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Value of fluid-attenuated inversion recovery sequences in early MRI of the brain in neonates with a perinatal hypoxic-ischemic encephalopathy

L.T.L. Sie[1], F. Barkhof[2], H.N. Lafeber[3], J. Valk[2], M.S. van der Knaap[1]

[1] Department of Child Neurology, University Hospital 'Vrije Universiteit', De Boelelaan 1117, NL-1081 HV Amsterdam, The Netherlands
[2] Department of Diagnostic Radiology, University Hospital 'Vrije Universiteit', De Boelelaan 1117, NL-1081 HV Amsterdam, The Netherlands
[3] Department of Neonatology, University Hospital 'Vrije Universiteit', De Boelelaan 1117, NL-1081 HV Amsterdam, The Netherlands

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Abstract. The aim of our study was to assess the usefulness of fluid-attenuated inversion recovery (FLAIR) sequences in comparison with conventional spin-echo and inversion MR imaging in neonates for evaluation of myelination and for detection of hypoxic-ischemic brain injury. We reviewed early MR scans of 18 neonates with suspected hypoxic-ischemic brain damage. Myelination could be evaluated with confidence using conventional MR imaging in all but 2 infants; however, the presence of myelin was very difficult to assess on FLAIR images. Overall, 53 lesions or groups of lesions were identified. The FLAIR technique was more sensitive in 11 of the lesions; especially (pre)cystic lesions could be identified much better and more cysts were found. Conventional MR imaging failed to identify 2 of the lesions and was more sensitive in 14 of the lesions; especially punctate hemorrhages and lesions in basal ganglia or thalami could be better determined. The FLAIR technique missed 3 of these lesions. In the remaining 28 lesions conventional MR and FLAIR images were equally diagnostic. The FLAIR technique and conventional MR imaging are complementary in detecting early sequelae of hypoxic-ischemic brain injury in neonates. The FLAIR technique is not suitable for assessing myelination of the neonatal brain; therefore, FLAIR cannot replace conventional MR imaging.

Key words: Neonates – Hypoxic-ischemic brain injury – Myelination – MRI – FLAIR

Introduction

In the past decade, early MRI has been used increasingly in neonates with a hypoxic-ischemic encephalopathy [1, 2, 3, 4, 5, 6, 7]. Several patterns of remaining posthypoxic-ischemic brain damage have been recognized. The most common pattern of posthypoxic-ischemic brain damage is periventricular leukomalacia (PVL), followed by bilateral lesions in the basal ganglia or thalamus, central cortico-subcortical damage, and multicystic leukomalacia [8, 9, 10, 11].

Fluid-attenuated inversion recovery (FLAIR) uses a conventional inversion recovery sequence with a long echo time in order to achieve T2-weighting, with an inversion time chosen specially to null the signal from cerebrospinal fluid (CSF) [12, 13]. The usefulness of FLAIR sequences has been reported in many disorders, including cerebral infarction, multiple sclerosis, mesial temporal sclerosis, subarachnoid space disease, and intracranial infections [14, 15, 16, 17, 18, 19, 20]. Recently, FLAIR imaging was used to evaluate late sequelae of perinatal hypoxic-ischemic brain damage. The FLAIR sequences were preferred to T1- and T2-weighted images for demonstration of PVL, cystic PVL, and subcortical lesions near the brain surface [21].

Until now, there have been no reports assessing the additional value of FLAIR images in the acute or subacute stage of a perinatal hypoxic-ischemic encephalopathy. It remains unclear whether this new sequence is able to detect more precisely the site and extent of the lesions as compared with conventional spin-echo and inversion MR imaging. In the present study, FLAIR sequences were compared with conventional MR images in order to assess their relative merits in detecting brain lesions and progress of myelination in neonates with a hypoxic-ischemic encephalopathy in the early stage.

