NÖRO PSİKİYATRİ ARŞİVİ
ARCHIVES OF NEUROPSYCHIATRY

RESEARCH ARTICLE

Arch Neuropsychiatry 2022;59:296–302
https://doi.org/10.29399/npa.27997

Neurodevelopmental Outcome in Patients with Typical Imaging Features of Injury as a Result of Neonatal Hypoglycemia

Emek UYUR YALÇIN[1], Hülya MARAŞ GENÇ[2], Asuman BAYHAN[3], Yonca ANIK[4], Bülent KARA[5]

[1]Department of Pediatric Neurology, Zeynep Kamil Maternity and Children's Diseases Training and Research Hospital, University of Health Sciences, İstanbul, Turkey
[2]Department of Pediatric Neurology, Ümraniye Training and Research Hospital, University of Health Sciences, İstanbul, Turkey
[3]Department of Pediatric Psychologist, Faculty of Medicine, Kocaeli University, Kocaeli, Turkey
[4]Department of Radiology, Faculty of Medicine, Kocaeli University, Kocaeli, Turkey
[5]Division of Pediatric Neurology, Department of Pediatrics, Faculty of Medicine, Kocaeli University, Kocaeli, Turkey

ABSTRACT

Introduction: Previous reports described a pattern of hypoglycemia-induced damage predominantly affecting the parieto-occipital regions. The long-term neurological sequelae of severe neonatal hypoglycemic encephalopathy include developmental delay, poor head growth, learning or behavioral difficulties, visual impairment, and epilepsy. This study reports neurodevelopmental outcome of children with neonatal hypoglycemia-associated parieto-occipital brain injury who were evaluated in our pediatric neurology outpatient clinic for different neurological complaints.

Methods: We retrospectively reviewed patients who were followed at Kocaeli University Hospital, Pediatric Neurology Department between 2007 and 2015. Patients (n=42) with predominately parieto-occipital lesions on magnetic resonance imaging (MRI) with the typical pattern of neonatal hypoglycemia were evaluated. Patients with documented hypoglycemia (n=21) were included in this study. Patients (n=9) with recurrent episodes of hypoglycemia longer than 12 hours were evaluated as prolonged hypoglycemia.

Results: Eleven patients (52.4%) experienced seizures in the neonatal period. Eighteen patients (85.7%) developed epilepsy during the follow-up. Refractory seizures were observed in 8 patients (38.1%). Nine patients (42.9%) manifested microcephaly, seven patients (33.3%) manifested cerebral palsy. Parieto-occipital involvement and the spasticity rate were statistically high in patients with prolonged hypoglycemia (p<0.01). Two patients had autistic features and four patients (19%) had attention deficit hyperactivity disorder. VEP studies could be performed in 18 of 21 patients. All patients had abnormal VEP results.

Conclusion: We are of the opinion that most patients of neonatal hypoglycemia are not always documented. Patients under risk and patients with symptoms of hypoglycemia should be vigorously screened and treated to prevent neurologic impairments including cerebral palsy, epilepsy and visual disturbance.

Keywords: Cerebral palsy, epilepsy, neonatal hypoglycemia, neurodevelopmental outcome, parieto-occipital brain injury, visual outcome

Cite this article as: Uyur Yalçın E, Maraş Genç H, Bayhan A, Anık Y, Kara B. Neurodevelopmental Outcome in Patients with Typical Imaging Features of Injury as a Result of Neonatal Hypoglycemia. Arch Neuropsychiatry 2022;59:296–302.

INTRODUCTION

Glucose is essentially important for brain metabolism and development. Although hypoglycemia is the most common metabolic disturbance in the neonatal period, brain injury resulting from isolated neonatal hypoglycemia is rare (1). Transitional hypoglycemia occurs after abrupt cessation of placental blood supply; glucose level decreases to the lowest levels within 1–2 hour after birth, increases within 2–4 hours and reaches the adult normal values after 48 hours. Such transitional hypoglycemia is common in the healthy newborn. However, some neonates with specific risk factors may experience a more prolonged and severe hypoglycemia. Blood glucose concentration <47 mg/dL was defined as the critical threshold associated with adverse neurodevelopmental outcomes in a multicenter study, enrolling infants less than 1850 g, by Lucas et al. in 1988 (2). This value of '47 mg/dL' has been widely accepted for definition of neonatal hypoglycemia for all infants, including term healthy infants with no risk factors (3). The Pediatric Endocrine Society (PES) and the American Academy of Pediatrics (AAP) have slightly different recommendations for

Highlights

- **Neonatal hypoglycemia-induced brain injury predominantly affects the parieto-occipital regions.**
- **It can cause developmental delay, microcephaly, epilepsy, behavioral and visual problems.**
- **Close observation is important as every newborn can experience hypoglycemia.**
- **There is no cutoff value below which brain injury definitely occurs.**
- **Early diagnosis and treatment determines the neurological prognosis.**

Correspondence Address: Emek Uyur Yalçın, Sağlık Bilimleri Üniversitesi Zeynep Kamil Kadın Doğum ve Çocuk Hastalıkları Eğitim ve Araştırma Hastanesi, Pediatri Anabilim Dalı, İstanbul, Turkey • **E-mail:** emekuyur@gmail.com
Received: 17.08.2021, **Accepted:** 21.11.2021, **Available Online Date:** 08.11.2022

evaluation and management of neonatal hypoglycemia. According to PES, a blood glucose level less than 50 mg/dL in the first 48 hours, and less than 60 mg/dL after 48 hours is suggested as abnormal. According to AAP, blood glucose at greater than 45 mg/dL (2.50 mmol/L) by age 24 hours is recommended (4, 5).

