Spongy degeneration in the white matter of the central nervous system in the newborn: pathological findings in three infants, one with hyperglycinaemia

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Infantile spongy degeneration of the white matter of the central nervous system is a rare disorder of unknown pathogenesis. Reported cases have generally been described under the heading of spongy degeneration of van Bogaert and Bertrand type or as Canavan’s type of diffuse sclerosis (see van Bogaert and Bertrand, 1967). The clinical and pathological features of the reported cases have been closely similar and a familial occurrence has been established; for these reasons it has been claimed that the disorder is a nosological entity (van Bogaert and Bertrand, 1967). However, a microscopic appearance in the central nervous system closely similar to that of van Bogaert and Bertrand’s disease may be seen in association with some amino-acidurias—notably in maple syrup urine disease (Crome, Dutton, and Ross, 1961; Silberman, Dancis, and Feigin, 1961; Diezel and Martin, 1964; Menkes, Philippart, and Fiol, 1965) and in hyperglycinaemia (Donohue, 1967; Rushton, 1968).

Pathologically, infantile spongy change is confined to white matter and myelinated grey masses; the vacuolation is usually associated with a considerable degree of myelin poverty, but products of myelin degeneration typical of a demyelinating disorder are not seen. These apparently incompatible findings have given rise to debate as to whether infantile spongy degeneration is primarily a myelin disease or an oedematous process with secondary myelin loss.

Severe spongy change of the white matter is described here in three infants who died in the first month of life: two were born prematurely; the third, who was born at term, suffered from hyperglycinaemia. A number of pathological findings peculiar to the occurrence of the disease at an age when the nervous system is normally actively myelinating provide evidence that infantile spongy degeneration is a primary myelin disorder and indicate that the poverty of myelin is at least in part due to a reduction in the rate of its formation.

MATERIAL AND METHODS

The brain and spinal cord and samples of other tissues were fixed in 4% formaldehyde in 10% saline. Tissue blocks were embedded in paraffin wax reinforced with 10% Alston dental wax (Dental Manufacturing Company) and 14% beeswax. The usual neuropathological staining techniques for paraffin sections were employed together with Palmgren’s method (1948) for nerve fibres and Gallay’s method (1963) for microglia.

Frozen sections from selected blocks were stained for myelin with the Kulchitsky-Pal method and the propylene glycol Sudan Black B method (Chiffelle and Putt, 1951), for neutral fat with the triethyl phosphate Oil Red O method, for microglia with the Weil-Davenport technique, and for astrocytes with Cajal’s gold sublimate method.

The volume proportions of myelinated nerve fibres and of other constituents of spinal cord white matter were measured in case 1 and in controls using an integrating eyepiece of the point-counting variety (Zeiss). In this analysis, frozen sections stained with Sudan Black B were examined with ×100 oil immersion objective. In each case, 1,000 eyepiece points were recorded over random microscopic fields within the posterior funiculus of the spinal cord. Seven infants without spongy change, born at 28 to 32 weeks gestation and dying within one to four days of birth, served as controls; the brain weight of these control cases ranged from 120 to 220 g.

CASE REPORTS

CASE 1 (Hammersmith Hospital no. 300304) M.G., a female infant, was the first liveborn child of English parents; the mother’s two previous pregnancies had ended at 14 and 24 weeks. This baby was born at 26 weeks gestation, weighing 980 g. She was in poor condition at birth and required resuscitation, but was breathing spontaneously by 15 minutes of age. In the first seven days of life she suffered some mild respiratory distress but gradually recovered from this. She made satisfactory progress until 10 days of age when she had a short apnoeic attack. Episodes of apnoea recurred at intervals.

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thereafter, becoming more frequent and less responsive to treatment. On the 24th day of life she became apnoeic and died despite resuscitative measures.

Neurological examination was carried out several times and no abnormality was detected. Palmar grasp and Moro reflexes were present, while the glabellar tap and pupillary light reflexes were absent, normal findings in an infant of less than 30 weeks gestation. Electroencephalogram recordings taken on the first and 15th days of life showed no unusual features.

