Published online: 31/05/2016 Published print: 06/2016

ORIGINAL PAPER

doi: 10.5455/medarh.2016.70.182-185
Med Arch. 2016 Jun; 70(3): 182-185
Received: JAN 25, 2016 | Accepted: APR 15, 2016

Predictors of Mortality in Neonates with Seizures; a Prospective Cohort Study

Suada Heljic[1], Sajra Uzicanin[1], Feriha Catibusic[2], and Smail Zubcevic[2]

[1]Neonatal Intensive Care Unit, Pediatric Clinic, UCC Sarajevo, Bosnia and Herzegovina
[2]Child Neurology Department, Pediatric Clinic, UCC Sarajevo, Bosnia and Herzegovina

Corresponding author: Prof. Suada Heljić, MD, PhD, Pediatric Clinic, UCC Sarajevo, Bosnia and Herzegovina, Tel.++38761865285; ORCID ID: orcid.org/0000-0003-3929-2541, E-mail: heljicsuada@hotmail.com

ABSTRACT

Objective: The aim of this study was to analyze prognostic indicators for mortality in neonates with seizures in a level III Neonatal Intensive Care Unit (NICU). **Patients and methods:** A cohort of 100 neonates with clinically manifested seizures hospitalized in the NICU during 4 years period was prospectively monitored for the first year of life. The cohort consisted of 33 preterm and 67 full-term babies with 60 male and 40 female infants. **Results:** The mortality rate in the first year of life of infants with seizures in the neonatal period was 23%. The most common cause of seizures was birth asphyxia for full-term infants and intra-periventricular hemorrhage for preterm infants. Death was more common in pre-term than term infants (p <0,005). Simple regression demonstrated statistically significant associations between death in the first year of life and a cluster of highly associated variables: resuscitation (p<0, 01), mechanical ventilation (p<0,01) and asphyxia (p<0,05). This cluster of variables significantly correlates with: gestational age (p<0, 05), birth weight (p<0, 05) and intracranial hemorrhage (p<0, 05). **Conclusion:** In this cohort of neonates with seizures asphyxia requiring neonatal resuscitation was the primary risk factor for death.

Key words: neonatal seizures, death, NICU, preterm infants, full-term infants.

1. INTRODUCTION

Seizures are the most common and distinctive clinical manifestation of neurologic dysfunction in the newborn infant. Neonatal seizures by definition occur within the first 4 weeks of life in a full-term infant and up to 44 weeks from conception for premature infants. Seizures are most frequent during the first week of life (1-3).

Seizures in neonates are relatively common, with variable clinical manifestations. Overall incidence is approximately 3 per 1000 live births; in a neonatal intensive care unit the incidence is as high as 8-15% (4). Their presence is often the first sign of neurologic dysfunction, and they are powerful predictors of long-term cognitive and developmental impairment. Newborns with seizures are at risk for neonatal death, neurologic impairment, developmental delay and later epilepsy (1-3). Causes of neonatal seizures include birth asphyxia, intracranial hemorrhage, metabolic disorders, infections, congenital malformations, benign familial seizures. The objective of this study was to describe the etiologic profile and prognostic indicators of mortality for infants with neonatal seizures in a level III NICU.

2. PATIENTS AND METHODS

During four years period a cohort of 100 neonates with clinical seizures was established with the intent to follow these infants until they reach age 3 years. This study is focused on infant mortality i.e. death prior to one year of age. Initial assessment was performed during their hospitalization in the NICU, further follow-up was done through regular visits to the outpatient facilities of the Department of Child Neurology. The inclusion criteria for the cohort were: Term neonates of <28 days age with manifested seizures and preterm babies with seizures prior to

44 weeks postconceptional age, EEG and neuroimaging (UZ, CT or MRI) performed during the neonatal period.

