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Long-term MRI findings of a case with persistent hyperinsulinemic hypoglycemia of infancy (nesidioblastosis)

Didem Aliefendioglu [a], Gulsah Bademci [b,*], Simay Kara [c]

[a] *Department of Pediatrics, Neonatology Unit, Faculty of Medicine, University of Kirikkale, Turkey*
[b] *Department of Neurosurgery, Faculty of Medicine, University of Kirikkale, Turkey*
[c] *Department of Radiology, Faculty of Medicine, University of Kirikkale, Turkey*

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Abstract

Background and purpose: To describe the sequential magnetic resonance imaging (MRI) findings in a neurologically handicapped newborn who had been suffered from neonatal hypoglycemia due to persistent hyperinsulinemic hypoglycemia of infancy (nesidioblastosis) and to evaluate the following changes in the long-term radiological follow-up.
Case: A case of newborn with severe hypoglycemia due to nesidioblastosis is reported. The patient was presented with poor feeding, irritability, and seizures. Nesidioblastosis was diagnosed on the basis of high intravenous glucose requirement, high insulin to glucose ratio, negative urinary ketones. Normoglycemia was maintained by a combined treatment including glucose infusions and steroid, and then somatostatin analoques. The patient was assessed neurologically and radiologically by sequential cerebral MRI within 2 years follow-up.
Results: The most striking findings were cystic lesions on corona radiata, parietooccipital deep white matter and diffuse subcortical involvement of the brain at the initial MRI. The lesions were recovered radiologically at the 5 months of age. Diffuse hyperintensity of the periventricular white matter and optic radiation suggests abnormal and delayed myelination at 1 year of age, and periventricular leukomalacia and ventricular irregularity at 2 years of age. More delayed neurologic sequelae included mental retardation and spasticity.
Conclusion: Neonatal hyperinsulinemic hypoglycemia must be suddenly and appropriately diagnosed and treated to prevent any further neurological dysfunction and damage. MRI studies are crucial in nesidioblastosis to define the characteristics and severity of cerebral lesions after hypoglycemia. Long-term radiologic follow-up should be further investigated to predict the neurologic outcome, although the radiologic recovery period was seen in acute or subacute phase of the disease.

Keywords: Hypoglycemia; Nesidioblastosis; Persistent hyperinsulinemic hypoglycemia of infancy; Magnetic resonance imaging

1. Introduction

Although hypoglycemia is a common disorder of the newborn, so much controversy still surrounds the definition, significance, and management of neonatal hypoglycemia. As a life-threatening form of neonatal hypoglycemia, nesidioblastosis, approximately known as "persistent hyperinsulinemic hypoglycemia of infancy (PHHI)" is a rare condition which remains to be elucidated but is associated with a high incidence of brain damage and mental retardation as a consequence of repeated episodes of severe hypoglycemia in pediatric patients.

With improved neuroradiologic techniques, such as magnetic resonance imaging (MRI) and positron emission tomography (PET) scanning becoming increasingly available, studies to determine the correlation between hypoglycemia and outcome will help to clarify issues surrounding the effects of hypoglycemia on brain pathology [1–4]. The topography of cerebral lesions on MRI correlates with the clinical severity of hypoglycemia during the neonatal period and subsequent neurologic sequelae.

Here we report the sequential neuroimaging features in a newborn with PHHI who presented with persistent and severe hypogylcemia. The chronological changes on MRI was also

* Correspondence to: Buketkent Mh. Iller Sitesi 9/9, Cayyolu, 06530 Ankara, Turkey. Tel.: +90 312 2415820; fax: +90 318 2252819.
E-mail address: bademci70@yahoo.com (G. Bademci).

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examined during either hyperinsulinemic hypoglycemia or normoglycemia in a long-term follow-up.

