Case Report

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Intractable Pyridoxine-Dependent Seizures (PDS) In A Neonate: A Rare Case Report.

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Abstract

Pyridoxine-dependent seizures (PDS) are a rare but treatable cause of neonatal seizures. PDS is characterized by intractable seizures in the neonatal period that respond dramatically to pyridoxine (vitamin B6) administration, making early recognition and intervention of paramount importance. This case report describes a 9-day-old male neonate referred to the neonatal intensive care unit (NICU) due to recurrent seizures beginning shortly after birth. Despite a full-term birth and an unremarkable prenatal history, the neonate exhibited abnormal quivering movements associated with shrill cry and altered sensorium. Initial investigations yielded normal results, and neuroimaging showed no structural abnormalities. Continuous electroencephalography (EEG) revealed a burst suppression pattern consistent with severe encephalopathy. Conventional antiepileptic drugs (AEDs) failed to control the seizures, prompting consideration of a broader differential diagnosis. Given the characteristic burst suppression EEG pattern and lack of response to AEDs, pyridoxine-dependent seizures (PDS) were suspected and confirmed upon a trial of intravenous pyridoxine. Genetic testing subsequently revealed compound heterozygous mutations in the ALDH7A1 gene, confirming the diagnosis of antiquitin deficiency, highlighting the genetic basis of this condition and its impact on pyridoxal phosphate metabolism.

Keywords: - Pyridoxine-Dependent Seizures, Antiquinin Deficiency, EEG, Burst Suppression.

INTRODUCTION

Pyridoxine-dependent seizures (PDS) are a rare but treatable cause of neonatal seizures. First described by Hunt et al. in 1954, PDS is characterized by intractable seizures in the neonatal period that respond dramatically to pyridoxine (vitamin B6) administration, making early recognition and interventio n of paramount importance.[1] Seizures in the neonatal period pose a diagnostic and therapeutic challenge, as they can be attributable to

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various aetiologies, ranging from benign to life-threatening. PDS is a rare underlying cause, accounting for less than 1% of neonatal seizures. The condition results from a deficiency of the enzyme α-aminoadipic semialdehyde dehydrogenase (antiquitin), which is encoded by the ALDH7A1 gene. This deficiency leads to the accumulation of α-aminoadipic semialdehyde (α-AASA), which acts as a neurotoxin, causing seizures. Clinical presentation of PDS is heterogeneous, with seizures typically occurring within the first few days to weeks of life. These seizures may manifest as subtle, focal, or generalized, making them difficult to differentiate from other neonatal seizure aetiologies. Some neonates with PDS may present with seizures refractory to conventional antiepileptic drugs (AEDs), further complicating the diagnostic process. Consequently, PDS is frequently underdiagnosed or misdiagnosed as other forms of neonatal seizures, delaying effective treatment. [2]

The diagnostic evaluation of neonates with suspected PDS necessitates a systematic approach. Initial investigations often include comprehensive metabolic and sepsis workups, as well as neuroimaging to rule out structural abnormalities. Routine electroencephalography (EEG) can demonstrate characteristic features such as burst suppression patterns, but it may not definitively establish the diagnosis of PDS. This diagnostic uncertainty underscores the importance of considering PDS when neonates present with early-onset seizures, especially if they fail to respond to conventional AEDs.[3]

The gold standard for diagnosing PDS is the response to a trial of intravenous or intramuscular pyridoxine. The dramatic cessation of seizures within minutes to hours of pyridoxine administration is a hallmark of PDS and can be life-saving. However, it is crucial to emphasize that the clinical response to pyridoxine may vary among patients, with some requiring continuous pyridoxine supplementation to prevent recurrent seizures.

