

Abnormalities of the Brain in Nonketotic Hyperglycinemia: MR Manifestations

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MR imaging in seven patients (4 days to 38 months old) with nonketotic hyperglycinemia showed age-related findings of progressive atrophy and delayed myelination. Parenchymal volume loss was found as early as 4 days after birth and increased in severity with increasing age to 27 months. Both supratentorial and infratentorial volume loss were present in the most severely affected patients. The corpus callosum was abnormally thin in all patients. The state of myelination of the CNS was assessed on T2-weighted images. Decreased or absent myelination within supratentorial white-matter tracts was detected in all four patients 10 months of age or older. Myelination of the brainstem and cerebellum progressed normally. No correlation was found between the degree of volume loss or abnormality of myelination demonstrated by MR and the concentration of glycine in the CSF or plasma.

Abnormalities shown by MR correlate well with known pathologic findings in patients with nonketotic hyperglycinemia.

Nonketotic hyperglycinemia (NKH) is a heritable disorder of amino acid metabolism in which large quantities of glycine accumulate in plasma, urine, and CSF [1]. Onset of the disease occurs most often in early infancy. Clinical manifestations include seizures, abnormal muscle tone and reflexes, and pronounced developmental delay. Death usually ensues before the age of 5 years [2]. The metabolic defect is in the glycine cleavage enzyme system, a four-protein complex responsible for the interconversion of glycine and serine. The activity of this enzyme system is deficient in the liver and brain of affected patients [3]. Autopsy studies on the CNS of patients with NKH have revealed vacuolation and decreased volume of myelin, thought to be due to myelinolysis combined with inadequate synthesis of protein precursors [4–8].

Only a few reports of radiographic findings in NKH are available [8–11]. Ventricular dilatation and porencephaly were visualized by pneumoencephalography in one patient [9]. Cerebral and cerebellar volume loss, with associated hypodensity of the periventricular white matter and internal capsule, was demonstrated by CT in two patients [8, 10]. Agenesis of the corpus callosum was found on CT in one patient [11]. The MR findings in NKH have not been reported previously. We describe a constellation of age-related findings in the CNS of seven patients with NKH studied with MR and neurologic examination.

Subjects and Methods

The seven subjects (four girls and three boys) were 4 days to 27 months old at the time of entry into this study. Careful neurologic evaluation was carried out in all patients. The concentrations of glycine in plasma, urine, and CSF were measured with an automatic amino acid analyzer [12]. Values reported were obtained before treatment with sodium benzoate.

Each patient had at least one MR examination performed with a 1.5-T superconducting magnet.* With multislice, multiecho, spin-echo pulse sequences, T2-weighted images, 1500–3000/70–100/2 (TR/TE/excitations), and proton-density-weighted images, 1500–3000/20–

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30, were acquired in the axial plane in all subjects. T1-weighted images, 600/20–25/2, were then obtained in the sagittal plane in all subjects. In two patients, additional T1-weighted images were obtained in the axial and/or coronal planes. Slice thickness was 5 mm with a 2.5-mm gap between successive slices. A 256 × 256 matrix was used in all examinations. A repeat MR study including identical pulse sequences was performed after an interval of 10–11 months in two subjects.

All MR examinations were evaluated in blinded fashion by two neuroradiologists experienced in pediatric neurodiagnosis. Subjective cerebral volume loss (atrophy) was recorded when enlargement of the ventricles and/or sulci was detected and graded as mild, moderate, or severe. The location of atrophy and the presence of focal parenchymal lesions were recorded.

The corpus callosum was measured on midline sagittal T1-weighted images. The thicknesses of the genu, of the body at middistance from the genu to the splenium, and of the splenium of the corpus callosum were measured with a magnifying glass and reticule. Accuracy was judged to be within 0.25 mm. These measurements were compared with the average MR measurements of the corpus callosum during the first 12 months of normal development reported by Barkovich and Kjos [13].

