Review Article

Research advances in neonatal hypoglycemic brain injury

Jun Su, Li Wang

Department of Pediatrics, the First Affiliated Hospital of Xinjiang Medical University, Urumqi 830054, China

Correspondence to: Jun Su. Department of Pediatrics, the First Affiliated Hospital of Xinjiang Medical University, Urumqi 830054, China. Email: sujunn2hny@163.com or lwang5266@yahoo.com.cn.

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Neonatal hypoglycemia is a common complication among preterm infants, small-for-gestational-age infants, and infants of diabetic mothers. Currently, these has been in-depth understanding of diagnosis and clinical intervention of neonatal hypoglycemia, but the glycemic threshold and time threshold values of neonatal hypoglycemic brain injury (NHBI) remain undefined. Persistent or recurrent hypoglycemia can result in neonatal permanent brain injury, leaving cognitive impairment, vision disturbance, occipital lobe epilepsy, cerebral palsy and other sequelae. NHBI has not yet been well understood by some clinicians, no diagnostic criteria have been available for NHBI due to the lack of specific clinical manifestations, although brain imaging studies are now an important diagnostic and prognostic tool, so it is also of necessity to establish criteria for its diagnosis (1).

This article provides a general review in hypoglycemic injury to the newborn brain, describes the pathological changes, pathophysiology and pathogenesis of NHBI, and reviews the clinical aspects of it. In addition, it involves issues related to diagnostic criteria and threshold values of NHBI, the relevance of "asymptomatic" versus "symptomatic" hypoglycemia, prevention and intervention.

History of research on hypoglycemia and an overview of NHBI

Neonatal hypoglycemia is a common clinical metabolic problem, which was reported over 100 years ago. In the 1920s, low blood glucose level in full-term infants or preterm infants were thought to be physiological. Significant neonatal hypoglycemia was first reported in 1937 (2). In 1959, Cornblath *et al.* reported 8 cases of "symptomatic neonatal hypoglycemia" (3). With the development of science and technology, neonatal hypoglycemia has been widely studied. Data have shown that if the neonatal hypoglycemia is not timely and properly treated, the infants may develop permanent brain injury, namely, neonatal hypoglycemic encephalopathy (4). In October 1989, the American Academy of Pediatrics discussed about the definition of hypoglycemia in newborns, especially in normal infants and low-birth-weight infants. In July 2004, after reviewing literature from CINAHL, MEDLINE and OVID databases, a *Guidelines for Management of Neonatal Hypoglycemia* (5) was developed by the Newborn Nursery QI Committee of Barbara Bush Children's Hospital at Maine Medical Center in the United States and revised on November 2007. Recently, in their Meta analysis of 18 clinical trials on the neurodevelopmental impact related to hypoglycemia, Boluyt *et al.* (6) found that by far no clinical research of high quality on the exact relationship between neonatal blood glucose levels and neurological outcome had presented convincing evidence. As medical technology and examination tools continue to develop, the definition of neonatal hypoglycemia is in continuous improvement. In the 1930s, clinical definition based on neonatal symptoms was adopted; during the 1960s-1980s, epidemiological definition based on the normal value of population was used. In fact, the rational definition of hypoglycemia has no specific values, but a threshold for abnormality of nerve function due to continuous decline of the blood glucose level, which varies greatly regarding hypoglycemia or its clinical situation. In recent years, as a result of EEG, endocrine and cerebral blood flow changes caused by hypoglycemia, physiological definition has started to be used and an intervention threshold of hypoglycemia has been put forward to guide clinical diagnosis and treatment of neonatal hypoglycemia (7). However, subsequent studies have shown that no definition of blood glucose was satisfactory and

the clinical symptoms were non-specific. The results of epidemiological survey simply recognize the threshold between normal blood glucose and hypoglycemia without enough attention to biological anomalies (from mild to severe) resulting from hypoglycemia; functional researches on the nervous system still lack adequate relevant research data. No prospective, randomized, controlled trial (RCT) has confirmed the long-term sequelae of hypoglycemia (8). So far, China has not yet developed criteria for routine diagnosis and treatment of neonatal hypoglycemia. Previous clinical definition or epidemiological definition has been using for diagnosis of neonatal hypoglycemia (9), which has comparatively low diagnostic threshold values.

