Sherwani *et al.*
Egyptian Pediatric Association Gazette (2023) 71:7
https://doi.org/10.1186/s43054-023-00158-x

Egyptian Pediatric Association Gazette

RESEARCH Open Access

Assessment of role of cranial ultrasound (CUS) in the evaluation of high-risk preterm and term neonates

Aliya Shabir Sherwani[1], Arshed Hussain Parry[2*], Mudasir Hamid Bhat[1], Tariq Ahmad Gojwari[1], Bashir Ahmad Charoo[3] and Naseer Ahmad Choh[1]

Abstract

Background Cranial ultrasonography (CUS) has become an important tool to depict normal brain anatomy and to detect the ischemic and hemorrhagic brain injury patterns in high-risk neonates. The present study aimed to assess the utility of CUS to diagnose the spectrum of brain injury patterns in high-risk preterm and term neonates admitted to the neonatal intensive care unit (NICU) and to find the association of CUS findings in various adverse antenatal and perinatal feto-maternal factors.

Results Out of the 200 neonates, 76 (38%) neonates had abnormal CUS findings and 124 (62%) had a normal CUS. Germinal matrix hemorrhage-intraventricular hemorrhage (GMH-IVH) (28/76; 36.8 %) was the commonest abnormality with GMH (grade 1) in 14/76 (18.4%), grade 2 in 7 (9.2%), grade 3 in 5 (6.5%), and grade 4 in 2 (2.63%). The other findings observed were cerebral edema (14/76; 18.4%), thalamic hyperechogenicity (10/76; 13.1%), periventricular leukomalacia (PVL) (4/76; 5.2%), and congenital anomalies (8; 10.5%). Abnormal CUS findings had a statistically significant association with birth weight <2000 g, prematurity, Apgar score <7, and adverse peri-natal fetal and maternal factors (all *p*-values <0.05). Abnormal CUS findings had a statistically significant association with poor cry, poor activity, abnormal tone, and presence of cyanosis (all *p*-values <0.05).

Conclusion In this cohort study of high-risk preterm and term infants GMH-IVH, cerebral edema, thalamic hyperechogenicity, PVL, and congenital malformations were the commonest lesions detected on CUS. Abnormal CUS findings were found to have a statistically significant association with various adverse peri-natal fetal and maternal factors.

Keywords CUS, High-risk neonate, Preterm neonate, GMH-IVH, Intraventricular hemorrhage, PVL

Background

Preterm neonates and term neonates with some underlying risk factors are at a heightened risk of abnormal neurological development owing to ischemic, hemorrhagic, and inflammatory insults to the neonatal brain [1]. To undertake or modify preventive measures it is essential to detect the ongoing brain injury at the earliest.

Magnetic resonance imaging (MRI) is a superior modality to accurately identify and characterize brain abnormalities in a neonate. However, owing to its cumbersome nature, limited availability, prohibitive cost,

*Correspondence:
Arshed Hussain Parry
arshedparry@gmail.com
[1] Department of Radiodiagnosis, Sher-i-Kashmir Institute of Medical Sciences, Srinagar, Jammu and Kashmir, India
[2] Department of Radiodiagnosis, Government Medical College, Srinagar, Jammu and Kashmir, India
[3] Department of Pediatrics, Sher-i-Kashmir Institute of Medical Sciences, Srinagar, Jammu and Kashmir, India

need for sedation, and transfer of neonate to MRI suite it is impractical for widespread use [2].

Cranial ultrasound (CUS) due to its widespread availability, cost-effectiveness, bedside availability, lack of radiation, and the provision of frequent use for monitoring has assumed a vital role in the diagnostic armamentarium of neonatology practice for depicting normal anatomy and pathological changes in the neonatal brain. This is possible as the open sutures and fontanelles allow an easy window to "peep" into the brain [3–6].

Any neonate regardless of gestational age or birth weight with exposure to adverse fetal, maternal, and placental factors is at an enhanced risk of morbidity or mortality and is categorized as a high-risk neonate. CUS plays an important role in guiding treatment and predicting the neurological prognosis of these high-risk infants [7–9]. The Quality Standards Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Science and the American Institute of Ultrasound in Medicine (AIUM) Practice Guidelines for the Performance of Neurosonography in Neonates and Infants recommend routine CUS screening for neonates born before 30 weeks of gestation and unstable neonates born after 30 weeks of gestation with indications for CUS [10, 11].

CUS, among a wide range of indications, appears to be most useful for the detection and follow-up of intraventricular hemorrhage, hydrocephalus, and periventricular leukomalacia (PVL). The advancements in neonatal intensive care have resulted in an improved outcome in high-risk neonates, thus highlighting the role of early detection of neurological subnormalities to modify the neurological outcome of these neonates [12, 13].

The future neuromotor and cognitive development and the potential risk of future development of cerebral palsy (CP) can be reasonably predicted based on abnormal CUS findings. A series of studies over a 30-year period have shown that a normal CUS can provide considerable confidence in predicting that an infant will have normal neurodevelopment [9, 14, 15]. In a typical large study, a normal ultrasound scan predicted normal cognitive function with a PPV of 77% (95% CI 74% to 80%), and the pooled probability of a normal cognitive outcome with a normal ultrasound scan is 82% (95% CI 79% to 85%) [16]. The association between CUS and neurodevelopmental outcome has been well studied. Echolucent and white matter lesions on CUS are associated with delayed mental and psychomotor development at 24 months of corrected age [12]. Moderate/severe ventriculomegaly was associated with a more than fourfold increase in the risk of psychomotor delay and an almost threefold increase in the risk of mental delay The highest RR for delayed mental development was associated with ventriculomegaly (RR: 2.70), followed by PVHI (RR: 1.90). Ventriculomegaly had the highest RR for delayed psychomotor development (RR: 4.40), followed by PVHI (RR: 3.90), echolucency (RR: 3.70), and cystic PVL (RR: 3.60) [12]. In a recent study of preterm infants, early CUS lesions were associated with poor attention, hypotonicity, and poor quality of movement at term-equivalent age [17].