Materials and methods

Patient data

We retrospectively reviewed MRI scans of all neonates with suspected hypoxic-ischemic brain injury who un-

Correspondence to: M.S. van der Knaap

derwent MRI in the acute or subacute stage as part of their clinical work-up between September 1996 and September 1998. In this period the FLAIR sequence was introduced and used on a regular basis. All infants included in the study had been admitted to the neonatal intensive- or high-care units of our hospital. Obstetric and clinical records of the children were evaluated for known risk factors for hypoxic-ischemic brain damage. Magnetic resonance imaging was performed when a persistent neonatal encephalopathy was present with convulsions or coma, according to the criteria of Sarnat and Sarnat [22], or when serious ultrasound abnormalities were present (bilateral diffuse increased echogenicity of the white matter, cortex, basal ganglia, or thalamus). Other ultrasound abnormalities, such as germinal matrix hemorrhage, mild PVL, intraventricular hemorrhage, or unilateral infarcts, were not considered an indication for MRI. All surviving infants received long-term follow-up at the Out-Patient Department.

MRI data

Neonatal MRI was performed as soon as the infants were in a stable respiratory and circulatory condition. They were sedated with chloral hydrate (75 mg/kg) orally. Heart rate and transcutaneous oxygen saturation were monitored.

The MRI was performed at 1.5 T (Siemens Vision, Erlangen, Germany) using a circularly polarized knee coil especially adapted for imaging small heads of neonates. For all images we used a 128×256 or 256×256 matrix, a field of view of 18–20 cm^2, and a slice thickness of 4 or 5 mm. T1-weighted spin-echo (SE) images (TR/TE = 480/20 ms) were obtained in the sagittal and axial planes. Inversion recovery (IR) images [TR/TE/inversion time (TI) = 4000/30/800 ms] and T2-weighted images [SE; TR/TE = 3000/30, proton-density (PD) weighted, – 60–120 ms] were obtained in the axial plane. Fast FLAIR images (TR/TE/TI = 9000/105/2200 ms) were obtained in the axial plane.

All scans were assessed and scored systematically for state of myelination, signal abnormalities, and (pre)cystic degeneration of white and gray matter structures, including periventricular and subcortical white matter, basal ganglia, thalami, cerebral cortex, brainstem, and cerebellum. The central sulcus was identified according to the formerly published criteria [23]. Myelination was assessed as normal, delayed, or not evaluable [24].

We interpreted the observed signal intensity (SI) changes according to previous publications [1, 2, 4, 5, 6, 25, 26] and assessed the images for the presence of the following lesions or groups of lesions:

1. Subtle band-like SI changes within the periventricular white matter relative to the remainder of the cerebral hemispheric white matter [26].
2. Punctate lesions in the white matter consistent with hemorrhages [2] in locations which are normally not myelinated at this age [24].
3. Larger focal lesions in the white matter consistent with hemorrhages.
4. Cystic lesions in the white matter, defined as well-demarcated areas with SI identical to that of CSF on all pulse sequences.
5. Precystic lesions in the white matter, defined as areas with SI close (but not identical) to CSF on all pulse sequences.
6. Extensive SI changes throughout the white matter with or without hemorrhagic or (pre)cystic aspect.
7. Signal changes in the basal ganglia or thalami with or without hemorrhagic or (pre)cystic aspect.
8. Signal changes in the (pericentral) cortex.

Images were reviewed and scored by consensus of two readers (L. T. L. S. and F. B.). The number, localization, and extent of the lesions were separately assessed on conventional and FLAIR images. Finally, FLAIR and conventional images were compared for each brain structure and the results of this were classified into five categories: (a) FLAIR imaging more diagnostic than conventional MR imaging; (b) FLAIR and conventional MR imaging equally diagnostic; (c) FLAIR imaging inferior to conventional MR imaging; (d) absence of lesions; and (e) not evaluable.

Results

Within the study period, 39 infants underwent MRI to evaluate the presence of hypoxic-ischemic brain damage. In 18 infants both conventional MR and FLAIR sequences were available and these infants were selected for the present study. The gestational age at birth of the infants was 34 ± 4.5 weeks (mean ± SD) with an age range of 28.5–42 weeks. Mean postnatal age at the time of MRI was 16 ± 11 days with a range of 3–40 days. Five infants did not survive the neonatal period. Clinical details of the infants are summarized in Table 1.

Myelination could be evaluated in all but 2 infants. Myelination was not evaluable in these 2 infants because of the presence of extensive hemorrhagic and cystic lesions. In the remaining 16 infants we found normal myelination patterns with conventional MR imaging (Fig. 1 a,b). However, the presence of myelin was difficult to assess on FLAIR images in all 16 infants (Fig. 1 c,d). Myelinated structures were hardly distinguishable as areas with minimally increased SI. Normal immature white matter appeared mildly hypointense or isointense relative to the gray matter on FLAIR sequences.

