Neurologic Aspects of Neonatal Hypoglycemia

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Abstract

Profound neonatal hypoglycemia is one of the leading causes of brain injury. Hypoglycemic encephalopathy is caused by lack of glucose availability to brain cells. Although sharing a similar pathogenesis with hypoxic-ischemic encephalopathy, hypoglycemic brain insult has distinctive metabolic, brain imaging, electroencephalographic and histopathologic findings.

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Neonatal hypoglycemia is a common condition. While most infants do not have neurologic sequelae, a few develop severe neurologic damage. Neonatal hypoglycemia is one of the leading causes of brain injury. The incidence of neonatal hypoglycemia depends on the definition of low blood glucose threshold. If the low blood glucose threshold in the first 2 days in term infants is defined as whole blood glucose ⩽40 mg/dl (the currently acceptable definition), or ⩽30 mg/dl (historical definition), the incidence will be 8.1% and 20.6%, respectively [1]. Many conditions are associated with neonatal hypoglycemia; these include common conditions [Table 1] as well as relatively rare conditions such as hormonal disorders, inborn errors of metabolism, glucose transporter deficiencies, and insulin-producing tumors. In this article we review the neurologic aspects of neonatal hypoglycemia; the pathophysiology, prevention and treatment of neonatal hypoglycemia are beyond the scope of this review.

Table 1. Common conditions associated with neonatal hypoglycemia*

Cause/ associated condition	Inadequate production of glucose**	Excessive utilization of glucose***	Comments
Prematurity	+	?	Mainly due to depletion of glycogen stores
IUGR infants	+	+	Hyperinsulinism in many infants, decreased gluconeogenesis, and rapid growth
IDM infants		+	Hyperinsulinism
Perinatal stress	+	+	Anaerobic metabolism, and depletion of glycogen stores
Polycythemic infants		+	Increased RBC mass causing excessive utilization
Non-IDM LGA infants			Cause not well established
Post-term infants	+		Depletion of glycogen stores
Sepsis	+	+	Decreased gluconeogenesis, and increased utilization
CHF and CHD		+	Increased utilization
Erythroblastosis fetalis		+	Increased insulin levels
High UAL		+	Increased insulin production due to excessive glucose perfusion of the pancreas
Maternal medications		+	Such as ritodrine, terbutaline and other medications

* Modified from ref. 1.
** Inadequate production of glucose secondary to lack of glycogen stores, decreased glycogenolysis and decreased gluconeogenesis.
*** Excessive utilization of glucose secondary to hyperinsulinism and/or an increased rate of anaerobic glycolysis.
IUGR = intrauterine growth restriction, IDM = Infant of diabetic mother, LGA = large for gestational age,
CHF = congestive heart failure, CHD = cyanotic heart disease,
UAL = umbilical artery line.

Neurologic overview

In theory, neuropathologic lesions of hypoglycemic encephalopathy should be very similar to those of hypoxic-ischemic encephalopathy because the essential substrates of oxidative phosphorylation, glucose and oxygen, respectively, are the limiting factors. As neurons have small reserves of glycogen but not oxygen, one might expect that lesions due to hypoglycemia would be somewhat slower in evolution and less severe. Nevertheless, prolonged, severe hypoglycemia in humans may induce extensive neuronal necrosis [2]. An important difference between HGE and HIE is that HIE is associated with severe lactic acidosis whereas HGE is not; lactic acidosis contributes significantly to neuronal degeneration. This capacity disappears with the progressive inability of lactate to enter the brain with maturation [3]. Neonatal resistance to hypoglycemic brain injury may be due to a combination of enhanced cerebral blood flow enabling cerebral uptake of glucose, enhanced ability to use alternative substrates (especially ketone bodies), lactate, and preservation of cerebral high energy phosphates [4]. Ketonemia is protective to the neonatal brain, which is subjected to hypoglycemia and hypoxia-ischemia, because of the substrate's ability to undergo oxidative decarboxylation and thus provide reducing

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HGE = hypoglycemic encephalopathy
HIE = hypoxic-ischemic encephalopathy

equivalents to mitochondria for energy production [5]. However, hyperinsulinemia, a common finding in infants of diabetic mothers, suppresses the production of ketone bodies and therefore decreases alternate fuel production. Additional protective mechanisms include glycogen stores in astrocytes [6] and a low cerebral metabolite rate for glucose, which are about 30% lower than in adults [7].

