

MRI Following Severe Perinatal Asphyxia: Preliminary Experience

Maja Steinlin, MD*, Regula Dirr*, Ernst Martin, MD†, Chris Boesch, PhD, MD‡, Remo H. Largo, MD‡, Sergio Fanconi, MD§, and Eugen Boltshauser, MD*

In 30 children suffering from severe perinatal asphyxia an attempt was made to determine the early prognostic signs of severe hypoxic-ischemic brain injury with magnetic resonance imaging (MRI). Ten early (1-4 days of age), 16 intermediate (2-4 weeks of age), and 38 late MRI (older than 1 month of age) procedures were performed on a 2.35 T MR-system. Severe cerebral necrosis was suspected by T₂ hyperintensity of the white matter, with blurred limits to the cortex in early MRI, and was confirmed by T₁ hyperintensity of the cortex in intermediate MRI. Severe cerebral necrosis was established at 3 months of age. Of the 11 children with this pattern (group A), 8 had severe and 3 had moderate cerebral palsy on subsequent examination. Thirteen children (group B) had normal late MRI scans; none developed severe cerebral palsy or marked mental retardation. Two children (group C) had focal ischemic lesions. Four children had intracranial hemorrhage (group D). Groups A and B did not differ in the severity of their perinatal histories and findings, suggesting that MRI during the first 3 months is of significant prognostic value.

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Introduction

Perinatal asphyxia still has an uncertain prognosis. It may cause hypoxic-ischemic brain injury and lead to later neurologic and mental deficits. Many studies have reported the lack of a clear relationship between biochemical and most clinical factors and the outcome of asphyxiated children. Although limited, the best prognostic indicator appears to be the duration and severity of encephalopathy during the first days of life and the neurologic findings on discharge [1-5]. Several studies have assessed computed

tomographic and/or sonographic findings during the first weeks of life in asphyxiated newborns and have demonstrated their prognostic value [6-9].

Experience with magnetic resonance imaging (MRI) in hypoxic-ischemic encephalopathy of the human newborn, however, is limited [10]; most studies demonstrated radiologic and clinical findings in preterm infants with periventricular leukomalacia [11,12]. We are aware of only 3 studies that compared MRI findings in term and preterm infants with their ultimate outcomes [13-15].

We report our experience using serial MRI to study severe perinatal asphyxia. We analyzed MRI patterns and their possible prognostic value by comparing the imaging findings with subsequent neurologic and developmental outcomes.

Methods

During 1986 to 1989, 30 children (13 girls, 17 boys) with histories of severe perinatal asphyxia underwent MRI scans. During the last 15 months of the period a study was begun to include all children referred to our neonatal intensive care unit (NICU) after severe perinatal asphyxia. The examinations were performed with the approval of the local ethics committee and the informed consent of the parents. Twenty-eight children were referred to our NICU immediately after birth; the remaining 2 were examined at our outpatient clinic because of neurologic problems. Twenty-three were born at term and 7 were preterm (mean gestational age: 37.8 weeks; range: 28-42 weeks). The relatively small number of preterm infants is a consequence of our exclusion criteria (see below).

Asphyxia is determined by ischemia and hypoperfusion and leads to a great variability of clinical symptoms which can be divided into the following:

- (1) Intrauterine signs of asphyxia: bradycardia (heart rate < 80/min) limited beat to beat variability, late decelerations, or meconium-stained amniotic fluid;
- (2) Peripartum signs: an Apgar score ≤ 5 at 5 min and ≤ 8 at 10 min, umbilical artery pH ≤ 7.1 , and base excess ≤ -10 mmol/L; and,
- (3) Postpartum signs of encephalopathy during the first 48 hours, such as seizures, lethargy, or pathologic spontaneous movements.

Because a clinical definition of asphyxia is not available [16], we assumed asphyxia to be severe when at least 1 criterion was fulfilled in 2 of 3 subgroups. Patients with dysmorphic syndromes or malformations and those who required surgery during the neonatal period or who had hyaline membrane disease were excluded from the study.

From the Departments of *Neurology, †Magnetic Resonance, ‡Growth and Development, and §Intensive Care; Children's University Hospital; Zurich, Switzerland.

