A Factor Analysis Model for Dimension Reduction of Outcome Factors in Neonatal Seizure Context

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Abstract

There is a controversial concept among many studies whether neonatal seizures are risk factors for neonatal death and/or neurodevelopment impairments (in case of newborn survivors). Multiple factors have been analyzed in literature, including perinatal factors, etiology factors, seizures characteristics factors, investigations findings factors, therapy-related factors. This paper aims to review the characteristics and the application context of different computational models developed for identifying both the risk factor of morbidity (epilepsy, cerebral palsy, development disability or their combination) and the mortality outcome after neonatal seizures. Consequently, we determined the groups of main risk factors using factor analysis. The vast majority of identified models are logistic regression models, but also decision tree models. In the literature, there is a large variation in establishing the risk factors determining poor or favorable outcome after a neonatal seizure, with similarities and inconsistencies. These findings could be a consequence of different approaches regarding inclusion criteria, methodologies used to identify seizure, seizures definition or description, analysis using computational models.

Keywords: neonatal seizures, risk factors, epilepsy, mortality, logistic regression, decision tree

1. Introduction

Presence of seizures and seizures control are very important aspects that clearly affect the intervention care phases and clinicians decision-making process. The differential diagnosis of neonatal and perinatal seizures is a complex task for a practitioner and it includes a lot of pathological conditions (epileptic and nonepileptic): 1. Nonepileptic (gastroesophageal reflux-Sandifer Syndrome, cyanotic breath-holding attacks, shuddering spells and jitteriness, pallid syncopal attacks-reflex anoxic attacks, hyperlexia, cardiac arrhythmias, subarachnoid hemorrhage, subdural hematoma, mitochondrial cytopathies, meningitis, encephalitis), 2.epileptic syndromes (benign, myoclonic, pyridoxine) (Cazan et. al., 2014; Cazan et. al., 2017). Hence, the differential

diagnosis algorithms should be undertaken carefully and efficiently in order to promptly intervene in the case management and to avoid any undesirable complication. Currently, there are many efforts to perform either noninvasive assessment of biomarkers in children with epilepsies or to apply different computational models to categorize the risk factors for susceptible cases (Shahar et. al., 2012; Choy, 2014; Azhibekov, 2015; Nicolae et. al., 2016; Pitkänen, 2016; Mahoney, 2016).

Different outcomes from neonatal period affect not only the suffering patient but the whole community. Multiple prognostic factors have been analyzed in literature, including perinatal factors, etiology factors, seizures characteristics factors, investigations findings factors, therapy-related factors Costea et. al. 2017). This paper aims to review the characteristics of different computational models developed for identifying the risk factor of outcomes after neonatal seizures and to determine the groups of main risk factors.

2. Methods

We examined NCBI databases (PMC, PubMed) using multiple search word combinations: neurological outcome, risk factors, neonatal seizure and neurological outcome, neonatal seizure, and epilepsy, neonatal seizure and mortality, selecting the articles including computational models analysis.

The information from each article was synthesized in three synoptic tables. Table 1 presents the reviewed studies description: author, year of publication, study period, type. We discussed the study concepts linked with the seizures description or definition, the inclusion or exclusion criteria and with other methodologies used to identify seizure and different risk factors. Table 2 offers details concerning the characteristics of these models designed to identify the risk factors. Table 3 provides further information about the identified outcomes and risk factors using different computational models.

Eventually, a factor analysis was implemented to define specific risk factors groups (table 4). Based on our previously presented work (Maniu et. al., 2017), we also considered in the factor analysis input (beside de reviewed studies from this paper) another five studies describing a different, scoring system based, approach (Ellison et. al., 1981, 1986; Pisani et. al., 2009; Garfinkle, & Shevell, 2011; Salamon et. al., 2014; Hur, & Chung, 2016).

3. Results

We have found ten new highly related studies from the literature review, published between 2005 and 2016, of which two were multicenter studies (considering 2 and 4 centers) while the rest were one hospital based case series (Miller et. al., 2005; Ambalavanan, 2006; Nunes, 2008; Pisani, 2012; Yildiz, 2012; Lai, 2013; Vargas, 2013; Anand, 2014; Shah, 2014; Pisani, 2016). Their brief description is presented in table 1.

