e-ISSN: 0975-1556, p-ISSN:2820-2643

Available online on www.ijpcr.com

International Journal of Pharmaceutical and Clinical Research 2024; 16(11); 946-951

Original Research Article

Biochemical Profile in Neonatal Seizures at a Tertiary Care Center at Rajasthan

Bhavna Vaishnav[1], Rajesh Kanwar[2], Pooja Verma[3], Mradul Varshney[4], Rajvi Fuletra[5]

[1,2]Senior Resident, Department of Pediatrics, Government Medical College and Bangar Hospital, Pali, Rajasthan

[3]Senior Resident, Department of Pediatrics, SMS Medical College, Jaipur, Rajasthan

[4,5]Resident, Department of Pediatrics, Government Medical College and Bangar Hospital, Pali, Rajasthan

Received: 25-08-2024 / Revised: 23-09-2024 / Accepted: 26-10-2024

Corresponding Author: Dr. Rajesh Kanwar

Conflict of interest: Nil

Abstract:

Introduction: Neonatal seizures, a prominent concern in neonatal neurology, represent an urgent clinical condition frequently stemming from various biochemical, structural, or infectious etiologies. The study, conducted at Government Medical College and Bangar Hospital, Pali, Rajasthan, investigates the biochemical profile of neonates presenting with seizures to aid in the early detection and management of underlying metabolic disturbances.

Methods: The study involved 1487 newborns admitted between June 2023 and May 2024, among whom 128 (8.6%) presented with or developed seizures. Data was systematically recorded, capturing each neonate's clinical history, maternal obstetric background, and onset details. Biochemical profiles, including glucose, calcium, sodium, magnesium, potassium, and phosphorus levels, were measured, with abnormal values indicative of potential seizure-related metabolic disturbances. The study distinguished primary metabolic seizures from those secondary to other etiologies, such as hypoxic-ischemic encephalopathy (HIE), intracranial hemorrhage (ICH), sepsis, and meningitis.

Results: Among the 128 neonates with seizures, HIE emerged as the leading etiology, accounting for 44.53% of cases, followed by primary metabolic disturbances (17.96%) and ICH (14.84%). Metabolic profiles revealed that 54% of neonates with seizures exhibited biochemical abnormalities, with hypocalcemia as the predominant disturbance in 56.52% of primary metabolic cases. Hypoglycemia was the next most frequent abnormality, constituting 17.39% of primary metabolic seizures. Notably, the incidence of seizures was higher in outborn neonates (70.31%) than in inborn neonates (29.68%), which may reflect limited perinatal care access in rural areas and higher rates of home deliveries. Subtle seizures were the most common type, observed in 46.09% of cases, followed by focal clonic (16.41%) and generalized tonic seizures (13.28%). Hypocalcemia and hypoglycemia were also significant in non-metabolic seizures associated with HIE, ICH, and other non-metabolic etiologies. Male neonates showed a higher incidence of seizures (59.38%), aligning with previous research highlighting increased neurological vulnerability in male infants.

Conclusions: The findings underscore the importance of prompt biochemical screening in neonates with seizures, as metabolic abnormalities like hypocalcemia and hypoglycemia are common and potentially modifiable contributors. The study's insights support the necessity for heightened neonatal monitoring, especially in outborn neonates from underserved regions. Furthermore, the predominance of HIE and metabolic abnormalities as seizure etiologies suggests that improving perinatal care quality and early intervention for metabolic disturbances could reduce neonatal seizure incidence and associated morbidities.

Keywords: HIE, Hypocalcemia, Hypogylcemia, and Seizures.

Introduction

Neonatal seizures have long captivated the interest of paediatricians due to their widespread occurrence and the myriad of conditions that can provoke them. They represent a common neurological challenge during the neonatal period, with a frequency ranging from 1.5 to 14 cases per 1000 births.[1] Neonates are particularly vulnerable to seizures due to various factors such as metabolic disturbances, oxygen deprivation, structural anomalies, and infections. Remarkably, around a quarter of cases present without an identifiable cause. [2] Early identification of the underlying cause of seizures is important. It provides an opportunity for active and prompt treatment, thereby mitigating the associated morbidity, mortality, and long-term consequences. The

