Original Article

Prenatal and Perinatal Determinants of Neonatal Seizures Occurring in the First Week of Life

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ABSTRACT

To evaluate prenatal and perinatal risk factors for early neonatal seizures, we conducted a case-control study including 100 newborns with neonatal seizures in the first week of life and 204 controls randomly selected from a list of healthy newborns born in the same hospital during the study period. Generalized tonic seizures were the most common seizures observed (29%), although the majority of newborns (71%) experienced more than one type of seizure. The most frequent presumed etiology of neonatal seizures was hypoxic-ischemic encephalopathy (30%). A history of epilepsy in first-degree relatives was found only for cases. Neonatal seizures were found to be associated with maternal disease in the 2 years before pregnancy, mother's weight gain > 14 kg during pregnancy, placental pathology, preeclampsia, low birthweight, low gestational age, and jaundice in the first 3 days of life. The need for cardiopulmonary resuscitation was found only for cases (37%). The causal pathways for neonatal seizures often begin before birth, and some of the factors identified may be preventable. (*J Child Neurol* 2001;16:651–656).

Neonatal seizures are considered important predictors of neurologic diseases and are also supposed to be indicators of the quality of perinatal care.[1] Although they have been attributed to many causes, the majority of cases are owing to only a few serious conditions, such as hypoxic-ischemic encephalopathy, intracranial hemorrhage, infections, and congenital malformations.[2,3]

Despite the fact that seizures represent the most frequent neurologic disorder among newborns, there still exists much controversy: seizures are difficult to recognize, there is a lack of uniformity of the case definition with different opinions on "what" has to be considered an epileptic seizure, and there are conflicting opinions as to whether seizures per se may cause brain damage.[4–7]

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Consequently, estimates of the frequency of neonatal seizures may be biased, with the estimated incidence rates varying greatly according to the level of confidence in the diagnosis.[8] As a result, the identification of risk factors has also been hindered. In fact, except for preterm birth and low birthweight, which have been reported as important risk factors,[8] little is known about other potential determinants, such as familial and maternal factors.

The objective of the present study was to evaluate familial, maternal, and neonatal risk factors for early neonatal seizures.

MATERIALS AND METHODS

We conducted a case-control study at the Neonatal Intensive Care Unit and Nursery of the University of Chieti, Italy. Cases were recruited over a 7-year period from January 1992 to December 1998. The cases consisted of 100 newborns with seizures in the first week of life, identified by systematic review of all clinical records. The controls (n = 204) were randomly selected from a list of healthy newborns born in the same hospital during the study period and who had been placed in the Nursery.

To evaluate exposure to potential risk factors, we collected information from clinical records and from face-to-face interviews with the mothers of the newborns. The main information collected from the clinical records was gestational age, birthweight, need for

intubation and cardiopulmonary resuscitation, clinical characteristics of seizures, electroencephalographic (EEG) findings, and diagnostic evaluation. All of the mothers of both cases and controls were interviewed by a single pediatric neurologist using a standardized questionnaire. The information collected included sociodemographic characteristics, a family history of epilepsy, maternal reproductive history (including diseases in the 2 years before pregnancy, number of miscarriages, stillbirths, death in the neonatal period, previous preterm births, and previous placental pathology), course of the current pregnancy (including the interval between previous and current pregnancy, order of birth, smoking, drug intake, bleeding, weight gain of > 14 kg, hypotension, hypertension, placental pathology, preeclampsia, and premature rupture of membranes), and modality of delivery (presence of umbilical cord around the neck, breech or shoulder presentation, use of forceps or vacuum extractor, cesarean section, and twin delivery).

