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Cranial ultrasonography can predict the neurodevelopmental outcomes in preterm neonates?

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ABSTRACT

Background: Preterm birth is correlated with cerebral lesions such as hypoxia-ischaemia and haemorrhage. It is important to fully provide their parents with the potential prognostic information for the neonates, and most do this with the role of some neuroimaging modalities. This study aims to evaluate if it is possible to predict the short-term neurodevelopmental outcomes in

preterm infants who develop hemorrhagic, ischemic or other brain lesions that are recognized on routine cranial ultrasound examinations? *Methods*. We prospectively evaluated the correlation of cerebral lesions found by cranial ultrasound and the developmental delays at the age of 6 months in 79 preterm infants (born before the 37th postmenstrual week). Cerebral ultrasound findings were reported as four categories: 1) Intraventricular haemorrhage; 2) Periventricular leukomalacia; 3) Ventricular dilatation; 4) Other lesions such as congenital anomaly, cystic lesion. Developmental evaluation at the age of 6 months was performed by Denver II screening test and during a neurologic examination. *Results*: Of 79 preterm infants, 24.1% had delayed mental or psychomotor development or both. Abnormal ultrasound findings, which were significantly correlated with the developmental delays, consisted of intraventricular haemorrhage (RR=9.6), periventricular leukomalacia (RR=10.3), ventricular dilatation (RR=18), congenital anomaly (RR=18) and cystic lesion (RR=18). Some perinatal factors such as Apgar score < 7at 5 mins, the disease of hyaline membranes, and mechanical ventilation were each correlated to increased risk of developmental delays. *Conclusion:* Cranial ultrasound is an excellent non-invasive modality for the screening of brain lesions in preterm newborns during hospitalization. Therefore, physicians could predict short-term neurodevelopmental outcomes.

Keywords: Cranial ultrasound, premature newborn, neurodevelopmental

1. INTRODUCTION

Premature birth is associated with brain lesions mostly resulting from hypoxia-ischaemiaand haemorrhage (Veyrac et al., 2006; Argyropoulou, 2010). Compared with full-term infants, preterm infants are in a state of continuous and immature brain development, are more vulnerable to injury and long-term disability, and are at high risk of death. Preterm birth is increasing and the rate of developmental impairment in survivors remains high (Cheong et al., 2012; Purisch et al., 2017; Vogel et al., 2018). Clinicians routinely need to provide parents and carers with prognostic information for their vulnerable infants, and most do this with the aid of some form of neuroimaging. Various imaging techniques, mainly ultrasound (US) and magnetic resonance imaging (MRI), have been used for this purpose (Veyrac et al., 2006; Argyropoulou, 2010). US is the most widely used cranial imaging modality in the neonatal intensive care unit. US machines are portable, the images can be acquired at bedside, and the cumbersome transport of the neonates to the computerized tomography (CT) or MRI suite is avoided. In addition, ultrasound is considered a safer modality in the pediatric population due to the lack of potential harming effect of ionizing radiation, as in CT, as well as avoiding the need for sedation frequently required for MRI. Ultrasound is the least costly of all cranial imaging modalities and is readily available in all intensive care units. Cranial ultrasound is cheap, safe and can be performed at the cot side by the attending neonatologist or paediatric radiologist.

In this prospective study, we evaluated if it is possible to predict the short-term neurodevelopmental outcomes in preterm infants who develop hemorrhagic, ischemic or other brain lesions that are recognized on routine cranial ultrasound examinations?

2. MATERIAL AND METHODS

Study population

Premature infants born before 37 weeks of gestational age (GA) and New Ballard score under 35 admitted into Neonatal Intensive Care Unitof Pediatric Center, Hue Central Hospital, Vietnam, were examined by ultrasound through anterior fontanel during the period from April 2017 to August 2018. This study was approved by the Hue Central Hospital institutional review board with the reference number of 157/2017-HCH. Informed consent was waived by the board.

