

Maternal and Fetal Risk Factors for Neonatal Hypoxic-Ischemic Encephalopathy: A Retrospective Study

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Background: Neonatal hypoxic-ischemic encephalopathy (HIE) leads to different degree of neurological sequelae. The incidence of HIE is relatively high, and the risk factors associated with HIE are still controversial. It is necessary to identify the risk factors associated with HIE.

Methods: A total of 258 neonates (110 HIE patients and 148 controls) were enrolled in this study. The characteristics of pregnant women and fetuses during pregnancy and delivery were compared between HIE patients and controls, and the risk factors of HIE were analyzed.

Results: The proportions of premature infants, low-birth-weight infants and the levels of 1-minute Apgar score, 5-minute Apgar score in HIE group were significantly lower than those in control group, while the proportion of amniotic fluid contamination in the HIE group was significantly higher than those of the controls. When HIE was taken as the end point of 1-minute Apgar score, and 5-minute Apgar score, the cut-off value of 1-minute Apgar score was 3, and 5-minute Apgar score was 7 by receiver operating characteristic (ROC) curve analysis. The results of multivariate logistic regression analysis showed that low birth weight (<2.5 kg) (OR 1.780, 95% CI: 0.124–25.463, $P=0.016$), amniotic fluid contamination (OR 3.223, 95% CI: 1.049–9.901, $P=0.041$), low 1-minute Apgar score (≤ 3) (OR 92.425, 95% CI: 15.522–550.343, $P<0.001$), and low 5-minute Apgar score (≤ 7) (OR 12.641, 95% CI: 2.894–55.227, $P=0.001$) may increase risk of HIE. In addition, amniotic fluid contamination, low 1-minute Apgar score (≤ 3), and low 5-minute Apgar score (≤ 7) may increase risk of HIE among newborns born to women without previous childbearing history, but not in newborns born to women with previous childbearing history.

Conclusion: Low birth weight (<2.5 kg), amniotic fluid contamination, low 1-minute Apgar score (≤ 3), and 5-minute Apgar score (≤ 7) may increase risk of HIE.

Keywords: hypoxic-ischemic encephalopathy, risk factors, clinical characteristics, newborns, birth weight

Introduction

Neonatal hypoxic-ischemic encephalopathy (HIE) refers to the various degrees of brain injury due to suffocation caused by partial or total lack of oxygen, reduce or suspend of the cerebral blood flow during the perinatal period.¹ It is a common central nervous system disease in fetuses or neonates, and severe children can be the legacy of different degree of neurological sequelae. Globally, the incidence of HIE in full-term live infants ranges from 1 to 8 per 1000, and even in developed countries, the incidence is 1.5 to 2 per 1000.² Around 400,000 babies develop neurodevelopmental disorders caused by HIE worldwide each year.³ HIE affects about 100,000 infants each year in China.⁴

HIE can be divided into different levels according to the evaluation system. At present, there are several major scoring systems for HIE evaluation in clinical practice. Thompson score is a scoring system created by Thompson et al in 1997 to predict the neurodevelopmental outcomes of HIE patients.⁵ While the Sarnat scoring system defines most

characteristics of the three stages.⁶ Apgar score was first introduced in 1952 by an American anesthesiologist named Virginia Apgar, and it is a widely utilized tool in neonates to describe an infant's condition after birth.⁷ Generally speaking, HIE can be divided into mild, moderate and severe hypoxic-ischemic encephalopathy.^{8,9}

At present, the risks of HIE are mainly based on the characteristics of pregnant women and fetuses during pregnancy and delivery. Due to maternal or fetal abnormalities, fetal dyspepsia leads to fetal brain asphyxia leading to neuronal destruction, which may evolve into ischemic hypoxic encephalopathy.¹⁰ One study has shown that the risk of HIE is higher in the presence of fetal growth restriction, nonreassuring cardiotocography, emergency cesarean section, meconium contamination, and chorioamnionitis.¹¹ Umbilical cord pathology, inflammatory changes in the placenta, and placental weight were associated with HIE.¹² Intrapartum period risk factors appear to be important for the development of HIE.¹³ Placenta previa, medicals during pregnancy, fetal distress, abnormal labor stage, Apgar score, amniotic fluid contamination, and cesarean section were independent risk factors for HIE.¹⁴ However, a study has found that mode of delivery and premature rupture of membrane have nothing to do with HIE.¹¹ There are still some inconsistent results in the study of HIE risk factors. It is necessary to identify the risk factors associated with HIE. Due to the variety of risk factors causing HIE, this study adopted the retrospective case-control study method to analyze the related factors in the whole perinatal period of pregnant women, and adopted the logistic regression analysis methods to screen the related risk factors.

