Magnetic resonance imaging in neonatal hypoxic-ischemic brain injury

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Chapter 4

Differentiation between peritrigonal terminal zones and hypoxic-ischemic white matter injury on MRI

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Abstract
The differentiation between terminal zones and pathological signal intensity changes on MRI of children and young adults is of diagnostic importance. We assessed the diagnostic value of several morphological features on MRI to differentiate between terminal zones and hypoxic-ischemic white matter injury. We selected all brain MRI examinations performed in subjects up to 20 years of age showing increased signal intensity on T2-weighted images in the peritrigonal areas. 75 individuals were assigned to a patient group (n=28) if there was evidence of hypoxia-ischemia during the perinatal period or a control group (n=47). Aspect, location, extent, shape, and borders of signal intensity changes in the peritrigonal areas were studied. Signal intensity of the peritrigonal areas was related to signal intensity of surrounding white matter. Presence of Virchow Robin spaces, hypoxic-ischemic abnormalities, and local atrophy were also recorded. Chi-squared tests assessed whether presence or absence of morphological characteristics differed between patients and controls. Logistic regression analysis studied which characteristics were best to discriminate between the two groups. Very high signal intensity of the peritrigonal areas on FLAIR (Odds Ratio 25) and presence of local atrophy (Odds Ratio 14.3) were best predictors to discriminate between the two groups.

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Introduction

The differentiation between terminal zones and pathological signal intensity changes on magnetic resonance imaging (MRI) of children and young adults is of diagnostic importance. Terminal zones are the last myelinating areas in the human brain (1-3). On T2-weighted MR images terminal zones are shown as areas of higher signal intensity in the peritrigonal areas compared to the surrounding white matter (1-3). The cause of this high signal intensity probably is late myelination of the fiber tracts in the association areas of the posterior and inferior parietal and posterior temporal cortex (3). Terminal zones may well be seen until the third decade of life (2-3). Terminal zones should be distinguished from hypoxic-ischemic white matter injury exhibiting similar increased signal intensity on T2-weighted images, such as gliosis resulting from periventricular leukomalacia (PVL) or infarction (1-2,4-6). PVL is a white matter disease mainly occurring in preterm-born subjects, the peritrigonal areas being one of the predilection areas (1-2,4-6). The high signal intensity in hypoxic-ischemic white matter injury on T2-weighted images is ascribed to dense fibrillary gliosis (7).

Barkovich formulated criteria to differentiate terminal zones from changes in the periventricular white matter caused by PVL on MR images (3). According to these criteria, terminal zones have hazy borders and a homogeneous aspect. Terminal zones occur in the deep white matter dorsal and superior to the level of the trigone. In some cases, there is rostral extension lateral to the ventricular body. The increased signal intensity is best visualized on T2-weighted MR images, and the signal intensity is lower than the signal intensity of changes due to PVL (3). Cowan described the presence of very high signal intensity on T2-weighted images due to gliosis resulting from PVL (2). Baker et al. described the existence of normal myelinated tissue interspersed between the ventricular system and terminal zones, while white matter changes resulting from PVL abut the ventricles (1).

To our knowledge, the diagnostic value of criteria to differentiate terminal zones from hypoxic-ischemic white matter injury have not been studied and systematically verified. Our aim was to assess the diagnostic value of the criteria described by Barkovich, Cowan, and Baker by applying these on MRI examinations of young subjects.

Materials and methods

We selected all brain MRI examinations performed over a 7-year period in our university hospital, a tertiary referral centre with a neonatal intensive care unit, in subjects up to 20 years of age at time of imaging. The institutional review board approved this study and did not require patient informed consent. From these MRI examinations, we selected only those showing increased signal intensity on T2-weighted images in the peritrigonal areas. Increased signal intensity in the

peritrigonal areas was defined as higher signal intensity of white matter located around the trigone than the surrounding white matter. MRI examinations of individuals, younger than 8 months of age, were excluded since in young infants the brain shows different contrasts compared to older individuals (3,8). To detect increased signal intensity on T2-weighted images in the peritrigonal areas, this has to stand out from the environment. In young infants, in our group younger than 8 months, the surrounding white matter is also of high signal intensity on T2-weighted images due to immaturity of the unmyelinated white matter. Thus, due to immaturity of the white matter, higher signal intensity in the peritrigonal areas compared to the surrounding white matter is not seen in young infants. After we selected the MRI examinations, the subjects were divided in a patient group with evidence of one or more hypoxic-ischemic events during the perinatal period and a control group.