Ultrasound Protocol and Findings

Each infant was prospectively screened by cUS examination for the presence of brain lesions at about 4 and 24 hours and 7 days of age. The anterior and posterior fontanels were commonly used. The mastoid and temporal fontanels were used to obtain axial images for evaluating posterior fossa. The transverse sinus can be examined through posterior fontanel or foramen magnum. Sono Site Sonomax ultrasound equipment with linear 5–7 MHz probe was used. All antiseptic precautions were taken and sterilized ultrasound gel was used. Transvaginal (TV) probe of 7–12 MHz (kept exclusively for cranial ultrasound) was used to evaluate quickly the areas of the brain near convexity. The examination time on an average was 5–7 min and another 1 min for TV probe to avoid heating effect (if at all it was there). Precaution was taken to avoid undue pressure of the probe on the fontanel. Scans were read by two independent readers aware only of the infants' birth weight and submitted to a third reader in case of disagreement as to the presence or absence or time of onset of a lesion.

cUS diagnoses were categorized as: 1) Intraventricular haemorrhage (IVH); 2) Periventricular leukomalacia (PVL); 3) Ventricular dilatation; 4) Other lesion (congenital anomaly, cystic lesion)

Developmental assessment at 6months

Families were invited to bring their child for developmental assessment close to the time when he or she would attain 6 months' corrected age. This assessment included the Denver II developmental screening test and a neurologic examination.

Statistical methods

All the numerical data are expressed as the means ±standard deviation. The chi-square test or Fisher's exact test was used for the analysis of categorical variables. To predict of short term developmental outcomes in preterm infants, we compared the US characteristics of the normal and developmental delay groups during the study period. The statistical analysis was conducted using SPSS Statistics version 20.

3. RESULTS

A total of 79 infants born at 24 through 36 weeks of gestation were included in this prospective cohort study. More than one-half of the entire cohort was male (55.7%). The mean gestational age 32.1±3.3 weeks, and their mean birth weight was 973.7±315.9 g (820-2,250 g). Of these preterm neonates, 54 (68.4%) had normal cUS findings and 25 (31.6%) had abnormal cUS findings. Among the abnormal cUS findings, 15 (19.0%) had intraventricular haemorrhage, 7 (8.9%) had periventricular leukomalacia,1 (1.3%) had ventricular dilatation,1 (2.5%) had congenital anomalyand 1 (2.5%) had cystic lesion. All children were performed by the Denver II Developmental Screening Test at the age of 6 months and found 19 (24.1%) cases had developmental delays. There was asignificant relationship between abnormal cUS findings (intraventricular haemorrhage, periventricular leukomalacia, ventricular dilatation, other lesion), Apgar score at 5 mins <7, hyaline membrane disease, mechanical ventilation and developmental delays (table 1 and table 2).

Table 1 Assocciation between cUS findings and developmental outcome

Characteristics	Developmental delays N=19	Normal development N=60	P value	RR
Intraventricular haemorrhage	8 (42.1)	7 (11.7)	<0.05	9.6
Periventricular leukomalacia	4 (21.1)	3 (5%)	<0.05	10.3
Ventricular dilatation	1 (5.2%)	0 (0%)	<0.05	18
Congenital anomaly	1 (5.2%)	0 (0%)	<0.05	18
Cystic lesion	1 (5.2%)	0 (0%)	<0.05	18

Table 2 Assocciation between newborn characteristics and developmental outcome

Characteristics	Developmental delays N=19	Normal development N=60	P value	RR
Sex				
Male	11 (57.9%)	33 (55.0%)	>0.05	
Female	8 (42.1%)	27 (45.0%)		
GA (week)				
<28	2 (10.5%)	0 (0.0%)	>0.05	
28-32	9 (47.4%)	21 (35.0%)		
≥32	8 (42.1%)	39 (65.0%)		
Birth weight				
<1500	10 (52.6%)	17 (28.3%)	>0.05	
1500-2499	8 (42.1%)	40 (66.7%)		
≥2500	1 (5.3%)	3 (5.0%)		
Multiple birth				
Multiple	4(21.1%)	15 (25.0%)	>0.05	
Singleton	15 (78.9%)	45 (75.0%)		
Apgar score at 5 mins			<0.05	2.96