Communications should be addressed to:
Dr. Steinlin; Children's University Hospital; Steinwiesstrasse 75;
CH-8032 Zurich, Switzerland.
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- [26] **Safdari H**, Boluix B, Gros C. Multifocal brain radionecrosis masquerading as tumour dissemination. *Surg Neurol* 1984;21:35-41.
- [27] **Breuer AC**, Blank NK, Schoene WC. Multifocal pontine lesions in cancer patients treated with chemotherapy and CNS radiotherapy. *Cancer* 1978;41:2112-20.
- [28] **Crosley CJ**, Rorke LB, Evans A, Nigro M. Central nervous system lesions in childhood leukemia. *Neurology* 1978;28:678-85.
- [29] **Cohen ME**, Duffner PK, Terplan KL. Myelopathy and severe structural derangement associated with combined modality therapy. *Cancer* 1983;52:1590-6.
- [30] **Locksmith JP**, Powers WE. Permanent radiation myelopathy. *Am J Roentgenol* 1968;102:916-26.
- [31] **Wara WM**, Phillips TL, Sheline GE, Schwade JG. Radiation tolerance of the spinal cord. *Cancer* 1975;35:1558-62.
- [32] **Pallis CA**, Louis S, Morgan RL. Radiation myelopathy. *Brain* 1961;84:460-78.
- [33] **Reagan TJ**, Thomas JE, Colby MY. Chronic progressive radiation myelopathy. *JAMA* 1968;203:106-10.
- [34] **Olsen JH**. Risk of second cancer after cancer in childhood. *Cancer* 1986;57:2250-4.
- [35] **Farwell J**, Flannery JT. Second primaries in children with central nervous system tumors. *J Neurooncol* 1984;2:371-5.
- [36] **Meadows AT**, Baum E, Fossati-Bellani F, et al. Second malignant neoplasms in children: An update from the Late Effects Study Group. *J Clin Oncol* 1985;3:532-8.
- [37] **Haymaker W**, Rubinstein LJ, Miquel J. Brain tumors in irradiated monkeys. *Acta Neuropathol* 1972;20:267-77.
- [38] **Krupp JH**. Nine-year mortality experience in proton-exposed macaca mulatta. *Radiat Res* 1976;67:244-51.
- [39] **Ron E**, Modan B, Boice JD, et al. Tumors of the brain and nervous system after radiotherapy in childhood. *N Engl J Med* 1988;319:1033-9.
- [40] **Chung CK**, Stryker JA, Cruse R, Vannuci R, Towfighi J. Glioblastoma multiforme following prophylactic cranial irradiation and intrathecal methotrexate in a child with acute lymphocytic leukemia. *Cancer* 1981;47:2563-6.
- [41] **Malone M**, Lumley H, Erdohazi M. Astrocytoma as a second malignancy in patients with acute lymphoblastic leukemia. *Cancer* 1986;57:1979-85.
- [42] **Kitanaka C**, Shitara N, Nakagomi T, et al. Postradiation astrocytoma. *J Neurosurg* 1989;70:469-74.
- [43] **Soffer D**, Gomori JM, Seigal T, Shalit MN. Intracranial meningiomas after high-dose irradiation. *Cancer* 1989;63:1514-9.
- [44] **Shapiro S**, Mealey J Jr, Sartorius C. Radiation-induced intracranial malignant gliomas. *J Neurosurg* 1989;71:77-82.
- [45] **Raventos A**, Duszynski DO. Thyroid cancer following irradiation for medulloblastoma. *AJR* 1963;89:175-81.
- [46] **Andrew DS**, Kerr IF. Carcinoma of thyroid following irradiation for medulloblastoma. *Clin Radiol* 1965;16:282-3.
- [47] **Horowitz ME**, Mulhern RK, Kun LE, et al. Brain tumors in the very young child: Postoperative chemotherapy in combined-modality treatment. *Cancer* 1988;61:428-34.
- [48] **Baram TZ**, Eys JV, Pack B. Optimal surgery and MOPP chemotherapy in infants with primitive neuroectodermal tumors of the posterior fossa. *Ann Neurol* 1986;20:423.

