

# Neurological and developmental outcome of children with neonatal hypoglycemic seizures

## Yenidoğan döneminde hipoglisemik nöbet öyküsü olan çocuklarda nörolojik ve gelişimsel prognoz

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### ABSTRACT

**Objective:** Neonatal hypoglycemia may lead to severe acute, and chronic neurological injuries. Hypoglycemic seizure usually follows long lasting periods of hypoglycemia and worsens cerebral injury as well as the prognosis. The aim of this study is to evaluate neurological and developmental outcomes of children with a history of neonatal hypoglycemic seizures.

**Methods:** 21 patients who had neonatal hypoglycemic seizures and followed up in Ege University Faculty of Medicine, Department of Pediatrics, Division of Child Neurology between January 1999 and May 2011 were included in this study. The electroencephalography, brain magnetic resonance imaging and visual evoke potential results of the patients were recorded. Mental and motor developmental outcomes were evaluated.

**Results:** The development of epilepsy, abnormal visual evoked potential responses and abnormal brain magnetic resonance findings in infants with a history of neonatal hypoglycemic seizures were found to be associated with poor neurodevelopmental outcome.

**Conclusion:** Newborns should be carefully monitored for hypoglycemia which causes severe and permanent but preventable neurological sequelae.

**Key words:** Neonate, hypoglycemia, epilepsy, prognosis

### ÖZET

**Amaç:** Neonatal hipoglisemi, hem akut hem de kronik dönemde ciddi nörolojik etkilenmelere neden olabilir. Hipoglisemik nöbet genellikle uzamış hipoglisemi süreci sonrası görülür ve serebral hasarlanmayı artırır. Bu çalışmanın amacı, yenidoğan döneminde hipoglisemik nöbet öyküsü olan çocukların, nörolojik ve gelişimsel sonuçlarının değerlendirilmesidir.

**Yöntemler:** Bu çalışmaya, Ege Üniversitesi Tıp Fakültesi Çocuk Hastanesi, Çocuk Nöroloji Polikliniğinde düzenli olarak takip edilmiş, 21 yenidoğan dönemi hipoglisemik nöbet öykülü çocuk dâhil edilmiştir. Olguların elektroensefalografileri, beyin manyetik rezonans görüntüleme ve görsel uyarılmış potansiyel sonuçları kaydedilmiş, gelişimsel ve nörolojik durumları değerlendirilmiştir.

**Bulgular:** Yenidoğan dönemi hipoglisemik nöbet öykülü çocuklarda, epilepsi gelişimi, anormal görsel uyarılmış potansiyel varlığı ve anormal beyin manyetik rezonans görüntüleme sonuçlarının hem nörolojik hem de gelişimsel açıdan kötü prognozla ilişkili olduğu saptanmıştır.

**Sonuç:** Yenidoğanlar, ağır ve kalıcı ancak önlenabilir nörolojik hasarlara neden olma olasılığı nedeniyle hipoglisemi açısından dikkatle izlenmelidir.

