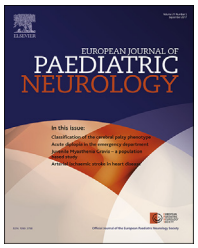
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Original article

Neonatal hypoglycemia: A wide range of electroclinical manifestations and seizure outcomes

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ABSTRACT

Purpose: We examined the various types of epilepsy in children with neonatal hypoglycemia in order to define electroclinical and prognostic features of these patients.
Method: We retrospectively reviewed the medical records of patients with a history of symptomatic neonatal hypoglycaemia who have been followed at Gazi University Hospital Pediatric Neurology Department between 2006 and 2015. Patients with perinatal asphyxia were excluded. Details of each patient's perinatal history, neurological outcome, epilepsy details, seizure outcome and EEG and brain MRI findings were reviewed.
Results: Fourty five patients (range 6 mo–15 y) with a history of symptomatic neonatal hypoglycaemia were included the study. Epilepsy developed in 36 patients and 23 of them had intractable epilepsy. All patients had occipital brain injury.
Conclusion: We observed that most of the patients, either manifesting focal or generalized seizures, further develop intractable epilepsy. This finding establishes neonatal hypoglycemia as a possible cause to be considered in any case of intractable epilepsy.

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1. Introduction

Glucose is the primary energy source of the human brain, therefore highly susceptible to hypoglycemic damage with a high risk of neurologic handicap including; cerebral palsy, intellectual disability, blindness and epilepsy.[1–4] Hypoglycemic brain injury is a recognized insult that triggers seizures and is typically associated with both focal and generalized epilepsy. The frequency of epilepsy after symptomatic neonatal hypoglycaemia is greater than 50%.[5–7] However, the spectrum of hypoglycemic brain injury resulting in epilepsy is unclear. Most of existing literature on this topic is focused on the incidence of seizures in large cohorts of epileptic patients after neonatal hypoglycemia with only a few studies describing the clinical, EEG, and syndromic aspects specifically.[5,7,8] To add to the knowledge base of this subject, in the

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present study, we examined the various types of epilepsy in children with neonatal hyperglycemia in order to define electroclinical and prognostic features of these patients. This information will enable earlier identification of patients, thereby preventing the progression. To our knowledge, this study is the largest report on a detailed analysis of the spectrum of epilepsy in neonatal hypoglycemia.

