# Long Term Neurological Outcomes of Patients with Neonatal Hypoglycemia

## Neonatal Hipoglisemili Hastaların Uzun Dönem Nörolojik Sonuçları

Ebru ARHAN, MD,[a]
Gülşen KÖSE, MD,[a]
Sevim ÜNAL, MD,[b]
Derya SOY, MD,[c]
Alev GÜVEN, MD,[a]
Eda ÖZAYDIN, MD,[c]
Esin KİBAR, MD,[c]
Meriç TÜZÜN, MD,[d]
Özgür ÖNER, MD[e]

Clinics of
[a]Pediatric Neurology,
[b]Neonatology
[c]Pediatrics
[d]Radiology,
[e]Child Psychiatry,
Ankara Dışkapı Children's Hospital, Ankara

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Yazışma Adresi/*Correspondence:*
Ebru ARHAN, MD
Ankara Dışkapı Children's Hospital
Clinic of Pediatric Neurology, Ankara, TÜRKİYE/TURKEY
petekarhan@yahoo.com.tr

**ABSTRACT Objective:** Symptomatic hypoglycemia in the newborn period is associated with long-term neurodevelopmental impairments. The nature of the hypoglycemic insult and long term neurodevelopmental outcomes and their relationship to brain injury patterns identified on magnetic resonance imaging were poorly defined. **Material and Methods:** Thirty nine patients with symptomatic neonatal hypoglycemia were included in the study. For the assessment of psychomotor development, percentage of developmental age was determined by Denver Developmental Screening test and Wechsler intelligence scale for children. All patients underwent magnetic resonance imaging as part of the follow-up. **Results:** Half of the patients had symptomatic partial epilepsy, six of them were medically intractable. Four children in the sample had language-cognitive delay, 5 children had fine motor development delay, none had gross motor development delay, and one of the children had social skills-self care development delay. There was no relationship between neurologic sequelaes and glucose levels. Ten patients suffered from visual impairment; four of them had optic atrophy, three had cortical blindness, three had alternating exotrophia. Sixteen patients demonstrated occipital lob injury, nine had parieto-occipital and five had parietal gliosis or volume loss. Imaging findings were normal in 5 patients. There was no relationship between magnetic resonance imaging findings and glucose levels. **Conclusion:** Neonatal hypoglycemia seems to play an important role in the development delay, especially on language-cognitive and fine motor development. Epilepsy, mental motor retardation, and visual impairments and are the most commonly reported outcomes associated with neonatal hypoglycemia Prompt recognition and treatment of neonatal hypoglycemia is essential to prevent and minimize future neurological sequelae. The patterns of injury associated with symptomatic neonatal hypoglycemia are more diverse and common than reported previously.

**Key Words:** Infant, newborn; hypoglycemia; magnetic resonance imaging

**ÖZET Amaç:** Neonatal semptomatik hipoglisemisi uzun dönem nörolojik gelişimsel bozukluklarla ilişkilidir. Hipoglisemik olayın niteliği, uzun dönem nörogelişimsel sonuçlar ve manyetik rezonans görüntülemede beyin hasarının şekli ile ilişkisi çok iyi tanımlanmamıştır. **Gereç ve Yöntemler:** Çalışmaya neonatal dönemde semptomatik hipoglisemi tanısı alan 39 hasta dahil edildi. Psikomotor gelişim değerlendirmesi için gelişimel yaş yüzdesi Denver Gelişimsel Tarama Testi ve Wecshler zeka ölçeği ile yapıldı. Bütün hastalara takiplerinin bir parçası olarak manyetik rezonans görüntüleme yapıldı. **Bulgular:** Hastaların yarısında semptomatik parsiyel epilepsi vardı, altısı tanesi tedaviye dirençli idi. Çalışmaya dahil edilen hastaların 4'ünde dil alanında gecikme, 5'inde ince motor gelişme geriliği vardı. Kaba motor gelişme geriliği olan yoktu ve bir hastada sosyal-kişisel bakım becerilerinde bozukluk vardı. Nörolojik sekeller ve kan şekeri seviyeleri arasında ilişki yoktu. On hastada görme bozukluğu; 4'ünde optik atrofi, 3'ünde kortikal körlük ve 3'ünde alternan ekzotropia mevcuttu. On altı hastada oksipital lob hasarı, 9 hastada parietooksipital ve 5 hastada gliyozis veya hacim kaybı mevcuttu. Beş hastanın ise görüntüleme bulguları normaldi. Manyetik rezonans görüntüleme bulguları ile klinik bulgular arasında bir ilişki yoktu. **Sonuç:** Neonatal hipoglisemi özellikle dil ve ince motor gelişim alanında olmak üzere psikososyal gelişimde önemli rol oynar. Epilepsi, mental retardasyon ve görme bozuklukları neonatal hipoglisemi ile ilişkili en sık bildirilen bozukluklardır. Gelecekteki nörolojik sekelleri önlemek ve en aza indirmek açısından neonatal hipogliseminin acil tanı ve tedavi edilmesi gerekmektedir. Neonatal hipoglisemi ile ilişkili hasar paternleri daha önce bildirilenlerden daha yaygın ve çeşitlidir.