The progress of CNS myelination was assessed in each MR examination in accordance with methods used by Barkovich et al. [14]. Myelinated white matter was recognized by its low signal intensity relative to gray matter in the basal ganglia or cerebral cortex on T2-weighted images. The state of myelination was evaluated separately in the dorsal pons and cerebellar peduncles, cerebellar hemisphere white matter, internal capsule, corona radiata, centrum semiovale, corpus callosum, and subcortical regions. Myelination of a region was judged to be normal when the degree and extent of white-matter hypointensity was similar to that expected in a normal patient of the same age [14]. Decreased myelination was diagnosed when white-matter hypointensity was present, but to a lesser degree or extent than appropriate for age. Myelination was labeled absent when the signal intensity of the white matter remained equal to (or greater than) that of the gray matter on T2-weighted images.

Results

Clinical Evaluation

The clinical and biochemical data of seven patients with NKH are summarized in Table 1. The onset of symptoms occurred before 72 hr after birth in each patient. With the

exception of case 2, each patient experienced an episode of apnea requiring neonatal ventilatory support. In case 2, the patient was lethargic at 2 days of life, but his symptoms and biochemical abnormality were sufficiently mild that the diagnosis was not made until the age of 9 months.

In another patient (case 7), an episode of *Staphylococcus aureus* bacteremia and septic shock occurred at the age of 5 months. A prolonged period (3 weeks) of ventilatory support followed, during which EEGs documented inactivity [16]. Hypoxic damage to the CNS was diagnosed clinically in this patient. In all other patients requiring ventilatory support (cases 1 and 3–6), intubation was performed at the first clinical signs of respiratory insufficiency; no episodes of significant hypoxia were diagnosed from recorded blood gases in this group.

Although head circumference was normal at birth, slowing of head growth was noted early in life in all patients. At the time of MR examinations, head circumferences were measured to be within 2 SD below the mean for age in all patients except one (case 7), whose head circumference was greater than 2 SD below the mean.

Elevated concentrations of glycine were found in the plasma, CSF, and urine in all patients (Table 1). The CSF concentrations of glycine ranged from 46.7 to 565.6 $\mu\text{mol/l}$. The ratios of CSF-to-plasma concentrations of glycine ranged from 0.06 to 0.37. Although absolute concentrations of glycine correlated poorly with clinical severity, a correlation was found between the ratio of CSF-to-plasma concentration of glycine and the frequency of seizures ($p < .05$ by Spearman's test [17]).

MR Evaluation

Parenchymal atrophy.—MR examinations of the brain demonstrated parenchymal atrophy in all patients. In six patients atrophy was detected on the initial MR study; a follow-up study demonstrated atrophy in the remaining patient (case 2) (Table 2). Atrophy of the cerebral hemispheres only was seen in cases 2–4 and 6. Both supratentorial and infratentorial structures were affected in cases 1, 5, and 7. Atrophy was detected as early as 4 days of age in case 1. A greater degree

TABLE 1: Clinical Findings in Nonketotic Hyperglycinemia

Case No.	Age at Diagnosis	Gender	Glycine ($\mu\text{mol/l}$) ^a		CSF/Plasma Glycine Ratio ^b	Neonatal Apnea	Seizures	
			CSF	Plasma			Age at Onset	Frequency ^c
1	2 d	M	565.6	1532.0	0.37	Yes	1 d	>15/d
2	9 mo	M	49.5	638.0	0.08	No	4 mo	<1/d
3	9 d	F	86.7	1067.0	0.08	Yes	2 d	<15/d
4	3 wk	F	180.0	781.9	0.23	Yes	2 d	>15/d
5	5 d	M	46.7	262.7	0.18	Yes	2 d	>15/d
6	3 wk	F	70.4	1096.6	0.06	Yes	5 d	<15/d
7	5 d	F	225.3	858.7	0.26	Yes	1 d	>15/d

Note.—d = day(s); wk = week(s); mo = month(s).

^a Normal ranges in our laboratory: CSF glycine, 3.0–10.2 $\mu\text{mol/l}$; plasma glycine, 92.0–514.0 $\mu\text{mol/l}$.

^b Upper limit of normal: 0.02 [15].

^c Before sodium benzoate therapy.

