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NEONATAL ENCEPHALOPATHY AT TERM- A CASE CONTROL STUDY

Ada Simeoni[1] and Edite Sadiku[2]
[1]Neonatology Department, International Hospital of Tirana, Albania
[2]University Hospital Centre "Mother Teresa" Tirana, Albania

Abstract: The causal pathway of neonataj enecephalopathy (NE) is poorly understood: in most cases there is no evidence of severe intrapartum asphyxia, and conversely, most infants with intrapartum signs of fetal distress do not go on to develop neurological sequelae. The aim is to evaluate perinatal factors potentially involved in the genesis of NE. We performed a retrospective case-controlled study of all term, nonmalformed live-born neonates at term delivered at our institution between 2015 and 2019. During the study period, 27 (0.09%) were diagnosed with NE, with moderate or severe NE in 14 cases (52%). Cases and controls were similar for maternal age, parity, race, gestational age at delivery, and incidence of premature rupture of membranes, but more women labored in the control group. As expected, the rates of CD and urgent or emergent CD were significantly higher among cases. Neonates destined to develop NE had higher rates of antepartum risk factors than controls (74% versus 18%, odds ratio OR]= 13.0, 95% confidence interval [CI] 4.4 to 40.4), including previous CD (OR = 4, 95% CI 1.2 to 15), abnormal amniotic fluid volume at ultrasound (OR= 6.8, 95% CI 1.5 to 29.5), and nonreactive FHR tracing before labor (OR = 49.0, 95% CI 5.4 to 1109. Future efforts to reduce the rates of NE should thus be directed toward the identification of antepartum risk factors. In a minority of such cases (such as fetal growth restriction), there may be a lower fetal threshold to hypoxic or ischemic events during the end of pregnancy or labor.
Keywords: Neonatal enecephalopathy, perinatal risk factors.

Introduction

The causal pathway of neonatal enecephalopathy (NE) is poorly understood: in most cases there is no evidence of severe intrapartum asphyxia, and conversely, most infants with intrapartum signs of fetal distress do not go on to develop neurological sequelae [1]. The largest study to date has shown that only a minority of cases of NE can be attributed to intrapartum events, suggesting that antenatal factors may be implicated in the causation of the majority of cases of NE [3,4]. However, a recent study utilizing neonatal magnetic resonance imaging as a means to time the occurrence of neonatal NE at term found that most cases of NE or early neonatal seizures resulted from events proximate to delivery, calling into question the role of antenatal insults [5]. To evaluate perinatal factors potentially involved in the genesis of NE, we have performed a casecontrolled study in which we included

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information on fetal heart rate (FHR) tracing. Indeed, a limitation of previous studies is the lack of information on FHR, information that is relevant because an abnormal FHR tracing before labor could suggest a causal role for antepartum events in the genesis of NE, and FHR tracing during labor would contribute to the knowledge of fetal intrapartum events.

Material and methods

We performed a retrospective case-controlled study of all term, nonmalformed live-born neonates at term delivered at our institution between 2015 and 2019. Our institution is a tertiary care center that serves as referral for a large geographic area. Neonates transferred from outside hospitals were excluded from analysis. We identified neonates who were subsequently diagnosed with NE. The diagnosis of NE was established by attending neonatologists after exclusion of other causes of encephalopathy, such as metabolic disorders, malformations, chromosome abnormalities, and viral infections. NE was classified in three grades according to Sarnat and Sarnat's criteria, [6,7] with mild NE characterized by hyperalertness and irritability, normal muscle tone, normal or hyperactive reflexes, ankle clonus, and no seizures; moderate NE with lethargy, decreased spontaneous movements, proximal muscular weakness, depressed primitive reflexes, and seizures; and severe NE with stupor or coma, markedly reduced muscle tone or flaccidity, and absent primitive reflexes. Presence of seizures was not a necessary criterion for the diagnosis. All cases of NE were prospectively compiled and audited on a yearly basis, thus maximizing the ascertainment and minimizing the risk of loss of cases. At least three controls for each case were selected from the cohort of singleton term infants born during the study period using computer-generated random numbers. Umbilical cord blood gas analysis, inclusive of pH and base excess values, was routinely obtained at the time of delivery in all neonates including controls. The occurrence of multiorgan failure8 and long-term outcome was recorded on all babies. Antepartum and intrapartum variables were evaluated by abstracting information from a review of the medical records. Every pregnant women in our clinic undergoes at least an ultrasound exam during the third trimester, as well as amniotic fluid volume evaluation at term; oligohydramnios was defined as an amniotic fluid index 8 cm. Small-for-gestational age was defined as a birth weight 180 beats/min, absent variability, moderate tachycardia with reduced variability, bradycardia [8,9].