**Anahtar Kelimeler:** Bebek, yenidoğan; hipoglisemi; manyetik rezonans görüntüleme



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Hypoglycemia is one of the most common clinical care issues in newborns. Hypoglycemia is associated with acute neurological dysfunction in a significant majority.[1-4] Increasing evidence indicates that neonatal hypoglycemia has also been associated with long-term neurological effects. Cerebral palsy, learning disabilities, mental retardation, intractable epilepsy, visual disturbance, and neuropsychiatry disorders can be seen in the prognoses of symptomatic infants. Magnetic resonance imaging (MRI) describes a pattern of hypoglycemia-induced injury affecting predominantly the occipital lobes and posterior parietotemporal regions.[5-7] Long-term follow-up regarding the clinical and radiological data of neonatal hypoglycemia cases in the literature are limited,[5-12] and to our knowledge our study is the one of the most extensive series to date.

The object of the present study is to investigate the long term effects of neonatal hypoglycemia on pschycomotor development and radiological brain injury in a large group of patients.

## MATERIAL AND METHODS

Infants who were referred to the Dıskapı Children's Hospital after ≥1 episode of hypoglycemia between January 2000 and December 2005 and followed up in the Paediatric Neurology Clinic, were identified. Study entry criteria were (1) ≥1 documented episode of symptomatic hypoglycemia (blood or plasma glucose concentration of ≤2.6 mmol/L) during the first postnatal month, (2) being followed up in pediatric neurology clinic of Dıskapı Children's Hospital properly, (3) MRI at postnatal age of >4 weeks. Exclusion criteria were congenital infections, major brain or other malformations, multiple dysmorphic features, chromosomal abnormalities, and evidence of severe hypoxic ischemic encephalopathy. A total of 39 patients with symptomatic neonatal hypoglycemia associated with epilepsy, cerebral palsy, mental retardation, visual abnormalities, microcephaly, neuropsychiatric abnormalities were investigated. Patients in whom hypoglycemia was detected but who had no neurological sequelae in their initial investigation were not included in the study. We discovered from the records that, during the same period, 71 cases were also being followed up because of both symptomatic and asymptomatic reasons in our Neonatal Intensive Care Unit. After being discharged, they did not come to routine follow-up examinations. Of these patients, were contacted. However, only 18 applied to the hospital for follow-up. No pathology was detected in their neurological examination.

Both the MRI and clinical records of 39 patients with neonatal hypoglycemia were reviewed retrospectively. Patients in the study ranged in age from 2 to 9 years at MRI. Patients files were examined with specific attention to the following: presence or absence of any type of seizure; presence or absence of motor deficit, developmental level and level of speech development. The clinical course and results of follow-up examinations were reviewed, with attention to perinatal parameters such as Apgar score, umbilical artery pH, base deficit, and the presence of signs and symptoms of neonatal hypoglycemia within the first few days of life. All neurological examinations were performed by an experienced pediatric neurologist who was blinded to the findings of the magnetic resonance studies. For the assessment of psychomotor development, percentage of developmental age was determined by Denver Developmental Screening test and Wechsler intelligence scale for children. Patients underwent magnetic resonance imaging as part of the follow-up.

MRI at a field strength of 1.5 T was performed on each patient. They were sedated by using orally administered chloral hydrate (30-50 mg/kg). Minimal image acquisition included a T1-weighted sequence in the transverse and sagittal planes and a T2-weighted sequence in the transverse plane. The locations and the degree of abnormal signal within the brain were recorded. The brain was also examined for the presence of any malformation or abnormality.