TABLE 2: MR Findings in Nonketotic Hyperglycemia

Case No.	Age at MR	Parenchymal Volume Loss			Width of Corpus Callosum in mm (% of normal) ^a		
		Brainstem	Cerebellum	Cerebrum	Genu	Body	Splenium
1	4 d	None	Mild	Mild	NM	0.7 (30)	2.0 (54)
2	8 d	None	None	None	6.7 (131)	2.2 (96)	3.5 (95)
	10 mo	None	None	Moderate	4.0 (52)	2.4 (57)	5.2 (68)
3	2 mo	None	None	Mild	2.7 (53)	1.3 (57)	2.7 (73)
4	4 mo	None	None	Moderate	2.7 (54)	1.1 (44)	2.7 (60)
5 ^b	23 mo	None	Severe	Severe	NM	NM	3.2 (39)
6	24 mo	None	None	Moderate	4.8 (62)	1.6 (38)	3.7 (45)
7	27 mo	Moderate	Severe	Severe	1.3 (17)	1.3 (31)	1.3 (16)
	38 mo	Moderate	Severe	Severe	NM	1.3 (31)	1.3 (16)

Note.—d = days; wk = weeks; mo = months; NM = not measured (due to local obscuration of margins of corpus callosum).

^a Normal values for the mean thicknesses of the genu, body, and splenium, respectively, of the corpus callosum [13]: 4–8 days old—5.1, 2.3, and 3.7 mm; 2 months old—5.1, 2.3, and 4.5 mm; 4 months old—5.0, 2.5, and 4.5 mm; 10 months old—7.7, 4.2, and 7.6 mm; 12 months old—7.8, 4.2, and 8.3 mm. (The 12-month-old values were used for cases 5–7.)

^b This was the only patient with a focal lesion, a retrocerebellar arachnoid pouch.

Fig. 1.—Case 5: 23-month-old boy. Axial MR image (600/25) shows gross dilatation of lateral ventricles (V) and sulci (arrows) of cerebral hemispheres compatible with severe volume loss.

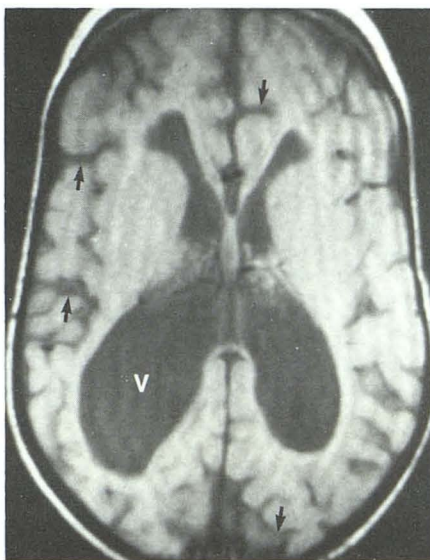


Fig. 2.—Case 4: 4-month-old girl. Sagittal MR image (600/20) shows that corpus callosum (arrows) is abnormally thin throughout its length. Classic findings of partial or complete corpus callosum agenesis are not present.



of volume loss was seen in the older patients (Fig. 1). Severe atrophy of the cerebrum and cerebellum was associated with a 5-cm retrocerebellar arachnoid pouch in case 5.

Measurements of the thickness of the genu, body, and splenium of the corpus callosum in each examination were compared with mean MR measurements of the normal developing corpus callosum during the first 12 months of life [13]. Corpus callosum measurements were well below normal in six of seven patients in our series at the time of the initial MR study (Fig. 2). In the remaining patient (case 2), the corpus callosum measured only 52–68% of normal on the follow-up MR study, decreased from 95 to 131% of normal at the time of the initial MR study. Accurate measurement of a portion of the corpus callosum was hampered by nearly equal signal intensities of white and gray matter in one neonate (case 1), and by volume averaging of adjacent CSF within dilated lateral

ventricles in two older patients with severe volume loss (cases 5 and 7). Otherwise, corpus callosum measurements were considered reliable. Classic MR findings of partial or complete corpus callosum agenesis [18] were not present in our patients.

Initial MR performed at 8 days of age in case 2 revealed normal parenchymal volume (Figs. 3A–3C) and normal or nearly normal measurements of the width of the genu, body, and splenium of the corpus callosum (Table 2). Moderate, diffuse supratentorial volume loss was demonstrated on a follow-up examination 10 months later (Figs. 3H and 3I); corpus callosum measurements decreased to approximately one-half of normal.

