Imaging the preterm infant's brain

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Chapter 6

Brain imaging findings in very preterm infants throughout the neonatal period: Part II. Relation with perinatal clinical data

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Early Human Development 2009; 85(2): 111-115

Abstract

This study describes the relation between frequent and clinically relevant brain imaging findings in very preterm infants (gestational age < 32 weeks), assessed with sequential cranial ultrasonography throughout the neonatal period and magnetic resonance imaging (MRI) around term age, and several potential perinatal risk factors.

For ultrasound findings during admission the following independent risk factors were identified: male gender for periventricular echodensities and intraventricular haemorrhage, postnatal corticosteroid treatment for cystic white matter lesions, and lower gestational age for post-haemorrhagic ventricular dilatation. For MRI findings around term age, including punctate white matter lesions, ventricular dilatation, decreased cortical complexity, and diffuse and excessive high signal intensity, no independent risk factors were found.

In very preterm infants, the risk factors for frequently found changes on cranial ultrasound have largely remained unchanged over the last decades, while no risk factors could be identified for subtle and diffuse white matter injury as seen on MRI around term age.

Introduction

Very preterm infants have a high risk of brain injury, including intraventricular haemorrhage (IVH), periventricular haemorrhagic infarction (PVHI), cystic periventricular leukomalacia, and more diffuse white matter (WM) injury. These abnormalities are associated with suboptimal or abnormal neurodevelopmental outcome.

Identification of potential risk factors for frequently occurring brain abnormalities in preterm infants may contribute to early detection and intervention, and possibly to prevention of injury and consequently of neurological sequelae. However, recent studies on risk factors for brain abnormalities in very preterm infants are limited, and the relation between more diffuse and subtle forms of WM injury and clinical data is still largely unknown.

In the first part of this study we described the incidences and characteristics of brain imaging findings up to term equivalent age (TEA), as assessed with modern neuro-imaging techniques, being a combination of sequential cranial ultrasound (cUS) and a single magnetic resonance imaging (MRI) examination, in a large cohort of very preterm infants recently admitted to a tertiary neonatal referral centre (1). In the second part of this study, in order to identify potential risk factors, we assessed the relation between the most frequently encountered and clinically relevant brain imaging findings and several well-defined perinatal clinical parameters that have been associated with brain injury in preterm infants (2-19). In addition, we wanted to evaluate whether risk factors have changed over recent decades.

Patients and Methods

Patients

Very preterm infants born at a gestational age (GA) of < 32 weeks who were admitted to the tertiary neonatal intensive care unit of the Leiden University Medical Center between May 2006 and October 2007, were eligible for a neuro-imaging study, including sequential, standardized cUS examinations throughout the neonatal period and one MRI examination preferably around TEA (40-44 weeks' postmenstrual age

(PMA)). Ethical approval for the study was given by the Medical Ethics Committee and informed consent from the parents was obtained for each infant. Exclusion criteria were congenital anomalies of the central nervous system, other severe congenital anomalies, chromosomal disorders, metabolic disorders, and neonatal meningitis.

For 133 very preterm infants (80 male, 53 female) informed parental consent was obtained. Mean GA and birth weight of included infants were 28.9 (range 25.6-31.9) weeks and 1176 (range 520-1960) grams. In 113 infants (68 male, 45 female) contemporaneous cUS and MRI were performed, at a mean PMA of 44.7 (range 40.0-55.9) weeks. Details on informed consent, infants' characteristics, neuro-imaging techniques and protocols, and cUS and MRI assessment procedures are described in the first part of this study (1).

Clinical parameters

For all very preterm infants included in this study, the following perinatal clinical parameters were collected retrospectively by an investigator, blinded to the cUS and MRI findings:

- Antenatal corticosteroid treatment for prevention of respiratory distress syndrome (RDS)
- GA at birth (weeks)
- Birth weight (grams)
- Gender (male / female)
- Plurity (singleton / twin / triplet)
- RDS, defined as requirement of mechanical ventilation and at least one dose of intratracheal surfactant
- Bronchopulmonary dysplasia (BPD), defined as oxygen dependence at 36 weeks' PMA (20)
- Postnatal corticosteroid (i.e. dexamethasone) treatment for BPD
- Patent ductus arteriosus (PDA), defined as present if requiring medical and/or surgical treatment
- Hypotension, defined as present if requiring inotropic treatment
- Postnatal sepsis, defined as present if positive blood culture, and/or necrotizing enterocolitis (NEC), defined as present if grade ≥ 2a according to Bell et al. (21)

The above mentioned clinical parameters were selected based on previous studies describing these parameters as potential risk factors for brain injury in very preterm infants. This enabled comparison of risk factors found in our study with those reported previously.