A universally accepted glucose level, which is sufficient to prevent unfavorable neurodevelopmental outcomes in the first 48 hours does not exist. Individual susceptibility to brain injury varies based on factors such as gestational age and ability of the infant to produce and use alternative cerebral fuels (6). The lower limit is likely higher when concomitant insults accompanying hypoglycemia, such as hypoxemia and ischemia, increase glucose requirement and cause brain damage (7). To sum up, many authorities believe that the definition of hypoglycemia must be individualized according to the infant's clinical condition.

Since the 1990s, many neuroimaging studies have described a correlation between neonatal hypoglycemia and brain injury involving the occipital lobes and posterior parieto-temporal regions (8–10). Although the breadth of involvement varies considerably depending on the degree and duration of hypoglycemia and concomitant insults, occipital predominance was underlined. Previous researchers reported that selective occipital vulnerability might be related to the high degree of axonal migration and synaptogenesis occurring within the occipital lobe during the neonatal period (8–11). It is well known that the long-term neurological sequelae of severe neonatal hypoglycemic encephalopathy include developmental delay, microcephaly, learning or behavioral difficulties, visual impairment, and epilepsy (6, 12–16). This study reports children with neonatal hypoglycemia-associated parieto-occipital brain injury who were evaluated in our pediatric neurology outpatient clinic for different neurological complaints.

METHODS

We retrospectively reviewed the medical records of outpatients who were followed at Kocaeli University Hospital, Pediatric Neurology Department between 2007 and 2015. Patients (n=42) with predominately parieto-occipital lesions on magnetic resonance imaging (MRI) with the typical pattern described for neonatal hypoglycemia were evaluated.

Patients whose hypoglycemia was documented with medical records (n=21) were included in this study. This study was approved by the Ethics Committee of Kocaeli University Hospital.

Patients with inborn errors of metabolism, congenital anomalies, brain malformation, or chromosomal abnormality were also excluded, even if they had a history of neonatal hypoglycemia. On the other hand, patients with preterm birth, fetal distress, and neonatal asphyxia were included because they are regarded to be associated with possible factors related to neonatal hypoglycemic encephalopathies. Hypoglycemia occurred between the first 2 hours and 7 days after birth in all patients. Patients with recurrent episodes of hypoglycemia longer than 12 hours were regarded as prolonged hypoglycemia. The educational status of the parents and whether they received breastfeeding counseling were questioned.

Perinatal history, onsets of epilepsy, major seizure types, clinical course of epilepsy, and electroencephalography (EEG) and neuroimaging findings were studied through medical records. Seizures and epileptic syndromes were classified according to the 2017 classification of the International League Against Epilepsy (ILAE) (17, 18). Asleep and awake interictal electroencephalograms were performed using the 10–20 international system. Magnetic resonance images, performed in all patients according to conventional techniques in different centers, were evaluated by the same child neuroradiologist (YA). Psychometric evaluation was performed by the same psychologist (AB), using the Wechsler Intelligence Scale for Children Revised (WISC-R) in patients aged 6–16 years and the Denver II test in patients ≤6 years old. WISC-R results were classified as average when the IQ was between 90 and 109, low average when it was between 80 and 89, borderline when it was between 70 and 79, mild cognitive impairment when it was between 50 and 69, moderate when it was between 35 and 49, and severe when it was below 34. In addition to the review of the medical records, neurologic evaluation, visual examination, visual evoked potential (VEP) testing were performed. The VEP results were classified as abnormal if cortical responses were poor or absent.

RESULTS

The data collected were statistically analyzed using the Statistical Package for Social Sciences (SPSS) software (version 15.0). In the analyses comparing the groups as well as the descriptive statistical methods (mean, standard deviation, minimum, maximum, etc.), the chi-square test and the Fisher exact test were used for categorical variables; the Mann-Whitney U test was used for comparisons of means between the groups. The results were assessed within a confidence range of 95%, considering significance to be at p<0.05.

Demographic Data and Perinatal Risk Factors

There were 21 patients; male to female ratio was 16:5. The ages ranged between 3 and 181 months (mean 87.71±47.25 months, median 84 months) in the last follow-up. The age at initial admission to our pediatric neurology clinic ranged between 3 and 122 months (mean 48.38±34.26 months, median 35 months). The mean duration of follow-up was 39.33±24.47 months (median 37 months, range 0–84 months) in 21 patients. One patient (patient 11) could be evaluated once, and no follow-up data was available. Prolonged hypoglycemia was detected in 9 (42.8%) patients.