In rats, hypoglycemic brain damage is minimized by the blocking of NMDA (N-methyl-D-aspartate) receptors to the acute neurotoxic effects of the release of large amounts of excitatory neurotransmitters [8]. Therefore, excitatory amino acids may play a role in causing brain damage. Hypoglycemia may induce neuronal death by interfering with mitochondrial energy production. Swelling and proteinaceous flocculent degradation of mitochondria are seen in hypoglycemic rat brains, in neuronal bodies and also in dendrites [9]. Apoptosis, which is programmed cell death and a major mechanism in neuronal loss, is triggered by a variety of stimuli including hypoglycemia [10]. Fas is a cell surface receptor that on activation initiates a cascade that leads to apoptosis. Caspases intracellular cysteine proteases are activated and convey an apoptotic signal in a proteolytic cascade of caspases, leading to degradation of cellular targets and apoptosis [11]. It was shown that the use of insulin-like growth factor-I and bcl-2 (B cell lymphoma-2), which are anti-apoptotic factors, can prevent or ameliorate hypoglycemic brain injury [10].

Neuropathologic findings

HIE and HGE have overlapping features but also differ substantially, in both the experimental animal and the human, where they are often concurrent conditions. The principal generalization from human postmortem, human and animal studies is that HIE often results in cerebral infarcts. In contrast, HGE tends not to cause extensive necrosis, but rather produces individual neuronal death throughout the brain with a characteristic vulnerability of certain neurons and resistance of others [9]. Some of the most vulnerable neurons to hypoglycemia are resistant to hypoxia, and vice versa. Even in human adults who died from pure hypoglycemic coma, the brain may exhibit selective neuronal loss without extensive tissue infarction [2]. The involvement of the occipital lobes found by magnetic resonance imaging and computerized tomography studies has been confirmed also by autopsy findings [12]. Selective swelling of dendrites is an early neuronal lesion in hypoglycemia. This feature resembles neurotoxic damage from sudden release of excitatory amino acids [9].

The human neonatal lesions traditionally described in textbooks of neuropathology include pyknosis and karyorrhexis of neuronal nuclei and neuronal loss in the cerebral cortex, Ammon's horn and the dentate gyrus of the hippocampus, basal ganglia and thalamus, particularly after multiple episodes of hypoglycemia. The cerebral cortex, brainstem and cerebellum appear to be more resistant to hypoglycemia [9,13,14]. While the dentate gyrus of the hippocampus is vulnerable to hypoglycemia, it is relatively resistant to hypoxia [2]. Laminar necrosis involving layers 2 and 3 of the cerebral cortex in human infants [15] and similar lesions in insulin-induced hypoglycemia in monkeys [16], with relative sparing of the cerebellar cortex and brainstem, were described in early neuropathologic studies. Brainstem neurons are remarkably resistant to irreversible injury by hypoglycemia. In global ischemia, by contrast, watershed zone infarcts often occur in the tegmentum of the midbrain, pons and medulla [17]. Selective degeneration of the pontine nuclei as pontosubicular degeneration is a characteristic and common lesion in premature infants who have suffered HIE but does not result from neonatal HE [14]. Neonatal rats rendered hypoglycemic for 18 days postnatally exhibited reduced brain weight, decreased myelin lipids and proteins, and cellular loss throughout the brain [18]. Mitochondrial swelling and degradation were shown to occur in neurons, including dendrites [9].

The predilection for the occipital lobes in HGE may be related to intensive axonal extension and synaptogenesis, which occur in the occipital lobes during the neonatal period, and are sensitive to glucose availability [19]. Of note, layer 4 of the primary visual cortex is larger, with more neurons and synapses than any other region in the cerebral cortex, and is therefore more susceptible to laminar necrosis [20]. A comparison of the neuropathologic lesions of hypoxia-ischemia and hypoglycemia is summarized in Table 2.

Based on published data [21,22], it is safe to conclude that human neonates who sustain profound hypoglycemia for hours may be at significant risk for an adverse neurologic outcome. Two studies delineated specifically the duration and the glucose levels that may cause brain insult. Seven newborns developed seizures when their plasma glucose levels were in the range of 2–11 mg/dl for a period of 12 hours or longer [21]. Two near-term infants had permanent abnormal brain imaging studies, after having PGLs as low as 2 and 4 mg/dl, and had a total length of hypoglycemia of 4 and 10 hours respectively [22]. According to one study [23], recurrent episodes of hypoglycemia are a more predictable risk factor for long-term sequelae than a single episode. A population meta-analysis of hypoglycemic infants showed that in more than

