Evaluation of risk factors for neonatal hypoxic ischemic encephalopathy

Neonatal hipoksik iskemik ensefalopati risk faktörlerinin değerlendirilmesi

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Abstract

Aim: Hypoxic ischemic encephalopathy (HIE) is a serious condition in neonates and is associated with neuromuscular dysfunction and death. In this study, we aimed to investigate potential risk factors for neonatal HIE.

Methods: A retrospective case–control study was conducted on infants admitted to our neonatal intensive care unit between 2015 and 2020. Infants born at ≥36 weeks of gestation and diagnosed with HIE were included in the case group. For each case, 4 gestational age-matched infants without HIE were selected and included in the control group. The groups were compared in terms of maternal demographic characteristics, pregnancy characteristics, and birth-related factors.

Results: The study included 75 infants with HIE and 300 controls. Nulliparity, history of antenatal care, medical complications during pregnancy, prolonged difficult birth, abnormal fetal heart rate, mode of delivery, and acute birth complications were found to be significantly associated with HIE in univariate analysis. In multivariate logistic analysis, the lack of antenatal care, abnormal fetal heart rate (FHR), and acute birth complication were the strongest factors associated with neonatal HIE.

Conclusion: Our findings demonstrated that the lack of antenatal care, abnormal FHR, and acute birth complications were risk factors for the development of HIE. Ensuring that pregnant women receive adequate antenatal care and applying necessary obstetric measures may help to reduce the HIE incidence.

Keywords: hypoxic ischemic encephalopathy; newborn; risk factors

Öz

Amaç: Hipoksik iskemik ensefalopati (HİE) yenidoğanlarda ciddi bir problem olup nöromüsküler disfonksiyon ve ölümle ilişkilidir. Bu çalışmada neonatal HİE için potansiyel risk faktörlerini araştırmak amaçlanmıştır.

Yöntem: 2015–2020 yıllarında yenidoğan yoğun bakım ünitemizde yatan bebekler üzerinde retrospektif bir vaka–kontrol çalışması gerçekleştirildi. Vaka grubu ≥36 gebelik haftasında doğan ve HİE tanısı alan bebeklerden oluşturuldu. Her vaka için, HİE'si olmayan, gestasyonel yaş bakımından eşlenik 4 bebek seçildi ve kontrol grubuna dahil edildi. Gruplar maternal demografik özellikler, gebelik özellikleri ve doğumla ilgili faktörler bakımından karşılaştırıldı.

Bulgular: Çalışma 75 HİE'li bebek ve 300 kontrol içerdi. Tek değişkenli analizde nulliparite, antenatal bakım geçmişi, gebelik sırasında tıbbi komplikasyon, uzun süreli zor doğum, anormal fetal kalp hızı, doğum şekli, ve akut doğum komplikasyonları HİE ile anlamlı olarak ilişkili bulundu. Çok değişkenli lojistik analizde antenatal bakım eksikliği, anormal fetal kalp hızı (FKH) ve akut doğum komplikasyonu neonatal HİE ile ilişkili en güçlü faktörler idi.

Sonuç: Bulgularımız antenatal bakım eksikliği, anormal FKH ve akut doğum komplikasyonlarının HİE gelişimi için risk faktörü olduğunu göstermiştir. Gebelerin yeterli antenatal bakım almalarını sağlamak ve gerekli obstetrik önlemleri uygulamak HİE insidansını azaltmaya yardımcı olabilir.

Anahtar sözcükler: hipoksik iskemik ensefalopati; risk faktörleri; yenidoğan

Received/*Geliş* : 11.06.2021
Accepted/*Kabul*: 18.07.2021

DOI: 10.21673/anadoluklin.951203

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INTRODUCTION

Hypoxic ischemic encephalopathy (HIE) is a serious condition in neonates and is characterized by central nervous system dysfunction in newborns after a hypoxic ischemic insult. The incidence of HIE has been reported to be 2 to 9 per 1000 live births (1). A 2008 study by the HIE Working Group of the Turkish Neonatology Society reported a HIE frequency of 2.6 per 1000 live births (2). HIE is associated with increased neonatal death and neurological disorders such as motor dysfunction, hearing loss, visual impairment, epilepsy, behavioral problems, and cerebral palsy (3,4). Therapeutic hypothermia is used as a standard treatment method in infants with moderate to severe HIE to reduce the risk of death and neurodevelopmental impairment (5,6). However, despite the use of therapeutic hypothermia, nearly half of the infants with HIE either die or survive with major disabilities (7).

