Case report

Nonketotic hyperglycinemia: A case report and brief review

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ABSTRACT

In encephalopathic infants, cerebrospinal fluid hyperglycinemia and elevated cerebrospinal fluid to plasma glycine ratio are considered pathognomonic of nonketotic hyperglycinemia (NKH). We present a case of NKH complicated by neonatal intractable seizures. Increased ratio of cerebrospinal fluid to plasma glycine concentrations of 0.28 was seen as a strong diagnostic indicator of nonketotic hyperglycinemia. Evaluating sick neonates with hypotonia, encephalopathy, and/or seizures is a diagnostic challenge. NKH should be considered; elevated cerebrospinal fluid/plasma glycine ratio will allow correct identification and treatment more often in the future.

1. Introduction

Glycine encephalopathy, also known as nonketotic hyperglycinemia (NKH), is an inborn error of glycine metabolism caused by deficiency in the glycine cleavage system (GCS) [1] and characterized by large quantities of glycine accumulated in all body tissues, especially in serum and cerebrospinal fluids. Most glycine encephalopathy cases occur during the neonatal period. The neonatal form manifests in the first hours to days of life with progressive lethargy, hypotonia, myoclonic jerks, hiccups, and apnea, which often lead to coma or death [2]. Outcome is usually poor, with mortality up to 50% during the first week of life [3]. Surviving infants have profound intellectual disability and intractable seizures. Atypical forms include milder disease, with onset from late infancy to adulthood, which presents various neurological symptoms: seizure, motor and/or cognitive impairments, aggressive behavior, and impaired work or school performance [2]. A rare transient form has been described in which newborns have elevated cerebrospinal fluid and plasma glycine, which is biochemically and clinically indistinguishable from the classic form. In the rare form, glycine levels normalize over time without pharmacologic intervention and often have few or no neurologic sequelae[4]. We present a case of NKH neonatal intractable seizures. Evaluating a sick neonate who presents with hypotonia, encephalopathy, and seizures is a diagnostic challenge; a high index of suspicion for timely diagnosis and treatment could prevent severe complications.

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2.   Case report

A two month-old girl was transferred to our hospital for evaluation and management of seizure. She was a full-term baby, her parents not consanguineous, pregnancy uneventful, and labor and vaginal delivery uncomplicated. Apgar scores at birth were 9 at 1 minute and 10 at 5 minutes birth body weight 3116 g (50th–75th percentile), birth height 52 cm (75th–90th percentile), head circumference 33.5 cm (50th–75th percentile). Physical and neurologic examinations were normal except for mild hypertonic muscle tone. Sudden onset of general convulsions accompanied by increased heart rate and oxygen desaturation appeared 3 hours after birth. Symptoms lasted about 3 to 4 minutes. One day after birth, general convulsions were noted every hour. Seizure frequency increased even under antiepileptic drug (AED) treatment. Laboratory examination showed that blood cell count, electrolyte, glucose, ammonia, and lactate were all within the normal range. Brain echography showed negative findings. Urine organic acid examination and blood liquid chromatography-mass spectrometry were unremarkable. The infant was transferred to the ward due to poor seizure control. After admission to our intensive care unit, she showed frequently paroxysmal general tonic postures, associated with oxygen desaturation and increased heart rate. Seizure was aggravated by touching. Phenytoin and phenobarbital were given, but in vain. Sleep EEG revealed paroxysmal sharp waves over both central areas. Video on long-term EEG monitor proved seizure associated with epileptic form discharges, particularly in the frontal region. Ictal recording showed general tonic seizure with tachycardia, associated with epileptic form spikes. Brain magnetic resonance imaging (MRI) showed no remarkable findings. Frequency and intensity of seizures did not improve after pyridoxine challenge and prescription of multiple AEDs. Under the impression of suspect NKH due to intractable seizures, cerebrospinal fluid examination was performed. Amino acid analyses (MRM mode) of glycine were as follows: CSF = 51.9μM; plasma = 183.0μM; and CSF/plasma ratio = 0.28 (Fig. 1). Diagnosis of NKH was strongly suspected. Regimen of frequent feedings, together with AEDs, including phenobarbital and clonazepam, sodium benzoate and dextromethorphan were prescribed. Episodes of seizures and apnea decreased, and the patient was followed-up at the outpatient clinic. Unfortunately, the patient expired at home when she was 5-month-old due to sudden onset of cardiac arrest and apnea.