Materials and Methods

Subjects

A total of 110 neonates with HIE admitted to Meizhou People's Hospital from January 2016 to May 2022 were selected as the observation group, including 76 males and 34 females. A total of 148 neonates without HIE in the same period were selected as the control group, including 99 males and 49 females. Neonates were diagnosed as HIE according to "Diagnosis of Hypoxic-ischemic Encephalopathy in Term Infants",¹⁵ "Guideline of Evidence-based Treatment for Hypoxic-ischemic Encephalopathy in Term Infants",¹⁶ and "Protocol of Hypothermia Treatment for Hypoxic-ischemic Encephalopathy in Neonates".⁴

Inclusion criteria were as follows: (1) all neonates met the diagnostic criteria of hypoxic-ischemic encephalopathy formulated by the neonatal Group of the Pediatric Society of Chinese Medical Association¹⁵; (2) all the neonates were confirmed as hypoxic-ischemic encephalopathy by magnetic resonance imaging (MRI) or computed tomography (CT) examination; (3) clinical data were complete. Exclusion criteria were as follows: (1) severe cardiac, liver and kidney dysfunction at birth; (2) neonates with hematological diseases; (3) neonates with congenital genetic diseases; (4) neonates with convulsions caused by childbirth injury and intracranial hemorrhage.

Observed Indicators

Clinical data of the two groups of neonates and their mothers were collected, including (1) maternal factors: pregnancy history, pregnancy conditions (amniotic fluid contamination, placental abnormalities, nuchal cord, pregnancy history); (2) fetal factors: gestational age, gender, birth weight, 1-minute Apgar score, and 5-minute Apgar score; and (3) delivery factors: delivery mode, and so on.

Statistical Analyses

Data analysis was performed using SPSS 21.0 (IBM Inc., USA). The measurement data were expressed as mean \pm standard deviation (SD), and the distributions of continuous variables were evaluated by Student's *t*-test or the Mann-Whitney *U*-test. Demographics and clinical characteristics of infants were calculated by χ^2 test. In this study, newborns were classified as premature infant (<37 weeks), full-term infant (37–42 weeks), and postterm infant (>42 weeks) according to neonatal gestational age at birth. Neonatal birth weight was categorized as low birth weight (1500–2499 g), normal birth weight (2500–4000 g), and macrosomia (>4000 g). When HIE was taken as the end point of birth weight, receiver operating characteristic (ROC) curve analysis was used to determine the optimal cut-off values of 1-minute Apgar score, and 5-minute Apgar score. Logistic regression analysis was applied to assess the association

between the characteristics of pregnant women and fetuses during pregnancy and delivery and HIE. $P < 0.05$ was considered statistically significant.

Results

A total of 258 neonates (110 HIE patients and 148 controls) were enrolled in this study, including 175 male neonates (67.8%) and 83 female neonates (32.2%). A total of 149 cases (57.8%) delivered by vaginal delivery, 109 cases (42.2%) delivered by cesarean section. There were 68 cases (26.4%) whose gestational age was <37 weeks at the time of delivery, and 190 cases (73.6%) whose gestational age was 37–42 weeks. There were 63 cases (24.4%), 186 cases (72.1%), and 9 cases (3.5%) with the birth weight <2.5 kg, 2.5–4.0 kg, and >4.0 kg, respectively. Sixty-one mothers (23.6%) of these newborns had a history of adverse pregnancy. Amniotic fluid contamination occurred in 81 cases (31.4%), nuchal cord occurred in 62 cases (24.0%), and placental abnormality occurred in 9 cases (3.5%). The 1-minute Apgar score and 5-minute Apgar score were 6.16 ± 3.54 and 7.91 ± 2.57 , respectively (Table 1).