Previous studies identified several prenatal and birth-related risk factors for HIE, including maternal age >35 years, nulliparity, maternal obesity, history of infertility treatment, pregnancy >41 weeks, intrauterine growth restriction, clinical chorioamnionitis, acute birth complications, and the presence of meconium and shoulder dystocia (8–13). Reported results vary depending on the characteristics of the study populations. It is important to update this information in view of the changes in population characteristics and obstetric and neonatal care over time. The identification of risk factors for HIE is fundamental in determining the preventive measures (14). Accordingly, in this study we evaluated several potential risk factors for HIE in newborns.

MATERIALS AND METHODS

A retrospective case–control study was conducted on infants who were admitted to the neonatal intensive care unit (NICU) of the Istanbul Medeniyet University Göztepe Training and Research Hospital between January 2015 and October 2020.

The case group consisted of infants born at ≥36 weeks of gestation and diagnosed with HIE. The HIE diagnosis was made based on the American College of Obstetricians and Gynecologists criteria, including the following: pH <7.0 or base deficit >16 mmol/L on blood gas analysis within the first hour after birth, a 10-minute Apgar score <5 or positive pressure ventilation for 10 minutes after delivery, and signs of encephalopathy in clinical evaluation (i.e., altered reflexes, hypotonia, lethargy, stupor or clinical seizures) (15). For each case, 4 gestational age-matched infants without HIE were selected and included in the control group. The exclusion criteria were gestational age <36 weeks or birth weight <2000 g and presence of diagnosed genetic defects, metabolic disease or major congenital anomalies.

The data used were obtained from electronic medical records and patient charts. Maternal characteristics such as age, parity, and history of antenatal care, smoking, chronic disease and medical conditions during pregnancy (gestational diabetes mellitus, preeclampsia/eclampsia, and intrauterine growth restriction) were collected. The presence of abnormal fetal heart rate (FHR) and chorioamnionitis was noted. Chorioamnionitis was defined as the presence of fever and treatment with intravenous antibiotics. Birth details (prolonged difficult birth, acute birth complications, and mode of delivery) were recorded.

Statistical analysis

Statistical analysis was performed using the SPSS (v. 22.0) software (SPSS Inc., Chicago, Illinois, USA). Continuous variables were expressed as means and standard deviations and compared by Student's t-test. Categorical variables were expressed as numbers and frequencies and analyzed by chi-square test or Fischer's exact test. Variables with a p value <0.1 in univariate tests were entered into the multivariate stepwise binary logistic regression analysis. $p<0.05$ was considered statistically significant.

Study ethics

The study protocol was approved by the Hospital Ethics Committee (2021/0242). Informed consent was obtained from the families of the included infants for all interventional procedures during the NICU admission. The study was conducted in accordance with the principles of the Declaration of Helsinki.

RESULTS

Of the 75 infants with HIE, 44 (58.7%) were male and 31 (41.3%) were female, while of the 300 controls 151

Table 1. Baseline characteristics

	Case group (N=75)	Control group (N=300)	*p*
Neonatal			
Gestational age (week) (mean±SD) (mean±SD)	38.2±1.5	38.3±1.7	0.77
Birth weight (gr) (mean±SD)	3102±507	3165±546	0.35
Sex, n (%)			
Male	44 (58.7)	151 (50.3)	0.19
Female	31 (41.3)	149 (49.7)	
Maternal			
Age (year) (mean±SD)	29.2±6.4	28.3±6.7	0.23
Smoking, n (%)			
No	65 (86.7)	272 (90.7)	
Yes	10 (13.3)	28 (9.3)	0.30
Parity, n (%)			
0	26 (34.7)	70 (23.3)	
≥1	49 (65.3)	230 (76.7)	*0.04*
Chronic illness, n (%)			
No chronic illness	62 (82.7)	267 (89)	
Thyroid disorders	4 (5.3)	12 (4)	
Hypertension	3 (4)	6 (2)	
Preexisting diabetes	1 (1.3)	3 (1)	
Others	5 (6.7)	12 (4)	
Chronic illness, n (%)			
No	62 (82.7)	267 (89)	
Yes	13 (17.3)	33 (11)	0.15

SD: standard deviation

Table 2. Pregnancy-related characteristics

	Case group (N=75)	Control group (N=300)	*p*
Antenatal care, n (%)			
Received	42 (56)	224 (74.7)	
Not received	33 (44)	76 (25.3)	*0.001*
Medical complication during pregnancy, n (%)			
No complication	63 (84)	276 (92)	
Preeclampsia/eclampsia	6 (8)	6 (2)	
Gestational diabetes	3 (4)	12 (4)	
Fetal growth restriction	3 (4)	6 (2)	
Medical complication during pregnancy, n (%)			
No	63 (84)	276 (92)	
Yes	12 (16)	24 (8)	*0.03*

(50.3%) were male and 149 (49.7%) were female. The case and control groups were similar in terms of maternal age and history of smoking and chronic diseases. The mothers of the infants with HIE had a higher rate of nulliparity than those of the controls (34.7% vs. 23.3%, p=0.04) (Table 1).

