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Imaging Patterns of Neonatal Hypoglycemia

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PURPOSE: Our purpose was to report the patterns of injury observed in five patients who suffered brain damage consequent to neonatal hypoglycemia.

METHODS: The imaging studies and clinical records of five patients with brain damage caused by neonatal hypoglycemia were reviewed retrospectively. Patterns of injury were compared with those described in the literature and those seen in neonatal hypoxic-ischemic injury.

RESULTS: Diffuse cortical and subcortical white matter damage was seen, with the parietal and occipital lobes affected most severely. Globus pallidus injury was present in one patient who had the most severe cortical injury.

CONCLUSION: We found a specific pattern of injury that correlates well with the sparse pathologic and imaging reports on neonatal hypoglycemia. We speculate that the patterns of damage are the result of regional hypoperfusion and excitatory toxicity with cell-type-specific injury.

Although hypoglycemia may be common among neonates (1), brain damage resulting from isolated neonatal hypoglycemia is rare. As a result, few cases have been reported in the pediatric, neurologic, or radiologic literature (1–6). We have recently had the opportunity to review the imaging studies of five infants who suffered brain damage as a result of neonatal hypoglycemia. All had similar patterns of damage to the brain. We report the imaging characteristics of these patients, compare the findings with those few cases reported previously, and attempt to relate the patterns to the underlying physiology.

Methods

The clinical records and imaging studies of five patients were reviewed retrospectively. Two were ultimately determined to have neonatal hyperinsulinemia, two were thought to have diminished glycogen and lipid stores as well as impaired gluconeogenesis subsequent to intrauterine malnutrition, and the fifth patient was ultimately determined to have a transient metabolic disorder.

Two patients had axial computed tomography (CT) studies (5-mm-thick sections) and all five had magnetic resonance (MR) imaging studies. MR examinations included sagittal 3- to 5-mm-thick T1-weighted sequences and axial 4- to 5-mm-thick spin-echo T2-weighted sequences in all patients, and coronal and axial 3- to 5-mm-thick T1-weighted sequences in three patients. Initial examinations were performed between the ages of 3 days and 26 days. Follow-up imaging studies (a total of two CT scans and two MR examinations) were obtained in three patients 10 days to 2 months after the original studies. All CT and MR studies were obtained without the use of intravenous contrast material.

Results

Clinical Data

All patients were neonates who were born after uneventful pregnancies and deliveries. The two undernourished neonates were classified as small for gestational age (less than 10th percentile) and the one with hyperinsulinemia was large for gestational age; the other two were considered normal in size. All had normal immediate postnatal courses, with 5-minute Apgar scores of 8 or 9. All initially presented as a result of seizure activity. In the two patients who were small for gestational age, seizures developed in the first day (one at 14 hours, one at 19 hours). One patient was still in the hospital when seizures developed; in the second, seizures developed at home and the infant was not brought back to the hospital for care until the age of 40 hours, when his increasing irritability began to concern his parents. In both cases, initial glucose levels, obtained with Chem strips, were zero. Serum glucose levels were obtained immediately, with values of less than 3 mg/dL for both patients. The patients were treated immediately with a bolus of 10% glucose followed by rapid drip infusion, but the hypoglycemia was difficult to treat and required continuous infusion for 36 hours in one patient and 48 hours in the other before glucose levels stabilized. Laboratory studies for underlying hormonal abnormalities and inborn errors of metabolism were negative.

FIG 1. Patient 1: *A–C* are from MR imaging study at age 13 days, *D* is from study at age 27 days.

A, Parasagittal spin-echo (550/11/2) image shows abnormal hyperintensity (*arrows*) of the parietal and occipital cerebral cortex.

B, Axial spin-echo (3000/120/1) image shows abnormal hyperintensity (*open arrows*) in the globi palladi and mixed hypointensity and hyperintensity (*solid arrows*) in the occipital cortex and white matter.

C, Coronal spin-echo (550/11/2) image shows hyperintensity of the globi palladi (*open arrows*). The cortex at the depths of the cortical sulci (*solid arrows*) is hyperintense as well.