All patients except one (patient 16) had risk factors that made them prone to hypoglycemia, including prematurity in 5 patients, being small for gestational age in 10 patients, being large for gestational age in 1 patient, low/high maternal age in 4 patients, gestational hypertension in 1 patient, maternal infection in 1 patient, preeclampsia/eclampsia in 4 patients, pathologic neonatal jaundice in 7 patients, polycythemia in 1 patient, sepsis in 9 patients, placenta previa and asphyxia in 1 (patient 14), necrotizing enterocolitis in 1 (patient 4), and feeding difficulties in 18 patients. Congenital hyperinsulinism was diagnosed in 1 patient (patient 11), who received sirolimus following glucose infusions, and steroid and diazoxide therapy. Seizure as a presenting symptom of hypoglycemic state occurred in 11 patients. In the other 10 infants, symptoms recorded included poor feeding, irritability, tremor, cyanosis, and hypoactivity. Demographic data, prenatal/postnatal problems and other risk factors (feeding difficulty, high/low maternal age, maternal infection, pathologic jaundice, neonatal sepsis, preeclampsia, necrotizing enterocolitis, gestational hypertension, congenital hyperinsulinism, polycythemia, placenta previa) were summarized in Table 1.

Thirteen mothers (61.9%) had received breastfeeding counseling. Fifteen infants had been initially fed with breast milk (71.4%) and 6 had been first fed with formula (28.6%).

Electro-clinical and Neuroimaging Findings

Eleven patients (52.4%) experienced seizures in the neonatal period. Eighteen patients (85.7%) developed epilepsy during the follow-up, 11 of them (52.4%) had neonatal seizures as a presenting symptom of hypoglycemia. The median age at onset of epilepsy after the neonatal period was 19 months, with a range of 2 months to 96 months (29.89±30.18 months). Three patients (14.3%) did not have epilepsy after the neonatal period despite abnormal MRI. Because of the small number of patients without epilepsy (n=3; patient no 4, 11 and 13), correlation

Table 1. Summary of the demographic data, risk factors, and prenatal/postnatal problems

Patient no	Age at initial admission (months)	Age (months)	Sex	Gestational age (weeks)	Birth weight	Delivery method	Risk factors	Asphyxia	Prolonged hypoglycemia	Neonatal seizure
1	46	92	M	40	LGA	VD	FD, HMA	–	–	–
2	50	134	F	40	AGA	CS	FD	–	–	–
3	35	66	F	38	SGA	CS	FD, PJ	–	–	+
4	29	53	M	36	SGA	CS	FD, PJ, NS, NEC	–	+	–
5	24	70	M	39	AGA	VD	FD, NS, LMA	–	–	+
6	80	160	M	32	SGA	CS	FD	–	–	+
7	28	84	F	37	SGA	CS	FD, MI, PJ	–	–	+
8	20	44	M	39	AGA	VD	FD, PJ, NS	–	+	–
9	113	181	M	40	SGA	VD	FD, GHT, PJ, HMA	–	+	+
10	86	90	M	32	AGA	CS	NS, PE	–	+	+
11	3	3	M	39	AGA	VD	FD, NS, LMA, CH	–	–	–
12	8	31	M	37	SGA	CS	FD, NS	–	–	+
13	10	23	M	38	SGA	CS	FD, PE	–	–	–
14	61	121	M	39	SGA	CS	FD, PJ, NS, P, PP	+	+	–
15	98	117	M	41	AGA	CS	FD, NS	–	–	+
16	25	95	M	39	AGA	CS	–	–	+	–
17	64	101	F	30	AGA	CS	FD, PE	–	+	–
18	32	80	F	38	SGA	VD	PJ, NS	–	+	+
19	49	58	M	36	AGA	CS	FD, PE	–	–	+
20	122	169	M	38	SGA	VD	FD	–	+	+
21	33	70	M	40	AGA	CS	FD	–	–	–

CH: Congenital Hyperinsulinism; CS: Cesarean Section; F: Female; FD: Feeding Difficulty; GHT: Gestational Hypertension; HMA/LMA: High/low Maternal Age; M: Male; MI: Maternal Infection; NEC: Necrotizing Enterocolitis; NS: Neonatal Sepsis; P: Polycythemia; PE: Preeclampsia; PJ: Pathologic Jaundice; PP: Placenta Previa; VD: Vaginal Delivery.

between MRI findings and neonatal seizures and epilepsy could not be evaluated statistically.

The most common type of initial seizure was focal aware seizure. Seven patients presented with focal aware seizures; 2 had focal impaired awareness seizures. One patient presented generalized tonic-clonic seizures. Six patients had generalized epileptic spasms and 1 patient had atonic seizure. The type of seizure type was not identified for 1 patient. Febrile seizure was noted in 3 patients, and all 3 developed epilepsy. Status epilepticus occurred in 5 patients during the follow-up.

The most common type of last seizure was focal impaired awareness seizure (*n*=6). Four patients presented focal aware seizures. Two patients presented generalized tonic-clonic seizures. Four had atonic seizures and 2 had myoclonic seizures. Six patients were diagnosed with West syndrome, two of them evolved to Lennox-Gastaut syndrome. Of these six patients with epileptic encephalopathy, 4 of them had prolonged hypoglycemia, two of them had a blood glucose of <20 mg/dL in the neonatal period.

