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Postencephalitic Porencephaly, Hydranencephaly or Polymicrogyria. A Review

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Summary. Twenty necropsy cases of the association of fetal encephalitis with porencephaly, hydranencephaly or polymicrogyria were reviewed including 5 from the authors' material. The latter include a basket brain, a porencephalic necrosis of recent date and a polymicrogyria in the formative state. The supratentorial lesions are often associated with cerebellar cortical dysplasias.

The pathogenetic interdependence of encephalitis and hemispheric defects or malformation is discussed. Examples are given in which the infection appears to be secondary to a pre-existent hemispheric lesion. For others the hemispheric lesions appear to be secondary to encephalitis. In these the encephalitis may produce secondary lesions by a variety of pathogenetic mechanisms.

Key words: Porencephaly – Hydranencephaly polymicrogyria – Encephalitis – Toxoplasma cytomegalovirus – Cortical dysplasias.

Etiology and pathogenesis of porencephaly and hydranencephaly are still controversial. Porencephaly has been considered a malformation ("schizencephaly") resulting from incomplete closure of the brain vesicle (Yakovlev and Wadsworth, 1946). More widely accepted is the opinion that both porencephaly and hydranencephaly are residual to the destruction of brain tissue from a failure in carotid circulation, and that they differ only in terms of the extent of damage. This interpretation is consistent with the classic experiments of Becker (1949) who produced porencephalic or hydranencephalic defects by arterial embolisation in puppies; similar lesions were produced by carotid occlusion in monkeys (Myers, 1969). Anoxia is implicated in the case of Bankl and Jellinger (1967) in which hydranencephaly was found in a fetus aborted 6 weeks after carbon monoxyde intoxication of the mother during the 24th week of gestation.

In apparent contradiction to these observations are scattered case reports on porencephaly or hydranencephaly associated with fetal encephalitis. Also, cavitary postencephalitic lesions were reported by Haymaker (1954), Booth et al. (1961) and Cordy and Shultz (1961). Experimental infection of fetal lambs with bluetongue virus may produce cavitary lesions having a superficial resemblance to porencephaly (Osburn et al., 1971).

The present paper reviews the data available on the association of fetal encephalitis with porencephaly or hydranencephaly in man, adding 5 own cases. It includes, in addition, data on polymicrogyria which often fringes porencephalic defects; fetal encephalitis has been claimed a cause polymicrogyria (Diezel, 1954). Some other types of cavitary lesions associated with encephalitis were also included for comparison even though they did not fit the strict definition of a porencephaly or a hydranencephaly. Based on this material the interdependence between fetal encephalitis and the production of hydranencephaly, porencephaly or of polymicrogyria may be reappraised.

Results

Nineteen cases were gathered from the literature (Table 1) and 7 from our own material (Table 2). From these 26 cases one may select 20 (1–14, 19–23) in which the association of hydranencephaly, porencephaly or polymicrogyria with fetal infection is reasonably convincing. The remaining cases (15 to 18; 24 and 25) will be dealt with in the discussion. Among the 20 qualifying cases there were 5 hydranencephalies, 1 basket brain, 8 porencephalies (5 of these had polymicrogyria), and 6 cases with polymicrogyria only. There were 11 girls and 7 boys (2 undefined). Ten infants were born premature. The age at death was one week or less for 7 infants, before the end of the first month for 5, and early infancy for the rest, the oldest case (15) being 34 months.

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Table 1. Published reports on hydranencephaly, porencephaly and polymicrogyria with encephalitis

