P-ISSN: 2664-3685
E-ISSN: 2664-3693
www.paediatricjournal.com
IJPG 2024; 7(2): 01-05
Received: 03-05-2024
Accepted: 07-06-2024

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Clinical-etiological profile of neonatal seizures and their outcomes in children's central teaching hospital

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DOI: https://doi.org/10.33545/26643685.2024.v7.i2a.233

Abstract
Background: The most common newborn neurological abnormality is seizures. Full-term babies get neonatal seizures within 4 weeks, whereas preterm babies can have them up to 44 weeks after conception. About 3-6 per 1000 live births. Objectives to study clinical types, time of onset and to determine the etiology of neonatal seizures and response to treatment.
Method: A prospective study of 78 neonates with clinically observed seizures was conducted at the neonatal ward in Child's Central Teaching Hospital, Baghdad, from May 1 to December 1, 2022. Detailed history and examination by a pediatrician were performed, analyzing variables such as age, sex, mode of delivery, seizure onset, presentation pattern, feeding method, maternal drug history, underlying causes, anticonvulsant response, and discharge state. Antenatal and prenatal histories, including maternal infections, gestational age, fetal distress, delivery complications, and hypoxic-ischemic encephalopathy, were documented. Laboratory and neuroimaging studies were conducted when indicated.
Results: 87.2% of 78 patients (male: female ratio 1.2:1) were born at term. Most seizures (43.6%) occur in the first 72 hours of birth. This study found that tonic seizures were the most prevalent form (50%), followed by subtle (25.6%), focal (14.1%), and multifocal (10. 3%).In this research, hypoxic ischemic encephalopathy (HIE) caused 28.2% of newborn seizures, followed by meningitis (21.8%), sepsis (14.1%), hypocalcaemia (14.1%), hypoglycemia (11.5%), kernel icterus (5.1%), IVH (3.8%), and TORCH (1.33%). Phenobarbital alone (86.3%) and phenytoin (13.7%) caused a reaction. IVH caused most of these individuals' 9% death.
Conclusion: Neonatal seizures are most prevalent in full-term male infants in their first 72 hours, and tonic seizures are the most common. Hypoxic ischemic encephalopathy causes most newborn seizures, followed by meningitis. Preterm newborns die most from intraventricular hemorrhage.

Keywords: Clinco-etiological, profile, neonatal seizure, outcome

Introduction
Neonatal seizures are abnormal electrical discharges in the central nervous system of neonates, usually manifesting as stereotyped muscular activity or autonomic changes [1]. These seizures occur within the first 4 weeks of life in full-term infants and up to 44 weeks from conception for premature infants [2]. The neonatal period is particularly vulnerable to seizures [3], with an incidence of 3-6 per 1000 live births [4]. Seizures occur due to excessive, synchronized depolarization of a large group of neurons. This can result from excessive excitatory amino acid release (e.g., glutamate) or deficient inhibitory neurotransmitter (e.g., gamma-aminobutyric acid [GABA]). Additionally, disruption of ATP-dependent resting membrane potentials can cause a flow of sodium into the neuron and potassium out [5, 6]. No racial preponderance is known, and sex-based frequency differences have not been described [7]. Neonatal seizures are most frequent during the first 10 days of life [7]. Neonatal seizures can be classified as follows [8, 9]: Focal clonic: Repetitive, rhythmic contractions of muscle groups in limbs, face, or trunk. Focal tonic: Sustained posturing of a single limb, asymmetrical posturing of the trunk, or sustained eye deviation. Myoclonic: Generalized, focal, or fragmentary arrhythmic shock-like contractions. Generalized tonic: Sustained symmetrical posturing of limbs, trunk, and neck. Subtle seizures: Include random eye movements, sucking, chewing, tongue protrusions, and limb movements like rowing or peddling. E.E.G Classification of Neonatal Seizures: Clinical seizures with associated EEG events: Seizure activity recorded on the EEG, includes focal clonic, tonic, and some

