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Characteristics of Hypoxic Ischemic Encephalopathy among Neonates in Sanglah General Hospital

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Abstract

Hypoxic ischemic encephalopathy (HIE) is a worldwide problem. It is a type of brain injury that occurs when the brain doesn't receive enough oxygen or blood flow occurring during pregnancy, labor and delivery or in the postnatal period. We aimed to investigate the characteristics of HIE among neonates admitted to Sanglah General Hospital. This observational retrospective study was conducted from January 2018 to December 2020 in Neonatology Ward of Sanglah General Hospital. This study was dominated by male subject, mild HIE (65.4%) with caesarian section (65.4%) and referred from other hospital (60.6%). Moreover the cases of seizure, neonatal sepsis and neonatal pneumonia accounted for 20.2%, 73.1%, and 34.6%, respectively. Mortality occurred in 28.8% neonates, but only 17.6% moderate HIE and 47.4% severe HIE got cooling therapy. Maternal characteristics were severe preeclampsia, placenta previa, previous abortion, hypertension, asthma and diabetes mellitus. This study demonstrated that HIE characteristics in neonates of Sanglah General Hospital mostly were mild stages, male gender, caesarean section as mode of delivery and majority was referred from other hospital.

Keywords: Hypoxic ischemic encephalopathy; Neonates; Characteristics

1. Introduction

Neonatal encephalopathy may resulted from variety of conditions. If encephalopathy caused by diffuse hypoxic ischemic brain injury, it can be mentioned as hypoxic ischemic encephalopathy (HIE). Hypoxic ischemic encephalopathy is one of the major causes of disabilities and deaths in newborns worldwide [1]. Hypoxic ischemic encephalopathy remains as major concern especially in developing countries with incidence 1.5-2 per 1000 live births with severe consequences, such as neonatal mortality and acute neurological injury with long-term neurodevelopmental disabilities [2-5]

Hypoxic ischemic encephalopathy is type of brain injury that occurs when the brain doesn't receive enough oxygen or blood flow. It may occur during pregnancy, labor and delivery or in postnatal period [6]. Hypoxic ischemic encephalopathy is a syndrome with nonspecific features, characterized by disorder of neurological function occurring in the first days of life in term and near-term neonates. Impact of neurodevelopmental occur mostly in neonates with moderate to severe forms of encephalopathy compared with mild HIE [7]. A proportion of brain injury in HIE occurs as result of primary hypoxic ischemic; however, the majority of postasphyxial brain injury occurs during secondary phase, after reestablishment of cerebral circulation and oxygenation [8].

Sarnat developed descriptive staging based on examination to classify infants from mild to severe encephalopathy. Recently some studies used modified Sarnat staging to exclude the heart rate variability that occurs during HIE treatment [7,9]. Sarnat stages can be used as predictor for long-term prognosis and as inclusion criteria for therapeutic

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hypothermia. In addition Thompson et al. developed a simplified scoring system based on Sarnat staging. The outcome of treatment depend on the stage whether its mild, moderate, or severe HIE [10].

A study of HIE in Japan showed risk factors of poor outcome includes birth weight, low APGAR score at 5 minutes and epinephrine usage. Laboratory abnormalities such as serum lactate, aspartate aminotransferase and alanine aminotransferase as well as abnormal brain magnetic resonance imaging (MRI) findings were also associated with poor outcome. Moreover study in Nepal also revealed that maternal infections, low socioeconomic status and multiple births were important risk factors for mortality in HIE especially in low resource settings [11].

Hypoxic ischemic encephalopathy is a serious condition. Randomized controlled trial showed that early cooling therapy improved neurodevelopmental outcome of newborns with HIE. The aims of this study is to investigate the characteristics of HIE among neonates admitted to Sanglah General Hospital.

