Periventricular leucomalacia in neonates

Complications and sequelae*

DAWNA ARMSTRONG and MARGARET G. NORMAN

From the Department of Pathology, The Hospital for Sick Children, Toronto, Ontario, Canada

Armstrong, D., and Norman, M. G. (1974). *Archives of Disease in Childhood*, 49, 367. **Periventricular leucomalacia in neonates: complications and sequelae.** Periventricular leucomalacia was examined in a total of 28 infants. These foci of infarction were attributed to episodes of failure of perfusion due to hypotension in a border zone between ventriculofugal and ventriculopetal circulations. We describe haemorrhage occurring into these infarctions as a complication occurring in 7 infants. In 2 infants with a bleeding diathesis the haemorrhage was massive and fatal. Descending degeneration of the corticospinal tract was present as a sequel of a large area of periventricular leucomalacia in another case.

Periventricular leucomalacia is the term used to describe cerebral infarctions occurring near the lateral ventricles in neonates. The lesion was first described by Virchow in 1867; and was re-emphasized and named periventricular leucomalacia by Banker and Larroche (1962) who described 51 cases and reviewed the published cases. This unusual site for cerebral infarction occurs in the watershed area between the ventriculopetal and ventriculofugal circulations described by Van den Bergh and Vander Eecken (1968). In neonates the infarction results from failure of perfusion (ischaemia). Periventricular leucomalacia is not by itself lethal but may produce spastic quadriplegia and mental retardation in babies surviving neonatal cardiorespiratory problems (De Reuck, Chattha, and Richardson, 1972).

Our purpose is to describe the haemorrhages, sometimes massive, into areas of periventricular leucomalacia, and the descending degeneration of long tracts with resulting spastic hemiplegia as a sequel to cavitation of the periventricular leucomalacia.

Materials and methods

Four cases of periventricular leucomalacia are described in detail to illustrate the complications. In addition, all cases of periventricular leucomalacia

occurring in 1971 and 1972 are listed in the Table. The incidence of periventricular leucomalacia in necropsies on neonates was 7%.

Case 1.

Clinical. A female was delivered by caesarean section because of prolonged labour and fetal distress at 42 weeks' gestation after a pregnancy complicated by toxæmia. The placenta was infarcted. Apgar score was 0, and meconium was recovered from her airway and stomach. The baby required assisted ventilation, correction of acidosis and hypocalcaemia, and developed seizures on the second day. These persisted until death on the 3rd day. She had thrombocytopenia.

Pathology. The brain (396 g) was mature and showed haemorrhage into the left centrum semiovale. The haemorrhage destroyed the corpus striatum and ruptured into the ventricular system, spreading to subarachnoid space (Fig. 1). Microscopical examination showed large areas of coagulation necrosis in the periventricular white matter of the frontal and parietal lobes, some capillaries contained fibrin thrombi, and there was recent haemorrhage. Astrocytosis was conspicuous in white matter around the entire ventricular system, extending into the subcortical zone. In some areas, macrophages and retraction balls could be found.

Remaining necropsy findings were hyaline membrane disease of lungs, abdominal, pericardial, and pleural effusions, and fatty change in the liver.

Comment. The presence of macrophages and of reactive astrocytes suggested that the damage occurred several days before birth, so the infarcted placenta may have contributed to cerebral ischaemia.

Received 8 October 1973.

*Presented in part at the Pediatric Pathology Club, Houston, Texas, 21 and 22 September 1973, and at the Canadian Association of Neuropathologists, Jasper, Alberta, 5 and 6 October 1973.

	No. of cases	Clinical			
		Abnormal pregnancy	Pregnancy (wk)	Delivery	Survival (days)
Placental problems	2	1 abruptio placentae 1 placenta praevia	32-36	2 caesareans	17-22
Intrapartum distress	5	1 bleeding first trimester 1 maternal diabetes	38-40	1 breech 2 caesareans	2-14
Congenital heart disease	5	1 surgery for bowel obstruction	36-40	1 precipitate	7-13
Miscellaneous congenital anomalies	3	1 abdominal pain first 5 mth	36-40	1 cord around neck	3-18
Metabolic disease (hypophosphatasia)	1		40		152
Premature 32-34 wk gestation	4	2 premature rupture of membranes 1 placental atrophy	32-34	1 breech	1-29
30 wk gestation	2	1 premature rupture	30	1 breech	63-84
24-27 wk gestation	2		24-27		31-50

The terminal massive haemorrhage into the brain may have resulted from the thrombocytopenia, with bleeding into an area of cerebral infarction which predisposed the infant to intracerebral haemorrhage. The diffuse gliosis of periventricular and subcortical white matter with cortical sparing is noteworthy.

