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Cerebellar haemorrhages and pons development in extremely low birth weight infants

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1. ABSTRACT

Neuropathological and Magnetic Resonance Imaging (MRI) studies showed a high frequency of posterior fossa abnormalities in preterms. To assess whether cerebellar haemorrhages (CH) diagnosed with ultrasound and/or MRI affect pons development in ELBW infants. The anteroposterior diameter of the pons was measured manually on the midline sagittal T1 MR image in 75 ELBW babies consecutively scanned at term postmenstrual age. Subjects with CH were identified and compared to babies with no posterior fossa bleeding. Nine ELBW infants with CH (CH-Group: median gestational age -GA- 26 wks, range 23-27; birth weight -BW- 680 g, 425-980) were compared with 66 babies with normal cerebellum (Control-Group: GA 28 wks, 23-33; BW 815 g, 430-1000). The two groups were comparable for BW ($p=0.088$) while GA was significantly shorter in CH babies ($p=0.005$). The pontine diameter was significantly lower in CH-Group compared to Control-Group (12.8 ± 2.2 vs 14.8 ± 1.2 mm; $p<0.001$). Conclusions: Cerebellar haemorrhages seem to affect the development of the pons in ELBW with the youngest GA.

2. INTRODUCTION

Cerebellar haemorrhages are known to be highly represented in post mortem studies of low-birth-weight infants although these lesions remain underdiagnosed in living premature infants due to difficulties in visualization of posterior fossa using conventional ultrasonography (US) (1). A number of studies have shown the association between cerebellar and pons abnormalities based on a developmental malformative nature but more recent observations have highlighted how this correlation is common also among preterm babies with acquired brain lesions (2). A small brain stem with flattened anterior curvature of the pons was detected with magnetic resonance imaging (MRI), performed between 2 months and six years of age, in 28 subjects born prematurely before the 30th week of gestation (3), and a reduction in the size of pons was described in babies with periventricular leukomalacia (4).

It remains unclear whether pontine development abnormalities are associated or not with cerebellar haemorrhages. Aim of the present study was to quantify,

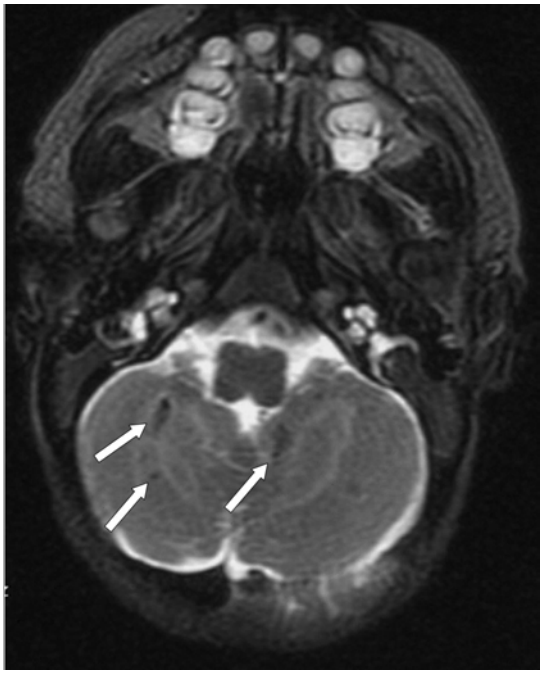

Figure 1. Axial T2-weighted MR image showing multiple punctate cerebellar haemorrhages (white arrows).

using a reproducible and easy to calculate method, the amount of pons flattening by measuring the anteroposterior pontine diameter in babies with and without cerebellar haemorrhages. The hypothesis to be tested was that cerebellar haemorrhages, mainly observed in extremely low birth weight infants (ELBW) (5) affect the development of the pons (6).

3. MATERIALS AND METHODS

According to the clinical protocol of the Department, ELBW infants, admitted to the Neonatal Intensive Care Unit, were brain scanned, by conventional MR imaging, at term postmenstrual age (PMA). Informed parental consent was obtained to enroll patients in the study. The babies were sedated for imaging with oral chloral hydrate (40-60 mg/kg) and pulse oximetry was monitored throughout the procedure. MR imaging was performed at 1.5 Tesla according to the internal standard protocol for imaging newborn babies, which included sagittal, axial and coronal 3 mm thick T2-weighted fast spin-echo (TR/TE = 6000/200 ms, fov = 180 mm, matrix = 320x320, nex = 2) and T1-weighted spin-echo (TR/TE = 600/15 ms, fov =180 mm, matrix = 256x256, nex = 3) sections. A dedicated 18 cm diameter quadrature head coil was used.

Cerebellar haemorrhages were defined as either multiple punctate haemorrhages ("Figure 1") or focal intraparenchimal haemorrhages ("Figure 2"); the first ones were detected by MR imaging while focal haemorrhages were first identified by cranial US in the early neonatal period and later confirmed by MR appearance of focal cerebellar parenchyma loss and hemosiderin deposits.