The proportion of premature infants in the HIE group was lower than that in the control group (16.4% vs 33.8%, $P = 0.003$). The proportion of low-birth-weight infants in the HIE group was lower than that in the control group (12.7%

Table 1 Comparison of Clinical Characteristics between the Two Groups

Variables	Total (n=258)	Control Group (n=148)	Neonatal Hypoxic-Ischemic Encephalopathy Group (n=110)	P value
Gender				
Male	175 (67.8%)	99 (66.9%)	76 (69.1%)	0.788
Female	83 (32.2%)	49 (33.1%)	34 (30.9%)	
Mode of delivery				
Spontaneous	149 (57.8%)	84 (56.8%)	65 (59.1%)	0.799
Cesarean section	109 (42.2%)	64 (43.2%)	45 (40.9%)	
Gestational age (weeks)				
<37	68 (26.4%)	50 (33.8%)	18 (16.4%)	0.003
37–42	190 (73.6%)	98 (66.2%)	92 (83.6%)	
Birth weight (kg)				
<2.5	63 (24.4%)	49 (33.1%)	14 (12.7%)	<0.001
2.5–4.0	186 (72.1%)	96 (64.9%)	90 (81.8%)	
>4.0	9 (3.5%)	3 (2.0%)	6 (5.5%)	
Adverse pregnancy history				
No	197 (76.4%)	108 (73.0%)	89 (80.9%)	0.142
Yes	61 (23.6%)	40 (27.0%)	21 (19.1%)	
Perinatal conditions				
Amniotic fluid contamination				
No	177 (68.6%)	119 (80.4%)	58 (52.7%)	<0.001
Yes	81 (31.4%)	29 (19.6%)	52 (47.3%)	
Nuchal cord				
No	185 (71.7%)	102 (68.9%)	83 (75.5%)	0.002
Yes	62 (24.0%)	44 (29.7%)	18 (16.4%)	
Unknown	11 (4.3%)	2 (1.4%)	9 (8.2%)	
Placenta abnormality				
No	224 (86.8%)	134 (90.5%)	90 (81.8%)	0.104
Yes	9 (3.5%)	3 (2.0%)	6 (5.5%)	
Unknown	25 (9.7%)	11 (7.4%)	14 (12.7%)	
1-minute Apgar score	6.16 ± 3.54	8.72 ± 1.80	2.72 ± 2.06	<0.001
5-minute Apgar score	7.91 ± 2.57	9.53 ± 1.05	5.72 ± 2.38	<0.001

vs 33.1%, $P<0.001$). And the proportion of amniotic fluid contamination in the HIE group was significantly higher than that in the control group (47.3% vs 19.6%, $P<0.001$), and the proportion of nuchal cord was significantly lower than that of the control group (16.4% vs 29.7%, $P=0.002$). In addition, the 1-minute Apgar score (2.72 ± 2.06 vs 8.72 ± 1.80 , $P<0.001$) and 5-minute Apgar score (5.72 ± 2.38 vs 9.53 ± 1.05 , $P<0.001$) were significantly lower in the HIE group than those in the control group. There were no statistically significant differences between the two groups in proportion of gender, mode of delivery, adverse pregnancy history, and placental abnormality (Table 1).

Receiver operating characteristic (ROC) curve analysis was used to determine the optimal cut-off values of 1-minute Apgar score, and 5-minute Apgar score. When HIE was taken as the end point of 1-minute Apgar score, and 5-minute Apgar score, the cut-off value of 1-minute Apgar score was 3 (the area under the receiver operating characteristic [ROC] curve [AUC] was 0.957) and for 5-minute Apgar score was 7 (the AUC was 0.930) (Figure 1). The results of multivariate logistic regression showed that low birth weight (<2.5 kg) (odds ratio (OR) 1.780, 95% confidence interval (CI): 0.124–25.463, $P=0.016$), amniotic fluid contamination (OR 3.223, 95% CI: 1.049–9.901, $P=0.041$), low 1-minute Apgar score (≤ 3) (≤ 3 vs >3 , OR 92.425, 95% CI: 15.522–550.343, $P<0.001$), and low 5-minute Apgar score (≤ 7) (≤ 7 vs >7 , OR 12.641, 95% CI: 2.894–55.227, $P=0.001$) may increase risk of HIE in infants (Table 2).

