

Cranial Ultrasonographic application in preterm baby as a predictive for white matter insult

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Abstract: Cranial Ultrasound is the most available and easily repeatable technique for imaging the neonatal brain. The quality and diagnostic accuracy depend on various factors; the suitability of the Ultrasound machine for neonatal cranial work, the use of optimal settings and probes, appropriate scanning protocols, the use of a variety of acoustic windows and last but not the least the scanning experience of the examiner. Knowledge of normal anatomy and the echogenicities of different tissues in normal and pathological situations as well as familiarity with the physiological and pathological processes likely to be encountered are vital. This paper assesses the value and appropriate use, safety and diagnostic accuracy of Ultrasound in evaluating the brain of the preterm born infants. This study group consisted of 308 preterm neonates, the gestational ages at birth ranged from 26 weeks to 34 weeks, and the birth weights ranged from 650 grams to 2250 grams, underwent cranial ultrasound in neonatal intensive care unit (NICU). 31 premature neonates were found to have PVL. Type of delivery, presence of perinatal asphyxia, gestation age and birth weight, were statistically insignificantly associated with PVL. Chorioamnionitis and neonatal sepsis and mechanical ventilation > 72 hours were the statistically significantly factors associated with PVL injury.

Keywords: Cranial Ultrasound, White Matter, Doppler, Periventricular Leukomalacia (PVL)

1. Introduction

The developing brain is susceptible to injury from variety of ischemic, infective, inflammatory, and neurotoxic factors. Preterm infants are at high risk of developing germinal layer hemorrhage (GLH), intraventricular hemorrhage (IVH), hemorrhagic parenchymal infarction (HPI), cystic periventricular leukomalacia and diffuse noncystic white matter (WM) injury. Infants with these abnormalities, excluding possibly GLH and small IVH, are at increased risk of developing motor, cognitive, and other impairment (1,2).

Periventricular Leukomalacia (PVL) is now considered the principal form of brain injury among preterm infants. PVL among very low birth weight infants is the major reason for their increased risk of developing a variety of neurologic sequelae, including motor dysfunction, delayed cognitive development, visual impairment, and epilepsy. The neurologic disabilities often result in cerebral palsy (CP), especially spastic diplegia (3). PVL has been defined as cyst formation with necrosis of myelinated fibers of the

white matter around the trigone that is situated dorsal and lateral to the external angles of the lateral ventricles. Several studies investigated the correlation between diffuse – type PVL and mental retardation and other neurologic disabilities (4,5).

Many authors have reported on the pathophysiologic features of PVL, which it is a complex process. PVL may occur because of ischemic / reperfusion injury to the periventricular area of the developing brain or because of cytokines induce damage following maternal or fetal infection (6), with infection and ischemia now being considered to underlie its development. Chorioamnionitis is reported to be associated with PVL, and umbilical cord inflammation (as detected in placental samples) is one of the risk factors for PVL (7).

Elevated interleukin – 6 levels in umbilical cord blood sometimes are associated with subsequent PVL (8). These reports suggest that PVL occurs in the prenatal period. However, it is well recognized that insufficient blood flow

in the watershed areas can induce white matter injury.

Impairment of cerebrovascular autoregulation, especially among premature infants, is associated with occurrence of PVL (9). This suggests that prenatal and postnatal pathophysiologic mechanisms can induce PVL. One report suggested a correlation between fetal inflammation and reduced postnatal blood pressure as the cause of PVL (10).

Cerebral blood flow (CBF) is autoregulated, being therefore uncorrelated to systemic arterial blood pressure. The brain in unhealthy preterm newborn does not autoregulate the CBF, and circulation then occurs through passive pressure. In this case, there is a direct linear relationship between CBF and mean arterial pressure. The association between the absence of CBF autoregulation and systemic hypotension has been implicated in the pathogenesis of cerebral white matter lesion (WML) and intraventricular hemorrhage (IVH) (11).

CBF measurement in preterm newborns provides useful information about cerebral perfusion and risks for intraventricular and germinal matrix hemorrhage and for WML (12).