Since healthy newborns are usually discharged within the third or fourth day of delivery, we investigated the occurrence of seizures after discharge and up to the end of the first week of life to avoid possible misclassification. Neonatal seizures were diagnosed based on the description on clinical records and on the evaluation of EEGs by a senior neuropediatrician. The clinical classification used was that proposed by Volpe, which includes focal clonic seizures, multifocal clonic seizures, generalized tonic seizures, myoclonic seizures, and subtle seizures.[2] Newborns with isolated subtle phenomena, such as subtle motor movements, autonomic changes, or apneas, were excluded from the study because of the possible misclassification owing to the low correlation between subtle phenomena and EEG-video monitoring.[7] The etiology of seizures was evaluated based on maternal and neonatal history, physical and neurologic examination, laboratory data (abnormal arterial gas values; acid-base balance; biochemical evaluation for serum calcium, magnesium, and glucose; blood cultures; and urine cultures), cerebrospinal fluid examination, EEG, and cranial ultrasound scans using a VINGMED, Sonda 7.5 Hz. All of the data mentioned above were taken from the clinical records. The definitions of the main variables investigated are provided in the Appendix.

Statistical Analysis

We performed a frequency distribution of the variables investigated as potential risk factors for neonatal seizures. Continuous variables, such as mother's education, weight gain during pregnancy, and age at delivery, were categorized according to biologic considerations or conventional cutoff points. Similarly, birthweight and gestational age were split into three strata (≥ 2500 g, 2499–1500 g, < 1500 g and ≥ 37 weeks, < 37 ≥ 32 weeks, < 32 weeks). To test and quantify the association between potential risk factors and neonatal seizures, crude odds ratios and their 95% confidence intervals (univariate analysis) were calculated for each exposure factor. To identify risk factors that were independently associated with neonatal seizures, variables significantly more frequent in cases than in controls at a univariate level ($P < .05$) were included in a logistic regression model.[9] When the results suggested the presence of confounding effects, owing to the strong association between different variables involved in a multistep chain of events, stratum-specific odds ratios were calculated (ie, if a noncausal association between factor C and the main outcome A was mediated through the association between risk factor B and C, the association between A and C in the presence or absence of B [ie, the possible confounding variable] was evaluated). Then, in case of confounding, and only if an effect modification could be ruled out, the variable was included in the final model.

RESULTS

Clinical Characteristics of the Cases

The majority of newborns (71%) experienced more than one type of seizure; subtle seizures were those most frequently associated with other seizures. Fifty-nine percent of the newborns experienced seizures in the first 2 days of life, 19% in the third and fourth days, and the remaining 22% from the fifth to the seventh day of life. Generalized tonic seizures were the most common seizures observed (29% of infants), followed by multifocal clonic seizures (13%), focal clonic seizures (9%), and myoclonic seizures (5%), all of which were associated with subtle seizures. The other combinations of seizures included generalized tonic and focal or multifocal clonic (8%), generalized tonic and myoclonic (2%), and focal clonic and multifocal clonic (5%). The remaining 29% experienced only one type of seizure: clonic (focal or multifocal) (19%), tonic (focal or generalized) (9%), or spasms (1%).

Interictal EEG was available for all of the newborns: in 20% of cases, it was normal; in 47% of cases, it showed asymmetries of background activity and/or background immaturity for gestational age; in 5% of cases, it showed a pattern-like burst suppression; and in 28% of cases, it showed depressed activity or episodic generalized voltage attenuation. The following etiologies were presumed to be responsible for neonatal seizures: hypoxic-ischemic encephalopathy (30% of infants), variably associated with hyaline membrane disease and metabolic disorders such as hypocalcemia, hypoglycemia, and hyponatremia; birth defects and chromosomal and metabolic diseases (cleft palate and lip, microcephaly, heart defects, trisomy 13, and glycogen storage disease) (11%); intracranial hemorrhage (subdural, intraventricular, periventricular, and miscellaneous) (10%); hypocalcemia and hypomagnesemia (9%); intracranial infections (bacterial and viral meningitis) or sepsis (8%); isolated hypocalcemia (5%); hypocalcemia associated with congenital anomalies (4%); isolated hypoglycemia (2%); miscellaneous (intrauterine growth retardation, benign neonatal convulsions) (4%); and unknown etiology (16%).