The neonatal brain develops rapidly. Persistent or recurrent hypoglycemia may lead to long-term visual disturbance, hearing impairment, cognitive abnormalities, secondary epilepsy, and other disorders in the central nervous system. The severities of such injuries can exceeds hypoxic-ischemic injury (10). NHBI depends on the severity and duration of hypoglycemia and on the existence of other comorbidities (11). Yang *et al.* (12) and Chen *et al.* (13) have reported that hypoglycemia before hypoxia-ischemia (HI) can further exacerbate hypoxic-ischemic damage in neonatal rats, while hyperglycemia before HI can significantly reduce the injury. Currently, it is believed that the glucose treatment threshold can be within the range of 2.2 and 2.6 mmol/L. Although the hypoglycemia treatment threshold range related to pediatric and adult insulin treatment is 3.3-3.8 mmol/L, large-scale prospective RCTs are still needed to address problems in neonates such as which blood glucose range can avoid future nervous system injury and whether the blood glucose level of 2.2-3.3 mmol/L may lead to brain injury and other problems (14,15).

Diagnostic criteria for NHBI

No uniform criteria for the diagnosis of NHBI has been available. Chen *et al.* (16) have proposed a method for evaluating brain maturity based on ultrasound technology. Sun *et al.* (17) reported that gestational diabetes may result in offspring brain maturation disorders, and cranial ultrasound can be applied to evaluate the results of neonatal gyrus width measurement. Liang *et al.* (18) observed that glucose metabolic disorders during pregnancy could cause a variety of neonatal diseases, brain immaturity, and brain injury. Mao Jian *et al.* (19) have presented the diagnostic bases of NHBI: (I) obvious hypoglycemia-related clinical manifestations or history of severe hypoglycemia (0-1.7 mmol/L) at admission; (II) whole blood glucose ≤2.0 mmol/L; (III) manifestations of nervous system dysfunction during hypoglycemia and for a period of time after the correction of blood glucose; (IV) obvious brain injury changes under magnetic resonance imaging (MRI); and (V) brain injuries caused by severe intracranial hemorrhage, intracranial infection, abnormal brain development, sepsis, congenital metabolic disorders and endocrine diseases are ruled out. Boluyt *et al.* (6) analyzed 18 studies on neurodevelopment following hypoglycemia and found that all but two studies had poor methodologies and no study could provide reliable evaluation on the effect of neonatal hypoglycemia on neurodevelopment. The diagnostic criteria proposed by Wang *et al.* (20) were as follows: (I) meet the diagnostic criteria of neonatal hypoglycemia; (II) other diseases (e.g., hypoxic-ischemic encephalopathy and infectious diseases) that may cause brain injury are ruled out; (III) clinical manifestations of symptomatic hypoglycemia such as paroxysmal cyanosis, tremors, convulsions, apnea, giant breast, and decreased responsiveness are observed; and (IV) brain injury is confirmed under imaging examinations. Therefore, the uniform criteria for diagnosis of NHBI still need further investigation.

Threshold values of NHBI

No experiment has confirmed the exact extent and duration of hypoglycemia that can cause brain injury. Animal experimental studies have suggested that when blood glucose declines from 1.36 to 0.12 mmol/L, EEG becomes smooth, predicting the start of necrotic brain injury (21). Koh *et al.* (22) have found that when the blood glucose level of full-term infants falls below 2.6 mmol/L, it resulted in reversible injury to the nervous system. Lucas *et al.* (23) have reported that when the blood glucose level of preterm infants falls below 2.5 mmol/L, it was closely related to the occurrence of adverse neurological outcome. After close monitoring of neonates and by combining the blood glucose levels with neurology, metabolism and physiology, Cornblath *et al.* (24) defined the neonatal hypoglycemia as: without considering birth weight and gestational age, blood glucose below 2.2 mmol/L within postnatal 24 h and below 2.2-2.8 mmol/L after 24 h; meanwhile, they argued that the concenpt of the "operational threshold" can be applied to guide the clinical diagnosis and treatment of neonatal hypoglycemia. In their multi-center study, Lucas *et al.* (23) followed 661 preterm infants till 18 months of age and found that the blood glucose <2.6 mmol/L could be used as an threshold value for intervention. Alkalay *et al.* (25)

conducted a meta analysis on 723 cases of healthy full-term neonates and found that the threshold values for hypoglycemia was 1.5 mmol/L within postnatal 1-2 h, 2.2 mmol/L within postnatal 3-47 h, and 2.5 mmol/L within postnatal 48-72 h. Filan *et al.* (26) reported that the minimum blood glucose values in 4 hypoglycemic neonates with occipital brain injury were 0.7-1.5 mmol/L. Analysis on 89 neonates with symptomatic hypoglycemia suggests that 21% of infants with plasma glucose below 1.40 mmol/L developed nervous system injury (95% confidence interval: 14%-27%) (27). Mao *et al.* (19) reported that the minimum blood glucose concentration during first detection was 0.98 mmol/L (≤1.70) on average. After reviewing the blood glucose value, imaging changes, and prognosis of 23 neonates with hypoglycemia, Alkalay *et al.* (28) found that the severity of nervous system injury not only related to the severity of hypoglycemia but also to the duration of hypoglycemia. Compared with blood glucose reduction, the duration of hypoglycemia has a larger effect on brain injury. Till now, when hypoglycemic symptoms or NHBI occurs, the blood glucose threshold remains unclear. However, if hypoglycemia occurs accompanied by hypoxia or ischemia when the brain needs more glucose, the threshold needs to be increased accordingly (29). Thus, it is important to develop a well-recognized clinical intervention value to reduce the occurrence of NHBI.