myoclonic seizures. These are more likely to respond to anticonvulsant drugs [10, 11]. Clinical seizures with inconstant EEG events: Seizures without corresponding EEG discharge, include all generalized tonic seizures and subtle seizures. These infants often have hypoxic-ischemic encephalopathy and do not respond well to anticonvulsants [10, 11]. Electrical seizures without clinical signs: Occur in comatose patients or after anticonvulsant administration without clinical signs [10, 11]. Etiology: Hypoxia-ischemia: The most common cause, occurring before, during, or after delivery [1]. Intracranial hemorrhage: Includes subarachnoid, intracerebral, and intraventricular hemorrhages [1]. Metabolic disturbances: Hypoglycemia: Defined as glucose concentration significantly below the mean for the population [12]. Hypocalcemia: Serum calcium level <7.5 mg/dL, can be early or late onset [8]. Hypernatremia or hyponatremia: Serum sodium level abnormalities [13]. Hypomagnesemia: Serum magnesium level <1.4 mEq/L [8]. Pyridoxine dependency: Rare familial cause of seizures due to increased pyridoxine requirement [14]. Amino aciduria: Includes phenylketonuria and other disorders. Infections: Sepsis, meningitis, and encephalitis caused by bacteria or viruses [15]. Developmental defects: Cerebral dysgenesis and other brain abnormalities [15]. Other causes: Drug withdrawal, hyperthermia, and familial benign neonatal seizure syndromes [16]. Evaluation begins with a detailed family history and physical examination [17]. Essential investigations include blood glucose, serum electrolytes, arterial pH, and EEG [18]. Management involves ensuring adequate ventilation, correcting metabolic disturbances, and initiating anticonvulsant therapy such as phenobarbital or lorazepam [19]. Aims of the Study is to investigate the causes of neonatal seizures, categorize the clinical types of neonatal seizures, determine the timing of seizure onset in neonates, and to assess the effectiveness of anticonvulsant treatments for neonatal seizures.

Method

A prospective descriptive study was conducted on 78 neonates at the neonatal ward in Child's Central Teaching Hospital, Baghdad, over seven months from May 1 to December 1, 2022. The study included neonates with clinically observed seizures or those who developed seizures during their stay in the ward, excluding those with jitteriness only.

Inclusion Criteria

- Seizures within the first 28 days of life.
- Seizures noticed by staff or referred with a history of suspected seizures, confirmed during hospital stay.

Data Collection

- Detailed history and physical examination by a pediatrician.
- Variables analyzed included age, sex, mode of delivery, seizure onset and pattern, feeding method, maternal drug history, underlying causes, response to anticonvulsants, and patient state on discharge.
- Antenatal history covered maternal infections, drug use, premature rupture of membranes, maternal diabetes, hypertension, fever, previous abortions, and antenatal sonography.
- Prenatal history included fetal distress indicators, decreased fetal movements, delivery complications, need for resuscitation, and Apgar scores. Babies with birth asphyxia symptoms were classified as hypoxic-ischemic encephalopathy.
- Gestational age was estimated using maternal history or physical examination based on the Ballard score.

Examination

- Comprehensive examination included gestational age, birth weight, vital signs, and neurological assessment (Fontanell status, consciousness, tone, reflexes).
- Systemic examination covered cardiovascular, respiratory, gastrointestinal, vision, hearing, occipito-frontal circumference, and signs of multisystem organ involvement.
- Congenital malformations or cutaneous markers were noted.

Investigations

- Serum calcium levels (<7 mg/dl considered hypocalcemia) and random blood sugar (<50 mg/dl considered hypoglycemia) were tested for all patients.
- Additional serum electrolytes, bilirubin levels, and jaundice workup were done as needed.
- Criteria for kernicterus included high indirect bilirubin, lethargy, hypertonia, opisthotonus, poor reflexes, and high-pitched crying, treated with exchange transfusion and anticonvulsants if convulsions occurred.
- Blood cultures were performed for all patients.
- Lumbar puncture (LP) was done for 58 patients with suspected meningitis (bulging fontanels, lethargy, vomiting, fever); 20 patients did not undergo LP.
- CSF analysis: cell count, protein, and sugar levels were evaluated.
- Neuroimaging: brain ultrasound (45 cases) and cranial CT-scan (37 cases) were conducted when necessary; some patients underwent both.
- TORCH screening was done for suspected congenital infections.

Results

We enrolled 78 hospitalised or home-delivered patients in our investigation. The majority of births (62.8%) were normal vaginal, while 29 (37.2%) were caesarean section. Forty-two infants (53.8%) were male and 36 (46.2%) were female. There were 68 full-term infants (87.2%) and 10 preterm births (12.8%). Sixty-six patients (84.6%) weighed >2500 g, two (2.6%) were less than 1500 g, and 10 (12.8%) were between 1500-2500 g. Weight ranged from 1200 to 4500 g, with a mean ± SD of 2.99±0.55 kg.

Table 1: Characteristics of Study Patients

Characteristic	Number	Percentage (%)
Mode of Delivery		
Normal vaginal delivery	49	62.8
Cesarean sections	29	37.2
Total	78	100

Sex		
Males	42	53.8
Females	36	46.2
Total	78	100
Gestation		
Term	68	87.2
Preterm	10	12.8
Total	78	100
Weight		
<1500 grams	2	2.6
1500-2500 grams	10	12.8
>2500 grams	66	84.6
Total	78	100

Table 2 and 3; illustrates the mode of delivery for the case and control groups. The control group consisted of 54 individuals, while the cases had a normal vaginal delivery at 49. The number of caesarian sections in the cases was 29, while the control group had 24. The p-value of 0.499 indicates that there is no risk factor associated with neonatal seizures. The study did not observe myoclonic seizures. Tonic seizures were observed in 39 cases (50%), focal (clonic) in 11 cases (14%), multifocal (Clonic) in 8 cases (10.3%), and subtle seizures in 20 cases (25.6%).

