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CRANIAL ULTRASOUND ALTERATIONS IN PRETERM NEONATES AND CORRELATION WITH PERINATAL RISK FACTORS

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ABSTRACT

Introduction: Preterm infants are exposed to a wide spectrum of brain injuries, many of which may be clinically silent. This highlights the important role of cranial ultrasound screening in preterm neonates. This study aimed to detect brain injuries in preterm infants using cranial ultrasound during the first week after birth and to evaluate the association between brain injuries and perinatal risk factors. **Methods:** A cross-sectional analytical observational study was conducted in the Neonatal Intensive Care Unit (NICU) at Latakia University Hospital. The study included 76 preterm infants admitted to the NICU, who underwent cranial ultrasound according to inclusion criteria. Various abnormal cranial ultrasound findings were recorded, and the relationship between these findings and perinatal risk factors was examined. **Results:** Out of the 76 preterm infants, 47.4% had abnormal cranial ultrasound findings. The most common finding was intraventricular hemorrhage (47.2%), followed by periventricular white matter hyperechogenicity (27.8%), cerebral edema (16.7%), periventricular white matter hypoechogenicity (5.8%), and ventriculomegaly (2.8%). Abnormal cranial ultrasound findings were significantly associated with a birth weight less than 1500 grams (P=0.0001) and gestational age less than 32 weeks (P=0.02). There was also a significant correlation between abnormal ultrasound findings and respiratory distress syndrome (P=0.005), sepsis (P=0.003), and perinatal hypoxia (P=0.01). **Conclusion:** This study has confirmed the role of cranial ultrasound as an important tool for early detection of many types of brain injury that are considered major causes of later motor, behavioral, and cognitive disorders. It has also demonstrated a significant association between abnormal cranial ultrasound findings and factors such as gestational age, birth weight, respiratory distress syndrome, perinatal hypoxia, and sepsis.

KEYWORDS: Cranial ultrasound, prematurity, perinatal risk factors.

INTRODUCTION

The high rates of preterm births worldwide represent a serious public health concern, as they are associated with an increased risk of numerous early childhood health problems such as motor delay, cerebral palsy, lower intelligence quotient, behavioral disorders, as well as respiratory diseases especially asthma. Furthermore, complications of prematurity are considered the leading cause of death in children under five years of age.[1,2]

It is well known that the morbidity rate among preterm infants during the early postnatal period is higher than that of full-term infants. Morbidity nearly doubles for each week of gestational age below 38 weeks. Moreover, the mortality rate among preterm infants is three times higher compared to full-term infants.[3]

The high susceptibility to brain injury in preterm infants has been well documented and is attributed to both external and internal factors. External factors are linked to the harmful effects of perinatal morbidities on the brain, most notably: Respiratory Distress Syndrome (RDS), sepsis, seizures, necrotizing enterocolitis (NEC), hypoglycemia, and perinatal asphyxia. Internal factors, on the other hand, are associated with the lack of morphological and functional maturation of the brain structures according to gestational age.[4]

Preterm infants are more vulnerable to ischemic and hemorrhagic brain lesions, including intraventricular hemorrhage (IVH), germinal matrix hemorrhage (GMH), periventricular hemorrhagic infarction (PVHI), and white matter injuries particularly cystic periventricular leukomalacia (cPVL) all of which play a significant role in morbidity and mortality.[5]

Cranial ultrasound was introduced in the late 1970s and remains a fundamental diagnostic tool in neonatology to this day.[6]

Cranial ultrasound reveals most cerebral hemorrhagic lesions such as (intraventricular hemorrhage, parenchymal hemorrhage) and ischemic lesions in addition to cystic lesions, calcifications, ventriculomegaly, cerebral infarction, cerebral edema, major congenital or acquired structural malformations, and periventricular hyperechogenicity. It also plays an important role in the early diagnosis of ischemic-hypoxic encephalopathy and assessing its severity and predicting the prognosis.[7]

Cranial ultrasound (CUS) is considered a safe imaging technique that does not require anesthesia and can be performed bedside.[8]

The importance of preterm screening by cranial ultrasound is sustained by the observation that a considerable proportion of preterm infants with abnormal cranial ultrasound findings were clinically asymptomatic.[9]

MATERIALS AND METHODS

Study Design: Cross-sectional analytical observational study.
Study area: Neonatal Intensive Care Unit (NICU) at the University Hospital in Lattakia**.**
Study Period: May 2023 – May 2024.
Inclusion Criteria: all preterm infants (with gestational age less than 37 weeks) who underwent cranial ultrasound through the anterior fontanelle within the first week after birth.

Exclusion Criteria

Preterm infants with congenital anatomical malformations of the central nervous system.
Preterm infants who died before cranial ultrasound could be performed.
Incomplete data.

Study Methodology

Detailed information was collected on each preterm infant, including sex, gestational age, birth weight, and the presence of perinatal risk factors (neonatal sepsis, respiratory distress syndrome, necrotizing enterocolitis, hypoglycemia, seizures, and perinatal hypoxia). Cranial ultrasound was performed during the first week of life by an experienced neonatologist using a SIEMENS-ACUSON X300 ultrasound machine, cranial ultrasound findings were recorded and correlated with perinatal risk factors.