2. Material method

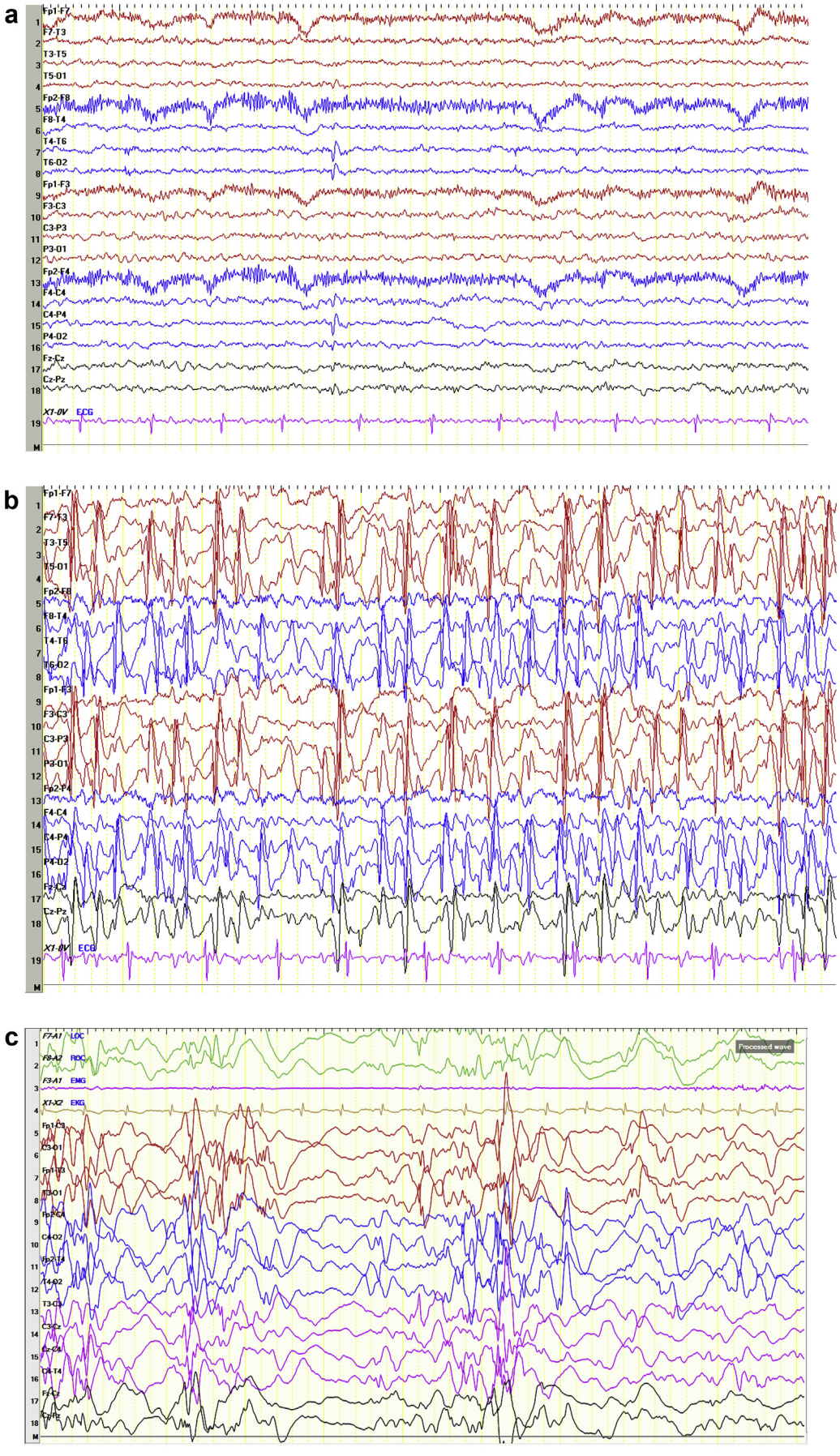
A retrospective electronic chart review using the key words "neonatal hypoglycemia", "epilepsy" was performed to identify patients who had a neurological handicap after neonatal hypoglycemia and subsequently followed at Gazi University Hospital Pediatric Neurology Department between 2006 and 2015. Gazi University Hospital Pediatric Neurology Department provides primary to tertiary levels of care for children with neurological disorders. The routine and video-EEG laboratories perform about 1500 pediatric EEGs per year. A total of 892 patients' charts were reviewed and, of these, 45 patients were found who were followed with neurological disorders after neonatal hypoglycemia. Of these, 36 patients were followed with epilepsy after neonatal hypoglycemia. These 36 subjects form the basis of the current report. Patients with a history of perinatal asphyxia and patients without documented hypoglycemia and apgar score at 5 min after delivery less than 7 were excluded from the study. Hypoglycemia, was defined as a whole blood glucose concentration of less than 47 mg per deciliter (2.6 mmol per liter). The study was approved by the hospital's ethics committee. A total of 36 subjects (26 male, 10 female, 11 mo–18 y 5 mo; mean age 10 y 5 mo, at the time of review) who developed epilepsy after neonatal hypoglycemia were identified. Multiple clinical variables in these 36 subjects were reviewed: neonatal hypoglycemia details, perinatal history, epilepsy details, imaging characteristics and neurological outcome. Neonatal hypoglycemia was classified by using a classification based on the clinical setting, the presence of symptoms, the duration and severity of hypoglycemia.[9,10] According to this classification, patients were divided into two groups[1]; Early transitional neonatal hypoglycemia: typically occurring in the first 6–12 h after sudden withdrawal of maternally derived substrate at birth and resolved within 5 days or[2] severe persistent neonatal hypoglycaemia, caused by specific primary enzymatic or metabolic-endocrine abnormalities involving glucose homeostasis. Neonatal hypoglycemia details included; risk factors (maternal conditions like gestational diabetes, preeclampsia, eclampsia), neonatal conditions (gestational age, gestational weight, sepsis, hyperbilirubinemia, intrauterine growth retardation), duration of hypoglycemia. Etiological investigation of neonatal hypoglycemia was performed by laboratory tests including; amino acid profile, thyroid hormones (T4/TSH), growth hormone, insulin, cortisol and acylcarnitines, and urine organic acids, ketone bodies. Hypoglycemia symptoms including seizures, poor feeding, hypothermia, apnea, altered consciousness, hypotonia were noted. Seizure onset, semiologic features, frequency, distribution, duration of the seizures, drug treatment, seizure outcome were analyzed from the medical records. Onset of epilepsy was accepted as the first seizure after the neonatal period. The epileptic syndromes were analyzed in detail. EEG of each patient was reviewed with respect to background abnormality (slowing of the background EEG rhythm, intermittent or continuous generalized, localized or regional slowing), the localization (generalized, focal, multifocal), morphology spike, polyspike, sharp wave, spike wave, sharp slow wave, and polyspike wave, and topography of interictal epileptiform discharges (IEDs). The classification of seizures was based on the clinical and EEG findings according to the criteria of International League Against Epilepsy.[11] In all cases, cranial MRI was performed with epilepsy protocol using superconducting magnets with multichannel head coils in the supine position with a 1.5 T MRI (GE SIGNA EXCITE, Milwaukee, USA). Epilepsy protocol included axial and sagittal T1 weighted, axial T2 weighted, oblique coronal FLAIR perpendicular to the long axis of both hippocampi, and 3D inversion recovery (IR). The whole brain volumetric series were acquired using a 3D IR technique with a slice of 1 mm thickness, zero interslice gap, 256 × 222 matrix size, and a single signal average. T2 weighted oblique axial images through the long axis of both hippocampi consisting of 20 slices were also obtained with 3 mm slice thickness and 0.75 mm interslice gap. All MRI slices were re-evaluated by K.A., who is most experienced and educated physician in MRI interpretation in the group.