According to the reproductive history of the mothers (with or without previous childbearing history) of these newborns, the subjects were divided into two groups: those with at least one childbearing history and those without childbearing history, and logistic regression analysis was conducted respectively. Among newborns born to women without previous childbearing history, the results of multivariate logistic regression showed that amniotic fluid contamination (OR 5.695, 95% CI: 1.345–24.120, $P=0.018$), low 1-minute Apgar score (≤ 3) (≤ 3 vs >3 , OR 32.518, 95% CI: 3.326–317.891, $P=0.003$), and low 5-minute Apgar score (≤ 7) (≤ 7 vs >7 , OR 15.411, 95% CI: 2.570–92.417, $P=0.003$) may increase risk of HIE. In newborns born to women with previous childbearing history, gender, mode of delivery, gestational age, birth weight, adverse pregnancy history, amniotic fluid contamination, nuchal cord, placenta abnormality, 1-minute Apgar score, and 5-minute Apgar score were not associated with HIE (Table 3).

Discussion

Many factors can contribute to the development of HIE. A series of fetal and maternal factors including fetal gender, mode of delivery, gestational age at birth, birth weight, adverse pregnancy history, amniotic fluid, umbilical cord, placenta, and Apgar score were included in this study. This retrospective cohort study showed that birth weight, amniotic fluid contamination, 1-minute Apgar score, and 5-minute Apgar score may have some effect on HIE. Specifically, the low birth weight (<2.5 kg), amniotic fluid contamination, low 1-minute Apgar score (≤ 3), and low 5-minute Apgar score (≤ 7) may increase risk of HIE in infants. In addition, in newborns born to women without previous childbearing history,

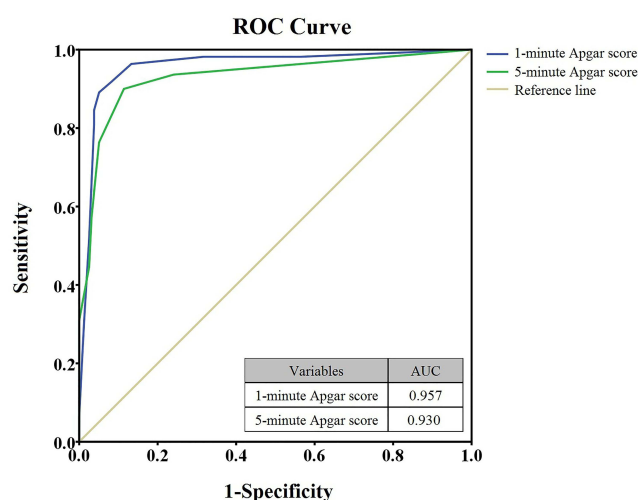


Figure 1 ROC curves of 1-minute Apgar score and 5-minute Apgar score for HIE.

Table 2 Logistic Regression Analysis of Risk of Neonatal Hypoxic-Ischemic Encephalopathy

Variables	Adjusted Odds Ratio (OR)	95% Confidence Interval (CI) for Adjusted Odds Ratio	P value
Gender			
Male	1.000 (Reference)		
Female	1.134	0.368–3.495	0.827
Mode of delivery			
Spontaneous	1.000 (Reference)		
Cesarean section	0.653	0.196–2.175	0.487
Gestational age (weeks)			
37–42	1.000 (Reference)		
<37	1.600	0.284–9.025	0.594
Birth weight (kg)			
<2.5	1.780	0.124–25.463	0.016
2.5–4.0	1.000 (Reference)		
>4.0	0.084	0.011–0.625	0.671
Adverse pregnancy history			
No	1.000 (Reference)		
Yes	0.392	0.102–1.509	0.173
Perinatal conditions			
Amniotic fluid contamination			
No	1.000 (Reference)		
Yes	3.223	1.049–9.901	0.041
Nuchal cord			
No	1.000 (Reference)		
Yes	0.379	0.106–1.359	0.136
Placenta abnormality			
No	1.000 (Reference)		
Yes	1.224	0.016–92.757	0.927
1-minute Apgar score			
>3	1.000 (Reference)		
≤3	92.425	15.522–550.343	<0.001
5-minute Apgar score			
>7	1.000 (Reference)		
≤7	12.641	2.894–55.227	0.001

amniotic fluid contamination, low 1-minute Apgar score (≤ 3), and low 5-minute Apgar score (≤ 7) may increase the risk of HIE in infants.