Pathological changes of NHBI

Energy metabolic disorders during hypoglycemia may lead to brain cell softening, swelling, necrosis, gyrus atrophy or white matter demyelination (30). Su *et al.* (31) have found that hypoglycemia and hypoxemia can induce similar changes in brain function but different intracerebral pathological changes. Hypoxic injury occurs more often in the watershed area, dominated by white matter injury in pre-term infants and gray matter in full-term infants; it can affect both gray matter and white matter during severe injury, which is often accompanied by varying degrees of cerebral hemorrhage. However, the distribution of pathological changes of NHBI does not match with that of brain blood vessels, when bilateral posterior parietooccipital brain tissue involvement is characteristic; usually the injury will not accompanied by cerebral hemorrhage, and the cerebellum and brainstem often will not be involved. Burns *et al.* (32) found that NHBI could be diversified in either form or location. Pathological reports have already confirmed the imaging features of brain injury. The most consistent performance of severe hypoglycemia is acute phase occipitoposterior cortex edema and chronic phase atrophy. However, these findings were mostly based on long-term severe NHBI and few imaging evidences have been available for short-term mild NHBI. NHBI can also be manifested as hemorrhage or middle cerebral artery infarction; parietooccipital cortex injury is most common, although the basal ganglia and thalamus can also be involved. Takeuchi *et al.* (33) found that the capsula interna, splenium of corpus callosum and corona radiata could also be involved during brain injury associated with hypoglycemia. Of 12 cases with hypoglycemia-related brain injury, abnormal MRI findings were observed at the splenium of corpus callosum (n=4), corona radiata (n=2), or crus posterius capsulae internae (n=1). After timely treatment, one case showed no abnormal signal during re-examination of the splenium of corpus callosum, suggesting that such injury be reversible (33-35). Brain injury related to neonatal hypoglycemia seldom involves deep gray matter nuclei (27). In that study (27), one patient only showed abnormal hyperintense diffusion-weighted imaging (DWI) signals at bilateral corona radiata, periventricular white matter, left caudate nucleus and globus pallidus, splenium of corpus callosum, and bilateral dorsal thalamus. The minimum value of blood glucose (1.6 mmol/L) in this infant was slightly lower than the upper limit (1.7 mmol/L) of the diagnostic criteria of hypoglycemia; it is therefore speculated that brain tissue injury of this infant might be jointly caused by hypoglycemia and, particularly, underlying hypoxia. White matter injury (diffuse cortical involvement) can be seen in severe adult NHBI (36,37), but rarely reported among neonates. Takeuchi has reported that among 12 cases, 6 had diffuse cortical injury combined with widespread involvement of the basal ganglia, thalamus, and white matter, which is clinically manifested as hypoxia-ischemia (33). It is also speculated that the diffuse white matter involvement may be characteristic for hypoxia-ischemia, whereas cortical injury is mainly associated with hypoglycemia.

Pathophysiology and pathogenesis of NHBI

The affected area of NHBI is mainly the cerebral cortex (nerve cells). Adult brain injury sites contain many N-methyl-D-aspartate (NMDA) receptors, inferring neonatal NHBI may be associated with anatomic distribution of specific excitatory amino acid receptors; Alfonso *et al.* (38) has proposed that vulnerability of the occipital lobe might be related to abnormal anatomy of the Willis ring. Cerebral blood flow increases during hypoglycemia; opposite to the

