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Ultrastructure of the Neuroglial Fatty Metamorphosis (Virchow) in the Perinatal Period

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Summary. The ultrastructure of neuroglial fatty metamorphosis (GFM) has been investigated in the telencephalic white matter of 12 premature and mature infants (gestational age 22–40 weeks; survival 0–96 days). GFM was found in all cases apart from a 22-week-old fetus, and involves predominantly astrocytic cells (68.8%), then glioblasts (43.5%), but only 7.4% of oligodendrocytes. GFM, therefore, seems to be independent of the myelination process and indicates the vulnerability of the immature neuroglial population in the metabolic and circulatory disorders of the perinatal period. Since GFM is found in almost all children dying within the early postnatal period, this subtle alteration reflects a special form of minimal brain damage. The relationship between GFM, astrocytic hypertrophy and periventricular leucomalacia and their role in the telencephalic leucoencephalopathy are discussed.

Key words: Neuroglial development – Fatty metamorphosis – Myelin formation – Perinatal period – Minimal brain damage.

Zusammenfassung. Die Gliazellverfettung im unreifen Großhirn-Marklager wurde bei 12 Kindern ultrastrukturell untersucht (Gestationsalter 22–40 Wochen; Überlebenszeit 0–96 Tage). Die „fettige Metamorphose" der Neuroglia (Virchow) fand sich in allen Fällen, ausgenommen den 22 Wochen alten Feten, und betrifft vorwiegend junge Astrozyten (68,8%), ferner zu 43,5% unreife Vorstufen, jedoch nur zu 7.4% die (z.Z. der Geburt erst in Erscheinung tretende) Oligodendroglia. Die Fett-Metamorphose der unreifen Glia stellt einen sensiblen Indikator für metabolisch-zirkulatorische Störungen der Perinatalperiode dar und erfolgt unabhängig von dem Prozeß der Markscheidenbildung. Zusammen mit einer oft auffälligen Astroglia-Proliferation ist die intracytoplasmatische Akkumulation nicht membrangebundener Lipide Ausdruck einer temporären Differenzierungsstörung der unreifen Neuroglia. Die resultierende Reifungsdissoziation mit Unterdrückung der oligodendrozytären Zellinie führt zur retardierten Markscheidenbildung und dem Bild der telencephalen Leucoencephalopathie.

Introduction

The nature of the glial fatty metamorphosis (GFM) in the immature telencephalic white matter (*fettige Metamorphose der Neuroglia* – Virchow, 1867, 1883) has been the subject of controversial interpretations (for review see Mickel and Gilles, 1970; Larroche and Amakawa, 1973; Sumi, 1974; Leech and Alvord, 1974; Friede, 1975). Many authors interpreted the lipid inclusions in glial cells as a physiological event preceding myelination and presumed that GFM mainly concerned precursors of the oligodendroglia. Other authors, however, stressed the pathological nature of GFM (Siegmund, 1923; Schwarz, 1924, 1926; Leech and Alvord, 1974; Schmidt, 1975; Gadsdon and Emery, 1976) as a phenomenon which is confined to certain structures of the immature human forebrain (corpus callosum, periventricular white matter), while other regions undergoing myelination or comparable structures of newborn animals fail to show GFM.

Little information is available concerning gliogenesis in the telencephalic white matter and the classification of the glial cell types which show lipid accumulation. Some ultrastructural aspects were reported by Sumi et al. (1973): The authors described lipid inclusions in glial cells of the telencephalic white matter of monkey fetuses which were stillborn or died spontaneously after birth. However, classification of the affected immature cells was not possible. In a previous ultrastructural study on human material, Schneider et al. (1975) found that lipid inclusions occurred mainly in young astrocytes and glioblasts. The aim of this study was to clarify the role of GFM during neuroglial differentiation and myelinogenesis in the telencephalon of mature and premature infants.