Table 1. Group A with diffuse MRI lesions

Patient No./Sex/GA	Early MRI	Intermediate MRI	Late MRI	Outcome
1/F/39	4 days: diffuse T ₁ /T ₂ hyperintensity, cortex limits disturbed	2 wks: T ₁ hyperintensity cortex, lack of myelination capsula interna	10 mos: severe cerebral necrosis, thin corpus callosum	Severe quadriplegia, microcephaly, hearing loss; DQ: 0.22 (9 mos)
2/F/39	—	2 wks: T ₁ hyperintensity cortex, cerebral liquefaction, lack of myelination capsula interna	19 mos: severe cerebral necrosis, thin corpus callosum	Severe quadriplegia, blindness, microcephaly; DQ: 0.16 (24 mos)
3/F/41	—	2 wks: T ₁ hyperintensity cortex, lack of myelination capsula interna	2 mos: cerebral necrosis, moderately disturbed myelination	Severe quadriplegia; DQ: < 0.3 (6 mos), ?blindness
4/F/38	1 day: cortex limits disturbed	2 wks: mild T ₁ hyperintensity cortex, T ₂ hyperintensities thalami	—	Opisthotonus, quadriplegia; DQ: < 0.5 (3 mos)
5/F/41	—	2 wks: mild T ₁ hyperintensity cortex	26 mos: T ₂ hyperintensities thalami, pallida; frontally enlarged fluid spaces	Severe quadriplegia, good visual/social contact; DQ: 0.25 (36 mos)
6/F/41	1 day: T ₂ hyperintensity frontally hypointense stripes in T ₂	—	3 mos: severe frontal atrophy	Mild quadriplegia, visual retardation (3 mos)
7/M/42	—	1 wk: T ₂ hyperintensities frontally	3 mos: delay of myelination occipital/frontal; 9 mos: frontal periventricular dysmyelination	Mild quadriplegia, DQ: 0.9 (9 mos)
8/F/39	—	4 wks: T ₁ hyperintensity cortex, cerebral liquefaction, lack of myelination capsula interna	28 mos: severe cerebral necrosis, degeneration of descending tracts	Severe quadriplegia, epilepsy; DQ: 0.1 (31 mos)
9/M/28	—	—	2 mos: mild T ₁ hyperintensity of the cortex; 5 mos: moderate, diffuse atrophy	Mild quadriplegia; DQ: 1.0 (5 mos)
10/M/40	—	—	75 mos: diffuse median cerebral necrosis, thin corpus callosum with disturbed myelination	Severe quadriplegia, blindness; DQ: < 0.2 (75 mos)
11/F/36	—	—	7 mos: diffuse subcortical cerebral necrosis, thin corpus callosum with disturbed myelination, lack of myelination capsula interna	Severe quadriplegia, epilepsy, blindness; DQ: < 0.2 (7 mos)

Abbreviations:

DQ = Developmental quotient = developmental age/chronologic age

GA = Gestational age

All children underwent 1-4 MRI examinations between the second day and sixth year of life. Not all MRI investigations were obtained at the same preferred time, mainly due to circumstantial reasons (i.e., limited access to MRI, lack of nursing staff, clinical instability). The timing of the investigations is defined as follows:

Early MRI – during the first 4 days of life;

Intermediate MRI – 2-4 weeks after birth; and,

Late MRI – after the first month of life.

Ten children were examined with early MRI scans, 14 were examined with 16 intermediate scans, and 29 were examined with 37 late

scans. The children were sedated for the examination using chloral hydrate (50-100 mg/kg body weight) and/or flunitrazepam (0.05 mg/kg body weight) administered either orally or rectally. T₁- (TR: 500; TE: 30) and T₂- (TR: 3,000; TE: 120) weighted images were performed on a 2.35 T superconducting MR-system, using a 256 × 256 imaging matrix [17]. All MRI scans were evaluated for gross morphology, stage of myelination [18], or bleeding [19] and ventricular size.

Twenty-seven of 30 infants were examined 1-3 times in neurologic follow-up. Twenty-five of these patients underwent developmental testing (Griffiths' test [20] or Snijder's Omen nonverbal intelligence test

[21]). Seven of them were evaluated between 3-6 months of age and 8 between 6-12 months. Nine children were tested during the second year of life and 1 child between 2 and 3 years of age. Two children died during the first year of life; autopsy was permitted only in 1 patient.

Results

Based on MRI findings, the patients were divided into 4 groups:

Group A – with diffuse brain injury;

Group B – with normal MRI findings or transient pathology;

Group C – with focal pathologic findings; and,

Group D – with intracranial hemorrhages.

Detailed analysis of perinatal data of groups A and B did not reveal significant differences (i.e., children in group A were not more severely affected).

Group A (N = 11)

The findings are summarized in Table 1. Eleven children had diffuse MRI abnormalities. Three early MRI scans demonstrated hyperintensities of the white matter in T₂-weighted images with blurred cortical margins (Fig 1).

Of 7 intermediate MRI scans, hyperintensity of the cortex in T₁-weighted images was evident in Patients 1-3 and 8 (Fig 2) and diencephalic T₂ hyperintensities in 1 patient.

Ten children had late MRI scans performed. Six MRI scans disclosed severe, diffuse necrosis of the cerebral hemispheres (Patients 1-3,8,10,11; Fig 3); 5 were predominantly in the occipital area (Fig 4). Myelination was disturbed or severely delayed in all 6 children. Lack of myelination of the internal capsule was manifest in all after the first month of life (Fig 4).

In 1 child with frontal hyperintensity visualized during intermediate MRI, retardation of myelination at 3 months led to patchy dysmyelination at 9 months (Fig 5).

Patient 5 exhibited T₂ hyperintensities in the thalamus and globus pallidum (Fig 6).

All 6 children with diffuse cerebral necrosis suffered from severe spastic quadriplegia and developmental delay (Patients 1-3,8,10,11). Both children with alterations in the diencephalon (Patients 4,5) already had severe spastic quadriplegia during the neonatal period.

