Original Article

Clinical neonatal hypoxic ischemic injury: Cranial ultrasound spectrum of findings in neonates admitted to a Newborn Unit in Nairobi, Kenya

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Abstract

Introduction: Birth asphyxia causes significant neurologic injury and neurodevelopmental delay in children. Cranial ultrasound (CUS) can be used for the diagnosis, early intervention, and prognostication of birth asphyxia. We determined the CUS findings among term neonates with clinical birth asphyxia and correlated sonographic findings with the modified Sarnat clinical grade.

Materials and Methods: We conducted a prospective cross-sectional analytical study in Kenyatta National Hospital New Born Unit (KNH NBU) between June 2018 and October 2018. Term babies, older than 24 h with clinical birth asphyxia, were recruited and CUS was performed. Statistical analysis was done using proportions, means, and frequencies. Chi-square tests were used to assess correlation between imaging findings and the clinical Sarnat grading of asphyxia.

Results: Periventricular deep white matter echogenicity and thalamus and/or basal ganglia deep gray matter was reported in 56.4% and 31.1%, respectively. Only 4.4% had cortical gray matter. Normal CUS findings were reported in 40.0% of the neonates. Prolonged labor and meconium-stained liquor were the predominant risk factors for perinatal asphyxia, seen in 58% of the neonates. Prolonged labor was independently reported in 43% of the neonates. Moderate and severe Sarnat grades correlated with abnormal sonographic changes of hypoxic ischemic encephalopathy (HIE) (Grades 2–8) ($P = 0.038$). There was a trend toward HIE severity with worsening Sarnat stages (trend test $P = 0.039$). Abnormal resistive indices (<0.5 and >0.8) were strongly associated with the presence of HIE brain changes ($P = 0.003$).

Conclusion: The correlation between birth asphyxia severity and CUS was more robust in Doppler evaluation of the deep cerebral arteries.

Keywords: Bedside, cranial ultrasound, hypoxic ischemic encephalopathy, Kenyatta National Hospital New Born Unit, term

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INTRODUCTION

Globally, perinatal asphyxia, also known as hypoxic ischemic encephalopathy (HIE), remains a common postdelivery complication occurring in 1–2/1000 live births in high-income countries.[1] With a much higher incidence in resource limited settings, it is the most common cause of neurologic injury and neurodevelopmental delay..[2]

The survivors of severe HIE usually have profound long-term neurologic impairment such as cerebral palsy, mental retardation, and epilepsy,[3] while majority of the infants with moderate HIE develop cognitive problems. These sequelae of hypoxic–ischemic brain injury require significant lifelong/long-term resources.[4]

The principal mechanism of pathogenesis underlying most of the neuropathology attributed to intrapartum hypoxia–ischemia is impaired cerebral blood flow.[3] The development of brain injury after hypoxia–ischemia is an evolving process, which is initiated during the hypoxic–ischemic insult and extends into the reperfusion period during recovery.[3] Following the hypoxic-ischemic insult, the brain damage develops after a symptom free interval or after a temporary clinical improvement.[5] The time before the full development of brain damage presents a window of opportunity for therapeutic interventions. It is essential to assess the severity of asphyxia in the newborn infant as soon as possible after birth or during the first hours after asphyxia to provide adequate care and treatment before the final damage develops.[6]

Neonatal cranial sonography is a relatively accessible modality for the assessment of neonatal brain, compared to computed tomography (CT) and magnetic resonance imaging (MRI) modalities that are expensive and relatively more inaccessible. Cranial ultrasound (CUS) can detect developmental abnormalities and exclude other causes of encephalopathy,[7,8] whereas Doppler ultrasound (US) provides additional evaluation of cerebral perfusion.[9] CUS is diagnostically more accurate compared to MRI and can be used to determine initial clinical management. In a study by Epelman *et al*. comparing the utility of US versus head MRI in perinatal asphyxia, the diagnostic accuracy of CUS was 95.7%, concluding that CUS was more accurate than previously reported.[7] US can be used to detect the most frequently occurring brain abnormalities in the preterm and full-term neonates, to study the evolution of lesions, and to follow brain maturation in preterm and term neonates.[7,8] The findings on sonography are of importance in HIE severity grading, appropriate patient management, and prognostication.