immature nervous system of newborns renders them susceptible to seizures even with minor provocations. [3] Seizures in newborns constitute a medical emergency, often indicating substantial damage to the central nervous system. Their clinical presentation, underlying causes, management, and prognosis significantly differ from seizures observed in older children. Defined as paroxysmal involuntary disturbances of brain function, seizures can manifest as various abnormalities including impaired consciousness, abnormal motor activity, behavioural changes, sensory disruptions, or autonomic dysfunction. [4] The presence of seizure does not constitute a diagnosis; seizures are a presentation of an underlying CNS disorder due to systemic or biochemical disturbances. Perinatal asphyxia, neonatal meningitis, and biochemical abnormalities are the most common etiologies of neonatal seizures. Biochemical abnormalities occur either as an underlying cause or as an associated abnormality. Biochemical abnormalities should be excluded in every case of neonatal seizure, even in the presence of other causes such as meningitis, asphyxia, and structural abnormalities. [5]

The most common metabolic abnormalities which can cause neonatal seizures are hypoglycemia, hypocalcemia, hypomagnesemia, hyponatremia, hypernatremia, and hypophosphatemia. Infants with sepsis and meningitis frequently have hypoglycemia, possibly due to inadequate intake, increased metabolic rate, and impaired ability to metabolize glucose. [6] Hypocalcemia (serum calcium levels <7 mg/dl) due to the use of high phosphate infant formula has been cited as a common cause of seizures in various studies. [7,8]

However, commonly hypocalcemia occurs in infants with trauma, hemolytic disease, asphyxia, and in infants of diabetic mothers (IDM) and usually coexists with hypoglycemia and hypomagnesemia, presenting at 2-3 days of life. [9] Hypomagnesemia (serum levels <1.5 mg/dl) can manifest with tetany and seizures at 2-4 weeks of age and has secondary hypocalcemia associated with it. In infants of diabetic mothers, hypomagnesemia appears to be a consequence of maternal magnesium depletion.[10] Hyperphosphatemia may be caused by ingestion of milk formulas containing high amounts of phosphorus, excessive parenteral administration of phosphorus, impaired renal function, and hypoparathyroidism. [11]

In a study on birth asphyxia, hypocalcemia with or without hyperphosphatemia occurred in around 12.5% of cases. [12] Hyponatremia as a result of fluid overload, renal compromise, and SIADH can be a frequent complication of birth asphyxia.[12] Similarly, SIADH can be a part of intracranial hemorrhage (ICH). [13]

Hence, the present study is conducted to study the biochemical abnormalities in neonatal seizures, which would help in early treatment and better prognosis.

Material and Method

This is an observational cross-sectional study done at Government Medical College and Bangar Hospital, Pali Rajasthan, India. Newborns both inborn and outborn who got admitted in NICU from June 23 to May 24 were included in the study as per the inclusion and exclusion criteria.

All newborns admitted during the study period to SNCU meeting the inclusion and exclusion criteria were included in the study. The clinical details like gestational age, birth weight, treatment progress, all investigations and outcomes were recorded in the birth register.

Data like child's demographic details, mother's obstetric history, any associated risk factors underlying preterm delivery like preeclampsia, fetal growth retardation, previous history of preterm births, etc., were noted. Details of onset of labour, mode of delivery, birth weight of the baby, and complications was recorded on designated formats.

Inclusion Criteria

1. All newborns, both inborn and outborn admitted to SNCU
2. And either presented with seizures or developed seizures during the course of admission.
3. The parents consented to be included in study.

Exclusion Criteria

1. Parents who did not consent for the study.
2. IUD and still births deliveries.
3. Incomplete medical records.

Definitions and Standard Values:

Prematurity was considered in any neonate born before 37 completed weeks, if the last date of monthly period was known or in infants whose estimated gestation by NBS (New Ballard Score) was less than 37 completed weeks (Eregie, 2000).

Term neonate was described as having gestational age between 37 to 41 completed weeks.

Primary metabolic seizures: seizures due to transient biochemical abnormalities in the absence of other etiologies for neonatal seizures (Sood *et al*., 2003).

Non metabolic seizures: For our study purposes we defined non metabolic seizures as seizures having biochemical abnormalities coincident upon other etiologies for neonatal seizures like birth asphyxia, meningitis, sepsis etc (Sood *et al*., 2003).

