

Risk of impaired cerebellar growth in preterm infants: a prospective mastoid fontanelle ultrasound study

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Abstract

Objectives: Recent studies realized with magnetic resonance imaging (MRI) showed impaired cerebellar growth in follow-up of preterm infants. Cerebellar injury may contribute to impaired motor, cognitive, language and behavioral dysfunction seen among this group. This study was designed to evaluate cerebellar growth in premature babies by ultrasound, a bedside imaging method, and to detect variables that could influence impaired cerebellar growth.

Material and methods: Postnatal cerebellar growth, measured by transverse cerebellar diameter (TCD), was prospectively assessed in 88 consecutive preterm infants born \leq 32 weeks of gestational age (GA). TCD was obtained via mastoid fontanelle (MF) ultrasound on a weekly basis, since the first week of life until 40 weeks postmenstrual age (p.m.a.). Variables that could influence cerebellar growth, such as GA, intrauterine growth restriction (IUGR), periventricular leukomalacia (PVL), peri-intraventricular hemorrhage (IVH), and posterior fossa hemorrhage (PFH) were evaluated.

Results: TCD could be measured by MF ultrasound in all patients. Cerebellar growth occurred linearly with postnatal age. At 40th p.m.a. week, TCD was smaller in IUGR group compared with no IUGR infants but their weekly cerebellar growth was similar. At term-equivalent age, cerebellar size was influenced by PFH, PVL and IVH severity.

Conclusion: TCD measured by MF ultrasound has demonstrated to be a bedside method for measuring the cerebellum in preterm babies. Impaired cerebellar growth seemed to be influenced by other brain lesions in these patients. We suggest that cerebellum should be studied in preterm infants born \leq 32 weeks gestation, at term equivalent age, using MF ultrasound.

Keywords

Cranial ultrasound, cerebellum, prematurity, mastoid fontanelle, cerebral growth, magnetic resonance imaging.

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Introduction

Impaired neurodevelopmental outcome is a major complication of surviving premature infants [1]. Survivors of premature birth need to be carefully assessed for neurodevelopmental impairment, in order to be referred to educational programs and subspecialty care with the goal of providing the best possible outcome. On attempting to implement correct strategies in the follow-up of preterm infant, it is essential to know the type and location of neurological damage in each patient.

In the last years, decreased cerebellar volumes have been described in follow-up of individuals born preterm, studied by volumetric magnetic resonance imaging (MRI) [2-5]. Disruption of cerebellar development has been associated to adverse neurodevelopmental outcome [6, 7]. More recent data have pointed out an important role for the cerebellum in the development of cognitive and social functions [8, 9]. This way, the idea of a role of cerebellum as only a center for motor coordination and execution has been abandoned [10].

The rapid cerebellar development from 24 to 40 weeks of gestational age (GA) makes the cerebellum vulnerable to multiple insults to which the premature infant is exposed [8]. At present, cerebellar impaired growth in the premature infant seems to be underappreciated. We hypothesized that ultrasound measurement of cerebellum, via mastoid fontanelle (MF), could give important information about its growth, becoming a useful and practical way to evaluate this structure in the preterm infant since MRI is not universally used in routine study of the neonatal brain. Cranial ultrasound using MF as an acoustic window has proven to be a useful tool for assessing the newborn cerebellum [11].

The aims of this study were: 1) to assess serial cerebellar growth with a bedside method, like cranial ultrasound, in a cohort of premature infants born ≤ 32 weeks gestation, until 40 weeks post

menstrual age (p.m.a.); 2) to compare cerebellar measurements at term equivalent age with term neonates born at 40 weeks GA; 3) to detect cases of impaired cerebellar growth and variables that could influence it.

Materials and methods

During 18 consecutive months (from January 2010 to July 2011), MF sonography was added to routine anterior fontanelle sonography in all consecutive premature neonates born ≤ 32 weeks GA in a neonatal tertiary care centre. A total of 88 consecutive neonates were included as study group. The control group consisted of 40 term newborns, born consecutively at 40 weeks GA, with adequate birth weight for GA. Infants with brain malformations, dysmorphic features, metabolic disorder and congenital anomalies were excluded. Infants were enrolled after birth, once written informed parental consent was obtained. The study was approved by the institutional ethics committee.

