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Shahnaz Ibrahim
Aga Khan University

KEEPING A HIGH INDEX OF SUSPICION OF NONKETOTIC HYPERGLYCINEMIA IN NEONATAL ENCEPHALOPATHY

Shahnaz Ibrahim
Department of Pediatrics and Child Health, Aga Khan University, Karachi ,Pakistan

Correspondence to: Department of Pediatrics and Child Health, Aga Khan University, P.O Box 3500, Karachi, 74800, Pakistan. Fax: 92-21-34932095, Email:shahnaz.ibrahim@aku.edu

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ABSTRACT

Inborn error of metabolism may present with a diverse spectrum of presentations varying from episodes of hypoglycemia, lethargy to full blown sepsis. Rarely may they present with subtle or obvious neurological manifestations ranging from seizure activity to encephalopathy.

We report two cases of nonketotic hyperglycinemia in infants who were born with an uneventful antenatal, perinatal course and developed lethargy, apnea and seizures. Both infants had history of one sibling death in the early neonatal period. Biochemical markers were normal. Neuroimaging was normal in both cases while one infant had pathological EEG suggestive of hypsarrythmia and infantile spasm.

Urine for organic acidemias was negative, while glycine levels in the plasma and CSF of both infants were high, with very high ratios conclusive of nonketotic hyperglycinemia
Both the infants are alive at two and a half years of age, on antiepileptic medications along with sodium benzoate for elevated levels of glycine. Both the children have significant global developmental delay with microcephaly

INTRODUCTION

Nonketotic hyperglycinemia (NKH), is a devastating metabolic disorder characterized by abnormally high levels of the glycine in the central nervous system. Glycine is an amino acid which also acts as a neurotransmitter. NKH, also known as glycine encephalopathy is caused by the shortage of an enzyme that normally breaks down glycine in the body. A lack of this enzyme allows excess glycine to build up in tissues and organs, particularly the brain, leading to neurological impairment.[1]

It is transmitted as an autosomal recessive disorder caused by defective activity of the glycine cleavage system . Mutations in the AMT and GLDC genes are associated with NKH. About 80% of cases of NKH result from mutations in the GLDC gene, while AMT mutations cause 10-15% of all cases. In a small percentage of affected individuals, the cause of this condition is unknown.[2,3]

Most patients with NKH have the neonatal phenotype, presenting in the first few days of life usually following an uneventful pregnancy and delivery with lethargy, hypotonia, and myoclonic jerks. Most affected newborns will have repeated episodes of severe and prolonged apnea, to which they succumb unless ventilator support is provided until normal spontaneous respiration resumes after several days or weeks. Those who regain spontaneous respiration develop intractable seizures.[1,2] The diagnosis of NKH is made by documenting raised glycine concentrations in CSF and in plasma, with an abnormally high ratio between CSF and plasma levels.[4]

Making a diagnosis of NKH beyond reasonable doubt requires awareness of this potentially lethal metabolic disorder. NKH is distinguished from other organic acid disorders by the absence of ketosis and this can only be confirmed by urine organic acid analysis. Confirma-

-tory tests include CSF and Plasma amino acid analysis looking for elevated levels of glycine and getting the CSF: serum glycine values, along with enzymatic analysis in liver tissue and / or mutation analysis.[5]

We report two cases presenting in the early neonatal life with seizures and encephalopathy.

CASE REPORT

Case 1: The first case was of a baby girl who was born term, with no antenatal or post natal complications. She had good APGAR scores and her birth weight was 3.5 kg. She remained stable for 24 hours and then developed lethargy and decreased movements.

Family history was significant for a sibling dying in the neonatal period with lethargy and presumed sepsis.

On examination she had normal vitals and her peripheral perfusion was good
Central nervous system examination showed that she was lethargic with poor suck and incomplete Moro. Fundus exam was normal. She was hypotonic and her reflexes were brisk. Rest of the systemic examination was normal.

She was started on intravenous fluids. Blood cultures and lumbar puncture were done, which were unremarkable. Initial investigations of complete blood counts, serum electrolytes, serum calcium, arterial ammonia and lactate were normal. Urine was negative for ketones. On the 3rd day she started having shallow breathing, therefore, she was electively intubated and ventilated. During intubation she had one episode of posturing for which she was given diazepam. Her EEG and MRI were done which were reported normal. On 7th day of life she again had multiple episodes of lip smacking, eye twitching and unrolling of eye balls therefore she was loaded with phenobarbitone. She was initially kept NPO and gradually gavages feeds were started .She was extubated on day 10th day of life. Her critical samples of blood and urine for organic acids were sent along with CSF for amino acids.

Keeping in mind the possibility of NKH, sodium benzoate and dextromethraphan were started after which she improved marginally and started showing some body movements. Table 1 shows the serum and CSF amino acid values in this child. CSF: serum glycine levels were also elevated at 0.13. This confirmed the diagnosis of NKH.

She has survived up to two and a half years of age. She is microcephalic, and is significantly delayed in achieving her milestones. She can sit with support and rolls over. She is seizure free for the last two years and her phenobarbitone is being weaned off.