Cranial ultrasound

cUS techniques and protocols, and assessment procedures are described in the first part of this study (1,22).

For the first part of this study, all sequential cUS scans were assessed for presence of brain imaging findings, including periventricular echodensities (PVE), cystic WM lesions, IVH, PVHI, post-haemorrhagic ventricular dilatation (PHVD), basal ganglia and/or thalamus abnormalities, and structural anomalies. Subsequently, the incidences and evolution of findings throughout the neonatal period were described. For details on classifications of PVE and IVH and definitions of various lesions, see part I (1).

For this second part of the study, only the brain imaging findings that were most frequently encountered on cUS during admission and/or have been suggested to be the most clinically relevant in very preterm infants, including PVE, cystic lesions in the WM, IVH, and PHVD, were assessed. As the number of infants with PVHI was small (n=7), this finding was not included in this part of the study. Details on the cUS findings are given in Table 1. As, in our opinion, homogeneous grade 1 PVE (the echogenicity of the periventricular WM being (almost) equal to that of the choroid plexus) may be a normal phenomenon in the preterm infant's brain, we decided to include only grade 2 PVE (the echogenicity of the periventricular WM exceeding that of the choroid plexus) and inhomogeneous grade 1 PVE for assessing the association between PVE and clinical parameters.

MRI

MRI techniques and protocols, and assessment procedures are described elsewhere in this issue (1,23).

For the first part of this study, all MRI examinations were assessed by at least two experienced investigators (LML, FTdB, GvWM, SJS) by consensus. The MR images were assessed for presence of punctate white matter lesions (PWML), diffuse and excessive

high signal intensity (DEHSI) (only on MRI scans performed between 40-44 weeks' PMA), other signal intensity changes in the WM, haemorrhage, PHVD, PVHI, basal ganglia and/or thalamus abnormalities, structural anomalies, and possible signs of atrophy (including ventricular dilatation (with the exception of PHVD), widened extracerebral spaces, and/or reduced complexity of gyration). Subsequently, the incidences of findings around TEA were calculated. For details see part I (1).

For this second part of the study, only the brain imaging findings that were most frequently encountered on MRI and/or have been suggested to be the most clinically relevant in very preterm infants around TEA, including PWML, ventricular dilatation, decreased complexity of gyration, and DEHSI, were assessed. Details on the MRI findings are given in Table 1. In order to make a clear distinction between mild abnormalities and more severe abnormalities with possible consequences for neurological development, we decided to include only multiple PWML (> 6) and severe ventricular dilatation, and not the milder spectrum of these abnormalities, for assessing associations with clinical parameters.

We regarded MRI as golden standard for the brain imaging findings around or shortly after TEA. The cUS findings obtained around TEA were therefore not used for this part of the study.

Table 1. Frequently encountered and clinically relevant neuro-imaging findings in very preterm infants during admission and around term equivalent age
(DEHSI, diffuse and excessive high signal intensity; IVH, intraventricular haemorrhage; n, number of infants; PHVD, post-haemorrhagic ventricular dilatation; PMA, postmenstrual age; PVE, periventricular echodensities; PWML, punctate white matter lesions; TEA, term equivalent age; WM, white matter)

Neuro-imaging findings	Number (%)
During admission (cUS; n=133)	
- PVE (excluding homogeneous grade 1 PVE)	87 (65.4)
- Cystic WM lesions	10 (7.5)
- IVH	37 (27.8)
- PHVD	21 (15.8)
Around TEA (MRI; n=113)	
- Multiple PWML (> 6)	19 (16.8)
- Severe ventricular dilatation (excluding PHVD)	12 (10.6)
- Decreased complexity of gyration	9 (8.0)
- DEHSI (of 70 infants with MRI between 40-44 weeks' PMA)	55 (78.6)

Data analysis

Statistical analyses were performed using SPSS software (version 14.0; SPSS inc., Chicago, Illinois, USA). The incidences of neuro-imaging findings during admission and around TEA were calculated for the first part of this study (1). For this part of the study, the incidences and means of clinical parameters were calculated.