2. Case report

A newborn boy weighing 4500 g with a gestational age of 40 weeks was delivered to a non-diabetic woman after uncomplicated pregnancy. The patient was the first child of consanguineous and healthy parents and transferred to our neonatal intensive care unit (NICU) on the third day of life because of hypoglycemia which was observed within the first hours of life. At the time of admission, he had poor feeding, irritability and seizures. Laboratory investigations including urine, complete blood count, blood biochemistry except glucose yielded normal results. Urinary ketones were negative. Sequential glucose concentrations were 18, 32, 38, 47 mg/dl (normal range: 40–60 mg/dl) while simultaneous plasma insulin consentrations were 201.9, 39.6, 85.3, 42.9 mIU/l (normal range: 3–20 μIU/ml), respectively. Glucagon test showed a normal response. Inappropriately raised plasma insulin concentration at the time of hypoglycemia were suggestive of PHHI. Abdominal ultrasonography was normal. No evidence of morphologic abnormality in the pancreas

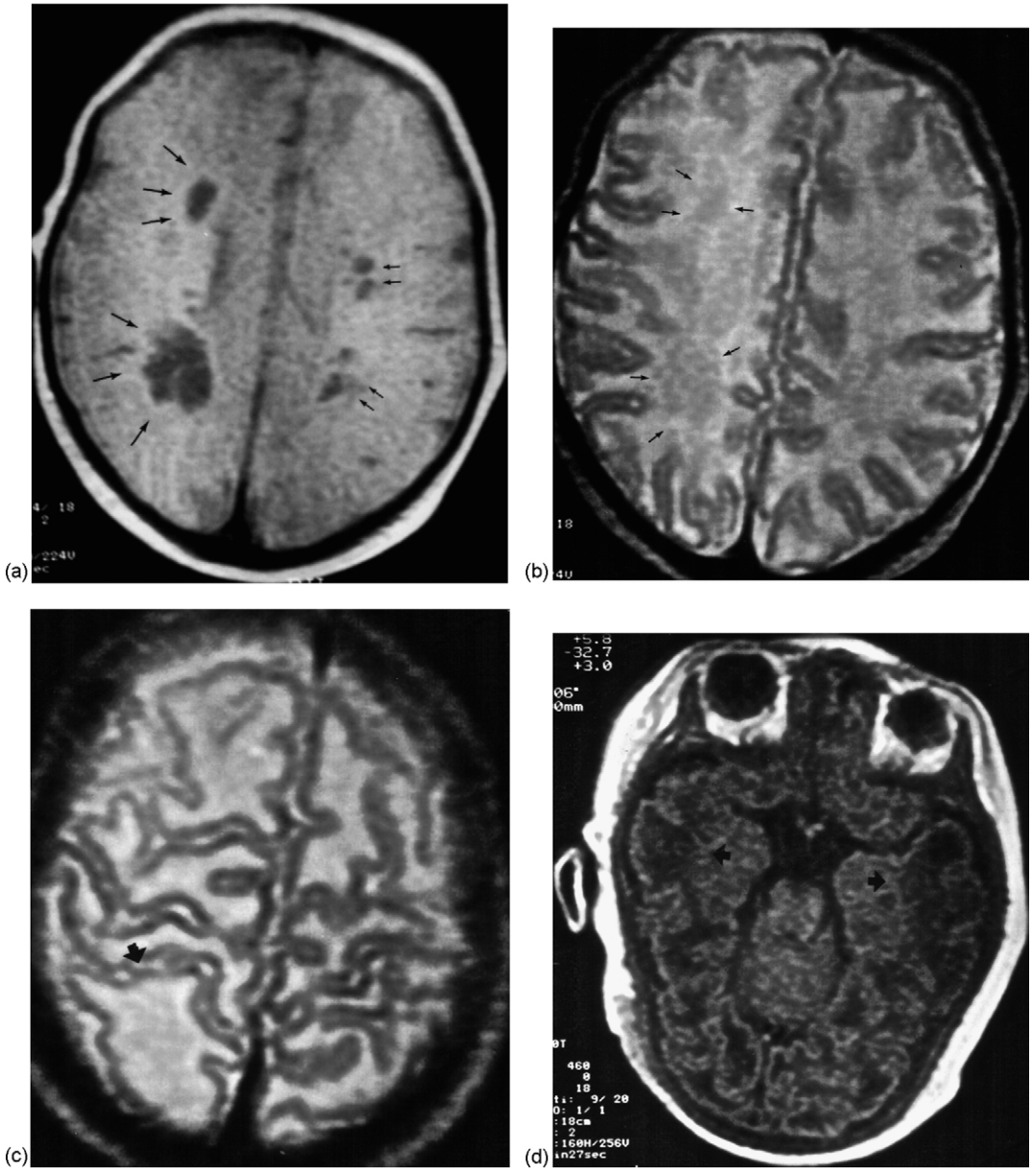

Fig. 1. (a) T1-weighted MRI shows hypointense lesions in right corona radiata, centrum semiovale and retrotrigonal parieto-occipital deep white matter (arrows). (b) T2-weighted MRI shows isointense appearance of the lesions located on centrum semiovale and deep parietooccipital lesions (arrows). (c) T2-weighted MRI showing right occipitoparietal hyperintensity indicating edema (arrows). (d) T1-weighted MRI demonstrating bitemporal edema (arrows).

was detected by abdominal CT. The newborn was evaluated for CMV, which can also cause cerebral white matter cystic changes.

Glucose infusion was continued as previously started at a dose of 12 mg/kg/min. An adequate glucose level could not be achieved with high glucose infusion rates, so intravenous corticosteroid was given additionally. As hypoglycemia persisted, he was commenced on long-acting somatostatin derivative Sandostatin (Octreotide, Sandoz; 10 mg/kg/day) treatment by continuous subcutaneous infusion. Normoglycemia was established within a few days of the treatment as well as his glucose requirement being reduced to 6 mg/kg/min. The patient was discharged on day 30, in a good clinical condition. The psychomotor development was retarded at the age of 6 months. There was hypertonisity with absence of head control. During the follow-up period, seizures were observed and controlled with medical treatment. Two years clinical follow-up showed cerebral palsy as a sequela of periventricular leukomalasia.