Material and Methods

The prospective telencephalic white matter was studied in 12 babies selected at random. Autopsy was performed within 2–5 h of death. Since several attempts of perfusion via the carotid arteries failed to achieve perfect fixation, immersion fixation was performed in most cases. Tissue samples for electron microscopy were taken from a coronal section through the precentral cortex (Fig. 1). Small cubes (< 1 mm) of the periventricular (I), central (II) and subcortical (III) white matter and the neocortex (IV) were osmificated, dehydrated with ethanol and embedded in micropal (Vestopal W). Semi-thin sections were stained with 5% Giemsa solution. Ultra-thin sections were treated with lead citrate and examined with the electron microscopes Zeiss EM 9 and Zeiss EM 10.

Ultrastructural studies were carried out on at least four blocks taken from zone II (Fig. 1) excluding all samples from necrotic regions. In seven cases the percentage of glial cell types and degree of lipid accumulation were determined by counting 100–140 glial cells in each case, using a 13,000-fold magnification of the electron micrographs.

For light microscopy coronal sections of both hemispheres were embedded in paraffin and celloidin; sections were stained with Nissl, H & E, Sudan black B, Heidenhain-Woelcke. Frozen sections were treated either with impregnation methods (Hortega, Cajal, Bielschowski) or stained with Sudan IV and Sudan black B for demonstration of lipid material.

Results

This group of infants included four mature babies, two premature infants of 38 weeks, five premature infants of 30–36 weeks and one 22-week-old fetus. Death occurred 0–5 days after birth in 9 children; the other children survived 20, 25 and 96 days respectively. Most infants died from cardiorespiratory insuffi-

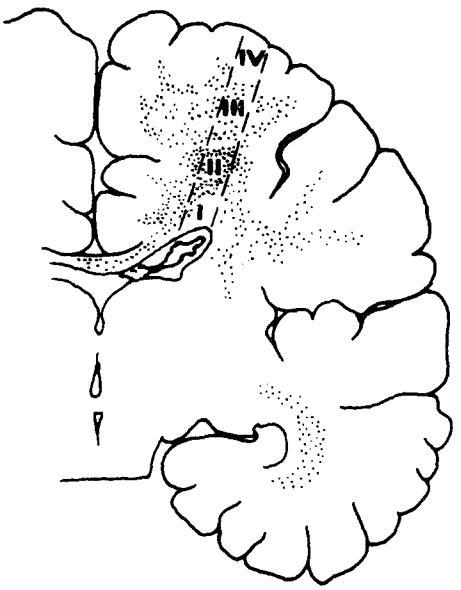

Fig. 1. Distribution of glial fatty metamorphosis in immature telencephalon. Zone I: subependymal zone. Zone II: central white matter. Zone III: subcortical white matter. Zone IV: cortex

ciency after perinatal asphyxia or complications due to malformations (i.e. diaphragmal defects, esophageal atresia). Neurological symptoms were prominent in three children; two of these developed hypotonia and respiratory depression before death. One child – a 28-week-old premature infant – survived severe intrauterine and postnatal asphyxia for 96 days and developed persistent opisthotonus, myoclonic jerks and microcephaly; the autopsy revealed marked microencephaly (brain weight 180 g), widespread lesions in the grey matter and sclerosis of the white matter.

The macroscopical aspects of the other brains varied corresponding to the gestational age. Venous congestion was common and slight subarachnoidal hemorrhages occurred in five infants. Five children showed focal necroses in the telencephalic white matter ("periventricular leucomalacia," PVL); one child demonstrated extensive confluent periventricular necroses.

Light Microscopy

At birth, the central telencephalic white matter (zone II, Fig. 1) contains an immature neuroglial population while the myelin formation is about to begin. The subcortical white matter (zone III) is comparable with zone II, whereas the glial population of the periventricular zone (I), including the subependymal cell layer, is rather heterogeneous. The predominant neuroglial cell type in zone II shows a large ovoid-round pale nucleus and an ill-defined, often vacuolated cytoplasm. Typical dark oligodendrocytes are only rarely found before the 40th week of gestation. A variable number of glial cells show regressive nuclear changes and pyknosis. The typical distribution of GFM was seen in 11 children, although in a variable intensity. The 22-week-old fetus showed no sudanophilic cells in zone II. Sudanophilic glial cells occur mainly in the deep (II) and subcortical