Sociodemographic Characteristics and Familial Predisposition to Epilepsy

The frequency distribution of demographic variables is shown in Table 1. No statistically significant differences were found between cases and controls with regard to family size or gender, although there was an excess of males among cases (63% vs 37%) compared with controls (56% vs 44%) and family size. The parents of cases tended to have a lower socioeconomic status than the parents of controls. The mothers of cases were two times more likely to have

Table 1. Frequency Distribution of Demographic Variables

	Cases (n = 100)	*Controls (n = 204)*
	n *(%)*	n *(%)*
Sex		
Male	63 (63.0)	114 (55.9)
Female	37 (37.0)	90 (44.1)
Ratio	1.70	1.27
Mother's age (yr)		
Median (range)	28 (20–41)	27 (18–40)
Mean (SD)	28.7 (5.4)	27.6 (4.4)
Number of siblings		
Median (range)	1.0 (0–5)	1.0 (0–5)
Mean (SD)	0.85 (1.0)	0.78 (0.93)
Mother's education (yr)		
≤ 8	61 (61.0)	85 (41.6)
9–13	36 (36.0)	98 (48.0)
≥ 14	3 (3.0)	21 (10.4)
Father's education (yr)		
≤ 8	56 (56.0)	77 (37.7)
9–13	38 (38.0)	92 (45.1)
≥ 14	6 (6.0)	35 (17.2)

attended school for 8 years or less compared with the mothers of controls (Table 2). A history of epilepsy in first-degree relatives was found for 4 cases (4 of the 285 first-degree relatives: 1 mother, 1 father, and 2 brothers) and for none of the controls (0 of 570 first-degree relatives) ($P < .05$) (data not shown). The 4 newborns with this history showed a combination of different types of seizures in the presence of hypoxic-ischemic encephalopathy (1 case), cleft palate and lip complicated by bronchopneumonia (1 case), and unknown etiology (2 cases).

Maternal Risk Factors

The maternal risk factors for neonatal seizures are shown in Table 2. Diseases in the 2 years before pregnancy (ie, diabetes mellitus, heart disease, ovarian cysts) were 6.1 times more likely to have occurred among the mothers of cases compared with the mothers of the controls. Although previous preterm birth was more common among the mothers of cases (8% vs 5.4% for the mothers of controls), the difference was not statistically significant (data not shown). As far as maternal factors during pregnancy were concerned, a weight gain of more than 14 kg showed the strongest association with neonatal seizures (odds ratio: 26.9; confidence interval: 10.3–70.5). Although the univariate analysis revealed an association for bleeding, this was not confirmed by the multivariate analysis.

When compared with the mothers of controls, the mothers of cases were 16.6 times more likely to have had a placental pathology (ie, placenta previa, meconium staining, placental infarction, retroplacental hematoma, abruptio placentae) and 5.1 times more likely to have presented preeclampsia. Premature rupture of membranes was 4.5 times more common among cases; however, after adjustment for the other variables, the odds ratio dramatically changed direction, becoming 0.1. This was owing to the confounding effect of low gestational age, which was strongly associated with premature rupture of membranes ($P < .0001$). After stratifying for gestational age, the odds ratio of neonatal seizures for premature rupture of membranes was 0.2 for term newborns and 0.5 for preterm newborns. Cesarean section was reported by 27% of the mothers of cases and by 22% of the mothers of controls. For 44% of the mothers of cases who had undergone cesarean section, the reason was evidence of fetal heart-rate abnormality (recorded by electronic monitoring during labor). This reason was not reported for any of the mothers of controls.

Neonatal Risk Factors

The neonatal risk factors for seizures are shown in Table 2. Cases were more likely than controls to have had a low birthweight (ie, < 2500 g). Both the crude and adjusted odds ratio were extremely high, although the lower confidence interval of the odds ratio for birthweight under 1500 g was lower than 1 at the multivariate analysis. Gestational age of <37 ≥ 32 weeks was also a significant risk factor for neonatal seizures, with an adjusted odds ratio of 20.6; the lowest gestational age (< 32 weeks) was only marginally associated with neonatal seizures at the multivariate analysis, probably owing to the small number of preterm newborns included in the study. Cases were more likely than controls to have experienced jaundice during the first 3 days of life (adjusted odds ratio >11). The proportion of twins among cases was more than twice that observed among controls (4% vs 1.5%), but the difference was not statistically significant (data not shown). With regard to being small for gestational age, there were no differences between cases and controls (7% of cases vs 6.4% of controls), although cases tended to be smaller than controls. The need for cardiopulmonary resuscitation was found only among cases (37%) and not among controls.