FIG. 1.—Case 1. Massive haemorrhage into centrum semiovale with rupture into ventricular system.

Case 2.

Clinical. A female was delivered vaginally after a 38½ week gestation complicated by mild toxæmia and fetal distress during labour. The cord was around the neck of the meconium-stained infant. In spite of an initial Apgar score of 9, the child became 'jittery' and developed a 'poor colour'. Hypoglycaemia and hypocalcaemia were corrected, but seizures, sepsis, and consumptive coagulopathy led to death on the 4th day of life.

Pathology. The brain showed haemorrhage into bilateral areas of softening around lateral ventricles (Fig. 2). The white matter was destroyed posteriorly on the left by a haemorrhage which had ruptured into the ventricular and subarachnoid system. Microscopical examination showed recent coagulation necrosis of periventricular white matter involving all lobes. The area of necrosis was extensive and recent. Haemorrhage was present in and near these areas. There were axonal swellings in some areas, but no macrophage or astrocytic response. A few of the small periventricular veins contained thrombi.

Other necropsy findings were haemorrhages in adrenals, lungs, heart, and kidneys.

Comment. This infant's brain showed very recent infarction of the periventricular white matter with axonal

leucomalacia, 1971 and 1972

Neuropathology				General pathology	
Periventricular leucomalacia		Haemorrhage into periventricular leucomalacia	Subependymal cell plate haemorrhage		Other
Gross	Micro				
2		1	0	1 cerebellar haemorrhage with dentato-olivary degeneration	1 lung abscess 1 chronic interstitial pneumonitis
1	4	1	0	1 infarction thalamus striatum; 1 heterotopia cerebellum	1 dysmature with infarcts kidney, adrenal; 1 amniotic fluid aspiration; 1 aspiration pneumonia and liver cell necrosis
2	3	1	0	1 heterotopia cerebellum	3 hypoplastic left heart; 1 hypoplastic aorta (repaired surgically); 1 tetralogy of Fallot (repaired surgically)
1	2	0	0		1 gastroschisis repaired (aspiration); 1 hypoplastic kidney and hyaline membrane disease; 1 left diaphragmatic hernia and multiple congenital anomalies
	1	0	0		Osteomalacia, nephrocalcinosis, craniosynostosis (repaired)
3	1	1	0	1 acute meningitis (<i>Esch. coli</i>); 3 minor subarachnoid haemorrhage	2 pulmonary haemorrhage; 1 hyaline membrane disease; 1 enterocolitis and pneumonia
1	1	0	2 (old)		1 oxygen toxicity of lungs with scarring; 1 did well till 'cot death' at 84 dy
1	1	1	1 (old)	1 old massive haemorrhage into ventricles with extension into arachnoid; old ventriculitis, arachnoiditis, hydrocephalus; old infarcts thalamus and central nuclei	

swelling but no cellular reaction. The change is consistent with an insult occurring after birth, perhaps during the seizures. The coexisting coagulation defect produced the massive terminal haemorrhage.

In this case the gross differential diagnosis is that of

subependymal cell plate haemorrhage. The maturity of the infant and the presence of coagulation necrosis of white matter suggest that the haemorrhage occurred into pre-existing areas of infarction in the periventricular white matter.

FIG. 2.—Case 2. Confluent streaky haemorrhages in left cerebral hemisphere, a few punctate haemorrhages in right hemisphere.

Case 3.

Clinical. A male was delivered vaginally at 28 weeks' gestation. The pregnancy had been complicated by vaginal bleeding caused by placenta praevia. The Apgar score at one minute was 4. On admission he had apnoea, hypotonia, acidosis, and hypoxia. He required high oxygen with artificial ventilation for 12 days during which time he developed radiological evidence of pulmonary oxygen toxicity and retrolental fibroplasia. He was 'jittery' and had an abnormal EEG (mainly left-sided abnormalities). No focal neurological deficit was detected during early examinations. He was subject to numerous respiratory infections and died at 6 months of age.