	Cerebral lesion	Type of infection and evidence	
		Cerebral	Generalized
A. Hydranencephalies			
1. Arey (1954) ? 12 mo	Hydranencephaly; persistent thalami and small cortical remnants	CMV, intravital in CSF	Signs of generalized infection
2. Lykke (1957) f, $5^1/_2$ mo	Hydranencephaly, remnants of medial, frontal and occipital cortex	Toxoplasma in tissue	Toxoplasma in kidney
3. Altshuler (1973) f, 1 week (32 wg)	Hydranencephaly, foci of necroses and mineralization in mesencephalon	Toxoplasma in brain stem and cord	Pseudocysts in kidney, pankreas and placenta
4. Villegas-Gonzales et al. (1976) ? 15 mo	Hydranencephaly of cerebral hemispheres	Toxoplasma pseudocysts	"Meningoencephalitis" at 20 days age
B. Porencephalies			
5. Diezel (1954) m, 42 d	Bilateral temporal porencephaly, widespread polymicrogyria	Cytomegalic cells in cerebrum and cerebellum	Generalized infection cytomegalic cells in liver and kidney
6. Born (1955) m, 2 d (38 wg)	Bilateral parieto temporal porencephaly; frontal and occipital microgyria	Cytomegalic inclusions subependymal	Generalized infection; cytomegalic cells in many organs
7. Crome and France (1959) f, 1 d (38 wg)	Porencephaly, central region, right; widespread polymicrogyria, bilateral	Suspected cyto-megalic inclusions	Generalized infection cytomegalic inclusions in many organs
8. Castleman (1963) f, 45 d	Photograph highly suggestive of nascent porencephalic lesions bilateral occipital	Toxoplasma pseudocysts and free organisms in brain tissue	Pseudocysts in retina only; positive titer in mother and child
9. Navin and Angevine (1968) f, (30 wg)	Porencephaly temporo-occipital right, polymicrogyria left	Cytomegalic inclusions in glia and neurons	Generalized infection, cyctomegalic inclusions in many organs
C. Polymicrogyria			
10. Hartmann (1948) f, 7 d	Polymicrogyria, paraventricular mineralization	None found	Generalized infection, cytomegalic inclusions in many organs
11. France (1951) f, 2 weeks	Polymicrogyria fringing cortical defects, right temporal, pre- and post-central; paraventricular necroses and mineralization	Cytomegalic inclusions para-aqueductal	Generalized infections; cytomegalic inclusions in many organs
12. Crome (1961) m, 8 mo case 1	Bilateral microgyria, necroses and mineralization periventricular and in basal ganglia	Not shown	Generalized infection, cytomegalic inclusion in many organs
13. Bignami and Appicciutoli (1964) f, 22 d case 1	Polymicrogyria frontal, temporal, parietal; cortical and subcortical cortical necroses with mineralization	Cytomegalic inclusions	Generalized infection, cytomegalic inclusions in lung, liver, kidney
14. case 2 m, 1 d (mature)	Extensive polymicrogyria frontal parietal and temporal	Cytomegalic inclusions	Generalized infections, inclusions in lung, liver, kidney
15. De Leon (1972) f, 34 mo	Widespread polymicrogyria	Multinucleated neurons; no organisms shown	Intravital dye test 1 : 64; no pseudocysts shown
D. Multifocal cystic encephalopathy			
16. Becker (1975) m, 5 mo case 1	Multifocal cystic encephalopathy	Multinuclear cells and inclusions	No generalized infection at autopsy
17. m, 4 mo case 2	Multifocal cystic encephalopathy	Cytomegalic inclusions and multinuclear cells	Cytomegalic inclusions in kidney

Table 1. *(continued)*

E. Lesions demonstrated by computer tomography			
18. Smith et al. (1977) m, 40 wg	Large cystic lesions, larger on left side than on right	CSF negative	Herpes simplex encephalitis during 2nd week of life; isolation of virus from skin; severe neurologic defects since then
19. Chalhub et al. (1977) m, 40 wg	Large porencephalic cysts left parieto temporo-occipital	Coxsackie A9 isolated from CSF	Acute encephalitis at 3 mo; severe neurologic defects since then