Results

During the study period, 27 (0.09%) were diagnosed with NE, with moderate or severe NE in 14 cases (52%). Their characteristics were compared with those of 100 randomly chosen

controls. Two of the 27 cases died (one in the neonatal period and one at 16 months) versus 0/100 controls, giving a neonatal case-fatality rate of 7%. Seventeen (63%) neonates with NE presented multiorgan dysfunction and four developed cerebral palsy at a mean follow-up of 84 37 months (range 39 to 144). Demographic and obstetric characteristics are shown in Table 1.

Table 1: Demographic and Obstetric Characteristics and Neonatal Outcome in Relation to NE

Variable	**NE Group (n ¼ 27)**	**Control Group (n ¼ 100)**	**p Value**
Maternal age (y)	32 5	32 4	0.8
Caucasian ethnicity	25 (93%)	97 (97%)	0.2
Nulliparity	19 (70%)	51 (51%)	0.08
Gestational age at delivery (wk)	39.8 1.1	39.7 1.0	0.7
Premature rupture of membranes	6 (22%)	35 (35%)	0.2
Cesarean delivery without labor	8 (30%)	8 (8%)	0.003
Labor	19 (70%)	92 (92%)	0.002
Spontaneous vaginal delivery	4 (15%)	86 (86%)	<0.001
Emergency cesarean delivery	11 (41%)	6 (6%)	<0.001
Apgar score <7 at 5 min	23 (85%)	0	<0.001
Apgar score <3 at 5 min	6 (22%)	0	<0.001
Umbilical artery pH	7.03 0.17	7.27 0.07	<0.001
Metabolic acidosis (pH <7 and BE <— 12)	11 (41%)	0	<0.001
Male sex	18 (67%)	61 (61%)	0.5
Birth weight (g)	3310 600	3375 404	0.5
Results are n (%) or mean standard deviation. BE, base excess; NE, neonatal encephalopathy.			

Cases and controls were similar for maternal age, parity, race, gestational age at delivery, and incidence of premature rupture of membranes, but more women labored in the control group. As expected, the rates of CD and urgent or emergent CD were significantly higher among cases, despite the fact that two cases who should have been eligible for CD without labor (one for severe fetal growth restriction and one for breech presentation) were in fact allowed

to labor. Neonates destined to develop NE had higher rates of antepartum risk factors than controls (74% versus 18%, odds ratio [OR] = 13.0, 95% confidence interval [CI] 4.4 to 40.4), including previous CD (OR ¼ 4, 95% CI 1.2 to 15), abnormal amniotic fluid volume at ultrasound (OR = 6.8, 95% CI 1.5 to 29.5), and nonreactive FHR tracing before labor (OR = 49.0, 95% CI 5.4 to 1109; In particular, 8/9 cases of nonreactive FHR on admission had also minimal or absent variability with decelerations. Decreased fetal movements were the indication for FHR monitoring in 6/9 cases. FHR abnormalities were the unique antepartum risk factors for NE in three cases, all associated with decreased fetal movements. NE cases had higher rates of intrapartum risk factors than controls (81% versus 19%, OR =18.7, 95% CI 6.4 to 54.0) including acute intrapartum events (OR = 24.5, 95% CI 4.4 to 180.5; whereas chorioamnionitis was not significantly different between cases with or without NE. Sixteen of 19 cases in the NE group admitted to labor and 55/92 of the controls admitted to labor underwent continuous electronic FHR monitoring (35 on admission to labor; in 20 cases the FHR monitoring was converted from intermittent to continuous during labor), and among those admitted to labor, higher rates of suspicious or ominous FHR (13/19 [68%] versus 9/92 [10%], $p < 0.001$, OR =19.9, 95% CI 6.2 to 64.0) was observed. Overall, 7/27 (26%) cases of NE in term infants had only antepartum risk factors, 6/27 (22%) had only intrapartum risk factors, and 12/27 (44%) had a combination of the two. In 2/27 (7%) cases, no risk factors were recognizable. Four of the 26 cases of NE who survived in the neonatal period developed cerebral palsy. One of them fulfilled all four of the necessary criteria outlined by American College of Obstetricians and Gynecologists (ACOG) for cerebral palsy caused by intrapartum events [10,11]. The second one presented only antepartum risk factors (decreased fetal movements and abnormal FHR on admission). The third case occurred in a patient with polyhydramnios, nonreactive FHR on admission, and a biophysical profile class of 6/10, who was allowed to undergo induction of labor, which was complicated by Boylan [12] suspicious FHR tracing and passage of meconium, and resulted in emergency CD at 8 cm of dilation. Neonatal birth weight was 3300 g, umbilical artery pH was 7.07 with base excess of 11, and Apgar scores were 0 and 6 at 1 and 5 minutes, respectively. The fourth case followed an uncomplicated pregnancy, and FHR tracing was reassuring throughout labor. Shoulder dystocia was encountered at delivery, with an interval-to-delivery of 8 minutes. The male infant weighed 3400 g, had umbilical artery pH of 7.20 with base excess of 6, and Apgar scores of 0, 0, and 1 at 1, 5, and 10 minutes, respectively.