Results of the qualitative radiological comparison between conventional MR images and FLAIR sequences are summarized in Table 2. We did not find lesions in brainstem or cerebellum on either conventional MR or FLAIR images.

1. Subtle band-like SI changes regarding the periventricular zone: conventional MR imaging and FLAIR were comparable in detecting mild periventricular white matter signal changes in 7 infants, showing a decreased

Table 1. Clinical details of the infants. *GA* gestational age in weeks; *BW* birth weight; *N* normal; *m* month(s); *y* year(s)

Case no.	Gender	GA at birth	BW (g)	Apgar 1/5/10 min	Risk factors/etiology	Persistent coma or convulsions	Outcome
1	M	39	4200	0,3,4	Fetal bradycardia	+	Dead
2	M	30	1025	6,8,9	Heart failure	+	Dead
3	M	28	1345	1,5,10	Sepsis	–	2 y: N
4	M	35	2000	8,9,?	Fetal bradycardia	+	6 m: hypertonia
5	F	39	2900	0,2,4	Fetal bradycardia	+	3 m: hypertonia
6	F	41	3620	3,4,5	Fetal bradycardia	+	Dead
7	M	41	3100	3,7,9	Fetal bradycardia	+	2 y: N
8	M	29	900	1,4,8	Twin-to-twin transfusion	+	4 m: N
9	M	37	4040	8,8,?	Meconium	+	Dead
10	F	41	4000	3,6,10	Meconium	+	2 y: tetraplegia
11	M	34	2480	0,1,3	Fetal bradycardia	+	Dead
12	M	29	840	7,7,?	Fetal bradycardia	–	2 y: N
13	F	42	3260	7,9,10	Traumatic delivery	+	2 m: hypertonia
14	F	36	2230	4,7,7	Solutio placentae	+	11/2 y: diplegia
15	M	35	1935	1,5,8	Fetal bradycardia	+	8 m: N
16	F	36	2385	9,9,?	Fetal bradycardia	+	11/2 y: N
17	M	31	960	6,8,9	Fetal bradycardia	–	11/2 y: diplegia
18	F	36	3000	7,9,?	Meconium	+	1 y: severe retardation

Table 2. The MRI findings in 18 infants with perinatal hypoxic-ischemic encephalopathy and comparison between FLAIR and conventional MR images. *SI* signal intensity; *CI* conventional MR imaging; *WM* white matter; *FL* FLAIR imaging

MRI lesions/groups of lesions	CI = FL	CI < FL	CI > FL	Normal	Not evaluable
Periventricular SI changes	5	1	1	7	4
Punctate WM hemorrhages	7	0	6	5	0
Focal WM hemorrhages	2	1	1	14	0
Cystic WM lesions	1	6	0	11	0
Precystic WM lesions	2	2	0	14	0
Extensive WM SI changes	2	0	1	15	0
Lesions in basal ganglia/thalami	3	0	4	11	0
Lesions in (pericentral) cortex	7	1	1	9	0

signal on T1-weighted SE, IR, and FLAIR images and increased signal on T2-weighted images as compared with the remainder of the hemispheric white matter. The remaining infants had either no zone of SI change (7 infants) or this zone was not evaluable because of the presence of extensive hemorrhagic or cystic lesions (4 infants).

2. Punctate lesions in the white matter: conventional MR imaging was more sensitive than FLAIR imaging in detecting punctate hemorrhagic lesions in 6 of the 13 infants. Hemorrhagic lesions have an increased SI on T1-weighted SE, IR, and FLAIR images and/or a decreased SI on T2-weighted images. These punctate high SI lesions were often more difficult to detect on FLAIR than on conventional MR images. However, whereas most lesions that were hyperintense on T1-weighted SE and IR images were also seen on FLAIR images, this latter pulse sequence frequently failed to identify lesions with low SI on T2-weighted images (Fig. 2). In 1 infant FLAIR also missed hemorrhagic lesions that were found on T1-weighted SE images. In 7 infants FLAIR and conventional MR images were equally diagnostic.

