J Radiol Sci 2011; 36: 177-181

Magnetic Resonance Findings in an Infant with Nonketotic Hyperglycinemia

Wei-Shiuan Chung[1] Mei-Chyn Chao[2,3] Fang-Ju Lin[1] Chun-Wei Li[4] Zi-Chii Tseng[1] Yi-Chien Tseng[1] Twei-Shiun Jaw[1,5]

Departments of Medical Imaging[1], Division of Genetics, Endocrinology and Metabolism[2], Department of Pediatrics, Kaohsiung Medical University Chung-Ho Memorial Hospital, Kaohsiung, Taiwan
Department of Medical Genetics[3], Departments of Radiology[5], School of Medicine, College of Medicine, Department of Medical Imaging and Radiological Sciences[4], College of Health Sciences, Kaohsiung Medical University, Kaohsiung, Taiwan

ABSTRACT

Nonketotic hyperglycinemia (NKH) is a rare disease caused by defects in the glycine metabolism, leading to accumulation of excessive glycine in the body, CSF, and brain. We report an infant with NKH who presented with poor sucking power, hypothermia, hyperreflexia, and hypotonia soon after delivery at the gestational age of 38 weeks, and progressed to respiratory failure, coma, and seizures. The diagnosis of NKH was established by laboratory data showing marked elevation of glycine levels in the plasma, cerebrospinal fluid (CSF), and increased CSF/plasma ratio of glycine levels. Genetic analysis demonstrated a missense mutation of GLDC gene (Exon 19) derived from her mother. Magnetic resonance (MR) imaging of the brain performed at the age of 70 days demonstrated thinning of the corpus callosum, symmetric distribution of restricted diffusion and abnormal signals on T2-weighted images in the white matters. A glycine peak at 3.55ppm was depicted on proton magnetic resonance spectroscopy (^{1}H-MRS) using time to echo of 144ms, supporting the clinical diagnosis of NKH. The combination of conventional, diffusion MR imaging, and ^{1}H-MRS, can be helpful in identification of white matter abnormalities in patients with NKH.

Nonketotic hyperglycinemia (NKH) is a rare autosomal recessive metabolic disorder caused by defects in the glycine cleavage system (GCS) in the body [1]. Defects in the GCS lead to accumulation of excessive glycine in the body, especially in the cerebrospinal fluid (CSF) system and brain [2]. Glycine is one of the important neurotransmitters [1]. In the most common classical neonatal type of NKH, lethargy, poor feeding, hypotonia, myoclonic jerks, and seizures may develop a few days after birth, and rapidly progress to apnea, respiratory insufficiency, coma and even death in early infancy [2]. Early diagnosis is crucial to guide clinical management though sometimes it is difficult due to non-specific presentations. Besides amino acid analysis, including glycine levels, in the plasma and CSF, the magnetic resonance imaging (MRI), including conventional sequences, diffusion weighted imaging (DWI), and the proton magnetic resonance spectroscopy (^{1}H-MRS), may help to diagnose NKH. We report a female infant with classical symptoms of NKH since her early neonatal period, presenting abnormally increased signal intensity on T2-weighted images, restricted diffusion in the white matter on MRI, and a glycine peak at 3.55ppm on ^{1}H-MRS.

Correspondence Author to: Twei-Shiun Jaw
Department of Medical Imaging, Kaohsiung Medical University Hospital, Kaohsiung, Taiwan
No. 100, Tz-You 1st Road, Kaohsiung 807, Taiwan

CASE REPORT

A full-term female baby was delivered spontaneously in a regional hospital without significant prenatal or perinatal abnormality except for weak crying. Her Apgar score was 8 and 9 at 1 and 5 minutes. Poor sucking power, general weakness, hypothermia, hyperreflexia, and hypotonia occurred soon after delivery and then progressed to apnea and coma. Endotracheal intubation was performed due to respiratory failure and pneumonia in the right lung. Her treatment continued at the regional hospital under the impression of floppy infant. Due to persistence of symptoms and signs, she was then transferred to the pediatric intensive care unit of our hospital at the age of 27 days. Some episodes of seizure occurred during this hospitalization.

