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Neonatal and obstetric risk factors are associated with the increased risk of neonatal intracranial hemorrhage

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Abstract

Background

In newborns, intracranial hemorrhage (ICH) is an acquired lesion with a high risk of morbidity, mortality, and long-term neurodevelopmental outcomes. Despite major improvements in newborn care and greater preterm infant survival in recent decades, ICH remains a serious concern. This study aimed to determine the prevalence of ICH in newborns and the various obstetric and neonatal risk factors linked to ICH development. This case-control study was conducted throughout the period from June 2017 to December 2017.

Patients and methods

This case-control research involved 240 infants admitted to Cairo University's Obstetrics and Gynecology Hospital's Neonatal Intensive Care Unit (NICU). We took detailed history, such as the maternal, obstetric, and delivery circumstances, laying stress on maternal and obstetric ICH risk factors. The general condition was assessed at 1 and 5 min using the Apgar score. Ballard score was used to determine gestational age. The birth weight was measured. A thorough clinical examination with a focus on neurological evaluation in accordance with the Sarnat phases was performed. The authors used cranial ultrasonography for imaging (CUS).

Results

Of 240 neonates, 78 neonates developed ICH (32.5%). Overall, 42.9% were males and 21.1% were females. Intraventricular hemorrhage was the commonest one (24.2%), and grade one intraventricular hemorrhage represented 13.4%. The prevalence of asymptomatic cases with ICH was 66.7%. The neonatal risk factors associated with increased ICH risk were prematurity, representing 67.4%; pneumothorax, representing 76.9%; and trauma, representing 77.3%. The sensitivity of CUS for detection of ICH was 84.6%, and the specificity of CUS was higher, representing 97.5%. Overall, 41.03% of ICH cases appeared on the first day of life and 76.9% on the third day by CUS.

Conclusion

The prevalence of asymptomatic cases with ICH was 66.7%. Certain neonatal risk factors are associated with increased risk of ICH such as birth weight, sex, gestational age, mode of delivery, and obstetric risk factors. CUS can be considered as a specific and sensitive indicator for the occurrence of ICH.

Keywords: Cranial ultrasound, gestational age, intracranial hemorrhage, intraventricular hemorrhage, neonatal intensive care unit, premature rupture of membrane

INTRODUCTION

Bleeding within the skull can occur external to the brain into the epidural, subdural, or subarachnoid space; into the parenchyma of the cerebrum or cerebellum; or into the ventricles from the subependymal germinal matrix (GM) or choroid plexus [1].

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Of all types of intracranial hemorrhage (ICH), germinal matrix-intraventricular hemorrhage (GM-IVH) is the most common and distinctive pathology [2]. Periventricular-intraventricular hemorrhage (PIVH) is a major cause of neurological disabilities in preterm newborns [3].

The incidence of IVH varies inversely with gestational age (GA), with an overall incidence of 15–42%, whereas severe IVH develops in 7–16% of VLBW infants [4]. Approximately 35% of VLBW infants with IVH develop posthemorrhagic hydrocephalus (PHH), and 15% of VLBW infants with IVH require intervention [5]. In Korea, however, no nationwide data for the incidences of IVH and PHH have been reported to date. IVH is graded based on the Papile classification system, but the grading of PHH is not yet standardized. Although some studies have suggested using the criteria for ventricular dilatation [6].

IVH occurs in preterm infants; however, the occurrence of this event is less frequent in term neonates. The main source of IVH in term neonates is choroid plexus; the most common clinical symptoms include seizure and poor feeding, and one-third of IVH events are graded as III–IV. Most affected neonates are discharged from NICU without CNS complication, ~10% need to refer to surgical interventions, and death occurred in a few neonates [7].

Although IVH is primarily specified to the preterm condition that might be detected in half of the preterm neonates, some studies have reported the evidence of IVH in about 3.5–5.0% of term neonates [1]. This discrepancy can be owing to the greater maturity of the brain at term and a lower rate of underlying risk factors predisposing to bleeding, such as coagulative disorders [8]. Although the main source and etiology of IVH in about half of the term neonates remained unknown, risk factors among mothers such as preeclampsia, urogenital tract infections, and chorioamnionitis and some neonatal risks including asphyxia, traumas, vitamin K deficiency, thrombocytopenia, and sinovenous thrombotic events have a major role in appearance of IVH [9].