Group B (N = 13)

Relevant findings are summarized in Table 2.

All 13 children had, by definition, normal late MRI scans.

Three of 6 early MRI scans were normal (Patients 12,13,15). Two had fine, hypodense centrifugal stripes periventricularly (Fig 7) and in the centrum semiovale (Fig 8) on T₂-weighted images (Patients 16,18). Myelination was normal in all 6.

Only 1 of 6 intermediate MRI scans in 5 children was judged to be normal (Patient 19); the others demonstrated either myelination problems or in 1 patient hypodense stripes.

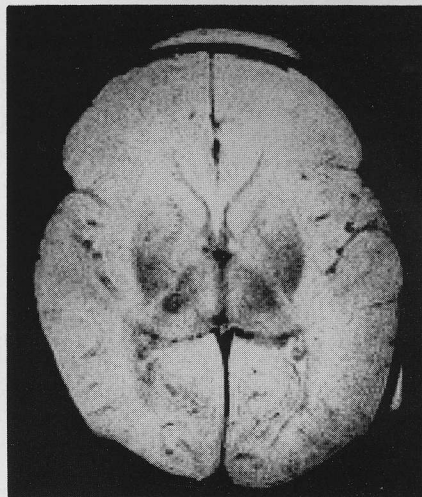


Figure 1. Diffuse hyperintensity of the white matter with blurred margin to the cortex. T₂-weighted (TR: 3,000; TE: 120) MRI of Patient 1 (group A) at 4 days of age.

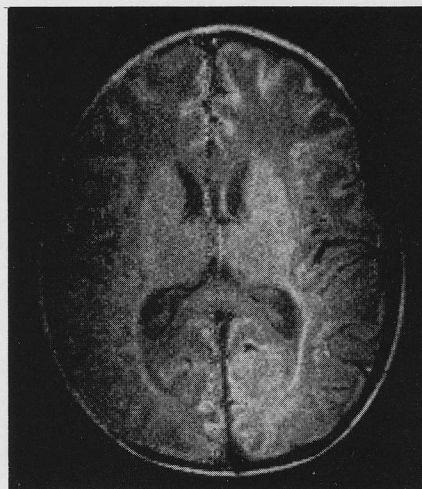


Figure 2. Relative hyperintensity of the cortex. T₁-weighted (TR: 500; TE: 23) MRI of Patient 2 (group A) at 11 days of age.

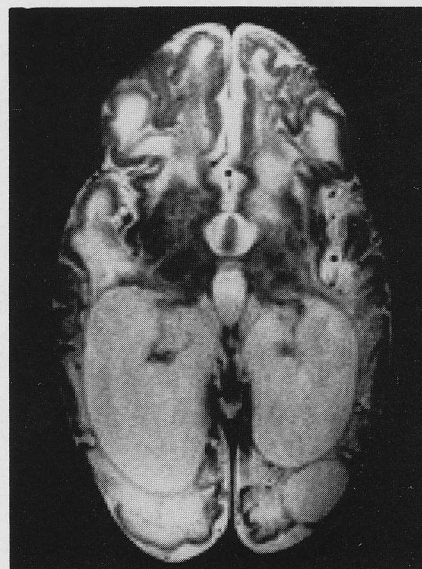


Figure 3. Extensive cerebral necrosis with enlarged ventricles and subarachnoid spaces. T₂-weighted (TR: 3,000; TE: 120) MRI of Patient 8 (group A) at 27 months of age.

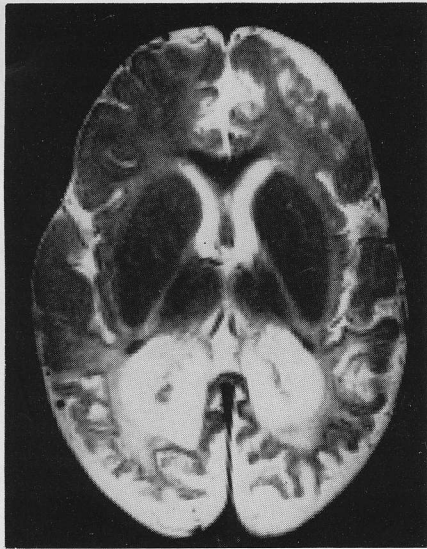


Figure 4. Occipitally pronounced cerebral necrosis, deficient myelination of the internal capsule. T₂-weighted (TR: 3,000; TE: 120) MRI of Patient 2 (group A) at 17 months of age.