Sepsis: Positive blood or CSF cultures. (Definite sepsis)

Possible Sepsis (WHO, 2005): Presentation with either one of the following: Abnormal temperature (>37.5ºC or <35.5ºC), respiratory distress, lethargy, feeding problems or seizures, premature rupture of membranes (PROM), foul smelling liquor, amnionitis. Positive septic screen i.e. presence of at least two out of the four parameters namely, total leucocyte count <5000/mm^3, bands to neutrophill ratio of >0.2, CRP >10ng/ml and micro-ESR of> 10mm in one hour.

Meningitis: Diagnosed on CSF examination as >20 WBC in CSF (John P. Cloherty *et al*., 2008) with predominance of polymorphonuclear leucocytes.

Neonatal Encephalopathy (Birth Asphyxia) No cry at birth, poor Apgar score 6 or <6 at 5 min (in hospital born neonates), an accompanying history of feeding problems, restlessness, agitation, hypotonia, seizures, and coma or similar symptoms and signs after excluding other possible diagnosis.

Intracranial Hemorrhage: It was diagnosed with a brain ultrasound or CT scan.

Criteria for diagnosing various biochemical abnormalities: (Kumar *et al*., 1995)

- Hypoglycemia: blood sugar < 40mg/dl
- Hypocalcemia: total serum calcium < 7mg/dl and ionized serum calcium< 4.4mg/dl
- Hypomagnesemia: serum magnesium < 1.5mg/dl
- Hypernatremia: serum sodium > 150meq/dl
- Hyponatremia: serum sodium < 130meq/dl
- Hypokalemia: serum potassium < 3.5meq/dl
- Hyperkalemia: serum potassium > 5.5meq/dl
- Hyperphosphatemia: serum phosphorus > 8mg/dl

Statistical analysis: Data was collected and entered into MS Excel 2019. Frequency and percentage were calculated and analysed. Taking, 95% confidence interval, and *P* value. *P* Value of <0.05 was considered significant.

Results

In the present study during the study period a total of 1487 newborns were admitted in the SNCU out of which 796 (53.53%) were inborn and 691 (46.47%) were outborn who were referred to our hospital from nearby centres. Out of 1487 newborns, the incidence of seizures was 8.60% (128 babies). These 128 babies were included in the present study. Out of the 128 babies who has seizures, 38 (29.68%) were inborn and 90 (70.31%) were outborn. [Image 1]. There were 76 (59.38%) male babies and 52 (4.63%) females. [Image 2] A total of 48 (37.5%) newborns presented with the chief complaints of seizures whereas rest of the newborns developed seizures during the course of admission.

