

# Neonatal Seizures in a Rural Iranian District Hospital: Etiologies, Incidence and Predicting Factors

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**Abstract-** Current study determined the overall incidence, common causes as well as main predictors of this final diagnosis among neonates admitted to a rural district hospital in Iran. This study was conducted on 699 neonates who were candidate for admission to the NICU. Study population was categorized in the case group, including patients exposed to final diagnosis of neonatal seizures and the control group without this diagnosis. Neonatal seizure was reported as final diagnosis in 25 (3.6%) of neonates. The most frequent discharge diagnosis in the seizure group was neonatal sepsis and in the non-seizure group was respiratory problems. No significant difference was found in early fatality rate between neonates with and without seizures (8.0% vs. 10.1%). Only gestational age <38 week had a relationship with the appearance of neonatal seizure. Low gestational age has a crucial role for predicting appearance of seizure in Iranian neonates.

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**Keywords:** Etiology; Gestational age; Incidence; Neonate; Neonatal seizure

## Introduction

Despite estimated incidence of neonatal seizures are notably high (1 to 3.5 per 1000 births in term newborns, even higher in preterm situation) its clinical management and diagnosis can be already challenging (1). The most prevalent known cause of neonatal seizures is hypoxic/ischemic encephalopathy which has been reported in approximately 1-2 per 1000 live births (2). This underlying etiologic factor can be occurred at term in the context of birth asphyxia, respiratory distress, congenital cardiac anomalies, sepsis, and multi-organ failure or less commonly as a complication of extracorporeal membrane oxygenation or surgical procedures for congenital cardiac disease (3-7). However, it has been suggested that the common developmental factors in the pathogenesis of neonatal seizures might be varied in different populations. The importance of appropriate managing neonatal seizures is mainly related to this fact that neonates with seizure diagnosis are potentially at risk for neonatal early mortality and survivors may have a high incidence of adverse neuro-developmental outcome including motor or cognitive disability (8). Therefore, early and accurate

detection of seizure and its clinical type is important for guiding antiepileptic drug therapy and helping to determine the risk of morbidity and mortality (9-13).

In this way, the primary step for appropriate managing neonatal seizure in each population is estimating overall incidence of neonatal seizure as well as determining its underlying prognostic factors. Based on our search among published reports, little data is available on the burden, etiologies and outcome of neonatal seizures in Iranian population. Therefore, current study came to address the overall incidence, common causes and immediate outcome of seizures as well as main predictors of this final diagnosis among neonates admitted to a rural district hospital in Iran.

## Materials and Methods

Current study was conducted on 699 neonates who were candidate for admission to the NICU ward for the first time and consecutively hospitalized in Fatemeh Hospital in Shahrood city, Semnan from January 2007 to January 2009. Study population was categorized in the case group, including patients exposed to final diagnosis of neonatal seizures and the control group without this

