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Neonatal Seizures in Iraq: Cause and Outcome

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During a daily neonatology practice, seizures are a continuous challenge as a common neurological disease with a wide range of underlying etiologies, and considerable risks of morbidity and mortality. This study aimed to clarify the rate, etiological factors and outcomes of neonatal seizures, and a possible foresight of neonatal death in Iraq. A prospective cohort study was conducted in neonates with seizures admitted to 3 major neonatology centers in Baghdad, Iraq, from 1st of December 2017 till the end of May 2018. Both term and preterm neonates affected by seizures were recruited with a total number of 203 patients. Perinatal asphyxia (n = 81; 39.90%), infection (n = 77; 37.93%), and metabolic abnormalities (n = 52; 25.62%) were most common causes for seizures. Death occurred in 66 neonates (32.51%), with higher mortality rates found in preterm neonates. Six adverse prognostic indicators were shown to be significant: positive pressure resuscitation, mechanical ventilation, perinatal asphyxia, infection, gestational age (preterm babies), and low birth weight (< 2,500 g). Neonatal seizures may be the first manifestation of neurological insults, and they are most commonly caused by perinatal asphyxia, followed by infection, and metabolic disturbances. Prevention of neonatal seizures is much more important than the treatment of them for the reduction of neonatal mortality. The effective strategies should therefore be proper medical care and management for mothers and neonates before, during and after delivery to prevent neonatal infections, perinatal asphyxia, low birth weight, prematurity, metabolic abnormalities, and other risk factors of neonatal seizures.

Keywords: etiology; Iraq; mortality prediction; neonatal fit; outcomes
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Introduction

Seizures are the most common clinical disorder of the central nervous system (CNS) during neonatal period with a global incidence of 1-5% (Nagaram et al. 2017). Clinical seizures are described as a paroxysmal difference in neurological function, either in one or all of behavioral, autonomic, and motor functions. They are not easy to investigate, and therefore identifying the causes and starting the treatment plan could be delayed resulting in poor outcome, such as cerebral palsy and epilepsy (Patil and Patel 2016). Neonatal seizures usually occur in early neonatal period. In about 20-33% of cases, seizures occurred on the first day of life, and in 50% within first three days (Galanopoulou 2015; Grinton et al. 2015).

Seizures affecting neonates have a wide range of etiology profiles including metabolic disorders, especially hypoglycemia and hypocalcemia, and frequently reflect a brain injury such as ischemia (hypoxic-ischemic injury and/or perinatal ischemic stroke), and sometimes intracranial infections (Li et al. 2016; Srikanth 2017).

The aim of the present study was to find out the rate, etiological factors and outcomes of neonatal seizures, and a possible prediction of neonatal death in Iraq.

Materials and Methods

This study was done in three major neonatology centers located in Baghdad city, the Iraqi capital; Al-Elwiyah Pediatric Teaching Hospital, Ibn Al-baladi Pediatric Hospital, and Medical City Pediatric Welfare Teaching Hospital, from 1st of December 2017 till the end of May 2018. All the neonates having seizures were included in the present study with a follow-up approach (through routine visits to the outpatient clinics of the hospitals) until two months after a hospital discharge. The present study was approved by the Ethical & Scientific Committee at Al-kindy College of Medicine, University of Baghdad, and informed consent was obtained from all participants (mothers and/or caregivers).

This study comprised neonates who had seizures (of any type) claimed by the mother or caregiver, witnessed by the neonatology centers' resident doctor, and confirmed by the attendant neonatologist, and were admitted to one of the above neonatology centers. All the term neonates were less than 4 weeks old, and preterm babies had less than 44 weeks of postmenstrual age (gestational age plus chronologi-

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cal age) (Engle et al. 2004).

Detailed histories (pre-, peri-, and postnatal) were obtained directly from the treating neonatologist, medical records, and the in-charge obstetrician. Regular antenatal care was identified with regard to World Health Organization (WHO) guidelines (WHO 2016).