D, Parasagittal spin-echo (550/11/2) image at age 27 days shows marked tissue loss, most prominently in the parietal and occipital lobes (*arrows*).
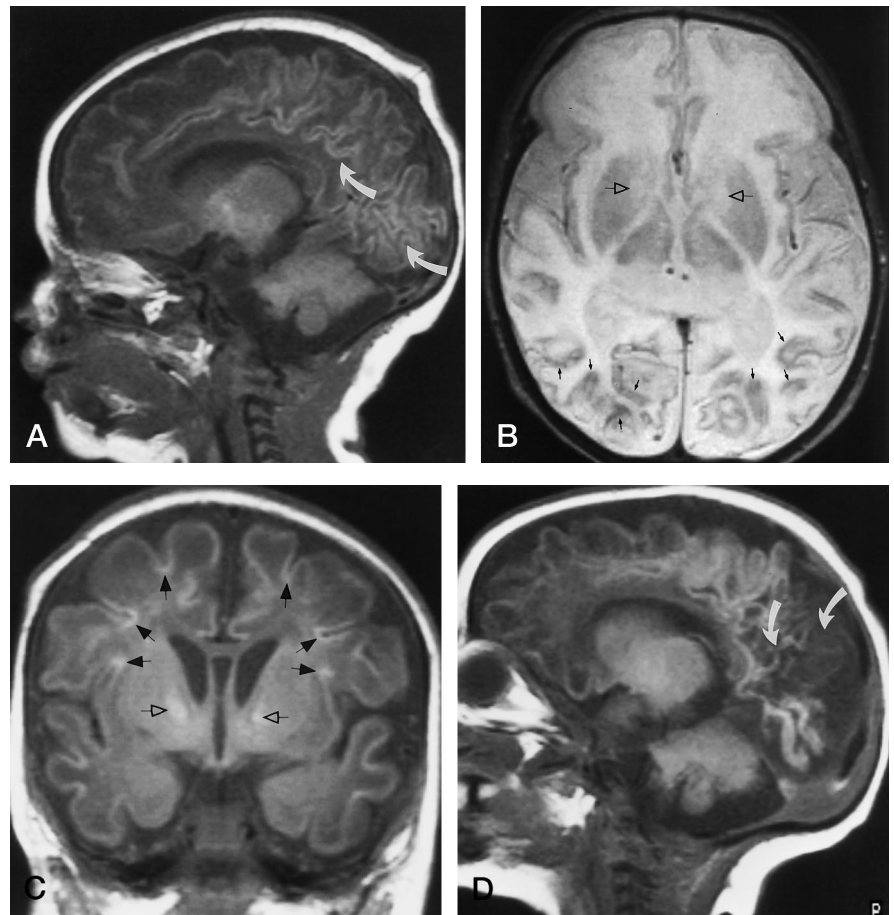
In the other three patients, who were not small for gestational age, poor feeding was reported to develop at age 2 to 3 days. Two were noted to have periods of apnea. One was discovered to have a large secundum atrial septal defect. Seizures, manifested as focal jerking of the arms or legs, developed between 40 hours and 80 hours after birth. Two of the patients were not brought to the hospital until the seizures started, whereas the third was already in the hospital undergoing a workup related to poor feeding and apnea. All three children in this group were somewhat slow to respond to intravenous glucose therapy; in two, the serum glucose levels did not stabilize, even after 2 days of glucose infusion. In both these infants, insulin levels were obtained and showed marked elevation. Ultimately, the diagnosis of congenital hyperinsulinism of the newborn, previously known as nesidioblastosis, was made in these patients, and near total pancreatectomies were performed. In the third patient, multiple abnormalities were present on the urine organic and amino acid screens; therefore, this infant was classified as having a generalized organic acidemia by the physicians on the child neurology and metabolic disease services. As the infant has matured, his ability to generate and metabolize glucose has normalized; he is normoglycemic without therapy at the present time.

None of the patients had episodes of hypotension or hypoxia during their neonatal course.