Controls

The control group consisted of children and adolescents who had been born at term and who had no clinical history associated with hypoxic-ischemic brain damage. They had no signs of infantile encephalopathy or other neurological symptoms, except for neurodevelopmental delay and/or epileptic seizures. And apart from the peritrigonal areas of increased signal intensity, no signal intensity abnormalities were found on MRI. This was checked with the original report of the attending neuroradiologists. According to the attending neuroradiologists, brain maturation as compared to known time tables (3,8) and brain parenchyma were normal in all children and adolescents from the control group.
In this group, frequent reasons for investigation were neurodevelopmental delay and/or epileptic seizures.

Patients

Subjects were included as patients if they fulfilled the following criteria:
1) born at a gestational age of more than 35 weeks, with a history of perinatal hypoxic-ischemic encephalopathy grade 2 or 3 according to Sarnat and Sarnat (9), and having neurodevelopmental delay, spasticity, and/or epilepsia,
2) born at a gestational age of less than 35 weeks if at least one of the following had been present during the neonatal period: a) prolonged artificial ventilation (more than one week), b) apnea attacks (apnea duration exceeding 10 s) with bradycardia (heart rate under 100 beats per minute in a non-ventilated infant), more than 10 episodes in 24 h, and c) septicaemia and/or necrotizing enterocolitis with circulatory instability, requiring volume expansion and/or vasomimetic therapy,
3) a) small for gestational age (birth weight for gestational age $p < 2,3$), or preterm born (< 37 weeks), and b) neurodevelopmental delay, spasticity, and/or epilepsia.
A pediatric neurologist (L.L.) assigned the subjects to the patient or control group based on the clinical data. She was unaware of the MRI findings.

MR imaging

Images were obtained with a superconducting magnet (Gyroscan ACS-NT 15, Philips Medical Systems, Best, the Netherlands) operating at a field strength of 1.5 T. T1-weighted spin-echo sequences (550-560/14-20 [repetition time msec/echo time msec], T2-weighted spin-echo sequences (2000-5500/100-120 [repetition time msec/echo time msec], and FLAIR sequences (6000-8000/110-120/ 2000 [repetition time msec/echo time msec/ inversion time msec] were performed in the subjects. T2-weighted and FLAIR images were obtained in axial planes. T1-weighted images were obtained in axial and sagittal planes. Slice thickness was 5 - 6 mm with an interslice gap of 0.5 - 0.6 mm.

Image analysis

The MR images were retrospectively evaluated by two experienced neuroradiologists (L.L. and F.W.-dB.) who reached consensus in all MRI examinations. They were blinded to the clinical history and the group to which the subjects had been assigned. Of each subject, all available sequences were studied together. Summarizing the criteria differentiating between white matter changes resulting from PVL or terminal zones as assessed by Barkovich, Cowan, and Baker, operational characteristics were formulated.