other parts, however, glucose utilization in the occipital lobe and cerebellum decreases, resulting in the vulnerability of these areas. Nevertheless, no literature up to now has reported hypoglycemia-induced cerebellar injury, suggesting that this view may be one-sided. Another hypothesis believes that too fast occipital axonal growth and synaptogenesis in the neonatal period require more blood glucose. Meanwhile, the occipital lobe receives blood supply from the posterior cerebral artery, which also supplies the brainstem, cerebellum, and part of the thalamus where metabolism is active. Compared to other cortices, the fourth lamina of visual cortex is thicker and has more neurons and synapses, thus requiring significantly more blood glucose and also is most susceptible to laminar necrosis (39). Although the pathogenesis of NHBI remains unclear, it is believed to be related to the following factors (40-43): (I) Excitatory amino acids increase the activation of NMDA receptors, causing the cellular ion channels to open and thus inducing cytotoxic edema. Hypoglycemia can not maintain brain glucose supply; in fact, it decrease brain electrical activity, induce free fatty acid and amino acid metabolism disorders, and thus increase the level of excitability neurotransmitter glutamic acid in the central nervous system. After binding to postsynaptic receptors, glutamic acid triggers the release of second messengers and alters cell membrane ion exchange through glutamate receptors of isomers. Some ionotropic receptors such as NMDA-type glutamate receptors are related with potassium, sodium, or calcium channels. The activity of normal levels of NMDA receptors plays a decisive role in brain tissue development. Excessive activation of NMDA receptors induces the excessive increase of the intracellular sodium and calcium ion concentrations; when they exceed the range that can be regulated by neuronal homeostasis, the transmembrane ion gradient changes. (II) Metabolism disorders and oxygen free radical injury may also be important causes of cellular edema. When hypoglycemia occurs, the lacking of ATP, creatine phosphate, and other energy matters deactivates the normal transmembrane concentration gradient recovery mechanism of energy-dependent sodium and calcium ions. Excessive calcium influx activates cell phosphatidase and protease, alters mitochondrial metabolism, triggers the formation of free radicals, changes the mode of synaptic transmission, and finally results in the necrosis of neurons. Special changes of mitochondrial function play an important role in NHBI in the early period. Tricarboxylic acid cycle reduces enzyme substrate flow, resulting in reduced mitochondrial molecular oxygen and increased oxygen free radicals and thus causing mitochondrial membrane and mitochondrial DNA injury. Mitochondrial DNA fragmentation interferes with the synthesis of the electron transport chain enzyme. The capability for cells to recovering the ATP level is therefore impaired and the local high-energy phosphate depletion can also alter calcium ion levels in and outside the mitochondrial membrane and induce apoptosis, thus directly leading to neuronal necrosis. And (III) Hypoglycemia can also aggravate brain injury under neonatal cerebral anoxia. High-energy phosphate depletion occurs during cerebral anoxia and the extracellular glutamic acid concentration increases; as a result, glutamic acid receptors are activated and intracellular sodium and calcium ion concentrations are increased. In addition, anoxic anaerobic glycolysis can also accelerate intracerebral glucose consumption. Hypoglycemia and cerebral anoxia synergistically accentuate neuronal injury. Hypoglycemia can also inhibit cerebral vasodilatation during hypoxia, which damages the compensatory mechanism via which the brain oxygen supply might have been improved during cerebral anoxia. Obviously, it is critically important to maintain normal blood glucose during neonatal respiratory distress or cerebral anoxia. Under physiological conditions, the maintenance of normal brain function highly depends on the ATP produced via the continuous supply of glucose; therefore, the transport of glucose into the brain becomes a key step for maintaining cerebral metabolism, which requires the regulation of glucose transporter (GLUT). GLUT gene over-expression has been observed in transgenetic rats with brain hypoxia-ischemia, and such overexpression has shown protective effect on the brain following hypoxic-ischemic injury, suggesting the utilization of glucose increases after hypoxia-ischemia (44). Another study also found that hypoglycemia before hypoxia-ischemia in neonatal rats down-regulated GLUT gene expression and synthesis and aggravated brain injury, while hyperglycemia prior to hypoxia-ischemia up-regulated GLUT gene expression and synthesis and improved brain injury (45). Therefore, it is important to maintain normal blood glucose during cerebral anoxia.

Clinical manifestations and risk factors of NHBI

Neonatal NHBI is asymptomatic or has nonspecific symptoms such as fatigue, becoming less active, feeding problems, being irritable, or even developing convulsions. These manifestations can also be explained by other pathological conditions such as birth asphyxia or severe infection. Disorders in ketogenesis in neonates with high

risks of hypoglycemia are liable to develop brain injury. Risk factors of NHBI include (40): (I) gestational age ≤36 weeks; birth weight less than small-for-gestational-age infants in the third percentile; (II) infants born to diabetic mothers and infants with Beckwith-Wiedemann syndrome or Rh hemolytic disease; (III) islet cell dysregulation syndrome, insulinoma; (IV) perinatal asphyxia; (V) impact of mothers' drugs, such as β-blockers; (VI) septicemia; and (VII) congenital metabolic disorders, lacking of enzymes for glycogenolysis, gluconeogenesis, and fatty acid β oxidation.

Imaging manifestations of neonatal NHBI

No diagnostic criteria have been available for NHBI due to the lack of specific clinical manifestations. Early detection of the imaging evidence for NHBI is important for the early judgment of the disease and assessment of prognosis.

Cranial ultrasound provides an accurate, rapid, convenient, X-ray-free, repeatable, and affordable tool for the diagnosis of NHBI. However, its specificity is lower than MRI; it is especially difficult to find parietoccipital brain injury. The diagnostic specificity of CT is low for NHBI; it is difficult to accurately reflect the pathological changes of nerve and will result in neonatal exposure to radiation.