A parallel management plan was applied to all recruited patients. Electroencephalography (EEG), and brain sonography were done in all patients during their stay in the hospital, and reviewed by a neurologist, while brain CT (computed tomography) scan and MRI (magnetic resonance imaging) were performed as needed. The following laboratory tests were done for all neonates: serum levels of calcium, glucose, magnesium, sodium, creatinine, urea and total serum bilirubin, arterial pH, examination of cerebrospinal fluid, culture of blood, urine, cerebrospinal fluid or umbilical swap, and chest x- ray. The criteria for identifying biochemical abnormalities were as follows (Madhusudhan et al. 2016): hypocalcemia; serum calcium level < 7.0 mg/dl; hypoglycemia; blood glucose level < 40 mg/dl; hypomagnesemia; serum magnesium level < 1.5 mg/dl; hyponatremia; and serum sodium level < 130 mEq/L.

Resuscitation through positive pressure or mechanical ventilation and management specifics were observed daily. Asphyxia diagnosis was made when Apgar score was ≤ 3 at five minutes after birth, metabolic acidosis (pH < 7) was observed, resuscitation went longer than usual, and Sarnat scale application showed moderate to severe encephalopathy (Sarnat and Sarnat 1976). Neonatal infection diagnosis was done clinically and confirmed through imaging studies when needed, and culture of blood, urine, cerebrospinal fluid and umbilical swap, as mentioned above. Kernicterus was diagnosed by an elevated critical serum bilirubin concentration (more than 20 mg/100 ml), presence of spasticity, opisthotonos and fever (van Praagh 1961). Moreover, neuroimaging studies were used to confirm intracranial bleeding based on the Papile classification (Papile et al. 1978).

Statistical analysis was performed using SPSS (Statistical Package for the Social Sciences), version 22. The p value of ≤ 0.001 was considered to be statistically significant.

Results

Total number of involved patients was 203 neonates (117 males; 57.64% and 86 females; 42.36%) (Table 1). Most of them (n = 139; 68.47%) were < 2,500 grams at birth, and the majority (n = 183; 90.15%) had seizures during the first week of life. Only one fifth of the patients (n = 43; 21.18%) had a regular antenatal care although about three quarters (n = 157; 77.34%) were from urban areas. Mothers gave birth normally (n = 150; 73.89%) rather than by surgery (Cesarean section). More than half of patients (n = 105; 51.72 %) required resuscitation by positive pressure and/or mechanical ventilation.

The most common cause of neonatal seizures was perinatal asphyxia (n = 81; 39.90%), followed by infection (n = 77; 37.93%), and metabolic disturbances (n = 52; 25.62%) (Table 2). In infection, septicemia was more frequent than meningitis. The other causes of neonatal sei-

Table 1. General features of 203 neonates.

Characteristics	Number (%)
Sex:	
• Male	117 (57.64%)
• Female	86 (42.36%)
Birth weight:	
• < 2,500 g	139 (68.47%)
• ≥ 2,500 g	64 (31.53%)
Seizures time points of presentation:	
• ≤ 7 days	183 (90.15%)
• > 7 days	20 (9.85%)
Residency:	
• Urban	157 (77.34%)
• Rural	46 (22.66%)
Regular maternal antenatal care	
• Yes	43 (21.18%)
• No	160 (78.82%)
Delivery mode:	
• Normal vaginal	150 (73.89%)
• Cesarean section	53 (26.11%)
Resuscitation (positive pressure ventilation):	
• Yes	110 (54.19%)
• Not needed	93 (45.81%)
Resuscitation (Mechanical ventilation):	
• Yes	105 (51.72%)
• Not needed	98 (48.28%)

Table 2. Causative factors of seizures in 203 neonates.