Signal intensity of the peritrigonal areas was related to signal intensity of surrounding white matter on FLAIR, T1, and T2-weighted images and scored on a 5-point scale. A much lower signal intensity than surrounding white matter was graded 1, slightly lower 2, equal 3, slightly higher 4, and much higher grade 5.
Aspect, extent, shape, and borders of the signal intensity changes in the peritrigonal areas were studied on the T2-weighted images. The aspect of signal intensity changes on T2-weighted images was assessed as either homogeneous or patchy. Extent of signal intensity changes was assessed in rostral-caudal and anterior-posterior directions. Rostral-caudal extension was assessed on a 5-point scale, anterior-posterior extension on a 9-point scale (Table 1). Shape was assessed as fan-shaped, rectangular, oval, or round. Borders were assessed as completely sharp, partially sharp, or hazy. Bordering with the ventricles was assessed on FLAIR images, because of better delineation of the ventricles on FLAIR images as compared to T2-weighted images, i.e. abutting the ventricles or normal myelinated tissue being interspersed between the area with altered signal intensity and the ventricles. The presence of Virchow Robin spaces in the peritrigonal areas was recorded. Signs of local atrophy (widening of the trigone, irregular contour of the trigone, deep regional cortical sulci, atrophy of the corpus callosum, especially the posterior corpus callosum, loss of regional white matter volume, or any combination of those) were recorded. Finally, the presence of hypoxic-ischemic abnormalities, such as arterial infarction, parasagittal watershed injury, abnormal signal intensity in the posterior limb of the internal capsule (PLIC), basal ganglia, and cortex, was assessed. These abnormalities were studied on all available images. All information was written on MRI score forms.

Table 1 Location of increased signal intensity in the peritrigonal areas on T2-weighted images in rostral-caudal direction and anterior-posterior direction.

1) **rostral-caudal extension:**
1= at trigone
2= at trigone with caudal extension to the posterior ventricular horns
3= at trigone with rostral extension to the ventricular body
4= at trigone with rostral and caudal extension as in 2 and 3
5= extension beyond 3 or 4

2) **anterior-posterior extension:**
1= directly posterior to the trigone
2= directly posterior to the trigone with rostral extension along the ventricular body
3= directly posterior to the trigone without rostral extension, but with dorsal extension as far as the U fibres
4= directly posterior to the trigone without rostral extension, but with dorsal extension including the U fibres
5= directly posterior to the trigone without rostral extension, but with dorsal extension including the cortex
6= directly posterior to the trigone with rostral extension and with dorsal extension as far as the U fibres
7= directly posterior to the trigone with rostral extension and with dorsal extension including the U fibres
8= directly posterior to the trigone with rostral extension and with dorsal extension including the cortex
9= extension beyond the ventricular body or U fibres

Statistical analysis

First, the frequencies in which each of the characteristics were seen on the MR images were calculated.
To study whether the frequencies of each of these characteristics differed significantly between the patient and control group, Chi-squared tests were used. In case a characteristic was ordered (having more than two outcome categories), a Chi-squared test for trend was used. This applied to the following characteristics: location/extent, aspect of borders, and signal intensity. To maintain a sufficient number of subjects in each group, the extent in rostral-caudal direction was divided in outcomes 1-3 versus 4-5, and the extent in anterior-posterior direction in outcomes 1-6 versus 7-9 (Table 1). All cases with partially hazy borders were combined with the cases with sharp borders. The two cases with equal signal intensity (grade 3) compared to surrounding white matter on the FLAIR images were combined with the cases that had slightly higher signal intensity (grade 4).
Logistic regression, using a forward stepwise selection procedure was performed to assess which characteristic(s) was/were best in discriminating between the patient and control group as (an) independent predictor(s).
To study whether there was difference in age at imaging between the two groups, a t-test was used.

Results

Clinical data

During the study period 455 brain MRI examinations were performed in subjects from 8 months up to 20 years of age. A total of 75 MRI examinations were selected for this study. The patient group consisted of 28 subjects (15 male), the control group of 47 subjects (28 male). Mean age at imaging in the patient group was 4.24 years (range 0.65-16.01), in the control group 3.8 years (range 0.83-12.73). There was no significant age difference between the two groups (p=0.57).

Characteristics of peritrigonal zones signal intensity

In 40/47 controls and in 17/28 patients, proton density images had not been performed and were therefore left out of further evaluations (3). In three patients FLAIR images had not been obtained. Table 2 shows the frequencies of the characteristics in patients and controls.

Table 2 Results in all 75 Subjects.