Statistic analysis was performed with the SPSS statistical analysis program using the x^2 test. P values of less than 0.05 were regarded statistically significant.

3. Results

3.1. *Clinical manifestations*

Twenty-nine patients were delivered at term, and seven patients were delivered prematurely. One infant was the product of twin pregnancy. All patients had Apgar scores >8 at 5 min. One patient had a history of exposure to valproate during the first three months of pregnancy. At presentation, all patients had signs and symptoms of acute neurological dysfunction associated with neonatal hypoglycaemia, with neonatal convulsions evident in 20 (18 of them in the first 72 h of life), apnea in 3 and irritability in 3. Ten patients had prenatal and perinatal problems (maternal diabetes (n:2), preeclampsia (n:4), prematurity (n:7)) that made them prone to hypoglycemia and/or medical problems other than hypoglycemia. Three patients were small for gestational age with birth weights of 2000–2250 g, delivered at term. Three patients had indirect hyperbilirubinemia requiring phototherapy; one patient had partial exchange transfusion for polycythemia. Neonatal sepsis was diagnosed in three patients with a positive blood culture in all. All infants had routine blood investigations performed for neonatal hypoglycaemia. Transient neonatal hypoglycaemia was diagnosed in 33 children, all of them had feeding difficulty. Persistent neonatal hypoglycemia was diagnosed in three children, two of them had hyperinsulinism and the other patient in the persistent group had panhypopituitarism. The minimum blood glucose ranged between 5 and 38 mg/dl (mean ± SD, 21.63 ± 1.33 mg/dl). Duration of neonatal hypoglycemia ranged from 6 h to 3 days


a
Fp1-F7
F7-T3
T3-T5
T5-O1
Fp2-F8
F8-T4
T4-T6
T6-O2
Fp1-F3
F3-C3
C3-P3
P3-O1
Fp2-F4
F4-C4
C4-P4
P4-O2
Fz-Cz
Cz-Pz
X7-0V ECG
b
Fp1-F7
F7-T3
T3-T5
T5-O1
Fp2-F8
F8-T4
T4-T6
T6-O2
Fp1-F3
F3-C3
C3-P3
P3-O1
Fp2-P4
F4-C4
C4-P4
P4-O2
Fz-Cz
Cz-Pz
X7-0V ECG
c
F7-A1 LOC
F8-A2 ROC
F3-A1 EMG
X1-X2 EKG
Processed wave

in the transient group whereas 2 days to 19 days in the persistent group.