Etiological factors	Number (%)
Perinatal asphyxia	81 (39.90%)
Infection:	77 (37.93%)
• Septicemia	45 (22.17%)
• Meningitis	32 (15.76%)
Metabolic disorders:	52 (25.62%)
• Hypocalcemia ± hypomagnesemia	28 (13.79%)
• Hypoglycemia	20 (9.85%)
• Hyponatremia	4 (4.43%)
Kernicterus	13 (6.40%)
Intracranial hemorrhage	13 (6.40%)
Central nervous system malformations	7 (3.45%)
Idiopathic (unknown)	5 (2.46%)

Table 3. Relation of neonatal mortality with sex and gestational age (term or preterm) in 203 neonates.

Gestational age with sex	Alive [n (%)]	Dead [n (%)]
Term male	74 (70.48%)	31 (29.52%)
Term female	49 (68.06%)	23 (31.94%)
Preterm male	10 (58.82%)	7 (41.18%)
Preterm female	4 (44.44%)	5 (55.56%)
Total [n (%)]	137 (67.49%)	66 (32.51%)

zures included kernicterus (n = 13; 6.40%), intracranial hemorrhage (n = 13; 6.40%), CNS abnormalities (n = 7; 3.45%) and idiopathic reasons (n = 5; 2.46%).

The relation of neonatal mortality with gestational age and sex is shown in Table 3. The present study included 177 term neonates (105 males and 72 females) and 26 preterm neonates (17 males and 9 females). The average age of gestation was 39.14 ± 2.46 (mean ± SD) weeks in term neonates and 32.51 ±17 (mean ± SD) weeks in preterm neonates, respectively. The percentage of mortality during neonatal period was higher in preterm neonates (n = 12; 46.15%) than in term neonates (n = 54; 30.51%). Moreover, the percentage of mortality during neonatal period was higher in female neonates (term neonates, 31.94%; preterm neonates, 55.56%) than in male neonates (term neonates, 29.52%; preterm neonates, 41.17%). Additional eight babies died after neonatal period (up to two months after discharge from the hospital) (3.94% of the total).

To find out if there were any correlations between neonatal seizures' mortality (extended up to two months after a hospital discharge) and different possible risk factors, a simple regression test was applied. We included the following factors (all of which showed a dichotomy pattern): death as a main outcome (positive alive vs. negative dead; 146 vs. 57), sex (positive male vs. negative female; 117 vs. 86), birth weight (positive < 2,500 g vs. negative ≥ 2,500 g; 139 vs. 64), delivery mode (positive normal vaginal vs. negative cesarean section; 150 vs. 53), gestational age (positive preterm vs. negative term; 26 vs. 177), resuscitation by a positive pressure ventilation (positive vs. negative; 110 vs. 93), resuscitation by a mechanical ventilation (positive vs. negative; 105 vs. 98), infection (positive vs. negative; 77 vs. 126), onset of seizures (positive ≤ 7 days (early) vs. negative > 7 days (late); 183 vs. 20), residency (positive urban vs. negative rural; 157 vs. 46), regular maternal antenatal care (positive vs. negative; 43 vs. 160), metabolic disorders (positive vs. negative; 52 vs. 151), kernicterus (positive vs. negative; 13 vs. 190), intracranial bleeding (positive vs. negative; 13 vs. 190), and central nervous system malformations (positive vs. negative; 7 vs. 196). A statistically significant association (p value ≤ 0.001) was revealed between death due to seizures during neonatal period and the following variables: positive pressure resuscitation, mechanical ventilation, perinatal asphyxia, infection, gestational age (preterm babies), and low birth weight (< 2,500 g).

Discussion

Neonatal seizures are a well-recognized cause of neonatal mortality, and the death rate from neonatal seizures was higher during the early sixties of the last century (around 40%), when compared with the recent reports (Ronen et al. 2007). Our data were not an exception with

its neonatal mortality rate (28%). However; a lower rate has recently been reported in United States (17%) (Glass et al. 2016). On the other hand, we observed higher mortality rates in preterm neonates rather than term neonates, consistent with the report by other investigators (Hall et al. 2006). The present study revealed that 3.94% of the studied neonates died after neonatal period (up to a couple of months after hospital discharge), confirming the idea on the high risk of neurodevelopmental delay and death beyond neonatal era (Tekgul et al. 2006; Jensen 2009).