Discussion

Our analysis of factors associated with NE in a prospectively collected cohort of term deliveries suggests that antepartum risk factors, alone or in combination with intrapartum events, are present in the majority of cases (74%), as reported in the largest study to date [13,44]. However, isolated antepartum risk factors are present only in a minority of cases (22%), suggesting that labor can act as trigger for events leading to NE in the presence of preexisting conditions. Of the factors we considered, those achieving statistical significance are obesity, history of a CD, and nonreactive FHR tracing before labor. Obesity has already been associated with higher rates of shoulder dystocia, low Apgar scores, and admission to the neonatal intensive care unit, [15–17] and we make the novel observation that it is also a risk factor for NE. Of interest, obesity was associated with an eightfold increased risk of NE despite its low prevalence in our population (3.8%). Centers with higher rates of obesity may confirm such an association and further investigate that factors mediate the adverse effect of obesity on neurological outcome. History of a CD was associated with a fourfold increase in risk of NE in our study, despite the absence of uterine rupture in any of our cases. This is also a novel observation, as an association between history of CD and NE has been reported in previous observational studies only among women suffering uterine rupture [18,19]. However, history of CD is an independent risk factor for stillbirth in the absence of uterine rupture, suggesting that presence of a uterine scar per se could have an effect on fetal well-being [20]. The third and most important antepartum predictor was abnormal FHR tracing on admission, which increased the risk of NE by nearly 50 times. A strength of our study is that FHR tracings, both on admission and during labor, were prospectively evaluated and classified, thus avoiding the risk of interpretation bias. Because all cases with abnormal FHR tracing on admission underwent immediate CD without labor, NE in such cases is likely the manifestation of damage already established in the antepartum period or at least not related to the delivery. Our rate of isolated intrapartum risk factors for NE (22%) is higher than that reported by Badawi et al [21] (4%). The discrepancy can be explained by the difference in availability of FHR tracing during labor in the two series, as it was only 50% in the series of Badawi et al and 84% in our NE cases. Although 40% of women in the control group did not undergo continuous FHR monitoring, the likelihood that an ominous pattern was missed in the absence of risk factors, decelerations, or changes in color of fluid is likely small. As nonreassuring FHR tracing during labor was the leading intrapartum risk factor for NE in our series (13/19 or 68%), the lack of a FHR tracing in half of cases in the series of Badawi et al

possibly led to failed recognition of intrapartum risk factors. Even though the predictive value of nonreassuring FHR for NE is poor in the general population [22] the sensitivity of the test (i.e., the proportion of NE cases with abnormal FHR tracing) is good, [19–21] which has led to the suggestion that some cases of intrapartum asphyxia could be prevented by an improved interpretation and management of FHR tracing [23].

Conclusion

Future efforts to reduce the rates of NE should thus be directed toward the identification of antepartum risk factors. In a minority of such cases (such as fetal growth restriction), there may be a lower fetal threshold to hypoxic or ischemic events during the end of pregnancy or labor. Timely intervention in such cases may minimize the fetal insult and the occurrence of NE. In the majority of cases, however, identification of individual risk factors is unlikely to alter clinical decision making and affect the rate of NE because of the rarity of NE and the fairly common occurrence of antepartum risk factors. Moreover, statistical association does not imply causality; further studies should evaluate which risk factors fulfill the criteria for a causal association with NE.