Statistical Analysis

Quantitative variables were presented as means with standard deviations, and qualitative variables were expressed as frequencies and percentages. The Chi-Square test was used to examine the association between qualitative variables. Results were considered statistically significant when the P value was less than 0.05.

RESULTS

The study sample included 76 preterm neonates, with gestational ages ranging from 25 weeks + 2 days to 36 weeks + 4 days, with a mean of 33.04 ± 2.5 weeks. Birth weights ranged from 775 to 2495 grams, with a mean of 1832.03 ± 445.49 grams. Males constituted 52.6% of the sample, and females 47.4%. No statistically significant association was found between sex and abnormal CUS findings, (P-Value=0.6).

Among preterm neonates with gestational age less than 32 weeks (n=21), 71.4% (n=15) had abnormal CUS findings, and 28.6% (n=6) had normal CUS findings. Whereas among preterm neonates with gestational age greater than 32 weeks (n=55), 38.2% (n=21) had abnormal CUS findings, and 61.8% (n=34) had normal CUS findings. Statistical analysis revealed a significant association between abnormal CUS findings and gestational age less than 32 weeks
(P-Value=0.02), as shown in Table (1).

Table (1): Distribution of CUS findings by gestational age in the study sample.

Gestational Age (weeks)	CUS Findings		P-Value
	Normal	Abnormal	
<28	0 (0%)	1 (100%)	
28-31.6	6 (30%)	14 (70%)	
32-33.6	10 (47.6%)	11 (52.4%)	**0.02**
34-36.6	24 (70.6%)	10 (29.4%)	

Among preterm infants with birth wieght less than 1500 grams (n=21), 90% (n=19) had abnormal CUS findings, and 10% (n=2) had normal CUS findings. Whereas among preterm infants with birth wight more than 1500 grams (n=55), 31% (n=17) had abnormal CUS findings, and 69% (n=38) had normal CUS findings. Statistical analysis showed a significant association between abnormal CUS findings and birth weight less than 1500 grams, as shown in Table (2).

Table (2): Distribution of CUS findings according to birth weight in the study sample.

Birth Weight (g)	CUS Findings		P-Value
	Normal	Abnormal	
<1000	1 (25%)	3 (75%)	**0.0001**
1000-1499	1 (5.9%)	16 (94.1%)	
1500-2499	38 (69.1%)	17 (30.9%)	

Among the abnormal CUS findings, intraventricular hemorrhage was the most common (47.2%), followed by periventricular white matter hyperechogenicity (27.8%), as shown in Table (3).

Table (3): Distribution of the 36 patients according to abnormal CUS findings.

Abnormal CUS Findings	Frequency n=36	Percentage (100%)
Intraventricular hemorrhage	17	47.2%
Periventricular white matter hyperechogenicity	10	27.8%
cerebral edema	6	16.7%
periventricular white matter hypoechogenicity	2	5.6%%
Ventriculomegaly	1	2.8%

Regarding the association between CUS findings and perinatal risk factors, there was a significant relationship between abnormal CUS findings and the following: respiratory distress syndrome, neonatal sepsis, and perinatal hypoxia, with statistically significant differences when P-Value < 0.05, as shown in Table (4).

Table (4): Distribution of CUS findings according to perinatal risk factors in the study sample.

Perinatal Risk Factors	CUS Findings		Total	P-Value
	Normal	Abnormal		
Neonatal Sepsis	29(47.4%)	10(25.6%)	39 (100%)	**0.003**
RDS	2 (13.3%)	13(68.7%)	15 (100%)	**0.005**
NEC	0 (0%)	2(100%)	2 (100%)	0.5
Neonatal Seizures	1 (50%)	1 (50%)	2 (100%)	0.9
Perinatal Asphyxia	2 (28.6%)	5 (71.4%)	7 (100%)	**0.01**
Hypoglycemia	0 (0%)	1 (100%)	1 (100%)	0.6
Others	6 (60%)	4 (40%)	10 (100%)	0.3

DISCUSSION

Cranial Ultrasound is the primary imaging method used in neonatal intensive care units (NICU) to assess the brain of neonates. While Ingale et al mentioned that cranial ultrasound has become a crucial diagnostic tool in modern neonatology to detect both normal anatomical findings and pathological changes in the neonatal brain, De Vries and Cowan suggested that cranial ultrasound and brain MRI are complementary methods to each other.[10,11]

In our study, the percentage of abnormal cranial ultrasound findings was 47.4 %, which is similar to the percentage reported in the study by Kinkar et al conducted in India in 2018, which included 100 preterm infants, where the percentage of abnormal cranial ultrasound findings was 47%.[12] On the other hand, in the study by Ballardini et al conducted in Italy in 2014, which included 724 preterm infants with gestational ages between 33 to 36 weeks, the percentage of abnormal cranial ultrasound findings was 13%.[13] This is lower than the percentage found in our study, which may be explained by the fact that the Ballardini study included preterm infants with a higher gestational age.