IVH is uncommon in term newborns. Asphyxia and hypothermia have been mentioned separately as possible risk factors of IVH as they might cause fluctuations of cerebral blood flow [10].

Aim

The aim was to find out how common IVH is and the many obstetric and neonatal risk factors linked to ICH development.

PATIENTS AND METHODS

From June to December 2017, participants in this case–control study were hospitalized in the Neonatal Intensive Care Unit (NICU) at Cairo University’s Obstetrics and Gynecology Hospital. The neonates in this study were separated into two groups: (1) cases involving the ICH group; and (2) cases that do not belong to the ICH group.

Each patient’s parents signed an informant written consent form.

Inclusion criteria:

The following were the inclusion criteria:

- (1) Preterm and full-term neonates.

Exclusion criteria:

The following were the exclusion criteria:

- (1) Extreme low-birth-weight newborns (<1000 g of birth weight).
- (2) Congenital malformation of the brain.
- (3) Neonatal sepsis such as meningitis and encephalitis.

Methods

All neonates were subjected to the following:

- (1) Thorough medical history taking, including maternal, obstetric, and delivery circumstances, with a focus on maternal and obstetric ICH risk factors.
 - (a) The Apgar score at 1 and 5 min was used to assess the general condition [11], and assessment of GA was done using the Ballard score [12]
 - (b) Anthropometric measurement (birth weight and head circumference).
- (2) Thorough clinical examination laying stress on neurological examination, according to Sarnat stages [13]. The assessment of the need for ventilator support was done.
- (3) Investigations: complete blood count, C-reactive protein, and arterial blood gases.

Cranial ultrasound

Trans-cranial ultrasound was used via anterior fontanel using GE LOG IQ3 probe, 8 MHz probe, 8 C (convex), 8 L (linear) (General Electric Company, 5 Necco Street, Boston, MA 02210).

PIVH was graded into four grades according to the Papile grading [14]:

Grade I: isolated GMH (no PIVH).

Grade II: PIVH without ventricular dilatation.

Grade III: PIVH with ventricular dilatation.

Grade IV: PIVH with parenchymal hemorrhage.

Statistical analysis

The data were coded, entered, and processed using SPSS (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp). The level *P* less than or equal to 0.05 was considered the cutoff value for significance.

Ethical considerations

All studies were completed according to local approval of the institutional review Board of Cairo University School Of Medicine. Informed consent for participation in this study was obtained from patients of all investigated cases in agreement with the declaration of Helsinki.

RESULTS

This case–control study was conducted on 240 neonates. They were admitted to the NICU of Gynecology and obstetrics Hospital Cairo University Hospital during the study period from June 2017 to December 2017. Overall, 78 of them (32.5%) represented the patient group, in which 54 cases (42.9%) were males and 24 cases (21.1%) were females. A total of 60 cases (44.1%) delivered via cesarean section and 18 cases (17.3%) vaginally. Their mean GA was 32.82 weeks, and their mean birth weight was 1.95 kg. Their mean Apgar score at 1 min was 2.00 and at 5 min was 3.38. A total of 162 individuals were without ICH as the control group, in which 72 of them (57.1%) were males and 90 were (78.9%) females. Overall, 76 of them (55.9%) delivered via cesarean section and 86 (82.7%) vaginally. Their mean GA was 36.33 weeks, and their mean birth weight was 3.03 kg. Their mean Apgar score at 1 min was 5.75 and at 5 min was 8.56 (Figs. 1 and 2).

The percentage of cases with ICH was 32.5% (78 cases), in which IVH was the commonest, representing 24.2% (58 cases), SAH was 2.5% (six cases), SDH was 2.5% (six cases), and IPH was 3.3% (eight cases). Grade one IVH was the commonest, representing 13.4% (32 cases), grade II was 4.2% (10 cases), grade III was 4.2% (10 cases), and grade IV was 2.5% (six cases) (Fig. 3).