The current study aimed to evaluate the CUS findings in high-risk preterm and term neonates admitted to a neonatal intensive care unit (NICU) and to find the association of CUS findings with various antenatal and perinatal feto-maternal parameters.

Methods

Study design and patient cohort

This was a single-center prospective study covering a 2-year study period from December 2018 to December 2020. The study was approved by the Institutional Ethical Committee (IEC) of our institution and informed consent was obtained from the parents or guardians. Two hundred high-risk neonates admitted to NICU for various indications were enrolled in the study on a non-randomized purposive sampling basis. Following neonates were included in the study:

1. All preterm neonates born before 34 weeks of gestation.
2. High-risk late preterm (≥34–36weeks) and high-risk term neonates with any of the following:
   (a) Neonatal seizures, (b) birth asphyxia, (c) neonatal encephalopathy including hypoxic-ischemic encephalopathy, (d) respiratory distress, (e) neonatal sepsis, (f) signs and or symptoms of central nervous system disorders like microcephaly, macrocephaly, hypotonia, unexplained poor feeding, (g) neonates born out of traumatic/instrumental labor, (h) suspected metabolic disturbances, (i) antenatally detected congenital malformations.

The study excluded babies admitted to the hospital after 28 days of life and term neonates not fulfilling the inclusion criteria.

Scanning protocol

Screening scans for babies born less than 34 weeks or less than 2000 grams were performed on days 1, 3, 7, and 14, and then fortnightly until 34 weeks, at 36 weeks, and at term equivalent age. In preterm infants >34 weeks CUS was performed on days 1, 7, 21, and at term equivalent age. In neonates with birth asphyxia scans were performed on days 1, 3–4, 7, and 10–14. In full-term neonates and neonates with neurological symptoms, CUS was performed at the earliest opportunity and

subsequent scans were based on the findings of the first scan and the clinical condition [18].

Data collection and scanning technique

A detailed antenatal history was obtained, and antenatal records were reviewed. Perinatal details were collected, and a detailed clinical examination was done. Routine investigations like metabolic and septic screens were performed. Other relevant investigations like a lumbar puncture in neonatal convulsions and neonatal sepsis and chest X-ray in all respiratory distress cases were done. Neonatal sepsis was defined as the presence of two positive bacterial cultures with a positive c-reactive protein.

CUS of the neonates fulfilling the inclusion criteria was performed in NICU. Proper antiseptic precautions were taken while performing the CUS examination because of the poor immune system of neonates, especially those born prematurely. Proper hand washing by the operator and disinfection of the transducer was done to reduce the transmission of infectious agents to the immunocompromised newborn. Special attention was given to the neonate's body temperature, as newborns are susceptible to rapid heat loss.

All ultrasound examinations were done by a single radiologist to avoid inter-observer variations and the images were reviewed by the same radiologist later without clinical information to check for intra-observer variations. The radiologist was a general radiologist, trained in neonatal sonography with an experience of 9 years. The neonates were divided into two groups based on gestation age (<32 weeks and >32 weeks) and on the basis of birth weight (<2000 g and >2000 g). The frequency of abnormal and normal CUS findings was compared between the two groups to calculate statistical association. Similarly, abnormal and normal CUS findings were compared between the neonates with an Apgar score of 7 or above and <7. Comparison was also made between the neonates with an adverse peri-natal risk factor and those without it.

All examinations were performed with LOGIQ P5 (GE Healthcare) ultrasound machine with high frequency (7–11 MHz) linear probe and low frequency (3–5 MHz) curvilinear probe. Proper depth of view was adjusted to ensure that no pathology is missed in the posterior fossa of the brain, and multiple focal zones were used to improve lateral resolution. Image quality was optimized by fine adjustment of available presets. Imaging was performed via the anterior fontanelle in sagittal and coronal planes. Imaging in the sagittal plane was done in the midline and then both right and left parasagittal areas were evaluated with probe angulation of 15 to 30° on either side. In the coronal plane, an examination was done through the frontal horns of lateral ventricles, Sylvian fissure, third ventricle, and occipital horns of lateral ventricles. Additional views were obtained through the posterior and mastoid fontanelle and the thin part of the squamous temporal bone.

Statistical analysis

Data were analyzed using the Statistical Package for the Social Sciences (SPSSInc. Chicago, IL, version 22.0). All the categorical variables were shown in the form of frequency and percentage. Chi-square test was used to examine the categorical variables. A p-value less than 0.05 were considered statistically significant.

Results

The study cohort consisted of 130 (65%) male and 70 (35%) female neonates. The mean age of the study population was 35.7 ± 6.2 weeks (mean ± SD). Of these, 24% were less than 32 weeks, 24% were between 33 and 36 weeks, and the rest 52% term neonates. The mean birth weight of the study population was 2406 ± 900 grams (mean ± SD). Among them, 152/200 (76%) had a birth weight ≥2 kg and 48/200 (24%) had a birth weight <2 kg.

Out of the 200 neonates, 76 (38%) neonates had abnormal CUS findings and in 124 (62%) neonates CUS findings were normal. Among neonates with abnormal CUS findings, 60 (78.9%) were males and only 16 (21.1%) were females. Distribution of high-risk neonates as per inclusion criteria is given in Table 1.

Timing of scan vs. CUS findings

A total of 154/200 (77%) neonates had their first CUS within the first 24 h of neonatal life. In 46/200 (23%) neonates, CUS was done greater than 24 h because they were referred from peripheral hospitals where facility of CUS was not available.