MRI is currently a more sensitive and specific screening method for diagnosing NHBI, which is superior to ultrasound and CT and can be used for early diagnosis (46) and follow-up (41). Currently, there are more advanced imaging techniques that can be used for diagnosis of NHBI. For example, DWI and apparent diffusion coefficient (ADC) images can both detect early brain injury; magnetic resonance diffusion tensor imaging (DTI) can detect abnormal myelination during mild brain white matter injury; and magnetic resonance spectroscopy (MRS) can be used for detection of other metabolites including lactic acid and kreatine.

DWI is sensitive for detecting intracellular water movement and the changes following tissue injury, which can display abnormalities within 24 h after hypoxic-ischemic encephalopathy; on the contrary, the conventional MRI needs 5-6 d to distinguish this. Kim *et al.* (42) have reported two cases respectively receiving MRI examination 3 and 7 days after the detection of hypoglycemia, where DWI show marked parietooccipital hyperintense signals, which were not clearly shown on the T1WI and T2WI of conventional MRI. Tam *et al.* (47) conducted a retrospective study on hypoglycemic newborns. The time interval from the beginning of DWI examination to the initial episode of hypoglycemia was greater than 6 d in 20 cases. Although hypoglycemia continued to progress in these patients, abnormal signal still could not be detected in the occipital lobe. Another 25 cases received MRI within 6 d after the episode of hypoglycemia, among whom 8 of the 16 full-term infants showed abnormal DWI changes, while 9 preterm infants showed no abnormal signal changes. Twenty cases received examination of visual evoked potential within 1 week after the initial episode of hypoglycemia, among whom 11 showed abnormal changes; abnormal changes in DWI were correlated with abnormal performance of visual evoked potential. Follow-up of 18 cases suggested that children with occipital abnormal DWI changes were more liable to develop cortical visual defects. In 2007, Yalnizogu *et al.* (48) reported the DWI results of 13 cases with NHBI, showing that the forms of brain injury were manifested by parietooccipital involvement, 3 unilateral and 10 bilateral. In 2008, Burns (33) reported the early DWI results of 35 cases with NHBI, indicating that 33 cases had abnormalities, among whom 10 developed transient cerebral edema and 28 had bleeding from the basal ganglia (n=14), white matter (n=10), and crus posterius capsulae internae (n=4). These results suggest that DWI plays an important role in early diagnosis and prognosis of neonatal NHBI. In recent years, ADC determination has also been applied in studies on neonatal NHBI. According to Tam *et al.* (47), ADC values were significantly decreased in patients with visual defects.

MRS is of great importance for the early detection of neuronal functions. Kim *et al.* (42) reported two infants with NHBI. They found that, expect for parietooccipital acute phase DWI (hyperintense) and chronic phase routine MRI (atrophy) anomalies, pathological changes in early MRS were manifested as increased lactic acid and fatty acid peaks and declined acetyl aspartic acid peak. DWI and MRS results can also be useful for the early assessment of the scope and state of nerve damage during neonatal NHBI. Based on current research on the cytological pathogenesis of hypoglycemic injury, phosphate MRS detection can also distinguish the changes of concentrations between ATP phosphate and lactic acid. ATP decreases and lactic acid increases during HIE, while ATP decreases but lactic acid does not increase during NHBI. Therefore, the ATP/lactic acid ratio can be useful for the differentiation between acute and (or) subacute hypoglycemia and the evaluation of hypoglycemia sequelae (43).

EEG changes of NHBI

The brain electrophysiology of hypoglycemia in neonates

has been rarely reported. It remains unclear whether hypoglycemia may induce specific brain electrophysiological changes. Early animal experiments (21) have found that hypoglycemia can induce slower brain electrical activity or equipotential/burst suppression. Recent studies have found early hypoglycemia can be manifested as increased density of frontal sharp transient (FST), delayed FST peak, or background electrical activity (49). Other studies have also found that, along with the decrease in blood glucose levels, brainwave frequency gradually slows down and its amplitude slowly declines, accompanied with clinical manifestation including anxiety and/or lethargy. When blood glucose falls below 1.36 mmol/L, the equipotential changes occur in electroencephalogram, indicating the occurrence of neuronal necrosis (50). In recent years, some authors have proposed that there can be no early EEG abnormalities in patients with asymptomatic hypoglycemia; however, if followed up to the school age, lower δ electric power and higher α electric power may occur in the frontotemporal and frontoparietal lobes, and its EEG changes are consistent with attention deficit hyperactivity disorder (ADHD) and attention deficit disorder (ADD). Other authors believe that EEG slow wave can be considered to be a subclinical manifestation of hypoglycemia. EEG amplitude and waveform changes can still reflect hypoglycemia and the severity of nervous system injury (50).