Pneumothorax, preterm, trauma, nonvertex presentation, ventilatory use, reduced blood pressure, and elevated CO₂ levels are all related with an increased risk of ICH in neonates. (Tables 1 and 2).

The neurological symptoms were discovered in 33.3% of cases with ICH in the current study, whereas 66.7% were asymptomatic (Table 2).

Cases with ICH showed significant differences in all blood gases parameters in the form of acidosis, hypoxia, hypercarbia, and low bicarbonate in comparison with the control group (Table 3).

There was a significant negative correlation on studying the correlation between birth weight, GA, and ICH (Table 4).

Logistic regression analysis was performed to identify the predictor factors. It demonstrated that GA and obstetric risk

factors were the most predictor factors for ICH ($P < 0.05$). The risk of ICH was nearly sixfold in the group with obstetric risk factors compared with those without obstetric risk factors, with hazard ratio of 6.11, 95% confidence interval (CI): 2.12–17.6, $P = 0.001$, and fivefold for GA less than 34 weeks than those greater than 34 weeks GA, with hazard ratio of 5.06, 95% CI of 1.82–14.08, $P = 0.002$ (Table 5).

The mortality rate was 33.3% in cases with ICH, whereas in the control group was 14.8%. On studying cranial ultrasonography (CUS) finding, it was found that 41.03% of cases of ICH appeared on the first day of life, 76.9% appeared on the third day of life, and 84.6% appeared at 1 week. On discharge, it was found that 80.8% of cases of ICH were resolved on CUS, and 19.2% of cases showed changes of squeals. The sensitivity of CUS for detection of ICH was 84.6%. The specificity of CUS was higher, representing 97.5%, and the positive predictive value of CUS for detection of ICH was 94.3% (Figs. 4–8: CUS of ICH).

DISCUSSION

Regarding the GA, we found a highly significant lower GA among cases with ICH ($P < 0.001$). This agrees with Lee *et al.* [3] who reported that lower GA was associated with a greater risk of high IVH occurrence, and the same relation was shown by Miranda [15].

In this study, it was found that there was a significantly lower birth weight among cases with ICH than the control group ($P = 0.01$). This finding was in agreement with the study done by Brouwer *et al.* [16] who was found that birth weight less than or equal to 1200 g was associated with PIVH. The same relation was shown by Mohamed and Aly [17].

Regarding the Apgar score, it was found that there was a highly significant lower Apgar score at one minute and 5 min among cases with ICH ($P < 0.001$). This finding was in agreement with Baumert *et al.* [18] who reported that a lower Apgar score was associated with a greater risk of high IVH occurrence.

On studying the sex relation to ICH, it was found that the male sex showed a significantly higher rate of ICH than female sex ($P = 0.01$), in which 52.5% of total studied newborns were males, and 42.9% of them had ICH, whereas 47.5%

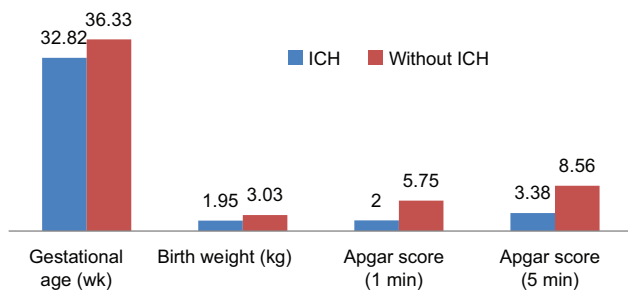


Figure 1: Gestational age, birth weight, Apgar score.

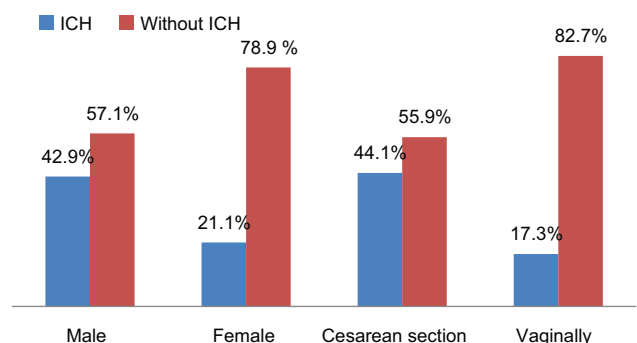


Figure 2: Sex, Mode of delivery (MOD) among patient and control group.

