of the brain (Benda, 1952).</td>
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<tr>
<td>Encephalomalacia with cavity formation (Ford, 1952).</td>
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<td>Multilocular encephalomalacia (Negrin and others, 1952).</td>
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</table>

I will summarize the findings of two cases of multilocular encephalomalacia which are interesting from an aetiological point of view.

Case Reports

Case 1.—The first child, a girl, of healthy parents was born by spontaneous vertex delivery. The mother was quite well throughout the pregnancy. Immediately after birth the child was motionless and only began to cry 24 hours later. After this she did not stop crying and slept only two to three hours a day. Soon after birth myoclonic jerks and epileptic fits started. She did not show any sign of psychic activity and the various types of epileptic fits continued in spite of anticonvulsive therapy. After a year she could swallow a little, but for the rest existed as a decorticated individual.

On examination at that age she showed the posture of decerebrate rigidity with a severe spasticity of both legs and there were athetoid movements of the hands. The skull was microcephalic and dolichocephalic. Tendon reflexes were exaggerated and there was a positive Babinski response on both sides. Laboratory investigations of the blood, cerebrospinal fluid, and urine showed no abnormalities. The Wassermann reaction was negative. At the age of 9 months an E.E.G. was made which showed almost no cortical activity whatsoever; only in the right parieto-occipito-temporal region variations of the spike-and-wave complex, 350 microvolts in amplitude, were found.

As she became older the general condition steadily grew worse. She died at the age of 1 year and 9 months from progressive impairment of the vegetative centres of the brain. Post-mortem studies were performed three hours after death.

Necropsy Findings.—The hemispheres were reduced to a flabby sac which slowly collapsed after the escape of an enormous amount of C.S.F. through an artificial opening. Macroscopically the basal ganglia, brain-stem, and cerebellum appeared normal. The total weight of the brain was 270 g. only. The blood vessels were normal.

![Fig. 1.—Transverse section through hemispheres of Case 1. Note the cysts in the white matter and the cortex and enormous dilatation of the ventricles.](http://jnnp.bmj.com/first-published-as-10.1136/jnnp.19.3.209-on-1-august-1956/downloaded-from-http://jnnp.bmj.com/)
FIG. 2.—Subependymal nodules of embryonic cells.

FIG. 3.—Group of immature cells in the neighbourhood of a blood vessel beginning cyst formation.

FIG. 4.—Loosening of fibrous glial tissue of the white matter resulting in cavitation.

FIG. 5.—Invasion of the cortex by fibrous glial tissue of the white matter.
and there were no thrombi in the dural sinuses. On transverse section the ventricles proved to be greatly enlarged, while innumerable cysts were scattered throughout the white and grey matter of the hemispheres (Fig. 1).

The alterations of the brain mantle were more pronounced in the right hemisphere than in the left and in general they were severe in the zones that myelinate late, moderate in the intermediate areas of Flechsig (Bailey and von Bonin, Fig. 1, p. 7), and very slight in those zones that myelinate earliest. In the latter zones the cysts were confined to the white matter, whereas in the intermediate zones a severe microgyria (better "sclerogyria") predominated. In the zones that myelinate still later there were no fissures and the pallium was transformed into a membrane.

Microscopic Studies.—The histological picture of the cysts as such did not differ much from that described by others. Some cysts were old and others more recent which made it evident that the process was still active at the time of death. This corresponds well with the clinical progress. In the neighbourhood of the ependyma of the anterior horns of the ventricles immature cells were found in great numbers. They were arranged in nodules, but were also more diffusely spread in the nervous tissue (Fig. 2). They could be traced from the ependyma into the direction of the cysts. Fig. 3 represents a small cavity at the border of a group of immature cells. It can be seen that the cavities do not develop exclusively around a vessel.

Serial slides were made of large parts of the brain which demonstrate well that the walls of the vessels themselves were always normal. The same immature, small, dark-staining cells were also found in the walls of large cysts and in the cortex.