**Anahtar kelimeler:** Yenidoğan, hipoglisemi, epilepsi, prognoz

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## INTRODUCTION

Neonatal hypoglycemia is a common disorder that can cause severe neurological sequelae in neonates, with incidence rates reported to range from 0.13 to 0.44% in term, and from 1% to 5.5% in preterm neonates <sup>(1,2)</sup>. Hypoglycemia is defined as blood glucose level below 47 mg/dl in the neonatal period <sup>(3)</sup>. If hypoglycemia is prolonged or recurrent, it may result in acute systemic effects and neurological sequelae <sup>(1)</sup>. Neurological sequelae may present as cerebral palsy, mental retardation, refractory epilepsy, microcephaly, ataxia, loss of vision and learning disability <sup>(4,5)</sup>. Transient low blood glucose level is common in the neonatal period and it is considered a normal feature of adaptation to extrauterine life <sup>(6)</sup>. Hypoglycemic encephalopathy is caused by lack of available glucose in brain cells. The neurological symptoms of neonatal hypoglycemia are nonspecific and may present with irritability, tremor, jitteriness, seizures, hypotonia, exaggerated Moro reflex, acute encephalopathy and lethargy. Hypoglycemic seizures usually present within the first 72 hours and usually appear after 12 hours of continuous or recurrent hypoglycemia <sup>(7,8)</sup>. Other risk factors including perinatal asphyxia and fetal distress are highly present in neonatal hypoglycemic encephalopathy <sup>(9-13)</sup>. Hypoglycemic encephalopathy and hypoxic ischemic encephalopathy may not be clinically distinguishable <sup>(11-13)</sup>. Cerebral infarct is common in hypoxic ischemic encephalopathy, whereas selective neuronal necrosis occurs in hypoglycemic encephalopathy and neurotoxicity occurs as a result of release of excitatory aminoacids. Seizures are usually the first symptom of profound hypoglycemia. Hypoglycemia accompanied by symptomatic seizures is worse in prognosis than hypoglycemia without seizures <sup>(8,14)</sup>. Seizures increase neuronal activity and energy consumption, which in turn increases the risk of injury <sup>(1,14)</sup>. A number of possible mechanisms for cell damage due to hypoglycemia have been proposed <sup>(1,9,15)</sup>. Activation of N-methyl D-aspartic acid (NMDA) receptors by excitatory aminoacids, increased mitochondrial free

radical production, the onset of apoptosis, and change in cerebral energy metabolism have been held responsible for the pathogenesis of neonatal hypoglycemia <sup>(16)</sup>. Elevated glutamate impairs calcium homeostasis, leading to excitotoxicity and cell death. The reason why the occipital cortex is sensitive to hypoglycemia in the neonatal period has not been elucidated yet <sup>(10)</sup>. However, qualitative and quantitative studies investigating the development of the visual cortex of animals revealed a marked increase in the number of synapses in the occipital cortex during the first 8 weeks of the postnatal life. Therefore, changes in glucose level are believed to increase predisposition to damage in the occipital cortex, which is also supported by previous studies <sup>(4,7,10,11)</sup>. In this retrospective study, we evaluated neurodevelopmental outcome of children with neonatal hypoglycemic seizures.

## MATERIAL and METHODS

A total of 21 patients (7 girls, 14 boys) with hypoglycemic convulsions in the neonatal period (simultaneously measured blood glucose level: < 47 mg/dl) who were followed up in Ege University Faculty of Medicine, Department of Child Neurology between January 1999 and May 2011 were enrolled in this study. Family history, birth history, demographic characteristics of the patients were examined, and results of physical and neurological examinations were recorded. The blood glucose levels of the neonates during seizure in the neonatal period and seizure semiology were recorded and data about ongoing seizures and antiepileptic drug history were obtained. Electroencephalographic (EEGs) examination results at last admission were recorded. The visual function of the patients was evaluated using visual evoked potential (VEP) performed between 6- 9 months of age. Brain magnetic resonance images (MRI) were taken in all patients between 12 and 24 months of age. Motor and mental development were assessed by Ankara Developmental Screening Test in patients younger than 6 years of age and by Wechsler

Intelligence Scale for Children-Revised (WISC-R) in patients older than 6 years of age. Ankara Developmental Screening Test is adapted from the Denver Test for Turkish children by Yalaz and Epir in 1983<sup>(17)</sup>. The test is appropriate for infants aged 0 to 72 months, and evaluates fine motor, and gross motor functions, language, and adaptive personal/social skills. Scores are given for these four skills and total development. Scores between age-normative values and 20% of those values are taken as near normal and refers to IQ scores over 80. Scores between 20 and 30% of age normative values are recorded as being borderline and refer to IQ scores of 70 to 79. Scores less than 30% of age normative values are scored as having significant delay. Total scores for general development are also recorded. Scores between 40 and 60 are appropriate for age, 21 to 39 shows mild -to-moderate delay, and  $\leq 20$  signifies severe delay<sup>(17,18)</sup>.

Study data were analyzed using the Statistical Package for the Social Sciences (SPSS Inc., Chicago, IL, USA) version 16.0. In one-way analysis, the relation between multi-categorical variables was analyzed using chi-square test. Mann Whitney U test was used for nonparametric data. A p value of  $<0.05$  was considered to be statistically significant.