Table 1: Neonatal risk factors among cases with ICH and control group

	Control group [n (%)]	Cases with ICH [n (%)]	χ^2	P
Prematurity	28 (32.6)	58 (67.4)	37.30	<0.001**
Pneumothorax	12 (23.1)	40 (76.9)	29.86	<0.001**
Trauma	10 (22.7)	34 (77.3)	24.62	<0.001**
Nonvertex presentation	36 (40.0)	54 (60.0)	24.83	<0.001**
Ventilatory use	44 (27.2)	44 (56.4)	9.70	0.002**
SBP (mean±SD)	67.02 (3.08)	51.23 (1.47)	t-test: 23.72	<0.001**
DBP (mean±SD)	43.94 (3.30)	33.72 (2.06)	t-test: 14.32	<0.001**
Increase CO ₂ (mean±SD)	37.21 (7.21)	61.85 (4.16)	t-test: 15.88	<0.001**

**Highly significant. ICH, intracranial hemorrhage; SBP, systolic blood pressure; DBP, diastolic blood pressure.

Table 2: Neurological signs among cases with ICH and control group

	Control group [n (%)]	Cases with ICH [n (%)]	χ^2	P
Negative	136 (83.95)	52 (66.7)	4.63	0.03*
Positive	26 (16.05)	26 (33.3)		

*Significant. ICH, intracranial hemorrhage.

Table 3: Blood gases parameters among cases with ICH and Control group

	Control group Mean±SD	Cases with ICH Mean±SD	t-test	P
pH	7.32±0.08	7.12±0.18	4.63	<0.001**
PCO ₂ (mmHg)	37.21±7.21	61.85±4.16	13.88	<0.001**
PO ₂ (mmHg)	58.26±4.75	33.40±3.36	20.05	<0.001**
HCO ₃ (mEq/L)	22.21±1.80	16.71±0.90	12.81	<0.001**
Base deficit	5.69±1.26	16.14±3.78	12.75	<0.001**

**Highly significant. ICH, intracranial hemorrhage.

Table 4: Correlation between birth weight, gestational age, and ICH

	r	P
Birth weight	-0.672	0.01*
Gestational age	-0.730	<0.001**

*Significant, **Highly significant. ICH, intracranial hemorrhage; r, correlation.

Table 5: Predictors of ICH

	P	HR	95.0% CI
Sex	0.18	1.89	0.75-4.75
Mode of delivery	0.09	2.34	0.88-6.19
Obstetric risk factors	0.001**	6.11	2.12-17.60
Gestational age	0.002**	5.06	1.82-14.08

**Highly significant. Bold Values, Obstetric risk factors and gestational age are highly significant predictors for ICH; CI, confidence interval; HR, hazard ratio; ICH, intracranial hemorrhage.

were females, and 21.1% from them had ICH. This finding was in agreement with Ou-Yang *et al.* [19] who found that the IVH was significantly higher in males compared with female neonates.

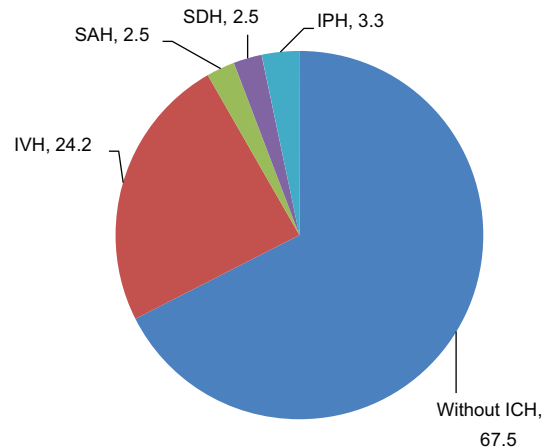


Figure 3: Frequency distribution of types of intracranial hemorrhage.

In the present study, of 240 neonates in NICU, 78 neonates developed ICH (32.5%). This was in agreement with the study done by Zakhary *et al.* [20], who reported that 24% developed ICH.