Table 2: Mode of Delivery for Case and Control

Mode of Delivery	Control	Case	P value
Normal vaginal delivery	54	49	
Cesarean section	24	29	0.499
Total	78	78	

Table 3: Neonatal seizure types distribution.

Type of seizure	No.	%
Focal (clonic)	11	14
Multifocal (clonic)	8	10.3
Tonic	39	50
Subtle	20	25.6
Myoclonic	-	-
Total	78	100

The study analyzed 78 cases of neonatal seizures, finding normal serum calcium levels in 67 cases (85.9%) and low levels in 11 cases (14.1%). Random blood sugar (RBS) levels were normal in 69 cases (88.5%) and low in 9 cases (11.5%). Blood cultures were negative in 50 cases (64.1%) and positive in 28 cases (35.9%). Lumbar puncture (LP) was performed in 58 cases (74.3%), with 40 showing normal results (69%), 17 abnormal (29.3%), and 1 traumatic (1.7%). Neuroimaging indicated that 44 of 45 brain ultrasounds were normal (97.8%), while cranial CT scans were normal in 32 of 37 cases (86.5%). The primary etiologies of seizures were hypoxic-ischemic encephalopathy (HIE) in 22 cases (28.2%), meningitis in 17 cases (21.8%), sepsis in 11 cases (14.1%), hypocalcemia in 11 cases (14.1%), hypoglycemia in 9 cases (11.5%), kernicterus in 4 cases (5.1%), intracranial hemorrhage (ICH) in 3 cases (3.8%), and TORCH infection in 1 case (1.3%). As in table 4.

Table 4: Etiology of neonatal seizures in the study group

Causes	No.	%
HIE	22	28.2
Hypocalcaemia	11	14.1
Hypoglycemia	9	11.5
IVH	3	3.8
Kernicterus	4	5.1
Meningitis and Encephalitis	17	21.8
Sepsis	11	14.1
TORCH	1	1.3
Total	78	100

Neonatal seizures were classified based on the day of onset into three groups: less than 3 days, 3-7 days, and more than 7 days. The majority (43.6%, 34 patients) experienced seizures within the first three days, primarily due to hypoxic-ischemic encephalopathy (HIE) (19/34). Seizures occurring between 3-7 days accounted for 30.8% (24 patients), with hypocalcemia being the cause in 8 cases (8/24). Late-onset seizures (>7 days) were observed in 25.6% (20 patients), mostly due to pyogenic meningitis (10/20). As in table 5 and 6.

Table 5: Studying etiology with respect to day of onset of seizures

	Age at Presentation with Seizures							
	< 3 days		3-7 days		8-28 days		Total	
Cause of Seizures	**N=34**	**100%**	**N=24**	**100%**	**N=20**	**100%**	**N=78**	**100%**
HIE	19	55.9	3	12.5	0	0.0	22	28.2
Meningitis	2	5.9	5	20.8	10	50.0	17	21.8
Sepsis	4	11.8	4	16.7	3	15.0	11	14.1
Hypocalcaemia	0	0.0	8	33.3	3	15.0	11	14.1
Hypoglycemia	8	23.5	1	4.2	0	0.0	9	11.5
Kernicterus	0	0.0	2	8.3	2	10.0	4	5.1
IVH	1	2.9	1	4.2	1	5.0	3	3.8
Cong Infection	0	0.0	0	0.0	1	5.0	1	1.3

Table 6: Distribution of study sample according to age of presentation

Age at Onset	< 3 days	34/78	43.6
	3-7 days	24/78	30.8
	8-28 days	20/78	25.6

Regarding the treatment of neonatal convulsions, 20 out of 78 patients (25%) were treated by correcting underlying causes, with 11 cases (14.1%) due to hypocalcemia and 9 cases (11.5%) due to hypoglycemia. Seven patients (9%) died before treatment could begin. Of the remaining patients, 51 (65.3%) required anticonvulsant drugs. These were divided into two groups: 44 patients (86.3%) responded to phenobarbitone alone, while 7 patients (13.7%) required the addition of phenytoin. The overall response to pharmacotherapy was 100%, as all 51 patients given anticonvulsants responded to the treatment. As in table 7.