Among the neonates in whom CUS was done in the first 24 h of life, 82 (53.2%) were normal and 66 (42.8%) were abnormal. In 46 neonates, CUS was done greater than 24 h of neonatal life among which 36 (78.3%) had a normal scan and 10 (21.7%) had abnormal findings.

Table 1 Distribution of high-risk neonates as per inclusion criteria

Inclusion criteria	Normal CUS	Abnormal CUS	Total
Preterm (<36 weeks)	56 (58.3%)	40 (41.7%)	96 (100%)
Birth asphyxia	48 (50%)	48 (50%)	96 (100%)
Birth trauma	4 (50%)	4 (50%)	8 (100%)
Neonatal sepsis	40 (76.9%)	12 (23.1%)	52 (100%)
Seizures	30 (71.4%)	12 (28.6%)	42 (100%)

CUS findings

Germinal matrix-intraventricular hemorrhage (GMH-IVH)

Out of 76 neonates who had abnormal findings, 28 (36.8 %) had GMH-IVH of which 14 (18.4%) had GMH (grade 1), 7 (9.2%) had GMH with intraventricular hemorrhage (IVH) without ventriculomegaly (grade 2), 5 (6.5%) had IVH with ventriculomegaly (grade 2), and 2 (2.63%) had parenchymal bleed (grade IV hemorrhage) (Figs. 1 and 2).

PVL

PVL was observed in 4 (5.2%) patients. On follow-up imaging, all four developed cystic PVL (grade 2 in 2 patients and grade 3 in the other 2 (Figs. 2 and 3).

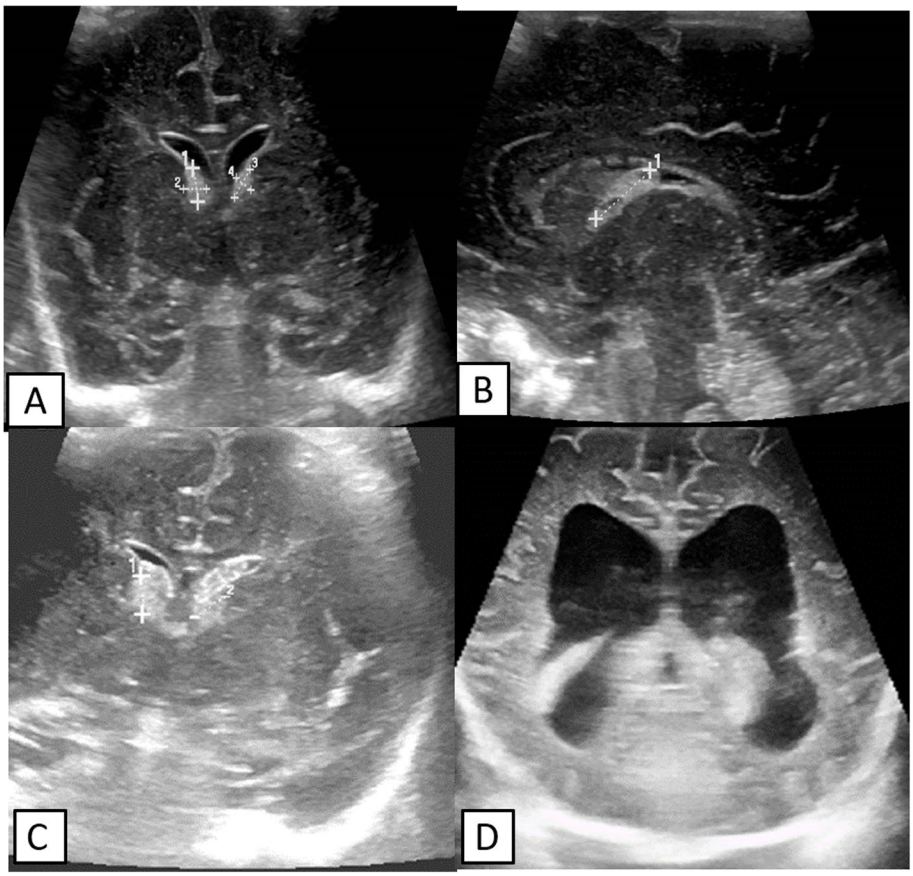

Fig. 1 CUS images in four neonates showing bilateral GMH without IVH with no ventriculomegaly (**A**), left GMH in para-sagittal scan (**B**), bilateral GMH with an intra-ventricular extension on the left side (**C**), and post-hemorrhagic ventricular dilatation (**D**)

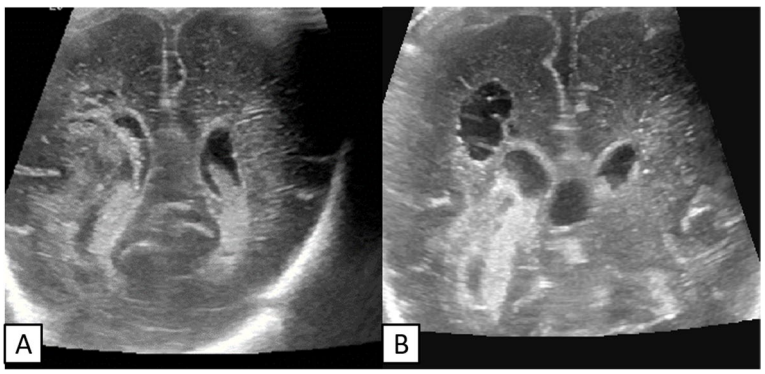

Fig. 2 CUS images in a pre-term neonate showing PVL (grade 2) (**A**) with progression into cystic PVL in a follow-up scan (**B**)

