MORPHOLOGIC FEATURES OF LESIONS IN THE WHITE MATTER OF THE CEREBRAL HEMISPHERES OF NEWBORN INFANTS WITH PERIVENTRICULAR LEUKOMALACIA AND SEPSIS

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A special form of lesion of the neonatal CNS is periventricular leukomalacia (PL), characterized by the onset of foci of necrosis, chiefly of coagulation type, in the periventricular zone of white matter of the cerebral hemispheres, and which are mainly distributed symmetrically and bilaterally. A random investigation of the frequency of PL in newborn infants showed it to be 19.5% [1]. In surviving infants PL leads to the development of cerebral infantile paralysis. All investigators agree unanimously that the genesis of foci of PL is ischemic and hypoxic in nature [6, 7, 12]. However, the pathogenesis of PL is not yet sufficiently clear. The mechanism of action of the various causative factors of this brain lesion has not been elucidated, nor have the ultrastructural changes in PL been studied. Incidentially, no adequate experimental model of PL has yet been devised. For instance, when asphyxia is induced in monkeys and their fetuses by various methods [10, 13], in some cases foci of necrosis develop in the brain substance, but these foci spread to the cortex and basal ganglia. Symmetrical lesions of the cerebral hemispheres have been reproduced in cats (by ligation of the basilar and carotid arteries) and in sheep fetuses exposed to asphyxia, but these did not correspond microscopically to PL [5, 10]. Meanwhile there are indications of the role of an infectious-toxic factor in the pathogenesis of PL [8, 9]. Clearly the answer to many questions requires a more penetrating investigation of newborn infants. In particular, the study of the morphology of lesions in the white matter of the brain in a group of neonates with sepsis could shed some light on the role of infection in the genesis of PL.

The aim of this investigation was a comparative study of the morphology of lesions in the white matter of the cerebral hemisphere in newborn infants with PL in groups with sepsis and without an infectious condition.

EXPERIMENTAL METHOD

Brains containing foci of PL in full-term neonates of two groups were studied: those without infection (17 cases) and those with sepsis (14 cases). Group 1 included infants dying during the first 4 days after birth from the following causes: birth trauma of the skull (five cases), pneumopathies (nine), birth trauma of the spinal cord (one), hemorrhages into the cerebral ventricles (one), and hemolytic disease (one). Group 2 included neonates with sepsis, the portal of entry of which was the umbilicus (nine cases), the lungs (four), and skin (one). In four cases intrauterine infection could be diagnosed. Most infants with sepsis died after the 11th day after birth, and in 9 of the 11 cases the sepsis was of the septicopyemic type.

Pieces of brain with foci of PL and surrounding white matter were studied histologically. The following staining methods were used: Nissl's, Cajal's, Miyagawa's, Favorskii', and Holtzer's. Myelin was detected by Lillie's method and fibrin by Shueninov's method. In two cases of early autopsies on neonates with sepsis foci of PL and perifocal areas of white matter of the brain were studied in the electron microscope. Ultrathin sections were stained suc-

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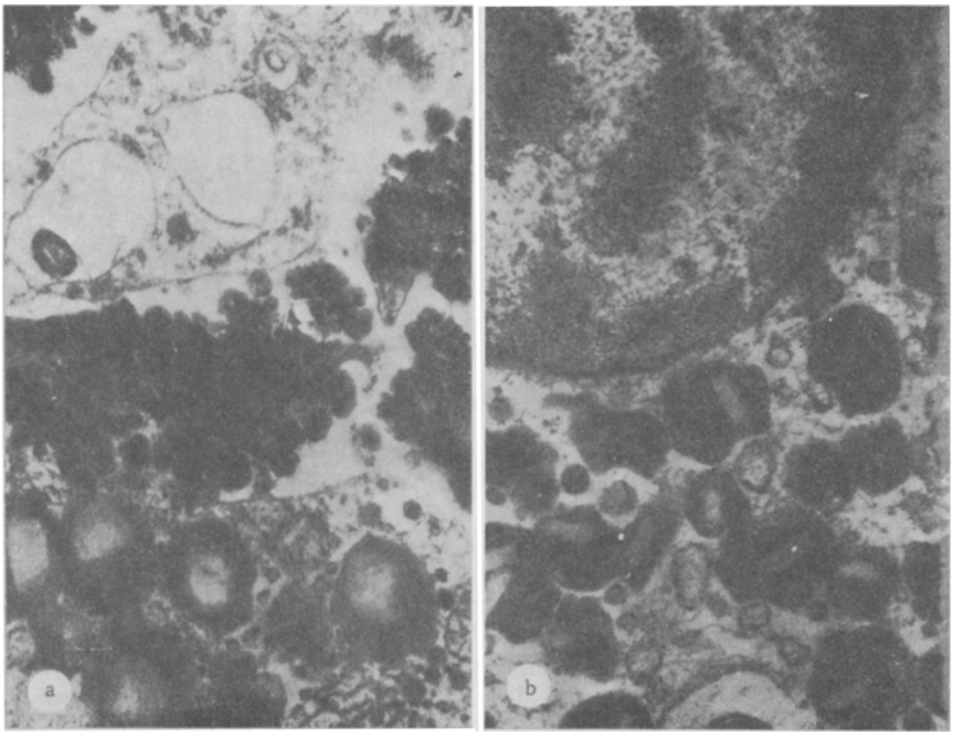