Table 7: Anticonvulsant Therapies in Neonatal Seizures

Type of Therapy	**No.**	**%**
No anticonvulsants use (but specific treatment)	20	25.6
Anticonvulsants	51	65.3
Phenobarbital	44	86.3
Phenytoin + Phenobarbital	7	13.7
Response to Anticonvulsant		
Responded to Phenobarbital alone	44	86.3
Required Phenobarbital + Phenytoin	7	13.7

Among all cases and exactly at time of discharge, 54 (69.2%) were improved and discharge well, 6 patients (7.7%) remained hypotonic, 11 patients (14.1%) became spastic and 7 patients (9%) were died, 3 cases due to IVH, 2 cases due to meningitis, 2 cases due to HIE. As in table 8.

Table 8: State of the patients at the time of discharge

State on Discharge	**Number**	**Percentage (%)**
Improve	54	69.2
Spastic	11	14.1
Hypotonic	6	7.7
Died	7	9
Total	78	100

Discussion:

The first four weeks of life represent a critical period with a high risk of seizures, which are associated with significant morbidity and mortality. In this study, 49 (62.8%) neonates were delivered by normal vaginal delivery, consistent with findings by Taksande AM *et al*. (2005) and Sweta LM (2002), reporting 65.4% and 64% respectively [20, 21]. Additionally, 42 (53.8%) of the cases were male, similar to Yaser's study (53.4%) [22]. Most patients (68, 87.2%) with neonatal seizures were full-term, aligning with Dr. Ashok Gupta's study (82.3%) [23]. The majority (84.6%) of these neonates weighed over 2500 grams, comparable to Sweta LM's findings (82.8%) [21]. Regarding seizure types, tonic seizures were the most common (50%), followed by subtle seizures (25.6%). This contrasts with Sweta LM's study, which found subtle seizures to be the most common (45%) [21]. The difference might be due to varying etiologies of neonatal seizures across studies, with sepsis being a major cause in Sweta LM's study. Age distribution showed that 34 (43.6%) neonates experienced their first seizure before 72 hours of age, similar to Dr. Ashok Gupta's findings (45%) [23]. However, this differs from Dr. Jasim M. ALMarzoki's study, which reported the first seizure between 3-7 days of life in 43.2% of cases [24]. This variation may be explained by the different common causes of neonatal seizures, with hypoxic-ischemic encephalopathy (HIE) being prevalent in early-onset cases in this study. HIE was the most common etiological factor, accounting for 22 (28.2%) cases, consistent with studies by Taksande AM *et al*. (2005), Eman F. Badran *et al*. (2007), and Watanabe K *et al*. (1980) [20, 25, 26]. Pyogenic meningitis was identified in 17 (21.8%) cases, a higher incidence than reported by Volpe [5] and Bergman *et al*. (3-8%) [27]. The increased incidence could be due to higher maternal risk factors for infection, such as premature rupture of membranes and poor antenatal care. Sepsis was found in 14.1% of cases, similar to Dr. Ashok Gupta (12%) [23] and James J *et al*. (13.5%) [28]. Hypoglycemia was present in 11.5% (9/78) of cases, higher than reported by Bergman *et al*. (7%) and Goldberg JH (6.2%) [29]. This higher incidence might be attributed to poor antenatal care for diabetic mothers. Kernicterus was reported in 5.1% of cases, higher than Dr. Ashok Gupta's study (2.94%) [23], likely due to late presentations and poor family awareness of severe neonatal jaundice consequences. Intraventricular hemorrhage (IVH) was observed in three cases (3.8%), higher than Dr. Ashok Gupta's report (0.98%) [23] but lower than findings by Taksande AM *et al*. (6.4%) and James J *et al*. (17%) [20, 28]. The differences may be due to the small number of preterm infants in this study. Treatment involved addressing treatable causes such as hypocalcemia (14.1%) and hypoglycemia (11.5%), similar to Yaser's study (21.5%) [22]. Anticonvulsant drugs were needed in 51 (65.3%) cases, with two seizure control groups identified: phenobarbitone alone (86.3%) and phenobarbitone with phenytoin (13.7%). The overall response to anticonvulsants was 100%, similar to Yaser's study [22], but inconsistent with Painter *et al*. (59%) and Gilman *et al*. (91%) [30, 31]. The differences could be due to the lack of electroencephalographic monitoring in this study. The mortality rate was 9%, with most deaths (42.9%) due to IVH, consistent with Taksande AM *et al*. (2005) [20].

Conclusion

Neonatal convulsions are most prevalent in full-term neonates, males, and those who are within the first 72 hours of life. The most prevalent pattern was tonic seizures. Meningitis is the second most prevalent cause of convulsions in newborns, following HIE. Preterm neonates are the primary victims of intraventricular haemorrhage, which was a significant cause of mortality.

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