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Risk factors for developing epilepsy after neonatal seizures

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ABSTRACT

Neonatal seizures are the most frequent neurological disorder in the neonatal period. The incidence is reported to be higher than at any other period in life. Because of the unique nature of neonatal brain anatomy, connections and the paradoxical nature of neurotransmitters, seizures in this age group vary in semiology from those in older children. They may cause irreversible changes to the synapses in the immature brain and progress to epilepsy.

The aim of the study was to analyse laboratory, clinical, neurophysiological and neuroimaging risk factors for epilepsy in a group of children who experienced seizures in the neonatal period.

A retrospective study of 176 newborns admitted to the Department of Neonatology, University Children's Hospital Ljubljana, due to seizures, was performed. Metabolic disorders and hypoxic-ischaemic encephalopathy were the most frequent aetiological factors associated with seizures. Epilepsy rate in the group was 18%. Pathological cardiotocography, reanimation after delivery, myoclonic type of seizures, more than one type of seizures, severely abnormal electroencephalography, abnormal neurological examination and neuroimaging, treatment with more than one antiepileptic drug and duration of treatment more than one month constituted statistically significant independent predictive factors for epilepsy ($p < 0.05$).

The results of our study further elucidate risk factors for epilepsy after neonatal seizures.

Key words: newborns, seizures, epilepsy, risk factors

Introduction

Seizures are the most common clinical manifestation of neurological dysfunction in newborns. They usually reflect a serious underlying condition such as hypoxic-ischaemic encephalopathy, stroke, haemorrhage, acute infection, hypoglycaemia or other metabolic disorder or brain malformations. (1) The estimated incidence of neonatal seizures is 2 - 3 per 1000 term newborns and 10 - 15 per 1000 preterm newborns. (2) The accumulating experimental data from animal studies suggest that seizures may lead to persistent neurological sequel by interfering with the proper construction of cortical neuronal networks. (3,4) Although mortality rates have been reduced, the morbidity rate remains high, with epilepsy being a frequent sequel. In addition, the development of epilepsy is strongly associated with other permanent neurologic disorders such as intellectual disability and cerebral palsy. (5-7) The occurrence of epilepsy after neonatal seizures varies in frequency, as reported in previous studies, from 3.5% to 56%. (2,8,9)

Clinical studies suggest that the aetiology of neonatal seizures is the most important factor influencing the outcome. (9) Other prognostic factors reported in the literature are interictal electroencephalographic features and early onset of seizures. (10,11) Establishing the risk factors that predict the development of epilepsy would allow clinicians to identify children at high risk and to plan long-term follow-up and health assistance.

The aim of this study was to analyse clinical, laboratory, neurophysiological and neuroimaging risk factors for epilepsy in a group of children with neonatal seizures.

Patients and Methods

The retrospective study included newborns admitted to the Neonatal

Department, University Children's Hospital, Ljubljana, Slovenia, between 1 January 1999 and 31 December 2009 due to neonatal seizures. Inclusion criteria were: clinical and/or neurophysiological seizures in the neonatal period (i.e., first 28 days of life) and at least two years of follow up in our hospital.

The diagnosis of neonatal seizures was based on direct observation of clinical and/or electroencephalography (EEG) events. Seizure types were categorized according to Volpe's classification as subtle, clonic, tonic and myoclonic. (1) Apnoea spells were considered as subtle seizures when concomitantly accompanied by other paroxysmal events and/or tachycardia. The time of occurrence of the seizures was categorized with respect to the age at onset: in the first 24 hours, between 24 and 72 hours and after 72 hours of life.

The aetiology was determined through the study of clinical history and examination, laboratory tests and neuroimaging studies (ultrasound, computed tomography (CT) and/or magnetic resonance imaging (MRI). The interictal background EEG activity was graded into four categories according to Holmes and Lombroso criteria: normal, mildly abnormal, moderately abnormal and severely abnormal. (11) Computed tomography scan or magnetic resonance was considered abnormal when there was evidence of hypoxic-ischaemic lesions, malformations, migrational disorders or alteration in myelination. Interictal neurologic evaluation was defined as normal, mildly abnormal, moderately abnormal or severely abnormal according to Amiel-Tison criteria. Information on treatment with anticonvulsive drugs and on the duration of treatment was collected.