2.1. Neuroimaging

Routine brain examination was performed with head coil, 1.5 T Philips Intera MRI machine. Transverse T1 TSE (460/18/2 = TR/TE/NEX), T2 TSE (4150/90/2 = TR/TE/NEX, field of view was 180 mm) and sagittal T1, coronal T2-weighted imaging were obtained.

Initial MRI scans at the age of 53 days demonstrated severe pathological changes in cortex and white matter, predominantly in the parieto-occipital region. Patchy hypointense lesions in the retrotrigonal area and parieto-occipital periventricular deep white matter, centrum semiovale, corona radiata, and entire subcortical white matter of temporal and frontal lobes on T1-weighted images and iso-hyperintense lesions on T2-weighted images were noted (Fig. 1a–d). These lesions especially in those corona radiata had a good tendency to recover radiologically 2 months later. The lesion on centrum semiovale was depressed while parietooccipital lesions showed developing atrophy with cystic gliomalacia (Fig. 2). At 5 months of age, the MRI of the brain showed complete recovery of the lesions located on centrum semiovale, corona radiata and entire frontal, temporal lobes and right parietooccipital white matter. But the volume of the centrum semiovale was still out of the normal range and hyperintense on T2-weighted images. The MRI showed microcystic encephalomalasia located in retrotrigonal area, hypointense on T1-weighted images and hyperintense on T2-weighted images (Fig. 3). At 1 year of age, MRI demonstrated hyperintensity in the bilateral optic radiation on T2-weighted images as a clue of delayed myelinisation. Hyperintensity and thinning of the corpus callosum were observed. It also showed persisting retrotrigonal cystic encephalomalasia in affected regions of the brain. Limited cortical necrosis occured at the depth of the parietooccipital sulcus suggested the

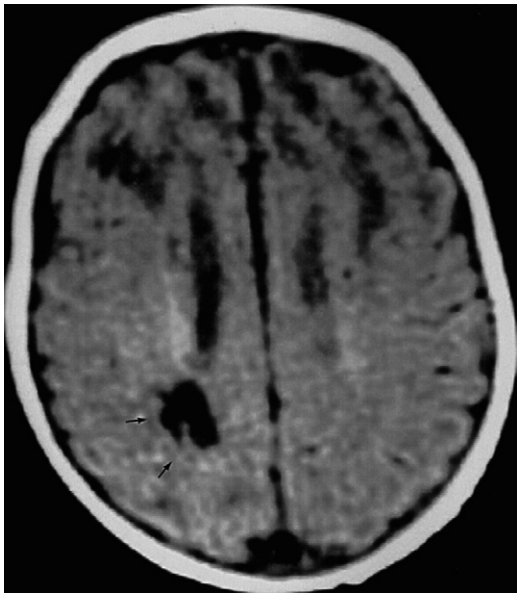

Fig. 2. T1-weighted MRI shows recovery of the lesion located nearby right corona radiata and right occipitoparietal subcortical hypointense gliomalasia (arrows).