In premature neonates, investigators have used a combination of xenon – 133 clearance and near infrared spectroscopy to study global cerebral blood flow and oxygen extraction. The regional nature of luxury perfusion suggests that determining regional cerebral blood flow may be more important clinically than measuring global cerebral blood flow (13). Recently, functional magnetic resonance imaging (MRI) and positron emission tomography have been used to study regional CBF (14).

When used to examine severely ill preterm neonates, MRI and positron emission tomography are limited by their expense and lack of portability (14). The method of choice for measuring CBF in the neonatal period consists in determining CBF velocity in the anterior cerebral artery, recorded by transcranial Doppler ultrasound, using the anterior fontanelle as acoustic window. It is sensitive, specific, bedside diagnostic tool, neither exposes newborn infants to ionizing radiation, no requires their sedation (15).

The sound waves given off by the transducer are reflected and their frequency travels proportionally to the velocity of circulating red blood cells in the vessel (11). Thus, the peak systolic and diastolic pressures are measured. In 1976, Pourcelot (16) introduced the concept of resistance index (RI), which is calculated by the following formula:

$RI = (S - D) / S$, where S and D stand for systolic and diastolic pressures, respectively. As its name itself suggests, RI measures vascular resistance. A high RI corresponds to vasoconstriction and low blood flow velocity, whereas a low RI is related to vasodilation and high blood flow velocity. In preterm newborns that are to develop hemorrhage, studies show that there is a fluctuating pattern in CBF velocity. Initially, CBF diminishes, with a high RI and vasoconstriction and probable infarction of germinal matrix vessels, followed by a low RI and vasodilatation with bleeding of germinal matrix vessels (17).

The aim of this study was to investigate cranial

ultrasound (US) within the first 28 days of life in preterm newborns, to correlate with cerebral white matter lesion especially PVL.

2. Patient and Methods

All surviving preterm neonates 34 weeks or less of gestation age, born from 2009 to 2012 were included in this study. Exclusion criteria were death before 14 days of life, presence of major congenital malformations or malformation of central nervous system, congenital TORCH infection (syphilis, toxoplasmosis, rubella, cytomegalovirus or herpes).

An informed consent form was read by parents before the first Cerebral Ultrasound Scan. Maternal and neonatal data include time of rupture of membranes, mode of delivery, birth weight, gestation age, sex, chorioamnionitis, placental abnormalities, Apgar score 1 and 5 minutes, exposure to hypoxia, prolonged exposure to hypocarbia and / or hyperoxia, maximum and minimum blood pressure in the first 7 days of life.

The study group consisted of 308 preterm neonates, the gestational ages at birth ranged from 26 weeks to 34 weeks, and the birth weights ranged from 650 grams to 2250 grams.

Cranial Ultrasound is regularly performed in neonatal intensive care unit (NICU) to premature babies on the first three days of life and on the 7th, 14th, 21st and 28th days of life, or after any clinical intercurrent event. All cranial ultrasound examinations were conducted by an experienced radiologist with great expertise in the management of newborns.

The scan was done using Philips Evisor C HD ultrasound machine with pediatric probe S 12 (2-5 MHz) for cardiac and cranial examination. First, we performed regular scan through anterior fontanel making the six regular scans in both sagittal, parasagittal and coronal views looking for the echogenicity, developing different part of the brain ventricular system, evidence of any intracranial collection and integrity of mid line structures. Then we got a scan for both middle cerebral artery and both side with measuring their flow profile.

The standard acoustic window used for imaging the neonatal brain is the anterior fontanel. However, the cerebellum, brainstem and posterior subcortical white matter may be poorly visualized using this approach. The detection of cerebellar abnormality via the anterior fontanel is complicated by the echogenic appearance of the tentorium and cerebellar vermis. The cerebellum is increasingly recognized as an important structure not only for motor control but also for cognitive and behavioral development. Abnormalities due to hemorrhage and infarction and poor growth [18-20] have gone under recognized. Scanning through the posterior fontanel (junction of the lambdoid and sagittal sutures) and mastoid fontanel (junction of the posterior parietal, temporal and occipital bones) can help to detect lesions and structural

malformations in these areas [21, 22, 23, 24]. Imaging through the temporal window allows good views of the mesencephalon and brainstem.