2. Material and methods

This descriptive observational study, retrospectively collected data from all neonates with HIE in Sanglah General Hospital during January 2018 to December 2020. Samples were collected consecutively. Data was collected from medical records. The accessible population were all HIE neonates admitted to neonatology ward of Sanglah General Hospital during study period and who fulfilled the inclusion criteria. Inclusion criteria include all neonates admitted to neonatology ward of Sanglah General Hospital with HIE from January 2018 to December 2020. Exclusion criteria was neonates with incomplete medical record. The sample size was determined by using total sampling method in the period of the study. The study results are shown descriptively in tables as number and percentage.

3. Results

The total neonates included in this study were 104 neonates with HIE and fulfilled inclusion criteria in the study. We performed retrospective study of all neonates with HIE admitted at our centre, started from January 2018 until December 2020.

Characteristics of neonates with HIE were showed in table 1. The number of cases for mild, moderate and severe stages were 65.4%, 16.3% and 18.3%, respectively. Seventy-four neonates (71.2%) were male and 30 neonates (28.8%) were female with ratio male-to-female 2.4:1. This study found HIE mostly occurred in term neonates (69.3%). Twenty-two neonates (21.2%) had birth weight below 2500 grams and 82 neonates (78.8%) had normal birth weight (≥ 2500 grams). The incidence of HIE was higher in newborns delivered by caesarean section (65.4%). Most neonates were born in other hospital (60.6%). There were 11.5% of multiple birth, 27.9% with fetal distress and 25.9% with PROM (Premature Rupture Of Membranes) $>12-24$ hours.

Table 1 Characteristics of neonates with HIE

Variables	Cases (n = 104) (%)
HIE stage	
Mild (1-10)	68 (65.4)
Moderate (11-14)	17 (16.3)
Severe (≥ 15)	19 (18.3)
Gender	
Male	74 (71.2)
Female	30 (28.8)
Gestational age	
< 37 weeks	30 (28.8)
37-42 weeks	72 (69.3)
>42 weeks	2 (1.9)
Birth weight	
<2500 grams	22 (21.2)
≥ 2500 grams	82 (78.8)

Mode of delivery	
Spontaneous	36 (34.6)
Caesarean section	68 (65.4)
Referrral	
Yes	63 (60.6)
No	41 (39.4)
Multiple birth	
Yes	12 (11.5)
No	92 (88.5)
Fetal distress	
Yes	29 (27.9)
No	75 (72.1)
PROM (premature rupture of membrane)	
None	72 (69.3)
> 12 – 24 hours	27 (25.9)
> 24 hours	5 (4.8)

Table 2 Maternal Characteristics of neonates with HIE

Variables	Cases (n = 104) (%)
Gravida	
1	64 (61.6)
2	28 (26.9)
3	10 (9.6)
>3	2 (1.9)
Severe Preeclampsia	
Yes	32 (30.7)
No	72 (69.3)
Placenta previa	
Yes	7 (6.7)
No	97 (93.3)
Previous abortion	
Yes	9 (8.6)
No	95 (91.4)
Gestational Hypertension	
Yes	22 (21.2)
No	82 (78.8)
Asthma	
Yes	4 (3.8)
No	100 (96.2)
Diabetes Mellitus	
Yes	2 (1.9)
No	102 (98.1)

Table 2 showed the maternal characteristics of neonates with HIE. Majority of neonates (61.6%) were born from primigravida mothers. Thirty-two mothers (30.7%) with severe preeclampsia. The number of cases with history of

placenta previa, previous abortion, hypertension, asthma and diabetes mellitus were 6.7%, 8.6%, 21.2%, 3.8%, 1.9%, respectively.

The comorbidities of neonates with HIE were showed in table 3. Seizure was found in 20.2% cases, neonatal sepsis in 73.1% cases and 34.6% neonates with neonatal pneumonia. Death occurred in 28.8% neonates.

Table 3 Comorbidities and outcomes of neonates with HIE

Variables	Cases (n = 104) (%)
Seizure	
Yes	21 (20.2)
No	83 (79.8)
Neonatal sepsis	
Yes	76 (73.1)
No	28 (26.9)
Neonatal pneumonia	
Yes	36 (34.6)
No	68 (65.4)
Mortality	
Yes	30 (28.8)
No	74 (71.2)

Table 4 showed cooling therapy in moderate and severe HIE. It found 17.6% moderate HIE cases and 47.4% severe HIE cases got cooling therapy.