Ultrasound studies

In the study group, a prospective postnatal cerebellar growth measurement by transverse cerebellar diameter (TCD) was assessed. TCD was obtained via MF ultrasound on a weekly basis, since the first week of life until 40 weeks p.m.a. Sonograms were obtained by using a Xario™ scanner (Toshiba Medical Systems, Otawara-shi, Japan), equipped with 5-8 MHz transducers. The studies were performed by an expert in neonatal and fetal neurosonography (F.C.) with 20 years of experience in neonatal and fetal cranial ultrasound imaging, and reviewed for cerebral and cerebellar abnormalities, including echogenicity changes in the cerebellar parenchyma (hemispheres and vermis) and abnormalities in echogenicity, size and shape of the fourth ventricle and posterior fossa cisterns. MF is located at the junction of the temporal, parietal and occipital bones and provides a wide acoustic window owing to its contiguity with the poorly mineralized squamous portion of the temporal bone and the parietotemporal suture. The neonate's head lies on one side and we used small, multifrequency (5-8 MHz) sector transducers. Full description of examination through MF approach was described by one of the authors' former group previously [12]. An axial view was obtained locating the transducer oriented at an angle of approximately 10° to the orbitomeatal line and placed above the

tragus, slightly separating the external auricle. The landmarks of the thalami, cavum septum pellucidum and third ventricle were identified thereby slightly rotating the transducer below the thalamic plane. The posterior fossa is revealed with the characteristic butterfly like appearance of cerebellum (**Fig. 1**). In all cases cerebellum was seen as two lobules on either side of midline in the posterior cranial fossa. The measurement of TCD was obtained by placing electronic calipers at outer margins of cerebellum. Inferior cerebellar vermis was included in the scan (**Fig. 1**). In the control group, one postnatal cerebellar growth measurement by TCD was obtained at the first week of life, at 40 weeks GA. The measurement of TCD was performed through MF, similarly to the one performed in the study group.

Conditions associated with impaired cerebellar growth

Variables that could influence cerebellar growth, such as GA, intrauterine growth restriction (IUGR, defined by nomograms, with the 10th percentile being used as the cut-off point) [13], periventricular leukomalacia (PVL, following de Vries classification) [14], peri-intraventricular hemorrhage (IVH, classification proposed by Volpe) [15] and posterior fossa hemorrhage (PFH, cerebellar and/or subarachnoid cisternal bleeding) [12] were evaluated. Infant growth parameters (e.g. weight and head circumference) were also obtained at birth and term equivalent age.

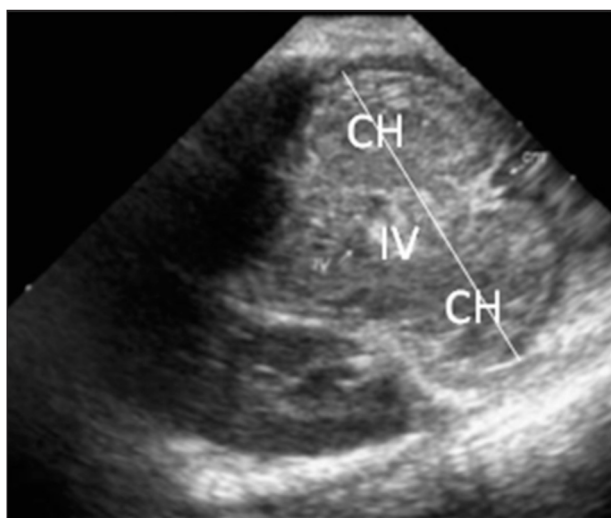


Figure 1. Cranial ultrasound of a preterm infant born at 29 weeks. Inferior-posterior view through the MF (mastoid fontanelle): butterfly like appearance of the cerebellum (full line: measurement of transverse cerebellar diameter. CH: cerebellar hemisphere. IV: inferior vermis).

Statistical analysis

Data analysis was performed using the SPSS® 16.0 (Statistical Package for the Social Sciences, Inc., USA), and a p-value less than 0.05 was considered significant. Continuous perinatal variables were summarized using means and Standard Deviations (SD) or medians and ranges; categorical variables were summarized using proportions. A percentile distribution of cerebellar growth by gestational age was obtained. Differences in postnatal cerebellar growth and IUGR were evaluated using the 2-sample t test. The relation between cerebellar size at 40 weeks p.m.a. and different variables was evaluated by multiple regression analysis. The association of cerebral lesions with cerebellar size was analyzed by ANCOVA adjusted for GA.