Case 2: Term AGA male baby with a birth weight of 2.8 kg was born to a gravida 2 para 0 mother by elective caesarian section due to previous scar. His APGARS at birth were 8/1 and 9/5. He remained well for 2 days then developed lethargy and poor suck and was found to be mildly hypotonic. His septic workup was sent, antibiotics were started and he was shifted to the neonatal intensive care area.

Mother's antenatal and postnatal course had been normal. The marriage was consanguineous and one older sibling had died at 5 days of age with apnea.

On examination, he had a birth weight of 3.5 kg and normal length and FOC. His perfusion was good but he was extremely hypotonic and lethargic. His anterior fontanelle was open and flat. Suck was poor. Moro was absent and deep tendon reflexes were decreased. Pupils were normal and face was symmetrical. His abdominal, respiratory and cardiovascular examinations were normal.

Initial investigations included a complete blood count, blood culture and lumbar puncture. These were normal. Electrolytes, serum calcium and sugar were also normal. There was no metabolic acidosis seen. Urine for ketones was negative. On 3rd day of life, the baby developed shallow respiration and episodes of apnea and he was then electively intubated and ventilated. He also developed seizures in the intensive care. He was then started on phenobarbitone and phenytoin and his seizures were controlled. A head MRI was done, which showed slight thinning of the corpus collosum suggesting hypoplasia of the corpus callosum (Figure 1). Since all the investigations were negative for infection and sepsis a suspicion of metabolic disorder was raised. A serum ammonia and serum lactate (arterial sample) was sent. Ammonia levels were borderline elevated and after saving critical samples for investigation for a metabolic disorder or a urea cycle disorder, sodium benzoate was started. His carnitine and acylcarntine levels, urine for organic acids and plasma for amino acids were sent for analysis. His plasma showed a significantly raised glycine and nonspecific elevation of taurine glutamic and aspartate.

He remained on the ventilator for another week and was then successfully extubated. He remained lethargic and hypotonic. He was readmitted with the same issues a couple of times and at the 3rd month of life restarted with seizures which were typically myoclonic in nature. His EEG was done which showed the classic hypsarrythmic pattern suggestive of infantile spasm. Suspecting NKH, serum and CSF amino acid levels were sent. CSF: serum glycine ratios were elevated at 0.2 strongly suggesting NKH (Table1).

Following this he was also started on dextromethorphan at high doses of 35 mg/kg and sodium benzoate was continued.

He was initially treated with Vigabatrin for 6 weeks for infantile spasms, and later switched to Injection ACTH for 6 weeks as there was no improvement. His seizures decreased in frequency and severity, but they did not completely abate. A repeat EEG done after ACTH showed improvement in background activity but the multiple independent multifocal spikes and wave pattern remained. He was then tried on multiple medications including topiramate, clobazam, valproate. Although, the seizures improved, they were never completely controlled.

His sodium benzoate and dextromethorphan were continued. He is now three years old and his development remains very poor with hardly any movement and no eye contact. He is extremely hypotonic with poor reflexes and continues to be gavage fed through a gastrostomy tube.

DISCUSSION

Classical NKH presents within hours or days of birth with lethargy, poor feeding, hypotonia, and hiccups. Neonates presenting with severe hypotonia and lethargy without an underlying etiology being identified should be suspected of having NKH.1,2 Hypotonia and lethargy were the main symptoms upon presentation in both our patients and although, sepsis was the initial diagnosis in both, the initial blood work was negative which raised the suspicion of NKH.

Neonatal seizures are a common presentation in the neonatal intensive care area, but if all investigations relating to sepsis are negative one should suspect NKH as seizures are strongly associated with NKH. The first baby had seizures; these were well controlled on phenobarbitone. The second baby went on to have the classic infantile spasms which were intractable. This is NKH is distinguished from a heterogeneous group of organic acid disorders by the absence of ketosis; although, this can only be confirmed by urine organic acid analysis. Both children had no ketosis or acidosis on initial presentation. Although, the second baby had borderline elevated ammonia, starting benzoate was actually beneficial to him as this also helps decrease the glycine level. Plasma and CSF amino acid profile in both patients were significant in showing raised glycine and the ratios of CSF: serum glycine was abnormal in both confirming the diagnosis.4 A transiently raised CSF glycine level may also be found in hypoxic–ischaemic encephalopathy maternal medication, and congenital infections.7,8 None of these confounding factors were seen in our patient.

MRI changes have been reported in literature. One of our children had partial agenesis of corpus collusom. This has been very well documented in literature along with gyral malformations.9 A recent paper from Turkey reported the use of MRS as a noninvasive method to detect high glycine levels in the brain thus helping in the early diagnosis and response to treatment.10 MRspectroscopy is a very new technology that has been incorporated in teaching centers across Pakistan. This would provide a rapid diagnosis needed as the counseling and prognosis for future needs to be done urgently. In a country where metabolic disorders abound and where metabolic testing is limited this would be an important tool for the early detection of NKH.