Table 4 Cooling therapy in moderate and severe HIE

	Moderate HIE (n = 17) (%)	Severe HIE (n = 19) (%)
Cooling therapy		
Yes	3 (17.6)	9 (47.4)
No	14 (82.4)	10 (52.6)

4. Discussion

Hypoxic ischemic encephalopathy is a serious condition that affects newborns. Asphyxia is one of the leading causes of mortality and significant neuromotor disability among survivors. Asphyxia can predispose newborn developing a large number disorders affecting every system of body in neonate. When asphyxia is followed by complex symptoms, a syndrome has been described known as HIE [12]. Hypoxic ischemic encephalopathy remains as serious problem due to adverse neurodevelopmental outcomes with lifelong consequences.

In this study, most neonates had mild HIE (65.4%). Hafza reported similar results with predominance of mild HIE [14]. This is similar to a study of 237 newborn in Ireland which showed 68,2% had mild stage of HIE. In addition, another study conducted in South India found the proportion of newborns with mild HIE was 56% [12,14] different with study from Pakistan which was dominated by moderate HIE [13]

This study found that 71.2% neonates with HIE were males. Although other studies also show male predominance but the number of males in our study were much more as compared to other studies [15,16], with ratio male to female was

2.4:1. This finding is similar with several studies which found male gender was conclusively found as risk factor for HIE [17, 18].

In this study, 28.8% of neonates with HIE were preterm babies. Azam stated prematurity increases HIE [19]. Niaz found 31% of HIE cases were preterm babies. However mortality is higher in term babies as compared to preterm babies with HIE (65% vs 35%). Prematurity is one of the major risk factor adversely affecting the outcomes of asphyxia babies. The brains of premature neonates are more fragile and susceptible to injury [20]. In this study, only 1.9% of neonates with HIE were postterm baby. In postterm condition, fibrosis of placenta can decrease blood flow from placenta to fetus and increase the risk of asphyxia [21]

Our study found that most deliveries were caesarean section (65.4%). Delivery by caesarian section is risky to asphyxia that lead to HIE. Some previous studies showed similar results [25]. Zulfiqar et al. in his study also described 66% of babies delivered by caesarian section had birth asphyxia as compared to 34% cases born by spontaneous delivery [26] Its similar with Liliana et al. found that most of HIE cases were caesarean section deliveries [27]. In our study, mostly caesarean section was performed because there were problems with mother, baby or both before delivery. Several studies reported that incidence of birth asphyxia was significantly higher in emergency caesarean section than elective caesarean section mostly because of the indications for emergency caesarean section as fetal distress, failure progress of normal labor, and cephalopelvic disproportion which endanger the neonates[28-30].

In this study, we found 11.5% of neonates were multiple birth, includes twin or triplet. Martinez et al. found that twin gestation was significantly associated with higher risk of HIE [36] however Nafisa et al. found that twin was not a significant risk factor for HIE, keeping with Curry et al [37,38]. Multiple birth are risky for HIE which occurs when there is insufficiency of oxygenated blood travelling to the baby's brain during or near the time of birth [36,38].

Fetal distress during maternal admission, indicates fetal impairment with unknown duration, might be a consequence from major preceding hypoxic ischemic events and is associated with neurological harm. The fetal distress on maternal is probably a sign of long lasting distressed fetus [39]. In our study, we found 27.9% neonates born from mother with fetal distress on admission.

In this study, the frequency of HIE in neonates who suffered premature rupture of membranes (PROM) >12 hours -24 hours and from PROM >24 hours were 25.9% and 4.8%, respectively. The same result was reported by Majeed et al. which showed that 24% babies whose mother had PROM developed HIE [40]. Premature rupture of membranes is not only association with increased incidence of emergency caesarian section but also with birth asphyxia and HIE [41]. Hafza et al. found that the frequency of HIE in PROM compared to other studies (24.9% vs 10%) [14].