<7 ≥7	9 (47.4%) 10 (52.6%)	14 (23.3%) 46 (76.7%)		
Hyaline membrane disease Yes No	 5(26.3%) 14 (73.7%)	 5 (8.3%) 55 (91.7%)	 <0.05	 3.93
Mechanical ventilation Yes No	 10 (52.6%) 9 (47.4%)	 4 (6.7%) 56 (93.3%)	 <0.05	 15.56

4. DISCUSSION

Both MRI and computerized tomography (CT) are proven to be the best neuroimaging; however, they are not the first-choice methods in our center for routine screening the cerebral lesions in preterm infants after birth. US is the most widely used cranial imaging modality in the neonatal intensive care unit because it can be repeatedly performed at bedside. This study does not aim to compare the predictive value between US and MRI or CT. Therefore, qualitative brain MRI was not included in the study. Periventricular brain damage, whether it is hemorrhagic, ischemic or both, can be associated with abnormalities in developmental outcome (Tudehope, 1985; Levene, 1988). Some of the earlier reports focused on infant outcomes associated with isolated germinal matrix hemorrhage (GMH) and/or IVH, but in most cases, infants with such lesions were not disabled (Aziz et al., 1995). The outcome abnormalities found in GMH and/or IVH with white matter damage, however, can range from subtle cognitive abnormalities to borderline or severe mental retardation (Ross et al., 1996; Whitaker et al., 1996). Motor abnormalities are reported often, particularly in association with disabilities such as cerebral palsy (Graham et al., 1987; Pinto-Martin et al., 1995; Hesser et al., 1997; Doyle et al., 2000), mental retardation (Wilkinson et al., 1996), or visual or hearing disturbances (Jacobson et al., 1996).