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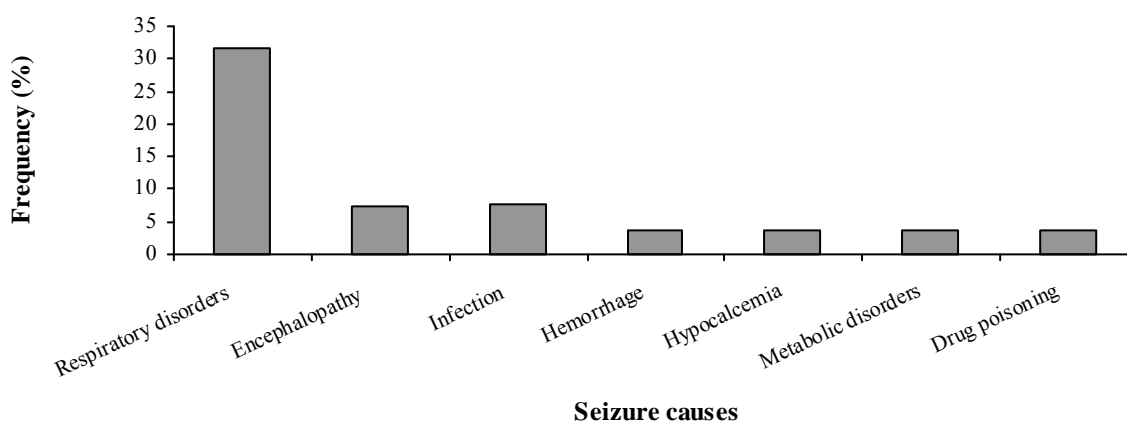
diagnosis. Baseline characteristics and clinical criteria of these subjects were extracted from hospital recorded files as well as face to face interviewing with their parents or physician if required and entered into a computerized database form. This information included neonates admission age and birth weight, gender, mother's age and parity, gestational age, type of delivery and inability to breast feeding. A neonate was defined as any child admitted aged 28 days or younger (14). Seizures were defined as reported or observed repeated involuntary muscle contractions, abnormal tonic extensions or jerky movements of any part of the limb, face or mouth that was not stimulus sensitive or repetitive abnormal chewing, ocular or pedaling movements (7). The discharging clinician made the final diagnosis (for example, neonatal sepsis, respiratory distress syndrome, meconium aspiration, pneumonia, neonatal jaundice, neonatal encephalopathy, prematurity or any congenital abnormalities) after review of the admission history, inpatient management notes and laboratory investigations. Early outcome endpoints were also described as neonatal mortality as well as total hospital stay. In order to calculate the incidence of neonatal seizures, the denominator, the total population of live births in the demographic surveillance area at the mid-point of the study was estimated based on a log-linear regression model of re-enumeration points. The rates are expressed as events per 1000 live births per year.

Results were reported as mean  $\pm$  standard deviation (SD) for the quantitative variables and percentages for the categorical variables. The groups with and without seizures were compared using the Student's t-test for the continuous variables and the Chi-square test (or Fisher's exact test if required) for the categorical variables. Predictors exhibiting a statistically significant relation

with the appearance of neonatal seizures in univariate analyses were taken for multivariate logistic regression analysis to investigate their independence as predictors. Odds ratio (OR) and 95% confidence intervals (CI) were calculated. *P*-values of 0.05 or less were considered statistically significant. All the statistical analyses were performed using SPSS version 13.0 (SPSS Inc., Chicago, IL, USA) and SAS version 9.1 for Windows (SAS Institute Inc., Cary, NC, USA).

## Results

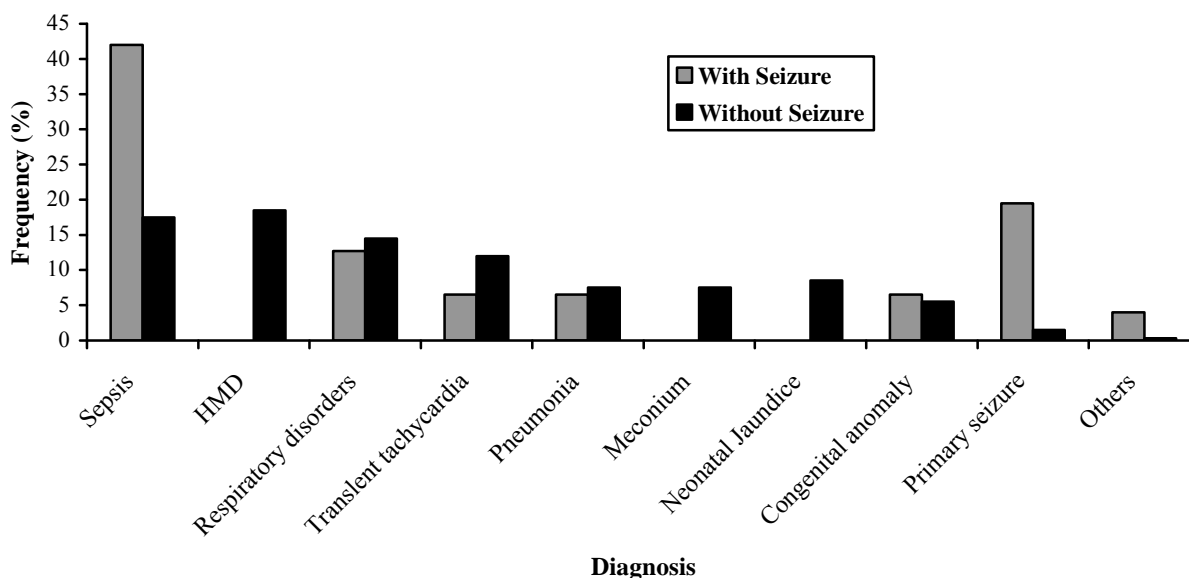
From January 2007 to January 2009, a total of 699 children were admitted to NICU ward of the Fatemeh Hospital in Shahrood city that neonatal seizure was reported as final diagnosis in 25 (3.6%) of them with the overall incidence rate 5 per 1000 live births per year. Fourteen of the 25 neonates (56.0%) had seizures within the first 24 hrs of life, 4 (16.0%) had seizures on days 3-7 and in the remaining 7 (28.0%), seizures occurred after the first week of life. The mean age of neonates with seizures was 2.79 days compared to 4.09 days for those without seizures. As shown in Table 1, neonates with and without seizures diagnoses were similar in terms of male to female ratio (1.5 versus 1.0, respectively), admission age, their mother's age, inability to breast feed and type of delivery. However, number of parity was significantly higher in those without seizure. The most prevalent etiologies of seizure was neonatal respiratory disorder (32%), followed by neonatal encephalopathy (8.0%), and infection (8.0%) (Figure 1). However, the most frequent discharge diagnosis in the seizure group was neonatal sepsis (46.6%) and in the non-seizure group was respiratory distress syndrome (19.3%) (Figure 2).