Investigation: A uniform protocol for diagnosis and management of neonatal seizures was used. Prenatal, perinatal and postnatal data were reviewed in detail from the medical records of the mothers and infants. An EEG was analyzed by a pediatric neurologist, for each infant in the cohort. Neuroimaging studies: Ultrasound was performed in all investigated infants. For term infants an MRI scan was generally performed after the acute period; if a more rapid scan in an acutely ill term infant was needed, CT scan was performed. The following laboratory investigations were performed routinely: glucose, calcium, magnesium, sodium, urea and creatinine, arterial pH, blood culture; lumbar puncture was performed if clinically indicated. Second line laboratory investigations were done if needed (virology, congenital infections screen, chromosomal analysis, blood ammonia, urine for maternal drugs, etc).

Diagnosis of seizures was based on observation by experienced NICU staff and confirmed by the neurologist, using conventional EEG registration (Silicon Biomedical Instruments BV). All babies were under rigorous physiological monitoring during the time of clinical seizures.

Diagnosis of asphyxia was based on metabolic parameters including severe metabolic acidosis (pH below 7,0, BE below -12), Apgar score ≤3 after 5 minutes, need for prolonged resuscitation and neurological assessment demonstrating moderate or severe encephalopathy based on the Sarnat scale (5).

Diagnosis of CNS inflammation was based on clinical manifestations, blood/liquor culture and neuroimaging studies. Diagnosis of intracranial hemorrhage was based on brain ultrasonography, and other neuroimaging techniques, if needed, using the anatomic classification of intra-periventricular hemorrhage by Papile (6).

For this study standard statistical analyses were used, using program SPSS version 14.0.

3. AIM

The aim of this study was to analyze: a) prognostic indicators for mortality in neonates with seizures in a level III Neonatal Intensive Care Unit (NICU), and b) mortality rate of those infants during first year of life.

4. RESULTS

The study included 100 infants with registered seizures during their hospitalization in the NICU. The investigated group consisted of 33 preterm and 67 full-term infants; 60 of them were male and 40 were female. Among 60 male patients 17 were born prematurely; among 40 female infants 16 were born prematurely. The majority of preterm infants (20/33) with seizures were born before 32 gestational weeks; 11 infants were post-term. Average gestational age of preterm infants was 30.47±3.22 GW; average gestational age of term infants was 39,51±1.22 weeks. Causative factors for seizures when apparent are summarized in Tables 1 and 2; at least one factor was present in 97 of the 100 infants. HIE was the most common cause of seizures in term infants; IVH-PVH was the most frequent cause in preterm infants.

Asphyxia	None Antepartum Postpartum	48 49 3
Intracranial hemorrhage	No Yes	70 30
Transient metabolic disturbance	No Hypocalcaemia+ hypomagnesiemia Hypoglycaemia Hypocalcaemia+hypoglycaemia Other	77 14 6 1 1
Infection/inflammation	No Sepsis Meningitis Sepsis + meningitis	65 27 6 2
CNS abnormalities	No Yes	95 5
Other causes (or unknown)	No Yes	97 3

Table 1. Etiologies of seizures in the entire cohort (n=100)

Term infants n= 67			Total (%)
HIE			34 (51)
Brain infarctions			4 (5,9)
Intracranial hemorrhage	Intraparenchymal	3	9 (13)
	Extraparenchymal	4	
	Combined	2	
Preterm infants (n=33)			Total (%)
IVH-PVH gr. I/II			7 (21)
IVH gr. III/IV			9 (27)
PVL (cystic)			9 (27)
PVL + IVH gr III/IV			5 (15)

Table 2. Results of brain imaging for term and preterm infants (n=100)

	Term infants		Preterm infants		Total
Survived	55 (82.1%)		22 (67.7%)		77 (77%)
	Male	Female	Male	Female	
	32	23	12	10	
Died	12 (17.9%)		11 (33.3%)		23 (23%)
	Male	Female	Male	Female	
	11	1	5	6	
Total	67 (100%)		33 (100%)		100

Table 3. Mortality rates by gestational age and sex

Table 3 summarizes mortality by gestational age and gender. Death was more common in this cohort among premature infants than term infants (X^2 = 29,160; df. = 1; p <0,005) and among male term infants than female term infants (X^2= 27,597 df=1 p<0,001).