Table 2. Own cases

Case 20 m, 33 h (30 wg)	Hydranencephaly, necrotizing foci in cerebellar cortex; brain weight 39 g (20% of normal)	Granulomatous mineralizing encephalitis with pseudocysts	Toxoplasma titer positive in mother and infant. Myocarditis; pseudocysts in adrenal
Case 21 f, 7 mo (wg)	Basket brain, mineralization in residual tissue, scars and focal dysplasias in cerebellar cortex (see text); brain weight 145 g (20% of normal)	Pseudocysts in thalamus	Generalized infection, toxoplasma titer 1 : 1024
Case 22 m, $4^1/_2$ mo (44 wg)	Large porencephalic cyst right temporal; extensive periventricular necroses and mineralization. Focal cerebellar cortical dysplasias; brain weight 240 g (32% of normal)	No cytomegalic cells or inclusions found	Generalized infection, serology 1 : 40, cytomegalic cells in urin and saliva. Necropsy: chorioretinitis, cytomegalic inclusions in many organs
Case 23 f, 19 d (31 wg)	Large porencephalies bilateral, central region; florid necrotizing encephalitis in cerebrum and cerebellum (see text); brain weight 150 g (53% of normal)	Toxoplasma pseudocysts in cerebral tissue near the defect	Predominantly central nervous signs, seizures. Necropsy: pseudocysts in heart, pancreas, adrenals
Case 24 m, 6 h (29 wg)	Large porencephaly right parietal; extensive polymicrogyria in status nascendi (see text); brain weight 103 g (59% of normal)	Many cytomegalic cells in subependymal granulomas	Cytomegalic cells in liver, pancreas, kidney and thyroid
Nonqualifying cases			
Case 25 m, 17 mo (36 wg)	Organizing multifocal periventricular infarcts, no mineralization, no inflammation (see text); brain weight 935 g (96% of normal)	Scattered pseudocysts in the glial scar tissue	Febrile disease with 16 mo; no signs of generalized infection at necropsy
Case 26 m, 5 w (40 wg)	Hydranencephaly, rudiments of basal ganglia; cerebellar atrophy, microphthalamus, retinal dysplasia, incomplete differentiation of cornea, synechias, cataract; brain weight 80 g (17% of normal)	None	Gripal infect 3rd month of gestation. Rubella titer 1 : 80 (not significant). Born with ocular malformations

Twelve infants were infected with cytomegalo virus, 8 with toxoplasma. Clinical signs of a generalized infection were present for most and involvement of viscera was documented at necropsy. Nearly all porencephalies and hydranencephalies had evidence of active infection either in the tissue adjacent to the defects or widespread in the CNS. Some cases of polymicrogyria had less direct evidence (cases 10, 12) the malformed cortex overlying periventricular calcified necroses of presumed encephalitic origin.

An effort was made to determine the frequency of associated infratentorial lesions since an encephalitis is unlikely to remain restricted to supratentorial structures. In 4 cases the cerebellum was described as normal. Three (5, 6, 23) had large necrotizing, asymmetric lesions and six (12, 13, 15, 20, 21, 22) had

