Cranial ultrasound findings in preterm infants predict the development of cerebral palsy

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ABSTRACT

INTRODUCTION: Our aim was to evaluate any association between gestational age, birth weight and findings on cranial ultrasounds during hospitalisation in very preterm infants and mortality and neurological outcome in childhood.

METHOD: This study was a retrospective cohort study based on a patient record review. The cohort consisted of very preterm born children (gestational age ≤ 32 + 0) born from 2004 to 2008. For each infant, we obtained results from all cranial ultrasounds performed during hospitalisation. In 2014, patient records were evaluated for cerebral palsy, Gross Motor Function Classification System, blindness and deafness.

RESULTS: A total of 249 infants were included. The mortality rate was 9.2%. In all, 217 children were evaluated at 5-9 years of age. Four children were diagnosed with germinal matrix haemorrhage – intraventricular haemorrhage grade 3 (GMH-IVH3) and periventricular haemorrhagic infarction (PVHI), of whom two developed cerebral palsy. Nine children were diagnosed with periventricular leukomalacia (PVL), of whom six developed cerebral palsy. Cerebral palsy was detected in 14 children (6.4%), and one (0.5%) child was in need of a hearing assistive device. Severe brain injury (GMH-IVH3, PVHI or PVL) (p = 0.000) and being of male gender (p = 0.03) were associated with cerebral palsy in childhood.

CONCLUSION: Severe brain injuries detected by neonatal cranial ultrasound in very preterm infants is associated with development of cerebral palsy in childhood.

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In the course of the past 30 years, medical science has significantly pushed the limits of viability of infants who are born extremely preterm, among others owing to the introduction of antenatal corticosteroids and treatment with postnatal surfactant [1]. Several studies show that the increased active perinatal care in the 1990s increased survival rates among very preterm infants. However, the improved survival might be associated with an increased risk of neurological sequelae such as cerebral palsy (CP), blindness and deafness, and developmental disorders [2-5]. Previous studies show that mortality and long-term neurodevelopmental disabilities increase with decreasing gestational age (GA) [6, 7].

The foetal brain continuously evolves. During GA 29-41, there is rapid brain growth and development [8]. Many factors negatively affect the development of the immature brain: e.g. insufficient nutrition, infections, intracranial bleeding and being born immature.

Germinal matrix haemorrhage – intraventricular haemorrhage (GMH-IVH) is graded 1-3. The association between GMH-IVH1-2 and adverse neurological outcome has been reported with divergent results [9, 10]. Periventricular haemorrhagic infarction (PVHI) (equivalent to GMH-IVH4) is a complication of GMH-IVH with periventricular haemorrhagic infarction. PVHI has been reported in 1-3% of preterm born infants [11]. GMH-IVH3 and PVHI have been shown to be associated with a high mortality and a high frequency of CP in childhood [12, 13]. Periventricular leukomalacia (PVL) has been shown to be associated with CP in childhood [14]. The most important pathogenesis of PVL is believed to be hypoxic-ischaemic and inflammatory injury in the preterm brain. The term "flaring" describes slightly echogenic periventricular zones, which are seen in many preterm infants in the first week of life. Flaring persisting beyond the first week of life is a sign of PVL.

Cranial ultrasound (C-US) is a routine bedside examination in neonatal intensive care units (NICU), which is performed to detect if GMH-IVH/PVHI and/or PVL has evolved. The result of this examination is used as part of the clinical evaluation and may guide the decision to continue intensive care of the preterm infant, but also to inform parents about their child's prognosis.

In this retrospective study, we evaluated if the results of the C-US, performed during hospitalisation in very preterm born infants, may be used by healthcare professionals to predict their neurological outcome later in childhood. We hypothesised the existence of a strong association between a low GA, low birth weight (BW), GMH-IVH or PVL and a severe neurological outcome such as CP.