presence of "*ulegyria*", hypointense on T1-weighted and hyperintense on T2-weighted images (Fig. 4a and b). At 2 years of age, MRI showed hyperintensity of the periventricular white matter and corona radiata on T2-weighted images. The white matter volume of periventricular region and centrum semiovale was extremely decreased. Focal hyperintensity lesions around periventricular white matter and corona radiata suggested "periventricular leukomalasia (PVL)". Atrophy of corpus callosum and irregularity of the lateral ventricles were markedly observed (Fig. 5a and b).

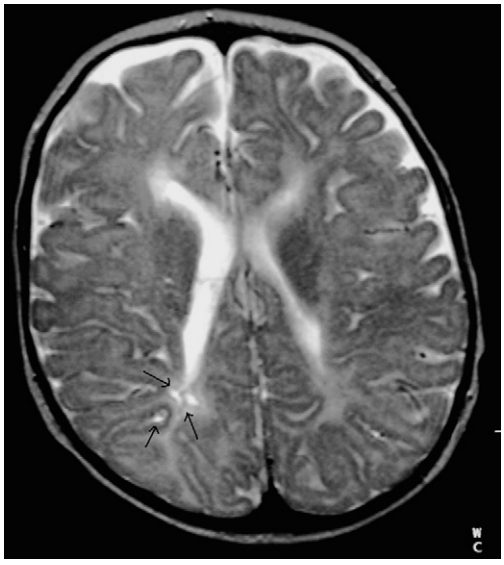

Fig. 3. Recovery of the lesion located in corona radiata. Retrotrigonal microcystic areas (arrows).

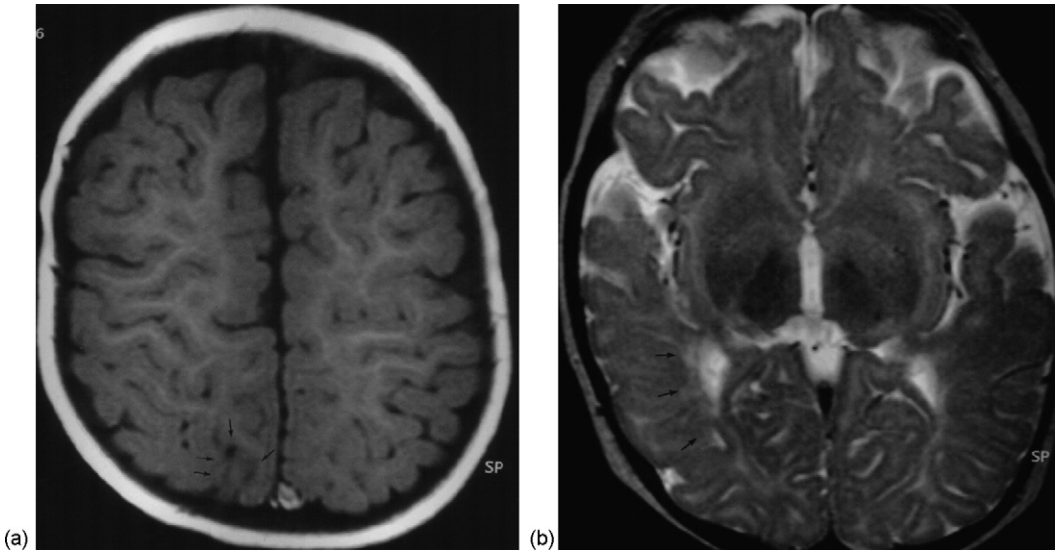

Fig. 4. (a) T1-weighted MRI shows limited cortical necrosis occuring at the depth of the parietooccipital sulcus suggesting the presence of ulegyria (arrows). (b) T2-weighted MRI shows hyperintense appearance in the optic radiation (arrows).