Glycine breath test recently reported from Japan is an alternative method to reach a diagnosis in NKH. It is a rapid, non-invasive test and would also be useful as a standard test for diagnosing NKH.11

Dextromethorphan a NMDA receptor antagnosist has been shown in some case reports to be beneficial by helping with seizures.12,13,14 We administered dextromethorphan in both our children. Although, the first baby remained seizure free, the second did not respond despite high doses. This may be because of the fact that the diagnosis was confirmed after 3 months of life when he developed infantile spasms and the CSF and serum amino acids were resent abroad for analysis. Death is imminent and has been reported to occur in the first year of life. Both children are surviving up to almost two and a half years of age.

CONCLUSION

In summary, NKH is an uncommon metabolic disorder but in our population where there is high consanguinity

Table 1. Demonstrating serum and CSF glycine levels in both patients

	CSF glycine (3.7-7.6umol/l)	Serum glycine (157-467umol/l)	CSF: serum glycine
Patient 1	187	1404	0.13
Patient 2	135	659	0.2

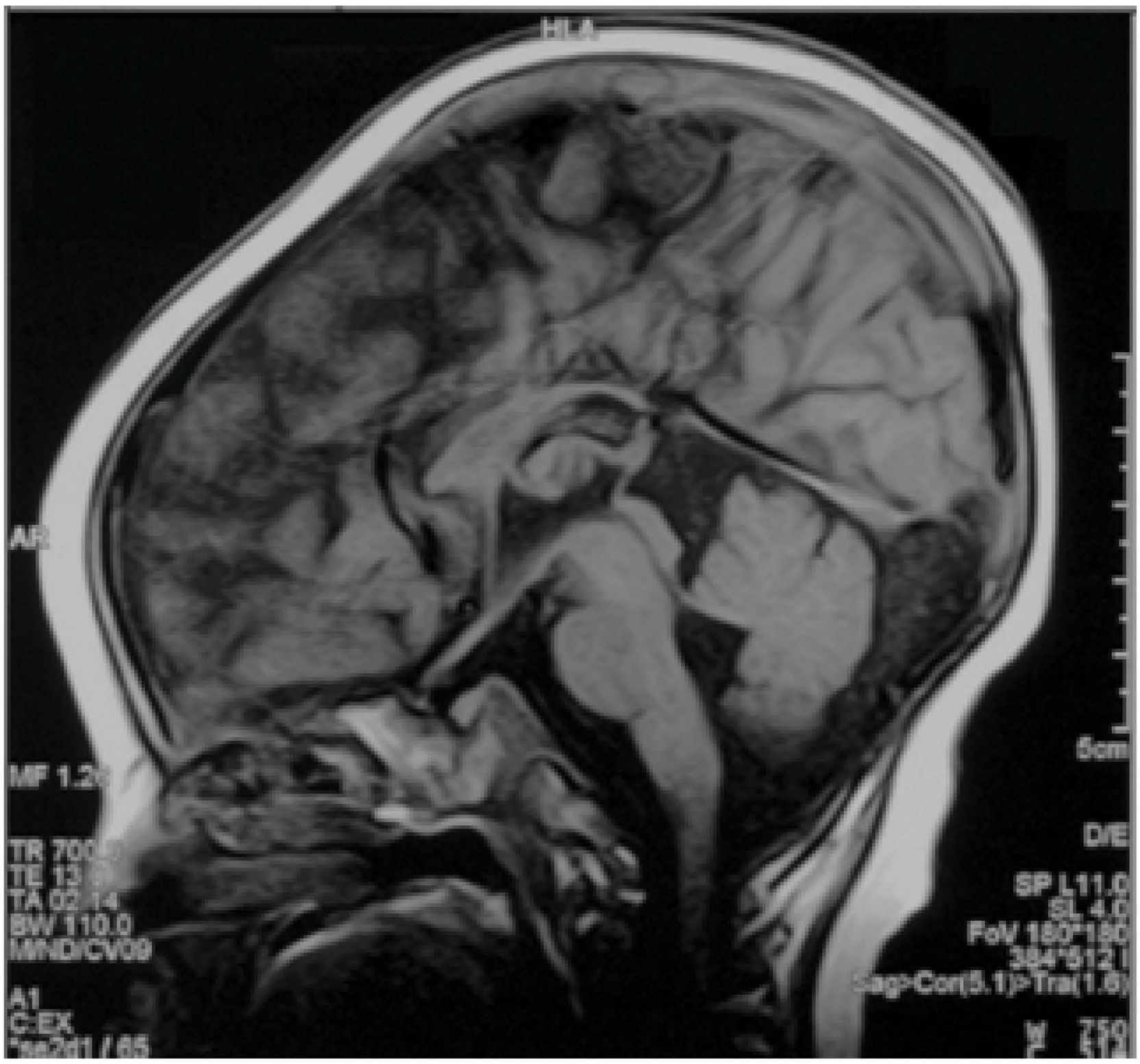

Figure 1. MRI showed slight thinning of the corpus callosum.

rate it should be suspected in hypotonic and encephalopathic infants. In light of the devastating nature of the disease, it is important to make the diagnosis early in so that appropriate counseling regarding prognosis can be given to the parents.

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