Pathology. The brain weighed 508 g (normal for age 660 g) and myelination was generally normal. Lateral to the left caudate nucleus was a cyst $1.3 \times 1 \times 1$ cm which communicated with the ventricle (Fig. 3). Posterior to the cyst was a separate linear cavity running into the internal capsule (Fig. 4). The walls of these lesions

FIG. 3.—Case 3. Old cavitated infarct at corner of left lateral ventricle.

FIG. 4.—Case 3. Old infarct in left internal capsule. Note enlargement of ventricle.

were firm and slightly yellow. The left lateral ventricle was three times as wide as the right at the level of the basal ganglia. Within the brainstem the left corticospinal tract was one-third the size of the right (Fig. 5). Microscopical examination showed diffuse gliosis around the old cavitated infarcts and accumulation of

FIG. 5.—Case 3. Marked atrophy of left pyramid in medulla.

haemosiderin pigment in a small subependymal zone. The left corticospinal tract was small and gliotic throughout the brainstem and cord. It lacked the early myelination seen in the right.

Necropsy showed pulmonary scarring, emphysema, and retrolental fibroplasia, the result of oxygen toxicity.

Comment. This brain showed the sequelae of ischaemic insult in a premature baby who survived 6 months. The cysts represented the site of early periventricular infarction which had become cavitated and surrounded by gliosis. The devastating effects on the ipsilateral corticospinal tract are expressed as descending degeneration and gliosis. This lesion is placed so that it could produce a spastic hemiplegia. Fibres of the corpus callosum were probably also interrupted.

Case 4.

Clinical. A 2100 g female was born to a 29-year-old gravida I diabetic. The pregnancy was complicated by toxæmia and hydramnios and was terminated at 32 weeks by caesarean section because of fetal distress. The Apgar score at birth was 2. The baby was cyanotic, the heart rate less than 50/minute. She required

resuscitation at birth and in the first 1½ hours had at least one cardiac arrest, and required resuscitation two more times as well. Persistent cyanosis, an enlarged heart and liver, and a loud systolic murmur were present. Congestive heart failure was treated with digitalis and diuretics. Bradycardia, hypocalcaemia, acidosis, hyperbilirubinaemia, and anaemia were all problems in the first 6 days of life. A cardiac catheterization was performed and a diagnosis of possible common atrium, small ventricular septal defect, tricuspid stenosis, persistent ductus arteriosus, bilateral superior vena cava, and left azygos continuation of the inferior vena cava was made. Subsequently she remained in heart failure, developed septicaemia, and was treated with antibiotics. She became hyponatraemic. In spite of ligation of the persistent ductus arteriosus she remained in heart failure, her PCO_2 increased, and she had episodes of apnoea. The heart rate varied, being sometimes slow and steady and other times irregular. She required assisted ventilation. She had developed pleural effusions and died on the 26th day of life.

Pathology. The brain contained lesions at two sites, some clustered 1–1.5 cm from the lateral angle of each lateral ventricle and the others in a line lateral to and paralleling the posterior horns. Some lesions were small, cavitated, rusty brown areas 0.2–0.3 cm in diameter, and the others were similar sized, white, and opaque. Microscopical examination showed older lesions to be cavitated, and containing foamy and haemosiderin-filled macrophages, reactive astrocytes, and irregular, lumpy basophilic strands (Fig. 6). A Holzer stain showed coarse fibrillary gliosis. Recent lesions were intensely eosinophilic and contained pyknotic nuclei and axonal swellings (Fig. 7). No cellular reaction was seen. The subependymal cell plate over the left caudate nucleus was honey-combed by a series of microcysts. Haemosiderin-filled macrophages and reactive astrocytes surrounded the cysts.

The remainder of the necropsy showed a complex cardiac malformation with an endocardial cushion defect, single atrium, atresia of pulmonary veins, with asplenia and other minor congenital anomalies.

FIG. 6.—Case 4. Old scar with astrocytes and 'encrusted' basophilic masses (arrows). (Haematoxylin and eosin. $\times 400$.)

FIG. 7.—Case 4. Area of very recent periventricular leucomalacia in lower right hand corner. (Haematoxylin and eosin $\times 136$.)