Characteristics	**Control group** (n=47)	**Patient group** (n=28)	**p-value**
SI of TZ compared to surrounding white matter on T1			0.025
Lower	1 (1%)	5 (7%)	
Equal	46 (61%)	23 (31%)	
SI of TZ compared to surrounding white matter on T2			0.000
Slightly higher	43 (57%)	9 (12%)	
Much higher	4 (5%)	19 (25%)	
SI of TZ compared to surrounding white matter on FLAIR		3 missing	0.000
Equal	1 (1%)	1 (1%)	
Slightly higher	44 (59%)	8 (11%)	
Much higher	2 (3%)	16 (21%)	
Location of peritrigonal area with increased SI: rostral-caudal extension			0.001
1	28 (37%)	10 (13%)	
2	5 (7%)	1 (1%)	
3	4 (5%)	0	
4	7 (9%)	4 (5%)	
5	3 (4%)	13 (17%)	

Table 2 Results in all 75 Subjects (continued).

Location of peritrigonal area with increased SI: anterior-posterior extension			0.006
1	35 (47%)	14 (19%)	
2	3 (4%)	3 (4%)	
3	3 (4%)	1 (1%)	
4	0	0	
5	0	0	
6	6 (8%)	5 (7%)	
7	0	1 (1%)	
8	0	0	
9	0	4 (5%)	
Shape			0.025
Fan-shape	46 (61%)	22 (29%)	
Rectangular-shape	1 (1%)	6 (8%)	
Aspect of borders			0.000
Hazy	42 (56%)	11 (15%)	
Completely sharp	0	15 (20%)	
Partially sharp	5 (7%)	2 (3%)	
Border with ventricles			0.001
Directly adjacent	1 (1%)	8 (11%)	
Not directly adjacent	46 (61%)	20 (27%)	
Virchow Robin spaces			0.007
Yes	44 (59%)	19 (25%)	
No	3 (4%)	9 (12%)	
Local atrophy	1 (1%)	11 (15%)	0.000
Widening trigone		8	
Irregular contour trigone	1	7	
Deep regional cortical sulci		1	
Atrophy corpus callosum		6	
Loss of regional white matter volume		6	
Signs of hypoxic-ischemic damage	0	12(16%)	
PVL	0	11	
Watershed injury	0	1	
Basal ganglia injury	0	1	
Peri-Rolandic injury	0	0	
Diffuse cortical injury	0	0	
PLIC: abnormal SI	0	0	
Brain stem injury	0	1	
Arterial infarction	0	0	
Hemorrhage	0	0	

Table 2 Results in all 75 Subjects (continued).

SI changes of surrounding white matter as compared to TZ	0	12 (16%)	
Equal	0	11	
Higher	0	1	

SI = signal intensity

TZ = terminal zones

Using forward logistic regression analysis in the 72 subjects in whom all MRI sequences had been performed, very high signal intensity of the peritrigonal areas on the FLAIR images (Odds Ratio 25, confidence interval: 5-142.9) and the presence of local atrophy (Odds Ratio 14.3, confidence interval: 1.4-166.7), were best independent predictors to discriminate between the patient and control group. Most differentiating was the presence of very high signal intensity of the peritrigonal areas on FLAIR (likelihood ratio test=61.22, p=0.000). This occurred very often in patients (21% of patients) compared to controls (3% of controls). After this most discriminating characteristic was entered in a logistic model, the absence of local atrophy had the second best discriminating power (p=0.012). Absence of atrophy occurred mainly in controls (99%) compared to patients (85%).

Based on the predictions from the logistic regression analysis, three categories of subjects were identified:

1) Children and adolescents with high predicted probability to come from the patient group. They had very high signal intensity of the peritrigonal areas on FLAIR. This group comprised 18 individuals, 16 were from the patient group (Figures 2a and b).
2) Children and adolescents with high predicted probability to come from the control group. They had equal or slightly higher signal intensity of the peritrigonal areas on FLAIR and no signs of local atrophy. This group comprised 51 individuals, 44 were controls (Figures 3a and b).
3) A third group had equal or slightly higher signal intensity of the peritrigonal areas on FLAIR and signs of local atrophy. They could not be allocated to one of the two groups with confidence. This group comprised three subjects, two were patients.

