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RISK FACTORS FOR HYPOXIC-ISCHEMIC ENCEPHALOPATHY IN FULL-TERM NEONATES

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ABSTRACT

Hypoxic-ischemic encephalopathy (HIE) is a clinically defined syndrome of disturbed neurological function in the earliest days of life in the term infants manifested by respiratory distress, subnormal level of consciousness, seizures and depression of tone and reflexes. The authors identified antepartum and intrapartum risk factors for HIE in full term newborns. Between January 1st, 2001 and December 31st, 2003, 54 term infants (gestational age ≥37 weeks) in NICU of the Clinic of Neonatology, Department of Obstetrics and Gynecology, Prof. Paraskev Stoyanov Medical University of Varna were retrospectively studied. All of them met the criteria for moderate or severe HIE (seizures, abnormal consciousness (stupor, coma), respiratory distress, difficulty feeding, abnormal tone and reflexes). Birth prevalence of moderate or severe neonatal HIE was 4,42% term live births. More important antepartum risk factors for HIE were infections, preeclampsia, bleeding in pregnancy, and postmaturity. HIE incidence in infants born after 42 weeks is by 2,5 fold higher. Significant intrapartum risk factors for HIE were intrapartum asphyxia (24% of cases with HIE - OR=6,91), operative vaginal delivery (OR=1,65) and emergency Caesarean section (OR=3,78). The study of the significant risk factors for HIE contributes to prevention of neonatal morbidity and mortality.

Key words: hypoxic-ischemic encephalopathy, intrapartum asphyxia, antepartum risk factors, intrapartum risk factors, prevention

Neonatal hypoxic-ischemic encephalopathy (HIE) is an important clinical problem associated with considerable morbidity, mortality and cerebral palsy in the neonatal period. HIE incidence ranges from 1,8% to 11,7% full term birth and the neonatal fatality is 2%-9% (2,3,5). HIE is a clinically defined syndrome of disturbed neurological function in the earliest days of life in the term infant manifested by respiratory distress, subnormal level of consciousness or coma, seizures and depression of tone and reflexes. Previous studies of newborn encephalopathy have focused almost exclusively on the intrapartum hypoxia. The assumption that, most often, neonatal encephalopathy is due to intrapartum asphyxia is, however, nowadays questioned. Recently, many studies suggest the contribution of factors before conception as well as the role of antepartum risk factors to HIE in full term neonates. Our objective was to investigate the role of adverse antepartum and intrapartum factors in the etiology of HIE in full term newborns.

MATERIAL AND METHODS

The newborns delivered in the region of Varna between January 1st, 2001 and December 31st, 2003 were studied. All of them were full term newborns (>37 weeks). The study contingent comprised 54 newborns with HIE. They were admitted in NICU of the Clinic of Neonatology, Department of Obstetrics and Gynecology, Prof. Paraskev Stoyanov Medical University of Varna, and during the first week of life they met the following criteria for HIE: seizures of any type or duration; abnormal consciousness - stupor, coma; difficulty maintaining respiration of central origin; difficulty feeding of central origin; abnormal tone and reflexes; altered responsiveness (decreased or increased) to stimuli for more than 24h, and ultrasound findings of periventricular leukomalacia or intraventricular hemorrhage. The severity of newborn HIE was graded as moderate or severe according to clinical criteria modified by Sarnat and Sarnat.

Criteria for severe (III grade) encephalopathy:

- Ventilation for more than 24 hours
- Coma or stupor
- Two or more anticonvulsant treatments
- Death in the neonatal period.

Controls were randomly selected from the population of term newborns delivered during the same period in the region of Varna and with the same birth weight, gestational age and gender. Retrospective antepartum and intrapartum data were collected from hospital records of the newborns and their mothers.

The following antepartal risk factors were considered: maternal conditions, family history of illness, infections,

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preeclampsia, eclampsia, postmaturity, congenital abnormalities, and intrauterine growth restriction. The following intrapartal risk factors were assessed: prolonged interval from rupture of membranes to delivery and/or maternal pyrexia; abnormalities of cord (nuchal cord, cord prolapse, cord around neck), ablatio/abruption of placenta; mode of delivery, acute intrapartum events and intrapartum fetal asphyxia.

RESULTS AND DISCUSSION

There were 11 427 full term deliveries in Varna region during the study period. The incidence of HIE was 4,72 per 1000 full term live births. In 31 newborns (57,4%) a severe neonatal HIE was established. According some literature data, there is a moderate or severe HIE in one-half to one-third of the cases (1,7). The mortality rate in the newborns with HIE was 20,37%, so this incidence was higher than that in published data.