A series of studies were arranged. Blood biochemistry, muscle biopsy and chromosome study were non-specific. The levels of serum creatine kinase, ammonia and lactate were within normal limit. No ketoacidosis or ketonuria was noted. Brain ultrasonography revealed thinning of the corpus callosum. Liquid chromatography-tandem mass spectrometry (LC- MS/MS) of the blood sample collected at the age of 35 days showed increase of plasma glycine (956 μmol/L) and several amino acids. Amino acid analysis of CSF and plasma using high-performance liquid chromatography (HPLC) at the age of 48 days revealed elevation

Figure 1

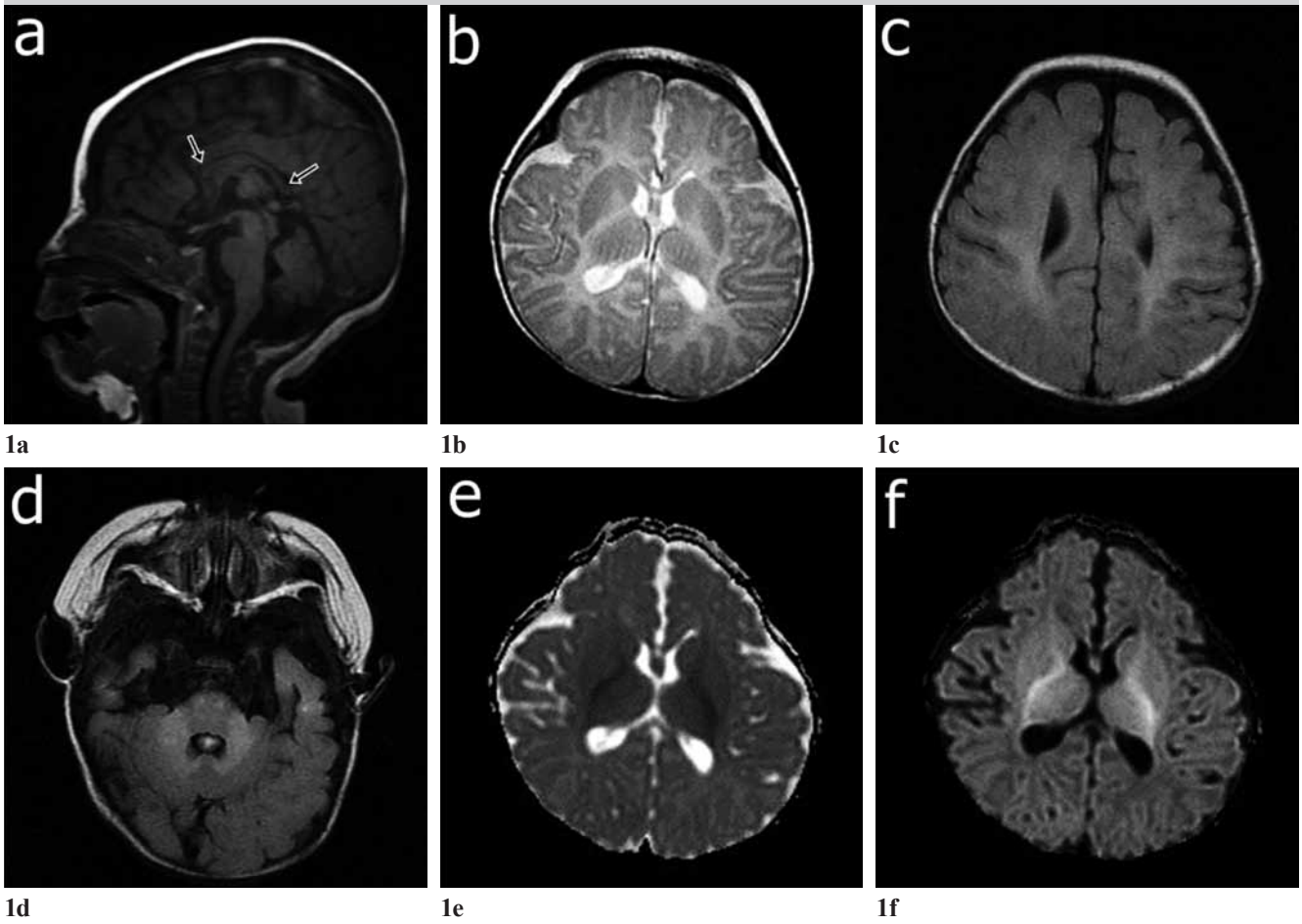

Figure 1. MRI of the brain at the age of 70 days: **a.** T1-weighted FLAIR (Fluid Attenuated Inversion Recovery) sagittal image (TR/TE/TI=2135.85/10.056/850 ms).; **b.** T2-weighted fast spin echo image (TR/TE = 8627/152 ms); **c.** and **d.** T2-weighted FLAIR axial image (TR/TE/TI = 8627/152/2100 ms); **e.** and **f.** ADC and EADC maps (TR/TE = 9650/94.6 ms). The T1-weighted sagittal image depicts thinning of the corpus callosum (arrows in a.). The T2-weighted images (b. to d.) show symmetric distribution of abnormal high signal intensity in the genua and posterior limbs of internal capsules, centra semiovales, cerebellar peduncles, and brain stem, suggestive of abnormal myelination. Restricted diffusions are demonstrated with decreased EADC and increased ADC values involving genua, anterior and posterior limbs of internal capsules (e, f).