The anteroposterior diameter of the pons was measured manually on the midline sagittal T1 MR image in 75 ELBW babies consecutively scanned at term postmenstrual age since January 2003. The measuring diameter of the pons was obtained by drawing a line passing through fastigium and hypophysis ("Figure 3").

All measurements were performed by two different operators (MG, ADC), blinded to the presence of CH, and the mean value was taken for statistical analysis. Interobserver agreement was evaluated with Bland-Altman plot. Nine subjects with CH were identified (CH-Group) and compared with 66 babies without any CH (Control-Group). Supratentorial abnormalities, defined as germinal matrix-intraventricular hemorrhage (GMH-IVH), periventricular leukomalacia (PVL), punctuate white matter (WM) lesions (7), detected at US and/or MRI, were also considered in the two groups.

3.1. Statistical analysis

Unpaired t-test (SigmaStat - Statistical Software version 2.0) was used to compare differences between the two groups. A p value of less than 0.05 was taken as significant. The interobserver agreement in pons measurement was estimated using the Bland-Altman method when measurement was obtained by two observers (MG, ADC). The Fisher exact test was used to compare the incidence of supratentorial lesions in the two groups.

4. RESULTS

Cerebellar haemorrhages were observed in 9 out of 75 (12%) ELBW infants. Babies with cerebellar haemorrhages (CH-Group) were therefore compared with 66 babies with normal cerebellum MR appearance (Control-Group).

Clinical, US and MR findings of babies with CH are shown in "Table 1". The two groups were comparable concerning birth weight (BW) (CH-Group: BW 680 g, 425-980, Control-Group: BW 815 g, 430-1000, p=0.088) while a statistically significant difference was observed in gestational age (GA) (CH-Group: median GA 26 wks, range 23-27, Control-Group: GA 28, 23-33 wks, p=0.005). The anteroposterior diameter of the pons was significantly shorter in CH-Group compared to Control-Group (12.8 ± 2.2 vs 14.8 ± 1.2 mm; $p<0.001$); individual values are shown in "Figure 4". The mean difference in pontine diameter, between the 2 observers, was 0.007mm (limits of agreement +2.43 and -2.42). No statistically significant differences (p=0.20) were observed in the incidence of supratentorial abnormalities which were detected in 4 out 9 babies in CH-Group and 14/66 infants in the Control-Group (details are shown in "Table 2").

5. DISCUSSION

In our cohort of ELBW infants CH were observed in 9 out of 75 babies (12%). A similar incidence of cerebellar lesions was observed in a different study with a population of preterm babies characterised by a high number of severe supratentorial lesions (8). Autoptic diagnosis of CH varies from 10% to 25% in very low birth

Table 1. Clinical and US/MR findings of babies with cerebellar haemorrhages

Subject	GA (wks)	BW (g)	Cerebellar haemorrhage (diagnosis by US and/or MRI)	Supratentorial abnormalities (diagnosis by US and/or MRI)
1	26	720	Multiple punctate CH (MRI)	None
2	25	500	Focal CH (US + MRI)	None
3	25	900	Focal CH (US + MRI)	GMH (MRI)
4	27	740	Focal CH (US + MRI)	None
5	26	980	Focal CH (US + MRI)	IVH + unilateral ventriculomegaly (US + MRI)
6	23	680	Focal CH (US + MRI)	IVH + ventriculomegaly (US + MRI)
7	26	575	Multiple punctate CH (MRI)	GMH, punctate WM lesions (MRI)
8	24	425	Multiple punctate CH (MRI)	None
9	27	680	Multiple punctate CH (MRI)	None

GMH = Germinal matrix haemorrhage (subependymal bleeding with no intraventricular involvement), IVH = Intraventricular haemorrhage, Punctate WM lesions = small multiple signal abnormalities of white matter defined as increased signal T1 and decreased signal T2 abnormalities in cerebral white matter and supposed to be milder forms of white matter damage (7).

Table 2. Incidence of supratentorial abnormalities detected at US and/or MRI in CH compared to Control-Group

	CH-Group (N=9)	Control-Group (n=66)	
GMH N (%)	2 (22)	2 (3)	
IVH N (%)	2 (22)	6 (9)	
Punctate WM N (%)	1 (11)	5 (7.5)	
PVL N (%)	0	2 (3)	
Total babies with supratentorial abnormalities (%)	4/9 (44.4)[1]	14/66 (21.2)[1]	p = 0.20 Fisher exact test

[1]In the CH-Group 1 baby developed both GMH and punctate WM lesions; in the Control-Group 1 baby showed IVH as well as punctate WM lesions.