Necropsy was performed 30 hours after death. A right-sided pneumothorax was present with pulmonary and mediastinal interstitial emphysema and with pneumopericardium. Microscopically, the lungs showed widely distended interlobular septae with collapse of most of the alveoli, but no evidence of parenchymal disease. No significant abnormality was found in other thoracic and abdominal organs.

NEUROPATHOLOGICAL FINDINGS

MACROSCOPIC The dura mater, venous sinuses, and the external aspect of the brain (205 g) and spinal cord appeared normal. The cerebral hemispheres had well formed secondary sulci, but no tertiary sulci. Coronal slices of the cerebrum showed no unusual features apart from two paraventricular foci of haemorrhage, both less than 3 mm in diameter, in the region of the terminal vein on each side; neither had ruptured into the lateral ventricle.

MICROSCOPIC The most striking pathological feature in the central nervous system was spongy change of the myelinated white matter. Affected areas contained a variable number of ovoid or cylindrical vacuoles measuring up to 100 μ in their smallest diameter and 300 μ in length (Figs. 1 and 2). In regions such as the white columns of the spinal cord most of the nerve fibres lie in parallel, the vacuoles were seen to be orientated so that their long axes followed the course of the fibres (Fig. 2). No material was demonstrable within the vacuoles in either frozen or paraffin sections. The cellularity of the spongy regions was not increased; astrocytes and oligodendroglia were normal in number and appearance, and there was no infiltration with microglial cells. Fibrous gliosis was not present. Nerve fibres were pushed aside by the vacuoles (Fig. 2), but features of axonal degeneration, such as fragmentation and nodular swelling, were not seen.

Many cells containing neutral fat were found in the posterior funiculus of the spinal cord, in the corpus callosum, and, to a lesser extent, in the centrum semiovale of the cerebral white matter—that is, in sites in which smaller although variable numbers of such cells are normally seen in infants dying in the neonatal period. These cells did not stain with the silver impregnation.
methods for microglia, and, compared with phagocytic cells, had a relatively scanty cytoplasm and lipid content (Fig. 5a). Except in the posterior columns of the spinal cord, the fat-laden cells were not associated with spongy change.

Comparison with other infants of 28 to 32 weeks gestation showed that there was generalized poverty of myelin (Figs. 3a, b), although the distribution of myelin within brain and spinal cord was normal. An estimate of the degree of myelin poverty was obtained using the integrating eyepiece (Zeiss) to measure the volume proportions of constituents of spinal cord white matter; the volume occupied by myelinated nerve fibres was found to be reduced by factors of 27% in the lumbar region and 37% in the cervical region compared with controls (Table). Vacuoles occupied 9% (lumbar) and 5% (cervical) of the total volume; if to that extent the spinal cord white matter was swollen the corrected reduction in proportional volume of myelinated fibres was 20% and 34% respectively. Since the myelin sheaths were not generally smaller than normal, the deficit was due to a decrease in their number. A few sheaths were

FIG. 3. Case 1. (a) Cervical spinal cord showing generalized poverty of myelin. Note that the spinal nerve roots stain heavily. (b) Normal appearance of the cervical spinal cord at 28 to 30 weeks gestation. Kulchitsky-Pal × 16

FIG. 4. Case 1. (a) Spinal cord white matter. The vacuoles have walls which stain in the same way as myelin. Myelin sheaths are reduced in number compared with normal shown in (b). Sudan Black × 850
Spongy degeneration in the newborn

abnormally large and there were all gradations between these and vacuoles, most of which had walls with tinctorial properties identical with those of myelin (Fig. 4a).

The spongy change was strictly confined to myelinated parts of the central nervous system and spared non-myelinated regions such as the cerebral white matter, and the optic, cortico-spinal (Fig. 1), and spino-thalamic tracts. In general, the spongy state was pronounced where myelin sheaths were most numerous and less remarkable in sites where myelin formation had recently begun.