3.   Discussion

In neonatal seizures, issues to consider include hypoxia-ischemia insult, hemorrhage or intracranial infarction, trauma, infection, cerebral malformations, neurocutaneous syndromes, drugs or toxic agents, and metabolic and idiopathic disorders. In our case, the birth course was smooth. Brain imaging study revealed no abnormal brain malformation or hemorrhage, yet refractory epilepsy was noted, which led us to survey for possible inborn errors. In many metabolic disorders, epilepsy may even dominate the clinical picture, especially in newborns and infants. One must always consider the possibility
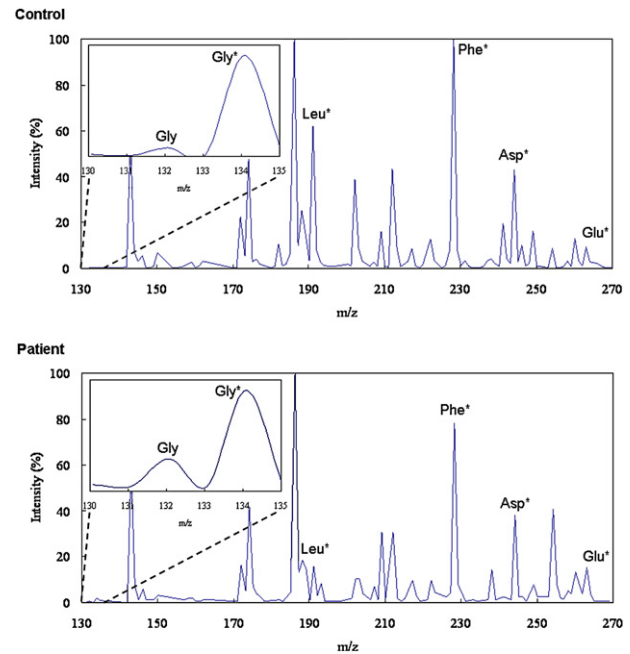

Fig. 1 – Amino acid profile of cerebrospinal fluid.

of inborn metabolic errors in neonates with unexplained and refractory epilepsy [1,2]. This patient's metabolic study showed unremarkable urine organic acid examination and blood liquid chromatography-mass spectrometry. Blood tests including electrolytes, glucose, ammonia, and lactate were within the normal range. Pyridoxine treatment was eventually ineffective, suggesting that pyridoxine-dependent epilepsy was unlikely. Therefore, further study of NKH was enrolled.

NKH is an autosomal recessive metabolic disorder characterized by glycine accumulating in the brain due to defective GCS. Incidence of glycine encephalopathy in British Columbia is 1:63,000 live births and 1:55,000 newborns in Finland [5]. Classically, NKH is associated with normal pregnancy and birth, then neonatal apnea, lethargy, hypotonia, and seizures occur, followed by severe psychomotor retardation in those who survive. While the present case manifested mild hypertonia, it may arise from severe encephalopathy. In the laboratory, NKH is characterized by elevated glycine concentrations in plasma, CSF, and brain with a CSF glycine to plasma glycine ratio greater than 0.08, which is diagnostic. A ratio of >0.04 is suggestive but require further confirmation through enzymatic analysis of liver or mutation detection. In our case, glycine CSF/plasma ratio is 0.28. Elevated cerebrospinal fluid glycine is reported in infants with encephalopathy: e.g., hypoxic ischemic encephalopathy, congenital stroke, central nervous system infection[3]. No perinatal insult or infection appeared in this case.