## RESULTS

Detailed clinical, radiological, electrophysiological and prognostic features of the patients are given in Table 1. The patients enrolled in this study were between 12 months and 13.5 years of age, with a mean age of 58 months. Seven patients (33%) were born by normal whereas 14 patients (67%) by cesarean delivery. Twenty patients were born at term, and one patient at 34 weeks of gestational age (patient no 6). The birth weights of the patients ranged from 1900 g to 3800 g (mean $\pm$ SD, 2738 $\pm$ 787 g). Blood glucose levels of the patients during convulsions ranged between 8-39 mg/dl (25.5 $\pm$ 9.7 mg/dl). The final EEGs were obtained between 6 and 96 months of age (35 months in average). The patients had hypoglycemic convulsions between at 1-7 days of

age (2.7 $\pm$ 1.4). Ten patients (47%) had perinatal asphyxia, 3 (14%) hyperbilirubinemia, 2 (9%) intra-uterine growth retardation and 3 (14%) sepsis. Four of them (19%) had no defined additional risk factors.

Seven patients (33%) had normal development. Eight of the patients (38%) had mild, 4 (19%) moderate and 2 (9%) severe mental motor retardation.

Thirteen of 21 patients (62%) showed seizure recurrences. Refractory epilepsy developed in six patients (patient no 1,2,5,7,15, and 19). Two patients (patient no 2, and 5) initially displayed West syndrome resulting in Lennox Gastaut syndrome. Three patients (patient no 1,15, and 19) had refractory generalized motor seizures (generalized tonic/clonic and generalized tonic), the remainder (patient no 7) had intractable partial seizures. Seven patients experienced either generalized or partial motor seizures which responded well to antiepileptic treatment. Two cases (patient no 3 and 9) had no seizures within the last two years, and one case (patient 6) had no seizures for the last seven years.

Five (62%) of 8 patients without seizure recurrences after the neonatal period had normal mental, and motor development. Psychomotor retardation was detected in eleven (84%) of 13 patients who developed epilepsy after the neonatal period. All six patients with refractory epilepsy had mental motor retardation which was severe in three. A statistically significant relationship was found between development of epilepsy, and psychomotor development ( $p<0.05$ ). Two patients with refractory epilepsy were also diagnosed with autism.

EEGs were normal in six patients (28%), four of whom (66%) also had normal mental and motor development. Thirteen patients (86%) had focal epileptic (parieto-occipital area) discharges on either bilateral or unilateral and two patients had similar discharges in temporal regions. Two of the patients (9%) with abnormal EEG findings, had hypersarrhythmia pattern on their previous EEGs. Three (20%) of 15 patients with epileptic foci on their EEGs had normal mental and motor development. No statisti-