DISCUSSION

We found neonatal seizures to be strongly associated with low gestational age and low birthweight, two related factors that have been shown to play an important role in predisposing newborns to seizures.[8,10,11] It is plausible that the effect of these factors is mostly mediated through hypoxic-ischemic events or intracranial hemorrhage, which have been reported to be the most important conditions associated with preterm birth and neonatal seizures.[12] This could explain our finding that 38% of newborns had a cranial ultrasound diagnosis of hypoxic-ischemic encephalopathy or intracranial hemorrhage. Neonatal seizures related to the above-mentioned conditions appear to have the same pattern of risk factors identified for other central nervous system disorders, such as cerebral palsy, symptomatic epilepsies, and mental retardation.[13,14] Given that the high risk of neonatal seizures in preterm newborns is high, therapeutic strategies for preventing and controlling seizures in these infants should be adopted. This is especially important when considering the results of a recent study among neonatal rats, which suggests that neonatal seizures increase

Table 2. Maternal and Neonatal Risk Factors for Early Neonatal Seizures

	Cases (n = 100)	*Controls (n = 204)*		
Risk Factors	n *(%)*	n *(%)*	*Crude ORs (95% CI)*	*Adjusted ORs (95% CI)*
Mother's education (yr)				
> 8	39 (39.0)	119 (58.3)	1.0	1.0
≥ 8	61 (61.0)	85 (41.7)	2.2 (1.3–3.7)	2.1 (1.0–4.6)
Diseases in the 2 years before pregnancy				
No	86 (86.0)	195 (95.6)	1.0	1.0
Yes	14 (14.0)	9 (4.4)	3.5 (1.4–9.3)	6.1 (1.7–21.6)
Mother's weight gain > 14 kg				
No	54 (54.0)	195 (95.6)	1.0	1.0
Yes	46 (46.0)	9 (4.4)	18.5 (8.1–43.4)	26.9 (10.3–70.5)
Bleeding				
No	86 (86.0)	194 (95.1)	1.0	1.0
Yes	14 (14.0)	10 (4.9)	3.2 (1.3–8.0)	2.9 (0.6–13.3)
Placental pathology				
No	89 (89.0)	202 (99.0)	1.0	1.0
Yes	11 (11.0)	2 (1.0)	12.5 (2.6–117.2)	16.6 (2.3–119.7)
Preeclampsia				
No	84 (84.0)	197 (96.6)	1.0	1.0
Yes	16 (16.0)	7 (3.4)	5.4 (2.0–15)	5.1 (1.4–18.9)
Premature rupture of membranes				
No	75 (75.0)	190 (93.1)	1.0	1.0
Yes	25 (25.0)	14 (6.9)	4.5 (2.1–9.7)	0.1 (0.0–1.2)
Birthweight (g)				
≥ 2500	60 (60.0)	196 (96.1)	1.0	1.0
2499–1500	34 (30.0)	6 (3.4)	18.0 (8.9–38.8)	12.5 (2.9–52.6)
< 1500	6 (10.0)	1 (0.5)	19.7 (4.2–93.4)	11.1 (0.5–258.4)
Gestational age (wk)				
≥ 37	57 (57.0)	196 (96.1)	1.0	1.0
< 37 ≥ 32	29 (29.0)	7 (3.4)	14.2 (5.7–40.1)	20.6 (1.6–257.3)
< 32	14 (14.0)	1 (0.5)	48.1 (6.9–2045)	19.0 (0.9–392.7)
Jaundice first 3 days				
No	79 (79.0)	198 (97.1)	1.0	1.0
Yes	21 (21.0)	6 (2.9)	8.8 (3.2–27.4)	11.7 (3.2–42.3)

the susceptibility of the developing brain to subsequent seizure-induced injury.[6]