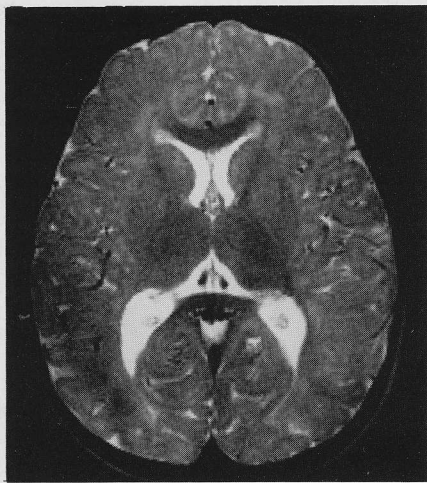


Figure 5. Patchy, irregular myelination of the frontal white matter. T₂-weighted (TR: 3,000; TE: 120) MRI of Patient 7 (group A) at 9 months of age.

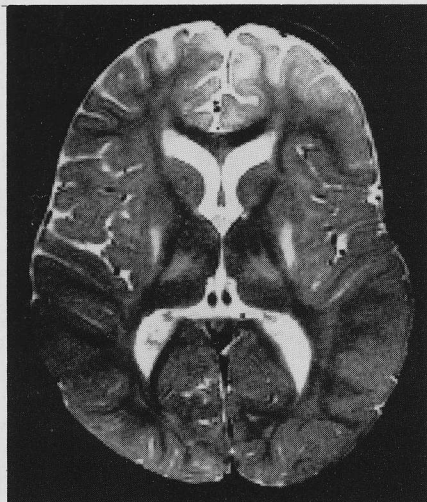


Figure 6. Hyperintensities of the lateral thalamus and striatum. Irregular appearance of the frontal white matter. T₂-weighted (TR: 3,000; TE: 120) MRI of Patient 5 (group A) at 22 months of age.

Sixteen late MRI scans were performed in 9 children. In 4 children we found diencephalic or occipital myelination problems resolving during subsequent examinations. All other MRI scans were normal.

Nine group B patients were neurologically abnormal on discharge from the NICU; 4 were considered to be normal.

Four children were normal during subsequent neurologic examinations (Patients 12,19,20,24). The others suffered from minimal signs of cerebral palsy.

Seven children (Patients 12,13,16,17,20,23,24) were normal and 2 (Patients 14,19) had minimally retarded development. In Patients 15, 21, and 22, retardation was not manifest, but testing was refused by the parents. Patient 18 has not yet been reassessed.

Group C (N = 2)

Only 2 children had focal ischemic infarcts.

Group D (N = 4)

Four children, 3 of whom were preterm, suffered from intracranial hemorrhage. Localization and degree of hemorrhage were variable.

Groups C and D were too small and too variable to draw any conclusions and will not be discussed further.

Discussion

Children of group A (i.e., diffuse hypoxic-ischemic brain injury) for whom early or intermediate MRI examinations were possible (N = 8) were born at term. They had the characteristic pattern of necrosis in the cortical and subcortical watershed regions, following the age-dependent development of the ventriculofugal arteries (Barkovich and Truwit [13]). Early MRI scans were characterized by diffuse hyperintensity of the white matter on T₂-weighted images with blurred limits to the cortex (Fig 1) and hypointensity of the white matter on T₁-weighted images with a sharp demarcation to a small cortex. These findings are probably due to increased water content as a consequence of ischemia and following severe edema and necrosis. In our experience, differentiation between edema and necrosis was not possible.

However, in all 6 intermediate MRI scans of children with verified severe cerebral necrosis, marked hyperintensity of a thin cortex on T₁-weighted images was manifest (Fig 2), probably because of the relative hypointensity of the white matter as a result of increased water content. We have never seen this pattern in the other groups; mild hyperintensity of the cortex in intermediate MRI may be a predictor of moderate cerebral necrosis.

Late MRI demonstrated that severe brain injury was established at 3 months of age (Fig 3). A lack of myelination of the internal capsule (Fig 4) was observed after the first month, while deficient myelination of the corpus callosum had become evident during the first year of life.

Of 9 children, 5 had parieto-occipitally (Fig 4) and 1 had frontally pronounced alterations, sustaining the notion of