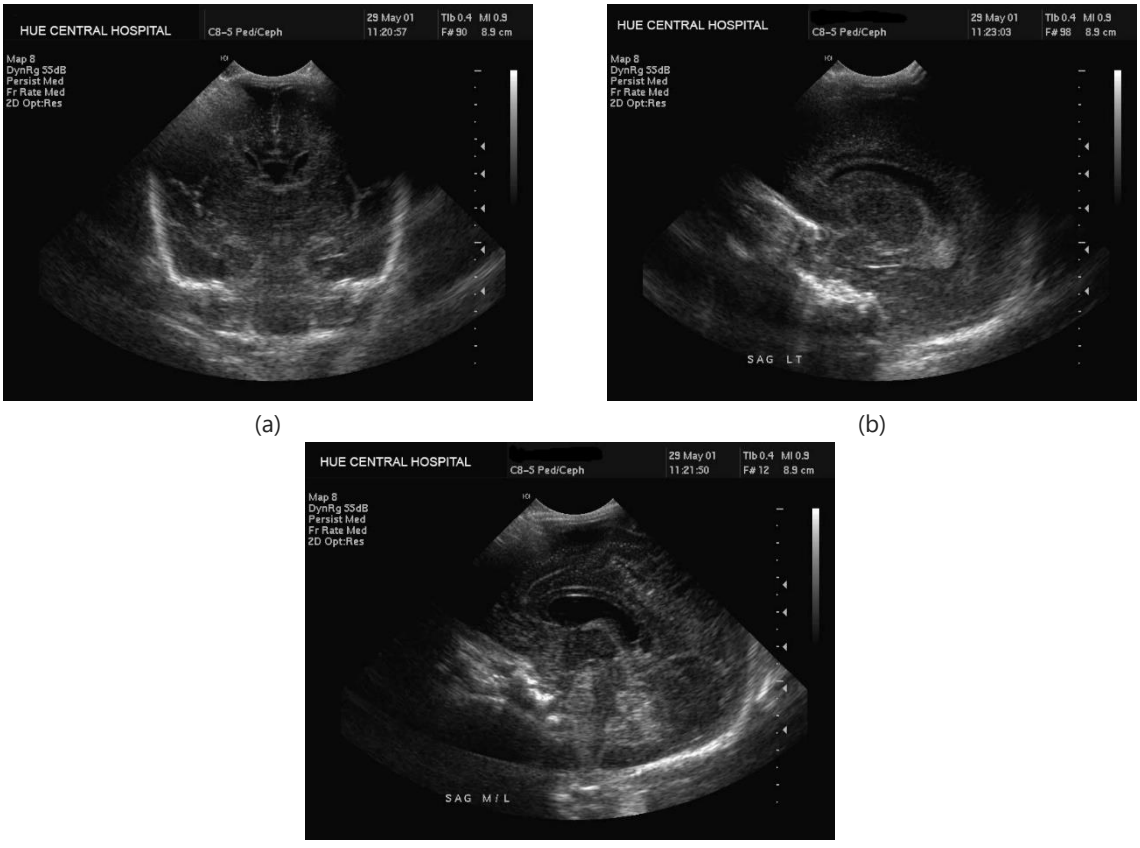


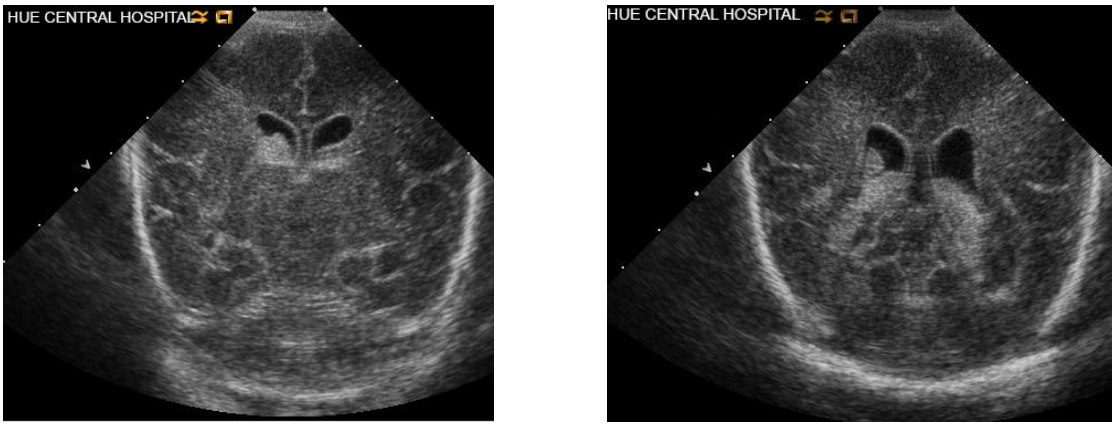
Figure 1 Periventricular leukomalacia on day 4 in preterm infant born at 29 week GA: (a)- Coronal view; (b) – Sagittal left view; (c) – Midline view.

The sensitivity of cranial ultrasound examinations as predictors of later developmental abnormalities has been reported as 16% at one and two weeks after birth, increasing to 53% at six weeks and 58% if performed when a child is at term-corrected age (Nwaesei et al., 1988). The specificity of cranial ultrasound examinations has been 99% to 100% in all age groups (Nwaesei et al., 1988). The presence of cysts has been reported as a predictor of cerebral palsy, with a sensitivity of 67% and a specificity of 96% (Graham et al., 1987). In most reports, estimates of the negative predictive value of cranial ultrasound examinations are consistent in that repeated normal examinations predict that an infant is unlikely to have cerebral palsy (Graham et al., 1987; Levene, 1990).

Our data analysis showed that, 54 (68.4%) had normal cUS findings and 25 (31.6%) had abnormal cUS findings. Among the abnormal cUS findings, 15 (19.0%) had intraventricular haemorrhage, 7 (8.9%) had periventricular leukomalacia, 1 (1.3%) had ventricular dilatation, 1 (2.5%) had congenital anomaly and 1 (2.5%) had cystic lesion. Neonatal hypoxic lesions and intracranial hemorrhagic lesions are classified into those that occur in preterm term infants and term neonates. In the former group, these lesions are GMH, intraventricular hemorrhage and PVL (Vergani et al., 2004). In term infant, hypoxic-ischemic encephalopathy and intracranial hemorrhage are the major manifestations. Sonography is highly accurate in detecting hemorrhage as well as for showing the resulting ventricular dilatation. Similarly, it is the technique of choice in the screening and follow-up of premature neonates for PVL. Multiple sequential examinations are necessary and sonography is ideal in this context.