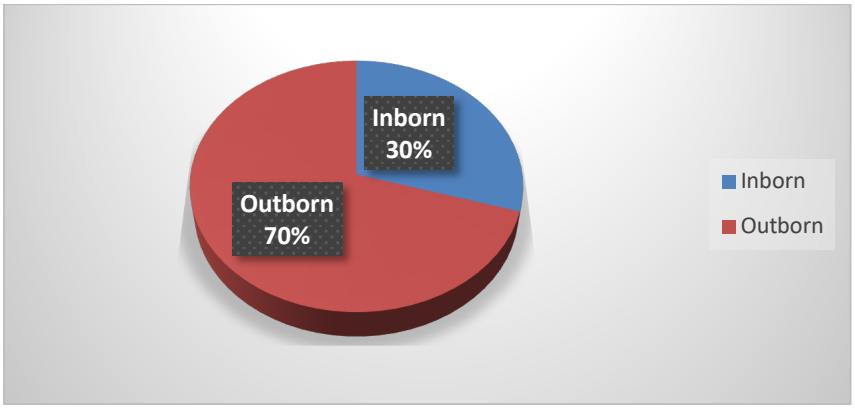

Figure 1: Inborn and Outborn cases in present study

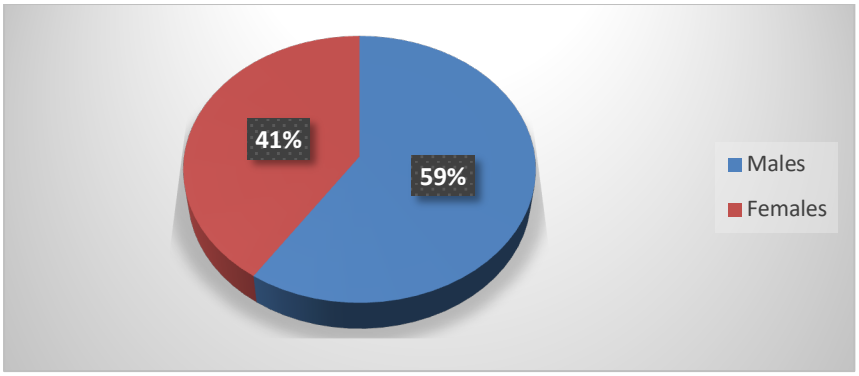

Figure 2: Gender wise distribution of cases

In the present study, Hypoxic-ischemic encephalopathy (HIE) is the most frequent cause, accounting for 44.53% (57 cases), followed by primary metabolic disorders, which make up 17.96% (23 cases). Intracranial bleeds contribute to 14.84% (19 cases), while encephalopathy, unrelated to HIE, is responsible for 8.59% (11 cases). Sepsis and meningitis are less common, representing 5.47% (7 cases) and 4.69% (6 cases), respectively. In 3.12% of cases (4 newborns), the cause remains unknown. [Table 3]

Subtle seizures are the most common, seen in 46.09% (59 cases), Focal clonic seizures, occurred in 16.41% (21 cases), while generalized tonic seizures account for 13.28% (17 cases). Multifocal clonic seizures, where multiple body parts are affected, represent 10.94% (14 cases). Seizures presenting as a combination of subtle with generalized tonic seizures (GTS) and subtle with clonic activity make up 7.03% (9 cases) and 6.25% (8 cases), respectively. [Table 4]

A total of 69 (54%) convulsing neonates had biochemical abnormalities. Twenty-three neonates (31%) had primary metabolic seizures, and 46 (69%) neonates had metabolic abnormalities superimposed or coincident on a primary illness such as hypoxic-ischemic encephalopathy, intracranial hemorrhage (ICH), meningitis, or sepsis. Fifty-nine (46%) neonates did not have any biochemical abnormality coincident with their etiology. In four (3.12%) neonates, the etiology could not be elucidated. Among the 23 neonates with primary metabolic seizures, 7 (24%) were preterm and 16 (70.6%) were term. Hypocalcemia was the most common biochemical abnormality in primary metabolic seizures, comprising 56.52% (n=13) of cases. Among these, preterm and term neonates each had 3 and 10 cases, respectively, making hypocalcemia the most common biochemical abnormality in both groups. Late-onset hypocalcemia was observed in 5 cases, while early-onset hypocalcemia was noted in 8 cases, including 4 cases in infants of diabetic mothers (IDM). Primary metabolic seizures except for late hypocalcemia had presentation in the first half of first week. Late hypocalcemia presented around the end of first week. Hypoglycemia was the next most common abnormality, comprising 17.39% (n=4) of the cases with primary metabolic seizures, including 1 IDM cases. Other cases included one large-for-date neonate, one preterm, one IUGR. Hypomagnesemia and hyperphosphatemia were seen in 13.04% (n=3) cases each of primary metabolic seizure cases.

Among the 46 cases of non-metabolic seizures, hypocalcaemia remained the most frequent abnormality with 21 cases, followed by hypoglycaemia in 11 cases. Hyponatremia was observed in 3 cases, while hyperphosphatemia and hypomagnesemia were present in 6 and 5 cases, respectively.

Table 1: Distribution of cases according to APGAR5, Gestational age and weight.

Characteristic		No. of Patients	Percent
Apgar Score at 5min	< 7	48	37.50%
	7 to 10	80	62.50%
Gestational Age (NBS)	Preterm	43	33.59%
	Term	85	66.41%
Weight	Appropriate for Gestation Age	96	75.00%
	Large for Gestation Age	8	6.25%
	Small for Gestation Age	24	18.75%

Characteristic		Value
Age of Onset of seizure (day)	mean ± SE	3.7 ± 0.4 (1, 25)
Head Circumference (cm)	mean ± SE	33.8 ± 0.1 (30, 37)
Length (cm)	mean ± SE	47.5 ± 0.3 (42, 53)

Table 2: Etiology of seizures in the present study

Etiology	No. of Cases	Percent
Hypoxic Ischemic Encephalopathy	57	44.53%
Intracranial Bleed	19	14.84%
Encephalopathy	11	8.59%
Meningitis	6	4.69%
Sepsis	7	5.47%
Primary Metabolic	23	17.96%
Unknown	4	3.12%
	128	100

