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Original Article

Risk Factors and Scoring System as a Prognostic Tool for Epilepsy After Neonatal Seizures

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ABSTRACT

BACKGROUND: Neonatal seizures may cause irreversible changes to the immature brain and. A scoring system for early prognostic information could be a useful clinical tool. The aim of the study was to analyze risk factors for epilepsy after neonatal seizures, to validate Garfinkle's scoring system, and to analyze whether a new scoring system is feasible. **METHODS:** A retrospective study of 176 newborns (59.1% boys, 40.9% girls, 70.5% term, 29.5% preterm; mean birth weight 2820 g), admitted to the Department of Neonatology, Division of Pediatrics, University Medical Centre, Ljubljana, because of neonatal seizures (clinical and/or neurophysiological), was performed. Epilepsy rate between 2 and 12 years of follow-up was 18.1%. Five independent predictors from Garfinkle's study and other known predictors were entered into hierarchical binary logistic regression models and analyzed through four steps to identify independent predictors of epilepsy. We tested whether any of the predictors was an effect modifier. **RESULTS:** Of five potential predictors from Garfinkle's score, electroencephalograph background findings and etiology were predictive. Etiologies, gestation, mode of delivery, duration of seizures, and other risk factors at birth were found to be independent predictors. Duration of seizures has a different effect on prognosis depending on the gestational age. **CONCLUSION:** Gestational age determines the association between duration of seizures and epilepsy. Scoring systems to predict development of epilepsy after neonatal seizures need to limit interaction between important predictor variables.

Keywords: newborn, seizures, epilepsy, risk factors, scoring system

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Introduction

Seizures are a common clinical manifestation of neurological dysfunction in newborns. They usually reflect a serious underlying condition such as hypoxic-ischemic encephalopathy, stroke, hemorrhage, acute infection, hypoglycemia, 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.[2,3] The accumulating data from animal studies suggest that seizures may lead to persistent neurological sequelae by interfering with the proper construction of cortical neuronal networks.[4,5] Although mortality rates have been reduced, the morbidity rate remains high, with epilepsy being a frequent sequela. In addition, the development of epilepsy is strongly associated with other permanent neurological disorders, such as intellectual disability and cerebral palsy.[6-8] The occurrence of epilepsy after neonatal seizures varies in frequency from 10% to 50% in previous studies.[9,10]

Clinical studies suggest that the etiology of neonatal seizures is the most important factor influencing the outcome.[11] Other prognostic factors reported in the literature are interictal electroencephalographic features, early

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onset of seizures, longer duration of seizures, and status epilepticus.[6,9,12-15] The prognostic significance of many other risk factors is equivocal and may reflect variation in data collection, classification, and analysis. Establishing risk factors and the development of prognostic scoring system that predict the development of epilepsy after neonatal seizures would allow clinicians to identify children at high risk and to plan long-term follow-up and health assistance. Until now, three studies have attempted to design risk score for adverse outcome after neonatal seizures: one almost 30 years ago analyzed clinical criteria only.[16] The other two are newer and one of them is focused only on term infants, but both are based on clinical, neuroimaging, and neurophysiological criteria.[17,18] Unfortunately, none of them has been broadly applied into daily clinical work.

In the score developed in the Garfinkle's study, five of 11 potential predictors of adverse outcome were shown to be independent predictors on binary logistic regression analysis: cesarean delivery, seizure onset on the first day of life, seizure type other than focal clonic, moderately to severely abnormal electroencephalograph (EEG) background findings, and etiology of either infection, postoperative, cerebral dysgenesis, inborn error of metabolism, or other genetic disorders. These five variables were used for the construction of scoring system with the minimum possible score of 0 and maximum of 5. A score of $\geq$3 was set as the cutoff of adverse outcome.[17]

Contrary to other studies, which were designed to study risk factors for different aspects of adverse neurodevelopmental outcome after neonatal seizures, our study focused only on risk factors for epilepsy. Our aim was to analyze clinical, laboratory, neurophysiological, and neuroimaging data; to validate the five point scoring system developed in the Garfinkle's study; and to analyze whether a new scoring system for the prediction of epilepsy in newborns with neonatal seizures is feasible.