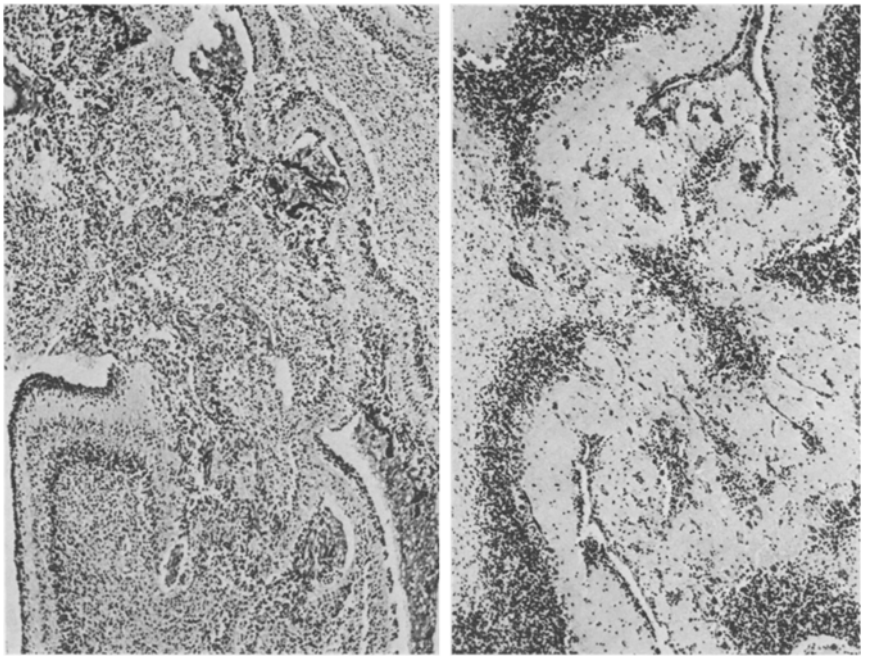

Fig. 1
Left: A focal granulomatous meningitis with lymphocytic and plasmocellular infiltrates destroys the superficial cortical layers of the cerebellum. Case 20, HE, 65×. Right: A focal cortical dysplasia without residua of an inflammatory process. Case 22, HE, 49×

circumscript focal dysplasias of cortical architecture, often multiple, of the type that is also known as "cerebellar polymicrogyria". For the remaining 7 cases the cerebellum was not mentioned in the description; the significance of these is dubious since focal cerebellar cortical dysplasias are easily overlooked on cursory examination. One may conclude that there is a relatively high incidence of cerebellar lesions, especially of focal cortical dysplasias, in this type of material.

The histopathologic findings in our case 20 shed light on the mechanism by which cerebellar cortical dysplasias form (Fig. 1): There was a subsiding focal leptomeningitis with nests of lymphocytes, a few plasma cells and macrophages within the proliferated leptomeningeal connective tissue. Bordering these foci there was rarefication or destruction of the superficial cerebellar granular layer and disorganization and rarefication of the deeper cell layers. The residual lesions in case 22 are shown for comparison (Fig. 1); here, there were only circumscript cortical dysplasias of the type seen in non-infected malformed brains. No recognizable remnants of an inflammatory process were found but the foci were distributed in the same haphazard manner as those in case 20. One may assume, therefore, that the focal cortical dysplasias are residual to destruction of superficial cortical layers by a focal granulomatous leptomeningitis with subsequent derangement of cortical development.

A few comments may define the criteria used for the selection of the supratentorial lesions in the cases in Table 1. The definition of porencephaly, basket brain, and hydranencephaly followed generally accepted criteria (Friede, 1975). The usage of the term polymicrogyria, however, is often ambiguous in the literature: Many authors use it or "microgyria" to describe small but well formed gyri having a normal laminar architecture; others use the terms for gyri reduced by tissue necrosis and scarring. For the present review only those cases were accepted in which either the text or the illustration made clear that the author had indeed described polymicrogyria in the sense of a specific cortical malformation characterized by an abnormally plicated cortex with fusion of the surfaces of adjoining microgyri, and an abnormal laminar architecture, corresponding to Crome's (1952) detailed description. The "microgyrias" reported by Mercer et al. (1953), Haymaker et al. (1954), Seifert (case 23, 1954), Verron (case 1 and 2, 1955), Mulatova (case 1, 1965) and Viçosa and Barbosa (1971) were not included in Table 1 even though some may well have been pertinent to this review.

Concerning our own cases, the data given in Table 2 may suffice to define the cases 20, 22, and 26. As to the others, a few additional comments may characterize their peculiar features.

ad 21: This appears to be the first account of a so-called basket brain associated with fetal encephalitis, unless Lykke's case is counted into this category. There were large bilateral, approximately symmetric, cystic hemispheric defects filled with clear fluid and covered with a thin translucent membrane (Fig. 2). The frontal poles were preserved, having a normal gyral pattern. There were median bridges of tissue formed by remnants of the cingular and parasagittal cortex. The