With regard to premature rupture of membranes, there was an association only at the univariate analysis. Gestational age was a confounder of the association between premature rupture of membranes and neonatal seizures, as shown by the inversion of the odds ratio. This was mainly owing to the unexpectedly high frequency of premature rupture of membranes in preterm controls (ie, seven of the eight preterm controls had premature rupture of membranes), which caused problems in estimating the odds ratios. These results make it difficult to disentangle the effect of premature rupture of membranes and low gestational age on neonatal seizures. The results of previous studies suggest that preterm premature rupture of membranes can be complicated by chorioamnionitis in up to 70% of cases, and infection is likely to result in termination of the pregnancy.[15] Furthermore, preterm infants exposed to chorioamnionitis are two to three times more likely to develop neurologic disorders, including seizures, compared with infants with the same gestational age but without a diagnosis of chorioamnionitis.[16] Jaundice was also found to be an important neonatal risk factor, and since hyperbilirubinemia has the potential to cause cerebral damage, an increased risk of neonatal seizures owing to its possible neurotoxicity cannot be ruled out. A previous study showed an independent association between hyperbilirubinemia and neonatal seizures only in infants with intracranial hemorrhage.[17] This finding is somewhat consistent with our results, which show a stronger association with hyperbilirubinemia in the preterm newborns (data not shown), who are at higher risk of intracranial hemorrhage.

With respect to maternal characteristics, we found an association between low educational level and neonatal seizures. Low educational level, which has been reported to be associated with other neurologic conditions, such as cerebral palsy, mental retardation, and newborn encephalopathy,[14,18,19] may play a role in the mothers receiving inadequate care during pregnancy and the lack of preventive interventions.

To our knowledge, this is the first study to report an association between excessive weight gain during pregnancy and neonatal seizures. Although excessive weight gain may be associated with diabetes and hypertension, in our study, the association remained even after controlling for these factors. However, it must be considered that excessive weight gain during pregnancy has been shown to be associated with increased incidence of induced labor, admission to neonatal intensive care, and perinatal mortality.[20]

Bleeding in the first trimester tended to be more common among mothers of cases, although the association was

not statistically significant on multivariate analysis. In previous studies, first- and second-trimester vaginal bleeding was found to be associated with neonatal seizures in term infants and was considered a risk factor for preterm delivery and subsequent neonatal complications.[21–23]

We found a strong association for placental pathology. To our knowledge, no studies have investigated the impact of this potential risk factor specifically for neonatal seizures, although numerous studies have examined the association between placental findings and preterm delivery, cerebral palsy, mental retardation, and epilepsy. Our finding is somewhat consistent with more detailed studies that show that various placental pathologic features, such as chorioamnionitis, are associated with preterm delivery or neurologic disorders other than neonatal seizures.[24]

A strong association was also found for preeclampsia. Chronic hypertension and pregnancy-induced hypertension associated with proteinuria are known risk factors for reduced uteroplacental perfusion and higher mortality in term growth-restricted fetuses.[25] Furthermore, chronic hypertension in the presence of proteinuria has been reported to be associated with adverse neonatal outcome, including neurologic disorders.[26]

Finally, a history of epilepsy and febrile seizures in first-degree relatives was more common in cases than in controls. Familial predisposition might reflect a genetic susceptibility to seizures. It should also be considered that a high proportion of our cases was at high risk of developing epilepsy owing to the underlying etiology, and neonatal seizures could represent the beginning of a true epileptic history. In this regard, it is already known that genetic susceptibility may increase the risk of symptomatic epilepsy associated with neurologic deficit presumed to be present at birth.[27] However, because of our limited sample size, we were not able to determine the extent to which familial predisposition to seizures contributes to neonatal seizures.

Before drawing conclusions, some limitations and possible biases of the study need to be addressed. First, it is difficult to disentangle the effects of specific exposures because they are often closely related. Furthermore, these exposures may occur at different times between the beginning of pregnancy and delivery, yet they usually coexist at some point. For this reason, the analysis of confounding effects is a necessary step, although it can hardly provide definitive results. Second, the risk factors identified in our study probably cannot be generalized to all of the diagnostic categories (ie, infections, metabolic disorders, etc) because of the high proportion of cases with hypoxic-ischemic encephalopathy and intracranial hemorrhage. This high proportion has been reported by most of the studies conducted to date and is likely to reflect the etiologic distribution of neonatal seizures, mainly those of early onset.[12] Larger studies are needed to identify risk factors specific for the minor diagnostic categories.

