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Case Report

# A Novel Co-Occurrence between Cerebral Sinovenous Thrombosis and Non-ketotic Hyperglycinemia in a Neonate-a Case Report

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## ABSTRACT

***Background:*** Cerebral venous sinus thrombosis (CSVT) is a relatively rare condition characterized by seizures, cerebral edema, lethargy, and encephalopathy. In neonates, lethargy often indicates central nervous system (CNS) dysfunction, necessitating a comprehensive evaluation for various potential diagnoses including cerebrovascular accidents, infections, and metabolic disorders. Non-ketotic hyperglycinemia (NKH) is an autosomal recessive disorder, also known as glycine encephalopathy, resulting from a deficiency in the enzyme responsible for glycine catabolism. This leads to elevated levels of glycine in the blood, urine, and cerebrospinal fluid (CSF), accompanied by severe seizures, hypotension, hiccups, apnea, and progressive lethargy, which may progress to encephalopathy or even death.

***Case Report:*** This report presents the case of a 3-day-old neonate admitted to the hospital with opioid toxicity, displaying reduced metabolic activity. Despite initial suspicion of ketotic hyperglycemia, further investigation revealed the presence of cerebral sinus thrombosis in addition to NKH.

***Conclusion:*** This case underscores the complexity of neonatal presentations and highlights the importance of considering multiple differential diagnoses, especially when faced with unusual or overlapping clinical features. Early recognition and appropriate management of CSVT and NKH are crucial in improving outcomes for affected neonates.

***Keywords:*** B-MRI, Case report, Cerebral venous sinus thrombosis, Neonates, Non-ketotic hyperglycinemia, Seizure

## Introduction

The neonatal symptoms of lethargy and seizures in infants are exigent conditions that demand immediate recognition and identification. It is therefore imperative to discern the potential differential diagnoses of these disorders to prompt early diagnosis and treatment. In the differential diagnosis of a lethargic neonate, infectious etiologies, metabolic aberrations, and cerebrovascular events should be contemplated (1). Non-ketotic hyperglycinemia (NKH) and cerebral venous sinus thrombosis (CVST) are two rare infantile disorders that may present with lethargy or seizures. NKH is an infrequent autosomal recessive disorder of glycine metabolism, and although it is a well-established condition, it can result in life-threatening complications in neonates. Neonates with NKH frequently experience escalating lethargy, severe seizures (primarily myoclonic), hypotension, hiccups, and apnea in the early weeks of life (2). CVST is an uncommon condition characterized by elevated intracranial pressure caused by

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inadequate cerebral venous drainage, which can have life-threatening ramifications (3). In this manuscript, we present the second case report of an infant with the concurrent affliction of NKH and CVST disorders. This manuscript was prepared following the CARE guidelines (https://www.care-statement.org).

## Case report

A 3-day-old male infant was admitted to the emergency department of Akbar Hospital, Mashhad, Iran, with lethargy, paleness, reduced consciousness, and feeding difficulties. He was delivered by cesarean section with a gestational age of 38 weeks, and the weight at the time of birth and hospitalization were 2400 and 2300, respectively. On physical examination, the infant had a heart rate of 130 beats per minute, a respirator orates of 31 beats per minute, and standard peripheral perfusion and palpitations. He was hospitalized immediately, and after 8 hours, the infant's condition deteriorated; bradycardia was 70, bradypnea was 8, and consciousness was reduced to less response to painful stimuli; thus, in order to prevent impending respiratory arrest, the infant was immediately connected to mechanical ventilation. He was the second child in the family and the first child was a 7-year-old girl with hypotonia with an unknown definitive diagnosis.

In consideration of the patient's clinical status, a comprehensive sepsis workup was undertaken. Naloxone was initiated based on the family history of opium toxicity; however, no discernible improvement was observed. Therefore, a diagnostic assessment was performed to elucidate the underlying etiology of the neonatal encephalopathy. The patient was prescribed Acyclovir at a dosage of 20 mg/kg every eight hours. Upon laboratory investigation, the serum levels of blood urea, creatinine, aspartate transaminase, alanine transaminase, glucose, and electrolytes were all found to be within the normal physiological range. The analysis of CSF elucidated normal protein and glucose levels, with no discernible cellular infiltration. Furthermore, the plasma concentration of ammonium and lactate were normal. The skull ultrasound imaging displayed no apparent pathological findings. In view of the neonate's hiccup-like movements during hospitalization, a CSF glycine analysis was conducted, revealing a marked elevation in glycine levels to 1805 µmol.