Cerebral hemispheres A few myelin sheaths were present in the globus pallidus and its efferent bundles, the nucleus lateralis ventralis of the thalamus, the subthalamic nucleus, and the red nucleus. Spongy change was represented only by occasional vacuoles in ansa lenticularis.

Cerebellum Vacuolation was prominent in the inferior cerebellar peduncles and in the central white matter of the vermis where a considerable quantity of myelin had been laid down. A small number of myelin sheaths was present in the superior peduncle, but this was not associated with spongy change. The middle peduncle and the intralobular white matter were non-myelinated and non-vacuolated.

Midbrain and pons The intramedullary part of the cranial nerve tracts, median longitudinal bundles, medial and lateral lemnisci were heavily myelinated and showed marked spongy change. A smaller number of vacuoles were present elsewhere in the tegmental region, while the ventral parts of both midbrain and pons were normal.

Medulla The vacuolation in the median longitudinal bundles and medial lemnisci was rather more severe at this level than in the pons, and was also pronounced in the tracts of the spinal divisions of the trigeminal nerves, in the lateral cuneate nuclei, and in the ventral part of the tegmental region. The floor of the fourth ventricle and cranial nerve nuclei, the medial cuneate nuclei, inferior olivary nuclei, and pyramids were spared. The ventral spino-thalamic tracts were identified at the level

TABLE

CASE 1: VOLUME PERCENT OF CONSTITUENTS IN SECTIONS OF SPINAL CORD WHITE MATTER (POSTERIOR COLUMNS)

<table>
<thead>
<tr>
<th></th>
<th>Myelinated nerve fibres</th>
<th>Vacuoles</th>
<th>Non-myelinated nerve fibres, nuclei, blood vessels</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cervical</td>
<td>40</td>
<td>5</td>
<td>55</td>
</tr>
<tr>
<td></td>
<td>(68.8 ± 5.0)*</td>
<td>(35.2 ± 5.0)*</td>
<td></td>
</tr>
<tr>
<td>Lumbar</td>
<td>44</td>
<td>9</td>
<td>47</td>
</tr>
<tr>
<td></td>
<td>(60.0 ± 1.4)*</td>
<td>(40.0 ± 1.4)*</td>
<td></td>
</tr>
</tbody>
</table>

*Mean values for controls, with 1 Standard Deviation.
of the decussation of the pyramids and were unmyelinated and free of vacuoles.

**Spinal cord**  Spongy change was marked in the myelinated parts of the spinal cord, but the grey matter and the non-myelinated tracts (Fig. 1), both crossed and uncrossed, were unaffected. In the spinal nerve roots the spongy change ceased abruptly at the attachment to the spinal cord; nerve roots beyond this point were heavily myelinated and appeared normal (Fig. 3a).

Nerve cells in all parts of the brain and spinal cord were normal. No unusual features were seen in posterior root ganglia, in peripheral nerves, or in skeletal muscle.

**CASE 2** (Hammersmith Hospital no. 313691) M.P., a female infant of Spanish parents, was born at 26 weeks gestation, weighing 900 g. She required resuscitation at birth but was breathing normally by 8 minutes of age. Short apnoeic attacks occurred on the second and third days of life, but at this time respiratory movements were easily restarted with gentle tactile stimulation. Increasing jaundice necessitated an exchange transfusion at 72 hours of age. On the sixth day of life apnoeic episodes became more frequent, pulmonary haemorrhage occurred, and there was cardiac slowing and death.

**Neurological examination** was performed on the first and third days of life and revealed no abnormality. The Moro response, plantar and palmar grasp reflexes were present. The glabellar tap reflex was absent and there was no pupillary reaction to light. These findings were in keeping with a gestation of 26 weeks.

**Necropsy** was done within 24 hours of death. The lungs were markedly haemorrhagic, and microscopically showed patchy resorption atelectasis with much recently shed blood in interstitial tissue, alveoli, and bronchi. Other thoracic and abdominal viscera appeared normal.