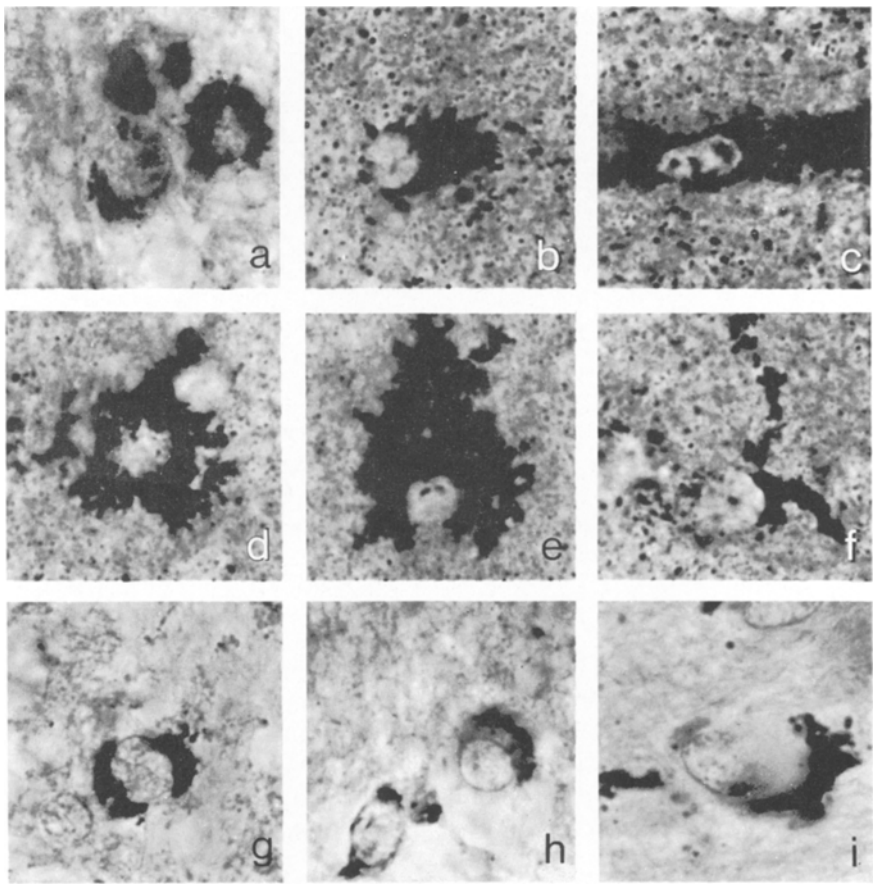

Fig. 2a–i. Various forms of fat laden neuroglial cells. Sudan black B; ×1000. All cells except **c** (corpus callosum) originate from zone II (Fig. 1). In reactive cells (**h, i**) lipid inclusions accumulate in cell periphery

(III) structures of the forebrain, including the temporal lobes, extending to the corpus callosum, superior parts of striatum and internal capsule, to a lesser degree also in the periventricular structures of zone I. Lipid material was found almost exclusively in large glial precursors (glioblasts) and cells of astroglial shape. Figure 2 demonstrates the variable distribution and density of the lipid material, ranging from few perinuclear droplets to massive accumulation in the whole cytoplasm. Many of these cells showed a star-shaped appearance resembling astrocytes (Fig. 2a, b, d–f). In the corpus callosum the fat laden cells have a bipolar configuration corresponding to the course of the fiber tracts (Fig. 2c). Figure 2g–i shows the lipid distribution in reactive glial cells which are characterized by loss of their cytoplasmic processes and hyperplasia of the perikaryon. Between the eccentric nucleus and the cap-like lipid accumulation an almost lipid-free cytoplasmic zone can be seen.