3.2. EEG findings

Interictal EEG showed posterior temporooccipital (23 cases), multifocal or generalized spikes, polyspikes, and spike/wave discharges (10 cases). Three patients had a normal initial EEG, and eight showed an hypsarrhythmic EEG associated with infantile spasms at seizure onset. Interictal EEG remained abnormal in 32 of 36 patients (88.8%). For the 23 patients that developed intractable seizures, interictal EEG remained abnormal in all cases and showed persistent multifocal or diffuse high-amplitude spikes mixed with irregular slow waves (Fig. 1a,b,c). 8/23 (34.7%) previously presented epileptic encephalopathy with infantile spasms and evolved to Lennox–Gastaut syndrome. For the 13 seizure-free patients, EEG was either normal[6] or showed normal background activity with focal occipital spikes in two cases and temporal spikes in one case.

3.3. First seizures

The age at onset of seizures ranged from 2 to 144 months (mean age, 18 months). Seizures started during the first 1 year of life in 26 patients (72%), at the median age of months. Neonatal seizures were reported in twenty patients, in the remaining six patients, seizures started within age 6 months and 12 months. Ten patients had onset of seizures after the age of one. First seizures were described as focal in 15 cases, spasm in 12, secondary generalized focal seizures in 2 patients, myoclonic/clonic in 3, generalized in 3 and tonic in 1.

3.4. Neuroradiological findings

Brain magnetic resonance imaging (MRI) was performed in all patients with epilepsy at the median age of 1.5 years (range 6 months–7 years). All patients had gliosis in the occipital white matter bilaterally, with occipital cortical atrophy in 28 (Fig. 2). Twenty two patients had additional gliosis in the parietal white matter (Fig. 3), with parietal cortical atrophy in four. One patient had pulvinar scarring (Fig. 3).

3.5. Treatments

Initially, patients were treated with carbamazepine or valproate in monotherapy, later, because of a worsening of seizures, antiepileptic polytherapy with a combination of different drugs (including phenobarbitale, valproate, carbamazepine, clobazam, leviteracetam, topiramate and vigabatrin) was introduced.

Strikingly, four patients (17.3%) developed encephalopathy with epileptic encephalopathy with continuous spike and wave during sleep and treated with intravenous methyprednisolone and clobasam. Vagus nerve stimulator was implanted in two of the intractable patients. Persistent neonatal hypoglycemia was diagnosed in three children, two of them had hyperinsulinism and eventually started on diazoxide following glucose infusions and steroid treatment and one of these patients had pancreatectomy at follow-up.

3.6. Clinical outcome and long term epilepsy evolution

At follow-up, 19 patients (52.7%) developed focal epilepsy with occipital features. Thirteen patients (36.1%) were progressively controlled with AEDs and became seizure free. On the other hand, six of these cases (19.4%) continued with daily to weekly seizures with a combination of generalized tonic, myoclonic, and atonic seizures. Discontinuation of antiepileptic drugs (AEDs) was carried out in three patients who became seizure-free during this follow-up period. Twenty-three (63.8%) patients have evolved intractable epilepsy and presented with multiple seizure types. They included generalized epilepsy with tonic and tonic–clonic seizures in 9 cases, myoclonic seizures in 3, complex partial seizures in 4, atonic seizures in 4, and epileptic spasm in 3 patients. 8/23 (34.7%) previously presented epileptic encephalopathy with infantile spasms and evolved to Lennox–Gastaut syndrome. Either due to hyperinsulinism or panhypopituitarism, all three patients with persistent hypoglycemia, presented with infantile spasms and developmental delay, all had hypsarrhythmia on EEG consistent with West syndrome and later evolved to intractable epilepsy. Because of small number, we could not make a statistical analysis for the risk factors.