Table 1. Reviewed studies description

First author Year / Country Study period / Study type	Study description
Miller 2005 / California 1994-2000 R, HB, MC	-173 term (GA>=36 wk) newborns with neonatal encephalopathy (2 centers, 121 (1994-2000) + 52) -gestational age median: 6 days (range 1-24 days) -magnetic resonance imaging (MRI)
Ambalavanan 2006 /Maryland -/MC	-205 neonates diagnosed as having hypoxic-ischemic encephalopathy - HT and control groups
Nunes 2008 / Brazil 1999-2003 P (3659), PB	-101 newborns with seizures -diagnosis of neonatal seizures was based on clinical observation -seizure etiology was based on positive clinical data, laboratory data and/or imaging studies (CUS, CT or MRI)
Pisani	-403 consecutive newborns with gestational age from 24 to 32 weeks

2012 / Italy 2000-2007 / R, HB	(preterm) -clinical and EEG-confirmed neonatal seizures
Yildiz 2012 / Turkey 2007-2009 / R,HB	-112 newborns (ages of 23-44 months) after manifesting seizures in their first postnatal 28 days
Lai 2013 / Taiwan 1999-2009 / R, HB	-232 term infants with clinical neonatal seizure - 17 related risk factors were analyzed - clinical neonatal seizure, EEG, CUS
Vargas 2013/Colombia 2008-2012 / CC, HB	-GA < 44 wk with neonatal seizures, treated with phenobarbital -20 case (without response), 35 control (with adequate response)
Anand 2014/India -/ R,HB	-108 newborns with seizure - EEG, USG, CT, MRI
Shah 2014 / UK 2007-2011 R,HB	- 85 neonates from 4 centers undergoing 72 h of TH - study hypothesis: seizure burden is associated with cerebral tissue injury independent of amplitude-integrated EEG (aEEG) background activity
Pisani 2016 / Italy 1999-2012 / R,HB	- 76 preterm newborns with seizure - video-EEG confirmed seizure - CUS

R retrospective, P prospective, CC case – control study, MC multicenter controlled trail, PB populational based, HB hospital based, C clinical, CT computed tomographic scan, MRI cerebral magnetic resonance imaging, CUS cranial ultrasonography / cerebral ultrasound, USG ultrasonography, EEG electroencephalogram (standard), CpH cord Ph, BpH blood Ph, HT therapeutic hypothermia

It can be noticed that seizure diagnosis was based on clinical grounds and functional explorations naming neuroimaging and/or EEG procedures (conventional EEG, aEEG, vEEG, CUS, MRI). The minimum number of newborns considered in these studies was 55, while the maximum was 403 with a mean of 148 (SD=86.75, median=112, IQR: (98,175)) and a total of 2226 evaluated cases.

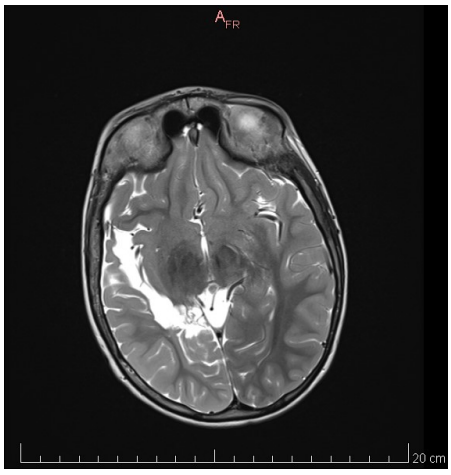

Figure 1. Pediatric epilepsy in the context of a cerebral malformation (Research and Telemedicine Center in Neurological Diseases, Pediatric Clinical Hospital from Sibiu, Romania)

The most frequently used computational model was the regression model, especially the binary logistic regression (table 2). The significance level considered varied significantly between studies (0.05-0.2). A few authors combined the significance level with OR (greater than 1). A few studies specified the model's performance using specific indicators such as correct classification

rates, sensitivity, and specificity. The performance values varied from 67% to 80% in case of death or disability and from 71% to 77% in case of death or 85.5% (in overall outcomes of the situation).