Table 3: Types of seizures in the present study

Type of Seizures	No. of Cases	Percent
Subtle	59	46.09%
Focal clonic	21	16.41%
Generalized tonic	17	13.28%
Multifocal clonic	14	10.94%
Subtle with GTS	9	7.03%
Subtle with clonic	8	6.25%
Total	**128**	

Discussion

Neonatal seizures are a common clinical issue during the first few weeks of life and often serve as the first indication of serious neurological dysfunction in newborns. Identifying seizures in neonates can be challenging due to their variable, disorganized, and often subtle presentation at this age. Early recognition is critical because seizures frequently represent the first sign of underlying neurological disease or dysfunction. Therefore, a comprehensive understanding of the incidence, natural history, clinical profile, and etiology of neonatal seizures is essential for accurate diagnosis and effective management, ensuring timely intervention to prevent further complications.

In the present study, out of total 1487 newborns who were admitted to the NICU, the incidence of seizures was 8.60% (128 babies). There were 76 (59.38%) male babies and 52 (4.63%) females. Out of the 128 babies who has seizures, 38 (29.68%) were inborn and 90 (70.31%) were outborn. A total of 48 (37.5%) newborns presented with the chief complaints of seizures whereas rest of the newborns developed seizures during the course of admission. The prevalence of seizures in inborn was 4.77% whereas in outborn it was quite high with 13.02% with cumulative prevalence of 8.6%. The incidence of seizures in this study (8.60%) is consistent with findings from previous studies, which report rates ranging between 1-20%, depending on the population and clinical setting. A study by Glass et al. (2016) [14] reported a seizure incidence of 10-15% in neonatal intensive care units (NICUs), which aligns closely with the present findings. However, the prevalence of seizures in newborns is higher in our study as compared to other previous studies done by Sharma R et al. [15] who reported the prevalence of 2.14%. With the increase in NICU infrastructure and access to level 2 and 3 NICU in government hospitals, the perinatal care has improved significantly however the higher incidence of neonatal seizures in our study may be due to the fact that a majority of patients coming to our facility are from rural and tribal background, who due to their believes and stigmas do not tend to seek medical care early and the delay in coming to the hospital may predispose to perinatal complications, leading to seizures in newborns.

Male predominance in neonatal seizures, as seen in this study (59.38% male vs. 40.63% female), is also commonly observed in literature. Several studies, including those by Pisani et al. (2008) [16] and Low et al. (2014) [3], reported a higher prevalence of seizures in male infants, which may be attributed to gender-related differences in neonatal brain vulnerability. A noteworthy finding in the present study is the significantly higher proportion of outborn neonates with seizures (70.31%) compared to inborn neonates (29.68%). This trend may reflect the large number of home deliveries being conducted at rural and tribal areas by untrained dais and no antenatal care being seeked by pregnant females. Limited access to adequate prenatal and perinatal care in the centers from which these outborn neonates were referred, resulting in higher incidences of complications such as hypoxic-ischemic encephalopathy (HIE) and infections, both of which are prominent causes of neonatal seizures. This observation aligns with earlier studies, such as Kumar et al. (2015) [17], which highlighted higher seizure rates in outborn neonates, particularly in resource-limited settings.

In the present study, HIE emerged as the leading cause of neonatal seizures (44.53%), followed by metabolic disorders (17.96%), intracranial hemorrhage (ICH) (14.84%), and sepsis/meningitis (10.16%). These findings corroborate those of earlier studies, such as the one by Tekgul et al. (2006) [4], which identified HIE as the most frequent cause of neonatal seizures, accounting for nearly 40-50% of cases. Furthermore, the prevalence of metabolic causes, particularly hypocalcemia and hypoglycemia, has been well-documented in studies by Volpe (2008)5 and Evans et al. (2010) [9], highlighting the importance of early identification and management of biochemical disturbances to prevent seizures.

Subtle seizures were the most common type, observed in 46.09% of neonates, followed by focal clonic (16.41%) and generalized tonic (13.28%) seizures. This distribution mirrors the findings of studies such as those by Clancy and Legido (2012) [2] and Murray et al. (2016) [18], who also found subtle seizures to be the most prevalent seizure type in neonates. Subtle seizures are often challenging to diagnose due to their non-specific clinical manifestations, emphasizing the need for

continuous monitoring and advanced neuroimaging in neonatal care.