Fig. 1. Ultrastructural changes in foci of PL. a) Remnants of disintegrating tissue consisting of lumpy osmiophilic mass and lipid granules in macrophage; b) lipid granules with bilirubin crystals in cytoplasm of macrophage from focus of PL. 14,000 ×.

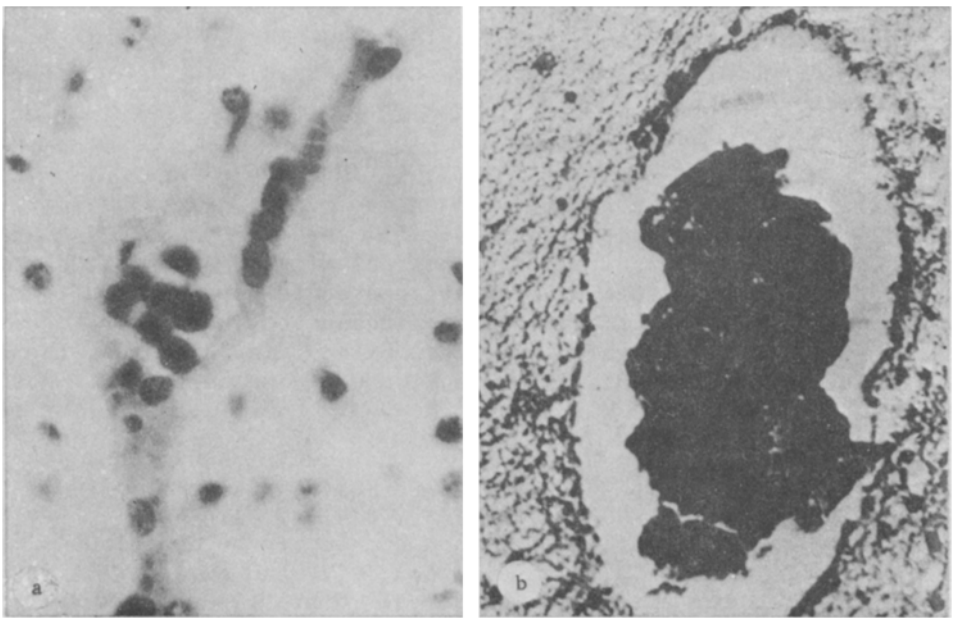

Fig. 2. Changes in vessels of white matter of brain alongside foci of PL. a) Stasis of erythrocytes, areas of emptying of capillary, swelling of endothelial cells. Cresyl violet, 400 ×; b) fibrin thrombus in subependymal vein. Shueninov's method, 200 ×.

TABLE 1. Frequency of Some Pathological Changes in Brain of Newborn Infants with PL in Group Without Infection and in Group with Sepsis

Character of pathological changes	Group of neonates without infection (17 cases)		Group of neonates with sepsis (14 cases)		P
	abs.	%	abs.	%	
Foci of PL:					
Stage I	8	47	—	—	<0,01
Stages I and II	3	17,6	4	28,6	>0,025
Stages I and III	—	—	2	14,3	>0,025
Stages I, II, and III	—	—	2	14,3	>0,025
Stage II	6	35,3	3	21,4	>0,025
Stage III	—	—	3	21,4	>0,025
Hemorrhages into foci of PL	6	35,3	3	21,4	>0,025
Perivascular hemorrhages around foci of PL	16	94,1	8	57,2	0,025—0,01
Subependymal hemorrhages	7	41,2	1	7,1	>0,025
Thrombosis of vessels in white matter of brain	2	11,7	12	85,7	<0,01
Diapedesis of leukocytes in individual foci of PL	—	—	4	28,6	>0,025

cessively with uranyl acetate and lead citrate and examined in the Tesla BS-500 electron microscope.