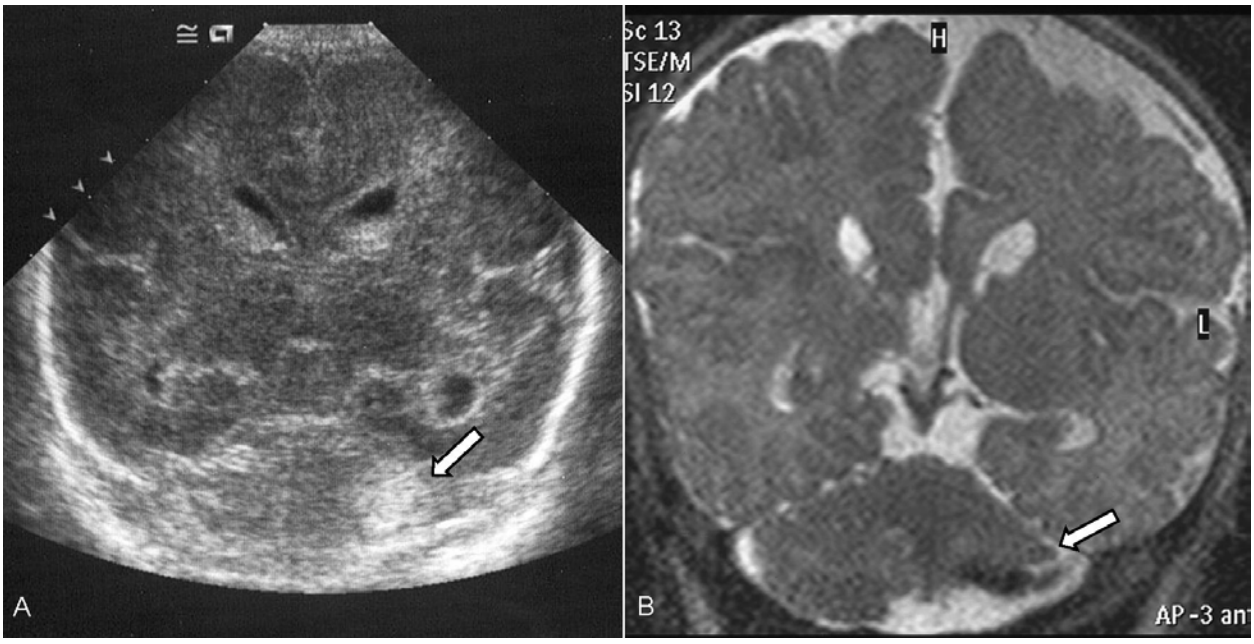

Figure 2. Cranial US appearance of intraparenchimal cerebellar haemorrhage in the early neonatal period (Figure 2A) as globular echolucency and coronal T2-weighted image at term postmenstrual age showing cerebellar atrophy and hemosiderin deposits (Figure 2B).

weight infants suggesting that posterior fossa haemorrhages may be underdiagnosed using traditional US (9,10). The pathogenesis is unknown although it has been historically associated with the use of CPAP mask requiring occipital bands (11). Two different patterns of cerebellar haemorrhage have been described at post-mortem study: a focal form usually associated with intraventricular haemorrhage and a milder form with small multiple punctate lesions, reported in up to 21% of neonatal specimens (10). These two patterns of CH appeared to be equally represented in our study and GMH-IVH was associated in four babies with the focal form. Cerebellar haemorrhages may be due to germinal matrix bleeding within the subpial external granule cell layer, particularly prominent at 24-30 weeks gestation when the layering pattern of the cerebellar cortex changes dramatically and any disruption of these developmental maturational steps of cerebellar development may have devastating consequences (12). At this getational age the vascular autoregulatory capacity of the cerebellum is even more

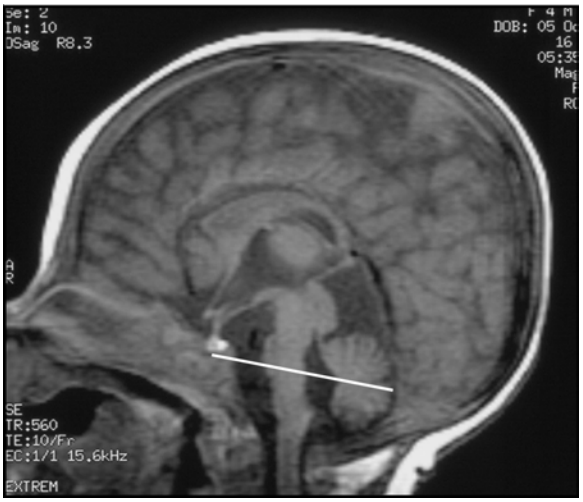

Figure 3. Sagittal midline T1-weighted MR image showing the measuring diameter of the pons in a baby with CH (patient 8, Table 1): a line was drawn passing through fastigium and hypophysis (white line) and the anteroposterior pontine diameter was measured manually according to this line. The flattening of the pons is evident.

