Reliability of qualitative assessment of brain magnetic resonance imaging in extremely premature infants*

Confiabilidade da análise qualitativa da ressonância magnética do encéfalo em prematuros extremos

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Abstract **OBJECTIVE: The present study was aimed at evaluating the reliability of the qualitative visual assessment of brain abnormalities using conventional brain MRI in extremely preterm infants. MATERIALS AND METHODS: A cohort of 45 consecutive infants with gestational age of 30 weeks or less (median of 27 weeks, ranging from 25 to 30 weeks) was enrolled in this study. Two independent, experienced neuroradiologists blindly reviewed MRI studies of the infants' brain for diffuse and excessive high-signal intensity (DEHSI), dilated lateral ventricles, intracranial hemorrhage, areas of abnormal signal in the basal ganglia and cortex, cyst-like areas, ventricular deformities, enlargement of subarachnoid spaces, early leukoencephalomalacia, and cortical abnormalities. RESULTS: Forty-one patients (91.1%) presented abnormalities at MRI. The most common findings were DEHSI in the white matter (75.6%) and ventricular dilatation (42.2%). The interobserver agreement was high ($\kappa > 0.60$) for most of the abnormal MRI findings. The kappa statistic values were moderate for enlargement of the subarachnoid space ($\kappa = 0.52$) and was only low for DEHSI in the white matter ($\kappa = 0.39$). CONCLUSION: Conventional MRI seems to be a reliable method for evaluating the most common brain abnormalities in extremely premature infants; however, the presence of DEHSI in the white matter demonstrated to be is a less reliable finding.**

Keywords: Preterm; Brain; Magnetic resonance imaging; Imaging; Hypoxia.

Resumo **OBJETIVO: O objetivo deste estudo foi avaliar a confiabilidade da análise visual qualitativa dos achados de imagem de ressonância magnética (RM) em recém-nascidos prematuros extremos. MATERIAIS E MÉTODOS: Uma coorte de 45 recém-nascidos de idade gestacional de 30 semanas ou menos foram inseridos neste estudo. Dois neurorradiologistas, cegos quanto aos dados clínicos, avaliaram de forma independente as RMs de crânio em relação aos seguintes achados: presença de hipersinal difuso e excessivo (DEHSI), dilatação dos ventrículos laterais, hemorragia intracraniana, áreas de sinal anormal em núcleos da base e córtex, áreas de aspecto cístico, deformidades ventriculares, dilatação do espaço subaracnóideo, leucoencefalomalácia precoce e anormalidades corticais. RESULTADOS: Quarenta e um pacientes (91,1%) apresentaram exame de RM anormal. Os achados mais comuns foram DEHSI (75,6%) e dilatação dos ventrículos (42,2%). A concordância interobservadores entre os dois experientes neurorradiologistas foi alta ($\kappa > 0{,}60$) para a maioria das alterações detectadas pela RM. O valor de kappa foi moderado ($\kappa = 0{,}52$) para alargamento do espaço subaracnoide e fraco ($\kappa = 0{,}39$) para DEHSI na substância branca. CONCLUSÃO: A avaliação qualitativa da maioria dos achados de imagem por RM de neonatos prematuros extremos foi considerada confiável, entretanto, a presença de DEHSI na substância branca demonstrou um grau de confiabilidade menor.**

Unitermos: Prematuros; Cérebro; Imagem por ressonância magnética; Imagem; Hipóxia.

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INTRODUCTION

Over the last decades, there have been significant advances in perinatal and neonatal care, which have dramatically improved survival rates for infants with very low birth weights. Nevertheless, there has been a increasing concern regarding the later neurodevelopmental challenges faced by surviving infants[(1)]. The developing

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brain is highly vulnerable to injury from a variety of ischemic, inflammatory, infective, and neurotoxic factors[(2)]. Extremely preterm infants are at higher risk of brain hemorrhage, white matter (WM) lesions, and poor cerebral development[(3)]. The central nervous system (CNS) damage increases the probability of neurological and developmental disabilities in this group of patients[(4)]. Conventional neuroimaging is usually employed to assess the presence and the extent of brain injury as well as to predict neurodevelopmental outcomes.

The two major neuroimaging modalities used in the evaluation of the premature infant's brain are cranial ultrasonography (US) and magnetic resonance imaging (MRI)[(5–8)]. Cranial US is reliable in the evaluation of hemorrhagic lesions, hydrocephalus, and cystic changes[(5,6)]. Such technique, however, is typically obtained through the anterior fontanel, which has a limited field of view. Moreover, cranial US is not accurate enough to evaluate diffuse or subtle brain injuries, specially in the WM[(5–8)]. MRI of the brain is more sensitive and specific than cranial US to detect hemorrhage, ischemia, and WM lesions[(5,6,9–11)]. It also provides better characterization of the most common brain abnormalities in preterm infants[(5,6,12)].