Neonatal hypoxia-ischemia is a common occurrence in low-birth-weight infants. Studies have shown that the infants who developed HIE had significantly lower birth weight than the infants who did not develop HIE.^{17,18} Low birth weight significantly increased the risk of neonatal moderate or severe HIE.¹⁹ Birth weight less than 3.0kg or greater than 4.0kg is a risk factor for moderate-to-severe neonatal HIE.²⁰ In the present study, low birth weight was an independent risk factor for HIE. Our results are consistent with those of previous studies. In one study, a cohort of infants with perinatal asphyxia was analyzed based on machine learning methods, and a predictive risk model for HIE was constructed using some clinical indicators such as Apgar score, maternal age, and infant birth weight.²¹

Amniotic fluid contamination was an independent risk factor for HIE.¹⁴ And meconium-stained amniotic fluid was significantly associated with HIE.²² Moderate-to-heavy meconium stained amniotic fluid is a risk factor for HIE.¹³

Table 3 Independent Risk Factors of Hypoxic-Ischemic Encephalopathy in Neonates Born to Women with or without Previous Childbearing History

Variables	Newborns Born to Women without Previous Childbearing History		Newborns Born to Women with Previous Childbearing History	
	Adjusted OR (95% CI)	P value	Adjusted OR (95% CI)	P value
Gender				
Male	1.000 (Reference)		1.000 (Reference)	
Female	0.966 (0.224–4.162)	0.963	1.507 (0.109–20.741)	0.759
Mode of delivery				
Spontaneous	1.000 (Reference)		1.000 (Reference)	
Cesarean section	0.722 (0.140–3.715)	0.697	0.541 (0.048–6.116)	0.619
Gestational age (weeks)				
37–42	1.000 (Reference)		1.000 (Reference)	
<37	1.391 (0.108–17.971)	0.800	/	0.994
Birth weight (kg)				
<2.5	1.068 (0.009–3.216)	0.236	/	0.994
2.5–4.0	1.000 (Reference)		1.000 (Reference)	
>4.0	/	0.999	7.085 (0.182–275.369)	0.294
Adverse pregnancy history				
Yes	/	/	1.000 (Reference)	
No	/	/	0.650 (0.090–4.682)	0.669
Perinatal conditions				
Amniotic fluid contamination				
No	1.000 (Reference)		1.000 (Reference)	
Yes	5.695 (1.345–24.120)	0.018	1.044 (0.112–9.728)	0.970
Nuchal cord				
No	1.000 (Reference)		1.000 (Reference)	
Yes	0.180 (0.030–1.091)	0.062	1.194 (0.086–16.650)	0.895
Placenta abnormality				
No	1.000 (Reference)		1.000 (Reference)	
Yes	/	0.999	/	0.998
1-minute Apgar score				
>3	1.000 (Reference)		1.000 (Reference)	
≤3	32.518 (3.326–317.891)	0.003	/	0.992
5-minute Apgar score				
>7	1.000 (Reference)		1.000 (Reference)	
≤7	15.411 (2.570–92.417)	0.003	/	0.995

Amniotic fluid contamination significantly increased the risk of neonatal moderate or severe HIE.¹⁹ Meconium stained liquor is a major risk factor for birth asphyxia, so amniotic fluid contamination is also one of the risk factors for HIE.²³ Our results are consistent with the results of these researches.