Results

The cohort perinatal characteristics and major ultrasound findings are expressed in **Tab. 1**. Mean GA was 29 ± 2 weeks and mean birth weight was $1,196 \pm 358$ g. IUGR was present in 29 (33%) of the sample. Patients were divided according to GA (≤ 28 weeks and > 28 weeks) (**Fig. 2**).

Measurements of TCD could be performed in all infants and all scans (including those at term age) were of sufficient quality. MF sonography added a maximum of 5 minutes to the total examination time.

TCD growth occurred linearly with p.m.a. (R Squared linear = 0.80; $p = 0.000$). At 40 weeks p.m.a., an average size of 53.5 mm was observed, with a minimum value of 33.5 mm and a maximum value of 58.8 mm (**Fig. 3**). In babies with reduced cerebellar diameter, 83.3% had a GA at birth ≤ 28 weeks.

TCD was smaller in the IUGR group, compared with no IUGR infants, from 28 weeks to 40 weeks p.m.a.; such difference was significant from 31 weeks p.m.a. ahead ($p < 0.05$) and was maintained when corrected for GA. On average, babies with IUGR have a TCD measuring less 2.1 mm than those without IUGR. There were no differences between the groups with/without IUGR regarding PFH and severity of PVL and IVH. The frequency of IVH and PVL in babies without IUGR was 40.6% and 23.7%, respectively. In patients with IUGR, the frequency of IVH and PVL was 44.8% and 27.5%, respectively. Cerebellar growth rate, excluding those born with 24-25 weeks GA, ranged from

Table 1. Study cohort characteristics and ultrasound abnormalities.

N = 88	Mean	SD	Median	min	max	N (%)
Gestational age (weeks)	29.07	2.23	30.0	24	32	–
Birth weight (g)	1,196	358	1,162	500	1,950	–
Male gender	–	–	–	–	–	41 (46.6%)
IUGR	–	–	–	–	–	29 (33%)
IVH	–	–	–	–	–	38 (43.2%)
IVH > 2	–	–	–	–	–	14 (17%)
PVL	–	–	–	–	–	24 (27.3%)
PFH	–	–	–	–	–	3 (3.4%)

IUGR: intrauterine growth restriction; IVH: peri-intraventricular hemorrhage; PVL: periventricular leukomalacia; PFH: posterior fossa hemorrhage.

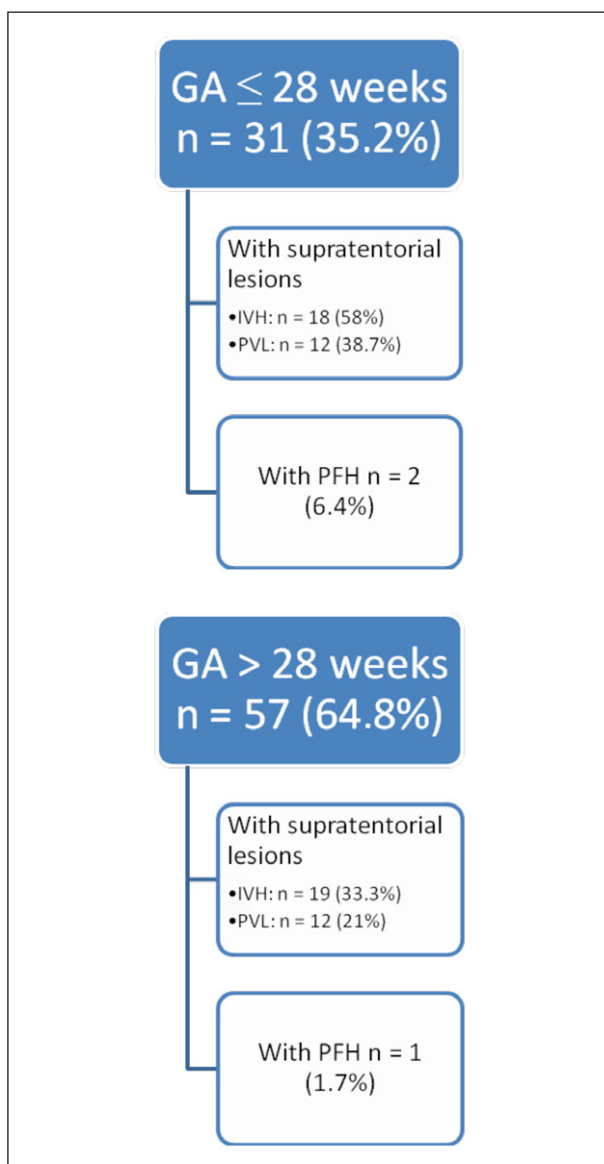


Figure 2. Study cohort according to gestational age and ultrasound abnormalities (GA: gestational age; IVH: peri-intraventricular hemorrhage; PVL: periventricular leukomalacia; PFH: posterior fossa hemorrhage).