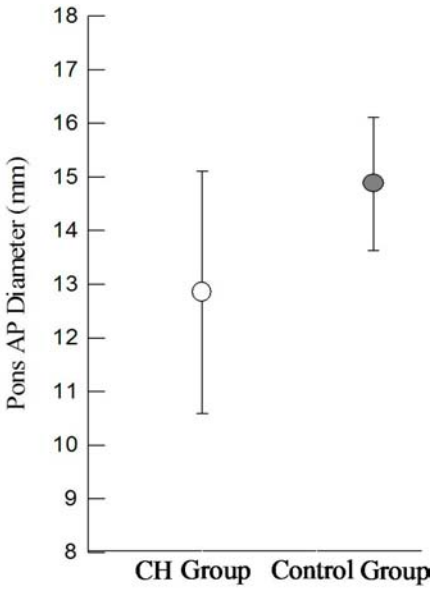

Figure 4. Anteroposterior diameter of the pons, calculated as average value of MG and ADC measurements, in babies with cerebellar haemorrhages (CH-Group, white circle) and without any CH (Control-Group, gray circle). Values are mean ± SD. A statistically significant difference was observed ($p<0.001$) between the two groups.

reduced than in the cerebrum, therefore ischaemia due to hypotension may be more common in the cerebellar watershed areas (13). A degree of pons atrophy has been observed in preterm babies with PVL (4) as well as a flattened anterior curvature of the pons, has been detected with MRI in 28 premature infants born before the 30th week of gestation (3). An acquired pontocerebellar atrophy should be differentiated from congenital pontocerebellar hypoplasia (association of pons, vermis and cerebellar hemispheres hypoplasia) revealing a neurodegenerative disorder. Acquired forms of pontocerebellar atrophy have been described in association with fetal drug exposure (14), sepsis in premature babies (15), twin-to-twin transfusion syndrome (16) and vascular undersupply (17). We used a reproducible and easy to calculate measurement of pons flattening, based on standard MR scans, to demonstrate that cerebellar haemorrhages are associated with pons abnormality in ELBW with the youngest. The results we obtained reinforce data from Argyropoulou et al. (4) in a more selected and younger population of babies scanned few weeks after birth. The causes of the association between impaired pontine development and CH remain to be understood. The cerebellum receives excitatory input from the frontoparietal cortex via the corticopontocerebellar tracts; the interruption, with secondary degeneration of corticopontocerebellar tracts could explain pontine atrophy linked to supratentorial lesions, as it has been reported in premature babies with little or no PVL (4). In the same way, primary cerebellar lesions can cause degeneration of pontine fibers due to the presence of pontocerebellar tracts but we are unable to demonstrate a sequential correlation beginning with cerebellar haemorrhage and causing pons atrophy, as the diagnosis of pons flattening was made with MRI performed once, at term PMA. A possible association of pontine hypoplasia and supratentorial lesions can not be excluded in our study, although no statistically significant differences were observed in the incidence of cerebral abnormalities in the two groups.

Another important feature of the developing brain of premature infants is the progressive myelination; this process spreads throughout the brain according to a preordered scheme of chronological and topographic sequences. Myelination proceeds centrifugally, from inferior to superior, and from posterior to anterior; in the brainstem it proceeds from the dorsal to the ventral areas. On MR myelination appears in the inferior cerebellar peduncles as early as 25 weeks, it is followed by the inferior colliculi, posterior brain stem, and ventrolateral nuclei of thalamus; between 26 and 35 weeks there is no evidence for new sites of myelination on MR imaging. Myelination is supposed to be a developmental event with highly demanding metabolism; this intrinsic vulnerability of the myelinating posterior fossa at low GA may contribute to explain pons impaired development. The majority of the babies represented in our population were born at extremely low gestational age, when myelination takes place in the posterior fossa. In conclusion we have shown that cerebellar haemorrhage is associated to an impaired development of the pons visualized at term corrected age. Considering the increasing survival of very preterm babies, the knowledge of this phenomenon may be useful when interpreting MRI scans of ex extremely low birth weight infants even in the absence of severe supratentorial lesions. Clinical follow-up studies are needed to investigate whether or not pons lesions are aggravating the outcome of babies with isolated cerebellar lesions.

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Abbreviations: ELBW: extremely low birth weight; MRI: magnetic resonance imaging; CH: cerebellar haemorrhage; US: ultrasound; PMA: postmenstrual age; GA: gestational age; BW: birth weight; GMH: germinal matrix haemorrhage; IVH: intraventricular haemorrhage; PVL: periventricular leukomalacia; WM: white matter

Key Words: ELBW, Brain MRI, Cerebellar haemorrhage, Pons

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