All patients with epilepsy received antiepileptic drugs after the first or second seizure, adrenocorticotropic hormone was used in 4 patients (%19) with West or Lennox-Gastaut syndrome. In addition to drugs, one patient received ketogenic diet (patient 16).

Refractory seizures were observed in 8 patients (38.1%). Seizures were well controlled in most of the patients (*n*=10, 47.6%) or recurred sporadically, suggesting a benign course. Two patients (9.5%) were seizure free and were no longer on antiepileptic drugs. Three patients (14.3%) did not develop epilepsy during the follow-up. The electroclinical findings are shown in Table 2.

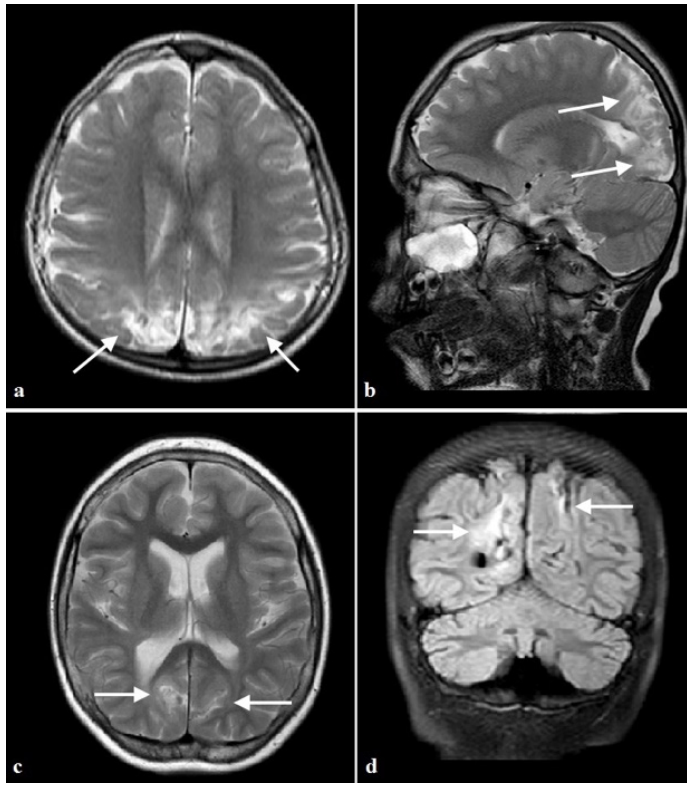

Figure 1. MRI of patient 9, T2-weighted axial images **(a)** and T2-weighted sagittal image **(b)** show bilateral parieto-ocipital encephalomalacia. MRI of patient 20, T2-weighted axial image **(c)**, and fluid-attenuated inversion recovery coronal image **(d)** show bilateral occipital encephalomalacia more prominent at the right hemisphere (*white arrows*).

MRI revealed unilateral cortical injury and white matter T2 prolongation in the occipital regions in 5 patients (23.8%) and bilateral in 6 patients (28.5%). Unilateral parieto-occipital involvement was detected in 4 patients (19.0%) and bilateral in 6 patients (28.5%), presenting as white matter hyperintensity on T2 sequences with or without cortical injury. Basal ganglia involvement was noted in 1 patient with a history of asphyxia, in addition to bilateral parietal-occipital involvement (patient 14). Periventricular leukomalacia (PVL) was detected as an additional feature in 3 patients. Cranial ultrasonography studies were performed during the neonatal period in 5 patients and the results were normal.

Parieto-occipital involvement on MRI and spasticity rate were statistically high in patients with prolonged hypoglycemia (n=9) ($p<0.01$). The neuroimaging findings are presented in Table 2. MRI findings of two patients are shown in Figure 1.

Neurologic and Visual Outcome

Nine patients (42.9%) manifested microcephaly. Seven patients were diagnosed with cerebral palsy; 1 with spastic diparesis, 3 with spastic hemiparesis, and 3 with spastic quadriparesis. No patients manifested ataxia or dyskinesia.