Typical microglial cells (macrophages) were found mainly in and around necrotic foci. In children also showing periventricular leucomalacia (PVL) the

Table 1. Neuroglial population and glial fatty metamorphosis in the telencephalic white matter (zone II) of 7 infants (gestational age 34–40 weeks). (Microglial cells and neurons excluded)

Neuroglial cell type	Neuroglial population		Glial fatty metamorphosis		
	No. of cells	%	No. of cells	Glial cell type (%)	All fatty glial cells (%)
Glioblasts	451	49	196	43.5	44.9
Astrocytes	328	36	225	68.8	51.5
Oligodendrocytes	27	3	2	7.4	0.4
Neuroglial necroses	110	12	14	12.7	3.2
Total cells	916	(100)	437	47.7	(100)

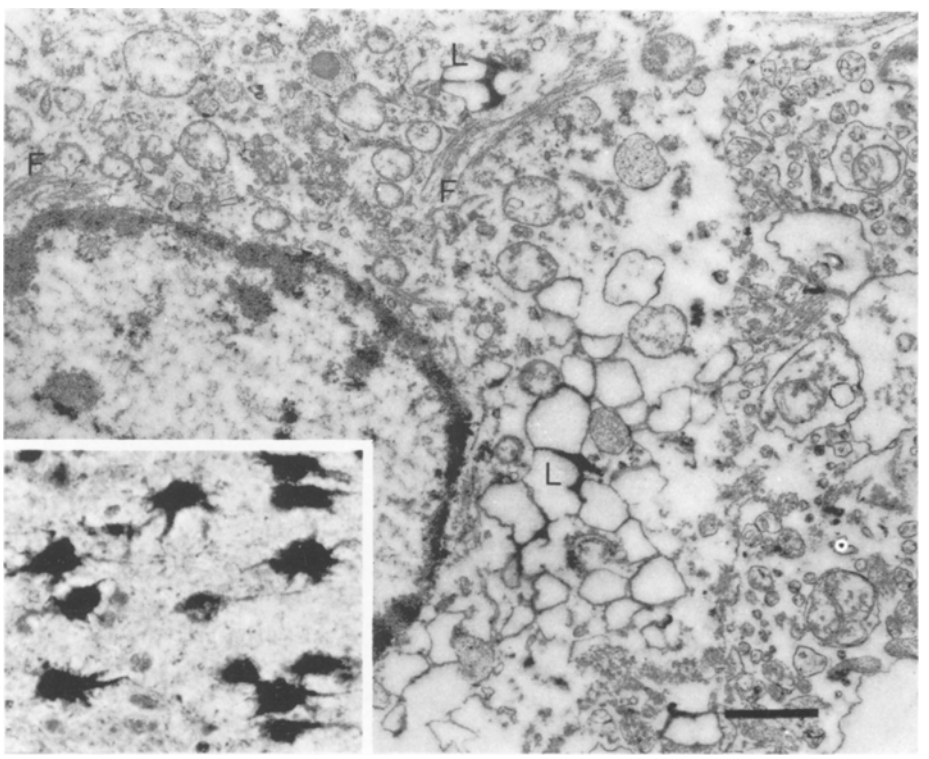

Fig. 3. Young astrocyte from zone II with perinuclear lipid inclusions (*L*) and bundles of filaments (*F*). Calibration 1 μm. *Inset*: astrocytes with short cytoplasmic processes; Cajal gold sublimate (× 440)

number of sudanophilic neuroglial precursors seemed to be increased in the intact white matter and in structures bordering the necrotic foci.

Electron Microscopy

Some quantitative aspects of GFM were studied in the brains of seven children (Tables 1 and 2) excluding brains with massive alterations. A total of 916 neuroglial