Pathologically, the findings in a term neonatal brain present in two main patterns: a basal ganglia–thalamus pattern involvement seen in severe injury and a peripheral pattern (also known as parasagittal or watershed) involving the cortical–subcortical white matter in milder injury.[10] Mild-to-moderate HIE demonstrates parasagittal watershed infarcts at ACA/MCA and MCA/PCA (ACA - Anterior cerebral artery; MCA – Middle cerebral Artery; PCA – Posterior Cerebral Artery) perfusion interfaces involving both the cortex and subcortical white matter. The parieto-occipital and posterior temporal lobes are the most affected, compared to the anterior lobes. Severe HIE mostly affects the metabolically active zones in the thalami, posterior putamen, hippocampi, brainstem, corticospinal tracts, and sensorimotor cortex. Basal ganglia injury portends a worse prognosis. More severe generalized hypoxemia leads to cerebral edema. Chronic findings include cortical atrophy, thinning, and multicystic encephalomalacia.[11,12]

This study aimed to build a local database on the pattern of brain US findings in birth asphyxia.

We determine the CUS spectrum of findings among term neonates clinically diagnosed with birth asphyxia and correlated the sonographic findings with the modified Sarnat clinical grade.

MATERIALS AND METHODS

This was a prospective cross-sectional analytical study conducted between June 2018 and October 2018 at the KNH NBU. A purposive sampling method was used to recruit participants who were term newborns ≥24 h old, born at ≥37 weeks gestation, and admitted with a clinical diagnosis of HIE. The neonates were studied for demographic details and risk factors for perinatal asphyxia. The infants were clinically graded for perinatal asphyxia severity using the modified Sarnat and Sarnat classification.[13] A CUS was performed by the principal investigator at first contact on all eligible participants. The white/gray matter changes were described with four standardized descriptors, as either: no echogenicity; periventricular or deep white matter echogenic changes; thalamus and/or basal ganglia deep gray matter echogenic changes; and/or cortical gray matter echogenic changes. Special note was made of whether the abnormalities were diffuse or localized. Any hemorrhagic changes and ventriculomegaly, if present, were recorded.

Color Doppler vascular study of the major cerebral arteries for peak systolic volume, end-diastolic volume, and resistive indices (RIs) was done and recorded appropriately.

The CUS findings were graded for HIE severity into eight grades as adapted from the classification by Mercuri *et al*.,[13] based on the predominant pattern and severity of changes.

For this study, the portable Mindray M7 US machine available within the KNH NBU unit was used to evaluate all the recruited babies. The machine cranial default protocol was used.

Statistical analysis was performed using SPSS version 25.0 (IBM Corp., Armonk, NY,) to determine mean, frequency distributions, standard deviations (SDs), proportions, and cross tabulations. A statistical test of proportion was used to assess the correlation between imaging findings and Sarnat clinical grading. All estimates were reported at 95% confidence level, and all comparisons were done at the 5% significant level.

Voluntary informed consent was sought from the parent/caregiver. Ethical approval of the study was obtained from the KNH-University of Nairobi (UON) Ethical Review Committee.

RESULTS

The participants were 45 consecutive term neonates admitted with a clinical diagnosis of perinatal asphyxia.

Majority of the mothers (86.7%) were aged below 35 years, with a mean age of 27.4 years (standard deviation [SD] ±4.7): the oldest was aged 36 years and the youngest was aged 18 years. The mean gestational age of the neonates at delivery was 38.8 weeks (SD ± 1.7): maximum 42 weeks and the minimum 37 gestational weeks. Majority of the participants were male (54%), with a male: female ratio of 1.2:1. The mean neonatal age at examination was 5.62 days (SD ± 3.8): the youngest was 2 days old and the oldest was 12 days old. The mean birth weight was 3120.8 g (SD ± 491.5): the heaviest weighed 4000 g and the lightest 2000 g; majority (88.9%) weighed ≥2500 g. The main mode of delivery was via spontaneous vaginal delivery (SVD) (71.1%), and the rest were delivered via cesarean section.

Risk factors for birth asphyxia

Prolonged labor and meconium-stained liquor were the predominant risk factors reported in majority (57.8%) of the participants (42.2% and 15.6% of the neonates, respectively). Three participants had both risk factors. Other risk factors observed are depicted in Figure 1.

Apgar scores and modified Sarnat stages

Majority (33.3%) of the neonates, as classified by their 5-min Apgar scores, had mild asphyxia, followed by 28.9% and 20% with moderate and severe asphyxia, respectively. The rest (8.9%) had normal scores (i.e., >7).