Apgar score is used as an indicator to judge the degree of neonatal asphyxia. The lower the Apgar score is, the more severe the degree of neonatal asphyxia is.²⁴ Some studies have shown that low Apgar score was an independent risk factor for HIE.¹⁴ 1-min Apgar score <7 significantly increased the risk of neonatal moderate or severe HIE.¹⁹ The Apgar score is the most commonly used score to quantify the postnatal state of the newborn, especially after fetal asphyxia.²⁵ In one study, a cohort of infants with perinatal asphyxia was analyzed based on machine learning methods to construct a predictive risk model for HIE, incorporating clinical indicators including Apgar score.²¹

In addition, gender of neonate, mode of delivery, gestational age, adverse pregnancy history, nuchal cord, and placenta abnormality were not associated with the risk of HIE in this study. Studies have shown that male fetuses are prone to HIE.^{26,27} The difference of HIE between males and females may be related to the difference of steroid hormone

level and motor function level between males and females.²⁸ About mode of delivery, cesarean section was an independent risk factor for HIE.¹⁴ Another study also showed that HIE was associated with mode of delivery other than unassisted vaginal birth.²⁹ However, the results of this study showed that delivery mode was not associated with the risk of HIE. In addition, gestational age was an antepartum risk factor for moderate-to-severe HIE.²⁰ Another study has shown that gestational age ≥ 41 weeks was associated with HIE.³⁰ In the present study, gestational age was not an antepartum risk factor for HIE. One study has shown that nuchal cord was associated with HIE,³⁰ but not shown in this study.

HIE is also associated with a number of other factors: gestational hypertension is positively associated with the risk of neonatal HIE³¹; maternal age ≥ 35 years as a potential risk factor for HIE³²; fetal blood advanced oxidation protein products (AOPP) and non-protein-bound iron (NPBI) can be used as early diagnostic markers of HIE.²⁷ HIE is associated with the polymorphisms in angiotensinogen (*AGT*) gene,³³ tachykinin receptor 3 (*TACR3*) gene,³⁴ caspase recruitment domain family member 8 (*CARD8*) gene,^{35,36} nitric oxide synthase 3 (*NOS3*) gene,^{37,38} oligodendrocyte transcription factor (*OLIG2*) gene,³⁹ but not associated with the polymorphisms in hypoxia-inducible factor 1 subunit alpha (*HIF1A*) functional polymorphisms.⁴⁰ Some non-coding RNAs may also play an important role in the development of HIE, such as microRNA-210,⁴¹ microRNA-30b,⁴² microRNA-204,⁴³ microRNA-374a-5p,⁴⁴ microRNA-139-5p,⁴⁵ microRNA-363-3p,⁴⁶ and so on.

Overall, the risk of HIE is associated with multiple factors, and more researches are needed to discover these risk factors and their associations with HIE. In clinical practice, the examination of pregnant women during pregnancy and perinatal period should be strengthened to detect risk factors as early as possible to prevent the occurrence of HIE. In detail, firstly, strengthen the examination before pregnancy and during pregnancy, actively treat the high-risk factors affecting fetal development such as gestational hypertension, diabetes, anemia, and try to remove the adverse effects on the fetus caused by prenatal and during pregnancy. Secondly, strengthen fetal monitoring during pregnancy, timely evaluate the child's intrauterine condition, and understand the growth and development of the fetus, such as the condition of amniotic fluid. Fetal distress in utero should be corrected, and termination of pregnancy should be considered if necessary. Thirdly, in the process of delivery, to prevent delayed labor caused by fetal or neonatal cerebral hypoxia, using appropriate delivery methods to shorten or end the process of labor, when necessary, appropriate relaxation of cesarean section indication, as soon as possible to end the delivery. In addition, medical institutions should standardize the resuscitation operation of neonatal asphyxia, fully prepare for the rescue of children with HIE, so that newborns with asphyxia after birth can be effectively treated at the first time.

Conclusions

In conclusion, the goal of analyzing the risk of neonatal HIE is to avoid HIE as much as possible. Based on the findings of this study, clinicians should take care to assess the risk of HIE based on fetal weight, amniotic fluid status, Apgar score at birth, and of course other reported risk factors. It is hoped that these findings will provide valuable information to obstetricians and neonatologists.

Data Sharing Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Ethics Approval

The study was performed under the guidance of the Declaration of Helsinki and approved by the Ethics Committee of Medicine, Meizhou People's Hospital, Meizhou Academy of Medical Sciences. The parents or legal guardians of all neonates signed informed consent forms.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no competing interests in this work.

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