METHODS

This study was a descriptive cohort study with retrospective review of patient records. The infants were born with a GA ≤ 32 + 0 at Odense University Hospital, Denmark, from July 2004 to August 2008. After discharge from the NICU, the children were followed at the

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outpatient clinic at HC Andersen Children's hospital in Odense. Excluded were children with severe congenital or chromosomal disorders and children who moved out of the region. Follow-up was based on patient record information at five to nine years of age (obtained in 2014).

The following information entered during the NICU stay was obtained from the patient records: gender, GA, BW, multiple birth or single birth, GMH-IVH1-3, PVHI and PVL detected by C-US, and survival until discharge from the NICU. Data obtained from the patient records from March to May 2014 included: CP, Gross Motor Function Classification System (GMFCS) 1-5, blindness and deafness.

According to NICU instructions, C-US will be performed routinely by a neonatologist in all very preterm infants within the first week of life and again at 4-5 weeks of age. If any pathology is observed on the C-US performed within the first week of life, further C-US will be performed. GMH-IVH1-3, PVHI and PVL are entered into the patient record.

All very preterm born infants with a GA < 32 and a BW < 1,500 g are followed at the neonatal outpatient clinic after discharge from the NICU and until 5-6 years of age. If BW > 1,500 g, the child will be followed until he/she can walk. If CP or other neurological problems are suspected, a physiotherapist and a paediatric neurologist will examine the child as well. According to the Follow-up Program for Cerebral Palsy, CP graduations are made according to GMFCS levels 1-5; from 1 for minimal restrictions to 5 for serious limitations.

All very preterm infants are also referred to an ophthalmologist at 4-5 weeks of age, but no earlier than GA 31, for screening of retinopathy of prematurity (ROP). If the child has ROP, visual impairment, strabismus or other eye disease, the ophthalmologist will continue to follow the child at the outpatient clinic. In this study, we recorded blindness defined as visual acuity in the best eye < 0.1. We did not record visual impairment, strabismus, etc.

In Denmark, all term born infants are offered a routine hearing screening a few days after birth. Preterm born infants are offered this hearing test at postmenstrual age close to term. In case of any abnormal findings, the child will be followed by an otolaryngologist at the outpatient clinic. In this study, we registered if the children were in need of assistive hearing devices and also recorded deafness in childhood.

Ethics

The project was reviewed and approved by the Danish Data Protection Agency, R.no. 2014-41-2809 and by the Danish Health Authority, R.no. 3-3013-634/1.

Statistics

Incidence of mortality, prevalence of CP, blindness and deafness were calculated. A group named "Severe brain injury" comprising cases of GMH-IVH3, PVHI and PVL was defined. Any association of the independent variables (GA, BW, small for gestational age (SGA), gender, multiple births, and severe brain injury) with CP was examined by multivariate logistic regression analyses. The statistical analyses were made using STATA statistical software (version 11). GA was divided into two groups; GA < 28 + 0 and GA ≥ 28 + 0. BW was divided into two groups; BW < 1,000 g and BW ≥ 1,000 g. SGA was defined as a BW Z-score below –2 standard deviation (SD) [15].

Trail registration: not relevant.

RESULTS

A total of 249 infants with a GA ≤ 32 + 0 were born during the inclusion period. A total of 22 infants died before discharge from the NICU, one child died during the follow-up period. Among the survivors, three children were excluded due to genetic diseases (Down's syndrome). Six children moved out of the region so follow-up was not possible. At follow-up in 2014, the children were between five and nine years of age. For the demographics of the group, see **Table 1**.

The mortality of the group was 9.2% (23/249). Mortality in the extremely preterm group (GA: 24-26)

ABBREVIATIONS

BW = birth weight
CP = cerebral palsy
C-US = cranial ultrasound
GA = gestational age
GMH-IVH = germinal matrix haemorrhage – intraventricular haemorrhage
NICU = neonatal intensive care unit
PVHI = periventricular haemorrhagic infarction
PVL = periventricular leukomalacia
ROP = retinopathy of prematurity
SGA = small for gestational age
WMA = white matter abnormality

TABLE 1

Demographics (N = 249).