At follow-up, two patients have attention deficit hyperactivity disorder, two autism, three mild intellectual disability, one severe intellectual disability and one moderate intellectual disability. Three children with epilepsy also had cortical visual impairment and five had intellectual disability and two had cerebral palsy.

When we evaluated the risk factors, severity, duration or the presence of neonatal seizures were not found related with long term seizure outcome, in the transient group (p: 0.673, 0.324, 0.89).

4. Discussion

Epilepsy is one of the main sequleas of neonatal hypoglycemia but the prevalence of epilepsy following neonatal hypoglycaemia is unknown, and predictors of the clinical course yet remains unclear. Clinical and electrophysiological features of epilepsy after neonatal hypoglycemia have been analyzed, in only a few retrospective studies with limited number of patients.[5,7,8] To the best of our knowledge, this is the largest study assessing the electroclinical features of epilepsy after isolated neonatal hypoglycemia and provides insight into the wide range of electroclinical variabilities in this group of patients. All patients in our series had occipital brain injury which mainly seems to be the suspectible cause of their epilepsy with a remarkable number of patients

Fig. 1 – a: EEG recorded at the age of seven showing sharp waves in the right parietooccipital region. b: Sleep EEG recorded at the age of nine showing electrical status epilepticus during sleep. c: Sleep EEG recorded at the age of three months showing hypsarrhythmia.

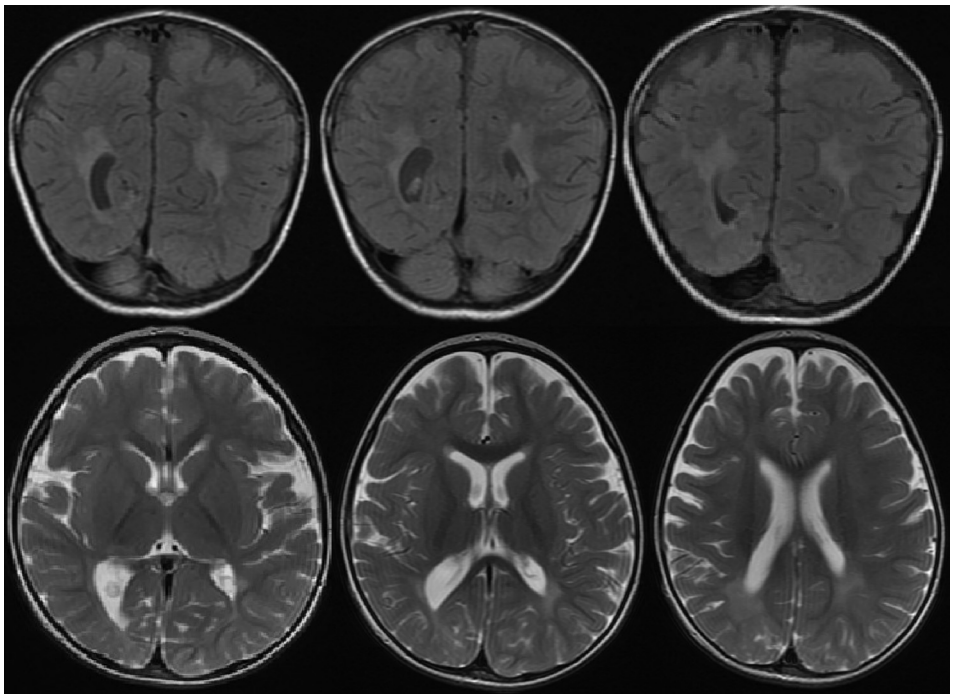


Fig. 2 – Coronal FLAIR and axial T2 imagings represent cortical atrophy and gliosis in the occipital lobes.

developing intractable epilepsy, which were not observed in the previously reported series. Seizure outcome was favorable in most of the children with occipital epilepsy, but in neither of the children with intractable epilepsy. The clinical signs of neonatal hypoglycemia are variable and the level of blood glucose concentration causing neonatal cerebral injury and leading to an acute neurological dysfunction is unclear. Therefore, the definition of hypoglycemia is still controversial.[6,7,9,10] Current guidelines report that neonates presenting with acute neurological dysfunction and a blood glucose level of 1–2 mmol/L warrant treatment of the neonatal hypoglycaemia.[12] Our findings showing all of the patients presenting with acute neurologic, corroborate this consensus.