of glycine, 94.3 μmol/L and 537.5 μmol/L respectively. (The normal glycine levels in newborn and infants are: 3-21 μmol/L in CSF and 153-318 μmol/L in plasma). The CSF/plasma ratio of glycine level elevated to 0.175 (normal < 0.02, classical NKH > 0.08). The results of amino acid analysis highly suggested the diagnosis of NKH. We extracted genomic DNA from peripheral lymphocytes of patient and parents, and screened mutations in the exon 1 to exon 25 of GLDC and exon 1 to exon 9 of AMT respectively. Genetic analysis demonstrated a missense mutation (c.2281G > A,p.Gly761Arg) of GLDC gene in the Exon 19 derived from her mother, supporting the diagnosis of NKH, despite no mutation in the AMT gene.

MRI of the brain was performed at the age of 70 days on a 3.0-Tesla scanner (Signa VH/I, GE Healthcare, Milwaukee, WI, USA) using a standard quadrature head coil. The conventional MRI revealed thinning of the corpus callosum (Fig. 1a). Abnormally increased signal intensities on T2-weighted images were noted symmetrically in the centra semiovales, coronae radiatae, genua, posterior limbs of the internal capsules, cerebellar peduncles, and pyramid tracts (Fig. 1b-1d). Symmetric distribution of restricted diffusion in the cerebellar peduncles, coronae radiatae, genua, anterior and posterior limbs of internal capsules was depicted on apparent diffusion coefficient (ADC) and exponential apparent diffusion coefficient (EADC) maps (Fig. 1e, 1f). A 2D MRS sequence with point-resolved (PRESS) volume pre-selection was used. Water suppression was accomplished using three preceding CHESS pulses. The field homogeneity was optimized automatically over the selected vision of interest (VOI) by observing the water signal. Spectra were acquired with repetition time (TR) 1500 ms, echo time (TE) 144 ms, Matrix size of 16 × 16 over a field of view (FOV) of 24 cm resulting a scan time of 6.4 min. A representative spectrum was obtained at the right centrum semiovale with a prominent peak at 3.55ppm detected, which is assigned to glycine (Fig. 2). The MR findings, especially the glycine peak at 3.55 ppm, supported the clinical diagnosis of NKH.

DISCUSSION

Nonketotic hyperglycinemia (NKH) is a rare autosomal recessive disorder of glycine metabolism caused by defects in the GCS, resulting in high glycine concentrations in the urine, plasma, and especially CSF and the brain [1]. Patients are classified into three clinical subtypes (neonatal, infantile, and late-onset) based on the onset of clinical symptoms [3]. Neonatal type of NKH is the most common. Patients usually manifest feeding difficulty, lethargy, hypotonia, hyperreflexia, apnea, and intractable seizures in the