Table 2. Group B with normal MRI findings or transient pathology

Patient No./Sex/GA	Early MRI	Intermediate MRI	Late MRI	Outcome (age at follow-up)
12/M/41	2 days: normal	—	9 mos: normal	Normal; DQ: 1.1 (9 mos)
13/M/40	4 days: normal	—	3 mos: normal	Minimal hypotonia, limited visual contact; DQ: 1.0 (3 mos)
14/M/40	—	2 wks: diencephalon, delayed myelination	6 mos: normal	Minimal hemisyndrome; DQ: 0.95 (18 mos)
15/M/40	3 days: normal	—	—	Normal by history
16/M/42	2 days: T ₂ hypointense stripes	—	3 mos: normal	Minimal quadriplegia; DQ: 1.0 (3 mos)
17/F/38	—	1 wk: T ₂ hypointense stripes	3 mos: normal	Minimal hemisyndrome; DQ: 1.0 (3 mos)
18/M/34	2 days: T ₂ hypointense stripes	—	—	Too young for follow-up
19/M/38	—	1 wk: normal	28 mos: normal	Neurologically normal; DQ: 0.85 (27 mos)
20/M/39	—	2 wks: diencephalon, delayed myelination	10 mos: normal	Neurologically normal; DQ: 1.0 (10 mos)
21/M/38	—	—	7 wks: normal	Lost to follow-up
22/M/39	—	—	46 mos: ?T ₂ hyperintensity thalamus	Minimal hemiparesis
23/M/35	—	1 wk: premature gyral pattern, hyperintense white matter	18 mos: minimal frontal atrophy	Minimal quadriplegia; DQ: 1.0 (18 mos)
24/F/39	4 days: white matter; T ₂ hyperintensity, T ₁ hypointensity	—	3 mos: T ₂ hyperintensities pallidum; 9 mos: normal	Neurologically normal; DQ: 1.1 (9 mos)

Abbreviations:
DQ = Developmental quotient = developmental age/chronologic age
GA = Gestational age

high sensitivity to ischemia of the posterior part of the brain.

In 2 children, diencephalic ischemic lesions were detected, combined with mild cortical necrosis (Fig 6) in 1 child confirmed later by autopsy findings. The typical clinical pattern was severe spastic quadriplegia evident soon after birth and less pronounced mental deficit. Only 1 of 2 children suffered complete circulatory arrest which could explain damage in the area with the highest metabolic requirements because of preserved vascular autoregulation, as observed by Barkovich and Truwit [14].

Cerebral myelination was delayed or even disturbed (i.e., patchy dysmyelination) in all 9 children with severe damage. Barkovich and Truwit reported that in severe insults, myelination delay can be detected in children up to 4 years of age [14]. Our oldest patient was 6 years of age; it appears that, with very severe damage, myelination retardation can persist. In 1 patient delayed myelination at 3 months of age was a predictor of periventricular patchy disturbed myelination in later scans.

Only 2 children in group A were preterm. The one born at 36 weeks gestation demonstrated the typical pattern of diffuse subcortical cerebral necrosis and less affected cor-

tex. The one born at 28 weeks gestation had moderate, diffuse atrophy with diminished white matter.

In all patients, the cerebellum and the brainstem were normal; infratentorial structures are most resistant to hypoxemia.

All 7 children with severe, diffuse cerebral necrosis suffered from prominent spastic quadriplegia and marked general developmental delay. Spastic quadriplegia was even more prominent in children with diencephalic lesions; general developmental delay was similar, but social and visual contact was better. Moderate atrophy and patchy disturbed myelination were combined with mild to moderate spastic quadriplegia and only mild developmental problems.

Early or intermediate MRI scans were found to be normal in 9 of 13 children in group B (by definition normal late MRI).

In 2 children we found moderate, diffuse T₂ hyperintensity of the white matter with early MRI, a sign of increased water content because of resolving edema.

Three patients had early or intermediate MRI hypointense centrifugal stripes, periventricularly near the frontal horns or in the centrum semiovale (Figs 7,8), which dis-

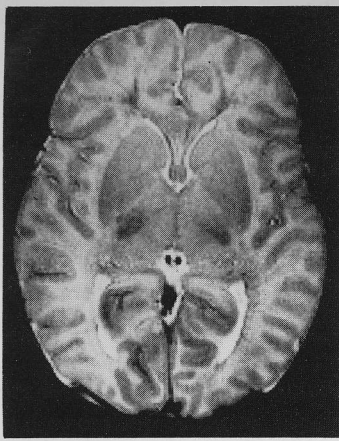


Figure 7. Centrifugal hypointense stripes in the deep frontal white matter. T₂-weighted (TR: 3,000; TE: 120) MRI of Patient 16 (group B) at 1 day of age.

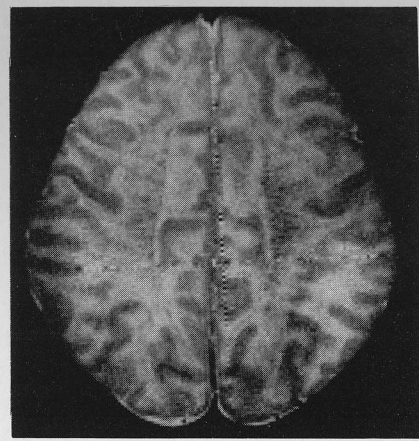


Figure 8. Hypointense stripes in the central corona radiata. T₂-weighted (TR: 3,000; TE: 120) MRI of Patient 16 (group B) at 1 day of age.

appeared without any sequelae in further studies. The anatomic pattern and intensity of these stripes on MRI are compatible with minimal intracerebral bleeding by diapedesis due to venous congestion after acute asphyxia.