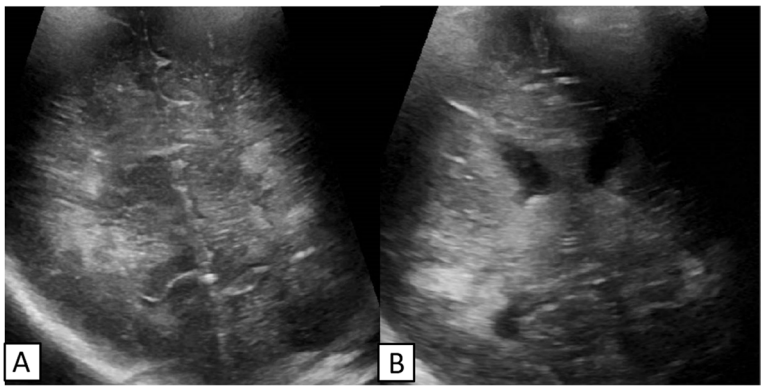

Fig. 3 CUS images at slightly different levels (**A**, **B**) in a pre-term neonate showing patchy hyperechogenicities in bilateral periventricular white matter suggestive of PVL

Cerebral edema

CUS detected brain swelling with slitlike ventricles and loss of visualization of the normal sulci with abnormally increased brain parenchymal echogenicity, consistent with brain edema in 14 (18.4%).

Thalamic hyperechogenicity, a marker of HIE was seen in 10 (13.1%) neonates. Of the neonates having thalamic hyperechogenicity, 8.4% were preterm and 5.3% were term neonates.

Congenital anomalies

Congenital anomalies were observed in 8 (10.5%) (Fig. 3), of which four had Dandy-walker malformation, two had hydranencephaly and two had hydrocephalus with associated meningomyelocele (Arnold Chiari malformation) (Fig. 4).

CUS and gestational age

Distribution of various CUS findings with gestational age is presented in Table 2. In neonates with gestation age <32 weeks (n=48) abnormal CUS findings were seen in 26 (54.1%) and 22 (45.9%) had a normal CUS. Whereas, in neonates with gestation age >32 weeks (n=152) abnormal CUS findings were seen in 50 (32.8%) and 102 (67.2%) had a normal CUS. On statistical analysis, significant association was found between gestation age <32 weeks and abnormal CUS findings (p-value=0.0081).

CUS and birth weight

In our study, 10% of neonates weighed less than 1500 g, 26.3% weighed between 1500 and 2000 g, and 21% weighed between 2000 and 2500 g. The overall incidence of abnormalities on CUS in low-birth-weight neonates was 68.9%. Out of neonates with a birth weight ≥2000 g (n=152) only 48 (31.6%) had abnormal CUS whereas, 104 (72.4%) had a normal CUS. In contrast, in neonates

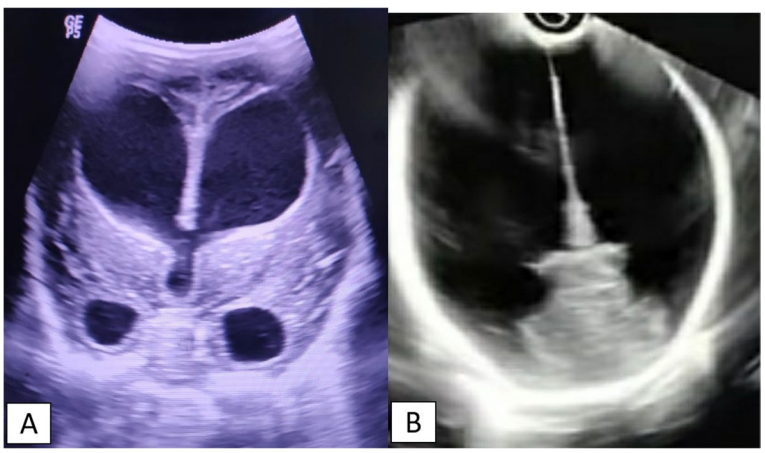

Fig. 4 CUS images in two different neonates showing congenital hydrocephalus (**A**) and hydranencephaly (**B**)

Table 2 Frequency of various CUS findings as per gestation age

Gestation age (weeks)	CUS findings								Total
	Norm al	GMH	IVH	CE	PVL	HCP	THE	Congenital anomalies	
28–32	22	12	8	0	2	0	2	2	48
	(45.8%)	(25%)	(16.7%)		(4.2%)		(4.2%)	(4.2%)	(100%)
33–36	34	2	4	2	2	2	2	0	48
	(70.8%)	(4.16%)	(8.3%)	(4.2%)	(4.2%)	(4.2%)	(4.2%)		(100%)
37–40	68	0	6	12	0	6	6	6	104
	(65.4%)		(5.8%)	(11.5%)	(0.0%)	(5.8%)	(5.8%)	(5.8%)	(100%)
Total	124	14	18	14	4	8	10	8	200

CUS cranial ultrasound, *CE* cerebral edema, *GMH* germinal matrix hemorrhage, *IVH* intra-ventricular hemorrhage, *PVL* periventricular leukomalacia, *HCP* hydrocephalus, *THE* thalamic hyperechogenicity

with birth weight <2000 g (n=48), 28 (58.3%) had abnormal CUS. There was a significant association between birth weight <2000 g and abnormal CUS findings (p-value=0.0008). The commonest abnormality in neonates weighing less than 2000 g was GMH-IVH and in neonates weighing more than 2500 g was cerebral edema followed by thalamic hyperechogenicity and hydrocephalus (Table 3).

CUS in perinatal asphyxia

Out of 92 patients with perinatal asphyxia, 46 (50%) had abnormal CUS whereas, 46 (50%) had a normal CUS. Among the study cohort, 44 (47.8%) had severe, and 48 (52.1%) had moderate perinatal asphyxia as per Apgar scoring. The frequency of CUS findings with the Apgar score is given in Table 4. Among neonates with an Apgar score of 7–10 (n=108), 30 (27.7%) had abnormal CUS whereas the rest 78 (72.3%) had normal CUS. In contrast, among neonates with an Apgar score <7 (n=92), 46 (50%) had abnormal CUS whereas 46 (50%) had normal CUS. There was a statistically significant association between Apgar score <7 and abnormal CUS findings (p-value=0.0012).