The aim of the present study was to evaluate the reliability of the qualitative visual assessment of brain abnormalities using conventional brain MRI in a cohort of 45 extremely preterm infants.

MATERIALS AND METHODS

Patient population

The Institutional Review Board of our Hospital approved the study and term of free and informed consent to perform MRI under sedation at term-equivalent age was obtained from the parents. A cohort of 45 consecutive infants with gestational age of 30 weeks or less (median of 27 weeks, ranging from 25 to 30 weeks) was enrolled in this prospective study. The gestational age was calculated from the date of the last menstrual period and confirmed with data from early US scans. The patients had a median birth weight of 890 g (ranging from 385 g to 1225 g). Critically ill patients were not considered for the study, at least until the neonatologist in charge of these patients confirmed that they could be submitted to MRI study at our imaging center affiliated to the hospital with no risk for the patient.

Imaging protocol

All the patients underwent MRI in a 1.5 T scanner (Magnetom Avanto – Siemens Medical Systems; Erlangen, Germany) using a head coil. The following sequences were obtained: T1-weighted sagittal three-dimensional gradient-echo (repetition time (TR)/echo time (TE) = 1770/3.9 ms, field of view (FOV) = 190 × 190 mm, matrix = 256 × 256, slice thickness = 0.7 mm), T2-weighted axial fast spin-echo (FSE) (TR/TE = 5610/159 ms, FOV = 180 × 180 mm, matrix = 256 × 256, slice thickness = 4 mm), and T2-weighted axial gradient-echo (TR/TE = 786/35 ms, FOV = 180 × 180 mm, matrix = 256 × 256, slice thickness = 4 mm, flip angle = 30°).

Imaging analysis

All the MRI studies were independently and blindly reviewed by two neuroradiologists (five and six years of experience). In cases of disagreement, a third neuroradiologist reviewed the images and final decisions were defined by consensus.

The following MRI findings were evaluated: 1) diffuse and excessive high-signal intensity (DEHSI), defined as areas of abnormal, diffuse high-signal on T2-weighted FSE images within the periventricular and/or subcortical WM (signal intensity similar to the CSF)[(7)]; 2) dilated lateral ventricles, if the transverse ventricular diameter was >10 mm, measured at the level of the atria[(13–15)], presence of intracranial hemorrhage defined as abnormal areas with signal characteristics compatible with blood products, classified according to its location in 3) intraparenchymal hemorrhage (IPH), 4) intraventricular hemorrhage (IVH), and 5) germinal matrix hemorrhage (GMH); 6) areas of abnormal signal in the basal ganglia and cortex; 7) cystic-like areas; 8) ventricular deformities; 9) enlargement of subarachnoid spaces overlying the cortical convexities (> 3 mm); 10) enlargement of the interhemispheric fissure (> 3 mm); 11) early foci of leukoencephalomalacia; 12) and gyri abnormalities[(7)].

Statistical analysis

Interobserver agreement in the MR images analysis was assessed with calculation of the kappa (κ) index, and the following ranges for agreement were used: 0.00, poor; 0.00 to 0.20, slight; 0.21 to 0.40, fair; 0.41 to 0.6, moderate; 0.61 to 0.8, substantial; and 0.81 to 1.0, almost perfect[(16)]. The p value of less than 0.05 was considered as statistically significant.

RESULTS

Prevalence of brain MRI abnormalities in extreme preterm infants

Among the 45 studied cases, only four patients (8.9%) had normal MR images (Table 1). The remaining 41 patients (91.1%) presented abnormalities on the MRI. The most common findings were DEHSI in the WM (75.6%) (Figure 1), lateral ventricles dilatation (42.2%) (Figure 2), GMH (31.1%) (Figure 3), IVH (28.9%) (Figure 4), ventricular deformities (24.4%) (Figure 5), and enlargement of the subarachnoid spaces (22.2%).

Reliability of qualitative visual assessment of conventional brain MRI

All the κ values obtained in the analysis of the interobserver variability were statistically significant. The interobserver agreement was high (κ > 0.60) for most of the abnormal MRI findings (Table 1). The κ statistic value was moderate for enlargement of the subarachnoid spaces overlying the cortical convexities (κ = 0.52) and was only fair for DEHSI in the WM (κ = 0.39).