In these 9 patients, normal early and intermediate myelination assessed by MRI was within the normal timetable, but most manifested slowed subsequent myelination. Myelination abnormalities were pronounced occipitally, although the myelination process in the occipital lobe is usually more advanced than in the frontal lobe. In 2 late MRI scans we found diencephalic T₂ hyperintensities that were not evident on repeated tests. These findings point to

the probability that perinatal asphyxia may lead only to transient retardation or disturbance of myelination with subsequent recovery. Our findings confirm those of Johnson et al. [13], although their myelination stages were defined in T₁-weighted images; however, in other respects comparison of our results with those of Johnson et al. is not possible. Their series included only 4 patients with hypoxic-ischemic encephalopathy and early and intermediate MRI scans usually were not performed.

In group B only 3 of 11 children were normal in all longitudinal neurologic examinations. Three patients had transient minimal cerebral palsy, while 5 had mild neu-

Birth Asphyxia

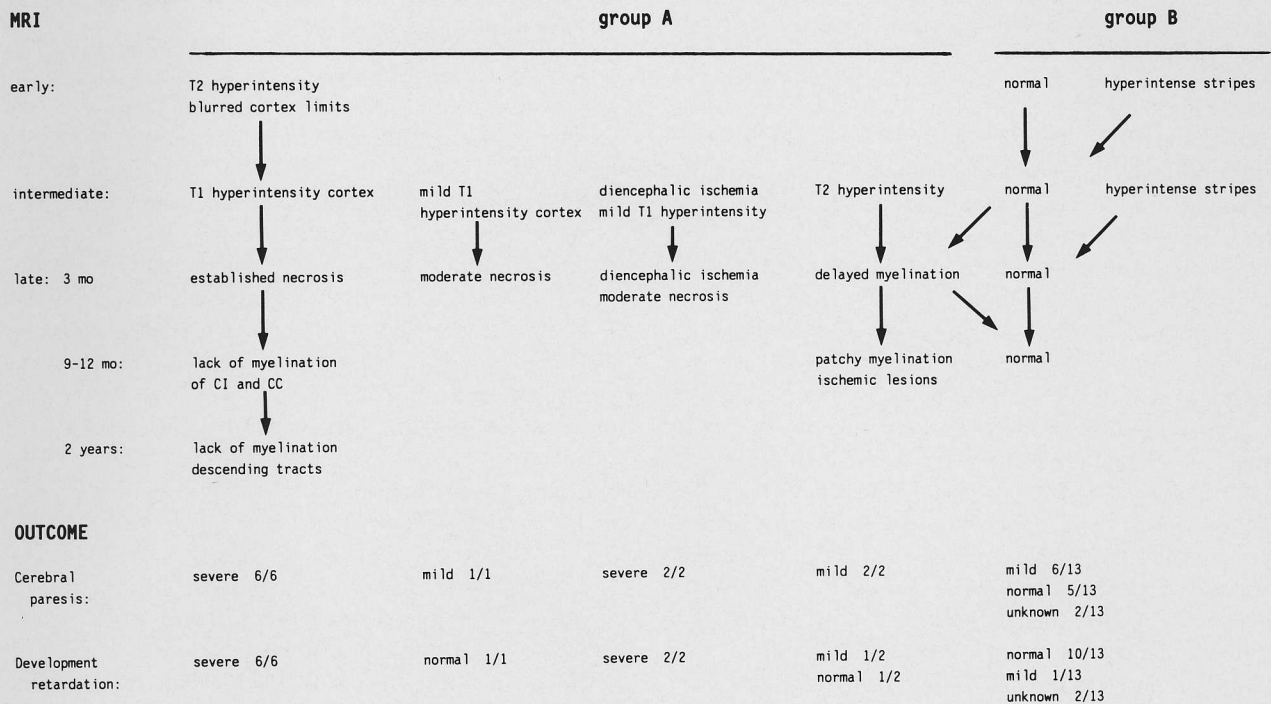


Figure 9. Summary of MRI patterns and outcomes following asphyxia in our series.

rologic abnormalities or developmental delay, but normal MRI at the last evaluation. An explanation for this observation could be the disappearance of lesions or minimal cerebral damage not visible by MRI. Transient pathologic findings could not be correlated with neurologic or developmental problems. Normal developmental assessments in 8 of 11 children should be taken with caution because of early testing age.