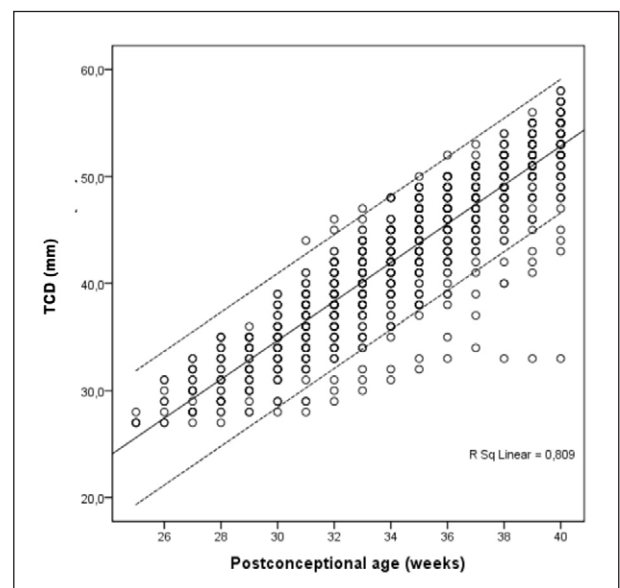


Figure 3. Study group cerebellar measurements according to postconceptional age (full line shows mean and dashed lines show 95% CI distribution).

1.1 mm/week to 2.0 mm/week, being the highest rates observed at 32-33 weeks and 39-40 weeks. Nevertheless, there was no difference in cerebellar growth weekly rate between IUGR and no IUGR babies.

The distribution of head circumference percentiles at 40 weeks p.m.a. showed a deviation in the normal curve to the left (Fig. 4).

When all variables that could influence cerebellar growth (such as GA, IUGR, IVH, PVL, PFH and head circumference percentile at 40 weeks GA) were included in the multiple logistic regression model, it was found that the head circumference at term equivalent age (Odds ratio 0.026; 95% CI [0.007-0.047]; p < 0.01) and the presence of PFH (Odds ratio

[-7.4]; 95% CI [-11.3]-[-3.5]; $p < 0.001$) were good predictors of the cerebellum size at 40 weeks p.m.a.

The analysis of the association between cerebral lesions and cerebellar size at term-equivalent age showed that the size of the cerebellum at 40 weeks was related to PVL severity ($F = 17.73$; $p = 0.000$), grade of IVH ($F = 3.22$ $p = 0.017$) and the presence of PFH ($F = 7.59$; $p = 0.007$) (Tab. 2). Concerning PVL, there was an association between impaired cerebellar growth at term equivalent age and PVL grades 2 and 3. None of our patients presented PVL grade 4. In patients with a reduced cerebellar diameter, the frequency of PVL and IVH was of 50% and 83%, respectively.

The average size (53.4 mm [43.0-58.8]) of the cerebellum in the study group at 40 weeks p.m.a. was lower than the control group (55.34 mm [50.5-58.7]) ($p < 0.001$; Mann-Whitney U test).

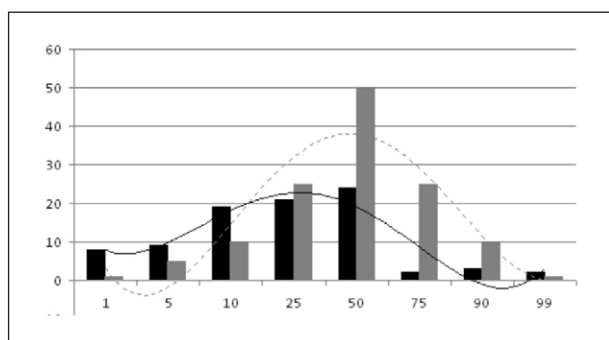


Figure 4. Percentiles distribution of head circumference in the study group compared with normal population (study group: black and full line; normal population: gray and dashed line).

