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Prognostic factors of the developmental outcome in neonates after hypoxic ischemic encephalopathy

Sana Abdulrazzaq Ibrahim*

Kawes Omer Zangana**

Abstract

Background and objective: The objectives of this study were to identify the etiologic profile and neurodevelopmental outcome of hypoxic-ischemic encephalopathy, and determine the usefulness of brain imaging to predict neurodevelopmental outcome.

Method: A prospective cross-sectional hospital based study was done on fifty term neonates admitted in the neonatal care. All the neonates included in the study were born on term (≥37 weeks of gestation) with perinatal asphyxia, admitted to the neonatal intensive care unit during the study period. All neonates included in the study underwent the first cranial ultrasonography at 6 month. Follow up of neurodevelopmental examination was done at 6 months of age, to determine the relationship between prognosis and the staging of encephalopathy with imaging methods.

Results: A total of 50 newborns enrolled in the current study with a mean APGAR Score ± S.D of 4.1 at first minute and 6.5 at fifth minutes consecutively. More than half of the mothers were primigraivda (64%), and most of them had normal vaginal delivery (76%) and 62% of them had prolonged labour. The majority (82%) of the babies had delayed initial crying after birth and 30% with abnormal brain ultrasonography. Half of the newborns (54%) had poor outcome as developmental delay.

Conclusions: This study showed a significant relationship between low APGAR score and perinatal asphyxia. This scoring system is based on clinical evaluation, brain imaging and prognosis or neurodevelopmental delay. Most of infants with abnormal brain ultrasonography at 6 months, had developmental delay while those of normal brain imaging had favorable outcome.

Keywords: Perinatal asphyxia; Developmental outcome; Brain ultrasonography.

* MBChB, KBMS Trainer pediatrics, Raparin Pediatric Hospital, Erbil, Iraq. Corresponding author: Sana Abdulrazzaq Ibrahim.

Email: sanaabdulrazzaq647@gmail.com

** Pediatric Assistant Professor, College of Medicine, Hawler Medical University, Erbil, Iraq

Introduction

Perinatal asphyxia is defined as the failure of the newborn to initiate and maintain adequate respiration after birth. It's a common and serious neonatal problem globally and it significantly contributes to both neonatal morbidity and mortality. According to the World Health Organization (WHO), between 4 and 9 million newborns develop birth asphyxia each year. Of those, an estimated 1.2 million die and at least the same number develop severe consequences, such as epilepsy,cerebral palsy and developmental delay[1].Perinatal asphyxia is estimated to be the fifth largest cause of under-five child deaths (8.5%), after pneumonia, diarrhea, neonatal infections and complications of preterm birth[2]. Asphyxia is the combination of the decrease in oxygen supply (hypoxia) and blood supply (ischemia) leads to a cascade of biochemical changes inside the body. These events lead to neuronal cell death and brain damage. Continuous asphyxia will also lead to multiple organ system dysfunctions[3]. The American College of Obstetricians and Gynecologists and the American Academy of Pediatrics assign a neonate to be asphyxiated if the following conditions are fulfilled: Umbilical cord arterial pH <7; Apgar score of 0-3 for longer than 5 min; neurological manifestations (e.g: seizures, coma, or hypotonic)and multisystem organ dysfunction,e.g:Cardiovascular,Gastrointestinal, hematological, pulmonary or renal system[4].Susceptibility of various organs to hypoxia varies depending on the gestational age. The newborn brain is generally resistant to hypoxia, but the process of auto regulation is not, loss of autoregulation leads to development of ischemia as a result of perinatal asphyxia[5].Classification system of Sarnat developed in1976 [6] is still widely used and is basis for most modern classification systems. According to the Sarnat system children are assigned a score of 1, 2 or 3 (1=mild NE; 2= moderate NE; 3= severe NE). Stage 1 lasts less than 24 hours and is characterized by hyperalertness, uninhibited Moro and stretch reflexes, sympathetic effects and a normal EEG. Stage 2 is marked by obtundation, hypotonia, strong distal flexion and multifocal seizures. Infants with the most severe stage of neonatal encephalopathy (stage 3) are stuporous and flaccid, and brain stem and autonomic functions are suppressed. The EEG shows abnormal patterns of brain activity[7].These

Encephalopathy scores have often been used to predict neurodevelopmental outcome[8]. The classification method of Sarnat and Sarnat has commonly been used to rapidly and correctly establish the severity of hypoxic ischemic encephalopathy. It can be suggested that patients with mild hypoxic ischemic encephalopathy are more likely to have better prognosis[9]. The objectives of this study were to identify the etiologic profile and neurodevelopmental outcome of hypoxic-ischemic encephalopathy (HIE), and determine the usefulness of brain imaging to predict neurodevelopmental outcome.