PGL = plasma glucose level

Table 2. Comparison between hypoglycemia and hypoxia-ischemia brain insult

Parameter	Hypoxia-ischemia	Hypoglycemia
Cause	Reduced oxygen availability	Reduced glucose availability
Serum lactic acid	Increased	Normal
Cerebral cortex	Infarction in watershed zones	Selective neuronal necrosis
Cerebral cortex	Layers	Middle laminae
layers 3, 5, 6	Superficial laminae	layers 2,3,4
Hippocampus	CA1, CA3	CA1, dentate gyrus
Cerebellum	Purkinje neurons	Absent
Brainstem	Tegmental watershed zone	Absent
Imaging studies	Non-specific	Occipital lobe
(occasionally parietal lobe)	EEG	Non-specific
Non-specific, or occipital lobe epilepsy		

CA = *cornu ammonis* (Latin), CA1 CA4 are parts of the hippocampus.

95% of newborn infants with hypoglycemia-associated severe neurologic sequelae, plasma glucose concentrations of <25 mg/dl were first detected at least 10 hours after birth. The incidence of severe neurologic injury in these infants is 28% with 95% confidence interval of 18 37% [Submitted].

Symptomatology

The neurologic symptoms of neonatal hypoglycemia are non-specific. Neurologic symptoms may appear gradually, with irritability, tremor, jitteriness, eye rolling, seizures, hypotonia, exaggerated Moro reflex, and progression to seizures and acute encephalopathy, lethargy and coma. The most common clinical finding reported by some authors is an altered level of alertness, characterized as a combination of jitteriness and stupor [24]. Seizures may start very early after onset of hypoglycemia, but usually appear after 12 hours of continuous or recurrent significant hypoglycemia. The presence of seizures correlates with severity of hypoglycemia. Occasionally, seizures have been described as focal jerking of the arms and legs, tonic or tonic-clonic. At follow-up, many of these patients persist with epilepsy of different types, including infantile spasms and partial seizures [24]. Although there is no pathognomonic symptomatology for neonatal hypoglycemia, the clinical findings that are depicted in Table 3 have been attributed to hypoglycemia, based mainly on resolution of hypoglycemia symptoms after treatment [25,26].

Jitteriness is not a very useful confirmatory sign for hypoglycemia since it occurs frequently in newborn infants. In fact it was reported in as many as 44% of 936 healthy full-term infants [27]. Tremor (tremor and jitteriness are terms that are often used interchangeably) is also a frequent neonatal sign. In the majority of healthy neonates (84 of 102) the tremor disappeared when consoled by suckling stimulation. Only those infants in whom the tremor continued during suckling stimulation had either hypoglycemia or hypocalcemia [28]. Jitteriness is not always physiologic however, and may indicate release of monosynaptic spinal cord stretch reflexes from corticospinal tract inhibition in term neonates, due to impaired function of the large inhibitory motor pyramid cells of layer 5 and 6 of the cerebral cortex [29].

Neurologic sequelae

At follow-up, neonatal hypoglycemia may lead to reduced head circumference, lower than expected psychomotor scores, motor deficit, and mental retardation [Submitted]. Neonates with recurrent episodes of hypoglycemia have lower scores in psychomotor development at follow-up than neonates with a single episode [23]. In a prospective controlled study, 39 treated hypoglycemic infants (PGL <25 mg/dl, mean ± SD weight 1,633 ± 578 g, gestational age 34.8 ± 4.7 weeks) and 41 matched controls were assessed for 5–7 years in terms of physical, neurologic, intellectual, developmental, and electroencephalographic findings. A larger number of hypoglycemic infants ($P < 0.05$) had IQ scores of <86 and significantly smaller mean head circumference as compared to the control infants [30]. In a multicenter study, in newborn infants (mean ± SD weight 1,337 ± 315 g, gestational age 30.5 ± 2.7 weeks) with moderate hypoglycemia (PGL <45 mg/dl), an abnormal neurodevelopmental outcome and increased incidence of cerebral palsy was found at the age of 18 months postnatally, as compared to matched euglycemic infants [31]. At age 8 years however, the incidence of cerebral palsy was not different between the two groups (authors' comment). The relative risk of neurodevelopmental impairment in newborns who were subjected to hypoglycemia during 5 or more days, compared with newborns without hypoglycemia, was 3 5:1 [32].

Table 3. Clinical manifestations of neonatal hypoglycemia*

Central nervous system response	Autonomic nervous system response
Apnea, tachypnea	Diaphoresis
Cyanosis**, dusky spells	Other rare autonomic responses such as:
Eye rolling, seizures	Instability of blood pressure
Jitteriness, tremor, irritability	Episodes of bradycardia
Lethargy	Increased bronchotracheal secretions
Tachycardia	Gastrointestinal paralysis
Poor feeding	Low temperature

* Modified from ref. 1.