Table 2. Electro-clinical and neuroimaging findings

Patient no	Febrile seizure	Onset of epilepsy (months)	First seizure type	Last major seizure type	First interictal EEG	Last interictal EEG	MRI findings	Seizure outcome
1	–	9	FAS	FIAS	Right O spikes	Right O spike and sharp waves	Bilateral O	Refractory, SE history
2	–	96	FAS	FIAS	Bilateral O spikes	Left O spikes	Bilateral O	Well controlled on monotherapy
3	–	30	FIAS	FIAS	No abnormalities	ESES	Bilateral O	Well controlled on monotherapy
4	–	–	No seizures	No seizures	Generalized abnormal background activity	Generalized abnormal background activity	Unilateral PO, PVL	No seizures
5	+	12	Unidentified	FIAS	Left O spikes	No abnormalities	Unilateral O	Well controlled on monotherapy
6	+	84	FAS	FAS	Left O spikes	No abnormalities	Unilateral O	No seizures no therapy
7	–	36	FAS	FAS	No abnormalities	Left O spikes	Unilateral O	Well controlled on monotherapy
8	–	14	GES	Atonic	Hypsarrhythmia	Multifocal independent spike and sharp slow waves	Bilateral PO	Refractory
9	–	2	GES	Atonic	Hypsarrhythmia	Slow (1.5-2.5 Hz) spike-and-wave pattern	Bilateral PO	Refractory
10	–	72	FAS	FAS	Bilateral O spikes	Left O spikes	Unilateral PO	Well controlled on monotherapy
11	–	–	No seizures	No seizures	Focal abnormal background activity	Focal abnormal background activity	Bilateral O	No seizures
12	–	3	GES	Atonic	Hypsarrhythmia	Right O spike and sharp slow waves	Unilateral O	Refractory, SE history
13	–	–	No seizures	No seizures	No abnormalities	Generalized abnormal background activity	Bilateral PO, PVL	No seizures
14	+	24	FIAS	FIAS	Bilateral O spikes	Bilateral PO spikes	Bilateral PO, PVL, basal ganglia	Well controlled on monotherapy
15	–	5	GES	GTCS	Hypsarrhythmia	Generalized abnormal background activity	Bilateral O	Refractory
16	–	3	GES	Myoclonic	Hypsarrhythmia	Slow (1.5-2.5 Hz) spike-and-wave pattern	Bilateral PO	Refractory, SE history
17	–	60	GTCS	GTCS	Left O spikes	No abnormalities	Unilateral PO	No seizures no therapy
18	–	1	GES	Atonic	Hypsarrhythmia	Multifocal independent spike and sharp slow waves	Bilateral PO	Refractory
19	–	48	FAS	FIAS	Right O spikes	No abnormalities	Unilateral O	Well controlled on monotherapy, SE history
20	–	8	Atonic	Myoclonic	Generalized discharge	Generalized discharge	Bilateral O	Refractory, SE history
21	–	30	FAS	FAS	Bilateral PO spike and sharp slow waves	Bilateral PO spikes	Unilateral PO	Well controlled on monotherapy

ESES: Electrical status epilepticus during slow sleep; FAS: Focal Aware Seizure; FIAS: Focal Impaired Awareness Seizure; GES: Generalized Epileptic Spasm; GTCS: Generalized Tonic-Clonic Seizure; O: Occipital; PO: Parieto-Occipital; SE: Status Epilepticus.

Table 3. Neurologic and visual outcome

Patient no	Microcephaly	Cerebral palsy	Mental and development level	ADHD	Specific learning difficulties	Autism spectrum disorder	VEP	Strabismus	Refractive error	Optic disc examination
1	–	–	Mild CI	–	–	+	ND	–	–	Normal
2	–	–	Normal	–	–	–	ND	–	–	Normal
3	–	–	Normal	–	–	–	No response	–	–	Normal
4	+	Quadriparetic	GDD	–	–	–	Elongated latency	+	–	Normal
5	–	–	Normal	+	+	–	Elongated latency	–	–	Atrophy
6	–	–	Normal	–	+	–	No response	–	+	Normal
7	+	–	Mild CI	+	–	+	No response	+	+	Normal
8	–	Hemiparetic	GDD	–	–	–	Elongated latency	–	+	Normal
9	+	Diparetic	GDD	–	–	–	Elongated latency	+	+	Pallor
10	–	–	Normal	–	+	–	No response	+	–	Normal
11	+	–	Gross motor delay	–	–	–	ND	+	–	ND
12	+	–	GDD	+	–	–	Elongated latency	+	–	Normal
13	+	Quadriparetic	GDD	–	–	–	Elongated latency	–	–	Pallor
14	+	Hemiparetic	Moderate CI	–	+	–	Elongated latency	+	+	Normal
15	–	–	Moderate CI	+	–	–	Elongated latency	+	+	Pallor
16	+	Quadriparetic	GDD	–	–	–	Elongated latency	+	–	Pallor
17	–	–	Normal	–	+	–	Elongated latency	+	+	Normal
18	+	–	GDD	–	+	–	Elongated latency	+	+	Pallor
19	–	–	Normal	–	–	–	No response	–	–	Normal
20	–	Hemiparetic	Mild CI	–	–	–	Elongated latency	+	+	Pallor
21	–	–	GDD	–	–	–	Elongated latency	+	+	Normal

ADHD: Attention Deficit Hyperactivity Disorder; CI: Cognitive Impairment; GDD: Global Developmental Delay; ND: Not Done; VEP: Visual Evoked Potential

Patients were evaluated with the Denver II test and 4 were evaluated with WISC-R according to age group. Only 7 patients (33.3%) were evaluated as normal in psychometric and developmental assessment. Global developmental delay was detected in 8 patients and isolated gross motor delay in 1 patient according to the Denver II test. Three patients had mild cognitive impairment and 2 had moderate cognitive impairment according to WISC-R. In addition, 2 patients had autistic features and 4 patients had attention deficit hyperactivity disorder. Specific learning disabilities were identified in 5 patients.

Thirteen patients (61.9%) had visual impairment with strabismus and 10 patients (47.6%) had refractory error. Severe cortical visual impairment was documented in 3 patients (14.3%). The optic disc was examined in 20 patients. Six of these patients had optic pallor and 1 had optic atrophy. During the last follow-up, VEP studies could be performed in 18 of 21 patients. All patients had abnormal VEP results; VEP demonstrated significantly increased latency in 13 patients, and a response could not be obtained in 5 patients. The neurologic and visual outcomes are shown in Table 3.