On studying the different types of ICH, it was found that 24.2% had IVH, 2.5% had SAH, 2.5% had SDH, and 3.3% had IPH, where IVH was the commonest. In agreement with our finding, a study done by Lee *et al.* [3] found that PV-IVH was 27.8%.

On studying the frequency of different grades of IVH, it was found that 13.4% had grade I, 4.2% had grade II, 3.3% had grade III, and 3.3% had grade IV. This was in agreement with Lee *et al.* [3], who found that 79.7% had grade I IVH, 6.9% grade II, 4.8% grade III, and 8.6% grade IV.

There are certain neonatal factors that are associated with increased risk of ICH, including pneumothorax, prematurity, trauma, nonvertex presentation, ventilatory use, lower blood pressure, and increased CO₂. These findings were in agreement with Crowther *et al.* [21] who stated that hypercarbia and hypotension were associated with PIVH.

Neurological symptoms were discovered in 33.3% of cases with ICH in the current study, whereas 66.7% were asymptomatic. This finding was consistent with that of Rooks *et al.* [22], who discovered a significant frequency of ICH in

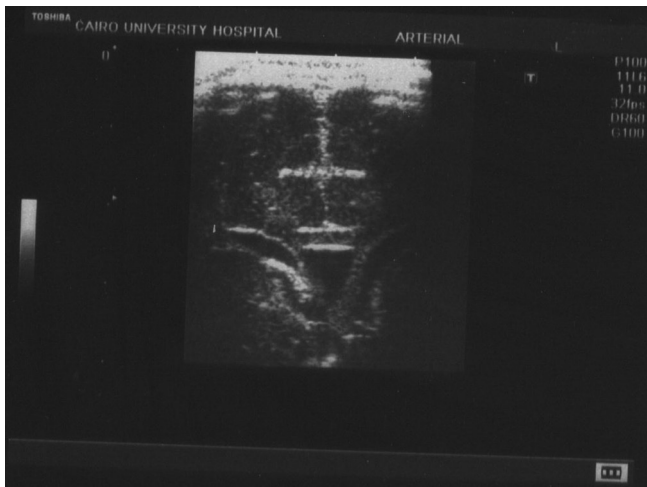


Figure 4: Right intraventricular hemorrhage (grade I), left intraventricular hemorrhage (grade II).

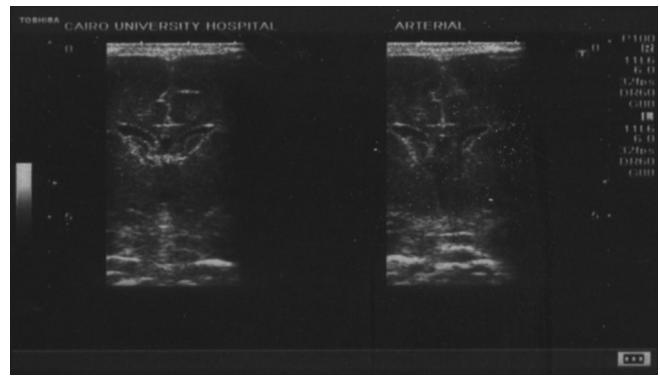


Figure 5: Grade II intraventricular hemorrhage.



Figure 6: Grade III intraventricular hemorrhage.

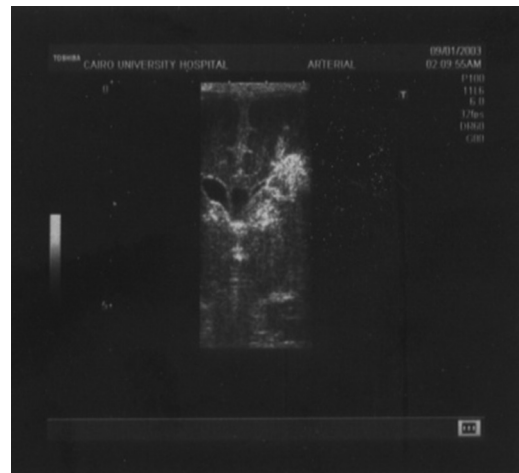


Figure 7: Grade IV intraventricular hemorrhage.

asymptomatic neonates and that ICH causes more subtle harm to the developing brain.

