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Neonatal Seizures: Clinical Presentation, Associated Pathologies and Therapeutic Approaches - A Clinical Study in aTertiary Hospital

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Abstract

Neonatal seizures are a significant neurological condition, occurring in approximately 2.29 per 1,000 live births, with higher incidence in preterm neonates. These seizures often signal serious underlying disorders and demand prompt evaluation. This retrospective observational study analyzed 97 neonates diagnosed with seizures during their stay in a Neonatal Intensive Care Unit from 2013 to 2023. Tonic seizures were the most common type, followed by myoclonic and clonic seizures. Hypoxic-ischemic encephalopathy was the leading cause in full-term neonates, and periventricular-intraventricular hemorrhage in the preterm group. Other etiologies included meningitis, ischemic neonatal stroke, and metabolic disturbances. Notably, genetic and structural abnormalities, such as polymicrogyria, were identified in a subset of patients, emphasizing the importance of genetic testing and advanced neuroimaging in diagnosis and management. Phenobarbital was the first-line treatment in all cases, with midazolam and levetiracetam used as second-line treatment. Electroencephalography was vital for diagnosis, though some patients exhibited normal EEGs despite clinical seizure activity. The findings underscore the complexity of diagnosing and treating neonatal seizures and highlight the need for early identification of underlying causes to improve long-term neurological outcomes.

Keywords: Neonatal Seizures; Preterm Neonates; Neonatology

Abbreviations: NICU: Neonatal Intensive Care Unit; ILAE: International League Against Epilepsy; EEGs: Electroencephalograms; GCP: Good Clinical Practice; HIE: Hypoxic-Ischemic Encephalopathy; CEEGs: Continuous EEG; SV2A: Synaptic Vesicle Protein 2A; MRI: Magnetic Resonance Imaging

Introduction

Neonatal seizures are a frequently encountered neurological condition in newborns. The estimated incidence of neonatal seizures has been reported as approximately 2.29 cases per 1,000 live births. However, higher rates are observed in preterm neonates compared to full-term infants, with preterm neonates having an incidence of 14.28 cases per 1,000 live births, while full-term neonates have a rate of 1.10 cases per 1,000 [1]. They are defined as sudden, abnormal, paroxysmal changes in brain electrical activity that occur from birth until the end of the neonatal period [2]. Due to the immaturity of the neonatal brain, seizures in this population exhibit distinct causes, electrographic patterns, and clinical presentations compared to those in older children or adults [3]. In many cases, neonatal seizures may be the first indication of a serious underlying disorder. Therefore, prompt recognition and evaluation are critical to identify the root cause, preventing further brain damage, and stopping the seizure activity [4].

Objectives

1. Identify the causes of neonatal seizures.

2. Review the clinical manifestations of neonatal seizures.

3. Promote information about possible etiologies, enhance care coordination and improve outcomes for newborns experiencing seizures.

Methods

A retrospective observational study was carried out using the hospital database. The cohort included a population of newborns with a diagnosis of seizures during neonatal intensive care unit (NICU) stay at Unidade Local de Saúde de Braga, Portugal, from January 2013 to December 2023. The diagnosis of epileptic seizures was established based on the International League Against Epilepsy (ILAE) classification. [5]. Patients with the first seizure after the neonatal period (defined as the first 28 days of life for term neonates and up to 44 weeks of corrected gestational age for preterm neonates) were excluded. Neonatal electroencephalograms (EEGs) were obtained based on clinical indications and were interpreted by neurologists attached to a tertiary hospital. Imaging in the neonatal period included cranial ultrasounds and magnetic resonance imaging in selected patients. Different variables were analyzed: birthweight and gestational age, etiology of the seizures (hypoxic-ischemic encephalopathy, structural, infectious, metabolic, genetic, vascular or undetermined cause), type, treatment and electro-clinical correlates. Statistical analysis was performed with SPSS v29.

Statement of Ethics

This study complies with the World Medical Association Declaration of Helsinki and was conducted in accordance with the principles of Good Clinical Practice (GCP). The study has been approved by the Unidade Local de Saúde de Braga Ethics Committee (nº 47/2024).

Results

During the study period, 104 patients were found to have the term 'seizure' noted in their problem list at some point during the NICU stay. However, 7 of these patients were excluded because either their first seizure happened after the neonatal period or the suspected seizures were not confirmed. As a result, the final study sample included 97 newborns. Of the 97 patients, the median gestational age at delivery was 38 weeks (IQR 30–39) and male-to-female ratio was 65.9:34.1. A significant percentage of the newborns were preterm, with 44 cases accounting for 45.4% of the total. The median birth weight was 2710 g.