CUS in neonatal sepsis

Out of 52 patients with neonatal sepsis 40 (77%) had a normal CUS whereas, 12 (23%) had an abnormal CUS. The findings included increased echogenicity in the periventricular and subcortical white matter (8/12; 66.6%), echogenic sulci (2/12; 16.6%), small discrete echogenic white matter lesions (2/12; 16.6%), ventriculomegaly (2/12; 16.6%) and cerebral hypoechoic lesion (2/12; 16.6%).

CUS in birth trauma

Among 8 patients with birth trauma, 4 (50%) had abnormal CUS findings. Two had intraparenchymal hemorrhages (1 in the temporal lobe and 1 in the frontal lobe) and two had IVH.

Table 3 Frequency of various CUS findings with birth weight

		CUS findings								Total
		Norma l	GMH	IVH	Cerebral edema	PVL	HCP	THE	Congenital anomalies	
Birth weight	<1.5 kg	0	4	4	0	0	0	0	0	8
			50.0%	50.0%						100.0%
	1.5–2.0	20	6	4	0	2	2	4	2	40
		50.0%	15.0%	10.0%		5.0%	5.0%	10.0%	5.0%	100.0%
	2.1–2.5	46	10	0	2	2	0	0	2	62
		74.2%	16.1%		3.2%	3.2%			3.2%	100.0%
	>2.5 kg	58	2	2	12	0	6	6	4	90
		64.4%	2.2%	2.2%	13.3%		6.7%	6.7%	4.4%	100.0%
Total		124	22	10	14	4	8	10	8	200
		62.0%	11.0%	5.0%	7.0%	2.0%	4.0%	5.0%	4.0%	100.0%

Table 4 Distribution of various CUS findings with Apgar score

Apgar score	CUS findings								Total
	Normal	GMH	IVH	Cerebral edema	PVL	HCP	THE	Congenital anomalies	
7–10	78	6	4	4	0	6	4	6	108
	72.2%	5.6%	3.7%	3.7%	0.0%	5.6%	3.7%	5.6%	100.0%
4–6	28	6	4	4	0	2	2	2	48
	58.3%	12.5%	8.3%	8.3%	0.0%	4.2%	4.2%	4.2%	100.0%
0–3	18	10	2	6	4	0	4	0	44
	40.9%	22.7%	4.5%	13.6%	9.1%	0.0%	9.1%	0.0%	100.0%
Total	124	22	10	14	4	8	10	8	200
	62.0%	11.0%	5.0%	7.0%	2.0%	4.0%	5.0%	4.0%	100.0%

Table 5 Incidence of abnormal clinical and their association with CUS findings

	Cranial ultrasound		Significance
	Normal	Abnormal	
Abnormal cry	20 (13.5%)	16 (30.8%)	0.049*
Poor activity	24 (16.2%)	20 (38.5%)	0.018*
Poor/abnormal tone	6 (4.1%)	10 (19.2%)	0.014*
Poor reflexes	8 (5.4%)	4 (7.7%)	0.673
Abnormal posture	6 (4.1%)	4 (7.7%)	0.464
Presence of pallor	2 (1.4%)	4 (7.7%)	0.103
Presence of icterus	38 (25.7%)	8 (15.4%)	0.283
Presence of cyanosis	36 (24.3%)	24 (46.2%)	0.037*
Tachycardia (HR >160)	6 (4.1%)	2 (3.8%)	0.963
Tachypnea (RR >60)	124 (100%)	76 (100%)	1.000
Abnormal temperature	8 (5.4%)	0 (0%)	0.226

CUS cranial ultrasound, *GMH* germinal matrix hemorrhage, *IVH* intraventricular hemorrhage, *PIH* pregnancy induced hypertension, *APH* antepartum hemorrhage, *GDM* gestational diabetes mellitus, *PVL* periventricular leukomalacia, *HCP* hydrocephalus

*indicates significant *p*-values

CUS findings in various clinical findings

Among the various clinical findings abnormal cry, poor activity, poor tone, and presence of cyanosis had a statistically significant association with abnormal CUS findings (Table 5).

Frequency of various adverse antenatal maternal factors with CUS findings is presented in Table 6. A higher percentage of neonates with at least one adverse perinatal factor had abnormal CUS in comparison to neonates with no adverse peri-natal risk factor (48.8% vs. 29%) (p-value=0.0053).

In the present study, 98 (49%) neonates were born via normal vaginal delivery (NVD), and 102 (51%) were born via lower segment caesarian section (LSCS). Out of 98 neonates born via NVD, 40 (40.8%) neonates had abnormal CUS findings and out of 102 neonates born via LSCS 36 (35.3%), neonates had abnormal findings.

Discussion

Although the pattern of brain injury may differ in preterm (<36 weeks of gestation) and term neonates (>36 weeks of gestation) depending on the severity and duration of hypoxia some overlapping features may exist. In preterm neonates, GMH-IVH and periventricular white matter injury are common lesions. In term neonates, watershed zones of the brain located at the borders of arteries and metabolically active tissues such as ventrolateral thalami, posterior putamina, hippocampi, brainstem, corticospinal tracts, and sensorimotor cortex are vulnerable to hypoxic injury [6].