**Table I. Clinical, radiological, electrophysiological and prognostic features of the patients.**

Patient	Age	Gender	Risk factor	Time of seizure	Blood Glucose level	Seizure frequency	MRI finding	EEG finding	Developmental delay	Abnormal VEP	Refractory epilepsy
1	9y	M	Hypoxia, polycythemia, hyperbilirubinemia	2nd day	8 mg/dl	1 seizure/month	Bilateral PO gliosis	Unilateral PO focus	Mild	-	+
2	13,5 y	M	Hypoxia	3rd day	11 mg/dl	1-2 seizure/day	Unilateral PO gliosis	Unilateral PO focus, hypsarrhythmia	Severe	+	+
3	4y 9/12m	M	Hypopituitarism	4th day	11 mg/dl	1 seizure/1 year	Cortical atrophy	Unilateral PO focus	Mild	-	-
4	3y 7/12m	F	Hypoxia	1st day	11 mg/dl	No seizures after the neonatal period	Normal	Normal	Normal	-	-
5	2y 1/12m	F	Hypoxia, sepsis	1st day	18 mg/dl	2-3 seizures/day	Bilateral PO gliosis	Bilateral PO focus, hypsarrhythmia	Moderate	+	+
6	12y	M	Hypoxia, prematurity	5th day	21 mg/dl	1 seizure/year	Bilateral PO gliosis	Unilateral temporal focus	Normal	-	-
7	10 y	M	-	5th day	22 mg/dl	3-4 seizures/months	Cortical atrophy	Unilateral temporal focus	Mild	-	+
8	2y5/12m	F	Hypoxia	2nd day	22 mg/dl	No seizures after the neonatal period	PVL	Normal	Mild	-	-
9	2 y 6/12m	F	IUGR, hypothyroidism	2nd day	22 mg/dl	Total 4 seizures	Bilateral PO gliosis	Bilateral PO focus	Mild	-	-
10	3y 2/12m	M	Hypoxia	2nd day	24 mg/dl	No seizures after the neonatal period	Normal	Unilateral PO focus	Normal	-	-
11	1 y	M	-	2nd day	25 mg/dl	No seizures after the neonatal period	Normal	Normal	Normal	-	-
12	6y 3/12m	F	Glycogen storage disease, hypoxia	3rd day	28 mg/dl	2 seizures/year	Bilateral PO gliosis	Unilateral PO focus	Moderate	-	-
13	2y 2/12m	M	Hyperbilirubinemia	3rd day	32 mg/dl	Total 1 seizure	Unilateral PO gliosis	Unilateral PO focus	Normal	+	-
14	1y	F	-	2nd day	32 mg/dl	No seizures after the neonatal period	Normal	Normal	Normal	-	-
15	2y	M	Hypothyroidism	3rd day	33 mg/dl	1 seizure/2 days	Unilateral PO gliosis	Unilateral PO focus	Severe	+	+
16	2y 8/12m	M	Hypocalcemia	3rd day	33 mg/dl	No seizures after the neonatal period	Normal	Normal	Normal	-	-
17	3y	M	Hypoxia	7th day	35 mg/dl	No seizures after the neonatal period	Bilateral PO gliosis	Normal	Moderate	+	-
18	2y9/12m	M	Cardiopathy	3rd day	35 mg/dl	No seizures after the neonatal period	Cortical atrophy	Bilateral PO focus	Mild	+	-
19	8y 7/12m	F	-	2nd day	36 mg/dl	2-3 seizures/day	Bilateral PO gliosis	Bilateral PO focus	Severe	-	+
20	1y 10/12m	M	Sepsis, hypoxia	1st day	39 mg/dl	1 seizure/3 months	Bilateral PO gliosis	Unilateral PO focus	Mild	+	-
21	7y3/12	M	Sepsis, hyperbilirubinemia	3rd day	39 mg/dl	1 seizure/2-3 months	Bilateral PO gliosis	Unilateral PO focus	Mild	-	-

M: Male, F: Female, IUGR: Intrauterine growth retardation, po: parietooccipital, PVL: periventricular leukomalacia, MRI: magnetic resonance imaging, EEG: electroencephalography, VEP: visual evoked potential

cally significant relationship was found between EEG results and psychomotor development ( $p>0.05$ ).

Brain MRI was normal in 5 patients (23%). Brain MRI revealed either bilateral or unilateral parieto-

occipital gliosis, periventricular leukomalacia, and cortical atrophy in twelve, one and three patients respectively. Mainly (75%). posterior cerebral structures were involved in our patients All patients with

normal brain MRI findings had no seizures after the neonatal period, and displayed normal mental and motor development. Only two (12%) of 16 patients with abnormal brain MRI findings had normal mental and motor development. A statistically significant relationship was found between MRI findings, and psychomotor development ( $p < 0.05$ ).

Although all of the patients with refractory epilepsy had abnormal brain MRI findings, 10 (67%) of 15 remainder patients had also abnormal MRI findings. No statistically significant relationship was established between MRI findings and the development of refractory epilepsy ( $p > 0.05$ ).

Abnormal VEP responses were found in seven patients (33%). Almost all of them (85%) had mental, and motor retardation whereas 8 (57%) of 14 patients with normal VEP response had mental motor retardation. There was a statistically significant relationship between abnormal VEP response and psychomotor development ( $p < 0.05$ ).