Glycine is an inhibiting neurotransmitter in the spinal cord and excitation modulator of N-methyl D-aspartate (NMDA) receptors in the telecephalon and cerebellum [6]. The GCS consists of four distinct (P, T, H, L) proteins. Over 80% of NKH patients show defects in the P-protein, as high as 15% human T-protein defect, with H-protein deficiencies being rare [7–9]. NKH can manifest one of four forms: classic neonatal, transient, infantile, and late; differences lie in time of onset, severity of

clinical presentation, and outcome [10,11]. The typical neonatal form presents in the first few days after birth with progressive lethargy, hypotonia, hiccups, and seizures, progresses to central apnea, and often death. Surviving infants often have profound developmental delay and intractable seizures. The infantile form occurs in the first few months of life and is also characterized by hypotonia, developmental delay, and seizures. Increased CSF glycine level (typically 20–30 times normal) along with elevated CSF/plasma glycine ratio, suggests diagnosis. Gold standard for diagnosis is still liver biopsy, but this is not feasible in many cases. A noninvasive [13] C-glycine breath test and screening system for genomic deletion with GLDC also help confirm diagnosis [12,13]. Genes known to associate with NKH are GLDC (encoding P-protein component of the GCS complex), AMT (encoding T-protein component), and GCSH (encoding H-protein component) [12]. Molecular genetic testing of all three genes is available on a clinical basis. Mutations associated with residual enzyme activity seem associated with a milder outcome and infantile presentation; two mutations with no residual enzyme activity seem linked with severe outcome and neonatal onset [14,15]. Initial EEG typically shows a burst-suppression pattern that evolves into hypsarrhythmia or multifocal spikes over the next few months.

MRI can show normal, agenesis of the corpus callosum, delay in myelination, vacuolation, gliosis, or, less frequently, retro-cerebellar cysts with subsequent hydrocephalus [16–18]. Prior reports revealed that hydrocephalus appears to predict poor outcome [2,17]. A glycine peak on magnetic resonance spectroscopy (MRS) result is seen in the most severely affected infants, carrying poor prognosis. MRS techniques may play a key role in assessing adverse outcome in NKH. Identification of NAA/Ins-Gly as an indicator of severity could be ultimately applied to monitor and predict evolution of NKH and fine-tune existing and future treatments [18].

To date, no effective treatment exists for NKH. The standard treatment strategies for NKH include sodium benzoate (to reduce plasma concentration of glycine) and NMDA receptor antagonists (ketamine, dextromethorphan, felbamate, and topiramate) [19]. Both sodium benzoate and dextromethorphan may improve alertness and decrease seizure frequency if prescribed during the newborn period [2]. Others focus on seizure control with AEDs. Among AEDs, valproate should be avoided in glycine encephalopathy, since it raises blood and CSF glycine concentrations by further inhibiting the GCS and may increase seizure frequency [20]. Higher glycine concentration would result in severe lethargy, seizures, chorea (especially in mildly affected patients), and coma p [21]. Other managements including gastrostomy tubation are used for feeding problems and physical therapy can prevent several complications. Surveillance developmental assessment is vital throughout the first years of life; molecular genetic and/or biochemical tests of at-risk symptomatic siblings are recommended to promote early diagnosis and treatment.

Acknowledgments

REFERENCES

[1] Tada K, Narisawa K, Yoshida T, Konno T, Yokoyama Y. Hyperglycinemia: a defect in glycine cleavage reaction. Tohoku J Exp Med 1969;98:289–96.

[2] Hoover-Fong JE, Shah S, Van Hove JL, Applegarth D, Toone J, Hamosh A. Natural history of nonketotic hyperglycinemia in 65 patients. Neurology 2004;63:847–53.

[3] Volpe J. Neurology of the newborn. 5th ed. 2008. p. 659–67.