In the present study, GMH-IVH was the commonest finding in preterm neonates whereas cerebral edema was the commonest finding in term neonates. This finding is in concordance with other studies [19–23]. GMH-IVH, parenchymal hemorrhagic infarction (PHI), and its sequel of post-hemorrhagic ventricular dilatation (PHVD) constitute the most dreaded complication in the vulnerable population of preterm and low-birth-weight neonates. The risk of GMH-IVH is related to the gestational age and is frequently seen in neonates born before 32 weeks. In neonates born before 28 weeks, the incidence varies in the range of 10–25%. In neonates born after 32 weeks, the incidence of GMH-IVH is less common and is usually a sequel of cerebral venous thrombosis. Germinal matrix attains its maximum size at 25 weeks of gestation and then gradually regresses with its remnants persisting until approximately 36 weeks. It has been demonstrated that immature fragile microvessels of the germinal matrix in the setting of fluctuations in cerebral blood flow owing to lack of autoregulatory mechanism in this population predispose them to GMH-IVH. GMH-IVH and PHI is almost exclusively immediate post-natal phenomenon

Table 6 Frequency of CUS findings in various adverse perinatal conditions

Perinatal risk factors	CUS findings								Total
	Normal	GMH	IVH	Cerebral edema	PVL	HCP	THE	Congenital anomalies	
None	46	12	0	8	4	6	6	8	90
	51.1%	13.3%	0.0%	8.9%	4.4%	6.7%	6.7%	8.9%	100.0%
PIH	22	4	6	2	0	2	2	0	38
	57.9%	10.5%	15.8%	5.3%	0.0%	5.3%	5.3%	0.0%	100.0%
APH	8	0	0	0	0	0	0	0	8
	100.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	100.0%
Twin preg	8	2	0	0	0	0	0	0	10
	80.0%	20.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	100.0%
PROM	18	0	4	0	0	0	2	0	24
	75.0%	0.0%	16.7%	0.0%	0.0%	0.0%	8.3%	0.0%	100.0%
GDM	18	2	0	2	0	0	0	0	22
	81.8%	9.1%	0.0%	9.1%	0.0%	0.0%	0.0%	0.0%	100.0%
Birth trauma	4	2	2	0	0	0	0	0	8
	50.0%	25.0%	25.0%	0.0%	0.0%	0.0%	0.0%	0.0%	100.0%

CUS cranial ultrasound, *GMH* germinal matrix hemorrhage, *IVH* intra-ventricular hemorrhage, *PVL* periventricular leukomalacia, *HCP* hydrocephalus, *THE* thalamic hyperechogenicity

with around 50% of events occurring in the first 24 h of life and 90% of events occurring in the first 3 days of life [6, 15–19]. The chances of hemorrhage drastically reduce after the first week of post-natal life presumably due to increased tissue oxygenation after birth which suppresses vascular endothelial growth factor and angiopoietin-2 thus reducing the formation of fragile new vessels [15].

The combined diagnostic accuracy of CUS ranges from 76 to 100% in detecting grade 1 hemorrhagic lesions greater than 5 mm and grade 2–4 hemorrhages [20, 21]. The present study found a significant association between birth weight <2000 g and abnormal CUS. Babies with low birth weight are at increased risk of intracranial hemorrhage [22]. There is an inverse relationship between GMH-IVH and birth weight.

Transient thalamic hyperechogenicity can be seen in a high percentage of neonates. However, the persistence of hyperechogenicity is a harbinger of white matter injury [23]. Basal ganglia or thalamus hyperechogenicity has a wide etiological profile including hypoxic-ischemic injury, hemorrhage, infection, calcifications, hypoglycemia, and chromosomal anomalies [24, 25].

In a study by Diwaker R et al. [6] consisting of one hundred preterm neonates, the different abnormalities detected in CUS included hydrocephalus in 12%, GMH-IVH in 6%, cerebral edema in 6%, PVL in 2%, choroid plexus cyst in 1%, intraventricular septa in 1%, and colocephaly in 1%.

In a study by Jha R et al. [26] consisting of 75 preterm neonates the incidence of CUS abnormalities was 25.4%. Abnormal findings were periventricular hyperechogenicity (10.6%), GMH-IVH (8%), PVL (4%), and cerebral edema (2.4%). CUS findings were significantly related to gestational age and birth weight. CUS findings had a significant association with APH, birth asphyxia, abnormal fetal activity, and abnormal tone. Our findings are in concordance with this study.

Fumagalli M et al. [21] included 1172 neonates for CUS. Periventricular hyperechogenicity was the commonest abnormality in 19.6% and 1% had severe abnormalities (4 GMH-IVH, 2 cystic PVL, 4 arterial strokes, 2 venous infarctions, 3 malformations). At the multivariate analysis, the combined gestational age/Apgar/comorbidities accurately predicted whether the neonate had normal or abnormal CUS (AUC 74.6).

Guan B et al. [27] detected variable incidences of abnormal CUS findings in term neonates with birth asphyxia. In neonates with mild HIE 25/54 (46.3%) had abnormal CUS whereas 58/60 (96.7%) of neonates with moderate HIE and 44/44 (100%) neonates with severe HIE had abnormal CUS.

Humsene et al. [28] observed positive sonographic findings in 120/165 (72.7%) neonates. 75% of preterm babies presented with GMH-IVH and follow-up scans showed communicating hydrocephalus in 75% and porencephalic cysts in 16%. In HIE, 74% had cerebral edema followed by periventricular echo densities. Infections presented with echogenic sulci or meningeal thickening in 38%.

De Vries LS et al. [29] conducted a large (n=2139) prospective study of preterm infants. Among preterm

infants <32 weeks (n=1639), 514 (31.3%) had abnormal CUS. Among them, 368 (71%) had PVL grade I–III, 128/514 (25%) had GMH-IVH (grade I–IV) and 12/514 (2.4%) had focal infarction. In the preterm group with a gestation age of 33–36 weeks (n=503) only 68 (13.5%) had abnormal CUS [42 (61.7%) had PVL grade I-IV; 10 (14.7%) had IVH (grade III-IV); 5 had focal infarction]. Seventy-six (5%) of the 1460 survivors in age <32 weeks developed CP. CUS abnormalities were present in 70 of 76 (92%) infants, being major in 58 (83%) and minor in 12 (17%). Twenty-nine (6%) of the 469 survivors in age 33–36 weeks developed CP. CUS abnormalities were present in 28 of 29 (96%) infants, being major in 25 (89%) and minor in 3 (11%). Considering the major CUS abnormalities, a specificity of 95% and 99% and a sensitivity of 76% and 86% were found for the two groups, respectively.