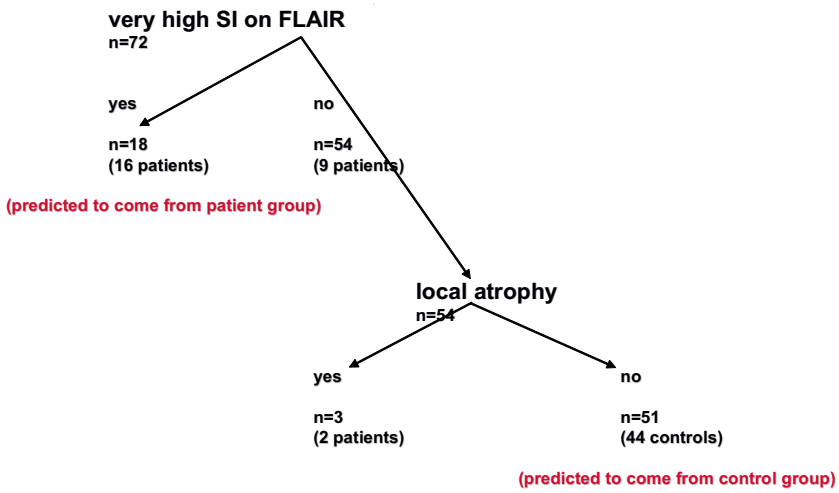


Figure 1 Flow-chart illustrating the prediction rule.
SI = signal intensity

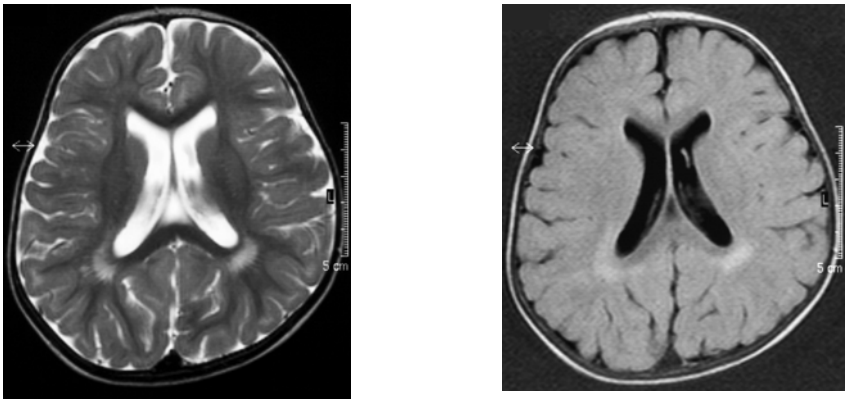
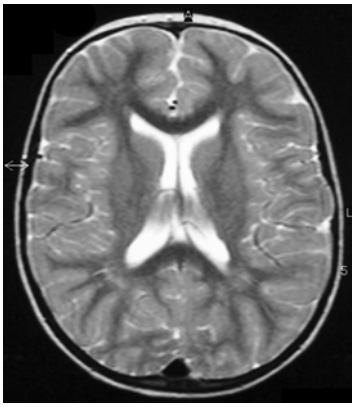
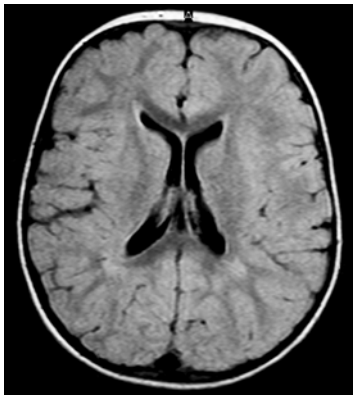