Table 2 Characteristics of different computational models developed for identifying the risk factors

Study	Computational models	Reported indicators
Miller 2005	Fisher exact test for qualitative (binary and non binary) variables	N, %, p
	Kruskal-Wallis tests, Spearman rank correlation, bootstrap modeling for non-normality investigation for numeric variables	Median (range), p
	Univariate linear regression	score change, 95% CI, p
	Multivariate model	score change, 95% CI, p
Ambalavanan 2006	early neurologic examination	correct classification rates
	logistic regression	OR
	scoring system	correct classification rates
	classification and regression tree analysis	correct classification rates
Nunes 2008	Fisher and chi square tests for qualitative (only binary) variables	N, %, RR, 95% CI, p
	Student's t test for numeric variables	M, SD, 95% CI, p
	multiple logistic regression model	β coefficient, t, p
Pisani 2012	Multivariate analysis	OR, 95% CI, p
Yildiz 2012	Multivariate logistic regression	OR, 95% CI
Lai 2013	Fisher and chi square tests for categorized data	N, %, p
	simple and multiple logistic regression models	N, %, OR, 95% CI, p
Vargas 2013	contingency tables, Fisher and chi square tests	M, SD
	logistic regression	OR, 95% CI, p
Anand 2014	Chi-square test	N, %, p
Shah 2014	Univariate and multivariate logistic regresion	OR, 95% CI, p
Pisani 2016	Student's t test for numeric variables	N,%
	chi square tests for qualitative variables	sensitivity, specificity
	multivariate logistic regression model	

Outcomes like death, brain injury, cerebral palsy, developmental delay and/or epilepsy were displayed in table 3 for further analysis in our review. In some studies, different comorbidities were individually evaluated determining risk factors for each outcome. In other reports they were considered together (overall outcomes). Only in three research papers, treatment factors were considered and identified as risk factors.

Table 3 Risk factors of outcomes and mortality in neonatal seizures

Study	Outcomes	Identified risk factors
Miller 2005	Brain injury	BW, intensive resuscitation, severe encephalopathy, severe seizure
Ambalavanan 2006	death or moderate/severe disability at 18 to 22 months or death as the outcomes	few components of the early neurologic examination were associated with poor outcomes
Nunes 2008	epilepsy (EP)	abnormal PNN, abnormal PEEG, BW Multivariate analysis – 0 factors
	developmental delay	abnormal NN, abnormal PNN, abnormal PEEG, earlier PNS, GA, BW

		Multivariate analysis: abnormal PN, abnormal PEEG
	mortality	GA Multivariate analysis – 0 factors
Pisani 2012	mortality brain damage	abnormal UBS, BW (<1000), cardiopulmonary resuscitation
Yildiz 2012	cerebral palsy, epilepsy, developmental delay	etiology, Apgar score, resuscitation, electroencephalogram, neonatal status epilepticus, cranial imaging findings, type/duration of antiepileptic treatment, response to acute treatment
Lai 2013	death, cerebral palsy, global developmental delay, and/or epilepsy	abnormal UBS, abnormal cerebral artery resistance index, abnormal EEG, presence of congenital heart disease
Vargas 2013	risk for therapeutic failure with phenobarbital and posible feature complications	*antecedents at birth/adaptation: seizure semiology* (more than one), latency to phenobarbital startup greater than 12 hours, subtle or tonic seizures, seizures longer than 5 minutes *postnatal antecedents*: low AS10, maternal intrapartum infection, neonatal shock
Anand 2014	Overall seizure outcome	Low GA, low BW, low AS5, etiology, SO, ST_EPI, abnormal radiological findings, abnormal EEG
Shah 2014	Overall seizure outcome	electrographic seizure burden
Pisani 2016	Overall seizure outcome (death, development delay, cerebral palsy, epilepsy)	BW, AS1, neurologic exam, EEG, UBS, presence of ST_EPI

AED - antiepileptic drug, CP - cerebral palsy, GDD - global developmental delay, GA - gestational age, BW- birth weight, RS - repeated/recurrent seizure, MD - type/mode of delivery, AS1 - Apgar score at 1 minute, AS5 - Apgar score at 5 minute, AS10 - Apgar score at 10 minute, SO - seizure onset, ST_EPI - status epilepticus, UBS - ultrasound brain scan, MSU- maternal substance used, MIS – maternal inflammatory state, PRM- prolonged rupture of membranes, PNN – postnatal neuroimaging, PNS – postnatal seizure.