The white matter was nowhere normal. It consisted of a stroma of glia cells, in which fragmented and swollen nerve fibres were embedded. Immature cells, akin to those underneath the ependyma, were dispersed among more mature ones and signs of cell division were met with. Mitotic cell division was very rare, amitotic forms being more frequent.

Evidently cysts arose primarily in the white matter as the formation of cysts was often found underneath a relatively normal cortex, but never a cystic cortex overlying normal white matter. Within more or less normal white matter homogeneous spaces devoid of axons (Bodian stain) were met with, independent of the course of blood vessels. Such spaces were altered by interstitial oedema into a loose network of glial fibres, from which by hydropic degeneration small cysts were formed. Meanwhile, at the border of the cysts a capsule of glial fibres appeared. Fig. 4 shows a cyst with some fat granule cells amidst a loose network of glial fibres, surrounded by a dense glial fibrillary capsule.

The relatively normal cortex had an embryonic appearance, as lamination was not distinct and nests of immature cells were present. A common finding was that the deepest part of the sulcus was not covered by a layer of cortex.

The cortical grey matter was invaded by fibrous glia cells, surrounding cysts in the white matter. Septa of fibrous glia isolated portions of cortical tissue (Fig. 5) which either underwent a process of softening and cyst formation or was replaced by a scar. Fig. 6 shows the fibrous glial tissue of the cortex, containing cavities filled with fat granule cells. It seems that these cells are transported to the perivascular spaces, the surrounding cysts, and the subarachnoid space. At last the cortex is replaced by a dense network of glia cells which show the same characteristics as those of the white matter between the cysts. Calcified neurons were found. The pia mater was thickened by an increase of collagenous fibres and was strongly adherent to the cortex. The blood vessels were normal and signs of inflammation were entirely lacking.

No lesions were found in the basal ganglia, the brainstem, or the spinal cord, except those resulting from secondary degeneration of the fibre tracts.

It happens that this child had an interesting family tree which was published by Biemond (1954). The cross-hatched circle (Fig. 7) represents this patient.
Two uncles of the father suffered from spinocerebellar degeneration. Moreover, four cousins of the father had some spinocerebellar disease.

The second case concerns the elder sister of the patient described under the title "Poliodysplasia Cerebri" (Kramer, 1953). The histopathological picture of poliodysplasia was the result of a disordered histogenesis, both of neurons and glial elements. These were under-developed and disorganized. A spongy disintegration of the fifth cortical layer was predominant, but the grey matter of the whole central nervous system was dysplastic and hypoplastic, whereas the white matter was relatively intact. It was supposed that these alterations were the result of a developmental disorder of the matrix, due to a toxæmia of pregnancy.

Case 2.—The mother had a similar toxæmia during the seventh month of her first pregnancy, when she was carrying the child I shall now discuss. This became worse during the last three weeks of pregnancy, necessitating its termination. The child was born in face presentation and in the beginning she was cyanotic. She cried for the first time when she was 19 days old. Thereafter there were no signs of any intellectual development. She did not fix objects with her eyes and did not react to people or stimuli, with the exception of music. She could not lift her head or trunk and a severe flexion contracture of both legs developed, necessitating orthopaedic measures. During the night she had screaming fits.

The skull was dolichocephalic and microcephalic. She was blind, with a nystagmus, but the optic discs were normal. There were spontaneous movements of the left arm only. The right arm was in extreme flexion contracture and displayed athetoid movements. Both legs were paralytic with exaggerated reflexes and a normal plantar response. During the examination she had small fits, with turning of the head and eyes to the left and jerking movements of all the limbs.

The cerebrospinal fluid was normal and other labora-

ory investigations showed no abnormalities. The Wassermann reaction was negative in the blood and C.S.F. of the patient and in the blood of both parents. It was impossible to make a good E.E.G. of the patient.

Necropsy Findings.—The child died suddenly at the age of 8 years and 9 months, and two hours after death, necropsy was performed. The weight of the brain was 810 g. The cerebellum was abnormally large as compared with the hemispheres. Blood vessels were normal and the venous sinuses were patent.