Maternal comorbidities like severe preeclampsia, placenta previa, previous abortion, hypertension, asthma and diabetes mellitus were predisposing risk factors for HIE. This study found 30.7% neonates were born from mother with severe preeclampsia. Mother with preeclampsia can increase the risk of HIE. Several studies found similar results that preeclampsia can be the risk factor of HIE [13,43,44]. In preeclampsia mother, abnormal trophoblastic invade both maternal decidual arteries, leads to reduction of placental perfusion and relative placental ischemia [45]. In this study, we also found 6.7% with history of placenta previa. Placenta previa may cause severe bleeding. The placenta prematurely tears away from uterus, directly and acutely result in fetal hypoxia and risky for HIE [43,45]

In this study, we found 1.9% neonates born from mother with diabetes mellitus. Diabetes mellitus may increase the risk of HIE by increasing risk of macrosomia, hypoglycemia, hypocalcemia, respiratory distress syndrome, polycythemia, hyperbilirubinemia, and cardiomyopathy. Maternal hypertension were also associated with the increased risk for HIE [42].

Seizures were found as common clinical feature in neonates with HIE, similar with other study which abnormal neonatal reflex and seizures, were the most frequent clinical features in neonates with HIE. Lee and Qureshi also reported similar results. This study found seizure in 20.2% of the babies with HIE [16,29,40].

There are several risk factors for the development of HIE and one of the most important is perinatal infection. Infection associated with perinatal hypoxia is not only as risk factor, but also causal factor in some cases and factor for poor prognosis of brain damage. Inflammatory response that is produced by infection causes brain damage [46]. In this study, we found other problems including neonatal sepsis and pneumonia neonatal in 73.1% and 34.6%, respectively.

Consequences of HIE ranging from cognitive, behavioural and memory problems to seizure and cerebral palsy of varying degrees and death. This consequences were rare in mild HIE but high in severe HIE. Morris et al. found that the outcome

of severe HIE is poor, with high portion of severe HIE dying or survive only for palliative care [47] Shankaran et al. found that neonates with moderate encephalopathy have 10 percent risk of death, meanwhile the survival group have 30 percent risk of disabilities. Sixty percent with severe encephalopathy die [48]. In severe HIE, the mortality rate is reported 25-50%. Multi organ failure is the etiology of most deaths which occur in the first week of life. Hypoxic ischemic encephalopathy with severe neurologic disabilities mostly die secondary to aspiration pneumonia or systemic infections [49]. In this study, the mortality rate was 28.8%.

Current evidence and guidelines suggest that newborn who are term or near term with evolving moderate to severe HIE should be treated with therapeutic hypothermia (cooling therapy) [50]. Neonates with moderate to severe HIE are risky for adverse events, such as cerebral palsy, neurodevelopmental disorders, or death. There is evidence from large randomized controlled trial that stated hypothermia is beneficial for neonates with HIE [50,51]. Multicenter studies also indicated that hypothermia treatment can significantly improve the prognosis of newborns with severe HIE, as well as window period of treatment <6 hours after birth [52]. Therapeutic hypothermia improves the survival and decreases the rate of disability of neonates with HIE [51]. Therapeutic hypothermia has multiple neuroprotective effects, including reduction of cerebral metabolism, prevention of seizures, stabilization of the blood brain barrier, inhibition of glutamate, selective reduction of apoptosis, and suppression of microglia activation. In this study, we found as many as 17.6% moderate HIE and 47.4% of severe HIE received cooling therapy.

5. Conclusion

In conclusion, this study demonstrated the characteristics of HIE in neonates at Sanglah General Hospital mostly were mild stage, male gender, caesarean section as mode of delivery and majority was referred from other hospital.

Compliance with ethical standards

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Disclosure of conflict of interest

No of interest statement.

Statement of informed consent

Informed consent was obtained from all individual participants included in the study.

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