Neuroimaging

The neuroimaging studies of all patients showed significant brain damage, with disproportionate involvement of the parietal and occipital lobes of the cerebral hemispheres. In one of the patients who was small for gestational age, the brain damage was more extensive, extending into the posterior portions of the frontal lobes and involving the globus pallidus (Fig 1). In the other four patients, the damage was restricted to the parietal and occipital lobes, involving both the cortex and underlying white matter (Fig 2). In two patients, CT scans were obtained in the first 5 days of life. They revealed edema in the parietal and occipital cortices (Fig 2), with normal-appearing basal ganglia. Ages at the time of the initial MR study ranged from 13 to 27 days. These studies showed T1 and T2 prolongation in the parietal and occipital white matter, with mixed signal intensity in the cerebral cortex (Figs 1 and 2). Some areas, particularly the deeper cortex, showed T1 and T2 shortening, whereas most of the affected cortex showed T2 prolongation (Fig 2). In the patient with the most extensive cerebral damage, T1 shortening and T2 prolongation were seen in the globus pallidus bilaterally (Fig 1). Short-term follow-up studies showed developing atrophy with cystic encephalomalacia in affected regions of the brain (Fig 1). The only available long-term follow-up study,
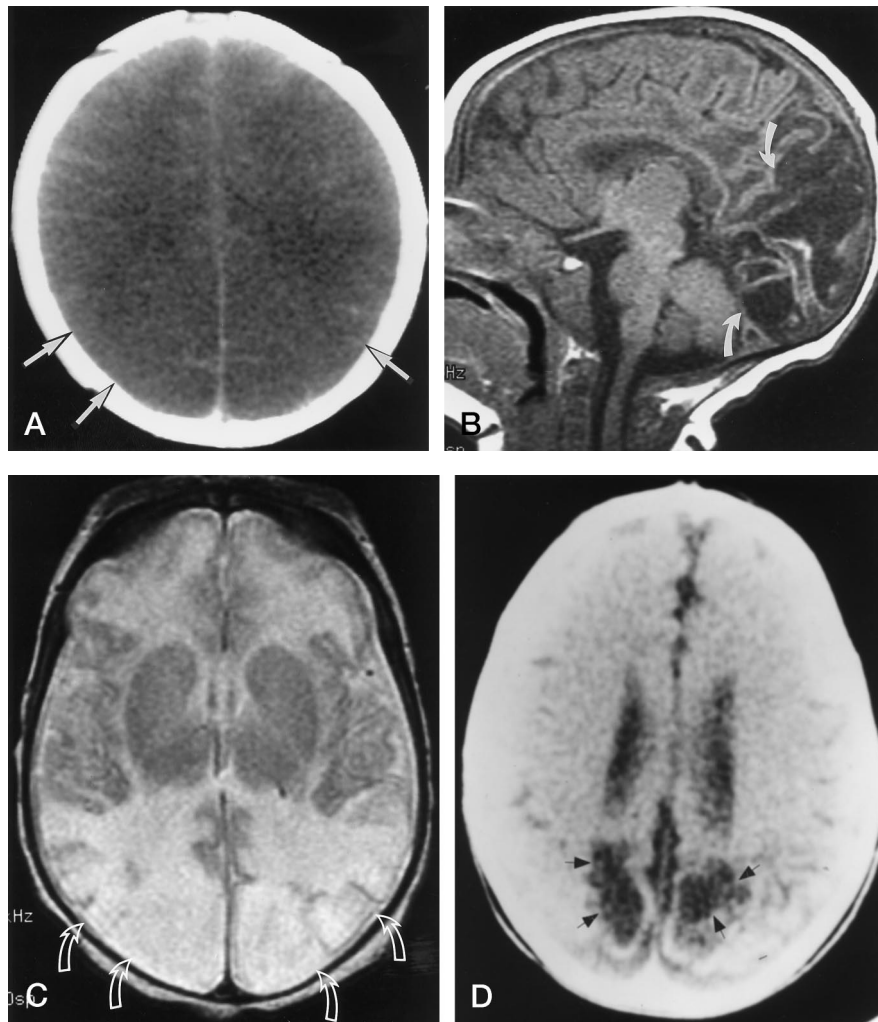
Fig 2. Patient 2.

A, Axial noncontrast CT scan on postnatal day 2 shows diffuse cortical edema, most severe in the parietal and occipital lobes (*arrows*).