Neonatal hypoglycemia may cause a well-defined pattern of brain injury with a tendency for the involvement of parietal and occipital white matter, as seen in all our patients.[13–16] The reason for the involvement of parietal and occipital lobes is not exactly known.[17–19] Excitatory neurotoxins active at N-methyl-D-aspartate receptors, increased mitochondrial free radical production, initiation of apoptosis and alterations in cerebral energy production are the possible mechanisms of hypoglycemia induced cellular injury.[20–23] It has been shown that during hypoglycemia regional glucose uptake of occipital lobes decreases due to the increased regional cerebral blood flow[24] A difference in regional blood flow may help hypoglycemic damage through either loss of autoregulation or delayed hypoperfusion. Neuronal injury in hypoglycemia may be limited to the areas with well-developed excitatory amino acid receptors.[15]

The neuronal injury in hypoglycemia develop epilepsy, mostly with a favorable prognosis and has been analyzed in previous papers. Recently, Fong et al. reported a benign outcome in 9 out of 11 patients with focal seizures in line with Caraballo and Montassir's reports.[5,7,8] In contrast to these, studies from Turkey and India reported intractable seizures in 12 out of 23 and five out of 12 children, respectively.[6,25] However, in these two studies patients had additional neonatal co-morbidities. Our study demonstrates a variable range of electrophysiological outcome ranging from benign occipital epilepsy to intractable epilepsy in children with isolated neonatal hypoglycemia. Although usually have a favorable outcome in previous studies, exceptionally it may diverge to intractable epilepsy and epileptic encephalopathy with continuous spike and wave during sleep, as seen in our group. Patients in our series had isolated hypoglycemia in the neonatal period, 23 out 36 had intractable epilepsy and four developed epileptic encephalopathy with continuous spike and wave during sleep. Occipital lobe injury alone does not typically cause continuous spike and wave discharges whereas damage to the neighboring cortex can be the real cause.[12,14,26] The reason why some of these patients have intractable seizures is not known. Infantile spasms, generalized seizures, focal seizures, and febrile seizures have been previously reported in these patients.[2] In our study, eight patients had infantile spasms. Abnormal discharges in the occipital lobe are thought to activate thalamus and reticular system causing infantile spasms.[26,27] The differences in outcome of our patients may reflect the higher proportion of children with infantile spasms and the severity or duration of neonatal hypoglycemia. Referral bias to our tertiary center specializing in epilepsy may also contribute to the capture of more unusual clinical presentations of this condition.

The seizure semiology and electrophysiological findings with stereotyped occipital interictal discharges with sleep activation, and a favorable outcome in thirteen patients are