The study found that 54% of neonates with seizures had biochemical abnormalities, with hypocalcemia being the most frequent. This is in line with previous reports from Rennie et al. (2007) [19] and Low et al. (2014) [3], where hypocalcemia was noted as a leading biochemical cause of seizures. Hypoglycaemia and other metabolic abnormalities, such as hypomagnesemia and hyperphosphatemia, were also prominent, further reinforcing the role of metabolic screening in the management of neonatal seizures.

Conclusions:

The findings underscore the importance of prompt biochemical screening in neonates with seizures, as metabolic abnormalities like hypocalcemia and hypoglycemia are common and potentially modifiable contributors. The study's insights support the necessity for heightened neonatal monitoring, especially in outborn neonates from underserved regions. Furthermore, the predominance of HIE and metabolic abnormalities as seizure etiologies suggests that improving perinatal care quality and early intervention for metabolic disturbances could reduce neonatal seizure incidence and associated morbidities.

Implications: The study emphasizes a strategic focus on metabolic profiling for neonatal seizures, particularly in settings with limited prenatal care access, and advocates for increased awareness of neonatal metabolic health to enhance early diagnosis and outcomes.

References

1. Scher MS, Painter MJ. Neonatal seizures: pathophysiology and outcome. J Child Neurol. 2005; 20(1):22-9.
2. Clancy RR, Legido A. The exact incidence of neonatal seizures: a quantitative review. Arch Dis Child. 2012; 67(10):1093-6.
3. Low E, Mathieson SR, Stevenson NJ, et al. Etiology and characteristics of neonatal seizures: a multicenter observational study. Epilepsia. 2014; 55(6):955-62.
4. Tekgul H, Gauvreau K, Soul J, et al. The current etiologies of neonatal seizures in the NICU. Pediatr Neurol. 2006; 34(2):85-92.
5. Volpe JJ. Neurology of the Newborn. 5th ed. Philadelphia: Saunders Elsevier; 2008.
6. Leaks P, Lum G, Moulder JE. Neonatal hypoglycemia in infants with sepsis. J Pediatr. 1981; 99(4):601-4.
7. Keen JH. Neonatal seizures associated with hypocalcemia due to phosphate formulas. Am J Clin Nutr. 1973; 26(3):280-4.
8. Interny AJ, Lombroso CT. The role of calcium in neonatal seizures. Pediatrics. 1969; 43(5):718-24.
9. Evans JR, Weiner SP. Neonatal hypocalcemia: clinical considerations and management. Neonatology. 2010; 97(3):231-6.
10. Kenner C. Comprehensive Neonatal Nursing Care. 5th ed. New York: Springer Publishing Company; 2007.
11. Kumar P, Dhakal A, Sood V, et al. Role of hypocalcemia in neonatal hypoxic-ischemic encephalopathy. Indian J Pediatr. 1995; 62(4):493-6.
12. Kumar P, Dhakal A, Sood V, et al. Role of biochemical abnormalities in neonatal seizures in HIE cases. Indian J Pediatr. 1995;62(4):493-6
13. Scher MS, Painter MJ. Syndrome of inappropriate antidiuretic hormone secretion in neonatal intracranial hemorrhage. Clin Perinatol. 1989; 16(1):243-55.
14. Glass HC, et al. Epidemiology of seizures in neonatal intensive care units. J Pediatr. 2016; 178:27-32.
15. Sharma DR. Seizure Pattern and Biochemical Abnormality in Neonatal Seizure. J Med Sci Clin Res. 2017; 5(9). doi:10.18535/jmscr/v5i9.104.
16. Pisani F, et al. Neonatal seizures: Aetiology, diagnosis and management. Acta Paediatr. 2008; 97(9):1308-17.
17. Kumar A, et al. Outborn versus inborn neonatal outcomes. J Trop Pediatr. 2015; 61(3):243-8.
18. Murray DM, et al. Neonatal seizures in hypoxic-ischemic encephalopathy. J Child Neurol. 2016; 31(1):27-34.
19. Rennie JM, et al. Biochemical abnormalities in neonatal seizures. Arch Dis Child. 2007; 92(7):641-4.