MR, performed initially at the age of 27 months in case 7, demonstrated severe supratentorial and moderate infratentorial atrophy (Fig. 4). This was the patient who experienced

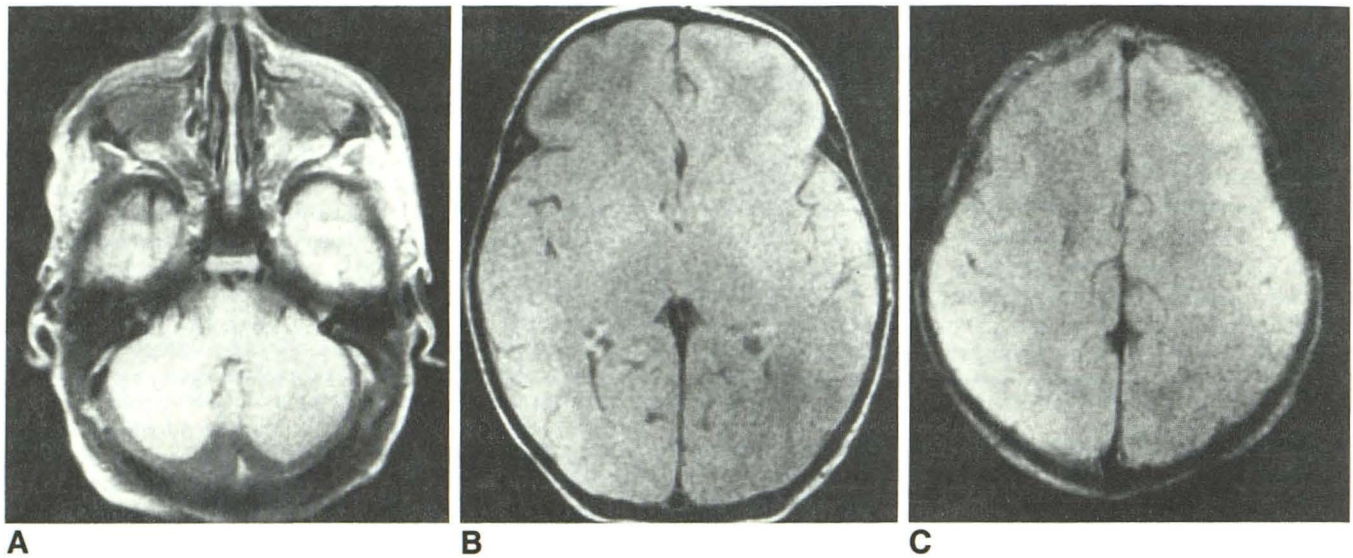


Fig. 3.—Case 2. A–C, Initial (8 days postnatal) axial T1-weighted MR images (600/20) show that ventricles and sulci are small, compatible with normal parenchymal volume.

D–F, T2-weighted MR images (3000/75, 8 days postnatal). Normal myelination of brain at this age is shown as decreased signal intensity limited to dorsal brainstem (b), ventrolateral thalami (t), and paracentral gyri of cortex (g). Forceps major and minor (f), internal capsule (i), and centrum semiovale (cs) are not myelinated at this age and appear hyperintense relative to cortex, as expected [14].

G–I, Follow-up (10 months postnatal) axial T2-weighted MR images (3000/70) show interval dilatation of ventricles (v) and subarachnoid spaces overlying hemispheres (s) compatible with moderate volume loss (compare with B and C). Decreased signal intensity within entire brainstem, middle cerebellar peduncles (p), and deep white matter of cerebellum reflects normal interval progression of myelination in these regions (G). However, white matter within forceps major and minor (f), external capsule (e), and centrum semiovale (cs) remains distinctly brighter than cortex and basal ganglia (H and I), indicating delayed myelination in these areas. (Cortex, underlying white matter, and basal ganglia regions should appear essentially isointense in a normal 10-month-old [14].)

sepsis and hypoxic injury at 5 months. The MR findings were unchanged on a follow-up examination done after an 11-month interval. The corpus callosum was severely atrophic in this patient (Table 2).