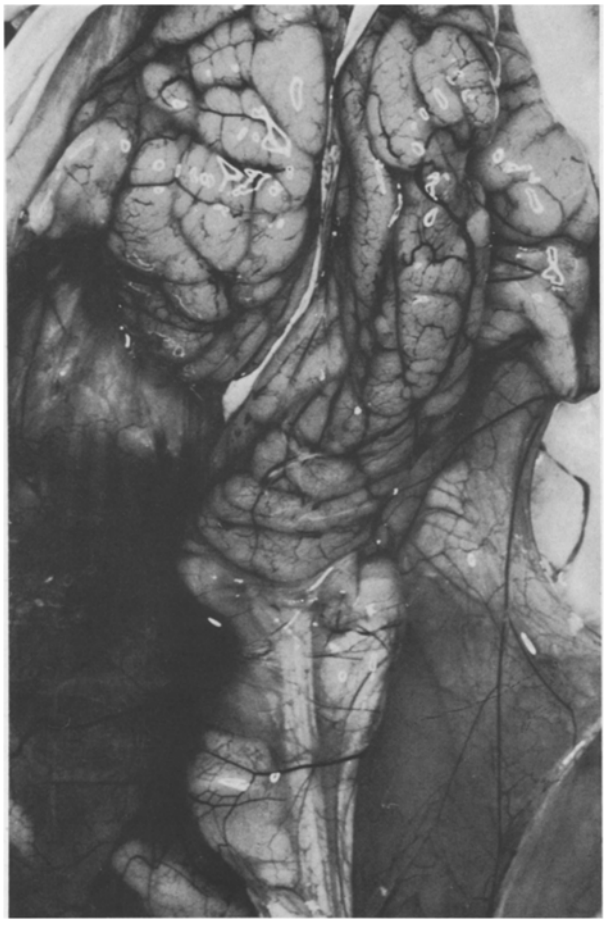

Fig. 2. Case 21: In situ appearance of the basket brain. The frontal lobes are seen in the upper half of the picture. A median bridge of cortical tissue projects occipitally between large pori covered with a thin, translucent membrane

occipital poles were absent but there were basal remnants of the temporal lobes. Microscopic examination showed a focal, subsiding encephalitis with sparse chronic inflammatory infiltrates, mineralization and dense glial scar tissue. Pseudocysts were sparsely scattered in the scar tissue.

ad 23: This case was thought to be unique in showing the status nascendi of a porencephalic lesion. The brain had large fluctuating defects bilateral in the centroparietal region. Both cavities combined contained approximately 100 ml creamy necrotic debris. Microscopic examination disclosed a florid granulomatous meningoencephalitis. Predominantly lymphocytic infiltrates were found in the cerebellar and cerebral leptomeninges. The parenchyma showed focal gliosis and massive lympho-, plasmo- and polymorphonuclear infiltrates with focal mineralization. Pseudocysts and organisms were found in the tissue. The choroid plexus was encompassed with granulation tissue. The pori corresponded to sharply delineated

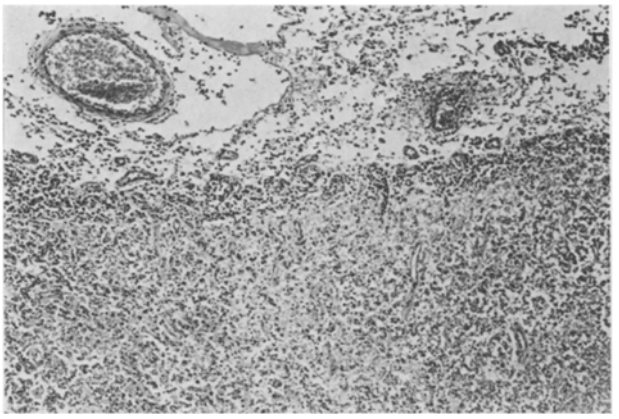

Fig. 3. Early stage in the formation of a porencephaly (case 23). There is transmural necrosis of the hemisphere sparing only the meninges. Chronic meningitis is evident; no occlusive vasculitis was found. The necrotic parenchyma contains nuclear debris; there is no evidence of a focal necrotizing encephalitis. HE 43×

large zones of ischemic necrosis destroying the entire width of the hemispheric wall. Only the leptomeninges and minimal residua of adjoining glial tissue had escaped necrosis. The edges of the necroses were sharp, with very little or without inflammatory changes in the adjoining non-necrotic tissue. There were no signs of inflammation within the necroses save a few small subpial foci of mineralization. The blood vessels in the meninges overlying the necrosis were without endarteriitis or vascular occlusions (Fig. 3). The necrotic districts were much larger than would correspond to the caliber of any of the overlying leptomeningeal arteries. It was thought unlikely that the necroses could have resulted from a secondary vasculitis, or from a focal necrosis within an inflammatory lesion.