** Cyanosis may be due to apnea, autonomic nervous system stimulation, or decreased pulmonary blood flow

Seizures are usually the first presenting symptom of profound hypoglycemia (PGL ⩽25 mg/dl) [Submitted]. Seizures that are associated with hypoglycemia have a worse prognosis than hypoglycemia without seizures [33]. Visual impairment due to profound neonatal hypoglycemia is associated with injury of the occipital lobes [Submitted].

Electroencephalogram

Changes in the EEG pattern in hypoglycemic infants reflect changes in the functional state of synaptic activity and, as with HIE, may have no distinctive features to be diagnostic. A recent study described 15 children (mean age 12 years) who developed severe neurologic sequelae after neonatal hypoglycemia. Thirteen had brain lesions in the occipito-parietal area, and 11 had occipital lobe epilepsy [34]. In another study of 20 newborns with symptomatic hypoglycemia, the EEG showed increased density of frontal sharp transient waves in all sleep stages when compared with controls. This increase was even higher in small for gestational age newborns [35].

Auditory evoked potentials

In five neonates studied with brainstem auditory evoked response and somatosensory evoked potentials during episodes of hypoglycemia, significant abnormalities (prolongation of latencies) were recorded [36]. Half of these patients were clinically asymptomatic. The abnormal findings returned to normal after the administration of glucose. However, a more recent and larger study [37] could not confirm and reproduce the results of the previous study. In the future, it remains to be seen if profound hypoglycemia is associated with hearing impairment.

Neuroimaging

Brain imaging studies in the acute phase demonstrate generalized edema and bilateral patchy hyperechogenic areas. Follow-up brain

Table 4. Neuroimaging, neurologic sequelae and hypoglycemia findings in newborns with persistent abnormal brain imaging studies [31]

	No. of patients (%)
Neuroimaging findings	17 (100%)
Occipital lobe involvement	14/17 (82%)
Dilatation of brain lateral ventricles	7/17 (41%)
Parietal lobe involvement	5/17 (29%)
Other brain parts involvement	2/17 (12%)
Neurologic sequelae	
Seizures as presenting symptom	12/17 (70%)
Motor and/or psychodevelopmental delay	11/17 (65%)
Visual impairment	7/17 (41%)
Microcephaly	6/17 (35%)
Hypoglycemia findings	
PGL (mg/dl) when hypoglycemia was first detected	
Median	7 mg/dl
Range	2–26 mg/dl
Postnatal time (hrs) when hypoglycemia was first detected	
Median	48 hrs
Range	1–72 hrs

CT and MRI scans showed parenchymal hypodensities, predominantly in the occipital lobes [19]. A review of 23 neonates with abnormal brain imaging studies due to profound hypoglycemia showed that the median and range of age at clinical presentation when hypoglycemia was first detected occurred at 30 hours and 1–72 hours respectively [Submitted]. The median and range of plasma glucose levels at that time was 14 mg/dl and 1–43 mg/dl respectively. Of the 23 patients, 6 (26%) showed only transient brain changes in imaging studies and normal follow-up studies, while 17 (74%) showed persistent brain insult in imaging studies. The cases with persistent abnormal imaging brain findings had a much higher likelihood for adverse neurologic outcome, as compared to the cases with transient findings ($P < 0.05$, Fisher's exact test). The imaging findings in these infants and their neurologic outcome are depicted in Table 4.

Advanced imaging technology [38,39], such as diffusion-weighted imaging and apparent diffusion coefficient mapping (for detecting early brain injury), diffusion tensor imaging (for detecting abnormal myelinization in small injuries of white matter), and magnetic resonance spectroscopy (for detecting lactate, creatine and other metabolites), may help in the future to delineate hypoglycemia injury earlier and with better accuracy and specificity. Based upon the present understanding of cellular pathogenetic events of hypoglycemia, future phosphate MRS studies will probably be able to delineate simultaneous alterations in adenosine triphosphate-high energy phosphorous vs. lactate concentrations. Hypoxic ischemic encephalopathy would be expected to reduce ATP-high energy phosphorous and elevate lactate, whereas HGE would be expected to demonstrate reduced ATP-high energy phosphorous without lactate elevation. Hence, an ATP-high energy phosphorous/lactate ratio may be useful in categorizing acute or subacute hypoglycemia brain injury and correlating with late sequelae.

MRS = magnetic resonance spectroscopy
ATP = adenosine triphosphate

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