No correlation was found between the degree of volume loss demonstrated by MR and absolute CSF or plasma glycine concentrations, or the ratio of CSF-to-plasma glycine.

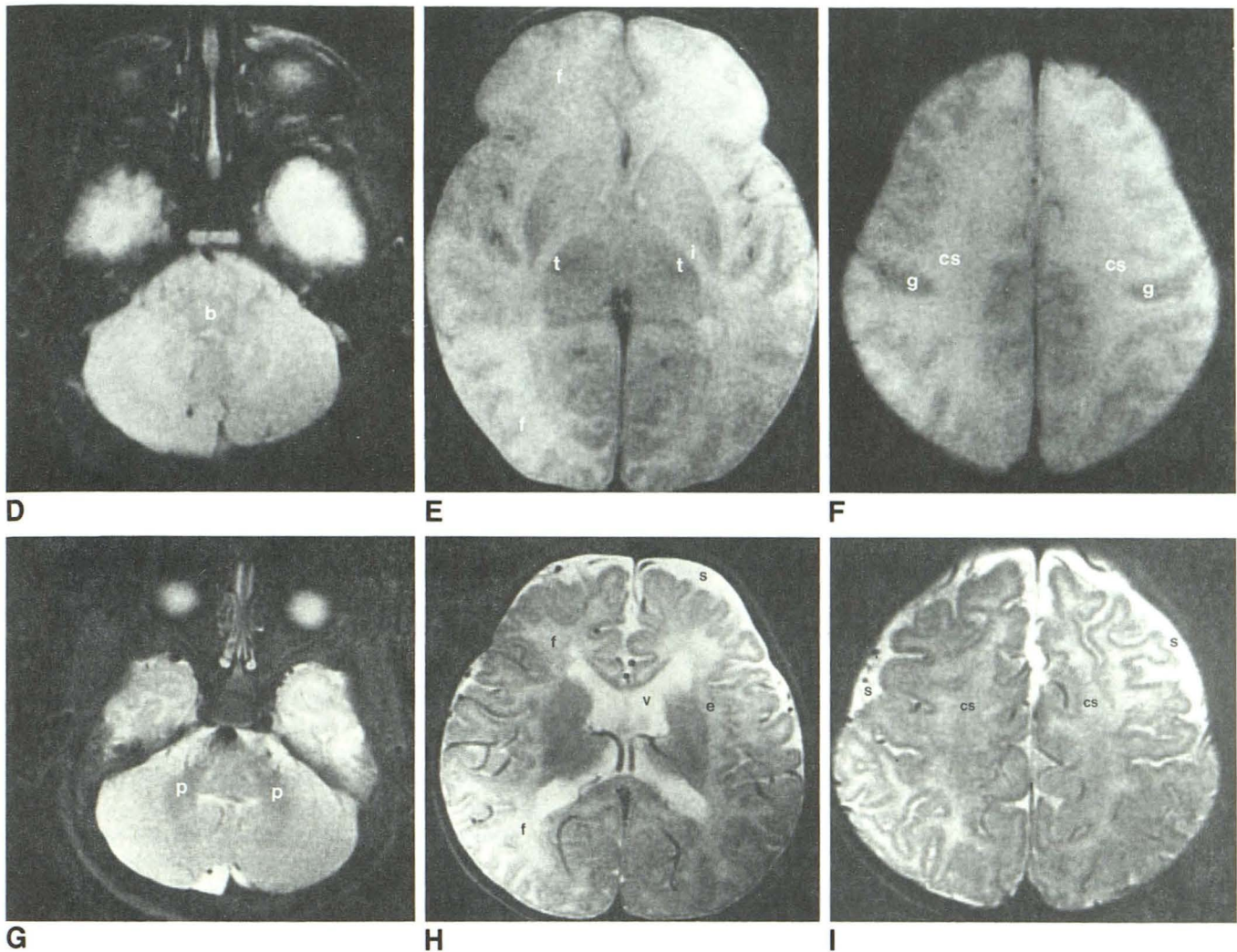
State of myelination.—In all patients, the state of myelination of the brain was graded on T2-weighted images [14]. Degree and extent of white-matter hypointensity were assessed in various brain regions (Fig. 5). Normal myelination of the brainstem and cerebellum was demonstrated by MR in four patients (cases 1–4) 4 days to 4 months old. MR in four patients (cases 2 and 5–7) 10–38 months old revealed decreased or absent myelination of supratentorial white-matter tracts including the internal capsule, corpus callosum, corona radiata, centrum semiovale, and subcortical regions.