3. Larger focal lesions in the white matter: conventional MR and FLAIR images were comparable in detecting larger hemorrhages in 4 infants. These lesions had an increased SI on T1-weighted SE, IR, and FLAIR images and a decreased SI on T2-weighted images.

4. Cystic lesions in the white matter: FLAIR images were more sensitive than conventional MR images in detecting cystic lesions in 6 of the 7 infants. Cystic lesions have SI identical to that of CSF on all pulse sequences, with a low SI on T1-weighted SE, IR, and FLAIR images (Fig. 3), and a high SI on T2-weighted images. In these 6 infants the cysts could be better demarcated and more cystic lesions were found with FLAIR sequences. In one of these 6 infants, a single cystic lesion found with FLAIR images was missed on conventional MR imaging (Fig. 2). In the remaining infant, FLAIR and conventional MR images were comparable.

5. Precystic lesions in the white matter could be distinguished much better with FLAIR images in 2 of 4 infants; in the other 2 infants both techniques were comparable.

6. Extensive SI changes throughout the white matter: conventional MR and FLAIR images were comparable in detecting extensive white matter SI changes in 2 infants. In another infant the different types of lesions were more clearly distinguishable with conventional MR imaging (Fig. 4). In general, conventional MR imaging provided better differentiation than FLAIR between ischemic changes (low SI on T1-weighted SE