The treatment regimen was augmented to include Sodium benzoate 250 mg every 8 hours, along with daily administration of 10 mg B1 tablets, 10 mg B6 tablets, 1 cc intravenous B12, 5 mg Biotin tablets, and 1 cc L-carnitine every 8 hours. Throughout the therapeutic course, the neonate demonstrated a noteworthy improvement in clinical status. Specifically, the normalization of breathing patterns was observed, leading to the discontinuation of endotracheal intubation. This is a significant milestone in the management of neonatal encephalopathy, as respiratory support is often required in the initial phase of treatment. Moreover, the neonate's reflexes and breast-sucking ability gradually returned to normal, indicating a restoration of neurological function.

To evaluate the neuromuscular electrical activity in the neonate, electromyography and nerve conduction velocity (EMG-NCV) studies were performed. The findings were consistent with chronic sensorimotor distal polyneuropathy with axonal characteristics, implying an underlying neuropathic process. Subsequently, electroencephalography (EEG) was conducted, which depicted wave patterns suggestive of a high likelihood of seizure activity. A brain magnetic resonance imaging (MRI) was carried out, revealing elevated T1 and reduced T2 signals in the middle and lower portions of the superior sagittal sinus (SSS), extending to the right transverse sinus, indicative of sinus thrombosis. Furthermore, the imaging displayed agenesis of the Corpus Callosum (ACC), manifesting as lateral ventricles with a parallel view, bat wings, colpocephaly, and the absence of the Corpus Callosum. In addition, augmented T1 signal intensities were observed on both sides of the periventricular white matter, suggesting hemorrhage or a TORCH infection.

The imaging study revealed a decrease in periventricular deep white matter intensity, which although it may be physiologically normal in infants, it may also signify the presence of myelination disorders. Additionally, soft tissue edema was observed in the frontoparietal cortex. The imaging findings further demonstrated cerebellar restriction and bilateral central tegmental tract involvement, which supported the diagnosis of NKH. Therefore, the neonate was initiated on dextromethorphan at a dose of 0.15 mg/kg/day. A brain MRI showed extensive venous sinus thrombosis (VST) and periventricular calcification, as evidenced by hyper-intensity at T1 and hypo-intensity at T2. In order to confirm the presence of calcification, a brain CT scan was performed that revealed a slight expansion of the extra-axial space. Although pachygyria was