Gestational age, weeks, median (range)	29 (24-32)
Birth weight, g, median (range)	1,257 (428-2,256)
Small for gestational age < –2 SD, %	27 [15]
Male, %	55
Multipara, %	43
Death, %	9

SD = standard deviation.

TABLE 2

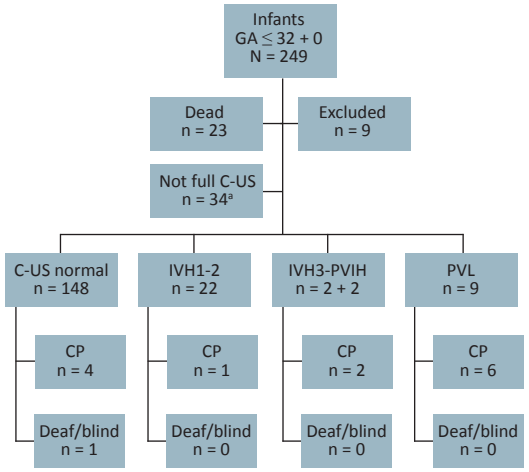
Mortality and severe brain injury (intraventricular haemorrhage grade 3, periventricular haemorrhagic infarction or periventricular leukomalacia) by gestational age.

GA, weeks	Total, N	Mortality, n (%)	C-US, total, n	Severe brain injury: IVH3, PVHI or PVL, n (%)
24	12	6 (50)	6	1 (17)
25	17	4 (24)	12	2 (17)
26	17	5 (29)	12	2 (17)
27	25	3 (12)	22	4 (18)
28	23	2 (9)	21	1 (5)
29	29	1 (3)	26	2 (8)
30	51	2 (4)	43	1 (2)
31	63	0	41	0
32	12	0	0	0
Total	249	23 (9)	183	13 (7)

C-US = cranial ultrasound; GA = gestational age; IVH3 = intraventricular haemorrhage grade 3; PVHI = periventricular haemorrhagic infarction; PVL = periventricular leukomalacia.

FIGURE 1

Profile of the study group compared with cranial ultrasound findings.



C-US = cranial ultrasound; CP = cerebral palsy; GA = gestational age, weeks + days; IVH = intraventricular haemorrhage; PVHI = periventricular haemorrhagic infarction; PVL = periventricular leukomalacia.
a) One infant with CP.

was 33% (15/46). In 22% (5/23), the primary cause of death was described to be IVH3, PVHI or PVL. Necrotising enterocolitis and PVHI were registered as competing causes of death in 8.7% (2/23). Among survivors with a GA 24 to 26, the rate of severe brain injury was 16% (5/31) and the rate of CP was 16% (5/31).

Data on mortality and severe brain injury (GMH-IVH3, PVHI or PVL) by GA are presented in **Table 2**.

A total of 14/217 (6.4%) children were diagnosed with CP. Overall, 4.6% (10/217) had severe disability (GMFCS 3-5). Among the children with CP 10/14 (71%) had severe disability (GMFCS 3-5). No children met the blindness criteria. One child, 1/217 (0.5%) was in need of hearing assistive devices. The child had no pathology on C-US and did not have CP.

A total of 183 (183/217) infants had a C-US performed as recommended within the first week of life and again at 4-5 weeks of age. Twenty infants (20/217) had no C-US performed. These infants were all born at GA 30-32 and none of them had neurological sequelae such as CP, deafness or blindness. Fourteen infants (14/217) had only one C-US during their first week of life. In this group, one child was subsequently diagnosed with CP GMFCS 1. This child was born at GA 30 and had no pathological findings in the C-US performed during the first week of life. In all, 22 children were diagnosed with GMH-IVH1-2, of whom 1/22 (4.5%) was diagnosed with CP. Four children were diagnosed with GMH-IVH3 and PVHI, of whom 2/4 (50%) had CP. Nine children were diagnosed with PVL, of whom 6/9 (66%) had CP.