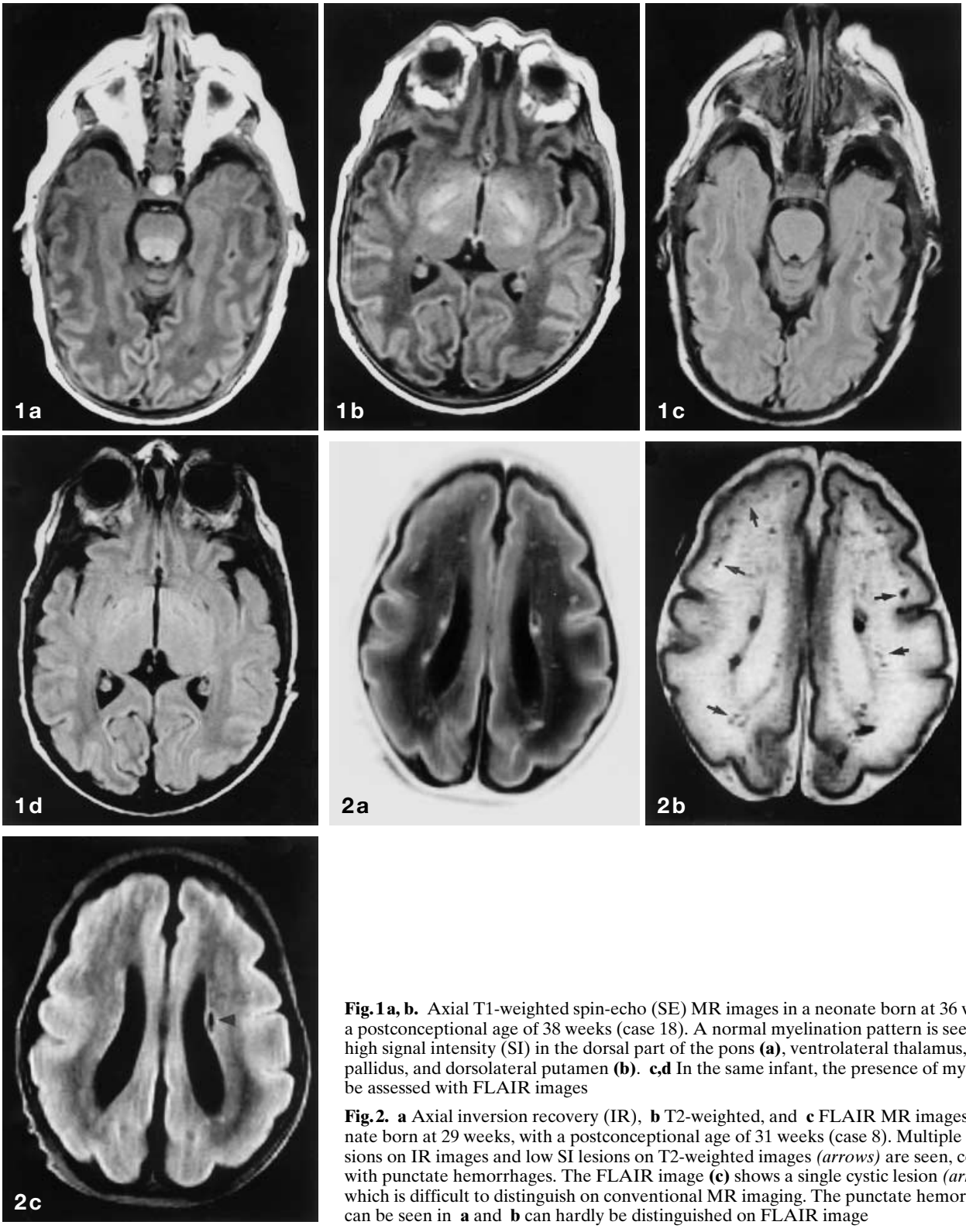

Fig. 1 a, b. Axial T1-weighted spin-echo (SE) MR images in a neonate born at 36 weeks, with a postconceptional age of 38 weeks (case 18). A normal myelination pattern is seen, with a high signal intensity (SI) in the dorsal part of the pons **(a)**, ventrolateral thalamus, globus pallidus, and dorsolateral putamen **(b)**. **c,d** In the same infant, the presence of myelin cannot be assessed with FLAIR images

Fig. 2. **a** Axial inversion recovery (IR), **b** T2-weighted, and **c** FLAIR MR images in a neonate born at 29 weeks, with a postconceptional age of 31 weeks (case 8). Multiple high SI lesions on IR images and low SI lesions on T2-weighted images *(arrows)* are seen, consistent with punctate hemorrhages. The FLAIR image **(c)** shows a single cystic lesion *(arrowhead)* which is difficult to distinguish on conventional MR imaging. The punctate hemorrhages that can be seen in **a** and **b** can hardly be distinguished on FLAIR image

and IR images and high SI on T2-weighted images) and hemorrhages (high SI on T1-weighted SE and IR images and low SI on T2-weighted images). In these cases FLAIR and also PD-weighted images showed a more diffuse hyperintense signal change, without much differentiation between ischemic and hemorrhagic changes. The cystic component could better be determined with FLAIR images in 1 infant (Fig. 4).

7. Signal changes in the basal ganglia or thalami: conventional MR imaging was more sensitive than FLAIR images in detecting lesions in this area in 4 of the 7 infants. These lesions had an increased SI on PD-weighted