ad 24: This was one of the uncommon cases of polymicrogyria in the status nascendi in a fetus of 29 weeks gestation. A large porencephalic defect in the right postcentral-parietal region was fringed by wide zones of cortex having an irregularly embossed surface pattern. The same surface pattern, without cavity, was present in the contralateral hemisphere. The frontopolar, occipitopolar and temporobasal cortex lacked gyri and had a microscopic structure normal for age. The polymicrogyric portions of the cortex were thinner than normal with an undulating surface (Fig. 4). Prongs of molecular layer projected into the depth. These were lined, on their inner surface, by a thin band of cortex consisting of a single dense sheet of cells, scattering toward the white matter. The polymicrogyric cortex was entirely free of inflammatory or granulomatous lesions. Its distribution at the outer face of the hemispheres corresponded to that of large mineralized, granulomatous foci at the ventricular face. Cytomegalic inclusion cells abounded in the latter. There was a severe, productive ependymitis. The abnormal, irreg-

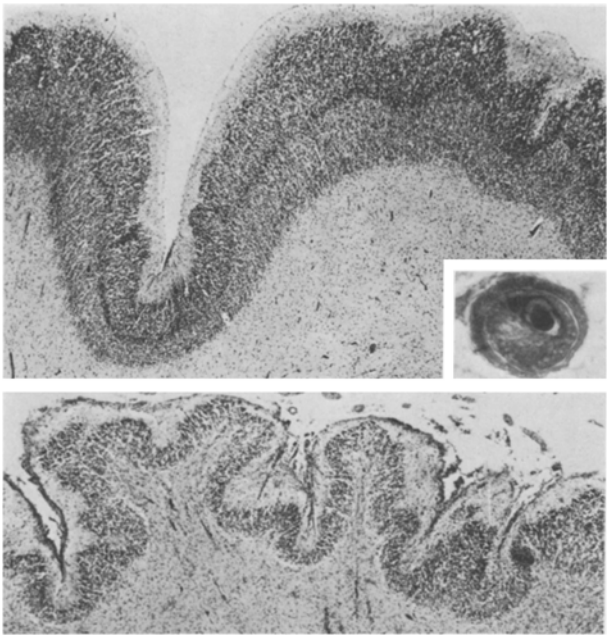

Fig. 4. Case 24. Top: Border of normal and polymicrogyric cortex. Bottom: Polymicrogyric cortex. Both cresylviolett 25×. Inset: Cytomegalic inclusion cell in the periventricular infiltrates. HE 660×

ularly folded polymicrogyric cortex of this case was found at an age when the adjacent normal cortex was flat and without any signs of commencing gyrus formation.

ad 25: This case is presented as an example of secondary infection of pre-existent lesions. The child had a trisomy 21. Nothing abnormal was known about his birth, nor were there any signs of a systemic infection with toxoplasma, except that the boy had passed through a febrile episode one month prior to death. His development was within expectation considering the chromosomal anomaly. The subependymal tissue of both cerebral hemispheres showed many cavitary lesions, measuring from a few mm to approximately 1 cm, scattered no more than 1,5 cm from the ventricular walls, most densely in the parieto-occipital segments of the lateral ventricles. No other lesions were found in the brain. Microscopic examination showed multiple infarcts with intense gliosis and residual organisation. There were no inflammatory infiltrates. There were scattered mineralized axons, and dust-like mineralized particles of the type often seen in periventricular infarcts. On scrutiny, a few pseudocysts were found in the scarred tissue and were interpreted as a dormant secondary infection of a glial scar.

Discussion

Twelve of the qualifying cases were infected with cytomegalovirus, 8 with toxoplasma. There are reports on large cavitary lesions associated with herpes simplex (case 18) or with Coxsackie encephalitis (case 19), but these were demonstrated by computer tomography without histopathologic verification. No report on large cavitary lesions or on polymicrogyria associated with rubella encephalopathy came to our attention.