Patients and methods

This is a prospective observational study conducted from the first of November 2018 to first of May 2019 on 50 term neonates who experienced clinical neonatal encephalopathy and were admitted to neonatal care unit in both Raparin Pediatric Teaching Hospital and Maternity Teaching Hospital, Erbil city, Kurdistan region, Iraq.All the neonates included in the study were born on term (≥37 weeks of gestation) with perinatal asphyxia, were admitted to the neonatal intensive care unit during the study period and followed up after 6 months of age. We included infants with evidence of a diffuse cerebral hypoxic insult that included: Severe metabolic acidemia (pH <7.0) on the umbilical cord or first neonatal blood sample, 5-minute Apgar score of <7, fetal distress (abnormal fetal heart rate<100beat /minute or meconium-stained amniotic fluid), neonatal seizures within the first 24 hours after delivery , need for assisted ventilation (mask/balloon or intubation),encephalopathy (lethargy/stupor, hypotonia and abnormal reflexes including an absent or weak sucking), and multiple organ dysfunction. Patients fulfilling at least two of the clinical findings were enrolled[9-10]. The patients enrolled were evaluated based on a number of factors which were; the presence of a medical condition in the mother during pregnancy, mode of delivery, APGAR scores, birth weight, meconium stained amniotic fluid, seizure onset age, clinical findings, and modified Sarnat hypoxic ischemic encephalopathy stage. Neonates with a gestational age <37 weeks, and neonates with intrauterine infections, trauma, central nervous system abnormalities, chromosomal abnormalities, or metabolic disorders were excluded. None of the neonates were treated with

hypothermia. All neonates included in the study underwent the first cranial ultrasonography at 6 months of age looking for any formation of cystic lesions of brain parenchyma, progressive ventricular dilatation and brain atrophy, with follow up of neurodevelopmental outcome to evaluate long-term prognosis for neonates diagnosed with hypoxic ischemic encephalopathy, and to determine the relationship between prognosis and the staging of encephalopathy and imaging methods.The developmental outcomes of infants were assessed by the Denver Developmental Screening Test ll. The test is appropriate for ages between 0 and 72 months, and evaluates fine motor, gross motor skills, language, and adaptive personal/social skills. The developmental outcome scores are set for these four skills and total development. Scores between age-normative values and 20% of those values were considered near-normal. Scores between 20% and 30% of age normative values were recorded as borderline (normal development), Scores higher than age-normative values (>30%) indicate the presence of a significant delay. In our study the patients whose scores were more than >30% of age-normative values according to Denver Developmental Screening Test were considered to have a developmental delay[11].The data were recorded on a specially designed questionnaire, collected and entered in the computer via Microsoft Excel worksheet (Excel 2010) and then analyzed using appropriate data system which is called Statistical Package for Social Sciences (SPSS) version 25 and the results were compared between patients with different variables, with a statistical significance level of < 0.05. The results presented as rates, ratio, frequencies, percentages in tables and figures and analyzed using ANOVA and Chi square tests.

Results

A total of 50 newborns enrolled in the current study had a mean APGAR score ± S.D of 4.1 at first minute and 6.5 at fifth minutes consecutively. More than half of the mothers were primmigraivda (64%), and most of them had normal vaginal delivery (76%) and 62% of them had prolonged labour. The majority (82%) of the babies had delayed initial crying after birth and 30% with abnormal brain US. Slightly more than half of the newborns (54%) had poor outcome as developmental delay, Table (1).

Table (1): Frequency and percentages of parity, mode of delivery, duration of labour, delayed initial crying, brain US and developmental delay.

Variables		No.	%
Parity	• Multigravida	18	36
	• Primigravida	32	64
Mode of delivery	• Caesarean section	12	24
	• Normal vaginal	38	76
Duration of labour	• Prolonged	31	62
	• Not prolonged	19	38
Delayed initial crying	• Yes	41	82
	• No	9	18
Brain US	• Normal	35	70
	• Abnormal	15	30
Developmental delay	• Favorable outcome	23	46
	• Poor outcome	27	54
Total		50	100

The results of able (2) show that there was a significant statistical association between degree of encephalopathy and developmental delay of the newborn. Only 7.1% of cases with mild encephalopathy, nearly 29.4% of moderate and 89.5% of severe encephalopathy patients had poor developmental outcome.