Figure 2 T2-weighted (a) and FLAIR (b) image of a subject from the patient group, showing much higher signal intensity of the peritrigonal areas compared to the surrounding white matter. Preterm-born infant with neurodevelopmental delay and mildly dysmorphic features. 1.5 years old at the time of imaging. T2-weighted image (5408/120; signals acquired, two; matrix, 253/256; section thickness, 5 mm; section gap, 0.5 mm; field of view, 20 cm) and FLAIR image (7000/120/2000; signals acquired, two; matrix, 253/256; section thickness, 5 mm; section gap, 0.5 mm; field of view, 20 cm).





a **b**

Figure 3 T2-weighted (**a**) and FLAIR (**b**) image of a subject from the control group, showing slighty higher signal intensity of the peritrigonal areas compared to the surrounding white matter. Subject with normal neurodevelopment. Pilocytic astrocytoma at the age of five years. 5.5 years old at the time of imaging for regular follow-up. The tumor was resected, no radiotherapy or chemotherapy was given. T2-weighted image (2500/120; signals acquired, one; matrix, 200/256; section thickness, 6 mm; section gap, 0.6 mm; field of view, 22 cm) and FLAIR image (7000/120/2000; signals acquired, two; matrix, 253/256; section thickness, 5 mm; section gap, 0.5 mm; field of view, 20 cm).

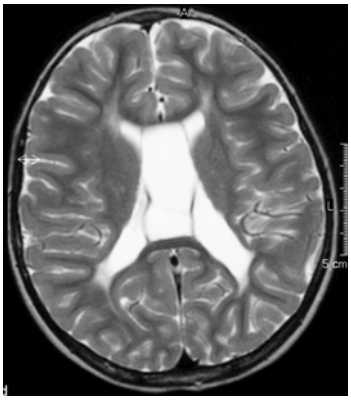


Figure 4 T2-weighted image (5408/120; signals acquired, two; matrix, 253/256; section thickness, 5 mm; section gap, 0.5 mm; field of view, 20 cm) of a subject from the patient group, showing local atrophy, abnormal signal intensity of the periventricular white matter caused by PVL, and a cavum septi pellucidi and cavum vergae. Preterm-born subject with neurodevelopmental delay and spastic tetraplegia. Almost 5 years old at the time of imaging.

Figure 1 shows a flow-chart of the prediction rule. For the whole group, positive and negative predictive values were, respectively, 89% and 83% if we assume the group difficult to predict to be controls. Positive and negative predictive values were, respectively, 86% and 86% if we assume the group difficult to predict to be patients.

Discussion

The differentiation between terminal zones and abnormal findings on MRI is of diagnostic importance. This is the first study assessing the diagnostic value of criteria differentiating terminal zones from hypoxic-ischemic injury of the periventricular white matter.

Very high signal intensity of the peritrigonal areas compared to surrounding white matter on FLAIR images and the absence of local atrophy were best independent predictors to discriminate between the patient and control group. They were used in a prediction model and we found high positive and negative predictive values. Subjects with very high signal intensity of the peritrigonal areas on FLAIR images were very likely to come from the patient group, while subjects with equal or only slightly higher signal intensity of the peritrigonal areas on FLAIR images and no signs of local atrophy were very likely to come from the control group. These results show that the existing criteria have good diagnostic value (1-3).
Frequency of several characteristics differed significantly between the control and patient group (see Table 2). On FLAIR and T2-weighted images much higher signal intensity in the peritrigonal areas was seen significantly more often in the patient group than in the controls. This is in agreement with results of Barkovich and Cowan who found signal intensity changes due to PVL to be higher than the signal intensity of terminal zones on T2-weighted images (2-3). Signal intensity of the peritrigonal areas compared to surrounding white matter was scored on a 5-point scale. We are aware of the fact this scale is a subjective one. The signal intensity of normal high signal intensity structures on T2-weighted images, such as cerebrospinal fluid and the eyebulb, is higher than the signal intensity changes we studied. However, very high signal intensity approximates the signal intensity of cerebrospinal fluid on T2-weighted images. Slightly higher signal intensity is of little bit higher signal intensity than the surrounding white matter.
On T1-weighted images, signal intensity in the peritrigonal areas was significantly more often lower in patients than in controls. Cowan described terminal zones to have low signal intensity on T1-weighted images, but not as low as the white matter changes resulting from PVL (2).