**NEUROPATHOLOGICAL FINDINGS**

**MACROSCOPIC**  The dural folds and venous sinuses were normal. The brain (120 g) had a convolutional pattern in keeping with 26 weeks gestation, with well-formed primary fissures but only a few shallow secondary sulci. There was a film of blood in the subarachnoid space over much of the surface of the brain. Coronal slices revealed a small intraventricular haemorrhage but no other abnormality.

**MICROSCOPIC** Findings were closely similar to those in case 1. Spongy change (Fig. 6) was present in all myelinated parts of the brain and spinal cord and was accompanied by generalized myelin poverty (Fig. 7), although the distribution of myelin in the various regions was appropriate for the gestational age. In frozen sections of spinal cord stained with Sudan Black B, myelin sheaths were seen to be less numerous than normal, some were abnormally large and many vacuoles had walls which appeared to be formed of myelin. Spongy change was not associated with astrocytic or microglial reaction and there was no fibrous gliosis. Axon degeneration was not seen. Unusually large numbers of glial cells carrying

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**FIG. 6.** Case 2. Tegmental region of medulla with median longitudinal bundle (arrows), showing severe generalized vacuolation.  
**H & E × 300.**

**FIG. 7.** Case 2. Lumbar spinal cord with marked myelin deficit. Compare with Figure 3 (b).  
**Kulchitsky-Pal × 16.**
neutral fat were found in those sites in which such cells are normally found in newborn babies. Except in the dorsal columns of the spinal cord, lipid-containing cells were not present in spongy areas.

Spongy change was most pronounced in parts where myelin sheaths were numerous, such as the medial and lateral lemnisci, median longitudinal bundles (Fig. 6), inferior cerebellar peduncles, intramedullary portions of cranial nerve tracts, and the reticular formation, but also involved tracts such as the brachium conjunctivum and the efferent bundles of the globus pallidus in which myelin formation had recently begun. Myelinated columns of the spinal cord were spongy, but the cortico-spinal tracts and grey matter were not affected. The cerebral white matter and intralobular white matter of the cerebellum were non-myelinated and free of vacuolation.

A few scattered neurones in the thalamus, red nucleus, substantia nigra, and reticular formation of the brainstem showed 'ischaemic' cell change, probably attributable to hypoxæmia. Nerve cells in the cerebral cortex, lentiform nucleus, cerebellum, and spinal cord appeared normal.

CASE 3 (Hammersmith Hospital no. 318680) R.H., a female infant of unrelated English parents, was born at term, weighing 3·5 kg. She was well at birth, but shortly afterwards developed muscular hypotonia and refused to feed. Hypotonia became progressively more severe, eventually leading to respiratory embarrassment with cyanosis. Continuous artificial respiration was started at the age of 4 days. A sibling was known to have died aged 4 days having shown similar clinical signs; for this reason, a hereditary systemic metabolic abnormality was suspected. On investigation the plasma glycine level was found to be 8 mg/100 ml. (normal less than 2 mg/100 ml.). Treatment with a protein-free diet was begun at 5 days of age. Subsequently there was an increase in muscular tone and by 9 days of age spontaneous respiration had returned; at this time the plasma glycine level had fallen to 6 mg/100 ml.

At the age of 15 days a number of fits occurred and a macular eruption appeared on the legs. Blood culture revealed Pseudomonas pyocyanea septicaemia. There was then progressive deterioration with death at the age of 20 days.

Neurological examination was made on several occasions. No abnormality was found apart from generalized hypotonia; cranial nerve function, tendon reflexes, and cutaneous sensation appeared normal. The electroencephalogram, which had previously been flat, showed increased activity after commencement of the protein-free diet.

Necropsy was carried out four hours after death. The basal regions of each lung were found to be consolidated; microscopically, the air spaces were filled with masses of microorganisms, fibrin, and mononuclear cells. The lower part of the aorta contained adherent mural thrombus presumably propagated by a catheter inserted through the umbilical artery. The thrombus extended into and occluded the iliac arteries and the right renal artery; the right kidney was totally infarcted.