The most frequently identified risk factors were the EEG findings (abnormal / severe electroencephalogram results), seizure characteristics (type, onset, duration, semiology), etiology, birth weight, Apgar score, cerebral ultrasound scan findings (abnormal) (Figure 2).

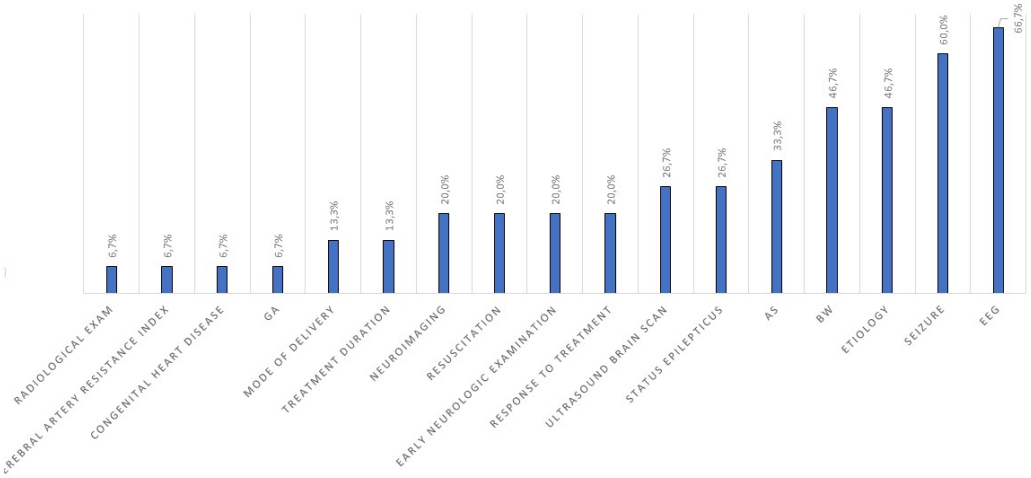

Figure 2. Identified risk factors hierarchy

As can be seen from Table 3, many different factors have been identified in previous studies as risk factors in neonatal seizures. In order to group these large number of factors, factor analysis was used. Factor analysis' main objective is to reduce many items into fewer latent factors by grouping similar variables into dimensions on the bases of pattern correlations.

We consider reducing the risk factors dimension using factor analysis with principal axis factoring extraction method and varimax with Kaiser Normalization rotation method in our attempt to identify latent risk factors. The principal component analysis finds for the initial data a new orthonormal basis having the axes ordered depending on variance (from high to low). The new ordered vectors (eigenvectors) are the principal components. The method generated 5 main factors, this number being extracted from the examination of scree plot and eigenvalues (over 1). First latent factor gathered the treatment and the resuscitation records, the second one included Apgar score and status epilepticus. Delivery mode, gestational age, and birth weight (medical history factors) were grouped as the third-factor category. The forth category comprised the etiology and seizure characteristics while the fifth considered functional and imaging data (EEG, ultrasound brain scans, neuroimaging -MRI, CT) (table 4).