Comment. Old lesions dating from the cardiac arrests suffered at the time of birth and very recent ones occurring during the terminal episodes of bradycardia and apnoea were present. The child was of 32 weeks' gestation, and had also suffered several weeks before death a small subependymal cell plate haemorrhage which had cavitated.

Results

In these cases the underlying diseases varied so widely that grouping was difficult. Gestational age and survival after birth also varied widely. About two-thirds of all the cases had arterial pH, PO_2 , and PCO_2 levels recorded at least once which indicated that at some time the infants were acidotic, hypoxic, or hypercapnic. Hypoglycaemia was not a significant factor, for all except 2 had blood sugars within the normal range. About half of the infants had hypocalcaemia and half had raised serum bilirubin. Blood pressure was rarely recorded so periods of hypotension are poorly documented.

The gross and microscopical pathology of the lesions was classic (Banker and Larroche, 1962;

De Reuck *et al.*, 1972). On gross examination white, opaque foci of coagulation necrosis, several mm in diameter lay just anterior to the lateral ventricles (corona radiata), around the lateral angles of the lateral ventricles anteriorly, and around the posterior horns of the ventricles in the parieto-occipital region (external and internal sagittal strata). The areas of necrosis were occasionally stained yellow in infants with hyperbilirubinaemia. In 11 of the cases the lesions were seen grossly, and in the rest of the cases were microscopical findings only. The lesions were not always bilateral. Microscopically the changes varied with the age of the lesion. The earliest change was coagulation necrosis shown by eosinophilia and homogenization of the fine fibrillar background of the brain (a change brilliantly shown in the Periodic Acid Schiff stain) with pyknosis and loss of nuclei. Axonal swellings might be seen before any other cellular reaction. Then a few microglia were evident. Macrophages and hypertrophied astrocytes appeared after a few days. The older lesions (as represented by an

incidental microscopical finding in an infant dying at 84 days of crib death) consisted of a cluster of vesicular astrocyte nuclei, a few lumpy basophilic rods (encrusted damaged axons), and fibrillary gliosis which was well shown in a Holzer stain.

It is impossible to date lesions precisely, and the age of the old gliotic ones can only be estimated in days or weeks. Most of the lesions seem to date from around the time of birth and correlate fairly well with clinically noted episodes of cardio-respiratory embarrassment (during which episodes blood pressure levels were not recorded). Case 4 is included to illustrate the occurrence of lesions of different ages in the same brain, some so recent there was no cellular reaction while others were older and contained macrophages and glial scarring.

A zone of reactive gliosis extended far beyond the focal area of necrosis, even to the subcortical zone in some cases. In some brains reactive astrocytes with prominent cytoplasm were the main lesion. This change always accompanied periventricular leucomalacia, and we considered it part of the reaction to injury. This may be 'telencephalic leucomalacia' (Gilles and Murphy, 1969; Leviton and Gilles, 1971, 1973).

We made additional observations. Haemorrhage in the areas of periventricular leucomalacia varied

from microscopical perivascular haemorrhages to petechiae (Fig. 8), to linear streaks of haemorrhage extending radially from the corners of the ventricle into white matter. Sometimes older haemorrhages, rusty brown grossly, contained haemosiderin-filled macrophages when examined microscopically. These small secondary haemorrhages occurred without recorded disturbances in coagulation. In several infants with thrombocytopenia or disseminated intravascular coagulation, massive fatal bleeding occurred into the brain and extended into the ventricles (Case 1, Fig. 1). These massive haemorrhages probably began as petechiae which increased and became confluent in the infarcted areas (Case 2, Fig. 2).

Cavities varied from microcysts to more than 1 cm in diameter. The cysts contained foamy macrophages early on; as they got older their walls came to consist of a mat of astroglial fibrils. These old infarcts with cavitation and gliosis represent one kind of 'porencephaly' (Norman, Urich, and Woods, 1958). Grossly visible descending long tract degeneration results when these infarcts are large and destroy enough axons in the internal capsule as it sweeps down by the corner of the lateral ventricles (Case 3).

Polymorphonuclear leucocytes were never

FIG. 8.—Cluster of petechiae at corner of left ventricle. Streaky haemorrhages and white areas (arrow) of periventricular leucomalacia on right.

present, unlike cerebral infarcts in adults. The reason for this is not clear.