Compared to the control group, the case group had a significantly lower rate of antenatal care (56% vs. 74.7%, p=0.001). Any medical complication during pregnancy was observed more frequently in the case group (16% vs. 8%, p=0.03). However, the groups did not differ in terms of subgroups of medical complications (Table 2).

Table 3. Delivery-related characteristics

	Case group (N=75)	Control group (N=300)	*p*
Fetal heart rate, n (%)			
Normal	55 (73.3)	281 (93.7)	
Abnormal	20 (26.7)	19 (5.3)	*<0.001*
Acute birth complication diagnosis, n (%)			
Enwrapped cord	8 (10.7)	2 (0.7)	
Cord prolapse	5 (6.7)	0 (0)	
Abruptio placentae	5 (6.7)	0 (0)	
Maternal collapse	4 (5.3)	0 (0)	
Acute birth complication, n (%)			
No	53 (70.7)	298 (99.3)	
Yes	22 (29.3)	2 (0.7)	*<0.001*
Prolonged difficult birth, n (%)			
No	57 (76)	280 (93.3)	
Yes	18 (24)	20 (6.7)	*<0.001*
Chorioamnionitis, n (%)			
No	73 (97.3)	297 (99)	
Yes	2 (2.7)	3 (1)	0.26
Mode of delivery, n (%)			
Spontaneous vaginal	23 (30.6)	135 (45)	
Operative vaginal	2 (2.3)	0 (0)	
Elective cesarean	0 (0)	157 (52.3)	
Acute cesarean	50 (66.7)	8 (2.7)	
Mode of delivery–categories, n (%)			
Spontaneous vaginal delivery	23 (30.6)	135 (45)	
Other	52 (69.3)	165 (55)	*0.02*

Table 4. The multivariate logistic regression analysis of risk factors for HIE

Parameter	OR[a] (95% CI)	*p*
No antenatal care	2.67 (1.14–6.28)	*0.02*
Abnormal FHR	3.46 (1.52–7.87)	*0.003*
Acute birth complication[b]	34.03 (7.32–158.28)	*<0.001*

FHR: fetal heart rate; HIE: hypoxic ischemic encephalopathy

[a] Adjusted for nulliparity, medical complication during pregnancy, prolonged birth, and mode of delivery.

[b] Enwrapped cord, cord prolapse, abruptio placentae, and maternal collapse.

In terms of birth-related characteristics, the case group was more likely to have prolonged difficult birth (24% vs. 6.7%, p<0.001), abnormal FHR (26.7% vs. 5.3%, p<0.001), and any acute birth complication (29.3% vs. 0.7%, p<0.001). The rate of chorioamnionitis was similar in the groups. Of the infants with HIE, 66.7% were delivered by cesarean section, 30.6% spontaneous vaginal delivery, and 2.7% instrumental vaginal delivery. In comparison, of the controls 45% were delivered by spontaneous vaginal delivery and 65% cesarean delivery (Table 3).

Stepwise logistic regression analysis showed that the lack of antenatal care (OR 2.67, 95% CI 1.14–6.28, p=0.02), abnormal FHR (OR 3.46, 95% CI 1.52–7.87, p=0.003), and acute birth complication (OR 34.03, 95% CI 7.32–158.28, p<0.001) were significantly associated with HIE development (Table 4).

DISCUSSION AND CONCLUSION

Despite all the advances in neonatal care, HIE continues to be one of the most important causes of neona-

tal morbidity and mortality. Many maternal, fetal, and delivery-related factors can affect the development of HIE. In this retrospective case–control study, we found that the lack of antenatal care, abnormal FHR, and acute birth complications were significantly associated with an increased risk of neonatal HIE.

