CASE REPORT

Neonatal non-ketotic hyperglycinemia

Hyperglycémie non cétosique néonatale

M. Nicolasjilwan, H. Ozer, M. Wintermark, J. Matsumoto

Introduction

Non-ketotic hyperglycinemia (NKH) is an autosomal recessive inborn error of metabolism due to a defect in the glycine cleavage system. It is characterized by the accumulation of large amounts of glycine in plasma and CSF. The elevated glycine levels result in the devastating neurological manifestations of the disease including hypotonia, myoclonus, seizures, poor feeding, and respiratory depression.

Case report

The female patient was born at 41 weeks gestation by spontaneous vaginal delivery and transferred to our institution at 5 days of age for workup and management of poor feeding, hypotonia, as well as myoclonic and tonic seizures. The diagnosis of neonatal onset non-ketotic hyperglycinemia (NKH) was made based on a markedly elevated CSF/plasma glycine ratio of 0.25 (normal ratio is less than 0.08) with a CSF glycine of 127 μmol/l (normal range 1.6–19.5 μmol/l) and plasma glycine of 504 μmol/l (normal range 224–514 μmol/l). Urine glycine levels were also markedly elevated at 39,781 μmol/g creatinine (normal range 0–7047 μmol/g creatinine). The diagnosis was confirmed by mutation testing that demonstrated homozygous mutation of the GLDC gene encoding for the P-protein of the glycine cleavage system complex. EEG demonstrated a burst suppression pattern, multifocal sharp wave discharges, diffuse slowing, and lack of state changes during a prolonged 90 minutes tracing. The patient was placed on dextromethorphan and sodium benzoate for control of hyperglycinemia, phenobarbital and levetiracetam for seizure control, and nasogastric tube feeding. She was unable to maintain sustained coordinated feeding effort for adequate oral intake to support her growth, and a gastrostomy tube

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KEYWORDS

Non-ketotic hyperglycinemia (NKH); Vacuolating myelinopathy; White matter restricted diffusion

Summary  The typical imaging findings of neonatal non-ketotic hyperglycinemia have rarely been described in the radiologic literature with only few individual cases or small series reported. In this article, we present a case of neonatal onset non-ketotic hyperglycinemia, imaged at 6 days of age, and discuss characteristic MRI and MR spectroscopic findings.

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Figures 1, 2  Absent T1 hyperintense (Fig. 1) and T2 hypointense (Fig. 2) signal of myelin in the posterior limb of the internal capsule in a term newborn indicates either lack of myelination or abnormal white matter signal.

Figures 3–6  Abnormal diffusion signal in the bilateral corona radiata (Fig. 3), posterior limbs of the internal capsules (Fig. 4), and ventral brainstem (Fig. 5) along the corticospinal tracts. There is also bilateral restricted diffusion in the dorsal brainstem (Fig. 5) and cerebellar white matter (Fig. 6).
was placed at 29 days of age. The patient was discharged at age 37 days. She is currently 14 months old with poorly controlled daily seizures and developmental delay.

Brain MRI performed at 6 days of age showed lack of normal myelination of the posterior limbs of the internal capsules, with absent T1 hyperintense and T2 hypointense signal of myelin at this level (Figs. 1 and 2). Diffusion imaging showed symmetrical restricted diffusion along the bilateral corticospinal tracts in the corona radiata, posterior limbs of the internal capsules, and ventral brainstem. There was also bilateral symmetrical abnormal diffusion signal in the dorsal brainstem and cerebellar white matter (Figs. 3–6), with corresponding T2 hyperintensity in the dorsal brainstem (Fig. 7). Agenesis of the anterior portion of the corpus callosum was also present (Figs. 8 and 9).

Discussion

The characteristic imaging findings of NKH include increased T2 signal and restricted diffusion confined to the white mat-

Figure 7  Axial spin echo T2 shows corresponding T2 hyperintense signal in the dorsal brainstem.

Figures 3—6  (Continued).
Figures 8, 9  Sagittal T1 sequence demonstrates absence of the anterior corpus callosum (Fig. 8), which is corroborated on coronal T2 sequence that shows absence of interhemispheric commissural fibers in the location of the anterior corpus callosum (Fig. 9). Small amount of T1 hyperintense blood along the interhemispheric falx is related to recent birth trauma (Fig. 8).

Intermediate tracts that are normally expected to be myelinated at a given age. At birth, when most patients present, these comprise the corticospinal tracts, including the posterior limbs of the internal capsules, dorsal pons, and cerebellar white matter. The underlying pathology consists of vacuolating myelinopathy that involves formed myelin sheaths with subsequent injury to the regions of expected normal myelination. The restricted diffusion observed is postulated to be secondary to the accumulation of fluid between the layers of the myelin lamellae [1]. In a case report by J. Mourmans et al. [2] of serial diffusion weighted and diffusion tensor imaging findings in a patient with neonatal onset NKH, restricted diffusion was observed in the topographic pattern of normal myelination at age 3 months with a normal fractional anisotropy on diffusion tensor imaging, compatible with axonal sparing. At 17 months, restricted diffusion disappeared, likely indicating coalescence of the myelin vacuoles and fractional anisotropy had decreased, indicative of axonal loss.

The pattern of diffusion signal abnormality in neonatal onset NKH and the absence of the normal T1 hyperintensity in the posterior limbs of the internal capsules in a term newborn may be mistaken for severe hypoxic ischemic injury. However, in NKH, there is no involvement of highly metabolically active structures including the lateral thalami, posterior putamina, hippocampi, and sensorimotor cortex, as is commonly present in neonates with severe hypoxic ischemic encephalopathy. The lack of brain swelling and sparing of the basal ganglia are important differentiating features from urea cycle disorders, organic acidemias, and mitochondrial disorders.

Structural cerebral abnormalities reported to be associated with NKH include callosal dysgenesis, cerebral atrophy, ventriculomegaly, and posterior fossa cysts [3–5]. The development of hydrocephalus in patients with NKH has been in particular associated with the presence of large retrocerebellar cysts [5,6].

Magnetic resonance spectroscopy in neonatal NKH

Although not performed in our patient, MR spectroscopy offers a noninvasive measure of the metabolic disturbance and elevated glycine levels in the brain of patients with NKH. Glycine is not present on MR spectroscopy of normal brain parenchyma. In vivo and at short TE, glycine resonance at 3.50 ppm is obscured by myoinositol resonance at 3.56 ppm. Longer TE MRS (TE = 135 ms) is preferable to demonstrate the typical glycine peak [7]. The changes in glycine and glutamate levels measured by MRS parallel the changes in plasma glycine levels.

Conflict of interest statement

There is no conflict of interest to declare.

References