Nervous system outcomes of NHBI and its follow-up

The prognosis of NHBI depends on the duration, severity, cerebral blood flow velocity, and cerebral glucose utilization ratio. Prompt diagnosis and treatment can warrant generally good prognosis (21). Sequelae mainly include visual disturbance, hearing impairment, cognitive abnormalities, and occipital lobe epilepsy. Follow-up has revealed that hypoglycemia did not induce psychomotor retardation in full-term healthy large-for-gestational-age infants at 4 years old (51). However, relevantly few clinical follow-up studies have been published. For these infants, neurodevelopmental conditions, intelligence quotient, reading ability, computing capability, exercise capacity, and others should be followed up. They should receive visual assessment at the adjustment age of 1 month and their growth, neurodevelopment, and visual and audiovisual conditions followed up at the adjustment age of 3, 6, 9, 12 and 18 months. Neurodevelopment can be evaluated by clinical psychiatrists using the WHO Disability Assessment Scale. Visual and auditory conditions can be respectively assessed through visual and auditory evoked potential.

Prevention and intervention of neonatal NHBI

Neonatal hypoglycemia may cause irreversible neurological sequelae (52). Persistent and recurrent hypoglycemia can severely impair brain growth and its function (53,54). Most cases of neonatal hypoglycemia can be asymptomatic or only have nonspecific clinical symptoms. Blood glucose testing conducted within postnatal 72 h is useful for the prevention and treatment of NHBI (55).

Early feeding is crucial for the prevention of NHBI; in other words, feeding should be initiated early to prevent NHBI (56). Changes in blood glucose should be closely monitored during hypoglycemia correction. Excessive correction of hypoglycemia may result in extensive fluctuations of blood glucose and even develop into hyperglycemia, which can also lead to brain injury (57).

Intervention of NHBI should be individualized, and parents should be guided to carry out proper training for their babies according to major neonatal functional disorders (58). When the situation of the disease becomes stable, neonates should be provided with hydrotherapy and composite finger-pressure therapy to improve blood circulation and promote the rehabilitation of the injured brain (59). The neonatal nervous system has strong plasticity. Early functional training can promote the functional reorganization of the central nervous system, promote the recovery and regeneration of injured brain cells, and alleviate the sequelae of neonatal brain injury (60). Studies have also shown that family intervention, in combination with Internet-based experience sharing, can facilitate the recovery of infants and meanwhile lessen the economic burden and mental stress of the family members (61).