In case 2, although normal cerebellar myelination occurred between the initial (8 days) and follow-up (10 months) MR studies, myelination of supratentorial white-matter tracts was decreased or absent on the latter examination (Fig. 3).

In case 7, myelination had proceeded only to the level of the internal capsule and basal ganglia by the age of 27 months, indicating a marked delay (Fig. 4). No progression of myelination was detected on the follow-up MR study at 38 months of age. The regions of the myelinated brainstem and basal ganglia appeared markedly hypointense relative to the nonmyelinated supratentorial structures in this patient.

Discussion

NKH represents a primary defect in the metabolism of glycine. The classic presentation is with life-threatening illness in the first days of life [1, 19]. An onset with lethargy, vomiting, or convulsions progresses rapidly to flaccidity, complete unresponsiveness, and episodes of apnea requiring ventilatory support. The majority of patients with NKH die in infancy. Those that survive are hypertonic and hyperreflexive, with frequent hiccuping, myoclonic convulsions, and little evidence of cerebral function. Atypical presentations have been described with a later onset of convulsions and a varying degree of mental retardation [1].



Dysfunction of the glycine cleavage enzyme system causes NKH. The four constituent proteins of this enzyme system catalyze the conversion of glycine to serine [3, 20, 21]. Activity of the cleavage system is undetectable in the liver and brain of patients with classical neonatal NKH; residual activity may be found in patients with atypical presentations [3]. Inadequate conversion of glycine to serine alters the cytoplasmic amino acid profile of myelinating oligodendroglia in patients with NKH. This may interfere with the synthesis of myelin [4].

Decreased brain weight and symmetric poverty of cerebral white matter have been reported on gross pathology in NKH [4, 5, 8]. Abnormalities of the corpus callosum include thinning (1- to 2-mm width) [4] and partial [21, 22] or complete [11] agenesis. There is preservation of the gray matter in most cases [6]. Rarefaction and vacuolation of myelin and variable gliosis with axonal preservation have been demonstrated on histologic sections. In neonates who die within the first month of life, spongy myelinopathy is most severe in those tracts

already myelinated at birth; that is, the brainstem and spinal cord [7, 8]. In older patients (24 and 36 months) the vacuolation of myelin is most evident in the bulky systems that myelinate after birth; that is, corpus callosum, optic radiations, and internal capsule [4]. Regions of predominant involvement may vary: sparing of the U fibers was reported in one patient [6]; involvement of the centrum semiovale but not the corona radiata was reported in two [4]. No derangement of the timetable of myelination has been detected in patients who die within the first several months of life [5, 8]. Delayed myelination in addition to the spongy state has been demonstrated in NKH patients who survive to 24 and 36 months of life [4].

Radiographic findings in patients with NKH have been described in a few case reports [8-10]. Porencephaly was detected by pneumoencephalography at 6 weeks of age in one patient [9]. Mild cerebellar and cerebral atrophy accompanied by hypodense foci within the periventricular white matter was noted by CT in an 11-year-old patient [8]. Similar