Risk factors for mortality

We used simple logistic regression to examine correlations for the entire cohort between 12 potential risk factors and the primary outcome of death before age 12 months (Table 4). All of the risk factors were dichoto-

	1	2	3	4	5	6	7	8	9	10	11	12	13
1. Death	1	0,17	0,11	0,05	0,11	0,17	0,23	0,32	0,36	0,24	0,00	0,17	-0,02
2. Prenatal history		1	0,58	0,07	-0,11	0,19	0,21	0,21	0,15	0,17	0,02	0,20	-0,12
3. Medications			1	0,01	-0,29	0,06	0,10	0,04	0,02	0,01	-0,10	0,12	-0,04
4. Manner of delivery				1	-0,14	-0,08	-0,17	0,10	0,00	0,15	-0,29	0,06	-0,10
5. Sex					1	-0,12	-0,07	0,17	0,11	0,20	0,13	-0,04	0,11
6. GA						1	0,85	0,24	0,31	0,25	0,29	0,65	-0,03
7. BW							1	0,21	0,27	0,26	0,32	0,54	0,04
8. Resuscitation								1	0,70	0,78	0,10	0,21	-0,20
9. MV									1	0,64	0,17	0,23	-0,12
10. Asphyxia										1	0,08	0,23	-0,19
11. Infection											1	0,18	-0,10
12. ICH												1	-0,11
13.Metabolic disord.													1

Table 4. Correlation between potential risk factors and death. **P<0,01 (yelow) *P<0,05 (green)

mous variables. The table also includes correlations between the risk factors examined. Due to the small number of cases, we excluded multiple pregnancy and developmental abnormalities of the brain from this analysis. Factors included in the analysis included: death (yes 23; no 77); prenatal complications (including chorioamnionitis or other maternal infection, chronic maternal disease, and prolonged rupture of membranes, positive 22; no 78); medications during pregnancy (yes 38; no 52); manner of delivery (cesarean section 36; vaginal delivery 64); sex (60 male; 40 female); preterm/term (preterm 33; full term 67); birth weight (<2500g yes 36, >2500g no 64); resuscitation (defined as a positive pressure ventilation yes 56; no 44); mechanical ventilation during hospitalization (yes 54; no 46); asphyxia (yes 52; no 48); infection/inflammation (yes 35; no 65); intracranial hemorrhage (yes 30; no 70) and transient metabolic disorders (yes 23; no 77).

5. DISCUSSION

Mortality rates for neonates with clinical seizures have declined over time, from approximately 40% in hospital based studies reported from the 1960s to more recent figures of 7-16% for term infants (7, 8). Mortality in our cohort is consistent with other cohort studies (e.g. 16% among term infants and 42% among premature infants in Ontario Canada) (9). In our study 20 (20%) infants died during their hospitalization in NICU and 3 after neonatal period, during first year of life. Despite improved survival, the risk of long term neurodevelopmental delay remains high with studies reporting a range from 28% to 46% (7-9).

Our cohort is similar to other reports in the following: increased risk of neonatal seizures among males (13, 14); increased risk of mortality in preterm infants (9, 15); increased risk of seizures among infants born post-term(16); and increased risk of seizures among neonates with perinatal asphyxia (1-3, 16-18).

Diagnosis of HIE depends primarily on recognition of the clinical syndrome using the Sarnat scale but also on a variety of neurodiagnostic techniques, including MRI and CT brain scans. In our study HIE was diagnosed by neuroimaging studies in 34/67 (50,7%) of full term infants. Similar results have been reported in other studies (7, 8). These seizures usually occur within the first 72 hours of life, may be seen in term and premature infants, and often remit after a few days. Other cerebrovascular insults including arterial and venous stroke, intracerebral hemorrhage and subarachnoid hemorrhage in term infants also frequently present clinically with seizures. In our study 13 full term infants had manifestation of such events. Therapeutic hypothermia has been demonstrated to decrease mortality and improve neurodevelopmental outcomes in term and late preterm infants with moderate and severe HIE (19, 20). In our cohort, 7/34 of the term infants with HIE received therapeutic hypothermia.