Intraventricular hemorrhage was the most common abnormal cranial ultrasound finding in our study, with a percentage of 47.2%. This was followed by periventricular white matter hyperechogenicity, with a percentage of 27.8%, which is similar to the results reported by Kinkar et al., where intraventricular hemorrhage was the most common abnormal cranial ultrasound finding at a rate of 40.4%, followed by periventricular white matter hyperechogenicity at 21.2%.[12] On the other hand, in the study by Jha et al conducted in India in 2017, periventricular white matter hyperechogenicity was the most common abnormal cranial ultrasound finding.[14]

In our study, a statistically significant relationship was observed between abnormal cranial ultrasound findings and both gestational age less than 32 weeks and birth weight less than 1500 grams ($p = 0.02$, $p = 0.001$, respectively). This aligns with the study by Aga et al conducted in Egypt in 2012, which included 80 preterm infants, and confirmed an increase in the percentage of abnormal cranial ultrasound findings in preterm infants with gestational ages less than 32 weeks and birth weights under 1500 grams, especially intraventricular hemorrhage.[15] This can be explained by the presence of

the germinal matrix, which is the primary source of intraventricular hemorrhage in preterm infants, as it is characterized by high blood perfusion, fragile blood vessels, and insufficient differentiation of the supporting structures, in addition to

The disorder of autoregulation of cerebral blood flow.
Our study showed a statistically significant relationship between Respiratory Distress Syndrome (RDS) and abnormal cranial ultrasound findings (P = 0.005), particularly intraventricular hemorrhage. This finding is consistent with the study by Fumagalli et al conducted in Italy in 2015.[16] This can be explained by the rapid changes in intrathoracic pressure caused by RDS, which affect cerebral venous pressure and cerebral blood flow.[17]

Preterm infants are more susceptible to sepsis compared to full-term infants due to the insufficient maturity of their immune systems, as well as the need for prolonged hospitalization and multiple medical interventions. Our study showed a statistically significant relationship between sepsis and abnormal cranial ultrasound findings in preterm infants (P = 0.003), which is consistent with the study by Ghoor et al conducted in South Africa in 2017.[18]

Sepsis predisposes to intraventricular hemorrhage through several mechanisms. It triggers an inflammatory response in which a range of factors, such as cytokines and other mediators, are released, causing disturbances in the coagulation system and a reduction in platelet count. Additionally, the instability of systemic arterial pressure in severe sepsis leads to cerebral blood flow disruption, thereby increasing the likelihood of hemorrhage.[17]

Sepsis also plays a role in white matter injuries through inflammatory mediators that cause a blockade in the maturation of oligodendrocyte precursor cells, leading to defects in myelin and hindering brain development programs."

Our study also revealed a statistically significant relationship between perinatal hypoxia and abnormal cranial findings (P = 0.01), particularly cerebral edema and intraventricular hemorrhage. This aligns with the studies of Kinkar et al[12] and Ballabh et al conducted in 2014[17], where hypoxia leads to anaerobic metabolism, metabolic acidosis, and disruption of the Na, K, ATPase system. This, in turn, causes disturbances in osmotic regulation across the neuronal cell membrane, resulting in the accumulation of sodium and water within the cells and the onset of cerebral edema.[20]

Additionally, hypoxia predisposes to intraventricular hemorrhage by promoting the increased secretion and activation of vascular endothelial growth factor (VEGF) and angiopoietin-2(ANGPT-2), in the germinal matrix. These factors, in turn, stimulate the rapid formation of new blood vessels that are abundant, fragile, and immature, thereby increasing the susceptibility to hemorrhage.

Declarations
Ethical approval and consent to participate: Ethical approval to study was obtained from the Scientific Research Ethics Committee at Latakia University in accordance with the Declaration of Helsinki.

Consent for publication: Not applicable.
Availability of Data and Materials: All the data generated or analyzed during this study are included in this published article. The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Competing interests: None.

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Author Contribution: zeinab alia, collected the data, checked the quality of the data collection, analyzed and interpreted the data, designed and coordinated the study, undertook and checked the quality assessment, produced the first draft of the manuscript, wrote and edited the manuscript and approved the final manuscript before submission. Oday jouni and mazen ghalia were the supervisor of the project; undertook and checked to the quality assessment, checked the quality of the collected data; analyzed and interpreted the data; checked the quality assessment; edited the manuscript and approved the final manuscript before submission.

CONCLUSION

This study confirmed the role of neonatal cranial ultrasound as an important diagnostic tool for the early detection of various brain injuries, which are significant causes of later motor, behavioral, and cognitive disorders. Early detection allows for timely intervention, thereby improving both short- and long-term clinical outcomes. The study also highlighted a significant relationship between abnormal cranial ultrasound findings and factors such as gestational age, birth weight, respiratory distress syndrome, sepsis, and perinatal hypoxia.

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