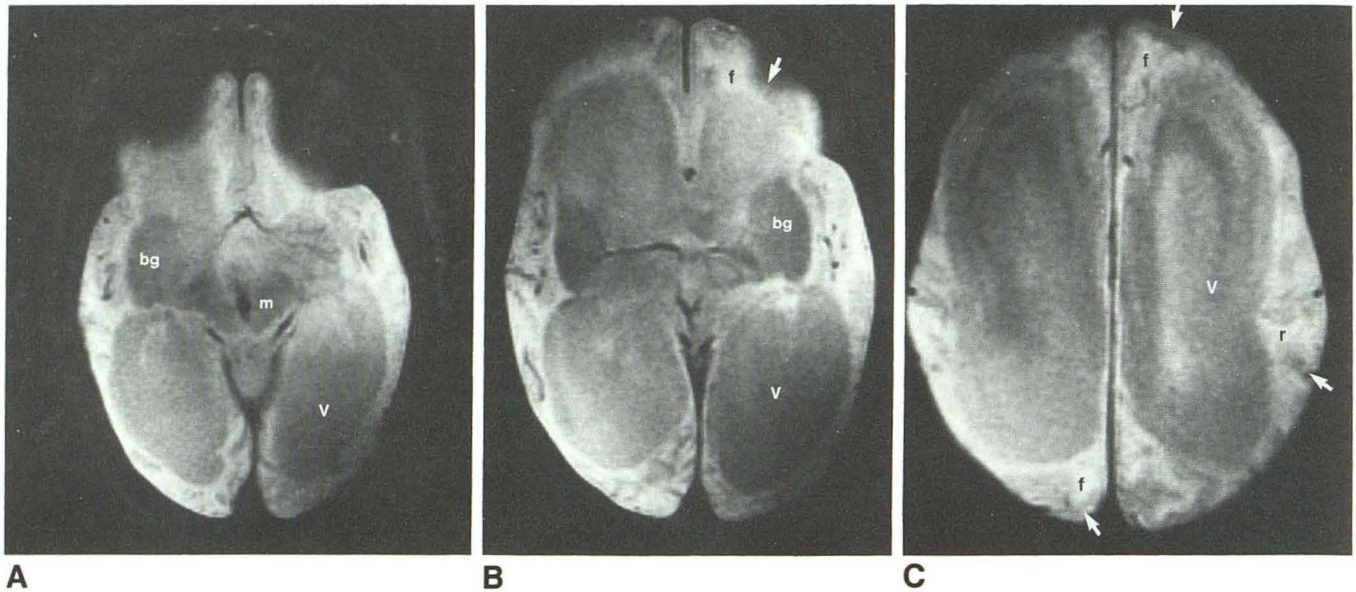


Fig. 4.—Case 7: 27-month-old girl. Axial MR images (3000/70) show marked ventricular dilatation (v) compatible with severe cerebral atrophy. Decreased signal intensity is limited to midbrain (m) and basal ganglia (bg) regions, indicating marked delay in progress of myelination [14]. White matter within fornice major and minor (f), corpus callosum, corona radiata (r), and centrum semiovale is abnormally hyperintense relative to thin cortical mantle (arrows). Follow-up examination at 38 months (not shown) demonstrated no change in degree of volume loss and myelination delay.

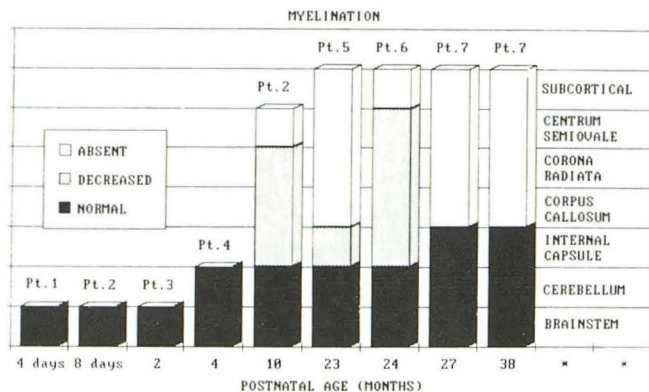


Fig. 5.—Degree of myelination (assessed on T2-weighted images) vs patient age at time of MR examination. Total height of each column represents degree of myelination expected in normal subject of the same age [14]. Four patients (cases 1–4) examined between 4 days and 4 months postnatally demonstrated normal myelination within brainstem and cerebellum. Four patients (cases 2 and 5–7) examined 10–38 months postnatally demonstrated varying degrees of delay in myelination within supratentorial structures including internal capsule, corpus callosum, corona radiata, centrum semiovale, and subcortical white-matter regions.

findings were demonstrated in a 10-year-old who had an atypical, delayed presentation [10]. Agenesis of the corpus callosum was reported on CT in a neonate with NKH [11].