Outcome

Children with post neonatal epilepsy were found through search of the Neurological Department records. Postnatal epilepsy was diagnosed if the child experienced more than two afebrile and unprovoked seizures after the neonatal period.

Table 1. Relationship between gestational age, perinatal factors and epilepsy.

	Without epilepsy	Epilepsy	Total	p
Gestational age				0.059
Term	94 (89%)	26 (21%)	120	
Preterm	47 (90.4%)	5 (9.6%)	52	
Apgar score				0.068
>5/7	97 (84%)	19 (16%)	116	
<5/7	40 (78.5%)	11 (21.5%)	51	
Birth weight				0.068
>2500g	103 (79%)	27 (21%)	130	
<2500g	35 (92%)	3 (8%)	38	
Perinatal factors				
pathological CTG	28 (69%)	13 (31%)	41	0.002 *
meconium aspiration	27 (82%)	6 (18%)	33	0.739
shock/haemorrhage/rupture	4 (100%)	0	4	0.372
LGA/IUGR	5 (83.4%)	1 (16.6%)	6	0.193
Measures at birth				
no measures at birth	62 (89%)	8 (11%)	70	0.358
inflation	27 (70%)	11 (30%)	38	0.053
resuscitation	24 (70%)	10 (30%)	34	0.044 *
intubation	26 (74%)	9 (26%)	34	

* $p < 0.05$; p based on chi-square or Fisher's exact test
CTG, cardiotocography; IUGR, intrauterine growth restriction; LGA, large for gestational age.

Statistical analysis

Statistical analysis compared data of children with neonatal seizures who developed epilepsy and those who did not. The analysis of clinical, neurophysiological and neuroimaging variables was performed by means of chi-square test and Fisher's Exact Test. A p-value of <0.05 was considered significant. Statistical analysis was performed using SPSS version 19.0.

Results

During the study period, 176 children, 72 (40.9%) female and 104 male (59.1%), with neonatal seizures were identified. Their birth weight was from 620 grams to 4500 grams, mean 2820 grams; gestational age from 24 to 41 weeks (mean 33 weeks); 52 (29.5%) were premature. Thirty-two children (18%) developed epilepsy. Adverse prenatal and perinatal events occurred in 115 (65.3%) patients though the groups of children with and without epilepsy were significantly different only in regard to pathologic cardiotocography (CTG) ($p=0.002$) and resuscitation after birth ($p=0.044$) (table 1).

The most common aetiological factor for seizures was hypoxic ischaemic encephalopathy followed by metabolic disorders which included transient electrolyte disorders, hypoglycaemia and inborn errors of metabolism (table 2); the groups of children with and

Table 2. Aetiology of neonatal seizures.

Aetiology	Number (%)
Idiopathic	3 (1.5%)
HIE	62 (35.4%)
intracranial haemorrhage	18 (10.4%)
Stroke	5 (3%)
sepsis	20 (11.2%)
metabolic disorders	47 (26.9%)
genetic disorders	6 (3.4%)
intracranial infection	4 (1.9%)
sinus venous thrombosis	1 (0.4%)
tumour	1 (0.4%)
developmental disorders	3 (1.5%)
Epileptic syndromes	1 (0.4%)
Unidentified	5 (8.8%)

HIE, hypoxic-ischemic encephalopathy.

Table 3. Seizures onset, type, duration of seizure and epilepsy.