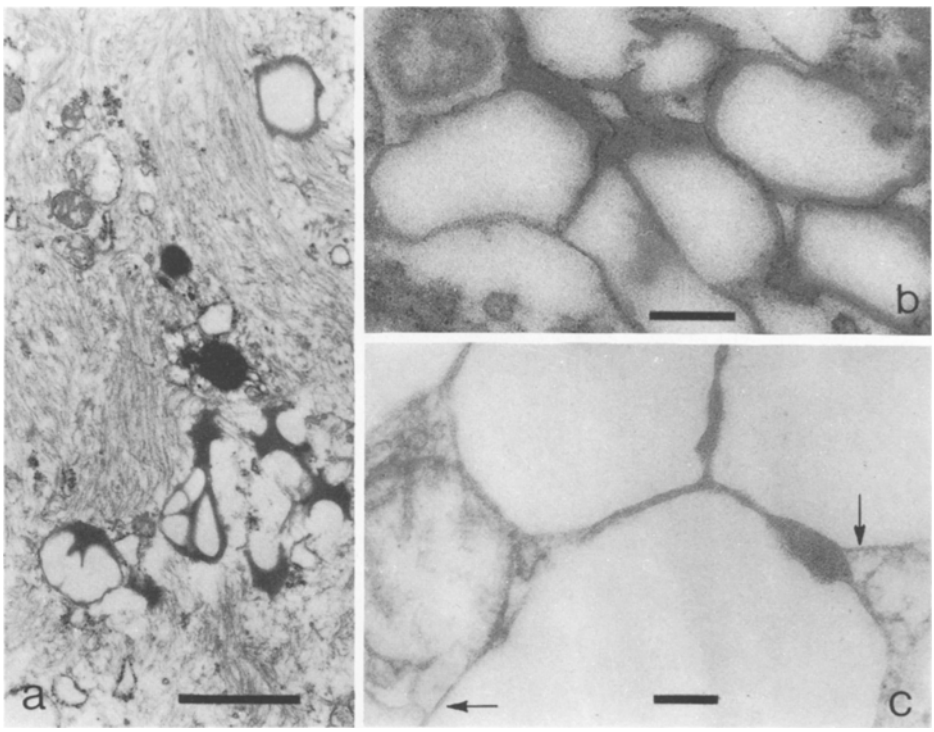

Fig. 4a–c. Various forms of lipid inclusions in astrocytic processes. Only in **c** a trilaminar membrane can be distinguished around lipid vacuoles (arrow). Calibration 1 μm in **a**; 100 nm in **b** and **c**

Table 2. Relationship of glial fatty metamorphosis to gestational age, brain weight, survival and periventricular leucomalacia (PVL) in 7 newborn infants

Case	Gestational age (weeks)	Survival (days)	Brain weight (g)	Glial fatty metamorphosis		Remarks
				Glioblasts (%)	Astrocytes (%)	
263	40	20	390	47	33	–
31	40	7	350	55	95	PVL
330	40	3	350	33	37	–
280	38	5	350	46	86	PVL
235	38	(1 h)	315	25	79	–
332	36	3	315	48	62	PVL
282	34	2	230	37	69	PVL

cells were counted (Table 1), of which 437 (47.7%) showed three or more osmiophilic inclusions within the cytoplasm. Only 2 of 26 oligodendroglial cells (7.4%) contained lipid droplets. Necrotic cells representing 12% of the glial population showed lipid inclusions in only 12.7%. The most remarkable finding was that GFM occurs mainly in astrocytes and glioblasts: 68.8% of the astrocytes and 43.5% of the undifferentiated precursor cells were involved by GFM. Together,