DISCUSSION

We evaluated patients (*n*=42) with predominately parieto-occipital lesions on MRI with the pattern typical for neonatal hypoglycemia. Most of the patients were born at other hospitals and were referred to our pediatric neurology clinic for various reasons. The neonatal medical records were missing or inadequate in most patients. Because identification of suspected hypoglycemia was a subjective decision by the pediatric neuroradiologist and neurologist, patients with documented hypoglycemia (*n*=21) according to medical records were included in this study.

In our series, male to female ratio was 16:5 (76.2% to 23.8%). Male predominancy was present in previous studies similar to our study (12–15). Various risk factors for neonatal hypoglycemia have been reported in previous studies. Low birth weight, neonatal feeding difficulties, and cesarean delivery were reported by Udani et al. (19). Similarly, in our study, low birth weight (n=10, 47.6%) and cesarean delivery (n=14, 66.7%) were found to be significant risk factors. We detected that most

of the patients (n=18, 85.7%) had feeding difficulties in the neonatal period. Unlike other reports, we investigated whether the mothers had received breastfeeding counseling. We found that 38% of our patients did not receive breastfeeding counseling despite intensive breastfeeding campaigns in our country.

We know that concomitant insults accompanying hypoglycemia, such as hypoxemia and ischemia, increase brain damage and may cause more serious and varied injuries (7, 20). Basal ganglia are found to be involved to a lesser extent (12, 21). In our study, additional lesions were noted in 3 patients, two of them were term babies, and one of them was late preterm. Basal ganglia involvement and PVL were detected in 1 patient with a history of asphyxia and PVL was detected in 2 patients. In addition; we found that parieto-occipital involvement on MRI and the spasticity rate were statistically high in patients with prolonged hypoglycemia (p<0.01). As can be expected, the severity of the radiological injury and clinical findings correlate with the duration of hypoglycemia (2). However, further studies are needed to evaluate the relationship between hypoglycemia duration and severity of the brain injury more clearly.

We observed a high rate of epilepsy (85.7%) and cerebral palsy (33.3%) in our study. Among seven patients with cerebral palsy, all patients were term babies except one, who was born at 36 weeks old. These higher rates may be attributed to the severity of neonatal hypoglycemia, concomitant insults and also our patient selection method that only included patients with radiologic sequel of neonatal hypoglycemia.

In our study, all patients with a history of neonatal seizures (n=11), and seven out of ten patients without a history of neonatal seizure developed epilepsy. The median age of onset of epilepsy after the neonatal period was 19 months, with a range of 2 months to 96 months (29.89±30.18 months) and the most common type of initial seizure was focal aware motor seizure. The typical seizure semiology for occipital lobe epilepsy including ictal vomiting was observed in only 6 of our patients (9.5%). The median age of seizure onset was 18–36 months and focal seizures were the major seizure type in other reports (7, 14, 15). Our findings were similar to these reports. Refractory epilepsy rate was 38.1% which is higher than refractory epilepsies in childhood epilepsies (6–14%) (22). Epilepsy rates were 80–92.3% and refractory epilepsy rates were 38.5–63.8% in other pediatric studies in Turkey where children with radiologic evidence of neonatal hypoglycemia were included (12, 23).

Although neonatal hypoglycemia is frequent, not all patients who experienced neonatal hypoglycemia are followed for possible neurodevelopmental risks. Children with important neurologic problems, particularly seizures or developmental delay, are brought to pediatric neurology clinics. So the underlying conditions can only be evaluated with prospective studies of children who had neonatal hypoglycemia. A large prospective study on newborns (gestational age ≥35 weeks) who are at risk for hypoglycemia and who underwent regular measurements of blood glucose for up to 48 hours of life was conducted and the newborns were treated to maintain blood glucose concentrations greater than 47 mg/dL regardless of postnatal age. Neurodevelopmental outcome at two years of age was similar between infants in whom intervention for hypoglycemia was provided compared to those without evidence of hypoglycemia (24). However, at 4.5 years of age follow-up assessment demonstrated that children who were treated for neonatal hypoglycemia had poorer executive and visual motor functions (25).

Stenninger et al. showed that hypoglycemic infants of diabetic mothers develop minimal brain dysfunction/deficit in terms of attention, motor control, and perception (26). Besides microcephaly, learning deficits, behavioral problems, and autistic behavior have been reported previously (12, 13, 15, 23, 27). In our report, 2 patients had autistic features and 4 patients had attention deficit hyperactivity disorder. Furthermore, specific learning disabilities were identified in 5 patients. In light of such information, we suggest that long-term neurodevelopmental follow-up of these infants is needed for early detection of potential learning and behavioral problems.

Previous reports found optic nerve hypoplasia associated with neonatal hypoglycemia (28). Per et al. documented esotropia/exotropia in 19 patients and optic atrophy in 11 of 60 patients (13). Similar to the previous reports, 6 of 20 patients had optic pallor and 1 had optic atrophy in our study. The high prevalence of abnormal VEP in our patients and in the literature even without clinical visual loss highlights the need to perform VEP in all patients with a history of neonatal hypoglycemia so that neonates with high risk can be referred for early rehabilitation.