In the right hemisphere the gyri of the parietal and occipital lobes were small and firm, the frontal and temporal lobes being normal. The left hemisphere was much more affected than the right. The left frontal lobe was much smaller and the sclerogyria (ulegyria) reached rostrally as far as area 9, area 4 being small and tortuous as well. The brain substance of the left parietal and occipital lobes (especially area 19) was reduced to a thin sheet, but the left temporal lobe was relatively normal. If one compares the affected parts with the myelogenetic map of the cerebral cortex of Flechsig no distinct correlation is found between these and the
Fig. 9.-Cortical convolution traversed by strips of fibrous glial tissue.

Fig. 10.—Subependymal gliosis.

Fig. 11.—Immature cells around a blood vessel.
period of myelogenesis. On transverse section of the hemispheres small cysts of the white substance of the altered parts were opened which contained a clear fluid (Fig. 8).

Microscopic Studies.—The leptomeninges was slightly thickened by an increase of connective tissue, while signs of inflammation were entirely lacking. Cysts were only found in the white matter. They developed by loosening of the pre-existing glial tissue, in which fat granule cells took no part. At the base of a fissure the "U" fibres degenerated primarily, contrary to what is found in diffuse sclerosis. The process of cavitation was especially found in places where the bottom of the fissure reached as far as the white matter, not covered by a layer of cortex. This phenomenon was interpreted as a sign of developmental disorder of fissuration. In the affected areas of the brain the glia seemed to have a tendency to proliferate. Immature cells were met with and amitotic division of cells was not uncommon. Moreover, binucleated cells were met with. The cortex was invaded by septa of fibrous glial tissue, coming from the underlying altered white matter (Fig. 9). The cortex was transformed into a dense glial tissue, without softened or cavitation. Fat granule cells were only found in small numbers in perivascular spaces. Also in this case an excess of subependymal cells was found in the region of the head of the caudate nucleus (Fig. 10), but also more peripherally (Fig. 11).

Discussion

A survey of the literature gives the impression that different causes give rise to cavitations which are morphologically the same. This is the reason why often one cause has been held responsible for all of them. Table II summarizes different aetiological possibilities which have been defended with more or less good arguments by the authors.

A primary softening of the brain parenchyma has usually been considered to be the cause of cavitation, followed secondarily by a glial proliferation. Therefore the genesis of multilocular encephalomacular has often been related to the encephalitis interstitialis congenita of Virchow (1867) and this is the reason why blood vessel pathology has received so much attention in the past.

Others have looked for a connexion with neuropathological cases, in which cyst formation, not accompanied by large amounts of fat granule cells, is also found, such as porencephaly, Wilson's disease, or poliodystrophia cerebri progressiva infantilis.

It is rather difficult and perhaps impossible to give an explanation of the development of the cysts in these cases, as it evidently began before birth, whereas the examination took place 21 months (Case 1) and 105 months (Case 2) after birth. The earliest structural abnormalities are hidden or removed during the ripening process of the brain and the development of the histopathological processes themselves. Nevertheless I will present the following explanation.

Case 1.—The family tree of this child makes it obvious that in this family a hereditary predisposition to degeneration of white matter existed. The "degeneration" in this case became manifest as a faulty development of the intermediate layer of His, from which the white matter is derived. I suppose that this was accompanied by a faulty development of the matrix. This assumption is based on the nodules of immature cells found in the neighbourhood of the ependyma and elsewhere. We have seen that this led to an excessive development of glia cells.

Subependymal nodules of cells were also found in similar cases by Schüle (1869), Obersteiner (1902), Dahllmann (1910), Ceelen (1920), Wohlwill (1921, a and b), Schmincke (1920), Siegmund (1923, a and b), Schwartz (1924), Jakob (1931), Diamond (1934), Fischl (1899), Ceelen (1920), and Schmincke (1920), thought that they were mesodermal (inflammatory), in nature, but His (1904), Ranke (1910 a and b), and Wohlwill (1921, a and b), proved their ectodermal origin. A second question was whether the