Figure 2

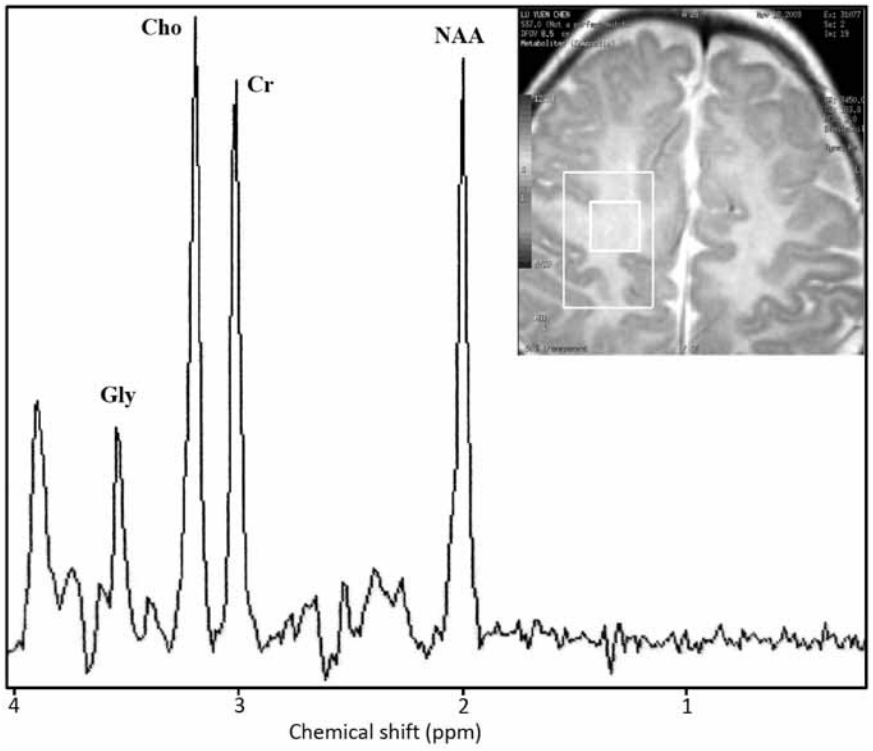

Figure 2. ^{1}H-MRS (TR/TE = 1500/144 ms) obtained at right centrum semiovale at the age of 70 days shows an abnormal glycine (Gly) peak at 3.55 ppm. Cho indicates choline; Cr, creatine; NAA, N-acetyl groups.

first few days of life [2]. Most patients die within a few weeks if left untreated [2]. In the infantile and late-onset form, most patients remain asymptomatic throughout the neonatal period, with subsequent neurogenic symptoms, mental, and developmental retardation [3]. According to the onset of clinical presentations, our case was classified as the neonatal type.

Highly elevated glycine in the CSF, plasma, elevated CSF/plasma glycine ratio, and absence of ketoacidosis are the clues to the diagnosis [4], as those found in our case. The GCS is one of the mitochondrial enzyme complexes, which is composed of four proteins encoded on four different chromosomes. Genetic defects in the GCS can be encoded by GLDC, AMT or GCSH [3, 4]. The gene analysis in this case demonstrated a missense mutation in GLDC gene derived from her mother.

Widespread spongiosis of myelinated white matter is the main histopathological feature of classical NKH of neonates, involving tracts undergoing active myelination during the neonatal period [2]. The ascending and descending tracts in the brain stem, posterior limbs of the internal capsules, the cerebellar peduncles, optic tracts, and optic chiasm are the mostly affected [2, 5-7]. The peripheral white matter in the centra semiovales, coronae radiatae, and corticospinal tracts are myelinated later in life and show no or mild spongiotic changes in previous studies. Electromicroscopic findings of NKH show intramyelinic microvacuoles formation and splitting of myelin lamellae. Other vacuolating myelinopathies include Canavan disease, maple syrup urine disease, proprionic acidemia, van der Knaap leukoencephalopathy, Creutzfeldt-Jakob disease, some mitochondrial diseases, and intoxications [7, 8].

Press et al. reported seven patients with NKH using conventional MR imaging which showed thinning of the corpus callosum, age-related findings of progressive atrophy and delayed myelination with pathological correlation [9]. Recent studies revealed evidence of restricted diffusion in the affected areas [7, 8]. The possible causes of restricted diffusion may be intramyelinic vacuole formation, or accumulation of fluid between the layers of splitting myelin lamellae [7,8,10]. DWI and conventional MRI can also show progression of disease with time [7]. MR findings of our case are similar to previous studies. The T2-weighted and diffusion-weighted findings may suggest vacuolating myelinopathy.

The distribution of abnormal signals on conventional and diffusion weighted imaging in our patient symmetrically involved periventricular and deep white matter, cerebellar peduncles and pyramid tracts, while the deep gray matter and subcortical white matter were spared. With this distribution, disorders of myelination should be considered. In this age group, some metabolic diseases may share similar pattern of early MR imaging findings. Metachromatic leukodystrophy occurs in older infants, children or adult, and it may appear more extensive white matter disease. Krabbe disease, clinically showing extremely irritability, involves periventricular, deep, and cerebellar white matter with a ring-like appearance around dentate nuclei. Typically, maple syrup urine disease shows edema with restricted diffusion in the cerebellar and brain stem more predominantly than in the supratentorial white matter. Urea cycle disorders may sometimes present similar pattern to that of NKH, mainly involves deep gray nuclei, deep cerebral sulci and subcortical white matter, with sparing of posterior fossa. Although the imaging pattern sometimes may not be specific in these diseases, patient presentations, clinical testing, and laboratory analysis can provide more clues for diagnosis.