The liver (152 g) showed no obvious macroscopic abnormality, but on histological examination vacuoles were seen in the cytoplasm of parenchymal cells. No material was identified in most of the vacuoles; glycogen was not demonstrable, and only a few cells around the portal triads contained excessive quantities of fat. There were no features of portal cirrhosis.

NEUROPATHOLOGICAL FINDINGS

MACROSCOPIC The dura mater and venous sinuses appeared normal. The leptomeninges over the base of the brain showed well-marked opacity and a substantial collection of pus was found in the cisterna magna. Other external features of the brain (420 g) were normal, there being no cortical atrophy or microgyria. No abnormality was seen in the cut surfaces of the brain or spinal cord.

MICROSCOPIC Evidence of two disease processes was found histologically. First, the presence of suppurative meningitis was confirmed; less intense inflammatory change was also seen in the ventricular system. Secondly, spongioform degeneration was found in myelinated regions of the brain and, to a lesser extent, of the spinal cord.

Features of the spongioform disease were similar to that in cases 1 and 2, except that astrocyte proliferation and hypertrophy was prominent and there was no myelin poverty. Ovoid vacuoles measuring up to 300 \( \mu \) in length were present in varying numbers in all myelinated areas, while non-myelinated parts of the cerebral white matter—that is, the centrum semi-ovale and the subcortical regions—were free of spongy change. Many large reactive astrocytes with abundant eosinophilic cytoplasm were found both in myelinated and non-myelinated white matter. There was no obvious myelin poverty or retardation of myelin formation, compared with other infants without spongy disease dying in the first month of post-natal life; myelination had begun in the cortico-spinal tracts and was associated with a mild degree of spongy change. However, lipid-filled glial cells of the same morphology as those seen in other newborn babies were present in excessive numbers in the corpus callosum and the central cerebral white matter (Fig. 8a), although not in the spinal cord.

Nerve cells and their processes were normal in appearance in all parts of the neuraxis. No abnormality was found in peripheral nerves, cervical sympathetic ganglia, or skeletal muscle.

DISCUSSION

Infantile spongioform degeneration is characterized microscopically by numerous vacuoles in the white matter, astrocyte proliferation and hypertrophy, myelin poverty, and an absence of products of myelin degeneration. Nerve cells appear normal in all parts of the neuraxis and axons are intact even where the myelin deficit is severe (van Bogaert and Bertrand, 1967). The histological features of the nervous system in the infants described in this communication, while limited in extent in the incompletely
myelinated brain, are closely similar to those previously recorded in spongy degeneration except that astrocytes were not increased in number in cases 1 and 2; these infants were born at 26 weeks gestation and the lack of glial reaction may be attributed to immaturity.

Perhaps the most important microscopic finding in the newborn is that the spongy change was limited to those parts of the brain and spinal cord in which myelin formation had begun. For example, in the spinal cords of cases 1 and 2, vacuolation was seen in the posterior columns, but the lateral columns, as yet unmyelinated, appeared normal. In each of the three cases the major part of the cerebral white matter was unmyelinated and free of spongy change. This is clearly evidence that infantile spongy degeneration is a disease of myelin and yet previous reports of spongy degeneration of the white matter in newborn infants (Sachs, Brown, and Aguilar, 1965; Rushton, 1968) have not laid emphasis on the freedom of non-myelinated areas from spongy change. Furthermore the demonstration in cases 1 and 2 of vacuoles with walls which stained as for myelin (Fig. 4a) indicates that the vacuoles are formed within the myelin sheaths. This observation is supported by the electron microscopic studies of Adachi, Wallace, Schneck, and Volk (1966) and Gambetti, Mellman, and Gonatas (1969), which have shown that the vacuolation in infantile spongy degeneration commences between the lamellae of the myelin sheath; the ultrastructural appearance is similar to that of experimental triethyl tin intoxication (Aleu, Katzman, and Terry, 1963) in which there is massive myelin vacuolization, and is quite different from human white matter oedema associated with inflammatory disease, infarcts, and tumours (Aleu, Samuels, and Ransohoff, 1966) in which fluid accumulation is largely extracellular and only occasional intramyelin vacuoles are seen.