Our findings are comparable with the study by Byrne et al. [15]. The authors performed serial MRI scans in patients with neonatal hypoxic-ischemic encephalopathy. In 6 of 8 infants with abnormal MRI scans at 4 months of age, cerebral palsy was found at 18 months; one of the remaining patients had findings suggestive of cerebral palsy, while the other one was normal. Three of 4 infants with normal MRI scans at 8 months had normal outcomes. Our observations are summarized in Figure 9. With considerable assurance MRI allows recognition of severe encephalopathy as early as the first week of life. This finding can be confirmed 10-14 days postpartum. The predictive value of early and intermediate MRI has to be confirmed in a larger patient sample.

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References

- [1] Robertson C, Finer N. Term infants with hypoxic-ischemic encephalopathy: Outcome at 3.5 years. *Dev Med Child Neurol* 1985;27:473-84.
- [2] Aylward GP, Verhulst SJ, Bell S. Correlation of asphyxia and other risk factors with outcome: A contemporary view. *Dev Med Child Neurol* 1989;31:329-40.
- [3] Vieneta R. Perinatal asphyxia, biochemical parameters as indices of asphyxia at birth and predictors of brain damage, and a trial of preventing damage by phenobarbital. Academic thesis, Helsinki, 1988.
- [4] Lupton B, Hill A, Roland E, Whitfield M, Flodmark O. Brain swelling in the asphyxiated term newborn: Pathogenesis and outcome. *Pediatrics* 1988;82:139-46.
- [5] Sarnat H, Sarnat M. Neonatal encephalopathy following fetal distress. *Arch Neurol* 1976;33:696-705.
- [6] Adsett DB, Fitz CR, Hill A. Hypoxic-ischemic cerebral injury in the term newborn: Correlation of CT findings with neurological outcome. *Dev Med Child Neurol* 1985;27:155-60.
- [7] Fitzharding PM, Flodmark O, Fitz CR, Ashby S. The prognostic value of computed tomography as an adjunct to assessment of the term infant with postasphyxial encephalopathy. *J Pediatr* 1981;99:777-81.
- [8] Flodmark O, Fitz CR, Harwood-Nash DC. Computed tomographic diagnosis and short-term prognosis of intracranial hemorrhage and hypoxic-ischemic brain damage in neonates. *J Comput Assist Tomogr* 1980;4:775-87.
- [9] Lipp-Zwahlen AE, Deonna T, Micheki JL, Calame A, Chrzanowski R, Cêtre E. Prognostic value of neonatal CT scans in asphyxiated term babies: Low density score compared with neonatal neurological signs. *Neuropediatrics* 1985;16:209-17.
- [10] McArdle CB, Richardson CJ, Hayden CK, Nicholas DA, Amparo EG. Abnormalities of the neonatal brain: MR imaging, part II. Hypoxic-ischemic brain injury. *Radiology* 1987;163:395-403.
- [11] Flodmark O, Lupton B, Li D, et al. MR imaging of periventricular leucomalacia in childhood. *AJR* 1989;152:583-90.
- [12] Dubowitz L, Bydder G, Mushin J. Developmental sequence of periventricular leukomalacia. Correlation of ultrasound, clinical and nuclear magnetic resonance functions. *Arch Dis Child* 1985;60:349-55.
- [13] Johnson MA, Pennock JM, Bydder GM, Dubowitz LMS, Thomas DJ, Young IR. Serial MR imaging in neonatal cerebral injury. *AJNR* 1987;8:83-92.
- [14] Barkovich A, Truwit CH. Brain damage from perinatal asphyxia: Correlation of MR findings with gestational age. *AJNR* 1990;11:1087-96.
- [15] Byrne P, Welch R, Johnson MA, Darrah J, Piper M. Serial magnetic resonance imaging in neonatal hypoxic-ischemic encephalopathy. *J Pediatr* 1990;117:694-700.
- [16] Hall D. Birth asphyxia and cerebral palsy. *BMJ* 1989;299:279-82.
- [17] Boesch C, Martin E. Combined application of MR imaging and spectroscopy in neonates and infants: Installation and operation of a 2.35 Tesla system in a clinical setting. *Radiology* 1988;168:481-8.
- [18] Martin E, Kikinis R, Zuerrer M, et al. Development stages of human brain: An MR study. *J Comput Assist Tomogr* 1988;12:917-22.
- [19] Zürrer M. Bestimmung von Alter und Ausdehnung intrakranieller Blutungen bei Neugeborenen und Säuglingen mittels Magnetresonanz. MD Thesis, Zürich, 1989.
- [20] Griffith R. Griffiths Entwicklungsskalen zur Beurteilung der Entwicklung in den ersten beiden Lebensjahren/dt. Bearbeitung Brandt I.: Beltz. Basel: Weinheim, 1983.
- [21] Snijders J, Snijders-Omen N. Snijders-Omen nicht verbale Intelligenztestreihe S.O.N. 2 1/2 -7. Groningen: Wolters-Nordhoff, 1977.