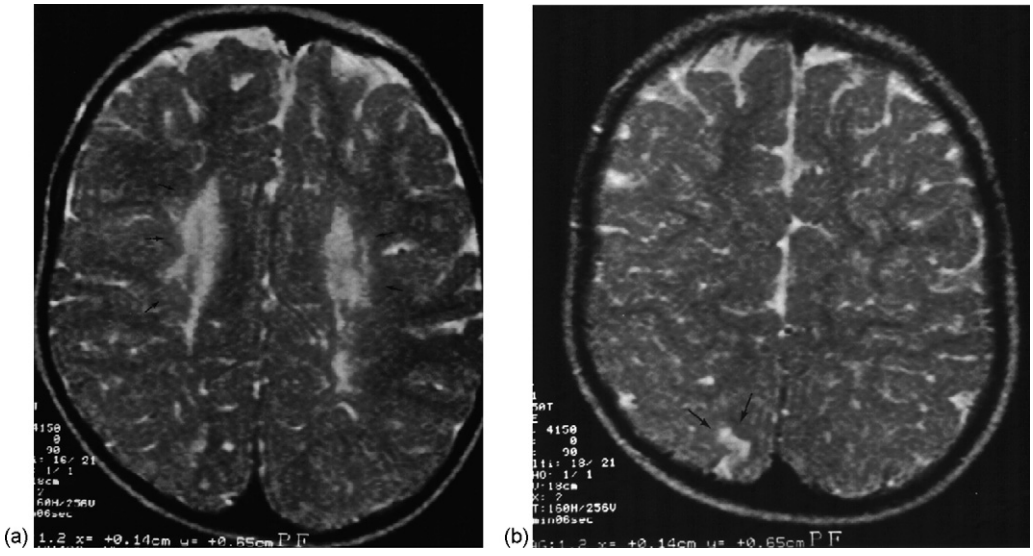

Fig. 5. (a) T2-weighted MRI shows periventricular leukomalasia (arrows). (b) T2-weighted MRI shows ulegyria (arrows).

3. Discussion

Metabolic disturbances such as anoxia and hypoglycemia may cause abnormalities in the brain function of the affected newborn and severe neurological sequellae have been reported after symptomatic neonatal hypoglycemia [5,6].

Congenital hyperinsulinism (CHI) as a cause of severe hypoglycemia in the neonatal and infancy period, is subdivided into two subtypes with diffuse and focal disease. The ability to distinguish diffuse from focal lesions has profound implications for therapeutic approaches, prognosis and genetic counselling. The focal form of the disease can be cured if the focal lesion can be accurately localized and surgically completely resected. (18)-F-DOPA PET is a promising non-invasive method for the identification and localization of the focal form of CHI [7].

PHHI, formerly termed nesidioblastosis, is a rare entity associated with a high incidence of neuronal death, brain damage and cognitive impairment due to repeated attacks of severe hypoglycemia. PHHI is caused by genetic defects in beta-cell regulation leading hypertrophy and hyperplasia of the islands of Langerhans [8,9]. Its diagnostic criteria are an extremely high demand for carbohydrates (more than 15 g/kg/day), an inadequately high plasma insulin level, and an inhibited production of ketone bodies. Treatment involves maintaining normal blood glucose levels; and modalities include high glucose infusion rates, medications, and

surgical interventions consisting in subtotal pancreatectomy [10]. The most important aim of continuous therapy is the prevention of irreversible brain damage. While prompt diagnosis and appropriate treatment can save many of them and can favourable influence the outcome of the disease; delayed detection and inappropriate treatment may lead a high risk of the development of cerebral palsy, impaired mental development, epilepsy or other forms of irreversible brain damage. Of importance is the fact that, the neurological outcome may be predicted with the aid of transient or persistent findings which would detected on MRI during long-term radiological follow-up.