A color Doppler examination (Doppler velocimetry) was performed together with the first Ultrasound examination for each patient with a sonograph with a 5.0 MHz sector transducer. The transducer was placed first on the anterior fontanel, and pulsations were observed in the anterior cerebral artery (ACA), in the bilateral internal carotid arteries (ICAs) alongside the sella turcica, and in the basilar artery (BA). In the trans – cranial plane, the transducer was placed in front of the ear, over the thin temporal window, to obtain a cross – sectional image of the brain and to allow the flow in the bilateral middle cerebral arteries (MCAs) to be measured.

PVL was diagnosed with Cranial Ultrasonography performed mainly at 21 or 28 days postnatally if a cyst of > 3mm was evident. Cranial Doppler resistance index (RI) was computed for each vessel according to the method of Pourcelot (16), as modified by Bada et al (25). RI is the mean peak systolic velocity (S) minus the end diastolic velocity (D) divided by peak systolic velocity, or $(S - D) / S$. Low RI (< 0.61), normal RI (0.61 – 0.85) and high RI (> 0.85).

After the serial ultrasound brain scans, patients were divided into two groups:

Group 1. Premature babies with diagnosis of PVL based on diffuse or cerebral cystic white matter injury.

Group 2. Premature babies without diagnosis of PVL, with cerebral echography negative for this condition.

The criteria for diagnosing PVL were the presence of diffuse periventricular hyperechogenicity that persisted for a period of more than 7 days, without forming cyst (diffuse periventricular white matter injuries) or the presence of cystic lesions of at least 0.3 cm in diameter, distributed bilaterally and located close to the external angles of the lateral ventricles or in white matter around the trigone (26).

The presence of ventricular dilatation without cerebral hemorrhage during any of the serial ultrasound scans was considered to be secondary to necrosis of the white matter present in the diffuse PVL component (27).

The following data were collected prospectively and later compared between the two groups. Sex, birth weight, gestation age, fifth minute Apgar score, antenatal steroid use, neonatal sepsis, peri-intraventricular hemorrhage, mean blood pressure in 1st 7 days and mean PCO₂ in the 1st 7 days of life. Observational clinical monitoring while in NICU allowed for assessment of possible risk factor for PVL.

Follow up cranial US were done later during the first 3 months post discharge from hospital for all infants diagnosed as having PVL with ultrasonography to detect atrophic changes in the cerebral parenchyma or ventriculomegaly.

The following non – parametric tests were carried out for the statistical analysis: chi square test, t test A $p < 0.05$ value (two tailed) were established as statistically significant.

3. Results

A total of 468 premature neonates were born during 3 years of this study, 308 of whom met the inclusion criteria and were followed up until their 3 months of age post hospital discharge or late death (after 28 days of life). A total of 24 premature neonates (8%) died while in NICU and 284 (92%) were discharged from the hospital.

Group 1 comprised 31 premature neonates 34 weeks or less with PVL, and was compared with 277 premature neonates without PVL, group 2 (Table 1). Type of delivery, presence of perinatal asphyxia, gestation age and birth weight, were statistically insignificantly between the two groups. Chorioamnionitis and neonatal sepsis and mechanical ventilation > 72 hours were statistically significantly more with PVL group.

Table 1. Shows comparison of possible risk factor between PVL +ve group (group 1) and PVL absent group (group 2).