The population of the present study had a higher proportion of males, indicating that male neonates had a higher risk of seizures, while mortality rates were higher in females. In addition, neonatal seizures occurred more frequently in term neonates rather than preterm neonates. These findings were consistent with the previous reports (Alcover-Bloch et al. 2004; Ehrenstein et al. 2007; Glass et al. 2009). Moreover, the lower birth weight was a great risk factor for neonatal seizures (Lanska et al. 1995; Nagaram et al. 2017). Most of our neonates had seizures during the first week of life, consistent with the previous report (Galanopoulou 2015).

Although most of our patients (77.34%) and their families came from urban areas, the majority of their mothers (78.82%) did not have a regular antenatal care. This would probably lead to an increase in the incidence of neonatal seizures, morbidity, and mortality consequences, as previously indicated by other authors (Glass et al. 2009). We assume that these consequences may be related to the low level of public health education of our community, giving less attention to such important issue. Most of the developing countries could have the same problem.

About three quarters of our studied neonates (73.89%) were delivered normally, like other reports (Minchom et al. 1987; AL-Naddawi et al. 2011). Assisted ventilation with its two forms, positive pressure and mechanical ventilation, was practiced widely for more than half of our neonates, and provided a vigorous support of breathing function, consistent with the recent report by others (Volpe et al. 2017).

In the present study, asphyxia was identified in 39.90% neonates representing a major etiological risk, which was also reported by many researchers (Jensen 2009; Patil and Patel 2016). Infection was a second risk factor (37.93%). Many previous reports indicated that infection has an important impact on survival and neurodevelopmental consequences (Göpel et al. 2006; Shah et al. 2008), particularly sepsis and meningitis (de Jonge et al. 2010), while other studies regarded metabolic disturbances as a second cause of neonatal seizures (Tekgul et al. 2006; Nagaram et al. 2017). The higher incidence of infection in our study may be due to poor antenatal care with resultant obstetrical problems, such as maternal prolonged rupture of membranes, dirty delivery settings, and missed management of other maternal conditions, which were previously mentioned (Göpel et al. 2006; de Jonge et al. 2010).

Kernicterus and intracranial bleeding had occurred in 6.40% of our neonates, CNS malformations had a less incidence (3.45%). These were consistent with other articles (Manent et al. 2011; AL-Naddawi et al. 2011).

Based on our results; we estimated that low birth weight (< 2,500 g), poor maternal antenatal care, and perinatal asphyxia which requires a respiratory resuscitation (positive pressure and/or mechanical ventilation) were at great risk of death that may occur up to 2 months after discharge from the hospital. Other investigators indicated that early onset of seizures was a predictor of poor prognosis of neonatal seizures (Ortibus et al. 1996; Nagaram et al. 2017). More extensive studies in different parts of the world may be required to emphasize on this important issue of mortality prediction.

In conclusion, main etiological factors for neonatal seizures are perinatal asphyxia, infection, and metabolic disorders. We could predict death outcome according to specific prognostic points.

According to the concept that prevention is better than treatment to decrease mortality in neonatal seizures, the present predictive finding may pave the way and encourage stakeholders to take further possible actions to improve some poor prognostic factors during future medical practicing, such as steps to prevent neonatal infections and perinatal asphyxia, with strict measures to prevent prematurity and maintain normal birth weight.

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Author Contributions

Hayder Al-Momen designed and performed research and also wrote the paper, Majed Kadhim Muhammed collected data, and Ali Abdulhussein Alshaheen analyzed data.

Conflict of Interest

The authors declare no conflict of interest.

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