Ballardini E et al. [19] in a retrospective study of 724 babies found intracranial lesions in 13% of neonates (3.7% at 36 weeks to 27.1% at 33 weeks of gestational age). Babies born at 33–34 weeks of gestational age were four times more likely to have an abnormal CUS than those at 35-36 weeks. A significant association was present between the head circumference less than the third percentile, the need for ventilation or surfactant, low Apgar index at the fifth minute, and neurological abnormalities.

Studies have found an association between antenatal maternal factors like PIH, Premature rupture of membranes and chorioamnionitis, and abnormal CUS findings [30–32]. Nicaise C et al. [31] reported CUS abnormalities in 11.7% of preterm born after premature rupture of membranes (PPROM).

In the present study, there was a statistically significant association between abnormal CUS and birth weight <2000 g, gestation age <32 weeks, Apgar score <7, and presence of adverse perinatal factors. Similarly, neonatal clinical examination findings of abnormal cry, poor tone, abnormal activity, and presence of cyanosis were also strongly associated with abnormal CUS. Studies have shown that poor neonatal reflexes, seizures and apnea, cyanosis, poor suck, high-pitched cry, and muscle twitching are significantly associated with abnormal CUS especially IVH [33].

This study has some limitations. Small sample size, single-center design, and lack of long-term neurodevelopmental outcomes are some of the important limitations of the study. A large sample size would be desirable to study the long-term outcome.

In conclusion, the robust information emanating from the routine use of CUS in neonatology practice can open new horizons in the precise understanding of pathophysiological mechanisms of neonatal brain injury and pave way for the development of efficient preventive measures.

Conclusion

This study underscores the role of CUS in the NICU setting. Early detection of brain damage in high-risk neonates guides management and helps in prognostication. In this cohort study of high-risk preterm and term infants GMH-IVH, cerebral edema, thalamic hyperechogenicity, PVL, and congenital malformations were the commonest lesions detected on CUS. Abnormal CUS findings are more common in low birth weight, prematurity, perinatal asphyxia, and adverse antenatal and perinatal events. Some clinical indicators like poor cry, poor activity, abnormal tone, and cyanosis have a statistically significant association with abnormal CUS.

Acknowledgements
The authors are grateful to the department of pediatrics for their support throughout.

Authors' contributions
S.A., P.A., B.M., G.T., C.B., and C.N. conceptualized the study and performed or assisted in the collection and analysis of data. P.A., S.A., and B.M. wrote the manuscript which was supervised and edited by C.N. and C.B. All authors have read and approved the manuscript and ensure that this is the case.

Funding
No funding was required for this study.

Availability of data and materials
The data is available from the first three authors.

Declarations

Ethics approval and consent to participate
The study was duly approved by the Institutional Ethical Committee (IEC) of Sher-i-Kashmir Institute of Medical Sciences, Srinagar, Jammu & Kashmir, India. A reference number was not applicable. Consent was obtained from the parent or guardian of the child.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

Received: 30 November 2021 Accepted: 27 January 2023
Published online: 13 February 2023

References

1. Volpe JJ (2008) Neurology of the Newborn. ed. Philadelphia, pa. Saunders, London
2. Wang LW, Huang CC, Yeh TF (2004) Major brain lesions detected on sonographic screening of apparently normal term neonates. Neuroradiology. 46(5):368–373
3. van Wezel-Meijler G. (2007) Cranial ultrasonography: advantages and aims. Neonatal Cranial Ultrasonography. 3-7.
4. A, Azzopardi DV. (2010) Confidence in the prediction of neurodevelopmental outcome by cranial ultrasound and MRI in preterm infants. Arch Dis Child Fetal Neonatal, Ed. 95: 388–390