<table>
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<th>Table II</th>
<th>AETIOLOGY OF ENCEPHALOMALACIA WITH OR WITHOUT CAVITATION IN THE NEWBORN</th>
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<tbody>
<tr>
<td><strong>Brain Parenchyma</strong></td>
<td><strong>Disease (degeneration) or inflammation (intra-uterine or post-natal)</strong></td>
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<tr>
<td>Henoch (1842), Hasch (1859), Roger (1866), Virchow (1867), Chiari (1880), Limbeck (1886), Salgo (1891), Hösé (1892),</td>
<td>Henschel (1889), Kohlbrandt (1930), Diamond (1934) or malnutrition: Parrot (1868), Hayem (1868).</td>
</tr>
<tr>
<td>Mechanical injury: Intra-uterine: Richter (1886), Seitz (1907), Birth trauma: Cruveilhier (1832), Cotard (1868), von Limbeck (1886), von Monakov (1895), Siegmund (1923), Schütz (1925), Schwartz (1924), Dollinger (1927), Sternberg (1930), Rydelberg (1932), Benda (1952).</td>
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<tr>
<td>Extra-uterine: Boëtter (1869), Herter (1870), von Kahllien (1895), Dean (1898), Landouzy and Labbé (1889), Congenital: Haschel (1868), Diamond (1934), Stevenson and McGowen (1942).</td>
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<tr>
<td>Hereditary: No data.</td>
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**Blood Vessels (intra-uterine or post-natal)** |
| Congenital aplasia: Haschel (1859), Ischaemic necrosis: Kundrat (1882), de la Croix (1884), Labbé (1884), Otto (1885),Binswanger (1885),Perina (1888). |
| Luetic degeneration of veins: Pommer (1931). |
| Luetic endarteritis: Takahashi (1921). |
| Sphincter of blood vessels: Dahllmann (1910), Meier (1912), Beneck. (1914). |
| Thrombosis or embolism: Heubner (1882), Kundrat (1882), Abercrombie (1847), Gowers (1888), Kreuer (1892), Beyer (1897), Wieglesworth (1897), Edgerley (1899), Scheffer (1900), Marburg and Casamajor (1944). |

**Meninges** |
| Primary affection: Schupfer (1901). |
| Skull Maldevelopment of the base of the skull and the callosal bony, resulting in atrophy of the white matter: Richter (1886). |
| Aplasia of temporal bone and compression of brain: Schaeffer (1896). |
formations of cells were pathological at all and if so, whether they were a sign of retardation in development or of active proliferation caused by a detrimental agent. And thirdly the problem arises about the relation between these cells and the pathological process. A critical survey of this material was also given by Guillery (1923).

In my opinion the nests of immature cells found in Case 1 were centres of proliferation, furnishing cells for the cystic growing process. The same significance was given to these subependymal cell nodules by Gohrbandt (1923), who examined the brains of 130 newborn infants with various histopathological alterations. In his opinion remnants of the matrix would keep their tendency to proliferate even during the first months of life.

Very little is known of the pathology of the foetal nervous system, but Patten (1952, 1955) described an overgrowth of the neural tube in human embryos, ranging from 7.5 to 30 mm. Factors which regulate the proliferating processes of the brain in embryos were studied by Källén (1955) who reported on the influence of the basal mesodermal plate of the skull on the cell division of the brain. In any case the causative mechanism of an early overgrowth of the neural tube is entirely different from a so-called "arrest of development".

Concerning Case 1, the question arises whether the glial proliferation started first in the matrix or whether the abnormal cell formation was the sequel of irritation of the matrix cells by some previous developmental abnormality of the white matter. Either possibility is difficult to prove, as only vestiges of the original malformation of the matrix and of the intermediate layer were left for us. However, both processes may have developed simultaneously.

Whatever the origin of the abnormal cells may be, the abnormality started rather late, as the general configuration of the brain was relatively normal.