PVL represents an ischemic injury involving the water shed area of the preterm brain, i.e., the periventricular white matter. There is no accurate way to diagnose PVL in the acute phase. Sonography is the best available imaging modality though it also remains fairly insensitive in early cases. Findings include focal areas of increased echogenicity in the superolateral periventricular areas, most prominent at the level of the atria. Pit fall already mentioned in this context is the normal periventricular flare due toanisotropic effect. Mild cases of PVL can resolve on follow-up sonography (figure 1). Chronic PVL results in ventriculomegaly, periventricular cystic change, and loss of deep white matter, with the sulci approximating the ventricular wall.

Most common site of hemorrhage in preterm neonates is a germinal matrix (Burstein et al., 1979). This is noted as echogenic areas in the caudothalamic groove. The hemorrhage can extend into the ventricles, former resulting in hydrocephalus (figure 2).



(a) (b)

Figure 2 Ultrasound images of a 2 day old premature infant born at 32 weeks.

Two contiguous coronal ultrasound images of the brain showing the echogenic focus of right intraventricular hemorrhage grade IIinvolving the right germinal matrix (top image) and then extending into the superior portion of the right lateral ventricle without ventricular dilation (bottom image). The echogenic substance filling the inferior portions of both lateral ventricles in the bottom image is the patient's normal choroid plexus. We evaluated the relationship between neonatal cranial ultrasound findings and standardized developmental as sessments in preterm neonates. As have others, we found that brain lesions diagnosed by cUS are powerful predictors of developmental delays in this cohort. They are intraventricular haemorrhage (RR 9.6) had periventricular leukomalacia (RR 10.3), ventricular dilatation (RR 18), congenital anomaly (RR 18) and cystic lesion (RR 18). Univaniate analysis revealed that several peninatal variables including afgar score at 5 mins < 7, hyaline membrane disease and mechanical ventilation are each associated with an elevated risk of developmental delays.

O'Shea et al. evaluated associations between ultrasound-defined lesions of the brain and developmental delays at 24 months' corrected age in 1017 children born before the 28th postmenstrual week. Ultrasound abnormalities were more strongly associated with low Psychomotor Development Index than with low Mental Development Index. Children without cranial ultrasound abnormality had the lowest probability (23% and 26%) of delayed mental or psychomotor development. Moderate/severe

ventriculomegaly was associated with a more than four fold increase in the risk of psychomotor delay and an almost threefold increase in the risk of mental delay. Echolucency was the next best predictor of delayed mental and psychomotor development. The probability of low scores varied with the number of zones involved and with the location of echolucency. At particularly high risk were infants with bilateral cerebellar hemorrhage, co-occurring ventriculomegaly and echolucency bilateral echolucency, or echolucency located posteriorly (O'Shea et al., 2008).

The most important implication of our study is that clinicians can use ultrasound markers of brain damage as predictors of developmental impairment. Children with these markers can be targeted for early intervention to improve developmental outcome. This use of ultrasound is part of the basis for the Practice Parameter for Neuroimaging of the Neonate in 2002 (Miller et al., 2002), which recommends cranial ultrasound screening for infants born before 30 weeks' gestation, at 7 to 14 days, and again at 36 to 40 weeks

5. CONCLUSION

Cranial ultrasound provides a good screening tool for detection of brain injury in preterm infants during hospitalisation. 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 toinform parents about their child's prognosis. Future studies are necessary to evaluate whether MRI of preterm infants can lead to a more accurate prediction of the neurodevelopmental impairment.

Abbreviation

cUS: Cranial ultrasound
RR: relative risk
MRI: resonance imaging
CT: computerized tomography
GA: gestational age
IVH: Intraventricular haemorrhage
PVL: Periventricular leukomalacia
GMH: germinal matrix hemorrhage

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Author contributions

All participated in the study design, data collection, and literature search. Data was analyzed by TNVA. TKH and TNVA wrote the paper. All authors read and approved the final manuscript.

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