[4] Aliefendioğlu D, Tana Aslan A, Coşkun T, Dursun A, Cakmak FN, Kesimer M. Transient nonketotic hyperglycinemia: two case reports and literature review. Pediatr Neurol 2003;28:151–5.

[5] Applegarth DA, Toone JR, Lowry RB. Incidence of inborn errors of metabolism in British Columbia, 1969-1996. Pediatrics 2000;105:10.

[6] Ichinohe A, Kure S, Mikawa S, Ueki T, Kojima K, Fujiwara K, et al. Glycine cleavage system in neurogenic regions. Eur J Neurosci 2004;19:2365–70.

[7] Toone JR, Applegarth DA, Coulter-Mackie MB, James ER. Biochemical and molecular investigations of patients with nonketotic hyperglycinemia. Mol Genet Metab 2000;70:116–21.

[8] Applegarth DA, Toone JR. Nonketotic hyperglycinemia (glycine encephalopathy): laboratory diagnosis. Mol Genet Metab 2001;74:139–46.

[9] Tada K, Kure S. Non-ketotic hyperglycinaemia: molecular lesion, diagnosis and pathophysiology. J Inherit Metab Dis 1993;16:691–703.

[10] Dinopoulos A, Matsubara Y, Kure S. Atypical variants of nonketotic hyperglycinemia. Mol Genet Metab 2005;86:61–9.

[11] Demirel N, Bas AY, Zenciroglu A, Aydemir C, Kalkanoglu S, Coskun T. Neonatal non-ketotic hyperglycinemia: report of five cases. Pediatr Int 2008;50:121–3.

[12] Kure S, Kato K, Dinopoulos A, Gail C, DeGrauw TJ, Christodoulou J, et al. Comprehensive mutation analysis of GLDC, AMT, and GCSH in nonketotic hyperglycinemia. Hum Mutat 2006;27:343–52.

[13] Kure S, Korman SH, Kanno J, Narisawa A, Kubota M, Takayanagi T, et al. Rapid diagnosis of glycine encephalopathy by 13C-glycine breath test. Ann Neurol 2006;59:862–7.

[14] Suzuki Y, Kure S, Oota M, Hino H, Fukuda M. Nonketotic hyperglycinemia: proposal of a diagnostic and treatment strategy. Pediatr Neurol 2010;43:221–4.

[15] Kikuchi G, Motokawa Y, Yoshida T, Hiraga K. Glycine cleavage system: reaction mechanism, physiological significance, and hyperglycinemia. Proc Jpn Acad Ser B Phys Biol Sci 2008;84:246–63.

[16] Mourmans J, Majoie CB, Barth PG, Duran M, Akkerman EM, Poll-The BT. Sequential MR imaging changes in nonketotic hyperglycinemia. AJNR Am J Neuroradiol 2006;27:208–11.

[17] Van Hove JL, Kishnani PS, Demaerel P, Kahler SG, Miller C, Jaeken J, et al. Acute hydrocephalus in nonketotic hyperglycemia. Neurology 2000;54:754–6.

[18] Viola A, Chabrol B, Nicoli F, Confort-Gouny S, Viout P, Cozzone PJ. Magnetic resonance spectroscopy study of glycine pathways in nonketotic hyperglycinemia. Pediatr Res 2002;52:292–300.

[19] Van Hove JL, Vande Kerckhove K, Hennermann JB, Mahieu V, Declercq P, Mertens S, et al. Benzoate treatment and the glycine index in nonketotic hyperglycinaemia. J Inherit Metab Dis 2005;28:651–63.

[20] Morrison PF, Sankar R, Shields WD. Valproate-induced chorea and encephalopathy in atypical nonketotic hyperglycinemia. Pediatr Neurol 2006;35:356–8.

[21] Hall DA, Ringel SP. Adult nonketotic hyperglycinemia (NKH) crisis presenting as severe chorea and encephalopathy. Mov Disord 2004;19:485–6.