The clinical data were compared between infants with and without the selected brain imaging findings, using a Fisher's Exact test for categorical variables and an unpaired t-test for continuous variables. Subsequently, the clinical variables in which the univariate analysis was demonstrated as $p < 0.1$ were entered into a stepwise logistic regression model to identify independent predictors of brain abnormalities. As several of the collected clinical parameters may be strongly related to GA at birth and, thus, GA may be a confounder, this parameter was always included in the model. The level of significance was $p \leq 0.05$.

Results

Clinical parameters

The characteristics of collected perinatal clinical parameters of all included infants are shown in Table 2.

Table 2. Characteristics of collected perinatal clinical parameters of all 133 very preterm infants included in the study
(BPD, bronchopulmonary dysplasia; GA, gestational age; n, number of infants; NEC, necrotizing enterocolitis; PDA, patent ductus arteriosus; RDS, respiratory distress syndrome)

Clinical parameters	
Antenatal corticosteroids, *n* (%)	82 (61.7)
GA (weeks), *mean* (range)	28.9 (25.6-31.9)
Birth weight (grams), *mean* (range)	1176 (520-1960)
Male gender, *n* (%)	80 (60.2)
Plurity, *n* (%)	43 (32.3)
Sepsis / NEC, *n* (%)	54 (40.6)
RDS, *n* (%)	72 (54.1)
BPD, *n* (%)	60 (45.1)
Postnatal corticosteroid treatment, *n* (%)	16 (12.0)
Hypotension, *n* (%)	43 (32.3)
PDA, *n* (%)	38 (28.6)

Neuro-imaging findings

The incidences of selected neuro-imaging findings on cUS during admission and on MRI around term are summarized in Table 1.

Relation between neuro-imaging findings and clinical parameters

cUS during admission *(n=133)*

The relation between cUS findings during admission and perinatal clinical parameters is shown in Table 3.

A significant association was found between presence of PVE and male gender. When entered into a logistic regression analysis, male gender was found to be independently associated with PVE (odds ratio (OR)=2.67; 95% confidence interval (CI) 1.26-5.63).

Infants with cystic lesions in the WM were significantly younger at birth and required significantly more often postnatal corticosteroid treatment than infants without these lesions. Only postnatal corticosteroid treatment was identified as independent variable (OR=6.06; 95% CI 1.50-24.52).

Presence of IVH was significantly associated with male gender, more RDS and more postnatal corticosteroid treatment, and there was a tendency towards less antenatal corticosteroid treatment and shorter GA at birth in infants with IVH. Logistic regression analysis only identified male gender as an independent risk factor for IVH (OR=2.52; 95% CI 1.07-5.95).

In addition, PHVD was significantly associated with shorter GA and lower weight at birth and more RDS, BPD, and postnatal corticosteroid treatment. Of these associated parameters, only GA at birth was identified as an independent variable (OR=0.63; 95% CI 0.47-0.48).

Table 3. Relation between neuro-imaging findings in very preterm infants and perinatal clinical parameters
(*, independent variable; BPD, bronchopulmonary dysplasia; DEHSI, diffuse and excessive high signal intensity; GA, gestational age; IVH, intraventricular haemorrhage; n, number; NEC, necrotizing enterocolitis; NS, not significant; PDA, patent ductus arteriosus; PHVD, post-haemorrhagic ventricular dilatation; PVE, periventricular echodensities; PWML, punctate white matter lesions; RDS, respiratory distress syndrome; TEA, term equivalent age; VD, ventricular dilatation; WM, white matter)

Clinical parameters	Neuro-imaging findings, *p-value* (finding present versus absent)							
	During admission (cUS; n=133)				Around TEA (MRI; n=113)			
	PVE (n=87)	Cystic WM lesions (n=10)	IVH (n=37)	PHVD (n=21)	Multiple PWML (n=19)	Severe VD (excluding PHVD) (n=12)	Decreased complexity gyration (n=9)	DEHSI (n=55)
Antenatal corticosteroids (%)	NS	NS	0.062 (51 vs. 68)	NS	NS	0.081 (42 vs. 67)	NS	NS
GA (weeks)	NS	0.037 (27.7 vs. 29.0)	0.099 (28.5 vs. 29.1)	0.000* (27.6 vs. 29.2)	NS	NS	NS	NS
Birth weight (grams)	NS	NS	NS	0.022 (1007 vs. 1208)	0.061 (1357 vs. 1183)	0.080 (1035 vs. 1231)	NS	NS
Male gender (%)	0.013* (69 vs. 45)	NS	0.046* (76 vs. 55)	NS	NS	NS	NS	0.059 (67 vs. 50)
Plurity (%)	NS	NS	NS	NS	NS	NS	NS	NS
Sepsis / NEC (%)	NS	NS	NS	NS	NS	NS	NS	NS
RDS (%)	NS	NS	0.040 (69 vs. 49)	0.033 (76 vs. 52)	NS	NS	0.062 (88 vs. 53)	NS
BPD (%)	NS	NS	NS	0.034 (67 vs. 42)	NS	NS	NS	NS
Postnatal corticosteroids (%)	NS	0.020* (40 vs. 10)	0.043 (22 vs. 9)	0.005 (33 vs. 8)	NS	NS	NS	NS
Hypotension (%)	NS	NS	NS	NS	NS	NS	NS	NS
PDA (%)	NS	NS	NS	NS	NS	NS	NS	NS