B, Sagittal spin-echo (550/11/2) MR image on postnatal day 19 shows low attenuation (*arrows*) of the parietal and occipital cortex and white matter.

C, Axial spin-echo (3000/120/1) image on postnatal day 19 shows abnormal hyperintensity (*arrows*), primarily in the parietal and occipital lobes.

D, Axial noncontrast CT scan at age 2 months shows large areas of encephalomalacia (*arrows*) in the parietooccipital regions bilaterally.

at age 3 months, showed large areas of cystic degeneration in the parietal and occipital lobes (Fig 2).

Discussion

The reported rate of occurrence of neonatal hypoglycemia varies considerably, depending on the definition of hypoglycemia and the population of infants studied (7). Neonatal hypoglycemia is probably underrecognized, because common symptoms, such as stupor, jitteriness, and seizures, may be lacking or inconspicuous in many affected neonates (1). The definition of hypoglycemia in infants varies with the maturational state of the brain: less mature infants can withstand lower glucose levels than more mature ones, and mature infants can withstand lower levels than adults. The most widely accepted definition of significant hypoglycemia in the newborn is a whole-blood glucose concentration of less than 30 mg/dL in term infants (a level of 30 mg/dL causes confusion and seizures in an adult [8], in whom normal levels are greater than 45 to 50 mg/dL) and less than 20 mg/dL in preterm infants (9). On the basis of these criteria, up to 8% of low-risk infants may suffer an episode of hypoglycemia, typically at 3 to 4 hours after delivery (7).

Cornblath and Schwartz (9) classified neonatal hypoglycemia into four clinical categories, which were adapted by Volpe (1) on the basis of prenatal maternal or fetal condition and the presence, severity, and time of onset of symptoms. Category one, transitional-adaptive hypoglycemia, is characterized by a very early postnatal onset of mild, brief hypoglycemia that responds rapidly to glucose administration. These infants often have diabetic mothers or erythroblastosis, and have difficulty adapting to the metabolic changes accompanying transition to extrauterine life. Category two, secondary-associated hypoglycemia, is characterized by onset of relatively mild hypoglycemia of short duration early in the first postnatal day, with rapid response to glucose. In general, these infants have been subjected to an associated disorder of the CNS, such as hypoxic-ischemic injury, intracranial hemorrhage, or bacterial sepsis. Category three, classic-transient hypoglycemia, tends to present toward the end of the first day with moderate to severe hypoglycemia that can be of prolonged duration and that requires large amounts of glucose before a response is noted. These infants are almost always small for gestational age, owing to intrauterine undernutrition, with resultant diminished glycogen and lipid

stores as well as impaired gluconeogenesis. Patients in category four, severe recurrent hypoglycemia, are usually born at term and present with severe, prolonged hypoglycemia. The time of onset of the hypoglycemia is variable, and the hypoglycemia may persist in spite of early glucose therapy. Most infants in this group have primary disorders of glucose homeostasis. Causes include Beckwith-Wiedemann syndrome, congenital hyperinsulinism of the newborn (nesidioblastosis), β-cell hyperplasia, endocrine deficiencies, and inborn errors of metabolism. Two of our patients seem to belong in category three and three in category four. Of importance is the fact that despite several different causes of hypoglycemia in our patients, the pattern of damage, with involvement of primarily the parietal and occipital lobes, was nearly identical. Therefore, the pattern of damage detected by neuroimaging seems to principally reflect injury from hypoglycemia and not that of an underlying disorder.

The causes underlying the ability of the less mature brain to withstand lower levels of glucose have not been completely established. In the mature (adult) brain, the levels of phosphocreatine and adenosine triphosphate (ATP) decrease very rapidly after the onset of severe hypoglycemia (10, 11). As a result, proteins and phospholipids are broken down to form endogenous amino acids and free fatty acids, respectively. These may then be channeled into oxidative pathways as alternative substrates for energy production. When proteins and free fatty acids are used as energy sources, ammonia and arachidonic acid (which generates free radicals) are produced, leading to cellular injury (10, 12, 13). With continued hypoglycemia, membrane homeostasis is lost, the electroencephalogram becomes isoelectric, and irreversible injury ensues.