In this cohort IVH-PVH was the most common cause of neonatal seizures among preterm infants. In our study the majority of preterm infants (23/33) had IVH-PVH or combination of hemorrhage with PVL , which is consistent with the literature (21).

Infection/inflammation during the neonatal period is a common cause of neonatal seizures and has a significant impact on neurodevelopmental outcome, regardless of etiology (22-24). In this cohort, sepsis and meningitis were diagnosed in 35% and 8% of infants with neonatal seizures respectively. Sepsis and meningitis are common causes of mortality in neonates (24). In this cohort 7% of infants died of sepsis and meningitis (20% of septic infants).

Metabolic disturbances responsible for neonatal seizures include hypoglycemia, hypocalcaemia, hypomagnesemia, and abnormalities of other electrolytes and amino acids. Many metabolic causes are readily treatable, and when such metabolic disturbances are the primary cause of neonatal seizures, they are rarely associated with significant long-term consequences. Analysis of metabolic disturbances in neonates with seizures: hypocalcemia / hypomagnesemia (14%), hypoglycemia (6%) and both – hypocalcemia and hypoglycemia (2%) are similar (8) to literature data. Symptomatic neonatal hypoglycemia is frequently associated with impaired neurodevelopmental (8).

Malformations of cortical development that frequently present with early life seizures include lissencephaly,

polymicrogyria, focal cortical dysplasia etc. Developmental abnormalities of the brain in our study were found in 5 infants: microcephalia in two cases (together with lissencephaly and Dandy Walker malformation) and in 3 cases of hemimegalencephaly. Unilateral macrencephaly–hemimegalencephaly, isolated or as a part of a syndrome is associated with severe refractory seizures in the neonatal period and often results in severe neurodevelopmental delay (25).

6. CONCLUSION

In this cohort of 100 infants with neonatal seizures, the mortality rate was high, consistent with previous reports. Seizures are the most prominent signals of a broad spectrum of neonatal neurological disorders most commonly related to brain injury associated with HIE in term infants and PVH-IVH in premature infants. Future studies of this cohort are planned including evaluation of neurodevelopment and prevalence of epilepsy and cerebral palsy at age 3, at entrance to primary school and at entrance to high school.

Author's contribution: Sajra Uzicanin: substantial contribution to acquisition of data, substantial contribution to analysis and interpretation of data, drafting the article. Feriha Catibusic: substantial contribution to conception and design, substantial contribution to acquisition of data, substantial contribution to analysis and interpretation of data. Smail Zubcevic: substantial contribution to acquisition of data, substantial contribution to analysis and interpretation of data. Suada Heljic: substantial contribution to conception and design, final approval of the version to be published.

- Conflict of interest: None declared.