Table 4. Factor analysis reduction factors rotated matrix

	Factor				
	1	2	3	4	5
treatment duration	.892				
response to treatment	.738	.510			
resuscitation	.715				
early neurologic examination	-.482				
status epilepticus		.937			
AS		.905			
mode of delivery			.847		
BW			-.631	.440	
GA			.627		
etiology				.863	
SO				.669	
ultrasound brain scan				-.454	-.404
EEG	-.439				.703
neuroimaging					.702

4. Discussions and conclusions

Prominently, the inclusion and exclusion criteria, the methodologies used to identify seizures, the description or the definition of seizures were different in these studies. Anand et. al. (2014) referred in their study to the clinical diagnosed seizures, newborns lacking the synchronized video EEG recordings. The affected newborns with very subtle or electrical only seizures might have been excluded. Lai (2012) had a similar approach analzying the patients with clinically evident seizures. On the other hand, Pisani et. al. (2016) studied only the newborns with confirmed video-EEG. A more complex analysis was presented in Shah 2014 study, where the aEEG and MRI were considered for diagnosis. Seizures pattern recorded on aEEG with corresponding 2-channel raw EEG (aEEG/EEG), were classified by severity of background and seizure burden; MR images were interpreted based on the severity of tissue injury.

Different risk factors related to the medical history were considered by different studies. Lai, 2014 considered 17 variables such as gender, delivery mode, small for date status, maternal illness, perinatal insults, meconium stained liquor, Apgar score at 1 and 5 minutes, seizure onset age, seizure type, etiology, electroencephalography (EEG) findings, antiepileptic drug efficacy, presence of metabolic acidosis, cranial ultrasonographic findings, and the presence of congenital heart disease. Conversely, Anand et. al. (2014) selected the following variables: time of onset of seizure, type, duration and frequency of seizure, neurological examination at the onset of the seizure, gestational age, type of delivery, birth weight, Apgar score at 1 and 5 min, resuscitation at the time

of birth. Biomarker assessment for these patients however such as routine chemistries including blood sugar, sepsis screen, lumbar puncture, serum electrolytes such as sodium, calcium, magnesium, EEG, neuroimaging (ultrasonography/computerised tomography/magnetic resonance imaging [USG/CT/MRI]), TORCH screening and inborn errors of metabolism screening were performed whenever indicated by the clinician and we couldn't recognize a systematic approach in this respect. In contrast, Ambalavanan used clinical and the laboratory variables (available within 6 hours of birth) to develop the model (both scoring system and decision tree).

As a consequence, distinctive computational models and distinctive approaches in using the models were employed in these reports with a predictable variability in the identified risk factors. In some analysis, univariate and multivariate regression techniques were applied only on categorical variables while in other studies there were both categorical and numerical variables. We didn't find any description of the categories selection. Moreover, we noticed differences in cut of points considered for the same variable (risk factor) between authors. Vargas et. al. (2013) considered that there was a higher risk with more than six medical antecedents at birth or with more than five postnatal medical antecedents. Miller et. al. (2005) findings pointed out that the measured prenatal risk factors did not predict the brain injury pattern types as neuroimaging biomarkers (watershed predominant, basal ganglia/thalamus predominant, and normal) but that the patterns of brain injury in terms of neonatal encephalopathy are associated with different clinical presentations and neurodevelopmental outcomes.

The large amount of factors identified in previous studies as risk factors for outcomes in neonatal seizures context make their analysis difficult to accomplish. We consider our approach to be an interesting and practical design for future computational models. It operates five major groups that cluster the most important studied risk factors on the reviewed studies. By using this type of data reduction technique, the large number of factors considered as risk factors for outcome in neonatal seizure context are restructured and we can identify derive groups of factors / underlying factors to be considered by the specialists in intervention care phases but also in prognostic and prediction of clinical outcome. Although there are controversial discussions regarding the use of factor procedure in case of categorical (binary) variables, the resulted groups have clinical relevance. Nonetheless, there are other limitations for this model related to the number of the included studies. Further work on metadata and considering also other modeling techniques (principal component analysis for categorical variables procedures (tetrachoric correlation), association rules) are needed to validate and optimize the risk factors groups.

Acknowledgment

This work has been conducted in the Pediatric Clinic Hospital Sibiu, within Research and Telemedicine Center in Neurological Diseases in Children - CEFORATEN project (ID 928 SMIS-CSNR 13605) financed by ANCSI with the grant number 432 / 21. 12. 2012 thru the Sectoral Operational Programme „Increase of Economic Competitiveness".

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