Our subjects included seven patients 4 days to 38 months old at the time of MR. Six patients had the classical form of NKH with neonatal onset. One patient had a milder form and delayed diagnosis. In this series, atrophy of the cerebral hemispheres was a common finding, occurring in all seven patients. In six patients, atrophy was noted on the initial MR study; a follow-up MR examination demonstrated the interval

appearance of supratentorial atrophy in the remaining patient with the milder form of NKH whose initial MR study was normal. Supra- and infratentorial structures were affected in three patients. The degree and extent of volume loss was greater in the older patients.

We compared our measurements of the corpus callosum in subjects with NKH with measurements of the corpus callosum recorded in a group of patients, 3 days to 12 months old, who had normal brain MR images [13]. By this standard, the corpus callosum was abnormally thin in six of seven of our subjects at the time of initial MR, and in the remaining subject at a 10-month follow-up study. It should be emphasized that three of our subjects (cases 5–7) were imaged between the ages of 23 and 38 months. Comparing their callosal measurements with those reported in normal subjects 10–12 months old (Table 2) most likely *underestimates* the true degree of atrophy of the corpus callosum in our subjects. Partial or complete agenesis of the corpus callosum was not seen in our subjects.

The ability of MR to assess postnatally the state of myelination of the developing brain [14, 23] was exploited also in our investigation. At birth, in normal neonates, the dorsal pons and portions of the superior and inferior cerebellar peduncles have decreased signal intensity on T2-weighted images (performed at 1.5 T), signifying normal myelination [23]. Myelination of the deep white matter of the cerebellar hemispheres usually occurs between 3 and 5 months after birth. White matter of the corpus callosum, internal capsule, corona radiata, and centrum semiovale myelinates during the first 4–11 months after birth. The subcortical white matter matures last, with myelination proceeding from the occipital region anteriorly to the frontal lobes from 11 to 18 months postnatally [14].

Our assessment by MR of the state of myelination in patients with NKH was remarkably similar to that reported on pathologic examination in this disease [4, 8]. T2-weighted images demonstrated normal myelination within the brainstem and cerebellum of subjects less than 4 months old. Above the age of 10 months, MR showed decreased or absent myelination within supratentorial white matter in all of our patients. The internal capsule, corona radiata, centrum semiovale, corpus callosum, and subcortical white-matter tracts were affected to varying degrees. Progression of myelination was delayed or absent in two patients in whom MR was repeated after 10- and 11-month intervals.

No foci of abnormal hyperintensity or other changes were noted on MR that indicated vacuolation or gliosis within regions of myelinated white matter. Similarly, no abnormalities of signal intensity were identified within the gray matter in our patients with NKH.

Striking similarities exist between NKH and other aminoacidopathies on pathologic and CT examination. The cerebral atrophy, spongy myelinopathy, and retarded myelination demonstrated at pathology in NKH are seen also in methylmalonic and propionic acidemia, maple syrup urine disease, tyrosinemia, phenylketonuria, and hyperbetaalaninemia [4, 7]. Moreover, the diffuse cerebral atrophy and deep hemisphere lucencies seen on CT in patients with NKH [8, 10] are among the abnormalities reported in methylmalonic and propionic acidemias [24, 25]. We speculate that the MR manifestations of NKH delineated in this report may also occur in patients with other aminoacidopathies.

In summary, our data indicate that MR findings of CNS atrophy and delayed myelination in patients with NKH are age-related and similar to those reported on pathologic examination. MR may detect atrophy of the brain as early as 4 days of life in neonates with NKH. Older subjects tended to have a greater degree of CNS atrophy. The volume loss increased in severity in one of two patients having a follow-up MR study. Both supra- and infratentorial structures were involved in the most severely affected patients. The corpus callosum was abnormally thin on initial or follow-up MR in all our patients with NKH. Myelination of the brainstem and cerebellum appeared normal through the age of 4 months when assessed on T2-weighted images. Decreased or absent myelination within supratentorial white-matter tracts was detected in patients more than 10 months old. No abnormality was detected by MR within the gray matter in patients with NKH.

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