Antenatal follow-up during pregnancy is extremely important in preventing risks and guiding delivery. High-quality antenatal care improves maternal health and promotes positive pregnancy outcomes. There is a well-established association between lack of antenatal care and adverse neonatal outcomes (16–18). Mundhra et al. (16) found a higher incidence of meconium-stained amniotic fluid, birth asphyxia, perinatal death, low birth weight, and 5-minute Apgar scores <7 in babies of mothers who did not receive antenatal care. In our case group, the rate of benefiting from antenatal care was 56%, which was comparable to the rate of 43.2% reported in a recent study by Gumus et al. (18). In a recent systematic review, inadequate antenatal care, young maternal age (<20 years), low levels of maternal education, non-hospital delivery, maternal hypertension, and anemia were reported as the most important maternal risk factors for birth asphyxia (19). In our study, multivariate analysis showed that the lack of antenatal care was related to an approximately 2.7-fold increased risk of HIE. We did not find a significant relationship between maternal age and medical conditions during pregnancy and the HIE risk. This can be attributed to the sample size and patient characteristics in our study.

In previous studies, nulliparity (20) and male sex (21,22) were found to be associated with birth asphyxia. It has been suggested that nulliparous women are at risk of prolonged second stage of labor, which leads to low Apgar scores and birth asphyxia (23). Although our case group had a higher percentage of nulliparous women, prolonged birth, and male infants, we did not observe a significant association between these factors and neurological injury. Some factors with a possible association with HIE, such as parity and sex, are not modifiable, but it is important to identify and consider them in risk evaluations.

FHR monitoring is common in current practice. Several studies reported a relationship between patterns of FHR and neonatal HIE and neurological outcomes (24,25). On the other hand, Graham et al. (26) reported that FHR was a poor predictor of cerebral palsy. In our study, abnormal FHR was significantly associated with an increased risk of HIE. Abnormal FHR is difficult to prevent, but it is critical to detect it and take immediate action.

In the present study, there were acute birth complications in a substantial portion of the case group, which was consistent with previous reports (8–13). In a cohort study of 36,086 pregnant women, Lundgren et al. (12) found that an acute obstetric event at birth was the most important factor for HIE. In a case–control study by Torbenson et al. (13), acute events including maternal collapse, cord prolapse, placental abruption, and amniotic fluid embolism were found to be significantly associated with HIE. These findings point to the necessity of regular training on acute obstetric conditions. While some sentinel obstetric events are unavoidable, prompt recognition and appropriate action can affect neonatal outcomes. Draycott et al. (14) reported decreased rates of HIE after the implementation of obstetric emergency training. In addition, Siassakos et al. (27) reported improved outcomes, such as less admission to the NICU and higher 5-minute Apgar scores, after the introduction of simulation training on management of cord prolapse. These studies show that outcomes of unavoidable emergencies can be improved by training.

Previous studies reported that chorioamnionitis and intrapartum fever were associated with HIE development (28). However, we found no significant difference between our case and control groups in terms of chorioamnionitis. This can be explained by diagnostic differences and our patient characteristics. In our case group, emergency cesarean section was the most common mode of delivery (66.7%), followed by spontaneous vaginal delivery (30.6%). There were only two cases of instrumental (use of vacuum or forceps) delivery. While Zulfikar et al. (29) reported a higher rate of birth asphyxia in cesarean delivery, Kiyani et al. (30) found that the mode of delivery was respectively vaginal, emergency cesarean, and instrumental delivery in 43%, 32%, and 23.4% of cases with birth asphyxia. In our study, multivariate analysis showed no significant association between mode of delivery and HIE development. This might be due to the considerably high rate of elective cesarean delivery in the control group.

Larger studies can be useful to explain the relationship between mode of delivery and risk of HIE.

Finally, the main limitations of our study include the retrospective design, the small sample size from a single center, and the risk analysis regardless of HIE severity despite the difference in risk of long-term neurological damage. Being a matched case–control study and including many possible factors for HIE are the strengths of our study.

In conclusion, our findings demonstrated that the lack of antenatal care, abnormal FHR, and acute birth complications were risk factors for the development of HIE. To reduce adverse pregnancy and neonatal outcomes, it should be ensured that pregnant women receive adequate antenatal care. Effective obstetric precautions should be taken by trained personnel during delivery to reduce the damage associated with acute birth complications. In the presence of abnormal FHR, deliveries should take place under close supervision. In addition, for intervention without delay, there should be sufficient personnel trained in neonatal resuscitation at the time of delivery.

Conflict-of-interest and financial disclosure

The author declares that she has no conflict of interest to disclose. The author also declares that she did not receive any financial support for the study.

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