The Academy of Breastfeeding Medicine (ABM) have guidelines for blood glucose monitoring and treatment of hypoglycemia in term and late preterm neonates. They do not recommend routine blood glucose monitoring in healthy term infants, which may harm the normal establishment of breastfeeding. Instead they emphasize that "at risk infants should be screened, followed up as needed, and treated if there are clinical signs or suggested thresholds are reached" (29). In this study, all patients were born in a health care center and almost all had risk factors for hypoglycemia, but they experienced brain injury secondary to neonatal hypoglycemia. We agree with the ABM recommendations in terms of blood glucose monitoring but health care workers should be more aware of infants at risk for hypoglycemia, recognize the clinical manifestations of hypoglycemia, and treat according to the guidelines. Because concomitant conditions such as hypoxia and ischemia markedly increase brain damage and exacerbate neurologic outcomes, safe blood glucose level should be individualized in every patient.

This study has some limitations. First, glucose levels were obtained from a retrospective chart review. Second, because of the small number of non-epileptic patients, we cannot investigate the relationship between the development/course of epilepsy and the severity of hypoglycemia.

It is well known that many patients with brain damage secondary to neonatal hypoglycemia face developmental delay, microcephaly, learning disabilities, behavioral problems, visual impairment, and epilepsy. The findings in our study confirm these data in many ways. We also believe that the number of patients with undocumented hypoglycemia is as large as the number of patients with documented hypoglycemia. We observe that some of these patients were diagnosed retrospectively when they applied to the pediatric neurology outpatient clinic with various neurological complaints at different ages.

CONCLUSION

It is well known that an overwhelming number of patients with brain injury secondary to neonatal hypoglycemia demonstrate developmental delay, poor head growth, learning or behavioral difficulties, visual impairment, and epilepsy. The findings in our study confirm these data in many ways. In addition, we believe that the number of patients with undocumented hypoglycemia is just as large as the number of patients with documented hypoglycemia. We observe that some of these patients were diagnosed retrospectively when they applied to pediatric neurology outpatient clinics at different ages with various neurological complaints.

Every newborn may develop hypoglycemia; close observation of all neonates is therefore necessary. There is no cutoff value below which brain injury definitely occurs, but recognition and early treatment of neonatal hypoglycemia is crucial to prevent or minimize long-term neurologic sequelae. In addition, the significance of breastfeeding

counseling needs to be highlights and parents must be informed about the symptoms of hypoglycemia. This way, it may be possible to prevent hypoglycemia secondary to feeding difficulties and to create awareness for parents of non-hospitalized neonates.

Ethics Committee Approval: This study was approved by the Ethics Committee of Kocaeli University Hospital (Date: 29.04.2014-10/3).

Informed Consent: Since this study has a retrospective design, patient consent was not obtained.

Peer-review: Externally peer-reviewed

Author Contributions: Concept– EUY, BK; Design– EUY, BK; Supervision– BK, YA; Resources– EUY, HMG, AB; Materials– EUY, AB; Data Collection and/or Processing– EUY, AB, YA; Analysis and/or Interpretation– EUY, HMG, YA, BK; Literature Search– EUY, HMG; Writing Manuscript– EUY, HMG; Critical Review– BK, YA.

Conflict of Interest: The authors declare no conflict of interest.