Neonatal HIE as a cause for newborn mortality was found out in 1,34‰ full term live births. According to other data, the incidence range varies between 2 and 9 ‰ (1,3,5). We enrolled 114 control infants born in this period in the region of Varna. Cases and controls were matched on gender, gestational age and birth weight.

Table 1. Distribution of principal entry criteria for HIE

Characteristics	Cases with HIE (n= 54)	
	n	%
Seizures	29	53,7
Irritability or lethargy	42	77,7
Abnormal tone	18	33,3
Abnormal reflexes	18	33,3
Respiratory distress	41	75,9
Difficult feeding	15	27,7
Stupor or coma	9	16,6
Mechanic ventilation ≥24h	34	31,2
Death in the neonatal period	11	20,37

Table 1 gives the observed distribution of the principal entry criteria for the affected newborns and the determination of the grade of HIE.

The most common pathology of the newborns with HIE includes seizures, irritability or lethargy and respiratory distress requiring mechanical ventilation during the first days after birth.

Antepartum risk factors

Severe preeclampsia, moderate or severe vaginal bleeding in pregnancy and a presumed infection were associated with an increased risk for HIE. The association of newborn HIE with intrauterine growth restriction was not proved in our study (OR=1,05) although the association of IUGR with neonatal seizures, HIE and cerebral palsy was important and it was already described in some publications (1-4).

Table 2. Antepartum risk factors for HIE

Risk factor	patients		controls		Odds ratio (OR)
	n	%	n	%	
1. IUGR	2	3,70	4	3,5	1,05
2. Preeclampsia	7	12,31	6	5,26	2,68
3. Infections	14	25,94	18	15, 7	1,86
4. Familial history	17	31,50	19	16,6	2,30
5. Malformations	5	9,26	1	0,87	11,53
6. Postmaturity	11	20,42	9	7,9	2,98

Different causes of growth restriction may differ in their capacity to cause neonatal HIE, or to predispose the fetus to the damaging effect of an intermediate factor. Although preeclampsia and EPH gestosis is a common cause of growth restriction they are important independent risk factors for HIE. Our findings suggest that the maternal preeclampsia and eclampsia was associated with a 2,3-fold higher risk of HIE in full term newborns (OR=2,68). Neonatal HIE was found to be by 1,7-fold more often in the cases with maternal infection during the pregnancy and in the full term newborns with fetal infection. The role of perinatal infection is of considerable etiological interest in neurological dysfunction of newborns. These neurological dysfunctions are, probably, related to different mechanisms of action of the infectious agent such as hyperthermia, inflammatory mediators or other pathophysiological responses who cause hypoxemic-ischemic damages of the brain (1,2,5,6).

There were 5 major congenital abnormalities in our contingent as well as two newborns with diabetic fethopathy. In 3 cases with major defects (2 infants with fetal hydrops and one infant with spina bifida) it is likely that HIE was due to the specific defect and these defects caused infant's death. Major congenital abnormalities are a significant risk factor for perinatal asphyxia and HIE (OR =2,30). In 17 (31,5%) cases and in 19 (16,6%) controls a history of bleeding in pregnancy, maternal thyroid disease, infertility treatment, diabetes, obstetrical failures, non preserving pregnancy were established. Similar results were reported in several reviews (1-3,5,6).

The postmaturity is an important risk factor. Gestational age ≥42 weeks is associated with 2,5-fold higher risk for HIE (OR=2,98).

Our findings suggest that sterility and its treatment are not an increasing risk factor for neonatal HIE. It is, probably, so because these pregnancies were accurately observed and most newborns were delivered by elective Caesarean section (1,2,5).

Table 3. Intrapartum risk factors for HIE

Risk factor	patients		controls		
	n	%	n	%	
1. Maternal pyrexia, prolonged interval from membrane rupture to delivery	17	31,5	24	21,1	1,72
2. Cord prolapse	14	25,9	16	14	2,17
3. Placental infractions	8	14,8	10	8,7	1,80
4. Mode of delivery					
- elective Caesarean section	5	9,2	22	19,3	0,42
- emergency Caesarean section	12	22,2	8	7,01	3,78
- operative vaginal	6	11,1	8	7,01	1,65
5. Intrapartum asphyxia	13	24	5	4,38	6,91

There were no recognized antepartum or intrapartum risk factors in a very small proportion of infants (2%). Antepartum risk factors only were identified in 9,26% of affected newborns, while intrapartum risk factors as cause of HIE were revealed in other 25 infants (46,3%).