MRI around TEA *(n=113)*

The relation between MRI findings around TEA and perinatal clinical parameters is shown in Table 3.

No significant associations were found between any of the findings on MRI and collected clinical parameters. In infants with multiple PWML there was a tendency towards a higher birth weight, and in infants with DEHSI towards more boys. In addition, there were strong but non-significant associations between severe ventricular dilatation and less antenatal corticosteroid treatment and lower birth weight, and between decreased complexity of gyration and more RDS.

Discussion

We assessed the relation between frequently occurring and/or severe brain imaging findings and several potential perinatal risk factors in a cohort of very preterm infants. Several risk factors were found for the selected brain imaging findings, detected on cUS during admission, which are partly consistent with those found in previous studies (2-12,14,17).

Male gender was identified as an independent risk factor for PVE during the early neonatal period. Cystic lesions in the WM, mostly detected after the first few postnatal weeks, were significantly associated with lower GA and postnatal corticosteroid treatment. Even when corrected for GA at birth, postnatal corticosteroid treatment was associated with a significantly higher risk of cystic WM lesions. None of the other clinical parameters were identified as risk factors for these WM findings. This is largely in agreement with previous studies, and supports the results of other authors demonstrating the negative effects of postnatal corticosteroid treatment on the developing WM in preterm infants (2,4-6,10-11,14,24).

IVH, the second most frequently encountered finding on cUS during the early neonatal period, was significantly associated with male gender, RDS and postnatal corticosteroid treatment. In addition, infants with IVH tended to be younger at birth, and, although not significant, antenatal corticosteroid therapy seemed to have a preventive effect on IVH development. When variables were entered into a logistic regression model,

including correction for GA, only male gender was identified as an independent risk factor for IVH. Again, our results are largely in agreement with those reported by others, who identified infection, lower GA and weight at birth, hypotension, PDA, and a more complicated respiratory course as potential risk factors and antenatal corticosteroid treatment as a potential protective factor for the development of IVH in preterm infants (3,6,8,10,12,14,17).

In contrast with several other studies (4-6,10,14), we did not find a significant association between presence of IVH and lower GA and weight at birth, which may be related to the fact that we only included preterm infants of < 32 weeks' gestation. In a study by Kadri et al. (17), no significant difference in incidence of IVH was found between infants of < 30 weeks' gestation and those between 30 and 34 weeks. However, they did find a significant difference in IVH incidence with older GA groups.

Our finding that male gender is associated with IVH has, to our knowledge, not been reported before. As regression analysis showed an independent association, influence of lower GA and/or more severe respiratory disease, as reported in boys, could thus be excluded. We therefore feel that male gender is an independent risk factor for brain injury in preterm infants.

IVH was complicated by PHVD in just over half of the cases. We found PHVD to be significantly more common in the younger and smaller infants, infants with RDS and/or BPD, and infants requiring postnatal corticosteroid treatment. Only GA at birth was identified as an independent variable, indicating that the other variables were related to the lower GA in infants with PHVD. This is partly in consistence with previous studies proposing hypotension and respiratory problems as risk factors and higher GA and weight at birth as protective factors for PHVD (6,9-10).

Severe lateral ventricular dilatation and decreased complexity of gyration, reported to be associated with WM injury and/or to represent loss of brain volume, were frequent MRI findings around or shortly after TEA (13,15). Although there was a tendency towards less antenatal corticosteroid treatment and lower birth weight in infants with severe ventricular dilatation, and towards more RDS in infants with decreased complexity of cortical folding, no significant associations were found between clinical parameters, and thus potential risk factors, and these findings. In a study by Ment et al. (7), dilatation of the lateral ventricles on cUS performed around TEA was associated with BPD, but

not with any other clinical parameter. However, they also included infants with mild-moderate lateral ventricular dilatation and in all their cases IVH was detected on cUS during the early neonatal period, while we only included infants with severe ventricular dilatation present around TEA and regarded PHVD as a separate finding.