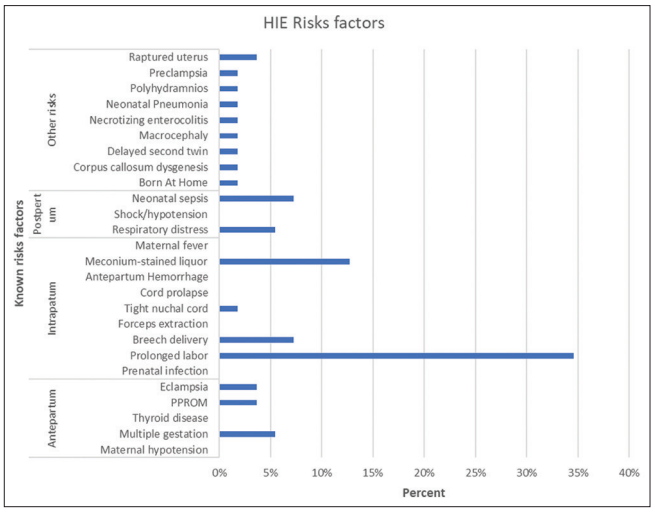

Figure 1: Hypoxic ischemic encephalopathy risk factors

As per the Modified Sarnat criteria, 44.4% of the neonates had Sarnat Stage II (moderate HIE), 37.8% had Stage 1 (mild HIE), while 17.8% had Stage III (severe HIE).

Spectrum of cranial ultrasound findings

Gray-white matter changes

Periventricular and/or deep white matter echogenicity was reported in 55.6% of the participants. There were no brain changes in 40% of the neonates. Thalamus and/or basal ganglia deep gray matter echogenic changes were the second common abnormal finding (31.1%) as shown in Figure 2.

Ultrasound grading for hypoxic ischemic encephalopathy severity

More than half (58%) of the participants had abnormal CUS findings consistent with HIE, where majority (28.8%) had moderate HIE, 26.7% had severe HIE, while only 2.2% had mild HIE. The rest (42.2%) did not show HIE-consistent CUS findings. The prevalence of all the specific HIE grades are depicted in Figure 3.

Color Doppler findings

Almost all (99.9%) the neonates with an abnormal RI range (<0.5 or >0.8) had abnormal CUS findings. Majority of the neonates (66.7%) had normal RI, as shown in Table 1.

Correlation of the Sarnat severity to the ultrasound findings, resistive index, and overall hypoxic ischemic encephalopathy grade

Abnormal US findings were more likely to be detected in Sarnat Stage III. Abnormal US findings were demonstrated in majority (87.5%) of the neonates with Sarnat Stage III,

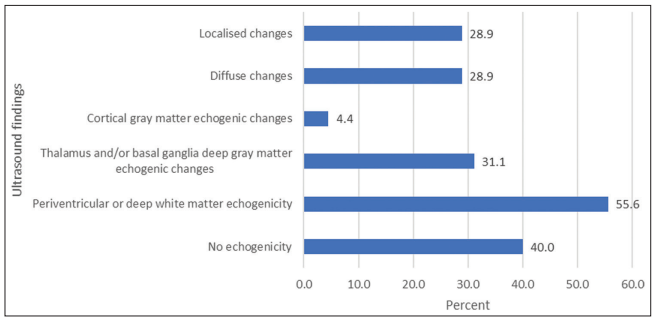

Figure 2: Spectrum of gray-white matter changes

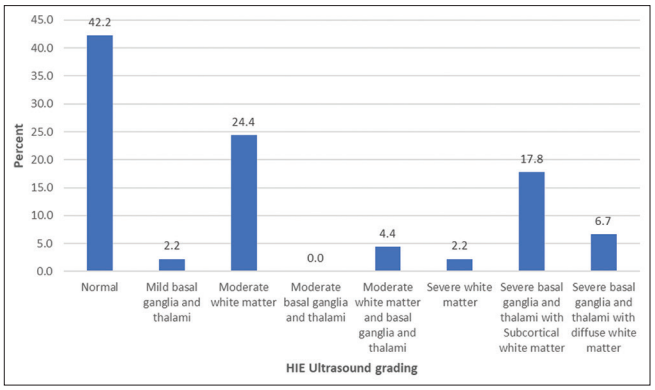

Figure 3: Hypoxic ischemic encephalopathy ultrasound grading (Grades 1 [normal] to Grade 8 [severe basal ganglia and thalami with diffuse white matter changes])

compared to 55% of the neonates with Stage II and 47.5% of Sarnat Stage I. A statistically significant trend toward severe HIE CUS findings was observed with worsening Sarnat scores, at 5% significance level (trend test $P = 0.039$).