In terms of the clinical manifestations (Table 1), most of the newborns (n=42, 43.3%) experienced the onset of seizures after the first 24 hours. More than one type of seizure was reported in 32.9% (n=32) of patients. The clinical manifestations of seizures varied. Tonic seizures were the most common, affecting 38 patients (39.1%), followed by myoclonic seizures in 32 patients (32.9%). Both automatisms and clonic seizures were observed in 30 patients each (30.9%). Less frequent manifestations included central cyanosis in 16 patients (16.5%), apnea in 13 patients (13.4%), and oxygen desaturation in 11 patients (11.3%). Epileptic spasms were the rarest, occurring in only one patient. All of the seizures involved exclusively focal or multifocal onset, and no generalized tonic-clonic seizures were described. In 11 patients (11.3%), EEG could not be performed. Of these, 4 patients died shortly after seizure onset, precluding the procedure. The remaining 7 patients required therapeutic hypothermia in another unit, due to hypoxic-ischemic encephalopathy, preventing EEG acquisition at our facility prior to transfer. Regarding the data from EEGs, 52 (53.6%) showed electro-clinical correlation and 34 (35%) showed normal background activity and no epileptiform patterns.

Table 1: Clinical Manifestation.

Clinical Manifestation	n= (%)
Tonic	38
Myoclonic	32
Automatisms	30
Clonic	30
Oxygen Desaturation	11
Apnea	13
Central Cyanosis	16
Epileptic Spasms	1

All seizures with electrical correlation (n=52, 53.6%) were treated. Of those that were purely clinical, 28 out of 30 (93%) were treated. Only one of the patients on whom it was not possible to perform an EEG was not treated. In all cases, phenobarbital was used as the first-line treatment. In order to control seizures, a second medication was required in some cases, with midazolam being used in 20 cases (20.6%) and levetiracetam in 16 cases (16.5%). In this study, the etiology of seizures will be analyzed by categorizing patients into two distinct groups based on gestational age: full-term and preterm neonates. This classification is essential because the underlying causes of neonatal seizures vary between these groups based on differences in brain maturation, susceptibility to injury, and perinatal risk factors.

Regarding the preterm group (n=44, 45.4%) (Table 2), seizures were attributed to periventricular-intraventricular hemorrhage in 19 patients (43.2%), periventricular leukomalacia in 8 (18.2%), venous infarction with secondary hemorrhage in 3 (6.8%), and other causes in 14 (31.8%). The other etiologies included meningitis (n= 3, 6.8%), congenital brain malformations (n=2, 4.5%), genetic syndromes (n=2, 4.5%), and acute ionic disturbances (n=2, 4.5%). Additionally, five patients (11.5%) had an unknown etiology. The brain malformation identified in both patients was polymicrogyria. Among those with a genetic etiology, one newborn was diagnosed with Ohtahara syndrome, while the other had Cardiofaciocutaneous syndrome caused by a *MAP2K1* pathogenic variant.

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Table 2: Etiology in Preterm Neonates.

Etiology in Preterm Neonates	n= (%)
Periventricular-Intraventricular Hemorrhage	19 (43.2)
Periventricular Leukomalacia	8 (18.2)
Venous Infarction with Secondary Hemorrhage	3 (6.8)
Meningitis	3 (6.8)
Congenital Brain Malformations	2 (4.5)
Genetic Syndromes	2 (4.5)
Acute Ionic Disturbances	2 (4.5)
Unknown Etiology	5 (11.5)

In the full-term group (n = 53, 54.6%) (Table 3), the most common cause of seizures was hypoxic-ischemic encephalopathy (HIE), affecting 28 patients (52.8%), followed by ischemic neonatal stroke in 4 (7.5%), intraventricular hemorrhage in 3 (5.7%), and periventricular leukomalacia in 1 (1.9%). Other causes accounted for 17 cases (32.1%) and included acute ionic disturbances (n=4, 7.5%), meningitis (n= 4, 7.5%), hypoglycemia (n=2, 3.8%), genetic syndromes (n=1, 1.9%), and metabolic disease (n=1, 1.9%). Additionally, five patients (9.4%) had an unknown etiology. The genetic etiology identified in one patient was developmental and epileptic encephalopathy due to an *HCN1* gene mutation (c.1172G>A, p.G391D). The metabolic disease case was diagnosed as severe Zellweger spectrum disorder.

Table 3: Etiology in Full-Term Neonates.

Etiology in Full-Term Neonates	n= (%)
Hypoxic-Ischemic Encephalopathy	28 (52.8)
Ischemic Neonatal Stroke	4 (7.5)
Intraventricular Hemorrhage	3 (5.7)
Periventricular Leukomalacia	1 (1.9)
Acute Ionic Disturbances	4 (7.5)
Meningitis	4 (7.5)
Hypoglycemia	2 (3.8)
Genetic Syndrome	1 (1.9)
Metabolic Disease	1 (1.9)
Unknown Etiology	5 (9.4)

Discussion

Neonatal seizures are a significant neurological concern in newborns. As the brain continues to develop during the neonatal period, seizures in newborns tend to present with distinct causes and clinical manifestations [6]. In this study, we reviewed a cohort of 97 newborns diagnosed with seizures during their NICU stay. Consistent with the literature, our findings highlight the variety of clinical presentations and etiologies associated with neonatal seizures, underscoring the complexity of their diagnosis and management.