Genetic testing to identify mutations in the ALDH7A1 gene can provide definitive confirmation of the diagnosis and guide long-term management. Early diagnosis is essential, as delayed initiation of pyridoxine therapy can result in developmental delays, intellectual disability, and even refractory epilepsy in affected individuals.[4]

his case report of 9-day old neonate found to have pyridoxine dependent seizures aims to shed light on the clinical presentation, diagnostic challenges, and therapeutic strategies employed in managing a neonate with PDS.

CASE REPORT

A 9-day-old male neonate was referred to our neonatal intensive care unit (NICU) with a history of recurrent seizures beginning shortly after birth. The neonate was born full-term via an uneventful vaginal delivery and had an unremarkable prenatal history. His family history did not reveal any known neurological disorders or seizure disorders. However, shortly after birth, the parents noticed abnormal movements characterized by sudden jerking motions of the arms and legs accompanied by altered sensorium.

Upon admission to the NICU, the neonate's physical examination was unremarkable, and vital signs were within normal limits. Initial investigations, including a complete blood count, electrolyte panel, and sepsis workup, yielded normal results. A lumbar puncture ruled out central nervous system infections. Neuroimaging, including cranial ultrasound and magnetic resonance imaging (MRI), did not reveal any structural abnormalities or intracranial lesions (Figure 1).

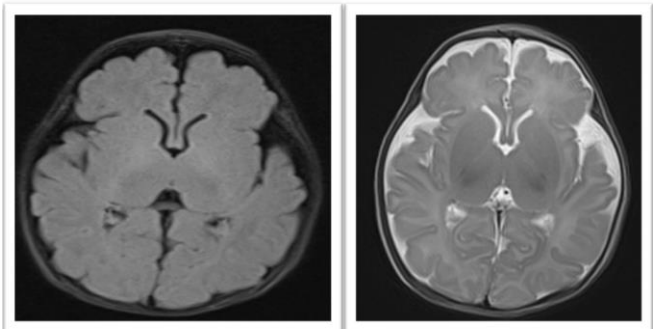

Figure 1: T1 W(Left) and T2W MRI images showed no significant abnormality.

Continuous electroencephalography (EEG) revealed a burst suppression pattern consistent with severe encephalopathy. Conventional antiepileptic drugs (AEDs), including phenobarbital and levetiracetam, were administered at maximum therapeutic doses, but the neonate's seizures remained refractory (Figure 2).

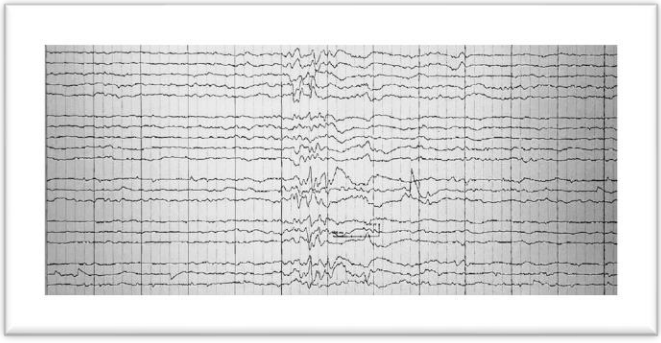

Figure 2: - Burst Suppression Pattern seen on EEG.

Due to the persistent and intractable nature of the neonate's seizures, a broader differential diagnosis was

considered. Given the lack of response to AEDs and the characteristic burst suppression EEG pattern, pyridoxine-dependent seizures (PDS) were suspected. A trial of intravenous pyridoxine was initiated at a dose of 100 mg.

Remarkably, within minutes of pyridoxine administration, the neonate's seizures ceased. Continuous EEG monitoring revealed a transition from burst suppression to normal background activity. The dramatic clinical and electrographic response to pyridoxine strongly supported the diagnosis of PDS.

Subsequently, genetic testing was conducted to confirm the diagnosis, which revealed compound heterozygous mutations in the ALDH7A1 gene, confirming the diagnosis of antiquitin deficiency. This finding underscored the genetic basis of the condition, resulting in impaired pyridoxal phosphate metabolism.