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Footnote

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References

1. Rozance PJ, Hay WW. Hypoglycemia in newborn infants:

Features associated with adverse outcomes. Biol Neonate 2006;90:74-86.
2. Cornblath M. Neonatal hypoglycemia 30 years later: does it injure the brain? Historical summary and present challenges. Acta Paediatr Jpn 1997;39:S7-11.
3. Cornblath M, Odell GB, Levin EY. Symptomatic neonatal hypoglycemia associated with toxemia of pregnancy. J Pediatr 1959;55:545-62.
4. Lou LF, Zhang J. Current Status of Diagnosis and Treatment in Hypoglycemic Encephalopathy. Yi Xue Zong Shu 2010;16:2008-10.
5. Newborn Nursery QI Committee. Neonatal hypoglycemia: initial and follow up management [DB/O]. [March 2010]. Available online: https://kr.ihc.com/ext/Dcmnt?ncid=51072065
6. Boluyt N, van Kempen A, Offringa M. Neurodevelopment after neonatal hypoglycemia: a systematic review and design of an optimal future study. Pediatrics 2006;117:2231-43.
7. Jain A, Aggarwal R, Jeeva Sankar M, et al. Hypoglycemia in the newborn. Indian J Pediatr 2010 ;77:1137-42.
8. Liu ZW, Chen HJ. Guideline for Management of Neonatal Hypoglycemia in United States. Shi Yong Er Ke Lin Chuang Za Zhi 2010;25:618-20.
9. Vannucci RC, Vannucci SJ. Hypoglycemic brain injury. Semin Neonatol. 2001;6:147-55.
10. Yue SJ, Wang MJ, Wang QH, et al. Congenital hyperinsulinism: a difficult and complicated case study. Zhongguo Dang Dai Er Ke Za Zhi 2006;8:391-4.
11. Shalitin S, Phillip M. The use of insulin pump therapy in the pediatric age group. Horm Res 2008;70:14-21.
12. Yang Y, Chen HJ, Qian LH, et al. Effect of glucose levels on the cerebral synthesis of glucose transporter (GLUT) 3 in neonatal rats with hypoxic ischemia. Lin Chuang Er Ke Za Zhi 2004;22:42-5.
13. Chen C, Chen HJ, Qian LH, et al. Influence of Different Blood Glucose Levels on Cerebral Pathology under Light Microscopy in Neonatal Rats with Hypoxic-Ischemic. Shi Yong Er Ke Lin Chuang Za Zhi 2006;21:894-897.
14. Jain A, Aggarwal R, Jeevasanker M, et al. Hypoglycemia in the newborn. Indian J Pediatr 2008;75:63-7.
15. McGowan JE, Price W, Hay WW Jr. Glucose homeostasis [M]//Handbook of Neonatal Intensive Care. 6th ed. St. Louis: Mosby Elsevier, 2006;382-4.
16. Chen XX, Zhou CL, Wang HM, et al. Study of the brain development in infants of diabetic mother. Zhong Hua Wei Chan Za Zhi 2005;8:300-3.
17. Sun LX, Zhou CL, Wang HM, et al. Effect of maternal diabetes mellitus during pregnancy on brain devel opment of the offspring. Zhong Hua Wei Chan Za Zhi 2004,7:346-8.
18. Liang KW, Zhou CL, Yang HX, et al. Abnormal glucose metabolism during pregnancy on outcomes in newborn. Zhong Gou Er Tong Bao Jian Za Zhi 2007,15:266-7.
19. Mao J, Chen LY, Fu JH, et al. [Clinical evaluation of neonatal hypoglycemic brain injury demonstrated by serial MRIs]. Zhongguo Dang Dai Er Ke Za Zhi 2008;10:115-20.
20. Wang L, Fan GG, Ji X, et al. MRI findings of brain damage due to neonatal hypoglycemia. Zhong Hua Fan She Xue Za Zhi 2009,43:42-3.
21. Auer RN, Olsson Y, Siesjö BK. Hypoglycemic brain injury in the rat. Correlation of density of brain damage with the EEG isoelectric time: a quantitative study. Diabetes 1984;33:1090-8.
22. Koh TH, Aynsley-Green A, Tarbit M, et al. Neural dysfunction during hypoglycaemia. Arch Dis Child 1988;63:1353-8.
23. Lucas A, Morley R, Cole TJ. Adverse neurodevelopmental outcome of moderate neonatal hypoglycaemia. BMJ 1988;297:1304-8.
24. Cornblath M, Hawdon JM, Williams AF, et al. Controversies regarding definition of neonatal hypoglycemia: suggested operational thresholds. Pediatrics 2000;105:1141-5.
25. Alkalay AL, Sarnat HB, Flores-Sarnat L, et al. Population meta-analysis of low plasma glucose thresholds in full-term normal newborns. Am J Perinatol 2006;23:115-9.
26. Filan PM, Inder TE, Cameron FJ, et al. Neonatal hypoglycemia and occipital cerebral injury. J Pediatr 2006;148:552-5.
27. Alkalay AL, Flores-Sarnat L, Sarnat HB, et al. Plasma glucose concentrations in profound neonatal hypoglycemia. Clin Pediatr (Phila) 2006;45:550-8.
28. Alkalay AL, Flores-Sarnat L, Sarnat HB, et al. Brain imaging findings in neonatal hypoglycemia: case report and review of 23 cases. Clin Pediatr (Phila) 2005;44:783-90.
29. Caraballo RH, Sakr D, Mozzi M, et al. Symptomatic occipital lobe epilepsy following neonatal hypoglycemia. Pediatr Neurol 2004;31:24-9.
30. Tam EW, Haeusslein LA, Bonifacio SL, et al. Hypoglycemia is Associated with Increased Risk for Brain Injury and Adverse Neurodevelopmental Outcome in Neonates at Risk for Encephalopathy 2012;161:88-93.
31. Su J, Chang GF. Research progress in hypoglycemic brain injury. Zhong Gou Jing Shen Ji Bing Za Zhi 2007;33:61-2.
32. Burns CM, Rutherford MA, Boardman JP, et al. Patterns of cerebral injury and neurodevelopmental outcomes