We can only guess how the earliest (primordial) cysts arose during the abnormal development of the intermediate layer. There is no justification for a mechanical explanation, nor do the indifferent cells themselves form cysts, such as we see in ependymomas. We have to be content with the acceptance of a primary loss of tissue within an abnormal cell stratum resulting in cavity formation (see the hypothesis of Lumsden, 1950). This cell stratum, being abnormal, found no pattern of blood vessels correlated with its needs and it is possible that this contributed to the formation of the cysts, as the fluid within them is apparently provided by blood vessels. Moreover, we have to remember that a loosening of nervous tissue and cysts is found in a certain stage in normal embryos (Gruenwald, 1945). The mechanism by which this disintegration and such cysts develop is not yet understood.

The formation of the cavities continued after birth and we have seen how cavities developed after homogenization, hydropic degeneration, and softening. The presence of undifferentiated cells and cell divisions found in the neighbourhood, and especially the invasion of the cortex by fibrous glial tissue, makes it evident that the glia cells play an active role.

Degeneration and proliferation are, however, combined in this case and it is impossible to disentangle the two processes on purely morphological differences.

This process bears much resemblance to the cyst-like changes in bone or the growth of a congenital cystic liver or kidney. That the growing process is to be compared with a benign tumour is supported by the clinical progress.

This pathogenetic view may throw some light on otherwise unresolvable questions, such as the progress, the localization in neopallial structures, and the development of the malacia independently of the blood vessels, or around normal vessels, etc.

Case 2.—The second case differed in many respects from the first one. The mother had a toxæmia of pregnancy which might have been the cause of abnormal developmental processes within the brain. In any case the cerebellum was relatively very large, which may have been the cause of the birth in face presentation. Whether the brain was damaged during birth remains unanswered, but the head was not large, as birth took place before term. Moreover, in many cases of multilocular encephalomalacia in the literature (Jakob, 1931; Dahlmann, 1910; Meier, 1912; Edinger and Fischer, 1913; Negrin, Lepow, and Miller, 1952) birth was normal.

Signs of impaired cerebral functioning were evident immediately after birth, as in Case 1, but there was no clinical progress, and the patient died accidentally.

The cysts were less numerous than in Case 1 and the lesions were less extensive. Cysts were confined to the white matter and a correlation with the time of myelination was not apparent.

The cortex was transformed into a dense network of glia cells originating from the underlying altered white matter.

Also in this case immature cells were found in the neighbourhood of the ependyma and around blood vessels in the white matter, though in a smaller number than in Case 1. This might be explained by the greater age of the patient and by the fact that the disease was not rapidly progressive. However,
there was some progress as amitotic division of cells was met with. That the process was less active than in Case 1 was also evidenced by the fact that signs of softening, with the formation of fat granule cells, were less marked.

In this second case the toxæmia of the mother may have damaged the brain in a state in which remnants of the matrix of the neopallium had the ability to proliferate. The cell proliferation was combined with the formation of a dense network of glial fibres. These formed a capsule around relatively normal brain tissue, which underwent a process of softening and cavitation as described. Contrary to Case 1 the proliferating process stopped at an early stage so that the clinical signs were not progressive.

It is interesting to note that the toxæmia of the mother impaired histogenesis during intra-uterine life of both children in a different way. In the first child, which was described under the title "multi-locular encephalomalacia", the matrix of the neopallium was stimulated to proliferation leading to cavitation and scarring of some parts of the white matter and cortex. However, in the second child (poliodysplasia) a disordered histogenesis led to an under-development of both the nerve cells and the glial elements in all parts of the brain. Thus, contrary to Lumsden (1950) I deny the heredodegenerative character of both disorders and I see no relation with Wilson’s disease, the condition described by Jakob and Creutzfeld.

Summary

Numerous cysts of different size and shape in both hemispheres of the brains of the newborn is a rare pathological condition. Such cases may be classified together on account of their gross morphology, but the cause is not always the same and the clinical features and the histological picture may differ as well.

The development of the pathological processes in two cases is described.

The first case, a child of 1 year and 9 months, was characterized as a familial, dysgenetic, progressive sclerosis of the hemispheres with cavity formation.

The second case was presented as an unprogressive, toxic, dysgenetic sclerosis of the hemispheres with cavity formation in a girl of 8 years and 9 months.

References