Discussion

Acquired cerebellar injury in the premature newborn is an increasingly recognized form of neonatal brain injury. Disrupted cerebellar development has been associated with significant deficits in cognition, communication, and social-behavioral function in premature babies, apart from those expected consequences of cerebellar dysfunction, such as ataxia, spasticity and dystonia [6, 7]. Moreover, cerebellar growth impairment seems to have a role in the genesis of spectrum autism disorders among preterm newborns, being this association currently under investigation [16].

Ultrasound detection of cerebellar growth

For all these reasons, there is a justified and urgent need for a bedside method to assess cerebellar growth. In premature newborn infants, who are still too unstable to be transported to the MRI unit, cranial ultrasound is the most widely used technique for imaging these babies owing not only to its accessibility, but also to its efficacy, safety and low cost [11, 12]. Furthermore, in most centers MRI is not even available. Ultrasound is routinely performed through the anterior fontanelle. Nevertheless, visualization of the infratentorial compartment is poor with this approach due to its location far from the transducer and orientation parallel to the sound beam. The use of MF as an acoustic window has proven to provide highly useful information of this region (particularly of the cerebellum), once it lies nearer to the probe and is approached at a more perpendicular angle [11]. TCD is well established in

Table 2. Risk factors associated to cerebellar size at 40 weeks corrected gestational age.

Source	Type III Sum of Squares	Df	Mean Square	F	Sig.
Corrected Model	606.86 ^a	9	67.42	10.32	0.000
Intercept	707.18	1	707.18	108.26	0.000
IVH grade	84.38	4	21.09	3.22	0.017
PVL grade	347.34	3	115.78	17.72	0.000
PFH	49.60	1	49.60	7.59	0.007
GA	25.79	1	25.79	3.94	0.050
Error	509.51	78	6.53	–	–
Total	249,922.20	88	–	–	–
Corrected Total	1,116.37	87	–	–	–

Tests of Between-Subjects Effects. Dependent variable: cerebellum at 40 weeks.

^aR Squared = 0.544 (Adjusted R Squared = 0.491).

IVH: peri-intraventricular hemorrhage; PVL: periventricular leukomalacia; PFH: posterior fossa hemorrhage; GA: gestational age.

the fetal ultrasound literature as a reliable parameter for estimation of GA in both singleton and multiple gestations [17, 18], even in the presence of IUGR [19]. TCD seems to be independent of head shape and inter-individual constitutional discrepancies. Consequently, it is considered a better marker for GA estimation compared to other clinical and biometric parameters, such as cavum septum pellucidum, anterior and posterior horns of cerebral ventricles and nuchal soft tissue measurements [20].

Cerebellar growth in study and control groups

Our study showed that TCD growth occurred linearly with p.m.a. A similar growth pattern is described in the fetus [21]. Cerebellar size of the study group at 40 weeks corrected age differed significantly from the control group. We postulate that such difference could be related to the relatively small cephalic perimeter in the study group (**Fig. 4**) or to lesions present in the preterm (control) group, or maybe both.

Risk factors associated to impaired cerebellar growth

Due to the nearly 5-fold increase in cerebellar growth between 24 and 40 weeks GA, certain insults occurring in that time could cause irreparable damage to this structure [8, 22]. Two major mechanisms have been proposed to explain cerebellar arrest of development in the premature baby: either a direct effect on the development of its cortex, or remote effects related to damage in remote but connected areas of the brain, the so-called diaschisis. These two mechanisms can exist simultaneously [8, 23].

Concerning the direct injury, hemosiderin deposition on the cerebellar surface is considered to be one of the most important risk factors for disruption of cerebellar development. Cerebellar volume reduction after superficial siderosis is known from MRI [24] and histopathological studies [25]. In one work, hemosiderin in the posterior fossa was even the main risk factor predicting disruptive cerebellar development in preterm infants less than 32 weeks of gestation, with a high positive and negative predictive value [6]. Hemosiderin can cause gliosis, neuronal loss and demyelination as well as necrotic and apoptotic mechanisms resulting from glutamate overload [6]. In our study, the presence of PFH negatively influenced cerebellar size at term equivalent age in the study group (**Tab. 2**).