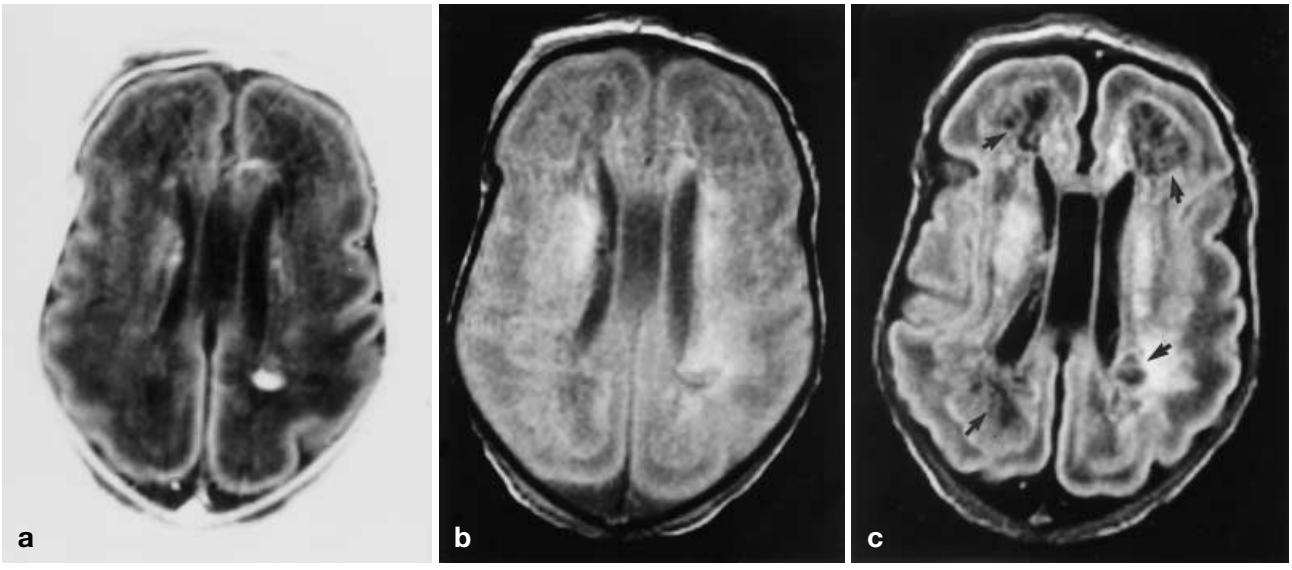

Fig. 3. **a** Axial IR, **b** Proton-density-weighted, and **c** FLAIR MR images in a neonate born at 31 weeks, with a postconceptional age of 33 weeks (case 17) show multiple SI changes throughout the periventricular white matter and a single high SI lesion in the left parietal region on all sequences; the latter is consistent with a focal hemorrhage. The IR and proton-density-weighted images show bilateral frontal and parietal precystic lesions with a SI almost identical to cerebrospinal fluid (CSF). These lesions are much better demarcated with FLAIR image and have an SI identical to CSF, consistent with cysts (*arrows* in **c**)

images, T1-weighted SE, IR, and FLAIR images, and sometimes a decreased SI on T2-weighted images. Conventional MR imaging was superior in differentiating hemorrhagic from ischemic changes, showing a combination of high and low SI changes on T1-weighted SE, IR, and T2-weighted images. The lesions were displayed with a more diffuse high signal on PD-weighted and FLAIR images (Fig. 4). In 1 infant the lesions were not seen on FLAIR images. In the other 3 infants both techniques were equally diagnostic.

8. Signal changes in the (pericentral) cortex: conventional MR and FLAIR images were comparable in detecting cortical lesions in 7 of 9 infants. The FLAIR and PD-weighted images often showed the same abnormal high SI, but FLAIR images were sometimes more difficult to assess. In 1 infant FLAIR failed to depict cortical lesions, which could be seen on PD-weighted images. In one other infant cortical lesions were missed on conventional MR imaging, showing only a diminished white and cortical gray matter differentiation. In this infant FLAIR images could identify an abnormal high SI of the white matter and low SI of the cortex.

Overall, 53 different lesions or groups of lesions were identified in our study population. The FLAIR technique was more sensitive in 11 of the lesions; especially cystic and precystic lesions could be identified much better and more cysts were found. Conventional MR imaging failed to identify 2 of these lesions: a cystic lesion and a cortical lesion. Conventional MR imaging was more sensitive in 14 of the lesions; punctate hemorrhages and lesions in basal ganglia or thalami could be identified better. The FLAIR technique missed 3 of these lesions: a punctate hemorrhage, a lesion in the basal ganglia and a cortical lesion. In the remaining 28 lesions or groups of lesions, conventional MR and FLAIR images were equally diagnostic. Furthermore, assessment of myelination was much easier with conventional MR than with FLAIR imaging.

Discussion

Early evaluation of the presence of perinatal hypoxic-ischemic brain injury is important for both clinical management and neurological prognosis. Ultrasound performed in the incubator is the primary imaging method in the early diagnosis of hypoxic-ischemic brain lesions. However, conventional MR imaging has been reported to be superior to ultrasound in determining the precise localization and extent of the lesions [27, 28]. Whenever a new technique becomes available, its merit with respect to perinatal hypoxic-ischemic brain injury has to be evaluated. In this paper we describe our experience with FLAIR.