Five patients with a blood glucose level lower than 20 mg/dl had displayed refractory epilepsy, mental motor retardation, and abnormal VEP response in three, four and two patients respectively. Sixteen patients with a blood glucose level between 20-40 mg/dl had refractory epilepsy, mental motor retardation, and abnormal VEP response in three, ten and five patients respectively. There was no significant relationship between blood glucose levels and the development of refractory epilepsy and mental motor retardation ( $p > 0.05$ ).

## DISCUSSION

The risk of developing a seizure is the highest during the neonatal period (1.8-5/1000 live birth) <sup>(19,20)</sup>. The seizure has diverse etiologies including, vascular, structural, genetic and metabolic causes. The etiology of the seizure, neurological examination, EEG and brain MRI findings are predictive factors for the long-term prognosis <sup>(21)</sup>. Hypoglycemia is responsible for only 2-3% of the neonatal seizures <sup>(19,20)</sup>. Neurological morbidity is seen particularly in severe,

prolonged or recurrent symptomatic hypoglycemia <sup>(5)</sup>. Experimental studies have demonstrated that immature brain is more resistant to the detrimental effects of hypoglycemia. Even though glucose is the primary fuel for cerebral oxidative metabolism, lactate and ketone bodies are used as alternative substrates for oxidative metabolism <sup>(22)</sup>. A compensatory increase in cerebral blood flow, low energy requirements due to low neuronal activity, increased endogenous carbohydrate stores, and an ability to consume organic substrates except for glucose are the factors that provide the resistance to hypoglycemia in neonates <sup>(5,15)</sup>.

The rate of epilepsy development following neonatal hypoglycemic seizures has been reported between 3%-56% <sup>(23-25)</sup>. However, Yalnizoglu et al <sup>(10)</sup> reported that except for one patient, all patients had symptomatic partial epilepsy, five were medically intractable and all of their patients had different degrees of developmental delay. In our group in 62% and 46% of the patients who developed epilepsy development had also refractory epilepsy. In that study all patients had abnormal MRI findings typical for neonatal hypoglycemia, where as we had patients with both normal and abnormal MRI findings. All of our cases with refractory epilepsy had mostly severe developmental delay and abnormal brain MRI findings ( $p < 0.05$ ).

Severe neonatal hypoglycemic encephalopathy involves not only the cerebral cortex but also posterior part of the subcortical white matter. Similarly, our patients displayed cerebral involvement mainly in posterior regions (75%) <sup>(1,9,11,15,26)</sup>. In a study by Burns et al <sup>(22)</sup>, in 33 of 35 infants with symptomatic neonatal hypoglycemia and without evidence of hypoxic ischemic encephalopathy white matter abnormalities occurred (94%), while cortical abnormalities occurred in 18 infants (51%), and 14 infants (40%) had basal ganglion lesions. In the abovementioned study, infants with prolonged or recurrent hypoglycemia were compared to those with transient hypoglycemia and it was concluded that early MRI findings were more valuable than the duration or

severity of hypoglycemia for predicting neurodevelopmental outcomes. Although Per et al. (4) reported that a statistically significant relationship existed between blood glucose levels, MRI findings and neurological sequelae, we did not find a relationship between blood glucose levels with either MRI findings or psychomotor development ( $p > 0.05$ ). However, our five patients with normal mental and motor development had normal brain MRI findings.

Visual impairment is caused by occipital injury associated with profound hypoglycemia (8). Previous studies on hypoglycemic neonates pointed out a visual injury rate changing from 18% to 53% (4,7,10,11). In this study, 33% of the patients had abnormal VEP response and a statistically significant relationship was found between abnormal VEP response and psychomotor retardation ( $p < 0.05$ ).

The presence of additional risk factors which may complicate the neurological outcome was the limitation of the study. For a better understanding of the effects of pure hypoglycemia on neurological outcome, prospective and long-term studies on homogeneous groups with isolated hypoglycemia using detailed ophthalmological examinations and neuropsychological tests are needed.

Even though the incidence of neonatal hypoglycemia has decreased with the improvement of neonatal intensive care, it still remains an important problem. During early neonatal period, all neonates should be monitored carefully for hypoglycemia which may result in permanent neurological sequelae such as developmental delay, learning/behavior disabilities, refractory epilepsy and visual impairment.

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