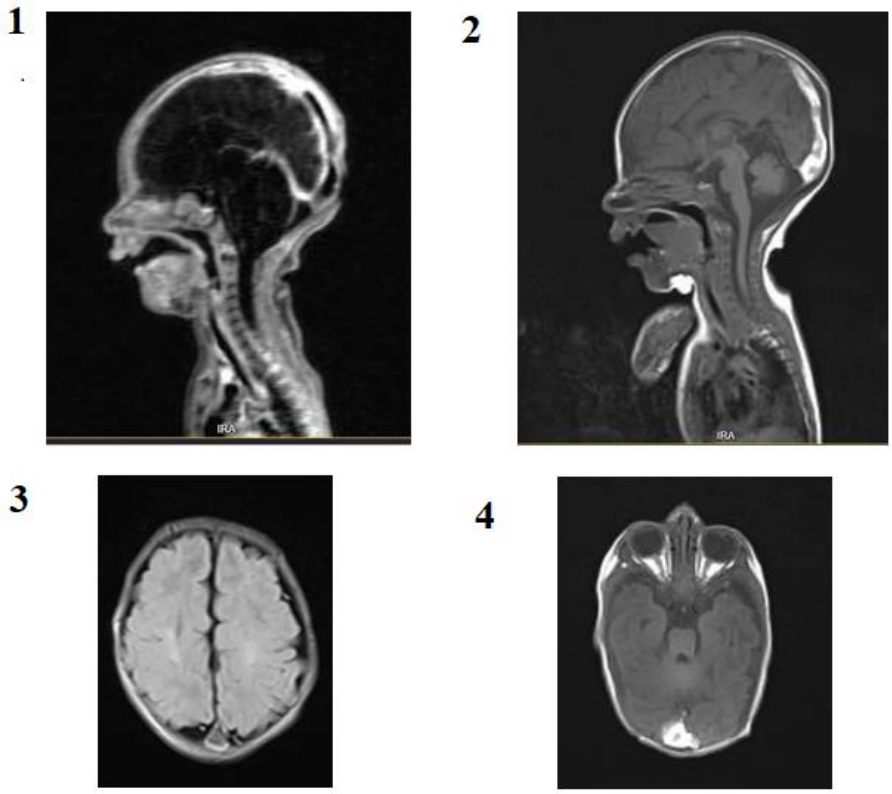


**Figure 1.** The inferior section of the superior sagittal sinus shows a longitudinal low signal filling deficiency due to thrombosis in the sagittal brain MRV image. Brain MRV sequences + Gd (1), T1W sequence in transverse and sagittal view (2), T2W sequence in transverse view (3), and T1W sequence in transverse and sagittal view (4) are employed.

observed, there was no indication of either parenchymal or periventricular calcification. Furthermore, neither microcephaly nor the absence of the Corpus Callosum was detected. Additionally, no significant midline shift was observed. The imaging findings were consistent with CSVT associated with the venous sinuses (Figure 1). To manage the CSVT, the neonate was initiated on low molecular weight heparin (LMWH; enoxaparin 1 mg/kg subcutaneously twice a day). Although the neonate's clinical condition improved over the following days, follow-up brain MRI with and without contrast and brain magnetic resonance venography (B-MRV) revealed persistent thrombosis. However, signs of recanalization were observed compared to previous imaging studies. Additionally, T1 signal amplification foci were noted in the periventricular white matter on both sides of the brain, indicating white matter injury of prematurity (WMIP) or subcortical heterotopias. MRV demonstrated thrombosis in the lower part of the sagittal sinus and at the beginning of the right transverse sinus (Figure 1).

Further investigations of serum amino acid levels and CSF glycine levels demonstrated increased glycine levels (serum: 1805 μmol/L, CSF: 227 μmol/L). The CSF/serum glycine ratio of 0.125 (greater than 0.08 diagnostic value) confirmed the diagnosis of NKH. Ultimately, the neonate's encephalopathy resolved, and he was discharged while continuing enoxaparin for two to four weeks.

### *Ethical Approval*

This case report does not contain any personal or identifiable information, and patient consent was obtained in accordance with institutional requirements. As per local regulations, ethics approval was not required.

## Discussion

This investigation details a case of a 3-day-old neonate presenting with seizures and lethargy, ultimately diagnosed with non-ketotic hyperglycinemia (NKH) and cerebral sinus venous thrombosis (CSVT) (2, 4). In light of the heterogeneity of clinical presentations of neonatal lethargy, a comprehensive differential diagnosis approach encompassing a broad range of potential

conditions, including but not limited to hyperbilirubinemia, infections, metabolic disorders, and CNS dysfunction-related diseases, is imperative. The evaluation of neonatal lethargy and encephalopathy warrants a thorough assessment of possible causes, including cerebrovascular accidents, metabolic derangements, infections, maternal pharmacological exposure, and intoxication. A meticulous family medical history inquiry can yield valuable clues to the underlying pathophysiology. In our case, the patient's family history included a previous instance of suspected cerebral palsy in a child exhibiting hypotension from birth, but who never manifested with recurrent, refractory seizures despite the absence of a formal diagnosis. The concurrence of CSVT and NKH implies that these are distinct etiologies that can correlate with encephalopathic features. The neonate displayed typical neonatal reflexes and exhibited an overall robust health status. The patient was maintained on enoxaparin and recommended to undergo a follow-up brain MRI examination in two weeks. This study represents, to the best of our knowledge, the second documented case of NKH with CSVT.