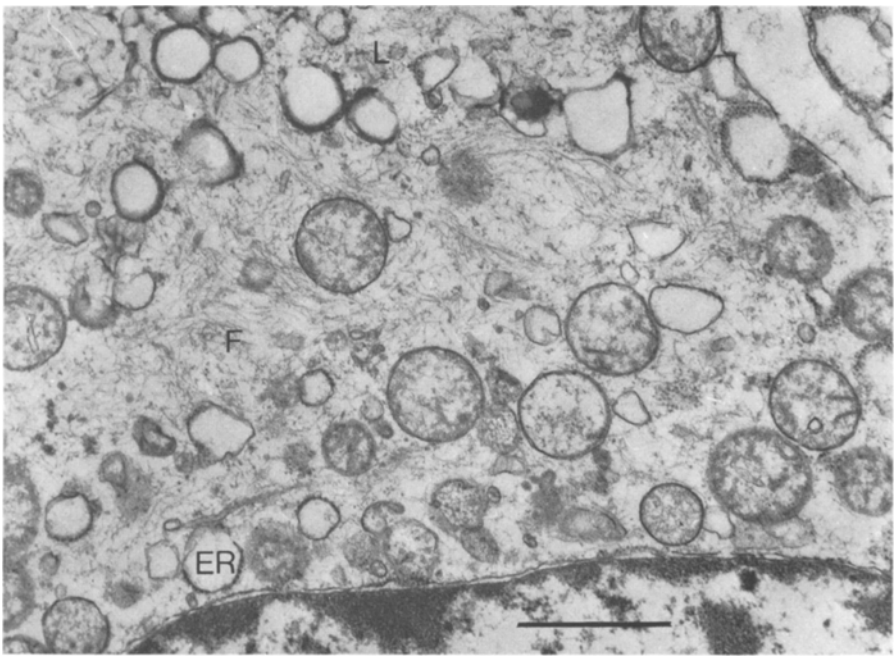

Fig. 5. Astrocyte from zone II with increased cytoplasmic density, containing filaments (*F*), many mitochondria and vesicular endoplasmic reticulum (*ER*). Lipid vacuoles (*L*) at cell periphery. Calibration 1 μm

astrocytes and glioblasts represented 96.4% of the whole neuroglial population undergoing GFM in the deep telencephalic white matter.

The neuroglial lipid inclusions were demonstrable mostly as vacuoles or as osmiophilic inclusions in astrocytes (Fig. 3–6). Often the osmiophilic material forms only a peripheral condensation as a halo around the vacuole (Fig. 4). Few vacuoles showed a surrounding trilaminar membrane (Fig. 4c) comparable with lipid inclusions in the multipotential glia (Vaughn et al., 1970). In some inclusions the outlines were blurred and disappeared in the cytoplasmic matrix (Fig. 4a). The droplets can be found in the perikaryon as well as in peripheral processes, but tend to accumulate in the perinuclear zone as clusters reaching several microns in diameter (Fig. 3).

Our data revealed remarkable individual differences in the number of fatty cells and the amount of lipid accumulation in astrocytes and glioblasts (Table 2). The great variability of GFM in individual cases could neither be explained by the gestational age nor by the survival time. The values in Table 2 suggest that children with periventricular leucomalacia tend to develop a higher rate of GFM. This probable correlation has not been statistically proved because of the great individual differences and the small number of cases.

In most children developing PVL the astrocytic population increases disproportionally. The proliferating astrocytes show a hypertrophic cytoplasm with an increased number of mitochondria and dispersed filaments (Fig. 5). Lipid inclusions are found more at the periphery of the cytoplasm (Figs. 2g–i, 5, 6).