While there have been some pathologic studies of the effects of neonatal hypoglycemia on brain development, reports of MRI findings in such infants have been rare. Imaging studies of neonatal hypoglycemia revealed a predominance of brain parenchymal loss in the occipital lobes with nearly complete absence of cortex in the posterior parietal and occipital regions and generalized thinning of the cortex throughout the brain [1,2,4,11,12]. Spar et al. reported progresive parenchymal loss and predominantly occipital involvement on CT and MRI of an infant at the age of 19 days [4]. Barkovich et al. reported similar CT and MRI findings of severe prolonged hypoglycemia in 5 neonates [2]. Aslan and Dinc presented diffuse parenchymal loss and infarction bilateral in occipital region and ventricular dilatation on MRI at the age of 10 days and atrophy of the occipital cortex at the age of 4 months [1]. Murakami et al. also reported parietooccipital deep white matter changes suggesting abnormal and delayed myelination areas in neurologically handicapped neonates suffering from hypoglycemia [12]. Kinnala et al. reported patchy hyperintense lesions in the occipital periventricular white matter and talamus. They also mentioned that these lesions have a good tendency to recover at 2 months [3]. Cakmakci et al. observed similar patterns on initial and 2 months US and MRI investigations of an hypoglycemic infant [11]. Although PHHI is a well-described disease and MRI findings are rarely reported, up to our knowledge, *long-term* MRI findings over 2 years of hypoglycemia due to nesidioblastosis has not been reported. Furthermore, it may be helpful to determine the long-term effects of nesidioblastosis on brain functions with neuroradiologic follow-up.

The topography of the predominant cerebral injury of hypoglycemia due to PHHI especially parieto-occipital cortex and subcortical white matter involvement shown by MRI was similar to that documented in the hypoglycemic infants, suggesting a non-spesific similarity in regional cerebral vulnerability to altered glucose metabolism. But, diffuse deep white matter involvement and corona radiata and optic radiation injury were remarkable and more severe in hypoglycemic damage of nesidioblastosis than other causes of hypoglycemic brain damage. Delayed myelinisation, leukomalasia and presence of ulegyria on MRI are the other significant characteristics of the chronic period of the disease. More delayed neurologic sequelae included mental retardation and spasticity were matched with the PVL.

Although the clinical relevance of these abnormal findings remains to obscure; both clinical and radiological follow-up may clarify the outcome. It is also worthwhile that parietooccipital lesions were tend to recover at 5 months in this patient; while periventricular lesions of hypoglycemia are usually reported to recover at 2 months, as reported in previous data. This observation supported the hypotesis that radiological findings of neonatal hypoglycemia varies considerably, depending on the degree, severity, duration and the effectiveness of treatment [11,12]. Despite this radiologic "recovery period" is similar with the literature, we observed that neurologic and particularly radiologic follow-up showed persistent findings. So, radiologic follow-up should be long-term investigated to consider the persistent neurologic findings, even "recovery period" was occurred on MRI in acute or subacute phase of the disease. Developing diffuse cerebral atrophy, microcystic encephalomalasia and periventricular leukomalacia detected on long-term MRI studies might be explain the persistency of subtle or obvious neurologic deficits.

Ultrasonography (US) is commonly used to screen neonates for white matter lesions. However, it is not a sensitive predictor of the milder spectrum of MRI defined white matter abnormalities, especially in premature infants. In fact, both US and MRI demonstrate specificity; but, parietooccipital lesions consequent to neonatal hypoglycemia are difficult to detect with US. The superiority of MRI over US in detecting parenchymal lesions is previously reported [3,11]. Furthermore, MRI is superior to cranial US to evaluate the prognosis of infants with non-cystic PVL lesions, as a predictor of outcome for CP. To conclude that, neonatal MRI is able to predict the precise localization and size of PVL on follow-up MRI and provides a good prediction of neurological outcome over 1.5 years.

We strongly speculated that it is necessary to follow the infants with severe hypoglycemia for obtaining long-term neuro-radiological outcome.

4. Conclusion

Hypoglycemia may be simply an epiphenomenon in a neonate with a serious disease. In such a case the underlying etiology rather than hypoglycemia may be more responsible for brain damage. MRI studies are essential to define the characteristics of cerebral lesions during and after neonatal hypoglycemia. MRI has also been shown to be effective in the choice and monitoring of treatment to reduce the brain damage. We speculated that cranial investigations are extremely helpful to follow the progression of disorder and to predict the neurologic outcome. As MRI increasingly available, correlation between hypoglycemia and outcome will help to clarify issues surrounding the effects of hypoglycemia on brain pathology.

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