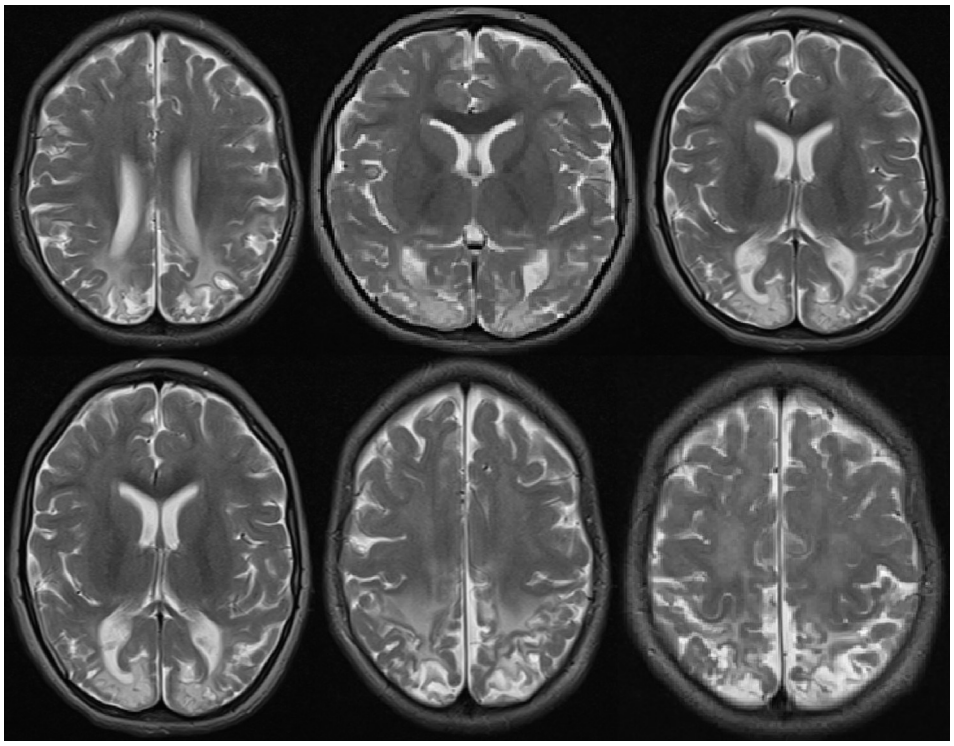


Fig. 3 – Axial T2 imagings: Gliosis in the bilateral parietal and occipital white matter with cortical atrophy.

suggestive of early-onset form of benign occipital epilepsy. Benign focal epilepsies, both occipital and centrotemporal spikes, are common in children with a variety of static brain lesions and developmental disabilities.[28–30] These benign focal epilepsies reflect an age related maturational instability phenomena and the relationship to the underlying neurodevelopmental disorder or lesion may be coincidental. It is important to make a syndromic conceptualization because of the age-limited nature.

Our data also emphasizes the importance of recognizing inadequate feeding in the first days of life as a potential cause of hypoglycemia. Transient neonatal hypoglycaemia due to inadequate feeding was diagnosed in thirty three children in our series. Because it may have devastating consequences such as intractable epilepsy and is a preventable state of hypoglycemia, it should be managed properly to avoid adverse outcomes. As a persistent cause in neonatal hypoglycemia, an early and rapid diagnosis of hyperinsulinemic hypoglycemia is essential for preventing brain damage. Two patients with hyperinsulinemic hypoglycemia in our series had infantile spasm, hypsarthymia on EEG and evolved to intractable epilepsy at follow-up. Studies regarding seizure outcome in hyperinsulinemic hypoglycemia are lacking. Similar to our patients, recently Fong et al. reported five patients with hyperinsulinemic hypoglycemia who presented with infantile spasm and have ongoing seizures despite treatment and reminded hyperinsulinaemic hypoglycaemia as a cause of persistent and recurrent neonatal hypoglycaemia.[8] Our series has several advantages over previous studies, such as large number, a homogenous group of isolated neonatal insult, and long follow-up term covering electroclinical aspects. Our results are quite different from previous studies.[5,8] The retrospective nature is the restrictive factor in our study. Because we did not have any knowledge regarding the time that passed before the patient applied to our clinic, no comment could be made on this issue. Further studies are needed for defining the reason why some patients have a intractable epilepsy and to develop a protocol for the prevention of permanent brain damage due to hypoglycemia.

5. Conclusion

To our knowledge, we present the largest group of epileptic patients with a single neonatal insult. This study establishes a wide range of electroclinical manifestation and seizure outcome may evolve as a consequence of neonatal hypoglycemia and can range from benign occipital lobe seizures to epileptic encephalopathy with continuous spike and wave during sleep and intractable epilepsy. In our study, we observed that most of the patients, either manifesting focal or generalized seizures, further develop intractable epilepsy. This finding establishes neonatal hypoglycemia as a possible cause to be considered in any case of intractable epilepsy. Magnetic resonance imaging studies are essential to define the characteristics of cerebral lesions secondary to neonatal hypoglycemia and to distinguish from other neonatal insults.

Conflict of interest

The authors have indicated they have no potential conflicts of interest to disclose.

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