	Without epilepsy	Epilepsy	Total	p
Seizures onset				
≤24 h	63 (78%)	17 (22%)	80	0.575
24 - 72h	42 (86%)	7 (14%)	49	
72h - 7 days	31 (84%)	6 (16%)	37	
Seizure type				
subtle	45 (82%)	10 (18%)	55	0.95
clonic	47 (76%)	14 (24%)	57	0.828
myoclonic	44 (74%)	16 (26%)	60	0.041 *
tonic	23 (74%)	8 (26%)	31	0.242
undefined	4 (48%)	3 (42%)	7	0.089
no data	8 (80%)	2 (20%)	10	0.896
More than one type	32 (65%)	17 (35%)	49	0.000 *
Duration of seizures				0.000 *
after neonatal period	32 (75%)	17 (35%)	49	

* $p < 0.05$; p based on chi-square or Fisher's exact test

Table 4. EEG, neuroimaging studies, neurologic assessment, therapy and epilepsy.

	Without epilepsy	Epilepsy	Total	p
EEG				0.001 *
normal	19 (100%)	0	19	
mildly abnormal	59 (91%)	6 (9%)	65	
moderately abnormal	51 (76%)	16 (24%)	67	
severely abnormal	13 (59%)	9 (41%)	22	
CT/MRI				<0.001*
normal	55 (94.9%)	3 (5.1%)	58	
abnormal	24 (59%)	17 (41%)	41	
Neurological assessment				<0.001*
normal	11 (100%)	0	11	
mildly abnormal	60 (96.7%)	2 (3.3%)	61	
moderately abnormal	56 (79%)	15 (21%)	71	
severely abnormal	13 (48%)	14 (52%)	27	

* $p < 0.05$; p based on chi-square or Fisher's exact test
CT, computed tomography; EEG, electroencephalography; MRI, magnetic resonance imaging.

without epilepsy were significantly different only in regard to the presence of metabolic disorders (p=0.028).
Almost half of the infants presented with seizures on the first day of life 80 (46 %) (table 3). In the majority of children clonic (57; 33%) and subtle (55; 32%) seizures were present, but only myoclonic seizures were significantly related to epilepsy (p=0.041). A clinical picture of more than one type of seizures was also highly significantly (p<0.001) related to epilepsy (table 3).
Amiel-Tison neonatal neurological assessment and EEG background activity were both found to be powerful predictors of adverse outcome (p<0.001, p=0.001). Normal and mildly abnormal EEG background activity was associated with a favourable outcome in 78 (45%) out of 84 infants (48%), whereas 16 (24%) infants with moderately and 9 (41%) with severely abnormal background EEG activity had an adverse outcome (table 4). Ninety-nine (56.2%) infants underwent brain imaging studies (CT and/or MRI) in the neonatal period. Infants with abnormal neuroradiology findings were more likely to develop postnatal epilepsy than those with normal findings (41% vs. 5.1%; p<0.001). Only 3 (5.1%) infants with normal brain imaging had an adverse outcome (table 4).
Seventeen infants (9.6%) with refractory

Table 5. Relationship between antiepileptic drugs and epilepsy.

	Without epilepsy	Epilepsy	Total	p
Anticonvulsive therapy				<0.001 *
without	10 (83.4%)	2 (16.6%)	12	
Phenobarbital	87 (82%)	19 (18%)	106	
Phenytoin / Phosphenytoin	31 (100%)	0	31	
combination	7 (42%)	10 (58%)	17	
Duration of therapy				<0.001 *
< one month	75 (98.7%)	1 (1.3%)	76	
> one month	49 (63%)	29 (37%)	78	

* $p < 0.05$; p based on chi-square or Fisher's exact test

seizures, who received a combination of anticonvulsant medications, developed epilepsy ($p<0.001$). The incidence of epilepsy among the group of infants with duration of therapy up to one month, and duration of therapy longer than the neonatal period was significantly different ($p<0.001$) (table 5).