The severity of HIE CUS grades was statistically significantly related to Sarnat Stages II and III ($P = 0.038$). The coefficient was 49.8% showing a strong correlation between the variables, as shown in Table 2.

Correlation of resistive indices to cranial ultrasound findings and hypoxic ischemic encephalopathy cranial ultrasound severity grades

Resistive indices to abnormal ultrasound findings

There was a strong correlation between abnormal RIs (<0.5 and >0.8) to the presence of abnormal CUS findings ($P = 0.003$), as shown in Table 3.

Resistive indices to the hypoxic ischemic encephalopathy severity

There was a positive correlation between abnormal RIs (<0.5 and > 0.8) to HIE severity ($P = 0.016$) as shown in Table 4.

Table 1: Color Doppler findings

Factors RI range	*n* (%)	CUS findings	
		Abnormal (%)	Normal (%)
Abnormal	15 (33.3)	14 (99.9)	1 (0.1)
Normal	30 (66.7)	12 (40.0)	18 (60.0)

CUS – Cranial ultrasound; RIs – Resistive indices

Table 2: Correlation of hypoxic ischemic encephalopathy cranial ultrasound grades to the modified Sarnat stages

Modified Sarnat stage	HIE CUS grades (Grade 1-8)			χ^2	df	*P*
	Mild	Moderate	Severe			
Moderate, severe	0	7	11	6.53	2	0.038
Mild	1	6	1			

χ^2 – Chi square test; df – Degree of freedom; *P* – *P* value (level of significance <0.05). CUS – Cranial ultrasound; HIE – Hypoxic ischemic encephalopathy

Table 3: Resistive indices to abnormal ultrasound findings

Factors		Ultrasound findings		X^2	df	*P*
RI Range	*n*	Abnormal	Normal			
Abnormal	15(33.3)	14(99.9)	1(0.1)	11.84	2	0.003
Normal	30(66.7)	12(40.0)	18(60.0)			

n-number; X^2 Chi square test; df- Degree of freedom: P- *P* value (level of significance<0.05)

DISCUSSION

Our study determined the CUS spectrum of findings among neonates admitted to the KNH NBU with a clinical diagnosis of perinatal asphyxia. Majority of the participants were male, and most of the mothers were below 35 years of age, which is similar to Tann *et al*.'s[14] study in Uganda with 63% of male participants and 87% of mothers under 35 years of age and Ugwu *et al*.'s[15] study in Nigeria which comprised 60% of male participants. Majority of the neonates were born via SVD and the rest via cesarean section, which is again similar to the findings from the study by Tann *et al*. with 66% of SVD rate. The weight range in this study was 2000–4000 g, which is similar to the findings from the Ugandan study by Tann *et al*., with 98% of the neonates weighing 2500 g and above.

Prolonged labor and meconium-stained liquor were the predominant risk factors for birth asphyxia in this study. Similar findings were reported by Ugwu *et al*. in Nigeria, where prolonged labor was a major risk factor in 51% of the neonates.[15] In contrast, a study in Iceland by Palsdottir *et al*. reported meconium-stained liquor and nuchal cord as the most common risk factors (50% and 41%, respectively).[16] Prolonged labor may not have been a major risk factor in Iceland study, likely due to better surveillance during labor.

Majority of the participants in this study scored either Sarnat Grade II (moderate asphyxia) (44.4%) or Grade III (severe) (37.8%), with only 17.8% Grade I (mild).

Table 4: Resistive indices to the hypoxic ischemic encephalopathy severity

HIE severity grading	RI range		χ^2	df	*P*
	Abnormal (<0.5 and >0.8)	Normal			
Normal (Grade 1)	1 (5.3)	18 (94.7)	24.72	12	0.016
Mild - severe HIE (Grades 2-8)	16 (57.1)	12 (42.9)			

χ^2 – Chi square test; df – Degree of freedom; *P* – *P* value (level of significance <0.05). RIs – Resistive indices; HIE – Hypoxic ischemic encephalopathy

This is similar to a study done in Lithuania by Ausrele *et al*.[17] and sub-Saharan African studies; This is similar to Ausrele *et al*. study in Lithuania[17] and to the Sub-Saharan Africa studies by Tann et al in Uganda and Ugwu et al in Nigeria. In the Tann et al study, moderate and severe HIE accounted for 89.7% of cases, while the same accounted for 61.8% of cases in the Ugwu et al study.[14,15]