In the immature (neonatal) brain, phosphocreatine and ATP levels in neurons are maintained despite low glucose levels (14). In fact, the cerebral metabolic rate for oxygen is unchanged in hypoglycemic neonates (15). Newborns are able to maintain consciousness at much lower glucose levels than are mature subjects (1). Probable reasons for the maintenance of energy profiles and neurologic function include the ability of the newborn brain cells to utilize lactate as an energy source (15, 16) and the low energy requirements of the immature neurons resulting from the low level of neuronal activity (1). A third factor contributing to the resistance of the newborn brain to hypoglycemia is the relatively minor effect of hypoglycemia upon cardiovascular function of the newborn (14). The immature heart has substantial stores of energy-rich carbohydrates that can be converted to glucose and, moreover, can use fuels other than glucose for energy (1, 17, 18); thus, cerebral perfusion and oxygenation is maintained during neonatal hypoglycemia.

The ability to utilize alternative energy sources and the maintenance of cardiac output and cerebral perfusion are likely to be the most important differences in the patterns of brain injury seen in neonatal hypoglycemia versus neonatal hypoxia (6, 19–23). When hypoxia occurs in the newborn, cardiac function is disturbed and cardiac output diminished. The diminished cardiac output, in conjunction with the impaired cerebrovascular autoregulation that accompanies hypoxia (24, 25), leads to ischemia and resultant lack of oxygen and glucose delivery to the brain. Thus, ischemic and hypoglycemic injury are superimposed. As hypoglycemia seems to potentiate the effects of hypoxia (1), the effects on the brain are devastating. This observation explains the identical pathologic patterns in infants with hypoxia and in those with combined hypoxia and hypoglycemia, as reported in the literature (26). In both groups of patients, in fact, the same sets of neurons suffer the same condition of combined hypoxia and hypoglycemia.

Hypoglycemia in adults leads to two patterns of damage: regional and cell-type specific. Insulin-induced coma in rats results in regional loss of autoregulation in the cortex, thalamus, hippocampus, and medial geniculate bodies, with preservation of the cerebellum, brain stem, and hypothalamus (27). Moreover, delayed hypoperfusion (25% to 40% of control cerebral blood flow) has been documented in the forebrain and hippocampus (28). Hypoglycemia disrupts protein synthesis in the superficial layers of the cortex, in the caudate, in the putamen, and in certain cell populations of the hippocampus (CA1 and CA3 pyramidal cells, dentate crest granule cells) (10), whereas cerebellar and brain stem protein synthesis is relatively unaffected. Rates of protein synthesis may simply reflect the available energy within the cell, with relative preservation in the cerebellum and brain stem due to a greater activity of glucose transport mechanisms in those areas (29). The contribution of selective changes in regional autoregulation and protein synthesis disruption have not been studied in neonatal groups.

Our findings of diffuse brain damage, with the most severe injury localized primarily to the parietal and occipital cortex of the brain, verify the observations of Banker (5), Anderson et al (3, 4), and Spar et al (2) concerning the diffuse nature of hypoglycemic brain injury in the newborn and the posterior cortical localization of the most severely injured regions. The reason that the parietal and occipital lobes are most severely affected is not obvious. The pattern of damage does not match the pattern of normal glucose uptake in neonates, as determined by positron emission tomography (30), indicating that it is not a simple matter of demand and supply of glucose as an energy source. One possible reason for the pattern of damage may relate to the development of receptors for excitatory amino acids (EAAs). The literature is replete with evidence that excessive release of excitatory amino acids (excitotoxins), such as glutamate and aspartate, into the synaptic cleft results in the selective death of the postsynaptic neurons (selective neuronal necrosis) in conditions such as hypoxia-ischemia, seizures, and trauma (31–34). Excitotoxins, particularly aspartate, also appear to be involved in neuronal injury resulting from hypoglycemia (35–38).

Moreover, experimental evidence indicates that the location of neurons with cell surface receptors for excitatory amino acids, such as *N*-methyl D-aspartate (NMDA), changes as development proceeds (39, 40). As cell injury does not occur in the absence of EAA receptors, the ontogenic changes in the receptor locations may explain the different location and pattern of damage in infants as compared with older children and adults (the corpus striatum and hippocampi [10, 41, 42]). Although the parietal and occipital cortices are not known sites of NMDA receptors in the neonatal period, the neonatal globus pallidus, which was injured in one of our patients, has high concentrations of receptors; the corpus striatum has high concentrations of NMDA receptors in adults (39, 40).