We found convincing anoxic neuronal changes in only 3 cases.

Discussion

De Reuck (1971) showed a watershed in the periventricular white matter where ventriculofugal and ventriculopetal arteries meet, and suggested that failure of perfusion is the cause of the lesion. De Reuck *et al.* (1972) pointed out that this periventricular site for infarction might be determined by the fact that in infants this is a metabolically active area (Davison and Dobbing, 1968) when compared with the same site in adults.

Extensive experimental work has been done on asphyxia (Brierley and Excell, 1966; Ames *et al.*, 1968; Cantu and Ames, 1969; Miller and Myers, 1970; Myers, 1969a, b, 1972), and it has been possible to vary the site of experimentally produced infarcts by varying the duration and severity of the ischaemic insult (Myers, 1972). The pattern of periventricular leucomalacia, however, is particularly human, and has been reproduced only in cats (Abramowicz, 1964) whose cerebral blood supply is similar to the human neonate.

The incidence of periventricular leucomalacia in our material is one-third that of Banker and Larroche (1962). This probably reflects improvement in neonatal intensive care over the last 11 years.

In examining the clinical data of our cases, which is similar to that of Banker and Larroche (1962) and De Reuck *et al.* (1972), it becomes evident that the element common to all was an episode of cardiorespiratory embarrassment. Though blood pressures were rarely recorded, hypotension is almost certainly present in these episodes and the resultant failure of perfusion causes ischaemia and infarction. It is probably significant that the commonest congenital heart lesion was hypoplastic left heart. In our material classic anoxic neuronal changes were rare, a finding similar to that of De Reuck *et al.* (1972) though Banker and Larroche (1962) recorded frequent cortical changes. The absence of the classic anoxic changes weigh in favour of regarding the cause of periventricular leucomalacia as a localized failure of perfusion rather than generalized hypoxia.

We found haemorrhage in a quarter of our cases. This was interpreted as bleeding into areas of infarction once circulation was restored. Bleeding was massive if a haemorrhagic diathesis was present. De Reuck *et al.* (1972) found no haemorrhages in their cases, an observation they used to deny Schwartz's (1961) suggestion that the lesions

resulted from obstruction in the Galenic system of veins. We agree with De Reuck *et al.* (1972) that these lesions are not the result of stasis in the Galenic system, but in our cases are secondary haemorrhages occurring into areas of infarction.

We differentiated the haemorrhagic lesions in our cases from germinal eminence haemorrhages which occur from the terminal vein into the subependymal cell plate of infants less than 32 to 33 weeks' gestation and may cavitate if the baby lives (Larroche, 1972). Periventricular leucomalacia and subependymal cell plate haemorrhage can coexist in the same brain, a good example being Case 4.

The cavities situated at the corner of the ventricle with resulting descending degeneration of the corticospinal tract (Case 4) form an anatomical basis for a spastic hemiplegia. If such a lesion occurred bilaterally, the basis for a spastic quadriplegia is present. All our cases were less than 6 months of age, and motor defects and mental function were not assessed. It is impossible to predict whether the early clinical observations of alterations in tone and seizures (in one-half the cases) would have correlated with altered mental function at a later age. In half our cases the lesion was found only on microscopical examination, and it is difficult to know whether these minute infarcts would have caused detectable clinical deficit later. In the group described by De Reuck *et al.* (1972), all those older than 6 months were retarded and had major motor deficits, but their cases had much more severe lesions as shown by considerable loss of cerebral tissue indicated by large ventricles or cavities. Clearly the lesion varies in size, and the large infarcts cause severe sequelae (De Reuck *et al.*, 1972).

Why were no polymorphonuclear leucocytes seen in the lesion? An infant is capable of reacting to infection with polymorphonuclear leucocytes. But, with infarction, even though large infantile infarcts cavitate, small ones often do not. Only a fibrillary glial scar in which the necrotic cell bodies and processes persist as basophilic structures is left. The tendency of microscopical infantile infarcts to show persistence of original structures which encrust and may ultimately calcify may be due to the lack of lytic enzymes from the polymorphonuclear leucocytes which react to necrosis in adult brains.