Contrast agents were not administered to any of the patients in this study.

Magnetic resonance images of all patients were reviewed separately by the same radiologist, wit-

hout knowledge of the clinical history of the patients. The clinicians were not aware of the results of the imaging findings. Electroencephalography was performed using Nihon Kohden 4421 EEG device, and the results were evaluated by the same pediatric neurologist (AG). Sleep and wakefulness interictal electroencephalograms were performed using the 10-20 international system.

### STATISTICAL ANALYSIS

Data were analysed by Statistical Package for the Social Sciences for Windows, version 13.0. The $\chi 2$ test was used to test for independence between rows and columns (glucose levels and magnetic resonance imaging findings, admission time and glucose levels, neurological sequelae and glucose levels) of a contingency table. The comparison of the association of neonatal hypoglycemia and psychomotor development was tested using the Fisher's exact test. Dichotomous variables were compared using the chi-square test with Yates' continuity correction (or Fisher's exact test, where appropriate). To be able to estimate odds ratios, 1 was added to each cell in the contingency tables that contained an empty cell. Continuous variables were analyzed with the t test or the Mann-Whitney U test, when appropriate. A p value < 0.05 was considered to be statistically significant.

## RESULTS

### PATIENT'S DEMOGRAPHICS

Of the 39 patients, 22 were male and 17 were female. Gestational ages ranged from 32 to 41 weeks (mean ± SD, 37.89 ± 2.43 weeks), and birth weights ranged from 1800 to 4000 g (3071.79 ± 568.88 g). The ages at the time of magnetic resonance imaging and neurodevelopmental assessment ranged between 2 to 9 years.

### HYPOGLYCEMIA CHARACTERISTICS

Blood glucose levels of patients on admission to the hospital were as follows: 10 to 20 mg/dL (median 16 mg/dL) in 8, 20 to 30 mg/dL (median 26 mg/dL) in 6, 30 to 40 mg/dL (median 34 mg/dL) in 17, 40 to 50 mg/dL (median 44 mg/dL) in 8. 17 patients were admitted within 24 hours, 12 between 24 and 48 hours, 6 between 48 and 72 hours, 4 between 72 and 96 hours. There was not any relationship between admission time and glucose levels ($p > .05$). All exhibited signs of hypoglycemia, characterised by poor sucking ability (n:20), seizures (n:4), apnea (n:11) and irritability (n:4) (Table 1). Etiologic factors and conditions accompanying hypoglycemia leading to hypoglycemia were grade I asphyxia in 3 patients, prematurity in 11, hyperbilirubinemia in 8, sepsis in 2, exchange transfusion in 2, congenital heart disease in 1, preeclampsia and eclampsia in 3, intrauterine growth retardation in 4, diabetic mother in 7 and oligohydramnios in 1 case. Other reasons detected in etiology were isolated cortisol deficiency in 7 patients; transient hyperinsulinism in 3; hypothyroid in 2; hyperammonemia, hyperinsulinism, hypoglycemia syndromes in 2; and nesidioblastosis in 2. Transient hyperinsulinism of the newborn was diagnosed in two patients and they were eventually started on diazoxide following glucose infusions and steroid treatment. Congenital adrenal hyperplasia was detected in two patients and mineralokortikoid therapy was given and they were followed at Pediatric Endocrinology Clinic. Conditions accompanying hypoglycemia were shown in Table 2.

**TABLE 1:** Hypoglycemia characteristics of the patients.

| Hypoglycemia features | n(%) |
|---|---|
| Presentation | |
| Poor sucking ability | 20( 51.2) |
| Seizures | 4( 10,2) |
| Apnea | 11(28.2) |
| Irritability | 4(10.2) |
| Concomittant diagnosis | |
| Hypoxic ischemic encephalopathy | 3(7.6) |
| Intrauterin growth retardation | 4 (10.2) |
| Prematurity | 11(28.2) |
| Hyperbilluribinemia | 8(20.4) |
| Sepsis | 2(5.1) |
| Exchange transfusion | 7(17.9) |
| Oligohydroamniosis | 1(2.56) |
| Transient hyperinsulinism | 2(5.1) |
| Congenital adrenal hyperplasia | 2(5.1) |