Patients and Methods

Patients

The retrospective study included newborns admitted to the Department of Neonatology, Division of Paediatrics, University Medical Centre, Ljubljana, Slovenia, between January 1, 1999, and December 31, 2009, because of neonatal seizures. Inclusion criteria were clinical and/or neurophysiological seizures in the neonatal period (i.e., first 28 days of life) and at least 2 years of follow-up in our hospital. The medical documentation was retrospectively reviewed, and clinical, neurophysiological, and imaging data were collected: gestational age, birth weight, mode of delivery, Apgar score at minute 5, need for resuscitation at birth, additional risk factors (meconium aspiration, pathological cardiotocography [CTG] or both), seizure type, time of seizure onset, etiology, interictal EEG, neuroimaging studies (computed tomography [CT] or magnetic resonance imaging [MRI]), Amiel-Tison neurological examination, treatment, and duration of seizures.

Methods

The diagnosis of neonatal seizures was based on the direct observation of clinical and/or EEG events. Seizure types were categorized according to Volpe's classification as subtle, clonic focal, clonic multifocal, tonic, and myoclonic.[1] Apnea spells were considered 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 and after 24 hours of life.

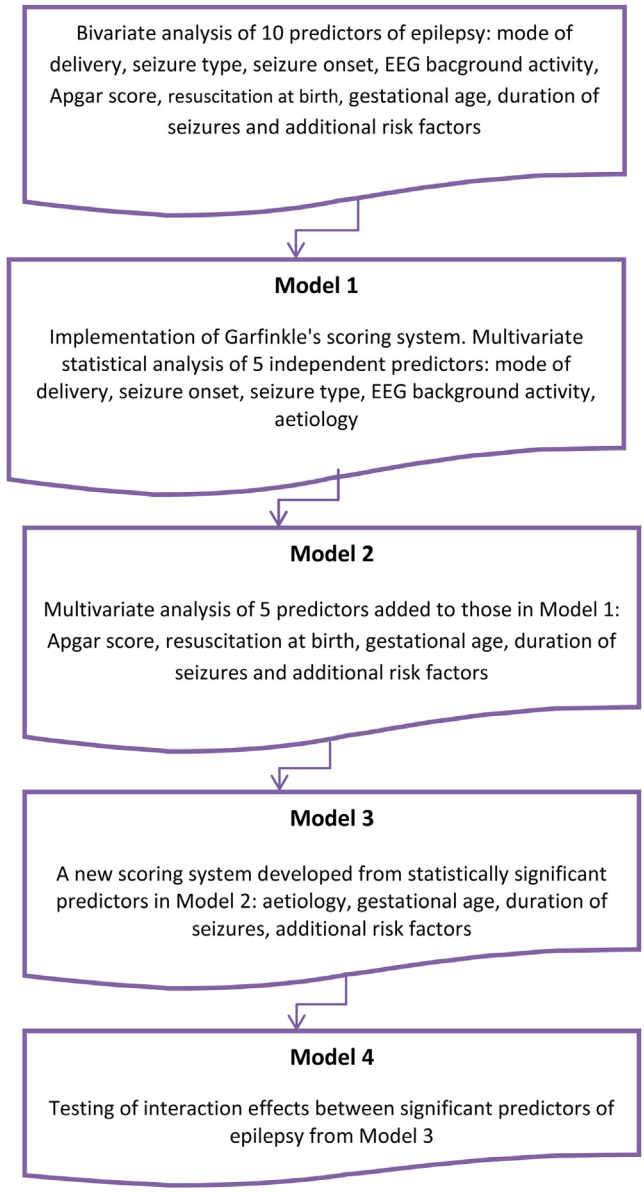

FIGURE 1.
Steps in the methodology of analysis.

The etiology was determined through the study of clinical history, examination, laboratory tests, and neuroimaging studies (ultrasound, CT, and/or MRI). It was defined as hypoxic ischemic encephalopathy, intracranial hemorrhage, cerebrovascular accident, infections, cerebral dysgenesis, inborn errors of metabolism, other genetic disorders, and postoperative ischemia.

The interictal background EEG activity was graded into four categories according to criteria used in Garfinkle's article: normal, mildly abnormal, moderately abnormal, and severely abnormal.[17,19] Duration of seizures was defined as a dichotomous variable with clinical seizures or EEG epileptiform activity for $\leq$1 month or $>$1 month.

CT or MRI scan was considered abnormal when there was evidence of hypoxic-ischemic lesions, hemorrhage, ischemic stroke, sinus thrombosis, white matter injury, infection, congenital anomalies, migrational disorders, or alteration in myelination.

Interictal neurological evaluation result was defined as normal, mildly abnormal, moderately abnormal, or severely abnormal according to the Amiel-Tison criteria.[20] Information on the treatment with anticonvulsive drugs was defined as treatment with phenobarbital, with more than one antiepileptic drug, or without treatment.