Clinical Manifestations and EEG Findings

Tonic seizures were the most common type, affecting 39.1% of the patients, followed by myoclonic seizures in 32.9%. The presence of multiple seizure types in over 30% of the cases highlights the clinical variability of neonatal seizures [7]. No instances of generalized tonic-clonic seizures were reported. This may be attributed to the incomplete development of arborization of axons and dendritic processes, coupled with the unmyelinated state of the neonatal brain, which causes a slower transmission of electrical activity and leads to fragmented seizures [8].

It is also notable that 35% of the patients had normal EEGs, indicating the challenges in diagnosing seizures based purely on clinical and electrographic data. This finding emphasizes the need for continuous EEG (cEEG) monitoring which is the best method for diagnosing and managing neonatal seizures. It should be used to identify seizures in high-risk clinical situations, to help differentiate between seizure-like events, avoid missing subtle or electrographic seizures and to monitor the effectiveness of treatments [9]. However, despite its clear advantages, cEEG in hospitals incurs significant costs for equipment and trained staff, as its benefits depend on expert interpretation [10].

The treatment approach in our cohort was consistent with current guidelines, with phenobarbital used as the first-line anticonvulsant [11]. Levetiracetam is increasingly used as a second-line treatment for neonatal seizures. It works by modulating neurotransmitter release through binding to the synaptic vesicle protein 2A (SV2A), and is typically preferred over other agents because of its better safety profile, ease of dosing, and reduced risk of respiratory depression. Midazolam works by enhancing the effect of the neurotransmitter GABA at the GABA-A receptor, similar to phenobarbital but with a quicker onset of action. It is often used in refractory seizures. The addition of levetiracetam or midazolam to phenobarbital offers a multimodal approach to seizure management, targeting different neurotransmitter systems. This combination can be crucial for refractory seizures and reducing the risk of prolonged seizures while minimizing the dose of phenobarbital, potentially reducing its associated neurodevelopmental side effects [12-14]. All patients with electro-clinical correlation received treatment, and nearly all clinical seizures were treated even in the absence of EEG confirmation. This treatment approach, particularly in cases where EEG was not available, likely reflects concerns about potential ongoing subclinical seizure activity and the risks of untreated seizures on the developing brain [15,16].

Etiology and Outcomes

Identifying the underlying etiology of neonatal seizures is critical for guiding treatment and prognosis. In our study, HIE was the most common cause of seizures in full-term neonates (52.8%), consistent with existing literature highlighting the strong association between HIE and neonatal seizures. In preterm

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neonates, periventricular-intraventricular hemorrhage was the leading cause (43.2%). Other frequently observed causes included neonatal ischemic stroke (7.5% in full-term neonates), meningitis (6.8% in preterm and 7.5% in full-term neonates), and metabolic disturbances (4.5% in preterm and 1.9% in full-term neonates) [17,18].

Beyond acute neurological insults, genetic and structural abnormalities also played a role. Polymicrogyria, one of the most common cortical development malformations, was identified in two cases. Previous studies estimate that epilepsy occurs in up to 87% of patients with polymicrogyria, highlighting its clinical significance. Magnetic resonance imaging (MRI) is a crucial diagnostic tool for neonatal seizures, as it enables early detection of structural abnormalities, which can influence long-term neurological outcomes, including motor and cognitive development. The extent of polymicrogyria seen on MRI can aid in prognostication and early intervention planning, providing valuable information for parental counseling [19,20]. Additionally, genetic causes, though less frequent, were identified in three cases. This underscores the importance of comprehensive genetic testing, particularly in neonates without an apparent acute etiology. Early diagnosis of genetic syndromes can significantly impact clinical management, prognosis, and treatment decisions, reinforcing the role of genomic medicine in neonatal neurology [21].

Conclusion

Neonatal seizures are a complex and critical neurological issue with diverse etiologies ranging from acute brain insults to underlying genetic and structural abnormalities. The clinical variability in seizure types in neonates further complicate the diagnosis and management of these patients. The identification of hypoxic-ischemic encephalopathy as the leading cause of neonatal seizures reaffirms its prominent role in neonatal neurological care. Additionally, MRI has proven indispensable in detecting underlying brain malformations, which are essential for guiding long-term care and counseling. The treatment regimen primarily involved phenobarbital, supplemented with levetiracetam and midazolam in more resistant cases, reflecting current best practices. Further research should focus on improving diagnostic tools and exploring new therapeutic options to enhance outcomes for neonates with seizures, particularly those related to genetic or structural causes. Early identification of these underlying factors is crucial to improving long-term neurodevelopmental outcomes.