5. De Vries LS, Groenendaal F (2002) Neuroimaging in the preterm infant. Ment Retard Dev Disabil Res Rev 8:273–280
6. Diwakar RK, Khurana O (2018) Cranial sonography in preterm infants with short review of literature. J Pediatr Neurosci 13(2):141
7. Nazparveen LA, Phirke DS (2017) Cranial ultrasound in critically ill neonates. J Med Res 3(6):290–293
8. Plaisier A, Raets MM, Ecury-Goossen GM, Govaert P, Feijen-Roon M, Reiss IK, Smit LS, Lequin MH, Dudink J (2015) Serial cranial ultrasonography or early MRI for detecting preterm brain injury? Arch Dis Child Fetal Neonatal Ed 100(4):F293–F300
9. Vollmer B, Roth S, Baudin J, Stewart AL, Neville BG, Wyatt JS (2003) Predictors of long-term outcome in very preterm infants: gestational age versus neonatal cranial ultrasound. Pediatrics. 112(5):1108–1114
10. Ment LR, Bada HS, Barnes P, Grant PE, Hirtz D, Papile LA, Pinto–Martin J, Rivkin M, Slovis TL. (2002) Practice parameter: Neuroimaging of the neonate:[RETIRED]: Report of the Quality Standards Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society. Neurology. 58(12):1726–1738
11. American Institute of Ultrasound in Medicine (AIUM): American College of Radiology (ACR); Society of Radiologists in Ultrasound(SRU) Collaborators (2014) AIUM practice guideline for the performance of neurosonography in neonates and infants. J Ultrasound Med 33(6):1103–1110. https://doi.org/10.7863/ultra.33.6.1103
12. O'Shea TM, Kuban KC, Allred EN, Paneth N, Pagano M, Dammann O, Bostic L, Brooklier K, Butler S, Goldstein DJ, Hounshell G (2008) Neonatal cranial ultrasound lesions and developmental delays at 2 years of age among extremely low gestational age children. Pediatrics. 122(3):e662–e669
13. van Wezel-Meijler G, Steggerda SJ, Leijser LM. (2010) Cranial ultrasonography in neonates: role and limitations. InSeminars in perinatology (Vol. 34, No. 1, pp. 28-38). WB Saunders.
14. Rademaker KJ, Uiterwaal CS, Beek FJ, van Haastert IC, Lieftink AF, Groenendaal F, Grobbee DE, de Vries LS (2005) Neonatal cranial ultrasound versus MRI and neurodevelopmental outcome at school age in children born preterm. Arch Dis Child Fetal Neonatal Ed 90(6):F489–F493
15. Parodi A, Govaert P, Horsch S, Bravo MC, Ramenghi LA (2020) Cranial ultrasound findings in preterm germinal matrix haemorrhage, sequelae and outcome. Pediatr Res 87(1):13–24
16. Nongena P, Ederies A, Azzopardi DV, Edwards AD (2010) Confidence in the prediction of neurodevelopmental outcome by cranial ultrasound and MRI in preterm infants. Arch Dis Child Fetal Neonatal Ed 95(6):F388–F390
17. Helderman J, O'Shea TM, Dansereau L, Check J, Hofheimer JA, Smith LM, McGowan E, Neal CR, Carter BS, Pastyrnak SL, Betz B (2022) Association of Abnormal Findings on Neonatal Cranial Ultrasound With Neurobehavior at Neonatal Intensive Care Unit Discharge in Infants Born Before 30 Weeks' Gestation. JAMA Netw Open 5(4):e226561
18. James AC (2018) Practical guide to neonatal cranial ultrasound (CrUS): basics. Paediatr Child Health 28(9):424–430
19. Ballardini E, Tarocco A, Baldan A, Antoniazzi E, Garani G, Borgna-Pignatti C (2014) Universal cranial ultrasound screening in preterm infants with gestational age 33-36 weeks. A retrospective analysis of 724 newborns. Pediatr Neurol 51(6):790–794
20. Raets MM, Sol JJ, Govaert P, Lequin MH, Reiss IK, Kroon AA, Appel IM, Dudink J (2013) Serial cranial US for detection of cerebral sinovenous thrombosis in preterm infants. Radiology. 269(3):879–886
21. Fumagalli M, Ramenghi LA, De Carli A, Bassi L, Farè P, Dessimone F, Pisoni S, Sirgiovanni I, Groppo M, Ometto A, Consonni D (2015) Cranial ultrasound findings in late preterm infants and correlation with perinatal risk factors. Ital J Pediatr 41(1):1–7
22. Kadri H, Mawla AA, Kazah J (2006) The incidence, timing, and predisposing factors of germinal matrix and intraventricular hemorrhage (GMH/IVH) in preterm neonates. Childs Nerv Syst 22(9):1086–1090
23. Luciano R, Bersani I, Mancini G, Vento G, Mercuri E (2020) Cranial ultrasound evaluation in term neonates. Early Hum Dev 143:104983
24. Parodi A, Morana G, Severino MS, Malova M, Natalizia AR, Sannia A, Rossi A, Ramenghi LA (2015) Low-grade intraventricular hemorrhage: is ultrasound good enough? J Matern Fetal Neonatal Med 28(sup1):2261–2264
25. Linder N, Haskin O, Levit O, Klinger G, Prince T, Naor N, Turner P, Karmazyn B, Sirota L (2003) Risk factors for intraventricular hemorrhage in very low birth weight premature infants: a retrospective case-control study. Pediatrics. 111(5):e590–e595
26. Jha R, Singh A, Jha R (2017) Cranial ultrasound in high risk preterm. New Indian J Pediatrics 6(1):26–32
27. Guan B, Dai C, Zhang Y, Zhu L, He X, Wang N, Liu H (2017) Early diagnosis and outcome prediction of neonatal hypoxic-ischemic encephalopathy with color Doppler ultrasound. Diagnostic Intervent Imaging 98(6):469–475
28. Humsene K, Krishnaveni N, Sarada B (2016) Transcranial perinatal neurosonogram for intracranial pathology: Study of 165 cases. J Med Sci Health 2(2):29–36
29. De Vries LS, Van Haastert IL, Rademaker KJ, Koopman C, Groenendaal F (2004) Ultrasound abnormalities preceding cerebral palsy in high-risk preterm infants. J Pediatr 144(6):815–820
30. Adams-Chapman I, Vaucher YE, Bejar RF, Benirschke K, Baergen RN, Moore TR (2002) Maternal floor infarction of the placenta: association with central nervous system injury and adverse neurodevelopmental outcome. J Perinatol 22(3):236–241
31. Nicaise C, Gire C, Fagianelli P, Debriere R, Thomachot L, d'Ercole C, Boubli L (2002) Neonatal consequences of preterm premature rupture of membrane (PPROM) at 24-34 WG: 118 singleton pregnancies. J Gynecol Obstet Biol Reprod (Paris) 31(8):747–754
32. Rovira N, Alarcon A, Iriondo M, Ibañez M, Poo P, Cusi V, Agut T, Pertierra A, Krauel X (2011) Impact of histological chorioamnionitis, funisitis and clinical chorioamnionitis on neurodevelopmental outcome of preterm infants. Early Hum Dev 87(4):253–257
33. Zhang XH, Qiu SJ, Chen WJ, Gao XR, Li Y, Cao J, Zhang JJ (2018) Predictive value of cranial ultrasound for neurodevelopmental outcomes of very preterm infants with brain injury. Chin Med J 131(8):920

Publisher's Note