DISCUSSION

Extremely preterm infants are at a high risk for adverse neurodevelopmental outcomes[(17–19)]. Previous studies have evaluated the main brain abnormalities seen at MRI performed in these patients at term-equivalent age[(6,7,12,20–23)]. The prevalence of brain MRI abnormalities was high in our patients cohort. Only four patients (8.9%) had normal brain MRI scans. The most common abnormalities were DEHSI in the WM (75.6%), ventricular dilation (42.2%), and hemorrhagic injury (GMH: 31.1% and IVH: 28.9%). This high prevalence of brain abnormalities observed in the present study

Table 1 Brain MRI findings at term-equivalent age in 45 extremely preterm infants.

Brain MRI finding	No. of infants (n = 45)	Kappa statistic value
Normal MRI	4 (8.9%)	1.00
DEHSI in the WM	34 (75.6%)	0.39
Dilated lateral ventricles	19 (42.2%)	0.653
Germinal matrix hemorrhage	14 (31.1%)	0.89
Intraventricular hemorrhage	13 (28.9%)	0.94
Ventricular deformities	11 (24.4%)	0.87
Enlargement of subarachnoid spaces	10 (22.2%)	0.52
Abnormal cortical signal	6 (13.3%)	0.90
Enlargement of the inter-hemispheric fissure	4 (8.9%)	0.84
Intraparenchymal hemorrhage	4 (8.9%)	0.84
Abnormal signal in the basal ganglia	3 (6.66%)	1.00
Early foci of leukoencephalomalacia	1 (2.2%)	1.00
Gyri abnormalities	1 (2.2%)	1.00
Cystic-like areas	1 (2.2%	1.00

MRI, magnetic resonance imaging; DEHSI, diffuse and excessive high signal intensity; WM, white matter.

with 45 extremely preterm infants is similar to previous studies[7,22].

Cranial US is less sensitive to demonstrate most of these WM abnormalities. Moreover, the significance of the US finding of WM echogenicity is controversial[1,5–9,20,21]. Inder et al.[21] have compared serial cranial US and brain MRI at term in a cohort of 96 extremely preterm infants. These authors emphasized the significant limitations of US for the detection of noncystic WM injuries. Additionally, cranial US failed to demonstrate subtle WM injuries between birth and term in a group of 32 preterm infants as compared with brain MRI[5]. In conclusion, US seems to have poorer sensitivity and specificity for the evaluation of WM abnormalities in extremely preterm infants as compared with MR imaging, and does not correlate with the clinical outcome[5,21]. Brain MRI is, thus, considered as the main imaging modality to predict neurodevelopment outcome in extremely preterm infants. It has been suggested that the severity of conventional MRI abnormalities is directly related to adverse long-term neurodevelopmental outcomes[20].

In our study, we assessed the reliability of the subjective visual assessment of conventional brain MRI performed at term-equivalent age in a cohort of 45 extremely preterm infants. The interobserver agreement was high ($\kappa > 0.60$) for most of the MRI findings, with the exception of the DEHSI in the WM. In our study, we observed a relatively low κ statistic value for DEHSI in the WM ($\kappa = 0.39$). Even though previous papers have defined the MR signal characteristics of DEHSI in the WM, it is still highly dependent on the radiologist's experience[1,7,22,23]. A thorough knowledge of the normal patterns of myelinization is essential when considering the possibility of DEHSI in the WM. Additionally, in some cases, CNS lesions were very severe and occurred early in the fetal development, making the evaluation of normal myelinization patterns even more difficult. This finding of relatively low interobserver agreement for WM DEHSI in our study may have relevant clinical implications because WM abnormalities have been reported as the main brain MRI abnormality related to the long- and short-term prognosis of extremely preterm infants; and clinical therapeutic decisions are frequently based on whether WM abnormalities are present or not[5,20].

We acknowledge some limitations to our study. Critically ill patients were not considered for the study to avoid additional risk for them. MRI was performed at the term-equivalent age, but not at birth, which

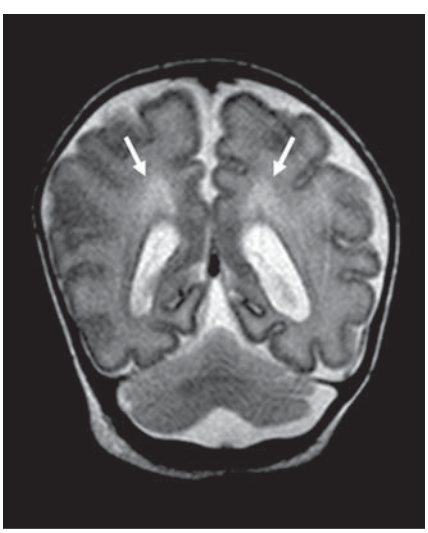

Figure 1. Coronal T2WI (5610/159) image demonstrates diffuse and excessive high-signal intensity, evidenced as areas of abnormal high-signal intensity within the periventricular white matter.