Heindel et al. found a large glycine peak at 3.55 ppm on the ^{1}H-MRS of two infants with NKH [12]. At short TEs, the signals of myo-inositol (3.56 ppm) overlap with those of glycine. Due to quick dephasing of the strongly-coupled protons of myo-inositol [13], using longer TE can reduce the signal of myo-inositol, making the glycine peak prominent. ^{1}H-MRS has the potential to be used as a noninvasive tool for monitoring the cerebral glycine level in patients with NKH, and as a tool in differential diagnosis of NKH from other metabolic disorders with hyperglycinemia [14]. If ^{1}H-MRS can be performed earlier in our case, it could suggest earlier use of amino acid analysis to diagnose the disease. The glycine peak can also be found in some brain tumors, including gliomas and central neurocytomas [15], which can be differentiated from NKH according to clinical history and imaging characteristics.

In summary, our case showed classical clinical presentations, typical MR findings in the white matter, and a glycine peak at 3.55ppm on ^{1}H-MRS, supporting diagnosis of NKH. Combination of MRI, DWI, and ^{1}H-MRS can help early identification of the abnormalities of the white mater, and provide a non-invasive method for monitoring clinical management in newborn infants with NKH.

REFERENCES

1. Kure S, Tada K, Narisawa K. Nonketotic hyperglycinemia: biochemical, molecular, and neurological aspects. Jpn J Human Genet 1997; 42: 13-22
2. Langan TJ, Pueschel SM. Nonketotic hyperglycinemia: clinical, biochemical, and therapeutic considerations. Curr Probl Pediatr 1983; 13: 1-30
3. Kure S, Kato K, Dinopoulos A. et al. Comprehensive mutation analysis of GLDC, AMT, and GCSH in nonketotic hyperglycinemia. Hum Mutat 2006; 27: 343-352
4. Applegarth DA, Toone JR. Nonketotic Hyperglycinemia (Glycine Encephalopathy): Laboratory Diagnosis. Mol Genet Metab 2001; 74: 139-146

5. Brun A, Börjeson M, Hultberg B, Sjöblad S, Akesson H, Litwin E. Neonatal non-ketotic hyperglycinemia: a clinical, biochemical and neuropathological study including electronmicroscopic findings. Neuropadiatrie 1979; 10: 195-205
6. Agamanolis DP, Potter JL, Herrick MK, Sternberger NH. The neuropathology of glycine encephalopathy: a report of five cases with immunohistochemical and ultrastructural observations. Neurology 1982; 32: 975-985
7. Poll B.T. The Sequential MR imaging Changes in Nonketotic hyperglycinemia. AJNR Am J Neuroradiol 2006; 27: 208-211
8. Khong PL, Lam BC, Chung BH, Wong KY, Ooi GC. Diffusion-weighted MR imaging in neonatal nonketotic hyperglycinemia. AJNR Am J Neuroradiol 2003; 24: 1181-1183
9. Press GA, Barshop BA, Haas RH, Nyhan WL, Glass RF, Hesselink JR. Abnormalities of the brain in nonketotic hyperglycinemia: MR manifestations. AJNR Am J Neuroradiol 1989; 10: 315-321
10. Culjat M, Benjak V, Dasovic-Buljevic A et el. Magnetic resonance findings in a neonate with nonketotic hyperglycinemia: case report. J Comput Assist Tomogr 2010; 34: 762-765
11. Osborn AG, Salzman KL, Barkovich AJ et al. Inherited Metabolic/Degenertative Disorders. In: Osborn AG, Salzman KL, Barkovich AJ et el. Diagnostic imaging: brain. 2nd ed. Philadelphia: Amirsys/Lippincott Williams and Wilkins, 2010; I-9-2-83
12. Heindel W, Kugel H, Roth B. Noninvasive detection of increased glycine content by proton MR spectroscopy in the brains of two infants with nonketotic hyperglycinemia. AJNR Am J Neuroradiol 1993; 14: 629-663
13. Hattingen E, Lanfermann H, Quick J, Franz K, Zanella FE, Pilatus U. 1H MR spectroscopic imaging with short and long echo time to discriminate glycine in glial tumours. MAGMA 2009; 22: 33-41
14. Huisman TA, Thiel T, Steinmann B, Zeilinger G, Martin E. Proton magnetic resonance spectroscopy of the brain of a neonate with nonketotic hyperglycinemia: in vivo-in vitro (ex vivo) correlation. Eur Radiol 2002; 12: 858-861
15. Bobek-Billewicz B, Hebda A, Stasik-Pres G, Majchrzak K, Zmuda E, Trojanowska A. Measurement of glycine in a brain and brain tumors by means of 1H MRS. Folia Neuropathol 2010; 48: 190-199