References

[1] American College of Obstetricians and Gynecologists, American Academy of Pediatrics. Neonatal Encephalopathy and Cerebral Palsy: Defining the Pathogenesis and Pathophysiology. Washington, DC: ACOG; 2003.

[2] MacLennan A. A template for defining a causal relation between acute intrapartum events and cerebral palsy: international consensus statement. BMJ 1999;319:1054–1059

[3] Badawi N, Kurinczuk JJ, Keogh JM, et al. Intrapartum risk factors for newborn encephalopathy: the Western Australian case-control study. BMJ 1998;317:1554–1558

[4] Cowan F, Rutherford M, Groenendaal F, et al. Origin and timing of brain lesions in term infants with neonatal encephalopathy. Lancet 2003;361:736–742

[5] Sarnat HB, Sarnat MS. Neonatal encephalopathy following fetal distress. A clinical and electroencephalographic study. Arch Neurol 1976;33:696–705

[6] Becher JC, Stenson BJ, Lyon AJ. Is intrapartum asphyxia preventable? BJOG 2007;114:1442–1444

[7] Shah P, Riphagen S, Beyene J, Perlman M. Multiorgan dysfunction in infants with post-asphyxial hypoxic-ischaemic encephalopathy. Arch Dis Child Fetal Neonatal Ed 2004; 89: F152–F155

[8] Parazzini F, Cortinovis I, Bortolus R, Fedele L. [Standards of birth weight in Italy]. Ann Ostet Ginecol Med Perinat 1991;112:203–246

[9] Fisher WM, Stude I, Brandt H. Ein Vorschlag zur Beurteilung des antepartualen Kardiotokogramms. Geburscht Perinatol 1976;180:116–120

[10] Catalano PM. Management of obesity in pregnancy. Obstet Gynecol 2007;109(2 Pt 1):419–433

[11] Cedergren MI. Maternal morbid obesity and the risk of adverse pregnancy outcome. Obstet Gynecol 2004;103:219–224.

[12] Boylan P. Intrapartum fetal monitoring. Baillieres Clin Obstet Gynaecol 1987;1:73–85.

[13] Perlow JH, Morgan MA, Montgomery D, Towers CV, Porto M. Perinatal outcome in pregnancy complicated by massive obesity. Am J Obstet Gynecol 1992;167(4 Pt 1): 958–962

[14] Landon MB, Hauth JC, Leveno KJ, et al; National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network. Maternal and perinatal outcomes associated with a trial of labor after prior cesarean delivery. N Engl J Med 2004;351:2581–2589.

[15] Spong CY, Landon MB, Gilbert S, et al; National Institute of Child Health and Human Development (NICHD) Maternal-Fetal Medicine Units (MFMU) Network. Risk of uterine rupture and adverse perinatal outcome at term after cesarean delivery. Obstet Gynecol2007;110:801–807

[16] Smith GC, Pell JP, Dobbie R. Caesarean section and risk of unexplained stillbirth in subsequent pregnancy. Lancet 2003; 362:1779–1784

[17] Nelson KB, Dambrosia JM, Ting TY, Grether JK. Uncertain value of electronic fetal monitoring in predicting cerebral palsy. N Engl J Med 1996;334:613–618

[18] Spencer JA, Badawi N, Burton P, Keogh J, Pemberton P, Stanley F. The intrapartum CTG prior to neonatal encephalopathy at term: a case-control study. Br J Obstet Gynaecol 1997;104:25–28

[19] American College of Obstetricians and Gynecologists. ACOG Practice Bulletin No. 106: Intrapartum fetal heart rate monitoring: nomenclature, interpretation, and general management principles. Obstet Gynecol 2009;114:192–202

[20] Larma JD, Silva AM, Holcroft CJ, Thompson RE, Donohue PK, Graham EM. Intrapartum electronic fetal heart rate monitoring and the iden

[21] Badawi N, Kurinczuk JJ, Keogh JM, et al. Antepartum risk factors for newborn encephalopathy: the Western Australian case-control study. BMJ 1998;317:1549–1553.

[22] Berglund S, Grunewald C, Pettersson H, Cnattingius S. Severe asphyxia due to delivery-related malpractice in Sweden 1990–2005. BJOG 2008;115:316–323.