The FLAIR imaging technique uses a long inversion time to suppress the signal from CSF and a long TE to produce heavily T2-weighted images. Advantages of FLAIR imaging include improved contrast between the SI of a variety of lesions that prolong brain T2 relaxation and the suppressed SI of the adjacent ventricular or subarachnoid CSF space [12, 13]. Many types of lesions result in signal increase on FLAIR, including pathology with T2-prolongation and T1-shortening [29]. The FLAIR technique is particularly useful in detecting subtle changes at the periphery of the hemispheres, in the brainstem, and in the periventricular region [12, 13, 19, 20, 30, 31, 32]. However, validation of the high sensitivity of FLAIR imaging is difficult, because histological confirmation is lacking in most cases [12]. The initial disadvantage of the FLAIR sequence has been the

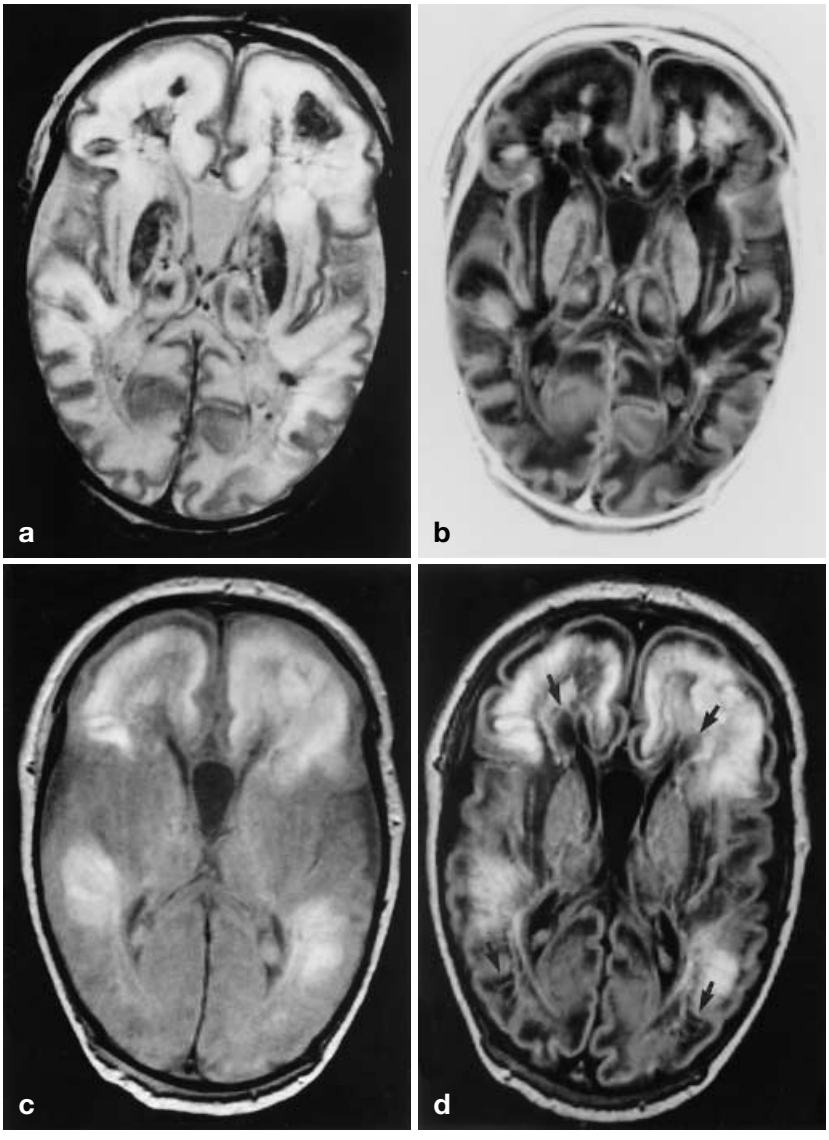

Fig. 4. **a** Axial T2-weighted, **b** IR, **c** proton-density-weighted, and **d** FLAIR MR images in a neonate born at 37 weeks, with a postconceptional age of 39 2/7 weeks (case 9) show extensive SI changes throughout the white matter and lesions in basal ganglia and thalami. Conventional MR imaging (**a, b**) is superior in differentiating these lesions into ischemic changes (low SI on IR images, and high SI on T2-weighted images) and hemorrhages (high SI on IR images, and low SI on T2-weighted images). Proton-density-weighted (**c**) and FLAIR (**d**) images show a more diffuse hyperintensity without much differentiation between ischemic and hemorrhagic changes, whereas the cystic component is better seen with FLAIR sequence (*arrows* in **d**). Diffuse white matter damage with large cystic lesions was confirmed at autopsy performed 4 days later

lengthy acquisition time [14], but recently the total acquisition time has been reduced to approximately 3 min by using a fast or turbo variant [29].