In evaluating these complex lesions three types of interdependence between the two disease processes need to be considered. First, they may be strictly coincidental. Secondly, encephalitis may be secondary to a pre-existing cavity or a malformation. Thirdly, the cavities or the malformations may be secondary to encephalitis. An effort will be made to untangle the evidence concerning these relationships, as far as the interpretation of histopathologic data permits.

1. It was extremely difficult to identify cases in which the infective process and the cerebral lesions were unequivocally coincidental. Case 26 was included as a potential example: the child had hydranencephaly and multiple eye malformations and a titer for rubella, which, however, was not considered diagnostic. Coincidence of two independent diseases becomes all the more difficult to prove if they develop during the same or during overlapping periods; in that case, some kind of interaction would inevitably occur.

2. A few cases could confidently be interpreted as superinfection of a pre-existent cerebral lesion. The damaged tissue may have presented a locus minoris resistentiae for the spread of an infection to the brain. Case 25, for example, had many subependymal cavities in a distribution characteristic of periventricular infarcts residual to perinatal asphyxia. The glial scar tissue bordering some of these contained a few toxoplasma-pseudocysts but had no inflammatory changes. There was neither a clinical history of toxoplasma infection, nor were there any other necropsy findings to document it. The case was interpreted as a local opportunistic, dormant infestation of glial scar with toxoplasma. The two cases published by Becker (cases 16, 17) are probably of the same type. Both had the characteristic lesions of multifocal cystic encephalopathy. In one (17) the birth had lasted for 50 h and the other (16) had passed through a critical episode with convulsions, apnea and opistotonus at the age of $1^1/_2$ months. There was no evidence of generalized infection in case 16 and it was sparse in case 17. Both cases are most probably secondary infections of residual lesions resulting from severe peri- or post-natal asphyctic-ischemic distress. There may well be several other instances of secondary infection among the 20 qualifying cases cited here because some of them had only sparse inflammatory changes confined to the scar tissue bordering the defect. Such findings are equivocal: they may either indicate a secondary infection of a scar, or else a smouldering remnant of an encephalitis that had been more widespread previously.

3. The third possibility is that fetal encephalitis causes cavities or cortical malformations. Perhaps the most convincing documentation of this type of interrelation is for a fetal brain having a polymicrogyria in the formative stage (case 24). Here, the malformed cortex was free of encephalitic lesions but corresponded in its distribution to the periventricular foci of a florid cytomegalovirus encephalitis. The latter had evidently disturbed the migratory patterns of cortical neurons.

A cause-effect relation is less evident for the large cavitary lesions, and a variety of pathogenetic factors may be considered. For example, the encephalitis itself may cause histotoxic tissue necrosis. This is unlikely considering the distribution of the encephalitic lesions, which tend to form multiple foci of variable sizes with a predilection for the periventricular tissue. The porencephalic tissue necrosis is transmural preferring the central region. Tissue necrosis may also result from a secondary vasculitis or from a thrombophlebitis, comparable to the large phlebothrombotic infarcts complicating neonatal leptomeningitis (Friede, 1973). Yet, obliterative arteriitis is not a typical feature of the acute meningoencephalitis and none was found in our case 24, in which the porencephalic necroses were recent. This case also lacked significant inflammatory changes within the necrotic tissue.

Pathogenetic mechanism may have to be searched for along different lines. Potential factors are anoxia-ischemia secondary to placental infection (case 9), infectious or toxic myocarditis (case 23), or failure of cerebral circulation from a severe brain edema either by the kincking of large arteries at their entrance into the cranial cavity (Lindenberg, 1967) or by some other mechanism. The pathogenesis of postencephalitic porencephaly may well be the same as that of porencephaly in the absence of encephalitis, the latter playing only the role of a triggering event.

One may conclude that the cause-effect relationship between fetal encephalitis and large cavitary lesions or cortical malformations still requires a cautious interpretation of the merits of each given case. Even those cases in which the cerebral lesions may be considered secondary to encephalitis may involve a variety of pathogenetic mechanisms.

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