Clinical Data for study group (n = 62)	Group 1 PVL present (n = 31)	Group 2 PVL absent (n = 277)	P value
Males (%)	17 (54.8%)	131 (47.3%)	NS
Birth weight	1010 ± 250	1174.46 ± 131.26	NS
Gestational age (weeks)	29.2 ± 2.5	30.16 ± 8.76	NS
Type of delivery:			
Vaginal	11 (35.5%)	78 (28.2%)	NS
Caesarian	20 (64.5%)	199 (71.8%)	NS
5 minute Apgar score	8 (6 – 9)	8 (7 – 9)	NS
Chorioamnionitis	14 (45.2%)	5 (1.81%)	0.05
Neonatal sepsis	24 (77.42%)	78 (28.16%)	0.01
Mechanical ventilation > 72 hours	27 (87.10%)	63 (22.74%)	0.01
Late neonatal mortality > 28 days	10 (32.26%)	10 (3.61%)	

Twenty six infants had grade I PVL, and these infants developed a mild diplegia. Three had grade II PVL and developed a mild diplegia. Two had grade III PVL, and all had severe diplegia; none were able to walk unaided. The Ultrasonographic signs ranged from ventricular dilatation, cystic leukomalacia, symmetric basal ganglia lesions, focal areas of infarction. Associated clinical signs are clues to confirm the radiological diagnosis such as neonatal sepsis, hypocarbia, dyspnea, and apnea. Unfortunately seventeen of 277 infants (6%) who developed neurological symptoms later one had normal neonatal US data. Grade III PVL was invariably associated with infantile neurological deficit. PVL I is a common finding, and only 3 of 26 (12%) infants developed a neurological deficit.

The maximal and minimal blood pressure and PaCO₂ value for infants in the first 7 days of life were measured. The only significant difference between the two groups in these parameters from day 0 to day 7 was in the mean PaCO₂ on days 1, 2 and 3 which was significantly lower for infants with PVL compared with no PVL group.

4. Discussion

The use of ultrasound for transfontanel diagnosis of PVL in neonates is already established in neurological practice, pediatric, and especially in newborns, due to its sensitivity and specificity in detecting this disease and also for follow up. This procedure does not need special preparation like anesthesia or sedation and there is no exposure of infants to radiation. The possibility to study the extent of blood flow velocity in cerebral arteries by Doppler technique, coupled with ultrasound examination in real time, expanded the applicability of this technique and enabled monitoring the changes of blood flow velocity in intracranial arteries.

De Vries *et al.* (28) in a tertiary unit setting used high-resolution, sequential cUS in preterm infants for predicting cerebral palsy (CP). In 29% of infants <32 weeks' GA cystic PVL, the most predictive marker for CP, was only detected after 28 days. This data gives evidence that cUS can detect most lesions leading to CP if scanning is performed frequently until discharge and again around TEA (term equivalent age) and supports the need for scanning all gestation preterm infants admitted to a neonatal unit.

In the current study, we followed the examination protocol according to Perlman *et al.* (29) recommendations; that preterm infants of birth weight (BW) <1000 g should be scanned between days 3–5, 10–14, around day 28 and pre-discharge; that those between 1000 and 1250 g are scanned between days 3–5, day 28 and pre-discharge and those between 1250 and 1500 g between days 3–5 and pre-discharge. Cystic PVL occurred in larger, more mature infants and was not always preceded by increased periventricular echogenicity (PVE). In 2/9 infants it was only detected on the pre-discharge scan. Ventriculomegaly was detected on the initial scan in 50% but only after day 28 in 33%.

In our study we evaluated 308 premature neonates evaluated by transfontanel doppler ultrasound technique, 31 premature neonates 34 weeks or less has PVL features.

We found that no statistically significant differences between the RI values of the cerebral arteries on both sides. Winberg *et al.* (30) studied the blood flow velocity in cerebral arteries using the transfontanel doppler ultrasound technique in two groups of normal infants at term and preterm. They found that, regardless of the technique, the values for the speed of blood flow in the intracranial internal carotid arteries were equivalent. Also they found no change in cerebral blood flow velocity related to the rotation of the skull, either, if the flow velocity was obtained in arteries located to the right or to the left

From the works of Bada *et al.* (25) and Pourcelot *et al.* (31) know that RI can be considered as a relative measure of blood flow velocity, should be indicative of vascular resistance. And that elevated RI correlates with vasoconstriction and low blood flow velocity, whereas low RI values correlate with high vasodilation and blood flow velocity.