Conclusions

Periventricular leucomalacia was examined in a total of 28 newborn infants. The lesions varied considerably in size. Secondary haemorrhage can occur into these periventricular infarcts and become massive. Either with or without haemorrhages there can be considerable cerebral damage which

results in gliotic cavitated cerebral infarcts which cause descending degeneration of long tracts. The infarcts are thought to result from failure of perfusion (ischaemia) in a watershed between ventriculopetal and ventriculofugal circulations.

The authors thank Drs. Paul Swyer and Graham Chance for access to the clinical records for these cases.

REFERENCES

- Abramowicz, A. (1964). The pathogenesis of experimental periventricular cerebral necrosis and its possible relation to the periventricular leucomalacia of birth trauma. *Journal of Neurology, Neurosurgery and Psychiatry*, **27**, 85.
- Ames, A., Wright, L., Kowada, M., Thurston, J. M., and Majno, G. (1968). Cerebral ischemia. II. The no-reflow phenomenon. *American Journal of Pathology*, **52**, 437.
- Banker, B. Q., and Larroche, J. C. (1962). Periventricular leukomalacia of infancy. A form of neonatal anoxic encephalopathy. *Archives of Neurology*, **7**, 386.
- Brierley, J. B., and Excell, B. J. (1966). The effects of profound systemic hypotension upon the brain of *M. Rhesus*. Physiological and pathological observations. *Brain*, **89**, 269.
- Cantu, R. C., and Ames, A. (1969). Distribution of vascular lesions caused by cerebral ischemia. Relation to survival. *Neurology*, **19**, 128.
- Davison, A. N., and Dobbing, J. (1968). The developing brain. In *Applied Neurochemistry*, p. 253. Davis, Philadelphia.
- De Reuck, J. (1971). The human periventricular arterial blood supply and the anatomy of cerebral infarctions. *European Neurology*, **5**, 321.
- De Reuck, J., Chattha, A. S., and Richardson, E. P., Jr. (1972). Pathogenesis and evolution of periventricular leukomalacia in infancy. *Archives of Neurology*, **27**, 229.
- Gilles, F. H., and Murphy, S. F. (1969). Perinatal telencephalic leukoencephalopathy. *Journal of Neurology, Neurosurgery and Psychiatry*, **32**, 404.
- Larroche, J. C. (1972). Sub-ependymal pseudo-cysts in the newborn. *Biology of the Neonate*, **21**, 170.
- Leviton, A., and Gilles, F. H. (1971). Morphologic correlates of age at death of infants with perinatal telencephalic leukoencephalopathy. *American Journal of Pathology*, **65**, 303.
- Leviton, A., and Gilles, F. H. (1973). An epidemiologic study of perinatal telencephalic leukoencephalopathy in an autopsy population. *Journal of the Neurological Sciences*, **18**, 53.
- Miller, J. R., and Myers, R. E. (1970). Neurological effects of systemic circulatory arrest in the monkey. *Neurology*, **20**, 715.
- Myers, R. E. (1969a). Brain pathology following fetal vascular occlusion. An experimental study. *Investigative Ophthalmology*, **8**, 41.
- Myers, R. E. (1969b). Cystic brain alteration after incomplete placental abruption in monkey. *Archives of Neurology*, **21**, 133.
- Myers, R. E. (1972). Two patterns of perinatal brain damage and their conditions of occurrence. *American Journal of Obstetrics and Gynecology*, **112**, 246.
- Norman, R. M., Urich, H., and Woods, G. E. (1958). The relationship between prenatal porencephaly and the encephalomalacias of early life. *Journal of Mental Science*, **104**, 758.
- Schwartz, P. (1961). *Birth Injuries of the Newborn*, p. 11. Hafner, New York.
- Van den Bergh, R., and Vander Eecken, H. (1968). Anatomy and embryology of cerebral circulation. In *Cerebral Circulation. Progress in Brain Research*, Vol. 30, p. 1. Ed. by W. Luyendijk. Elsevier, Amsterdam.
- Virchow, R. (1867). Zur pathologischen Anatomie des Gehirns. I. Congenitale Encephalitis und Myelitis. *Virchows Archiv für Pathologische Anatomie und Physiologie und für Klinische Medizin*, **38**, 129.

Correspondence to Dr. M. G. Norman, Department of Pathology, The Hospital for Sick Children, 555 University Avenue, Toronto M5G 1X8, Ontario, Canada.