On studying the correlation between birth weight, GA and ICH, it was found that there was a significant negative correlation. These findings were in agreement with Kadri *et al.* [23], who stated that the incidence of IVH among preterm neonates was inversely related to the weight and the age of the newborns. Brouwer *et al.* [16] found that birth weight less than 10th percentile was more at risk for ICH. Miranda [15] found that the incidence of IVH increases as the GA decreases; higher grade hemorrhages occurred more frequently in low-birth-weight neonates.

Multivariate logistic regression analysis was performed to identify the predictor factors; it was demonstrated that GA and obstetric risk factors were the most predictor factors for ICH ($P < 0.05$). The risk of ICH was nearly sixfold in the group with obstetric risk factors compared with those without obstetric risk factors, with hazard ratio of 6.11, 95% CI of 2.12–17.6, $P = 0.001$, and fivefold for GA less than 34 weeks than those greater than 34 weeks GA, with

hazard ratio of 5.06, 95% CI of 1.82–14.08, $P = 0.002$. These findings were in agreement with a study done by Roze *et al.* [24] who was found that GA and maternal intrauterine infection were predictors, with hazard ratio of 12.2, 95% CI of 1.2–127.0, $P = 0.04$. The same relation was shown by Khodapanahandeh *et al.* [25].

On studying CUS finding, it was found that 41.03% of cases of ICH appeared on the first day of life and 76.9% appeared on the third day of life. These findings were in agreement with Volpe [2], who stated that postnatally, most hemorrhage occurs when the neonate is younger than 72 h, with 50% hemorrhage occurring on the first day of life. The extent of hemorrhage is greatest when the neonate is aged ~5 days.

The sensitivity of CUS for detection of ICH was 84.6%, the specificity of CUS was higher, representing 97.5%, and the positive predictive value of CUS for detection of ICH was 94.3%. This finding was in agreement with Khan *et al.* [26] who stated that CUS examination provides a relatively sensitive and highly specific means of detecting IVH. CUS is not reliable in the detection of nonmatrix-related hemorrhage. Computed tomography was found to be more sensitive in detecting extra-axial hemorrhage, and computed tomography was also better in detecting nonmatrix-related IPH.



Figure 8: Mild frontal subdural collection.

In the present study regarding discharge, it was found that 80.8% of cases of ICH were resolved on CUS, and 19.2% of cases showed changes of squeals. This finding was in agreement with Roze *et al.* [24] who found that PVHI was seen in 10–15% of preterm infants with GMH. Lee *et al.* [3] found that PV-IVH is one of the major causes of the development of neurological impairment and the incidence ranges from 15 to 40%.

In the present study, it was found that the mortality rate of total neonates was 20.8%. Overall, 33.3% occurred among cases with ICH, in which the higher mortality rate of 41.4% was found in cases with IVH and 50% in IPH ($P = 0.001$). Gomella [27] reported that the mortality rate in cases with mild to moderate PIVH was 5–10%, 20% with severe PIVH, and 50% with severe PIVH and parenchymal involvement. Brouwer *et al.* [16] reported 24.5%, and Lee *et al.* [3]. reported 35.6%.

In this study, blood gases parameters showed a statistically significant difference between the patient and control groups ($P < 0.001$), especially hypoxia, hypercarbia, and acidosis among cases with ICH. This finding was in agreement with Khodapanahandeh *et al.* [25], who reported that hypoxia hypercarbia was associated with PIVH. Roze *et al.* [24] reported that the perinatal and neonatal risk factors, including umbilical cord PH less than 7.1, increase the risk of ICH. The same relation was shown by Lee *et al.* [3].

CONCLUSION

The prevalence of asymptomatic cases with ICH was 66.7%. There are certain neonatal risk factors that are associated with increased risk of ICH such as birth weight, sex, GA, mode of delivery, and obstetric risk factors. CUS can be considered as a specific and sensitive indicator for the occurrence of ICH.

Recommendations

Good perinatal care and avoidance of instrumental delivery should be done. Routine screening using CUS should be recommended for all infants born at 34 weeks of gestation or earlier and for all VLBW infants (<1500 g of birth weight).

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Conflicts of interest

There are no conflicts of interest.

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