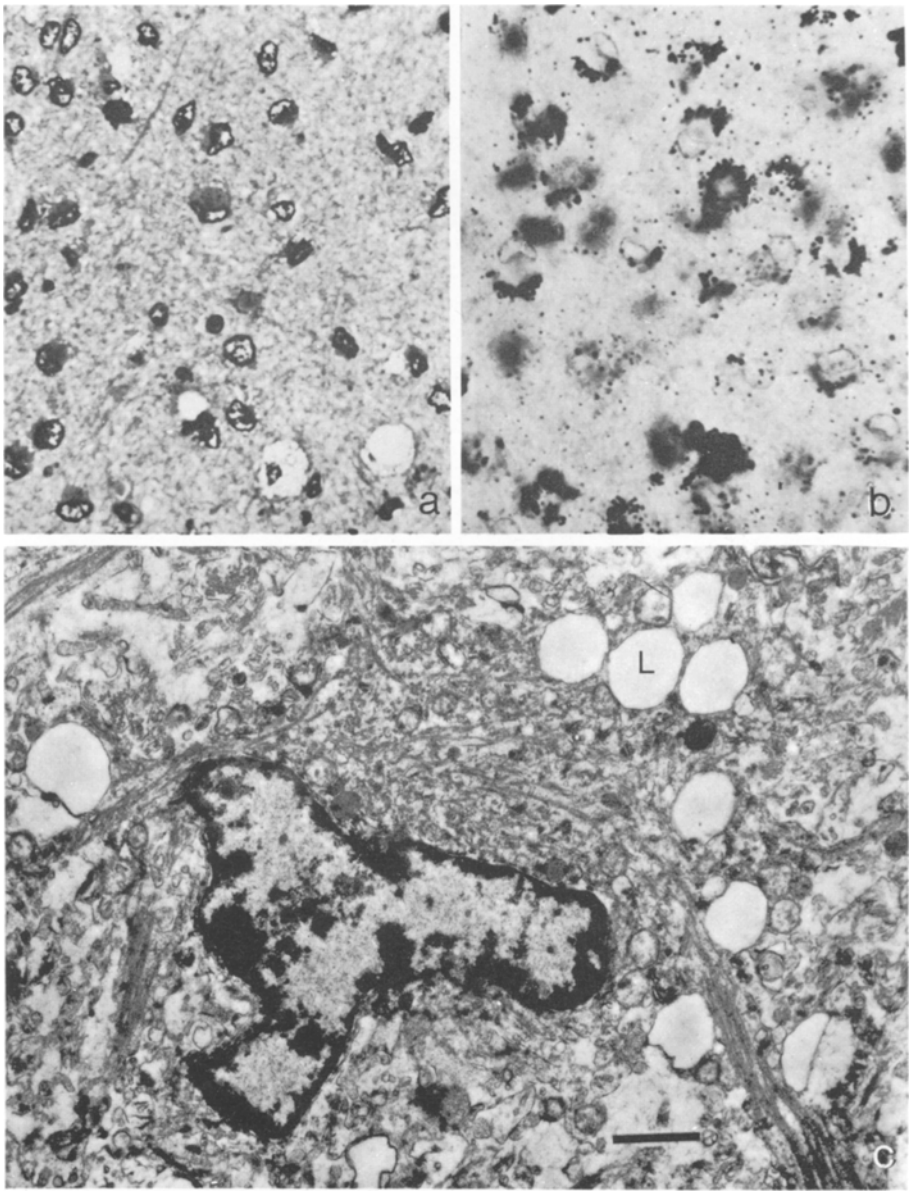

Fig. 6a–c. Fatty metamorphosis in hypertrophic astrocytes in micrencephalic brain with marked sclerosis. Lipid vacuoles (*L*) are found mainly at periphery of protoplasmic astrocytes. **a** and **b** ×440; **c** calibration 1 μm

Massive astroglial fatty metamorphosis was found in a child with microcephaly and sclerosis of the white matter after severe intrauterine and postnatal asphyxia (Fig. 6). In the telencephalic hemispheres the excessive astrocytic proliferation was combined with lipid accumulation in most of the hypertrophic astrocytes and complete absence of oligodendroglial differentiation and myelin formation.

Discussion

The different types of sudanophilic cells and their significance in the immature brain have first to be considered. The heterogeneity of the sudanophilic cells has been stressed by Merzbacher (1910) as a plausible explanation for the divergent interpretations of the phenomenon of GFM. There are several different conditions in which intracytoplasmic lipid accumulation can be observed:

1. Gliogenic macrophages are related to "programmed cell death" during embryonic development (O'Connor and Wyttenbach, 1974). Neuroglial cell necroses occur also in the fetal period during myelination in the spinal cord (Hildebrand, 1971; Phillips, 1973) or in the brain of adult mice (Korr et al., 1973). The high number of neuroglial cell necroses during gliogenesis (12% Table 1) in our study is independent of GFM or periventricular leucomalacia.

2. Typical scavenger cells occur in and around foci of periventricular leucomalacia (PVL) as found in five of our cases. They represent cells with variable lipid accumulation, phagosomes, dense cytoplasmic matrix and cytoplasmic processes engulfing necrotic material. Whether they originate from the multipotential glia (Vaughn et al., 1970; Vaughn and Pease, 1970) or represent true microglial cells, they differ clearly from fatty neuroglial cells.

3. Perivascular accumulation of lipid laden macrophages is found regularly in infants who have died within the first 6 postnatal months (Jellinger et al., 1971).

4. The dysmyelination in the mouse mutant "Jimpy" is characterized by abnormal oligodendroglial development, increased number of cell necroses and lipid-containing immature glial cells (Farkas-Bargeton et al., 1972; Privat et al., 1972; Meier and Bischoff, 1975).