Discussion

Many studies have demonstrated that neonatal seizures are a significant cause of death and adverse neurodevelopmental outcomes, such as cerebral palsy, developmental delay and epilepsy. (11) The follow up period in our cohort was from one to almost ten years and we found that 18% of children who experienced neonatal seizures developed epilepsy. The result is similar to previous contemporary cohorts that used broad clinical and/or electrographic definitions for neonatal seizures. On the contrary, some studies that included only children with seizures confirmed by EEG found a lower incidence rate, which reflects problems in the definition of neonatal seizures as the same epileptic discharges may not be detectable by surface EEG studies. (12,14-16)

Neonatal seizures usually reflect underlying aetiology. The majority of seizures in our population were symptomatic, and different factors from a broad spectrum of aetiologies were identified. Hypoxic-ischaemic encephalopathy (HIE) was identified in the majority of infants in our group. It has also been the leading cause for neonatal seizures in previous studies, though the incidence varied, probably as a result of inconsistent diagnostic criteria used. (9) However, HIE was not associated with an adverse outcome and this was also demonstrated in previous reports, where neonatal seizures and the severity of hypoxic-ischaemic encephalopathy were independently associated with eventual outcome. (17,18) Pathologic CTG, reflecting a hypoxic ischaemic event, also proved to be independently associated with epilepsy in our study. Among other aetiological factors for neonatal seizures, metabolic disorders - inborn error of metabolism and hypoglycaemia - were significantly associated with epilepsy. There are several putative mechanisms for hypoglycaemia-induced cellular injury, including excitatory neurotoxins active N-methyl-d-aspartate receptors, increased mitochondrial free radical generation and initiation of apoptosis and altered cerebral energetic characteristics. (19) Authors who have studied outcomes associated with neonatal hypoglycaemia have reported visual impairments and epilepsy, with the parietal and occipital lobes being affected most severely. (19)

Although the exact prognostic value of the presence of specific seizure types remains a challenge for the clinician, a number of studies converge in reporting that patients with other than focal seizures have a worse outcome compared to those with focal seizures. (20,21) Our results support this observation as myoclonic seizures were statistically significant for developing epilepsy. We also proved the correlation between the myoclonic type of seizures and an underlying metabolic aetiology, so in our future work, we should further elucidate a possible classification of epileptic syndrome (Early myoclonic epileptic encephalopathy). (22)

The severity and pattern of neuroimaging studies are known risk factors for neonatal seizures and subsequent epilepsy, and we also showed a clear relationship between the results of neuroimaging studies and epilepsy. This relationship is the result of preexisting brain abnormalities, which lead to seizures but there is controversy from animal studies regarding whether neural injury can cause changes in excitability, sufficiently to result in unprovoked seizures beyond the neonatal period. (23)

Neurologic assessment across the studies is highly predictive for long-term outcome. (9) The Amiel-Tison neurologic assessment proved to be useful in recognizing children who have normal development despite different perinatal risk factors, and in identifying those children who have adverse neurological outcomes and delayed developmental performance. (24,25) Our study also proved the value of this method of assessment for identifying children with epilepsy.

The high predictive value of abnormal EEG background activity for outcome in neonates with seizures is already well known and was also proved in our study. (9,10,26) Some other studies showed that sequential EEG recordings have better predictive value; they demonstrated that sequential EEG background activity was strongly correla-

ted with postnatal death, neurodevelopmental delay and epilepsy. (27)
Despite the low efficacy reported, infants with seizures end up being given maintenance antiepileptic drugs . The duration and need of a combination of antiepileptic drugs are indicators of clinical severity and are related to an unfavourable outcome. In the cohort we observed a strong association between the need for chronic drug therapy and the development of postnatal epilepsy was found.

Conclusion

Epilepsy is an outcome following neonatal seizures in the setting of different neurologic dysfunctions in the neonatal period. Our data provide further information for clinicians and parents planning long-term care for children with neonatal seizures. Children with metabolic disorders, those who needed resuscitation after birth and had a pathologic CTG, those with myoclonic or more than one type of seizures, and those in whom seizures persisted after the first month of life and needed treatment after the neonatal period, are at a high risk for epilepsy. In the future, new neuroprotective and antiepileptic agents should be studied in neonates with the presented risk factors.

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