Financial Disclosure: None

REFERENCES

1. Volpe JJ. Hypoglycemia and brain injury. In: Volpe JJ, editor. Neurology of the Newborn, 4th ed. Philadelphia: WB Saunders; 2001. p.497–520.
2. Lucas A, Morley R, Cole TJ. Adverse neurodevelopmental outcome of moderate neonatal hypoglycaemia. BMJ 1988;297:1304–1208. [Crossref]
3. Adamkin DH. Neonatal hypoglycemia. Semin Fetal Neonatal Med 2017;22:36–41. [Crossref]
4. Thornton PS, Stanley CA, DeLeon DD, Harris D, Haymond MV, Hussain K, et al. Pediatric Endocrine Society Recommendations from the Pediatric Endocrine Society for Evaluation and Management of Persistent Hypoglycemia in Neonates, Infants, and Children. J Pediatr 2015;167:238–245. [Crossref]
5. Adamkin DH; Committee on Fetus and Newborn. Clinical report-postnatal glucose homeostasis in late-term and preterm infants. Pediatrics 2011;127:575–579. [Crossref]
6. Burns CM, Rutherford MA, Boardman JP, Cowan FM. Patterns of cerebral injury and neurodevelopmental outcomes after symptomatic neonatal hypoglycemia. Pediatrics 2008;122:65–74. [Crossref]
7. Caraballo RH, Sakr D, Mozzi M, Guerrero A, Adi JN, Cersósimo RO, et al. Symptomatic occipital lobe epilepsy following neonatal hypoglycemia. Pediatr Neurol 2004;31:24–29. [Crossref]
8. Barkovich AJ, Ali FA, Rowley HA, Bass N. Imaging patterns of neonatal hypoglycemia. AJNR Am J Neuroradiol 1998;19:523–528. http://www.ajnr.org/content/ajnr/19/3/523.full.pdf
9. Murakami Y, Yamashita Y, Matsuishi T, Utsunomiya H, Okudera T, Hashimoto T. Cranial MRI of neurogically impaired children suffering from neonatal hypoglycemia. Pediatr Radiol 1999;29:23–27. [Crossref]
10. Filan PM, Inder TE, Cameron FJ, Kean MJ, Hunt RW. Neonatal hypoglycemia and occipital cerebral injury. J Pediatr 2006;148:552–555. [Crossref]
11. McDonald JW, Johnston MV. Physiological and pathophysiological roles of excitatory amino acids during central nervous system development. Brain Res Rev 1990;15:41–70. [Crossref]
12. Yalnizoglu D, Haliloglu G, Turanlı G, Cila A, Topcu M. Neurologic outcome in patients with MRI pattern of damage typical for neonatal hypoglycemia. Brain Dev 2007;29:285–292. [Crossref]
13. Per H, Kumandas S, Çoşkun A, Gümüs H, Öztop D. Neurologic sequelae of neonatal hypoglycemia in Kayseri. J Child Neurol 2008;23:1406–1412. [Crossref]
14. Montassir H, Maegaki Y, Ohno K, Ogura K. Long term prognosis of symptomatic occipital lobe epilepsy secondary to neonatal hypoglycemia. Epilepsy Res 2010;88:93–99. [Crossref]
15. Karimzadeh P, Tabarestani S, Ghofrani M. Hypoglycemia-occipital syndrome: a specific neurologic syndrome following neonatal hypoglycemia. J Child Neurol 2011;26:152–159. [Crossref]
16. Tam EWY, Widjaja E, Blaser SI, MacGregor DL, Satodia P, Moore AM. Occipital lobe injury and cortical visual outcomes after neonatal hypoglycemia. Pediatrics 2008;122:507–512. [Crossref]
17. Fisher RS, Cross JH, French JA, Higurashi N, Hirsch E, Jansen FE, et al. Operational classification of seizure types by the International League Against Epilepsy: position paper of the ILAE Commission for Classification and Terminology. Epilepsia 2017;58:522–530. [Crossref]
18. Scheffer IE, Berkovic S, Capovilla G, Connolly MB, French J, Guilhoto L, et al. ILAE classification of the epilepsies: position paper of the ILAE Commission for Classification and Terminology. Epilepsia 2017;58:512–521. [Crossref]
19. Udani V, Munot P, Ursekar M, Gupta S. Neonatal hypoglycemic brain injury: a common cause of infantile onset remote symptomatic epilepsy. Indian Pediatr 2009;46:127–132. http://www.indianpediatrics.net/feb2009/127.pdf
20. Salhab WA, Wyckoff MH, Laptook AR, Perlman JM. Initial hypoglycemia and neonatal brain injury in term infants with severe fetal acidemia. Pediatrics 2004;114:361–366. [Crossref]
21. Anderson JM, Milner RD, Strich SJ. Effects of neonatal hypoglycemia on the nervous system: a pathologic study. J Neurol Neurosurg Psychiatry 1967;30:295–310. [Crossref]
22. Arts WF, Brouwer OF, Peters AC, Stroink H, Peeters EAJ, Schmitz PIM, et al. Course and prognosis of childhood epilepsy: 5-year follow-up of the Dutch Study of Epilepsy in Childhood. Brain 2004;127:1774–1784. [Crossref]
23. Arhan E, Öztürk Z, Serdaroğlu A, Aydın K, Hirfanoğlu T, Akbaş Y. Neonatal hypoglycemia: A wide range of electroclinical manifestations and seizure outcomes. Eur J Paediatr Neurol 2017;21:738–744. [Crossref]
24. McKinlay CJ, Alsweiler JM, Ansell JM, Anstice NS, Chase JG, Gamble GD, et al; CHYLD Study Group. Neonatal Glycemia and Neurodevelopmental Outcomes at 2 Years. N Engl J Med 2015;373:1507–1518. [Crossref]
25. McKinlay CJD, Alsweiler JM, Anstice NS, Burakevych N, Chakraborty A, Chase JG, et al; Children With Hypoglycemia and Their Later Development (CHYLD) Study Team. Association of Neonatal Glycemia With Neurodevelopmental Outcomes at 4.5 Years. JAMA Pediatr 2017;171:972–983. [Crossref]
26. Stenninger E, Flink R, Eriksson B, Sahlen C. Long term neurological dysfunction and neonatal hypoglycemia after diabetic pregnancy. Arch Dis Child Fetal Neonatal Ed 1998;79:F174–F179. [Crossref]
27. Cowan F. Neonatal hypoglycemia: role in infantile epilepsy. Indian Pediatr 2009;46:122–123. http://www.indianpediatrics.net/feb2009/122.pdf
28. Fahnehjelm KT, Jacobson L, Hellstrom A, Lewensohn-Fuchs I, Ygge J. Visually impaired children with posterior ocular malformations: pre- and neonatal data and visual functions. Acta Ophthalmol Scand 2003;81:361–372. [Crossref]
29. Wight N, Marinelli KA; Academy of Breastfeeding Medicine. ABM clinical protocol #1: guidelines for blood glucose monitoring and treatment of hypoglycemia in term and late-preterm neonates, revised 2014. Breastfeed Med 2014;9:173–179. [Crossref]