Archer *et al.* (32) assessed by transfontanel doppler ultrasound technique, a group of 43 term infants with clinical manifestations of perinatal hypoxia. These newborns were evaluated from the first hours of life with subsequent monitoring and objectives of this study were to correlate possible changes in RI is determined in the first 48 hours of life, could predict neurological late in this group of patients. Concluded that those infants with hypoxemia, compared with normal newborns, the US-Doppler technique was able to predict late neurological sequelae, with accuracy 86 %. These authors reported that some infants after perinatal hypoxia showed low values of RI, and that all abnormal RI were observed before 72 hours of life. Our results are matching with archer *et al.*, conclusions.

Although sequential CUS is clearly very important, its potential hazards and burden for the often sick and unstable newborn infant should be kept in mind. These include extra handling, applying pressure and cold gel to the fontanel, the risk of dislodging tubes or lines or introducing infection from equipment that is not kept clean or from the operator. Most of these issues are relatively easy to prevent when appropriate safety and hygienic precautions are taken. All ultrasound equipment for use on a neonatal unit must be kept regularly cleaned, the probes wiped with a damp cloth. We also use hard surface wipes that contain some alcohol but these are not suitable for all probes and the manufacturers should be consulted (33).

5. Conclusions

Many factors that act before, during, and after delivery can produce PVL thus sequential cranial US scanning at optimal times gives high accuracy. Whilst MRI does have advantages over cranial US, cranial US facilitates early bedside diagnosis and monitoring of pathology in a way that is relatively easy and not disturbing and safe for the newborn infant.

6. Figures Labels

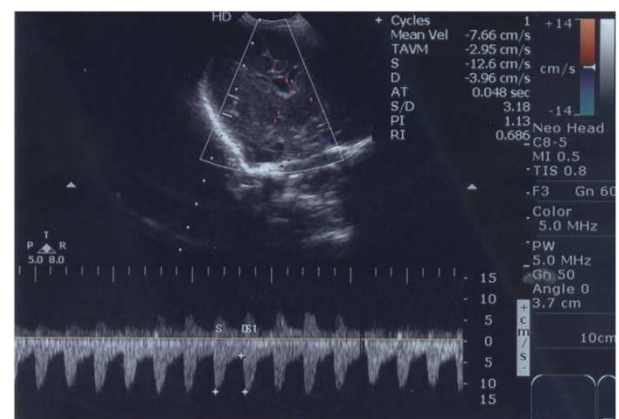


Fig 1. Ultrasound coronal scan through temporal window enabling visualization of the right middle cerebral artery show normal wave flow pattern with high resistive index

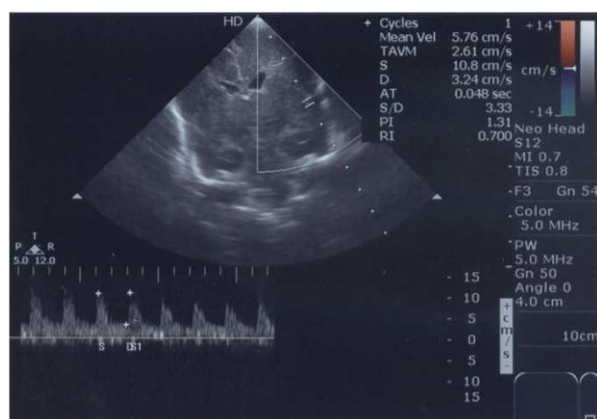


Fig 2. Ultrasound coronal scan through temporal window enabling visualization of the right middle cerebral artery show normal wave flow pattern with high resistive index

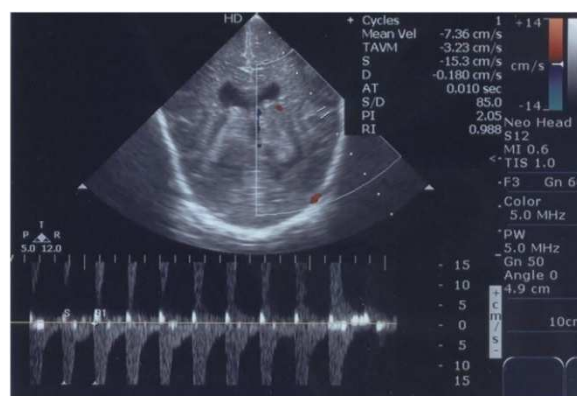


Fig 5. Ultrasound coronal scan through temporal window enabling visualization of the right middle cerebral artery normal high resistive index with periventricular, cortical hypoechogenicity