**TABLE 2:** Magnetic resonance imaging findings and glucose levels

| | Glucose levels ( mg/dl) | | | |
|---|---|---|---|---|
| | 10-20 (n:8) | 20-30 (n:6) | 30-40 (n:17) | 40-50 (n:8) |
| Magnetic resonance imaging findings | | | | |
| Occipital region (n:16) | 4 | 3 | 6 | 3 |
| Parietooccipital region(n:9) | 2 | 1 | 5 | 1 |
| Parietal region (n:5) | 1 | 2 | 2 | - |
| Multicystic encephalomalacia (n:2) | - | - | 1 | 1 |
| Periventricular encephalomalacia (n:2) | 1 | - | 1 | - |
| Normal (n:5) | - | - | 2 | 3 |

## MAGNETIC RESONANCE IMAGING RESULTS

The most characteristic result on examination of the MRI findings was abnormally high intensity on T2-weighted images in the periventricular deep white matter and/or adjacent atrophy in the cerebral cortex with loss of gray white matter differentiation in the occipital region in 16 patients and in the parietooccipital lobes in 9 (Figure 1 and 2). Parietal involvement was seen in 5 patients. Imaging findings were normal in 5 patients. Two patients showed cystic encephalomalacia. Two patients had periventricular leukomalacia. Posterior fossa structures and basal ganglias appeared normal in all patients. There were no relationships between magnetic resonance imaging findings and glucose levels ($p > .05$) (Table 2). There was no relationship between neurologic sequelae and magnetic resonance imaging findings (Table 3).

## NEUROLOGICAL SEQUELA

Four children in the sample had language-cognitive delay, 5 children had fine motor development delay, none had gross motor development delay, and one of the children had social skills-self care development delay. The neurological sequelae detected were mental motor retardation and microcephaly in 5 patients; mental motor retardation and epilepsy in 5; epilepsy in 13; mental motor retardation in 7; attention deficiency hyperactivity disorders in 2; microcephaly in 4, and autistic behaviour in 4. There were no relationships between neurologic sequelae and glucose levels ($p < .05$; Table 4).

Eighteen patients had abnormal EEG features. Common EEG features were epileptiform activity originating from occipital(n:12), parietal(n:2) and parieto-occipital regions(n:4). Twelve patients had symptomatic partial epilepsy, six were medically intractable. Five patients had Lennox-Gastatut syndrome with compatible EEG findings.

Ophthalmologic sequelae were present in ten patients; four of them had optic atrophy, three had cortical blindness, three had alternating exotrophia.

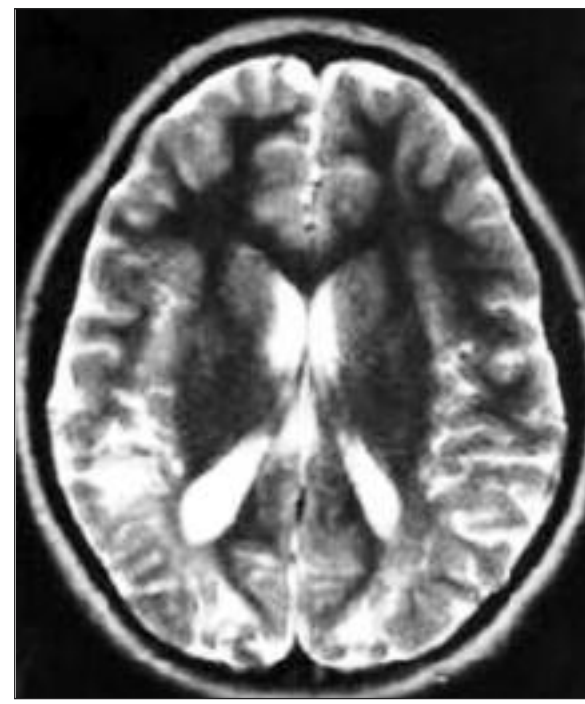

**FIGURE 1:** T2 weighted axial magnetic resonance shows marked atrophy in the parietal and occipital cortex and underlying cerebral white matter.