**Figure 1.** The most prevalent primary etiologies of seizure at the admission time.

**Table 1.** Baseline characteristics of study neonates with and without seizure.

Characteristics	Total (n=669)	Seizure group (n=25)	Non-seizure group (n=674)	P-value
Admission age (days)	2.79±0.16	4.09±1.52	2.74±0.15	0.113
Male gender (%)	375 (53.7)	15 (60.0)	341 (50.6)	0.483
Birth weight (kg)				
< 1.5 kg	127 (18.2)	2 (8.0)	125 (18.5)	
1.5-2.5 kg	154 (22.0)	4 (16.0)	150 (22.3)	0.085
> 2.5 kg	418 (52.8)	19 (76.0)	399 (59.2)	
Gestational age	37.16±3.74	37.10±3.78	39.00±1.27	0.025
Mother's age (year)	27.32±5.85	29.09±7.03	27.26±5.79	0.240
Number of parity				
1	495 (70.8)	13 (52.0)	482 (71.5)	
2	138 (19.7)	18 (32.0)	130 (19.3)	0.048
3 or more	66 (9.5)	4 (16.0)	62 (9.2)	
Breast feeding (%)	451 (64.05)	19 (76.0)	432 (64.1)	0.222
Type of delivery				
Normal vaginal delivery	254 (36.3)	10 (39.0)	244 (36.2)	
Aided vaginal delivery	422 (60.4)	14 (56.5)	40 (58.4)	0.892
Cesarean section	23 (33.0)	1 (4.0)	22 (33.0)	



**Figure 2.** The most frequent discharge diagnosis in the seizure and non-seizure group.

Regarding early outcome of study neonates, total length of hospital stay was similar in the groups with and without neonatal seizure (5.63±4.61 versus 5.68±4.59 days,  $P=0.959$ ). Two of the 25 (8.0%) neonates in seizure group and sixty eight of the 674 (10.1%) neonates in non-seizure group died. There was no difference in case fatality between neonates with and

without seizures ( $P=0.731$ ). Both two neonates with seizures who died had birth weight > 2.5 kg. Multivariable logistic regression analysis showed that among studied mother's and neonate variables, only gestational age < 38 week had a relationship with the appearance of neonatal seizure (OR=-0.714,  $P=0.041$ ) (Table 2).