In this study the merit of FLAIR sequence in the acute stage of perinatal hypoxic-ischemic brain damage was that it could depict cystic and precystic lesions in the white matter much better than conventional MR imaging, even when these lesions were abutting a CSF border. Since the white matter is immature during the neonatal period, and SI of unmyelinated white matter is as high as that of cystic lesions and CSF on T2-weighted images, T2-weighted images are less useful in detecting cystic lesions. This was also found by others [21]. On the other hand, conventional MR imaging was definitely superior to FLAIR images in detecting small hemorrhages, and lesions in the basal ganglia or thalamus, because high signal changes on T1-weighted and low signal changes on T2-weighted sequences are complementary. The relatively decreased sensitivity for punctate hemorrhages may in part result from the use of the fast SE version of FLAIR vs conventional T2-weighted SE images. Spin-echo is known to be more sensitive to susceptibility artifacts than fast SE, because the latter has additional refocusing 180 pulses. Frequently, FLAIR and PD-weighted images were comparable in appearance and gave equally diagnostic information, especially in hypoxic-ischemic brain lesions with high SI changes on both sequences. In the more chronic stage, Okuda et al. [21] found FLAIR to be superior to conventional MR imaging in detecting areas with gliosis (high SI changes) and cystic (low SI changes) PVL in 13 patients with a history of perinatal hypoxic-ischemic encephalopathy (aged 1 month to 3.6 years).

In our study, myelination patterns in neonates were readily established with conventional MR images [24, 33], but not with FLAIR imaging. Recently, Ashikaga et al. [34] reported that myelination can be accurately assessed by FLAIR images without using other SE sequences. They identified two stages: the early stage (first 6 months of life), when signal intensities of gray and white matter are approximately similar to those on T1-weighted SE images, and the late stage, when the

pattern of myelination is similar to that on T2-weighted SE images. Contrary to the findings of Ashikaga et al. [34], we found that FLAIR sequences are not well suited to evaluate myelination in the early neonatal stage. The presence of myelin could hardly be assessed with this technique and additional SE sequences are needed. This discrepancy may be related to the fact that we studied a younger population (neonates). Murakami et al. [35] assessed normal myelination patterns of the pediatric brain with FLAIR imaging in 29 developmentally normal children (aged 1–42 months). They found on T2-weighted images that the white matter progressed from hyperintense to hypointense relative to adjacent gray matter over the first 2 years of life. An analogous, although slightly delayed, sequence of maturation was observed on FLAIR images with the exception of the deep cerebral hemispheric white matter, which followed a triphasic sequence of development. On FLAIR images the deep cerebral white matter was hypointense relative to gray matter in the young infant (similar to T1-weighted SE images), became hyperintense in the first few months of life, and then reverted back to hypointense during the second year of life (similar to T2-weighted SE images). It is difficult to make a comparison with our findings, because Murakami et al. [35] did not assess the presence of myelinated structures in infants younger than 1 month of age.

More recently, diffusion-weighted (DW) MR imaging has been introduced into neonatal medicine [36, 37, 38]. Johnson et al. [38] examined the effectiveness of echo-planar DW imaging in detecting hypoxic-ischemic brain injury compared with turbo T2-weighted and FLAIR imaging in a cohort of 26 neonates and infants. They found that echo-planar DW images revealed a greater extent of and a larger number of abnormalities compared with both T2-weighted and FLAIR images in 11 of 12 (92%) patients with abnormalities on DW images. Undoubtedly, DW imaging is a more sensitive MR method for detection of hypoxic-ischemic brain injury in the first hours after the asphyxia, but at the time of performance of this study it was not available to us.

In conclusion, all MR sequences used (T1-weighted SE, T2-weighted SE, and FLAIR) are complementary and should all be applied if maximal diagnostic information is needed. Although FLAIR might be used as a stand-alone sequence in the evaluation of late sequelae of perinatal hypoxic-ischemic brain damage, FLAIR cannot replace conventional T1-, PD-, and T2-weighted images in the early stage.

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