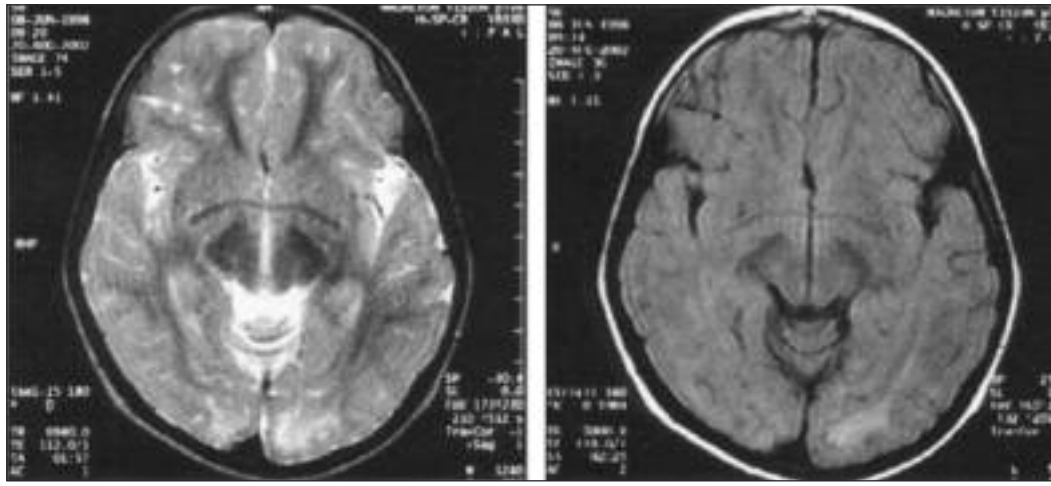

**FIGURE 2:** T2 weighted **A.** and FLAIR **B.** imagings showing hyperintensity in medial occipital lobes.

**TABLE 3:** Magnetic resonance imaging findings and neurological outcomes.

| | Neurological outcomes | | | | | | |
|---|---|---|---|---|---|---|---|
| | Motor mental retardation+ Microcephaly | Motor mental retardation + Epilepsy | Epilepsy | Motor mental etardation | Attention deficiency hyperactivity syndrome | Microcephaly | Autism |
| Magnetic resonance imaging findings | | | | | | | |
| Occipital region (n:16) | 3 | 3 | 6 | 2 | 1 | 1 | - |
| Parietooccipital region(n:9) | 1 | 1 | 2 | 1 | 1 | 2 | 1 |
| Parietal region(n:5) | - | - | 2 | 2 | - | 1 | - |
| Multicytic encephalomalacia(n: 2) | - | 1 | 1 | - | - | - | - |
| Perventricular leucomalacia(n:2) | - | - | 1 | 1 | - | - | - |
| Normal(n:5) | 1 | - | 1 | 1 | - | - | 2 |

**TABLE 4:** Glucose levels and neurological outcomes.

| | Neurological outcome | | | | | | |
|---|---|---|---|---|---|---|---|
| | MMR+Microcephaly (n:5) | MMR+epilepsy (n:5) | Epilepsy(n:13) | MMR(n:7) | ADHD(n:2) | Microcephaly (n:4) | Autism(n:3) |
| Glucose levels | | | | | | | |
| 10- 20(8) | 2 | 1 | 3 | 1 | - | 1 | - |
| 20-30(6) | 1 | 1 | 2 | - | 1 | - | 1 |
| 30-40(17) | 2 | 2 | 6 | 3 | 1 | 2 | 1 |
| 40-50(8) | - | 1 | 2 | 3 | - | 1 | 1 |

MMR: Mental motor retardation, ADHD: Affention deficiency hyperactivity syndrome.

## DISCUSSION

This is one of the few studies of a large cohort of newborns with hypoglycemia that assesses magnetic resonance imaging injury patterns, clinical presentations and neurodevelopmental outcomes. In line with previous reports, most of our patients showed diffuse brain damage, with the most seve-