In cases 1 and 2 there was generalized poverty of myelin. Measurements made on spinal cord white matter in case 1 showed that this amounted to a 20 to 34% decrease compared with other infants, at the same stage of gestation. However, the distribution of myelin was approximately normal and was advanced enough to be appropriate at least to the gestational age at birth. It was not possible to determine whether myelination was topographically retarded after birth, even in case 1 who survived for 24 days, since normal parameters of neonatal myelin formation for intervals of less than one month have not been established. Consequently there was no microscopic evidence in
cases 1 and 2 to indicate whether the disease process commenced before or after birth. Neither were clinical findings helpful in this respect; abnormal neurological signs were not detected despite repeated examination, but in such immature babies there is normally nearly complete muscular hypotonia and only limited reflex activity (Robinson, 1966).

Case 3, who suffered from hyperglycinaemia, showed no obvious myelin deficit, although surviving for 20 days. In some disorders of aminoacid metabolism, such as phenylketonuria and maple syrup urine disease, there is evidence that the nervous system is not affected until after birth, presumably because the mother detoxicates the infant while in utero. This is probably true of hyperglycinaemia as well, in view of the clinical history of well-being in the first hours of life followed by sudden and progressive deterioration. The hyperglycinaemic infants described by Rushton (1968) survived for no more than two weeks and yet showed considerable myelin poverty. This suggests that in case 3 dietary measures were effective in arresting the white matter change. Further evidence for this is the remarkable improvement in the electroencephalogram record.

All three cases showed an abnormal accumulation of sudanophilic lipid which is not a feature of older children with spongy disease. A variable but small amount of lipid is present in the cerebral white matter of all babies dying in the neonatal period; the cells which carry the fat do not have the appearance of microglia but are thought to be astrocytes and oligodendrocytes (Wohlwill, 1921; Rydberg, 1932). The fat-containing cells are always found in the same distribution in the newborn baby’s brain, being plentiful in the corpus callosum and centrum semiovale and absent from the subcortical white matter. The significance of this lipid accumulation is not known, but it seems likely that it is a normal process concerned with the growing brain. In each of the three infants with spongy disease the quantity of lipid present was very much greater than normal, yet it was found only within the normal distribution, and the morphology of the fat-containing cells was normal and was not that of phagocytic microglia. Spongy change and fat cells were not found in the same regions except in the spinal cord. These findings, taken together with the myelin poverty, suggest that in infantile spongy disease there is a diminished rate of incorporation of lipid into the myelinating brain.

It must be emphasized that van Bogaert and Bertrand’s disease has many clinical and pathological features in common with the neurological disorders described in association with various hereditary aminoacidurias. In maple syrup urine disease, for example, there is invariably pronounced vacuolation at all levels in the central nervous system, myelin loss with swelling of myelin sheaths but without the production of neutral fat, astrocyte proliferation, and an absence of neuronal and axonal damage (Crome et al., 1961; Silberman et al., 1961; Diezel and Martin, 1964; Menkes et al., 1965). In this communication severe spongiform change is described in an infant (case 3) with hyperglycinaemia. Similar findings have previously been reported in hyperglycinaemia (Donohue, 1967; Rushton, 1968) and in tyrosinaemia (Donohue, 1967). Spongiform degeneration has been described in phenylketonuria by Malamud (1966), although widespread spongiform change was not present in a larger series of phenylketonurics reviewed by Crome and Pare (1960). In addition, the clinical presentation of maple syrup urine disease may be indistinguishable from that of van Bogaert and Bertrand’s disease (Silberman et al., 1961). The earlier descriptions of infantile spongiform degeneration (van Bogaert and Bertrand, 1949; Meyer, 1950) were recorded before the discovery of maple syrup urine disease (Menkes, Hurst, and Craig, 1954) and hyperglycinaemia (Childs, Nyhan, Borden, Bard, and Cooke, 1961) but only one of the later reports of infantile spongiform degeneration lists aminoacid chromatography among the investigations performed; in this case (Donohue, 1967), no abnormal urinary aminoacids were found. Banker, Robertson, and Victor (1964) postulated that spongiform degeneration was associated with a systemic metabolic abnormality largely on the grounds of the characteristic and very remarkable astrocytosis. Sachs et al. (1965) thought that the clinical history of their newborn infants suggested a genetically-determined metabolic abnormality and the clinical course they describe is exactly that of hyperglycinaemia or maple syrup urine disease presenting in the neonatal period.