One child with CP had a C-US in the first week of life that demonstrated "flaring"; no further changes were detected at the C-US performed at five weeks of age. Another child with CP was diagnosed with hydrocephalus during hospitalisation due to an aqueductal stenosis. The hydrocephalus was well treated by surgical insertion of a shunt system. Two of the 14 children (14%) with CP had normal findings on their C-US. The profile of the study group compared with C-US findings is provided in **Figure 1**.

A total number of 183 children with all data available were included in the two multivariate regression analyses. The first analysis showed that male gender (odds ratio (OR) = 12.7, p = 0.03), and having severe brain injury (OR = 141.6, p = 0.000) were significantly associated with CP. See **Table 3**.

The second analysis (not shown) included the variables SGA, multiple birth, gender, IVH1-2 and severe brain injury. In this analysis, only severe brain injury (OR = 86.0, p = 0.000) was significantly associated with CP. Of the 183 children, 28% were born SGA (< – 2 SD) [15].

DISCUSSION

We found an overall mortality rate of 9.2%, with a trend towards a higher mortality with decreasing GA. Overall, 6.4% were diagnosed with CP, none were blind, and 0.5% were in need of a hearing assistive device. In our study, 4.6% were diagnosed with severe disability in childhood (GMFCS 3-5, deaf or blind). Male gender and severe brain injury increased the risk of developing CP in childhood.

TABLE 3

Multivariate logistic regression analysis performed to investigate independent variable association with cerebral palsy in children (N = 183 with full cranial ultrasound, 13/183 with cerebral palsy).

	n (%)	Odds ratio (95% CI)	p-value
Gestational age < 28 weeks + 0 days	52 (28)	0.21 (0.02-2.41)	0.21
Birth weight < 1,000 g	57 (31)	3.74 (0.41-33.8)	0.24
Male	97 (53)	12.7 (1.28-127.0)	0.03
Multiple birth	81 (44)	1.70 (0.31-9.20)	0.54
IVH1-2	27 (15)	0.76 (0.10-5.73)	0.79
Severe brain injury: IVH3/PVHI/PVL	13 (7)	141.6 (15.7-1,277)	0.000

CI = confidence interval; IVHX = intraventricular haemorrhage grade X; PVHI = periventricular haemorrhagic infarction; PVL = periventricular leukomalacia.

For comparison, Serenius et al found an overall mortality of 31% with a significantly higher mortality with decreasing GA: 7% with CP, 0.9% with blindness, 0.9% deafness and 11% diagnosed with severe disability (includes children with severe mental retardation). These infants were born with a GA < 27, between 2004 and 2006 [6].

Leversen et al found an overall mortality of 42% (incl. stillbirths): 11% with CP, 2% with blindness, 1% with deafness and 6% with severe disability (including children with severe mental retardation). These infants were born at GA < 27, between 1999 and 2000. Leversen et al showed that an increased risk of neurological sequelae was strongly associated with a GA of less than 26 weeks [7].

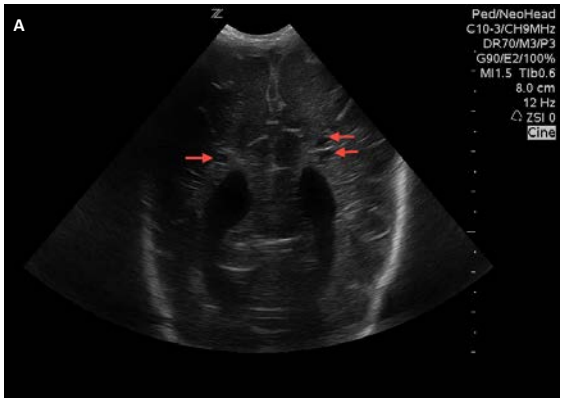
Bolisetty et al determined that GMH-IVH3-4, male gender and PVL are independent factors associated with moderate-to-severe neurosensory impairment. Bolisetty et al found that even GMH-IVH1-2 can adversely influence long-term neurodevelopmental outcomes in extremely preterm infants [9].