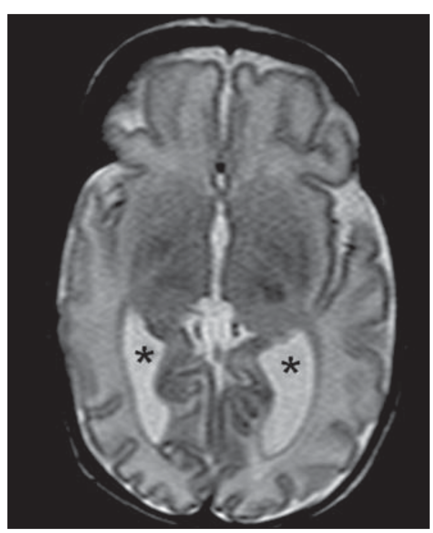

Figure 2. Axial T2WI (5610/159) image demonstrates lateral ventricles dilation measured at the level of ventricular atria (> 10 mm) (*).

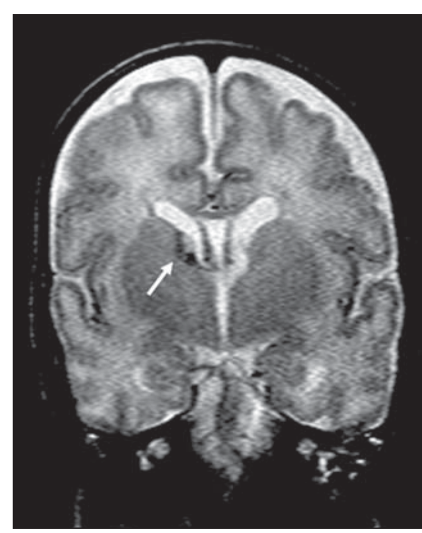

Figure 3. Coronal T2WI (5610/159) image demonstrates germinal matrix hemorrhage evidenced as low-signal intensity material in the subependymal zone (arrow).

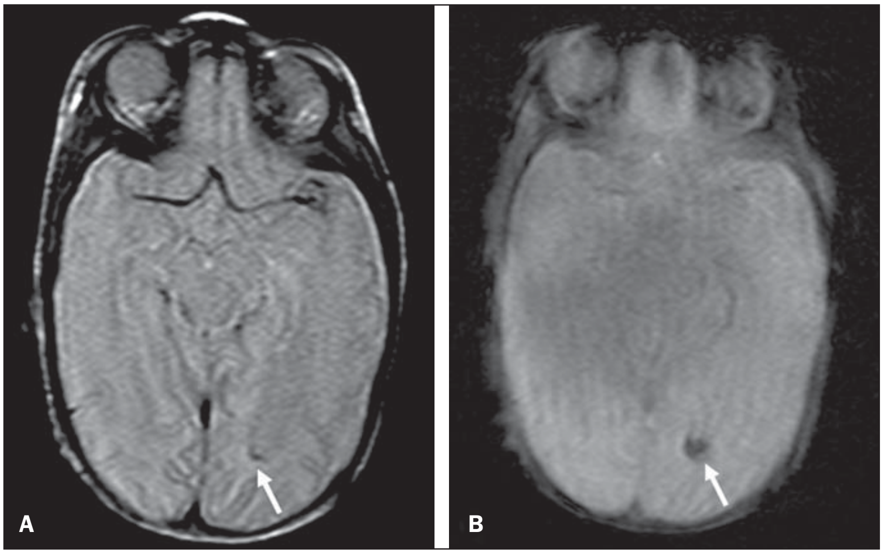

Figure 4. (**A**) Axial T2WI (5610/159) and (**B**) axial gradient-echo image (1770/3.9; flip angle = 30°) demonstrate low-signal intensity material layering in the occipital horn of the left lateral ventricle (arrows). Note marked blooming of the susceptibility effect from blood products on the gradient-echo image.

Figure 5. Axial T2WI (5610/159) image demonstrates ventricular deformities evidenced as irregular ventricular walls (arrows).

is similar to other studies(6,7,12,20–23). Finally, as the aim of our study was to assess the reliability of brain MRI abnormalities, we did not correlate the MRI findings with the long-term outcome, which has already been studied(20).

In conclusion, conventional MRI is usually employed to assess brain abnormalities in extremely preterm infants. The most common brain MRI findings at term-equivalent age in extremely preterm infants were DEHSI in the WM, ventricular dilation, GMH, and IVH, which have been associated with adverse neurodevelopmental outcome. According to the present study, conventional MRI seems to be a reliable method for evaluating the most common brain abnormalities in extremely premature infants; however, it seems that the presence of DEHSI in the WM is a less reliable finding.

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