REFERENCES

1. Volpe JJ. Neurology of the Newborn 5th ed. Saunders, Philadeplphia, 2008, 203-37
2. Rennie JM, Boylan GB. Neonatal seizures and their treatment. Curr Opin Neurol. 2003; 16: 177-81.
3. Hill A. Neonatal seizures. Pediatrics in Review. 2000; 21: 117-21
4. Sheth RD, Hobbs GR, Mullett M. Neonatal seizures: incidence, onset, and etiology by gestational age. J Perinatol. 1999; 19(1): 40-3.
5. Sarnat HB, Sarnat MS. Neonatal encephalopathy following fetal distress. A clinical and electroencephalographic study. Arch Neurol. 1976; 33: 696-705.
6. Papile LA, Burnstein J, Burnstein R, et al. Incidence and evolution of subependymal and intraventricular hemorrhage: a study of infants with birth weights less than 1,500 gm. J Pediatr. 1978; 92: 529-34.
7. Jensen FE. Neonatal Seizures: An Update on Mechanisms and Management Clin Perinatol. 2009; 36(4): 881-900.
8. Tekgul H, Gauvreau K, Soul J, et al. The current etiologic profile and neurodevelopmental outcome of seizures in term newborn infants. Pediatrics. 2006; 117: 1270-80.
9. Ronen GM, Buckley D, Penney S, et al. Long-term prognosis in children with neonatal seizures: a population-based study. Neurology. 2007; 69(19): 1816-22.
10. Brunquell PJ1, Glennon CM, DiMario FJ Jr, Lerer T, Eisenfeld L. Prediction of outcome based on clinical seizure type in newborn infants. J Pediatr. 2002 Jun; 140(6): 707-12.
11. Scher MS, Aso K, Beggarly ME, et al. Electrographic seizures in preterm and full-term neonates: clinical correlates, associated brain lesions, and risk for neurologic sequelae. Pediatrics. 1993; 91: 128-34.
12. Pisani F, Copioli C, Turco EC, Sisti L, Cossu G, Seri S. Mortality risk after neonatal seizures in very preterm newborns. J Child Neurol. 2012; 27(10): 1264-9.
13. Hall DA, Wadwa RP, Goldenberg NA, Norris JM. Maternal risk factors for term neonatal seizures: population-based study in Colorado, 1989-2003. J Child Neurol. 2006; 21: 795-8.
14. Glass HC, Pham TN, Danielsen B, Towne, Glidden D, Wu YW. Antenatal and intrapartum Risk Factors for Seizures in Term Newborns: A Population-Based Study, California 1998-2002. Pediatr Neurol. 2012; 46(2): 111-5.
15. Holanda Manoel RR, de Melo AN. Comparative clinical study of preterm and full term newborn neonatal seizures. Arq Neuro-Psiquiatr. 2006; 64 (1): 45-50.
16. Ehrenstein V, Pedersen L, Holsteen V. et al. Postterm delivery and risk for epilepsy in chilhood. Pediatrics. 2007; 119: 554-61
17. Bergamasco B, Penna P, Ferrero P, et al. Neonatal hypoxia and epileptic risk: A clinical prospective study.Epilepsia. 1984; 25: 131-46.
18. Graham EM, Ruis KA, Hartman AL, Northington FJ, Fox HE. A systematic review of the role of intrapartum hypoxia-ischemia in the causation of neonatal encephalopathy. Am J Obstet Gynecol. 2008; 199(6): 587-95.
19. Azopardi DV, Strohm B, Edwards AD, Dyet L, Halliday HL, Juszczak E. et al. Moderate hypothermia to treat perinatal asphyxial encephalopathy. N Engl J Med. 2009; 361: 1349-58.
20. Shankaran S, Pappas A, Laptook AR, McDonald SA, Ehrenkranz RA, Tyson JE et al. Outcomes of safety and effectivness in a multicenter randomized, controlled trial of whole-body hypothermia for neonatal hypoxic-ischemic encephalopathy. Pediatrics. 2008; 122: 791-8.
21. McCrea HJ, Ment LR. The diagnosis, menagment and postnatal prevention of intraventricular hemorrhage in the preterm neonate. Clin Perinatol. 2008; 35(4): 777-92.
22. Shah DK, Doyle LW, Anderson PJ, Bear M, Daley AJ, Hunt RW, et al. Adverse neurodevelopment in preterm infants with postnatal sepsis or necrotizing enterocolitis is mediated by white matter abnormality on magnetic resonance imaging at term. J Pediatr. 2008; 153: 170-5.
23. Gopel W, Hartel C, Ahrens P et al. Interleukin 6-174- genotipe, sepsis end cerebral injury in very low birth weight infants. Genes Immun 2006; 7:65-8.
24. De Jonge RCJ, van FurthM, Wassenaar M, Gemke RJBJ ,Caroline B,Terwee CB. Predicting sequelae and death after bacterial meningitis in childhood: A systematic review of prognostic studies. BMC Infect Dis. 2010; 10: 232.
25. Manett JB, WangY, Chang YJ, Paramasivam M, LoTurco JJ. Dcx Re-expression Reduces Subcortical Band Heterotopia and Seizure Threshold in an Animal Model of Neuronal Migration Disorder. Nat Med. 2009; 15(1): 84-90.
26. Foley ME, Alrab M, Dalay L, Keane D. MacQuillan, Oherlihy C. Term neonatal asphyxial seizures and periparum deths: lack od correlation with rising cesarean delivery rate. Am Jour of Obst and Gynec. 2005; 192: 102-8.