Infantile spongiform degeneration also has some pathological similarity to Border disease of sheep. This is a congenital disorder with a nervous system lesion characterized by myelin poverty and astrocytic proliferation at all levels in the brain and spinal cord, preservation of axon cylinders and nerve cells, and, in lambs less than 6 months old, accumulation of sudanophilic lipid (Hughes, Kershaw, and Shaw, 1959; Barlow and Dickinson, 1965). Spongiform change of the white matter has not been described, but vacuolation within the lamellae of the myelin sheaths is seen on electron microscopy (Cancilla and Barlow, 1968). In animals which survive, the lesion is ultimately repaired and consequently the myelin deficit is thought to be due to retardation of
myelin formation rather than demyelination. Border disease has been found to be transmissible by the inoculation into pregnant ewes of extracts of tissues from affected foetuses and newborn lambs (Dickinson and Barlow, 1967; Shaw, Winkler, and Terlecki, 1967), indicating that an infective agent is operating during intrauterine life. This raises the possibility that at least some infants with spongy degeneration may be suffering from a transmissible disease.

The significance of spongiform change in the infant's brain has recently been questioned by Feigin, Pena, and Budzilovich (1968) who argue that vacuolation may be due to rapid post-mortem release of carbon dioxide as a result of glucagon lysis. However the localization of the spongiform change within the myelinated parts of the incompletely myelinated brain and the finding that the vacuoles are sited mainly within myelin sheaths provide strong evidence that infantile white matter spongiform change is a genuine feature of a myelin disorder. It seems probable that the lesion may be produced by a number of different pathological influences acting on the myelinating brain. This conclusion receives support from the chemical analysis of cerebral white matter and isolated myelin from two children with spongiform degeneration reported by Kamoshita, Rapin, Suzuki, and Suzuki (1968) in which no specific abnormality was found.

**SUMMARY**

Spongy degeneration of the white matter is described in three newborn infants. In two premature infants who showed no clinical abnormality, the aetiology is unknown. A third infant, who was born at term and presented with progressive muscular weakness, had hyperglycinemia.

Vacuolation was found only in myelinated regions of the brain and spinal cord, confirming that infantile white matter spongiform change is a feature of myelin disorder. An excessive accumulation of non-phagocytic lipid-filled glial cells in the parts of the brain and spinal cord in which smaller numbers of such cells are normally found in newborn babies suggests that the myelin poverty is at least in part due to a slowing in the rate of myelinogenesis. It is postulated that infantile white matter spongiform degeneration may be caused by a number of separate disease processes affecting the myelinating brain.

I am grateful to Professor P. M. Daniel, Professor J. P. M. Tizard, and Dr. Sabina J. Strich for their criticism of this study, to Mr. R. Sallis and staff for technical assistance and to Mr. P. M. Taylor for printing the photographs. The necropsy on case I was performed by the late Dr. M. J. R. Dawkins. The necropsies on cases 2 and 3 were carried out by Dr. J. S. Wigglesworth. The study was undertaken while the author was in receipt of a grant from the Nuffield Foundation.

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J Neurol Neurosurg Psychiatry 1969 32: 328-337
doi: 10.1136/jnnp.32.4.328

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