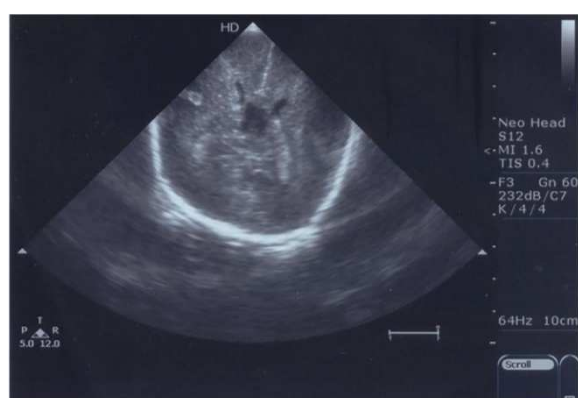


Fig 3. Cranial ultrasound coronal scan shows periventricular and cortical diffuse hypoechogenicity

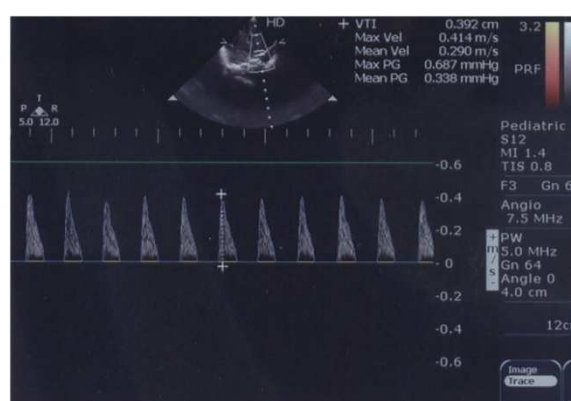


Fig 6. Ultrasound coronal scan for middle cerebral artery show abnormal wave flow pattern with no diastolic flow.

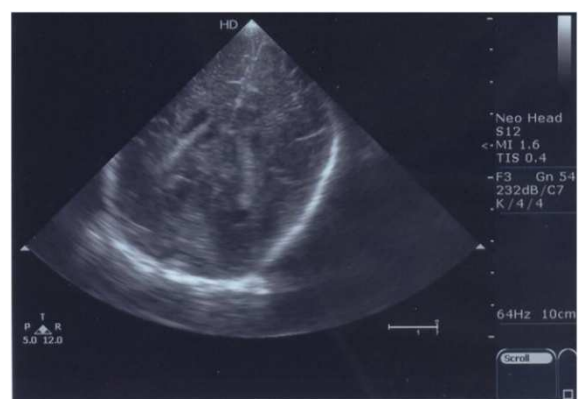


Fig 4. Cranial ultrasound coronal scan shows periventricular and cortical diffuse hypoechogenicity and abnormal echogenicity with loss of definition of the cerebellum suggestive of haemorrhage

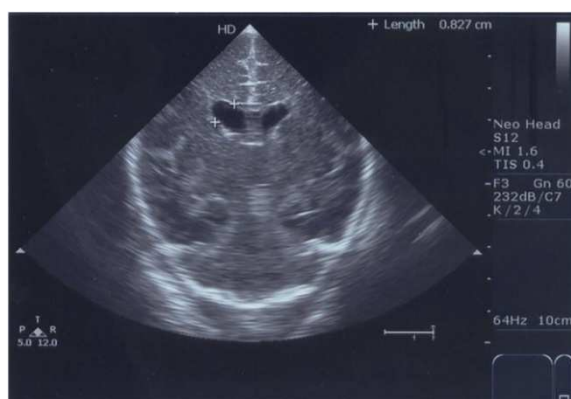


Fig 7. Cranial ultrasound coronal scan show cortical diffuse hypoechogenicity as well as dilated frontal horns of the lateral ventricles

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