Periventricular and deep white matter echogenicity was the most common CUS finding, accounting for 55.6% of the changes, whereas basal ganglia and/or thalamus deep gray matter echogenic changes accounted for 31.1%. These findings are consistent with the patterns of injury seen in term neonates, with a basal ganglia–thalamus pattern involvement seen in severe injury, a peripheral pattern involving the cortical–subcortical white matter in milder injury, and worsening involvement of the deep white matter tracts portending more severe injury.[10] Forty percent of the participants had no detectable brain changes, which is consistent with HIE findings where a good percentage of the affected brain may not demonstrate structural changes, for instance, Barseem *et al*. in Egypt reported normal findings in 48.5% of their participants. Similar findings have been reported in many other studies on HIE.[7,13,18]

We observed that abnormal US findings were more likely to be detected in Sarnat Stage III when compared to Sarnat Stages I and II. There was a trend toward severe HIE CUS findings with worsening Sarnat scores. A statistically significant correlation between moderate and severe Sarnat stages with the presence of abnormal CUS changes ($P = 0.038$) was also observed. While we could not find similar studies directly correlating these two outputs, many authors have shown a correlation between clinical neurological deficits and CUS HIE severity.[17,19-23] A study in Lithuania observed that in the presence of watershed, thalamus, and basal ganglia injury, CUS showed 100% sensitivity in predicting spastic quadriparesis (85% specificity, 33% positive predictive value [PPV], 100% negative predictive value [NPV], and 100% sensitivity) in predicting long-term severe mental development (80% specificity, 31% PPV, and 100% NPV).[17] Martinez-Biarge *et al*. showed a strong association between the severity of basal ganglia and thalamus involvement and the severity of motor impairment and its ability to predict death and specific motor outcomes.[20]

Abnormal RIs (<0.5 or >0.8) were a strong indicator of the presence of abnormal brain changes of HIE, with a significant correlation to mild, moderate, and severe HIE grades of US brain changes. This may indicate that RI value may predict HIE severity. The majority of the neonates (66.7%), however, had normal RIs. Similar findings have been reported by Barseem *et al*., Kirimi *et al*., and Liu *et al*.[18,24] Liu *et al*. further showed later brain death at RI values >1.0.[25] Kirimi *et al*. showed that neonates with significantly elevated RI at <12 h after birth developed cerebral palsy and neural and mental impairment at 1 year of age.[26] Barseem *et al*. also demonstrated Neurodevelopmental impairment at 1 year of age for neonates who had significantly elevated RI (>0.70) at <12 h of birth.[21] Kudreviciene *et al*. demonstrated that neonates with reduced RIs (evaluated within 24 h of birth) had severe mental retardation at 1 year of age.[17]

To achieve the best outcomes in perinatal asphyxia, early diagnosis and intervention is of extreme importance. The therapeutic window during which interventions may significantly influence brain damage is estimated at between 2 and 6 h by many studies.[6] Advances in supportive care include therapeutic hypothermia; optimizing neonatal resuscitation protocols (such as delayed cord clumping prior to routine cooling); and the potential use of neuroprotective agents such as magnesium, nitric oxide, and calcium channel blockers among others.[27]

Limitations

We are cognizant of the study limitations, key of which was the different neonatal age at imaging. The different timing could account for some of the differences in the conspicuity of abnormal echogenicity in the brain.

CONCLUSION

This study showed that prolonged labor and meconium-stained liquor were the predominant risk factors for HIE. Periventricular and deep gray matter echogenicity was the most common sonographic finding in term neonates with HIE. The modified Sarnat grade severity correlated significantly with sonographic HIE

severity. The correlation between birth asphyxia severity and CUS was more robust in Doppler evaluation of the deep cerebral arteries. Our findings demonstrated that HIE clinical severity was associated with abnormal cerebral arterial RIs, which have been shown to be predictive of poor neurodevelopmental outcomes. Even though Sarnat staging has been shown to be valuable in the clinical grading of HIE, we observed significant CUS findings in neonates whose clinical HIE scores were mild to moderate. This observation suggests and reaffirms the need for brain imaging to evaluate HIE severity even where the clinical findings suggest otherwise. Imaging, therefore, remains of utmost importance in the ultimate assessment of the degree of encephalopathy in all degrees of perinatal asphyxia.

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Conflicts of interest

There are no conflicts of interest.

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