Barkovich described homogeneous signal intensity on T2-weighted images in the peritrigonal areas in subjects with terminal zones. In all the subjects (both patients and controls) we studied, the peritrigonal areas with increased signal intensity were homogeneous, thus homogeneity not being a discriminating characteristic between terminal zones and pathology (2).
Increased peritrigonal signal intensity was seen in the control group in the same area as has been described by Barkovich and Cowan for terminal zones: above and at the level of the trigone, extending from the trigone backwards (2-3). The extent of the area of increased peritrigonal signal intensity was less in the control group than in the patient group. Presuming that this area was pathological in patients and consisted of normal terminal zones in the control group, this finding was what we expected, normal terminal zones being small and pathological white matter changes in the same area being larger than terminal zones (Figure 4).
Borders of the peritrigonal areas with increased signal intensity were significantly more often hazy in the control group than in the patient group. The presence of completely sharp borders was seen only in the patient group. These findings are in agreement with Barkovich, who found PVL lesions to be more sharply defined (3).
The increased signal intensity in the peritrigonal areas abutted the ventricles in 29% of patients and in 2% of controls. Baker et al. described the existence of normal myelinated tissue interspersed between the ventricles and terminal zones (1). We found this very often in controls (98%), but still in 71% of patients. Thus, this phenomenon did not discriminate between terminal zones and pathology.

Possibly, this difference can be explained by the fact that more recent MRI machines provide better image quality and resolution than the MRI systems used in the eighties, therefore enabling better detection of normal myelinated tissue, even in subjects with pathological white matter changes. Another explanation may be that in the eighties, the subjects imaged had more profound changes due to PVL compared to the subjects in our groups (inclusion bias). MRI examinations are nowadays more widespread available, not only for the severely affected patients. In addition, there has been a steady decline in the incidence of severe PVL during the last decade (10). Probably we included less patients with severe forms of PVL.

Virchow Robin spaces were seen significantly more often in the control group. This is contrary to what we expected. Virchow Robin spaces are found in older people with loss of white matter volume and a normal finding in young children (6,10). An explanation may be that in patients with white mater damage the pathologic changes in the periventricular white matter may mask these subtle spaces, which may therefore not show as separate entities.
In 12 patients we found signal intensity changes in the non-peritrigonal white matter, probably due to hypoxic-ischemic damage. Pathological white matter changes may be due to a variety of conditions, such as infarction and PVL. These conditions can cause volume loss and scarring, resulting in local signal intensity changes (Figure 4). In almost all of them (11/12) the increased signal intensity in the peritrigonal areas had the same signal intensity as the abnormal areas in the non-peritrigonal white matter, supporting our presumption that in these patients the increased signal intensity in the peritrigonal areas was also of pathological origin.

We are aware of the fact that the subjects from our control group were not healthy subjects, they underwent imaging for reasons such as headache, epilepsy, or neurodevelopmental delay. However, the subjects were carefully selected not to have hypoxic-ischemic cerebral damage. According to the attending neuroradiologists, apart from the peritrigonal areas of increased signal intensity, no signal intensity abnormalities were found on MRI in the control group. Brain maturation as compared to known time tables and brain parenchyma were normal in all children and adolescents from the control group (3,8).
This study provides guidelines permitting distinction between terminal zones and hypoxic-ischemic white matter injury in daily clinical practice. The differentiation between terminal zones (normal variation) and abnormal findings is of diagnostic importance, especially since the changes in pathological periventricular white matter can be subtle and easily confused with terminal zones. The clinical significance and prognostic value of this differentiation still needs to be evaluated by correlating neurodevelopmental outcome with neuroimaging findings in subjects with increased signal intensity of the peritrigonal areas.

Conclusion

The signal intensity of the peritrigonal area on FLAIR images is the most important characteristic to distinguish between terminal zones and pathology in young subjects.

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