Another direct mechanism described as associated to cerebellar underdevelopment is IUGR [8]. Follow-up MRI studies in IUGR babies have documented reduced overall brain volume, specifically decreased cortical gray matter and hippocampal volumes [26, 27]. Being born small for GA (SGA) is associated with long-term impairment in cognitive, executive, motor and behavioural functions [28, 29]. As far as we know, cerebellum was not studied separately in MRI studies performed in former SGA preterm infants. A prenatal 3D ultrasound work did not find differences in cerebellar volumes between SGA and appropriate for GA (AGA) fetuses [30]. Meanwhile, experimental studies in fetal sheep and guinea pigs demonstrated an association between IUGR and decreased cerebellar growth [8].

In our study, we found that, at 40th p.m.a. week, TCD was smaller in the IUGR group compared with no IUGR infants. Nevertheless, there was no difference in the weekly cerebellar growth between IUGR and no IUGR babies. So, our results suggest that IUGR infant's cerebellum is smaller than no IUGR infants' cerebellum; this is maybe due to SGA babies' smaller global size and that cerebellar growth rate is similar in SGA and AGA babies, at least until a corrected age of 40 weeks is reached.

IVH has been also significantly associated to reduced cerebellar growth in preterm infants, which was explained by the diaschisis process. Our results are comparable to those of previous MRI studies [2, 31], which found a significant association between cerebellar measurement and the severity of IVH in the study group (**Tab. 2**). It was suggested that not only the crossed cerebral-cerebellar lesion process would be involved in this association, but also the toxicity of blood breakdown products in the CSF as a result of supratentorial hemorrhage [31, 32, 35].

Some studies support the hypothesis that alterations in cerebellar structural development in preterm infants are influenced by the presence and severity of disturbance in cerebral white matter and there is accumulating evidence that cerebral white matter disease results in a global cerebral structural alteration including the cerebellum [8, 33]. A secondary reduction in cerebellar volumes could result from axonal loss, Wallerian degeneration and/or cerebellar neuronal differentiation since PVL alters fiber tract integrity into the corticospinal tracts [33]. Despite some works did find a strong relation between cerebellar arrest of development and PVL [2, 33-35], others

did not [31]. These differences could be related to the milder degree of PVL found in the last ones. In our study group, cerebellar size was negatively influenced by PVL severity (**Tab. 2**).

Limitations

Our study has some limitations. Firstly, as our work is an ultrasound study and the classification of PVL used was that of De Vries [14], non-cystic leukomalacia which is diagnosed by MRI was not considered. This is important once its frequency is much higher than cystic leukomalacia. Nevertheless, the exact relationship between white matter disease and impaired cerebellar growth can only be elucidated by MRI studies [36]. Some punctate cerebellar hemorrhages can also be missed by cranial ultrasound, even when using mastoid fontanelle [12]. Secondly, when comparing cerebellar growth between IUGR and no IUGR infants, we did not exclude the cases with brain injury and we have to postulate the hypothesis that the results might be different. Nonetheless, there were no differences between the groups with/without IUGR regarding severity of brain injury. Another limitation of our study was that, as the included infants were born between 24 and 32 weeks GA, in later weeks values of postnatal linear growth there are more values than in first weeks values (i.e. more values at 30 weeks than at 24 weeks). However, we could not avoid it since it was important to include all preterm babies at risk for impaired cerebellar growth according to MRI studies, i.e. born \leq 32 weeks GA.

Conclusions

Disruption of cerebellar development is a well-known but underappreciated condition in the preterm infant born \leq 32 weeks GA. Transverse cerebellar diameter measured by MF ultrasound has demonstrated to be a bedside quantification method for measuring the cerebellum and, consequently, has the potential to be used in the routine neonatal cranial ultrasound in the preterm patient. This is very important once MRI is not available in the majority of neonatal intensive care units. Impaired cerebellar growth seemed to be influenced by other variables, as suggested by MRI studies. We suggest that cerebellum should be studied by MF ultrasound and/or MRI in the premature infant born \leq 32 weeks GA, at least at term equivalent age.

Abbreviations

AGA: appropriate for gestational age
GA: gestational age
IVH: peri-intraventricular hemorrhage
IUGR: intrauterine growth restriction
MF: mastoid fontanelle
MRI: magnetic resonance imaging
PFH: posterior fossa hemorrhage
p.m.a.: postmenstrual age
PVL: periventricular leukomalacia
SGA: small for gestational age
TCD: transverse cerebellar diameter

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Declaration of interest

The Authors declare that there is no conflict of interest.

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