Impaired growth of the cortical gray matter in preterm infants on term equivalent MRI has been reported to be associated with postnatal corticosteroid (i.e. dexamethasone) treatment (24). Our results could not confirm this. However, in those studies cortical growth was quantified using volumetric MRI techniques, while we visually assessed complexity of cortical folding. In another study, no associations were found between cortical gray matter development and perinatal clinical data (13). Finally, in a study by Horsch et al. in preterm infants (16), signs of atrophy on cUS at discharge were significantly associated with lower GA and weight at birth, and more respiratory problems and postnatal corticosteroid treatment.

Finally, subtle changes in the WM, including PWML, in particular multiple (> 6), and DEHSI, were frequent findings on MRI around term; no cUS-correlate was found for these MRI phenomena (1). Although there was a tendency towards a higher birth weight in infants with multiple PWML and more boys in the group of infants with DEHSI, no significant associations were found between clinical parameters and these MR imaging findings. Our results are largely in agreement with those of scarce previous studies, which did not find associations between either PWML or DEHSI and any of the clinical parameters assessed by us (15,18-19).

Although the risk factors for changes in the preterm infant's brain, particularly those detected on cUS during the early neonatal period, found in this study are largely consistent with those reported in other studies, our results do not confirm all the previously proposed risk factors. There are several possible explanations for this inconsistency. Firstly, the associations between brain imaging findings and clinical parameters depend on the homogeneity of the population studied. We only included very preterm infants with a GA of < 32 weeks, being a relatively homogeneous group with respect to severity of illness and occurrence of cerebral abnormalities. In addition, the definitions of brain imaging findings and the criteria for including findings, and the definitions of clinical parameters and the inclusion criteria may have been different between our and some previous studies (2-7,10-12,14). Finally, in our study, in order

to identify independent risk factors for brain findings, correction for GA at birth and logistic regression analysis were applied, resulting in loss of statistical significance of associations in the univariate analysis. This was true for associations between IVH and PHVD and RDS, BPD and postnatal corticosteroid treatment. However, not in all studies these additional analyses were applied (2,10,17).

We appreciate several limitations of our study. Firstly, as was expected when studying very preterm infants, our number of preterm infants without any abnormal brain imaging finding was small. Secondly, we did not take co-occurring findings into account when assessing associations between brain imaging findings and clinical parameters. In consistence with previous studies (12-13,15), IVH and changes in the periventricular WM often co-existed in our infants, and therefore IVH may have confounded the associations with clinical parameters found for WM changes, and vice versa. However, as these two brain findings may have common or overlapping aetiologies in preterm infants, and can therefore be expected to be associated with common or overlapping clinical parameters, and our results are largely consistent with those of previous studies, we feel that this will not have influenced our results considerably. Some of the brain imaging findings, including decreased complexity of gyration and cystic lesions in the WM, were only detected in a small number of infants. This may partly have caused the lack and/or the inconsistency with previous studies in significant associations with clinical parameters. In addition, we regarded MRI as golden standard for the brain imaging findings around TEA. This may have contributed to our lack in association between decreased complexity of gyration and clinical parameters, especially as this finding was more often scored on contemporaneous cUS. However, we feel that we rather overestimated this finding on cUS than underestimated it on MRI (1). We did not match our infants for GA and weight at birth. However, as we corrected for GA and applied multivariate logistic regression analysis, this will not have influenced our results considerably. Finally, we only collected the most frequently proposed, well-defined perinatal risk factors for brain injury in preterm infants. Therefore, we may have missed some relevant associations, and thus risk factors, for the imaging findings.

In conclusion, this study has shown that male gender is an independent risk factor for the development of IVH and PVE, while a lower GA is independently associated with PHVD. Finally, postnatal treatment with corticosteroids for BPD is significantly associated

with cystic WM lesions. Despite advances in neonatal intensive care and changes in the distribution of WM injury in preterm infants, the risk factors for frequently occurring and clinically relevant findings in the preterm infant's brain are still largely the same as those reported in the past, while no risk factors could be identified for subtle and diffuse WM injury as seen on MRI around term age.

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