In conclusion, we found an association between neonatal seizures and some important familial, maternal, and neonatal exposures. The causal pathways for neonatal seizures seem to begin before birth. However, whether there is a "continuum" of exposure, through familial, maternal, and neonatal factors, remains to be determined. Additional studies are needed to determine the extent to which the removal of specific risk factors can reduce the incidence of neonatal seizures.

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APPENDIX

- Family history of epilepsy: maternal report of two or more unprovoked seizures not related to a specified acute underlying cause
- Diseases in the 2 years before pregnancy: maternal report of any major illness in the 2 years before pregnancy
- Bleeding: maternal report of bleeding during pregnancy lasting at least 24 hours
- Placental pathology: maternal report of physician diagnosis of placenta previa, meconium staining, placental infarction, retroplacental hematoma, abruptio placentae
- Preeclampsia: pregnancy-induced hypertension associated with proteinuria
- Premature rupture of membranes: rupture of membranes before the onset of labor
- Small for gestational age: birthweight less than the 10th percentile for gestational age
- Hypoxic-ischemic encephalopathy: defined according to Sarnat and Sarnat's criteria[28]
- Hypocalcemia: total calcium < 8 mg/dL (birthweight > 2500 g); < 7 mg/dL (birthweight < 2500 g)
- Hypomagnesemia: < 1.6 mg/dL
- Hypoglycemia: < 35 mg/dL (birthweight > 2500 g) in the first 72 hours of life; < 25 mg/dL (birthweight < 2500 g) in the first week of life; < 40 mg/dL (any weight) at the end of the first week of life
- Hyponatremia: < 130 mEq/L

Vignette

Schistosomiasis in Madagascar

Schistosomiasis is a leading infectious disease in Madagascar, ranking just below malaria and tuberculosis. Both *Schistosoma mansoni* and *Schistosoma haematobium* infections are prevalent. Touch preparation of rectal tissue is a common test performed to diagnose intestinal schistosomiasis.

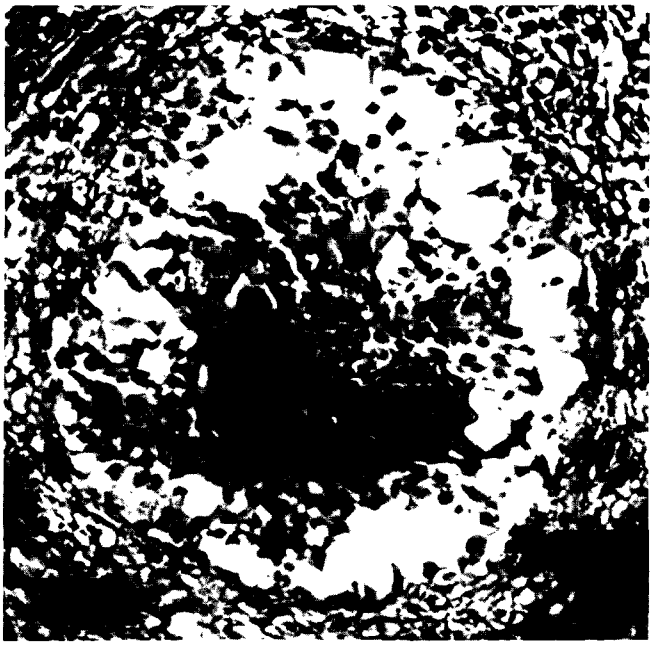

Figure 1. Histologic section of hemorrhoidal tissue showing *Schistosoma mansoni* encased by granulomatous inflammation. (Hematoxylin and eosin stain; original magnification ×100.)

Figure 2. Touch preparation of rectal biopsy demonstrating numerous *Schistosoma mansoni* ova with their characteristic lateral spines. (Iodine stain; original magnification ×400.)

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