after symptomatic neonatal hypoglycemia. Pediatrics 2008;122:65-74.
33. Takeuchi S. [Reversible increased signal intensities in the splenium on diffusion-weighted imaging caused by transient hypoglycemia]. No To Shinkei 2005;57:420-1.
34. Kim JH, Koh SB. Extensive white matter injury in hypoglycemic coma. Neurology 2007;68:1074.
35. Kim JH, Roh JH, Koh SB. Reversible injury of internal capsule and splenium in a patient with transient hypoglycemic hemiparesis. Cerebrovasc Dis 2006;22:282-3.
36. Lo L, Tan AC, Umapathi T, et al. Diffusion-weighted MR imaging in early diagnosis and prognosis of hypoglycemia. AJNR Am J Neuroradiol 2006;27:1222-4.
37. Aoki T, Sato T, Hasegawa K, et al. Reversible hyperintensity lesion on diffusion-weighted MRI in hypoglycemic coma. Neurology 2004;63:392-3.
38. Alfonso I, Rerecich A. Neonatal hypoglycemia and occipital cerebral injury. J Pediatr 2007;151:e1-2.
39. Alkalay AL, Sarnat HB, Flores-Sarnat L, et al. Neurologic aspects of neonatal hypoglycemia. Isr Med Assoc J 2005;7:188-92.
40. Straussman S, Levitsky LL. Neonatal hypoglycemia. Curr Opin Endocrinol Diabetes Obes 2010;17:20-4.
41. Mao J, Chen LY, Fu JH, et al. Clinical evaluation by MRI on the newborn infants with hypoglycemic brain damage. Zhonghua Er Ke Za Zhi 2007;45:518-22.
42. Kim SY, Goo HW, Lim KH, et al. Neonatal hypoglycaemic encephalopathy: diffusion-weighted imaging and proton MR spectroscopy. Pediatr Radiol 2006;36:144-8.
43. McGowan JE, Chen L, Gao D, et al. Increased mitochondrial reactive oxygen species production in newborn brain during hypoglycemia. Neurosci Lett 2006;399:111-4.
44. Lawrence MS, Sun GH, Kunis DM, et al. Overexpression of the glucose transporter gene with a herpes simplex viral vector protects striatal neurons against stroke. J Cereb Blood Flow Metab 1996;16:181-5.
45. Chen C, Chen HJ, Qian LH, et al. [Effect of different blood glucose levels on the expression of cerebral GLUT3 mRNA in neonatal rats with hypoxia-ischemia]. Zhongguo Dang Dai Er Ke Za Zhi 2006;8:395-401.
46. Yanagawa Y, Isoi N, Tokumaru AM, et al. Diffusion-weighted MRI predicts prognosis in severe hypoglycemic encephalopathy. J Clin Neurosci 2006;13:696-9.
47. Tam EW, Widjaja E, Blaser SI, et al. Occipital lobe injury and cortical visual outcomes after neonatal hypoglycemia. Pediatrics 2008;122:507-12.
48. Yalnizoglu D, Haliloglu G, Turanli G, et al. Neurologic outcome in patients with MRI pattern of damage typical for neonatal hypoglycemia. Brain Dev 2007;29:285-92.
49. Nunes ML, Penela MM, da Costa JC. Differences in the dynamics of frontal sharp transients in normal and hypoglycemic newborns. Clin Neurophysiol 2000;111:305-10.
50. Auer RN. Hypoglycemic brain damage. Metab Brain Dis 2004;19:169-75.
51. Brand PL, Molenaar NL, Kaaijk C, et al. Neurodevelopmental outcome of hypoglycaemia in healthy, large for gestational age, term newborns. Arch Dis Child 2005;90:78-81.
52. Hume R, Burchell A, Williams FL, et al. Glucose homeostasis in the newborn. Early Hum Dev 2005;81:95-101.
53. Ding GF. [Hypoglycemic brain injury in premature infants]. Zhonghua Er Ke Za Zhi 2006;44:828-30.
54. Jin F, Qian SY. Research Progress of Pathoglycemia and Brain Injury in Neonates. Shi Yong Er Ke Lin Chuang Za Zhi 2008, 23:1116-8.
55. Sinclair JC, Bottino M, Cowett RM. Interventions for prevention of neonatal hyperglycemia in very low birth weight infants. Cochrane Database Syst Rev 2011;10:CD007615.
56. Hay WW Jr. Strategies for feeding the preterm infant. Neonatology 2008;94:245-54.
57. Cryer PE. Hypoglycemia, functional brain failure, and brain death. J Clin Invest 2007;117:868-70.
58. Yager JY, Armstrong EA, Black AM. Treatment of the term newborn with brain injury: simplicity as the mother of invention. Pediatr Neurol 2009;40:237-43.
59. Li Y, Cheng R, Xu ZZ, et al. Early intervention and the prognosis of the neonates with hypoxic ischemic encephalopathy. Lin Chuang Er Ke Za Zhi 2006,24:188-90.
60. Chen YH, Liu L, Chen MR, et al. Effects of Early Intervention on Growth Associated Protein-43 and Neuron Cells Apoptosis in Brain of Neonatal Rats. Shi Yong Er Ke Lin Chuang Za Zhi 2007,22:1083-4.
61. Wade SL, Wolfe C, Brown TM, et al. Putting the pieces together: preliminary efficacy of a web-based family intervention for children with traumatic brain injury. J Pediatr Psychol 2005;30:437-42.

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