The ontogenic changes in NMDA receptor location have also been suggested as a cause of the changing patterns of brain injury resulting from profound hypoxic-ischemic injury in infants, since the locations of EAA receptors are similar to those damaged in hypoxia and ischemia (21, 22). The pattern of damage in neonatal hypoxic-ischemic injury, however, is distinct from that in neonatal hypoglycemia. This apparent discrepancy can be explained by taking into account the decreased cerebral perfusion that accompanies asphyxia. As discussed earlier, cardiac output and, thus, global cerebral perfusion are maintained in hypoglycemia. Therefore, one possibility is that a difference in regional blood flow may contribute to hypoglycemic damage through either loss of autoregulation or delayed hypoperfusion, as discussed above. Alternatively, neuronal injury in hypoglycemia may be restricted to those areas with well-developed EAA receptors able to be excited by elevated levels of aspartate. In contradistinction, hypoxia is almost invariably accompanied by decreased cardiac output and compromised autoregulation, resulting in decreased cerebral perfusion (24, 25). Location of brain injury in hypoxia, therefore, is determined by the degree of cardiac impairment, metabolic requirements of the cells (which are dependent on the state of regional metabolic activity), availability of collateral blood flow, and developmental state of the EAA receptors, particularly those for glutamate.

The question arises as to why the globi palladi were injured in just one of our five patients. Based on the fact that the patient with injury to the globus pallidus was the one with the most extensive and severe cortical injury, we speculate that the neonatal globus pallidus is less susceptible to hypoglycemic injury than is the parietooccipital cortex, but more so than the rest of the structures in the brain. If this is so, then this patient presumably had hypoglycemia of greater severity or greater duration than the other patients. However, we have no good records of precisely how long the hypoglycemia was present in any of these patients, so this remains pure speculation. One might also venture that there may have been a component of hypoxia in this patient that was not present in the others and that the combined hypoxic-hypoglycemic injury was responsible for the globus pallidus injury. However, no documented hypoxia was present in any of our patients.

The cause of the T1 and T2 shortening of the MR signal arising from damaged cerebral cortex is most likely the same as in hypoxic-ischemic injury. This issue has been discussed in articles on hypoxic-ischemic injury (21, 22, 43), and does not need a lengthy discussion here. Likely possibilities include calcification, petechial hemorrhage, and myelin degradation. The exact cause of the signal changes awaits direct pathologic-radiologic correlation.

The differential diagnosis of this pattern of damage in the neonatal brain is not very extensive. Severe sagittal sinus thrombosis can cause bilateral paramedian brain injury involving gray and white matter; however, the thrombosed sinus can be identified by MR imaging and, in addition, sinus thrombosis in neonates is usually an incidental finding that does not cause brain damage (44–46). Bilateral posterior cerebral artery compression resulting from cerebral edema may cause bilateral occipital infarction (47), but the pattern is different from that seen in the patients reported here, as the calcarine regions are specifically involved in arterial infarction but are spared in neonatal hypoglycemia. Of importance, neonatal hypoxic-ischemic injury (48, 49) does not cause the pattern described here and, therefore, can be clearly separated from neonatal hypoglycemia on the basis of the imaging appearance of the injuries. It is equally important to note that all the patients in this study had an underlying problem that made them susceptible to severe, prolonged hypoglycemia; there is no evidence here or elsewhere indicating that neonates without underlying problems, such as growth retardation or disorders of glucose homeostasis, can sustain brain injury from hypoglycemia.

Conclusion

We have described the imaging findings in five patients who suffered brain damage as a result of neonatal hypoglycemia. CT and MR studies showed damage primarily to the parietal and occipital lobes of the cerebrum. Possible mechanisms of brain damage, the reasons for the location of the damage, and potential reasons for the difference in location from that in hypoxic-ischemic injury and adult hypoglycemic injury have been discussed.

Acknowledgments

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