Cerebral sinovenous thrombosis (CSVT) is an uncommon but severe cerebrovascular condition mainly affecting infants and children, with a frequency of around 0.6 per 1,000,000 per year(5-7). The age of the patients with CSVT plays a critical role in the disease's etiology, symptoms, and long-term outcome. The most prevalent underlying causes of children's CSVT are acute infections of the head and neck, such as mastoiditis, followed by chronic disorders, such as nephrotic syndrome, malignancy, and inflammatory bowel disease. Also, neonatal diseases such as anemia, cyanosis, heart disorders, bacterial sepsis, and dehydration are risk factors for CSVT(6, 8). Maternal risk factors described for CSVT include pre-eclampsia and gestational diabetes, which were not present in our patient. In infants, the most prevalent signs of CSVT are seizures and impaired mental state; however, in children and adolescents, the most prevalent symptoms are headache, vomiting, and lethargy, occasionally accompanied by sixth nerve palsy(7). In our patient, respiratory problems, hypotension, and lethargy were prominent findings. The long-term outcome of CSVT in children varies depending on not only the age of the incident illness but also the existence of concomitant disorders and the occurrence of acute complications. Approximately 50% of these neonates and is associated with parenchymal lesions. The treatment of CSVT in infants is still controversial (9). Anticoagulant therapy limits clot formation and possibly the development or enlargement of parenchymal lesions. Several studies have shown the benefits of treatment with LMWH. Neonatal CSVT usually involves the sagittal and transverse sinuses; in 50-70% of cases, multiple sinuses can be involved. Venous congestion is usually followed by a bleeding infarction. In our infant, thrombosis was detected in the lower part of the sagittal sinus and the beginning of the right transverse sinus. Despite having a thrombus in the sagittal sinus, our patient had no signs of a bleeding infarction.

NKH develops more often in elderly individuals with mild diabetes or as the first clinical sign of diabetes. Nevertheless, Neonatal NKH often presents in the first few days of birth as malnutrition, significant lethargy and hypotension, encephalopathy, and severe seizures (10). According to previous studies on NKH, 19% of individuals with NKH develop focal seizures, which are primarily simple motor seizures (11). The occipital lobe is the most often reported site; however, the frontal and parietal lobes have also been observed. NKH detection needs plasma and CSF amino acid analyses, which is defined by a glycine to CSF to plasma glycine ratio greater than 0.08. In addition to the lack of ketoacidosis, excluding other organic acidemias is required to diagnose NKH. Our patient lacked acidosis, and his urine organic acids analysis was normal. An elevated glycine level verified our patient's diagnosis in the blood and plasma glycine ratio of 0.125. A definitive diagnosis of NKH is based on mutations and enzymatic analysis. Many studies have shown that approximately 80% of patients with NKH are deficient in the activity of glycine decarboxylase, one of the four enzymes in the glycine breakdown system (12). Regrettably, in the present case, the NKH diagnosis could not be confirmed using enzyme measurements and associated mutation analysis due to technical difficulties and poor economic conditions. Similar to CSVT, the treatment of NKH remains a subject of debate, and no conclusive treatment has been established for NKH. The current management strategies for NKH are primarily aimed at reducing the levels of glycine and inhibiting N-methyl-D-aspartate receptors (NMDAs). Sodium benzoate and dextromethorphan have been utilized for this purpose(10).

White matter parenchymal volume abnormalities and agenesis or corpus callosum

hypoplasia are among the many anatomical abnormalities of the brain linked with NKH (10, 13). Our patient had further anatomical anomalies, including agenesis of the corpus callosum. NKH often causes abnormal brain MRI results. Long-term proton magnetic resonance spectroscopy revealed that glycine levels in the brain were consistently associated with clinical outcomes. Imaging studies may assist in monitoring patients' progress when they are treated with sodium benzoate or dextromethorphan for NKH(9).

In conclusion, a comprehensive differential diagnosis that encompasses a spectrum of plausible etiologies, including toxicities, metabolic aberrations, septicemia, cerebrovascular accidents, and, notably, a meticulous inquiry of the patient's family medical history is requisite when assessing neonatal lethargy. A comprehensive and meticulous scrutiny of the patient's family medical history can significantly expedite the identification of CSVT and NKH, facilitating timely and appropriate intervention and management. Thus, integrating family history inquiry into the differential diagnosis approach can serve as an invaluable tool in the early identification and management of CSVT and NKH, potentially enhancing the outcomes of affected neonates.

## Conclusion

In this case report, we present a rare co-occurrence of cerebral sinovenous thrombosis (CSVT) and non-ketotic hyperglycinemia (NKH) in a neonate. This case highlights the complexity of neonatal encephalopathy and emphasizes the importance of a thorough differential diagnosis when confronted with symptoms such as seizures and lethargy. Early recognition of these conditions, followed by prompt intervention, can significantly improve clinical outcomes. The multidisciplinary approach adopted in this case, including metabolic, imaging, and family history investigations, was key in reaching a timely diagnosis and facilitating effective treatment.

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None.

## Conflicts of interest

The authors declare that they have no conflicts of interest regarding the publication of this case report.

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