EXPERIMENTAL RESULTS

Foci of PL could be differentiated into three stages: development of necrosis, resorption, and the formation of a glial scar or fist which, in some general features, corresonded to the stages of cerebral infarction [3, 4]. Stage I was characterized by predominantly coagulation necrosis. Large foci had an oxyphilic zone around the periphery, in which there were thickened, deformed, and fragmented axis cylinders. Necrosis of glial cells, karyorhexis, swelling, fragmentation, and disintegration of the nerve fibers, with accumulation of myelin disintegration products and cellular debris were observed. At the end of stage I proliferation of astrocytes and microglia was found around the foci. Many lysosomes and polymorphic cytolysosomes with a labilized membrane could be distinguished among the microgliocytes, evidence of high acid hydrolase activity and of intensive catabolism. In stage II the macrophagal reaction reached its climax, disintegration products of brain tissue and bilirubin (in cases of jaundice) were phagocytosed. Macrophages contained excessive numbers of lipid inclusions, ingested fragments of myelin and other membrane structures, and also bilirubin crystals (Fig. 1a, b). Many axonal spheres, some which had undergone phagocytosis, were found. However, diapedesis of leukocytes, characteristic of cerebral infarcts in adults, was not observed. Astrocytes took part in autophagocytosis of the disintegrating tissue, as was confirmed by the large number of cytolysosomes, vacuoles, and lipid structures in the cytoplasm. A glial scar and cyst formed in stage III.

Pathological changes in glial cells and nerve fibers and disturbances of the microcirculation were found in the white matter of the brain around foci of PL. Emptying of the capillary system with collapse and death of the capillaries was found. Stasis of erythrocytes, discrete areas of sludging, and fibrin thrombi were observed in the arterioles, venules, and capillaries (Fig. 2a, b). Permeability of the endothelioctye and basement membrane was considerably increased, as shown by increased hydrophilicity and separation of the layers of structures surrounding the vessels, and also swelling of the basement membrane of the vessels. Veins in the subependymal zone of white matter of the brain were diluted and, in some cases, they were associated with fibrin thrombi (Fig. 2b) and perivascular hemorrhages.

The changes described, like other brain lesions, were found with different frequencies in neonates of the two groups studied (Table 1). An important feature of the group of children with sepsis is that although most of the neonates lived longer than 11 days, in 7 of 14

cases foci in stage I were discovered and they lasted until about the third day. Since these foci developed postnatally, accompanied by marked manifestations of sepsis the role of sepsis in their genesis can be assumed. The results of the investigation also points to the importance of thrombosis of blood vessels in the white matter of the brain in the genesis of PL foci in stage I. The presence of leukocytes in individual foci was perhaps connected with the hematogenous spread of microorganisms into them. This mechanism is definitely present in complications such as suppuration of foci of PL, which was discovered in one newborn infant with umbilical sepsis. Foci of PL in sepsis may be combined with foci of encephalitis, which were found in two cases.

Irrespective of the group studied, foci of PL at different stages of development were discovered in the new born infants (Table 1), indicating that the lesions appeared at different times and that the process was progressive. This was particularly evident in the group of neonates with sepsis, in which no case with foci only in stage I was present. It can be postulated that sepsis promotes persistence of PL. In some cases sepsis developed against the background of a previous lesion of the brain, in the form of PL, and could predispose to the onset of new foci of ischemic necrosis of the white matter of the brain, whereas in others PL developed against the background of sepsis, which can be regarded as one of the etiologic factors of PL.

It can thus be concluded from the results of this investigation that PL does not arise at a single moment, i.e, neither during birth [2, 11] or after birth [7], as some authorities consider, but it is a dynamic and persistent process. Neonatal sepsis also promotes progression of PL and the formation of new pathological foci even after the 10th day of life; one of its mechanisms, moreover, may be thrombosis of vessels in the white matter of the brain.

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