Table (2): Association between degree of encephalopathy and developmental delay***.**

Degree of encephalopathy	**Developmental delay**		**Total**
	Poor outcome No. (%)	**Favorable outcome**	
Mild	1(7.1%)	13 (92.9%)	14 (100%)
Moderate	5 (29.4%)	12 (70.6%)	17 (100%)
Severe	17 (89.5%)	2 (10.5%)	19 (100%)
Total	**23 (46%)**	**27 (54%)**	**50 (100%)**

* p-value = 0.001

Discussion

Birth asphyxia or hypoxic ischemic encephalopathy is one of the common neonatal problems in our country, despite major advances in monitoring technology and knowledge of fetal and neonatal pathologies. Perinatal asphyxia remains a

serious condition, causing mortality and long term morbidity. It is a tragedy for a normally developed fetus to sustain cerebral injury during the last hours of intrauterine life and exist for many years with major handicap12. Neonatal neurologic syndrome is of essential importance in indicating the severity of hypoxic ischemic injury and prognosis. Increased risk for complications is particularly associated with increased severity and duration of neurologic abnormalities13. Moreover, our study has revealed the maternal and neonatal factors associated with perinatal asphyxia. About 64 % of mothers were primigravide and 36% were multigravida this was in concordance with this studies14 and with other study which come in conclusion that birth asphyxia more common among primigravida15.Regarding the mode of delivery, in our study the results showed that vaginal delivery was strongly associated with birth asphyxia (76%) in comparison to caesarean section (24%) which is supported by various studies with16, but in contrast to the study that was done in Turkey which revealed that emergency caesarean section was also strongly associated with birth asphyxia in comparison to vaginal delivery, and various other studies supported it with different study designs19. Our study also reveals thatvaginal delivery is associated with abnormal brain imaging more (36.8%) in comparison to caesarean section (8.3%). Because cephalopelvic disproportion is a frequent cause of obstructed labor, which increased risk for birth asphyxia mortality24-25.In this study, the APGAR scores were low (<7) in most of the patients at 1 minute the mean of APGAR score was (4.1) and at 5 minute the mean was (6.5). These results found significant relationship between low APGAR score and birth asphyxia, which is compatible with another study15.In our study, there is a significant relationship between degree of encephalopathy and APGAR score at 1 min and 5 min (p-value=0.001).In sever encephalopathy the means of APGAR score at 1 min was (3.21) and at 5 min was (5.74), so a high incidence of neurological abnormality or (poor outcome) has been observed among children with low APGAR scores at 1 min18, while this is disagreement of another study9 who established that results of APGAR score were insufficient to determine the correlation with neurodevelopmental outcome. Moreover, a number of factors, such as prematurity, drugs used by the mother, anesthetic agents

used during delivery, trauma, infections, cardiopulmonary disorders, and congenital abnormalities affecting the neuromuscular system, may also lead to depressed Apgar scores19. Our study suggested that patients with mild hypoxic ischemic encephalopathy are more likely to have better prognosis due to the high negative predictive value (92.9%), which is compatible with the result of other study9 (90.9%).In our study, 89.5% of sever neonatal encephalopathy put the newborn at risk for poor. Neurodevelopmental sequelae.In comparison to moderate encephalopathy, 29.4% were at risk for poor . Neurodevelopmental sequelae which is compatible with this study 21, and in our study those with sever encephalopathy (63.2%) had abnormal brain ultrasonography after 6 months follow up, which is compatible with this study whereas (66%) infant with sever encephalopathy had parenchymal lesions on brain imaging10. cranial ultrasonography is sensitive enough to identify most abnormalities that are known to be associated with adverse neurologic outcome22. Cranial ultrasonography is cost-efficient and noninvasive, and its prognostic value for later neurologic sequelae has already been suggested by several studies23. Regarding brain imaging and prognosis, about 93.3% of infants that had abnormal brain ultrasonography at 6 months had developmental delay. This is in comparison with those of normal brain imaging (74.3%) who had favorable outcome. It is compatible with another studies9-10. Therefore, brain imaging findings had the strongest correlation of neurodevelopmental outcome in infants with hypoxic ischemic encephalopathy. In this study, results indicated that 54% of total infants had a favorable neurodevelopmental outcome, and 46% of total infants had a significant degree of developmental delay or neurodevelopmental deficit at 6 months which is nearly compatible with other study20 that 57.1% of total infants had a favorable neurodevelopmental outcome and 38.1% of total infants had a significant degree of developmental delay or neurodevelopmental deficit at 12 months. However, several studies showed higher or lower degree of poor neurodevelopmental outcome in HIE. These results could be caused by the different criteria for enrollment and relatively heterogeneous patient group in the other study14.

Conclusions

In the review of this study, we can conclude that perinatal asphyxia is associated with acute neurologic morbidity in term neonate. Primigravide, vaginal delivery, and prolonged labour were the factors associated with low APGAR score at 1and 5 minute, these are the major causes of moderate and sever neonatal encephalopathy. This study shows a significant relationship between low APGAR score and poor neurodevelopmental outcome. Most of infants with abnormal brain ultrasonography had developmental delay.

Conflicts of interest

The authors report no conflict of interest.

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