DISCUSSION

Pyridoxine-dependent seizures (PDS) represent a rare yet treatable cause of neonatal seizures, characterized by seizures that are refractory to conventional antiepileptic drugs (AEDs) but respond dramatically to pyridoxine (vitamin B6) administration. However, neonatal seizures often present diagnostic challenges due to their diverse aetiologies and non-specific clinical manifestations. Distinguishing PDS from other seizure disorders, such as hypoxic-ischemic encephalopathy or metabolic disorders, can be particularly challenging in the absence of pathognomonic clinical features.[5]

The diagnosis is usually made on the basis of refractory seizures not responding to usual doses of anticonvulsants. Continuous EEG monitoring is indispensable in the evaluation of neonatal seizures. The characteristic burst suppression pattern observed in PDS, as demonstrated in this case, can serve as a a valuable diagnostic clue. However, it is essential to

acknowledge that this pattern is not exclusive to PDS and may also be present in other severe encephalopathic conditions. Thus, EEG findings should be interpreted in conjunction with clinical and laboratory data.[6]

The hallmark of PDS diagnosis is the rapid cessation of seizures following intravenous pyridoxine administration. As observed in our case, this therapeutic trial is both diagnostic and potentially life-saving. The prompt administration of pyridoxine, ideally as soon as PDS is suspected, can prevent further neuronal injury and reduce the risk of long-term neurodevelopmental deficits. Definitive confirmation of PDS is achieved through genetic testing, which identifies mutations in the ALDH7A1 gene, responsible for encoding antiquitin. Genetic testing is crucial, as it not only confirms the diagnosis but also helps predict the risk of PDS recurrence in future pregnancies. Furthermore, it has implications for genetic counselling for affected families.[7]

The cornerstone of PDS management is lifelong pyridoxine supplementation. Although the neonate in this case demonstrated a dramatic response to intravenous pyridoxine, continuous oral pyridoxine therapy is essential to maintain adequate vitamin B6 levels and prevent recurrent seizures. Monitoring pyridoxine levels and adjusting the dosage as needed is crucial to ensure therapeutic efficacy.[8]

Beyond its diagnostic and therapeutic aspects, PDS raises important clinical and ethical considerations. While the identification of PDS through genetic testing allows for precise diagnosis and management, it also necessitates comprehensive genetic counselling for affected families. It is essential to educate parents about the autosomal recessive inheritance pattern of PDS, the potential risk of recurrence in future pregnancies, and the availability of prenatal testing options. PDS is just one of several metabolic and genetic disorders that can present with neonatal seizures. Pyridoxamine 5'-phosphate oxidase (PNPO) deficiency and folinic acid-responsive seizures share clinical features with PDS and should be considered in the differential diagnosis. Accurate differentiation among these conditions is crucial, as each may require distinct therapeutic approaches. [9]

The neonatal intensive care unit (NICU) serves as the primary setting for managing neonatal seizures, where complex evaluations are conducted to determine the underlying cause. PDS emphasizes the significance of a systematic approach to neonatal seizures, with heightened awareness of rare yet treatable conditions.

Timely recognition and diagnosis within the NICU are critical to optimizing outcomes for affected neonates.[10]

CONCLUSION

In conclusion, pyridoxine-dependent seizures in neonates represent a rare but treatable cause of early-onset seizures. The clinical heterogeneity and lack of specific diagnostic markers often lead to delayed or missed diagnosis. This case report highlights the importance of considering PDS in the differential diagnosis of neonatal seizures, especially when conventional AEDs prove ineffective. Early recognition, prompt initiation of pyridoxine therapy, and genetic confirmation are critical to ensuring optimal outcomes for affected neonates and preventing long-term neurodevelopmental sequelae. Healthcare providers must remain vigilant in their approach to neonatal seizures, recognizing the potential for PDS, and advancing our understanding of this complex clinical entity.

Conflict of interest

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