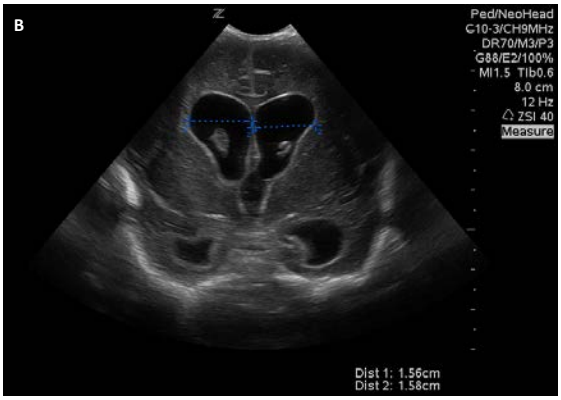
Unfortunately, we have not registered mental retardation as an important neurodevelopmental outcome in our study. Mental retardation is a well-known risk in extremely preterm born infants, as described in the studies above. In our study, we can only compare on development of CP, being blind or deaf.

A strength of our study is the low exclusion rate of 9/249 (3.6%). It is a weakness that we did not include mental retardation as an outcome variable. The study is a retrospective cohort study, and this type of study requires a large sample for rare outcomes. A total of 34 infants did not have two routine C-US performed. This is found to have a minimal impact on the results as the majority of these infants were born with a GA of 30-32. One of these 34 children developed mild CP; none of these children were blind or deaf.

C-US is an inexpensive, easy and quick way to examine and diagnose cerebral abnormalities in very preterm infants, and it is helpful because it yields a prognosis for every child. Nevertheless, some uncertainty remains with respect to the use of C-US. This uncertainty includes inter-observer reliability and accuracy and the fact that several determinants may not be picked up, i.e. white matter abnormality (WMA) and cerebellar lesions. In our study, 27% (3/11) of children with PVHI or PVL did not develop CP. Roze et al found that 24% of children with PVHI developed no neurological sequelae [12]. Furthermore, we found that 2.7% (4/148) of the children with no pathological findings on C-US developed CP.

Hintz et al assessed the inter-observer reliability of C-US interpretations between two central readers, and accuracy between central and local readers. Reliability and accuracy were found for highly unfavorable C-US findings, but not for WMA or mild-to-moderate GMH-IVH [16]. Determinants that may not be picked up by C-US include brainstem and hippocampal hypoxic injury, cerebellar haemorrhage or ischaemia, a diffuse non-cystic form of PVL, and WMA, which have been shown to be associated with an adverse outcome [17, 18]. Additionally, the C-US findings cannot provide answers to whether the child will develop a cognitive impairment or not.





The question also remains whether GMH-IVH1-2, if accurately and consistently diagnosed with C-US, could be a risk factor for later neurodevelopmental impairment. An additional benefit seems to arise if cerebral magnetic resonance imaging (MRI) is included in scanning protocols to enhance the reliability in predicting preterm infants' neurodevelopmental outcomes. Increasing severity of WMA and significant cerebellar lesions on MRI have been demonstrated to be associated with adverse outcomes [17-19].

C-US provides a good screening tool to detect severe brain injury resulting in an adverse outcome. On the other hand, however, MRI with improved discrimination of WMA and other brain injuries will probably give a more precise prediction of the neurodevelopmental impairment of every single preterm born infant. MRI might be complementary and necessary to more accurately predict preterm infants' outcomes and help design a precise follow-up programme for each child. This needs to be addressed in future studies.

CONCLUSION

In conclusion, we found that C-US detecting GMH-IVH3, PVHI or PVL and male gender were associated with CP in childhood. C-US provides a good screening tool for detection of severe brain injury in very preterm infants during hospitalisation. Future studies are necessary to evaluate whether MRI of preterm infants can lead to a more accurate prediction of the neurodevelopmental impairment.

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