**Table 2.** Factors predicting neonatal seizure with the presence of potential cofounders.

Item	Multivariable <i>P</i> -value	Odds ratio	95% Confidence interval
Male gender	0.878	1.084	0.390-3.009
Admission age	0.247	0.948	0.865-1.038
Birth weight	0.628	1.000	0.999-1.001
Apgar score	0.431	0.979	0.928-1.033
Type of delivery	0.876	0.941	0.440-2.012
Gestational age	0.041	0.714	0.518-0.986
Mother's age	0.645	0.977	0.885-1.079
Parity	0.640	0.865	0.472-1.585

Hosmer-Lemeshow goodness of fit:  $\chi^2 = 10.945$ ,  $df = 8$ ,  $P=0.205$

## Discussion

The main finding of current study is partially high incidence rate of neonatal seizure among our study population in total live births probably due to the high prevalence of risk factors for neonatal brain insult in this community such as low birth weight, pre-maturity, maternal medical conditions, perinatal obstetrical complications, and access to high-quality obstetrical and neonatal care (15). However, our study suggests that the incidence of neonatal seizures in NICU is much lower than that reported from developed nations (16). The incidence of neonatal seizure varies widely, depending on the gestational age, neonate weight and underlying causes of appeared seizure. In the present study, gestational age is a main predictor for seizure, but no significant relationship was observed between the appearance of seizure and body weight. However, some studies suggested that in preterm infants with birth weigh less than 1.5 kg, the incidence ranges from 19 to 57.5 per 1,000 live births, but in infants who weigh more than 2.5 kg, the incidence rate is as low as 2.8 per 1,000 live births (17).

Our study showed that the most prevalent etiologies of neonatal seizure were respiratory problem, followed by encephalopathy and infection. Intracranial infections, accounting for 5% to 10% of seizures, are the most common cause in developing countries. Viral infections caused by herpes simplex virus, cytomegalovirus, and rubella as well as bacterial infections by group B *Streptococcus*, *Listeria*, and *Escherichia coli* have been commonly found in infection-related neonatal seizures. Therefore, prompt recognition and initiation of appropriate treatment can be effectively resulting in the best outcome in affected neonates (18). Regarding seizures originated from respiratory disorders, it seems

that hypoxic-ischemic encephalopathy caused by respiratory distress is mainly responsible for high incidence of neonatal seizure in our study subjects. It has been revealed that cerebral hypoxia/ ischemia can occur at term in the context of birth asphyxia and respiratory distress disorder (2).

Based on our findings, hemorrhage and metabolic disturbances are less common underlying etiologies of neonatal seizure. It has been previously shown that intracranial hemorrhage accounts for about 10% of cases. Additional causes of seizure include structural brain malformations, hypoglycemia, hypocalcemia, hypomagnesemia and hypo- and hypernatremia as well as inborn errors of metabolism such as aminoacidopathies, urea cycle defects, mitochondrial disorders, beta-oxidation defects and pyridoxine dependency (19,20).

The most frequent final diagnosis of seizure in our survey was neonatal sepsis. Although in similar studies neonatal sepsis was a common diagnosis, it was not independently associated with seizures (7). In fact, isolation of a pathogenic organism in blood alone might not be associated with seizures. However, neonatal infection is a preventable condition that its preventing can lead to reduce the burden of neonatal seizure and therefore can decrease its-related neonatal morbidity.

Although we could reveal common causes of neonatal seizures in our population, the seizure etiologies may not be identified despite clinical evidences of brain injury or encephalopathy or any risk factors or family history that has been identified as an idiopathic type. It seems that the etiologies of these seizure types are part of genetically determined epileptic syndromes such as benign familial neonatal convulsions and benign non-familial neonatal convulsions.

## Neonatal seizures, incidence and predictors

In summary, neonatal seizure in the study rural sample of Iranian neonates was reported in 3.6% of them with the overall incidence rate 5 per 1000 live births per year. The most common etiologies of seizure in neonates were neonatal respiratory disorder, neonatal encephalopathy; whereas the most frequent final diagnosis in the seizure group was neonatal sepsis. Among mother and neonates parameters, low gestational age has a crucial role for predicting appearance of seizure in Iranian neonates.

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