5. The fatty neuroglial metamorphosis, as described in this study, represents a transient and probably reversible fatty degeneration of the neuroglia in the prospective telencephalic white matter. This interpretation is consistent with recent assumptions of Leech and Alvord (1974), Sumi (1974), Friede (1975), Schmidt (1975) and Gadsdon and Emery (1976) that GFM reflects the sensitivity of metabolically active immature glial cells in a vulnerable region of the forebrain. Lipid accumulation is generally absent in young oligodendrocytes, and is not time-related to myelination. Our findings could be interpreted to suggest that the lipid material is available for myelin formation but has accumulated in incompetent neuroglial cells (mainly preexisting astrocytes) but also in glioblasts whose transformation into oligodendrocytes may be inhibited.

It should be noted that the ultrastructural details presented in this study underline the exact descriptions of previous authors, who called the affected neuroglial cell *Sternenzelle* (Merzbacher, 1910), *Fettspinnenzelle* (Wohlwill, 1921) or *hypertrophische strahlige Gliazelle* (Schwartz, 1924). Rydberg (1932), Alpers and Haymaker (1934) and Tuthill (1938) confirmed that cells predominantly of astroglial shape undergo GFM.

Our ultrastructural study demonstrated that most lipid inclusions are not membrane-bound and cannot be interpreted as phagosomes, particularly as necrotic structures are absent. In areas with periventricular leucomalacia, however, phagocytic activity of astrocytes can be observed. The astrocytic heterophagosomes and autophagic vacuoles differ clearly from the intracytoplasmic fat accumulation (Schlote, 1967; Vaughn and Pease, 1970; Schneider et al., 1976).

In our material the telencephalic white matter of 30-week-old fetuses already contains young astrocytes, whereas the first oligodendrocytes appear near term. In the 40th week the ratio glioblast/astrocyte/oligodendrocyte is approximately 55/40/5. It has to be taken into account that in this study some immature "light" oligodendrocytes (Mori and Leblond, 1970) were visualised as glioblasts, so that the proportion of oligodendrocytes undergoing fatty change may in fact be higher than 7.4%. Nevertheless, our data indicate clearly that the majority of fatty glial cells are astrocytes. Therefore, any positive correlation between GFM and myelination can be ruled out, excepting the hypothesis that the young astrocyte participates actively in the myelination process. Our findings, however, suggest that there is a close relation between GFM and the pathological reactions of the astroglial cell line in the perinatal period. We suppose that perinatal brain damage mainly endangers the transformation of glial precursors to the oligodendroglial cell line, whereas preexisting astrocytes are stimulated to proliferate. The appearance of proliferating astrocytes indicates a "false" transformation of the glial precursors.

Astrocytosis and suppression of the oligodendroglial cell line with retarded myelin formation was described as perinatal telencephalic leucoencephalopathy (PTL) by Gilles and Murphy (1969). PTL as a diffuse glial abnormality is different from periventricular leucomalacia (PVL), hemorrhagic necrosis, or subependymal matrix infarction, but – like these lesions – a sensitive indicator of the exceptional vulnerability of the telencephalic white matter in the perinatal period. GFM as a rather common finding in stillborn infants and newborn babies dying shortly after birth, represents a special form of a subtle perinatal brain damage at the cellular and subcellular level, a "minimal brain damage," so to speak. GFM thus indicates a transient disturbance of neuroglial differentiation with retarded oligodendroglial maturation and impaired myelinogenesis, a sort of a mostly reversible "telencephalic leucodystrophy" in the perinatal period.

So far, no comprehensive concept of the neuroglial abnormalities in the immature telencephalic white matter exists. Some of our data suggest a close relationship between GFM and hypertrophic astrocytosis in the way that lipid inclusions appear predominantly in reactive astrocytes around leucomalacic areas (Table 2).

A broad spectrum of telencephalic leucoencephalopathies is conceivable, extending from delayed neuroglial differentiation to irreversible myelin deficit due to necrosis or astrocytic hypertrophy (sclerosis). During recent years some experimental approaches have been started (Sumi, 1974; Gilles et al., 1976) and more information on glial reactions in the immature brain can be expected. On the other hand, ultrastructural and biochemical studies on human autopsy material seem to be indispensable for better insight into the abnormal reactions of the "myelination glia."

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