References

1. Yozawitz E (2023) Neonatal Seizures. N Engl J Med 388(18): 1692-1700.
2. Kim EH, Shin J, Lee BK (2022) Neonatal seizures: diagnostic updates based on new definition and classification. Clin Exp Pediatr 65(8): 387-397.
3. Spoto G, Saia MC, Amore G, Gitto E, Loddo G, et al. (2021) Neonatal Seizures: An Overview of Genetic Causes and Treatment Options. Brain Sci 11(10): 1295.
4. Stieren ES, Rottkamp CA, Brooks-Kayal AR (2024) Neonatal Seizures. Neoreviews 25(6): e338-e349.
5. Zuberi SM, Wirrell E, Yozawitz E, Wilmshurst JM, Specchio N, et al. (2022) ILAE classification and definition of epilepsy syndromes with onset in neonates and infants: Position statement by the ILAE Task Force on Nosology and Definitions. Epilepsia 63(6): 1349-1397.
6. Pisani F, Spagnoli C (2018) Acute symptomatic neonatal seizures in preterm neonates: etiologies and treatments. Semin Fetal Neonatal Med 23(3): 191-196.
7. Shellhaas RA, Wusthoff CJ, Tsuchida TN, Glass HC, Chu CJ, et al. (2017) Profile of neonatal epilepsies: Characteristics of a prospective US cohort. Neurology 89(9): 893-899.
8. Carrasco M, Stafstrom CE (2018) How Early Can a Seizure Happen? Pathophysiological Considerations of Extremely Premature Infant Brain Development. Dev Neurosci 40(5-6): 417-436.
9. Sandoval Karamian AG, Wusthoff CJ (2021) Current and Future Uses of Continuous EEG in the NICU. Front Pediatr 9: 768670.
10. Ryan MAJ, Malhotra A (2024) Electrographic monitoring for seizure detection in the neonatal unit: current status and future direction. Pediatr Res 96(4): 896-904.
11. Pressler RM, Abend NS, Auvin S, Boylan G, Brigo F, et al. (2023) Treatment of seizures in the neonate: Guidelines and consensus-based recommendations-Special report from the ILAE Task Force on Neonatal Seizures. Epilepsia 64(10): 2550-2570.
12. Sharpe C, Reiner GE, Davis SL, Nespeca M, Gold JJ, et al. (2020) Levetiracetam Versus Phenobarbital for Neonatal Seizures: A Randomized Controlled Trial. Pediatrics 145(6): e20193182.
13. Rao LM, Hussain SA, Zaki T, Cho A, Chanlaw T, et al. (2018) A comparison of levetiracetam and phenobarbital for the treatment of neonatal seizures associated with hypoxic-ischemic encephalopathy. Epilepsy Behav 88: 212-217.
14. Van den Broek MP, Van Straaten HL, Huitema AD, Egberts T, Toet MC, et al. (2015) Anticonvulsant effectiveness and hemodynamic safety of midazolam in full-term infants treated with hypothermia. Neonatology 107(2): 150-156.
15. Holmes GL (2016) Effect of Seizures on the Developing Brain and Cognition. Semin Pediatr Neurol 23(2): 120-126.
16. Lin K, Stafstrom CE (2022) Cognition, Behavior, and Psychosocial Effects of Seizures in the Developing Brain. Curr Top Behav Neurosci 55: 3-15.
17. Emily S. Stieren, Catherine A Rottkamp, Amy R Brooks-Kayal (2025) Neonatal Seizures. Neoreviews 25 (6): e338-e349.
18. Zhou KQ, McDouall A, Drury PP, Lear CA, Cho KHT, et al. (2021) Treating Seizures after Hypoxic-Ischemic Encephalopathy-Current Controversies and Future Directions. Int J Mol Sci 22(13): 7121.
19. Catherine Shain, Sriram Ramgopal, Zianka Fallil, Isha Parulkar, Richard Alongi, et al. (2013) Polymicrogyria-associated epilepsy: a multicenter phenotypic study from the Epilepsy Phenome/Genome Project. Epilepsia. 54(8): 1368-1375.
20. Sintia Kolbjer, Daniel A Martín Muñoz, Anne K Örtqvist, Maria Pettersson, Anna Hammarsjö, et al. (2023) Polymicrogyria: epidemiology, imaging, and clinical aspects in a population-based cohort. Brain Commun 5(4): fcad213.
21. Kaur S, Pappas K (2020) Genetic Etiologies of Neonatal Seizures. Neoreviews 21(10): e663-e672.

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