Table 4. Immediate characteristics of newborns with HIE and controls

Characteristics	cases with HIE		controls	
	n	%	n	%
Apgar at 1 minute				
0 - 3	16	29,6	2	1,75
4 - 6	24	44,4	18	15,8
Apgar at 5 minute				
0 - 3	13	24,07	0	0
4 - 6	19	35,2	9	7,9
Airway resuscitation				
- none	3	5,5	70	61,4
- oxygen	11	20,4	24	21,1
- bag and mask	27	50	20	17,5
- intubation and MV	13	24,07	0	0
Birth trauma-related	8	14,8	3	2,63

Intrapartum risk factors for HIE were the following:
Maternal pyrexia in labour and prolonged interval between rupture of membranes and delivery were more common, but statistically insignificantly, in our cases with HIE when compared with the controls. The most striking finding relates to mode of delivery.

A vital distinction not made in most other studies is the differentiation between elective and emergency Caesarean section. In these cases there was no significant prevalence of non-elective section in the newborns with HIE (1-3). Elective and emergency section was performed on a similar proportion of HIE cases and controls - in 31, 4% of the cases with HIE versus 26,4% of controls. Compared with the elective section, the operative vaginal delivery and the emergency section were associated with an increased risk of HIE. The frequency of delivery by emergency section (OR=3,78) or forceps (OR=1,65) is by two times higher in HIE cases. Only 9,2% of the infants with HIE versus 19,3% of the controls were delivered by elective section. Elective Cesarean section had a protective effect on neonatal HIE (OR=0,42). A lot of studies support the view that most risk factors for neonatal HIE lie in the intrapartum period. Criteria for intrapartum asphyxia are: abnormal intrapartum cardiotocogram; fresh meconium in labour; one-minute Apgar score of less than a 3- and a 5-minute Apgar score of less than 6.
Newborns with HIE were also more likely than controls to have fresh meconium during labour. Significant prevalence of neonatal complications such as meconium aspiration syndrome and pneumothorax was revealed in infants with signs of HIE compared to controls.
Much more HIE cases than controls had low one- and 5-minute Apgar score. HIE cases also tended to take longer to achieve regular respiration. There were considerable differences between HIE cases and controls with regard to time to first gasp, oxygen or intubation after delivery and pharmacological resuscitation, too.
Cord pH was not measured because of technical troubles. However, we accepted the following indices: pO_2 , pCO_2 , pH, and O_2 saturation up to 30th minute after birth.
Some authors conclude that the clinical signs of intrapartum asphyxia (such as low Apgar score, abnormal cardiotocogram, meconium-stained liquor or need for ac-

tive resuscitation) may simply reflect previous antenatal neurological compromise, or they are the first clinical manifestation of neonatal HIE in some cases.

We ascertain that intrapartum asphyxia is a very important risk factor for HIE in full term newborns because we find out that intrapartum factors are single cause for HIE in 24% of cases (OR=6,91).

Birth trauma is a very serious problem in our hospital. It causes severe intrapartum asphyxia with a long term hypoxia and acidosis. Besides it results in mechanical injuries of the brachial plexus or rupture of falx cerebri. We established a birth trauma in 15% of the newborns with HIE and only in 2,6% of the controls. Therefore, the choice of mode of delivery is very important precondition for the prevention of HIE in newborns.

CONCLUSIONS

1. The causes of HIE in full term infants are heterogeneous. Significant risk factors for HIE are: perinatal infections, maternal pyrexia, a prolonged interval from rupture of membranes to delivery, bleeding in pregnancy, preeclampsia, eclampsia, postmaturity, and mode of delivery.

2. It is necessary to continue research on the role of intrapartum asphyxia as it is an important risk factor for HIE and relates to the high level of obstetric interventions and mode of delivery. Intrapartum asphyxia is a consequence of antepartum effects and intrapartum factors are merely markers of damage associated with adverse events before birth causing decompensation of adaptive fetal capabilities.

3. Based on our data we could conclude that postmaturity, perinatal infections, intrapartum asphyxia and operative vaginal delivery are more significant risk factors for HIE.

4. Conforming to these results, we propose the following measures for prevention of neonatal HIE: prophylaxis of infections; choice of eligible and non-traumatic mode of delivery; diminution of the birth trauma and the risk of intrapartum asphyxia; adequate and timely cardio-pulmonary resuscitation and oxygenation for the newborns with signs of asphyxia. In this way we could prevent the prolonged hypoxia and severe metabolic acidosis that cause hypoxic-ischemic brain injury.

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