re injury localized primarily to the occipital and parietal cortex of the brain.[10,13-15] Barkovich et al. reported a specific pattern of injury in neonatal hypoglycemia in five newborn infants showing diffuse cortical and subcortical white matter damage affecting parietal and occipital lobes most severely.[15] Yalnizoglu et al reported patients with typical neuroimaging features following neonatal hypoglycemia.[16] The rationale that the parietal and occipital lobes are most severely affected is not evident. One possible reason for the pattern of damage may relate to the development of receptors for excitatory amino acids. Excessive release of excitotoxins, particularly aspartate, into the synaptic cleft results in the selective death of the postsynaptic neurons in sensitivity is related to increased glucose demands due to intensive axonal growth and synaptogenesis, which occurs within the occipital lobes during the neonatal period. These processes are exceptionally sensitive to glucose availability.[10,17] Although the occipital lobes can be involved in multiple brain injury mechanisms, the pattern of bilateral occipital cortical injury is quite specific for neonatal hypoglycemia. In our study, the most characteristic MRI finding was areas of abnormally high intensity on T2-weighted images in the periventricular deep white matter and/or adjacent atrophy in the cerebral cortex, with loss of gray white matter differentiation in the occipital region in 16 patients and in the parietooccipital lobes in 9. Parietal involvement was observed in 5 patients.

As reflected in other studies, neonatal hypoglycemia was strongly associated with impaired neurological development.[5,11,12,16,18-20] Mental retardation and motor clumsiness are the most reported neurologic sequelae in the follow-up of newborn patients with hypoglycemia. Per et al. detected cognitive functional disorders, behavioral and learning disabilities in 44 of 60 patients.[12] Most studies on long-term outcome report similar incidences of neurological impairment.[5,11,18] Our patients had mild to severe developmental delays, or learning and behavior problems with variable degree. Two of our patients showed hyperactivity and attention problems, three had autistic features.

Visual impairments and epilepsy were common, and both are reported outcomes associated with neonatal hypoglycemia.[18,21] In line with the literature, our patients developed epilepsy as the most common neurologic problem. Intractable epilepsy seems to be the most important prognostic factor in the clinical outcome of patients with neonatal hypoglycemia. Approximately half of our patients had epilepsy, six were medically intractable. Five patients had Lennox-Gastatut syndrome with compatible electroencephalographic findings. Murakami et al detected epilepsy in 7 of 8 patients, Yalnizoglu et al. in 23 of 24, Alkalay et al. in 12 of 17, Caraballo et al. in 12 of 15 (2 of whom were resistant to anticonvulsants drugs), Traill et al. in 2 of 2, and Menni et al. in 16 of 90.[7,11,13,18,21] These findings suggest that neonatal hypoglycemia may cause severe partial epilepsy and this may be due to additional neonatal disorders other than hypoglycemia.

Because it is recognized that there can be occipital injury after neonatal hypoglycemia, it was postulated that there would be a correlation with abnormal early VEPs and later visual function. Previous reports found optic nerve hypoplasia associated with neonatal hypoglycemia.[22] In newborn patients who are affected by hypoglycemia, visual disturbance may be observed.[16,18,20,21,23] In the present study, ophthalmologic sequelae were present in ten patients; four of them had optic atrophy, three had cortical blindness, and three had alternating exotrophia. The majority of our patients with abnormal vision have involvement of the occipital cortex; however, some with severe occipital injury had apparently normal visual development.

A limitation of our study was that we cannot tell the exact onset, duration and severity of hypoglycemia. We cannot keep out the presence of hypoglycemia starting earlier in life with mild symptoms that were not recognized by the parents or care givers because most of our patients were brought to the hospital with poor sucking and irritability on the first few days of life. Also, most of our patients had additional neonatal insults that might have contributed to the effects of hypoglycemia in newborn brain.

## CONCLUSION

Although the level of the glucose leaving sequelae is not exactly known, neonatal hypoglycemia seems to play an important role in the psychosocial development delay, especially on language-cognitive and fine motor development. Epilepsy, mental motor retardation, and visual impairments are the most common reported outcomes associated with neonatal hypoglycemia. Prompt recognition and treatment of neonatal hypoglycemia is essential to prevent and minimize future neurological sequelae. The patterns of injury associated with symptomatic neonatal hypoglycemia are more diverse than reported previously. These results from a child neurology center would be subject to a follow up bias. On the basis of our results, we suggest that additional, prospective studies are necessary to determine the true incidence of abnormal neuroimaging studies and subsequent adverse neurologic outcomes that result from neonatal hypoglycemia. These future studies will help to better delineate the association between low blood glucose concentrations and the duration of hypoglycemia leading to brain damage.

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