ORIGINAL ARTICLE

Determining Potential Risk Factors for Epilepsy in Children with Neonatal Hypoglycemia

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ABSTRACT

Objectives: Identifying neonates at risk for hypoglycemia and establishing treatment protocols to prevent potential neurological complications are essential. This study aims to investigate the possible risk factors for epilepsy in children with a history of neonatal hypoglycemia in North Khorasan Province.

Materials & Methods: This case-control study analyzed 64 children with a previous history of neonatal hypoglycemia between 2017 and 2021 in North Khorasan Province. Nineteen children with epilepsy were selected as the case group, and their MRI data were extracted from medical records. In the control group (45 individuals who did not develop epilepsy), children were randomly selected, and their data were also collected. The researchers completed the ages and stages questionnaire (ASQ) for both case and control groups at follow-up. Pregnancy, delivery, and neonatal health information was obtained from hospital records using a checklist. Statistical analysis was performed using SPSS v20, with data entry and coding accuracy ensured before analysis.

Results: This case-control study was conducted on 64 children (19 with epilepsy and 45 without epilepsy) with neonatal hypoglycemia. The mean age for the case and control groups were 4.1 and 4.6 years, respectively. An association was observed between epilepsy prevalence (58%) and familial history ($p<0.05$). Children who developed epilepsy had more extended periods of hypoglycemia and NICU stays ($p<0.05$). The age when hypoglycemia starts has a significant impact on the development of epilepsy, with an eight times higher risk for every extra day of life at the time of hypoglycemia ($p<0.05$). The ASQ findings revealed significant deficiencies between case and control groups ($p<0.05$). MRI results demonstrated that ~82% of children with epilepsy displayed irregularities, predominantly gliosis, and encephalomalacia in the occipital area (abnormal pathologic findings).

Conclusion: Neonatal hypoglycemia significantly raises the likelihood of developing epilepsy in later childhood. This risk is particularly high when the newborn requires an extended stay in the NICU, experiences delayed onset of hypoglycemia, or has a family history of epilepsy. Prompt recognition and focused intervention for newborns with these risk factors are essential to minimize the chances of developing epilepsy and related neurodevelopmental issues.

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Introduction

Neonatal hypoglycemia, characterized by abnormally low blood glucose levels, is a prevalent metabolic disorder that can have severe neurological consequences. Glucose is essential for brain metabolism, specifically in neonates, as their brain

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relies heavily on glucose for proper functioning. The threshold for neonatal hypoglycemia is defined as a blood glucose level of less than 25 mg/dL within the first 4 hours of life, less than 35 mg/dL between 4 to 24 hours, and less than 45 mg/dL after 24 hours of life (1, 2). If untreated or prolonged, neonatal hypoglycemia can lead to brain damage, manifesting as epilepsy, developmental delay, and other neurological impairments (3). Despite its common occurrence, the long-term effects of neonatal hypoglycemia on neurodevelopment, including epilepsy, are not entirely understood, necessitating further investigation into the associated risk factors (4, 5).

Studies have demonstrated that the duration and severity of hypoglycemia are critical determinants of neurological outcomes (6-9). In neonates, prolonged hypoglycemia can lead to irreversible damage, particularly in the occipital lobe, often resulting in visual impairments and epilepsy (10). The association between hypoglycemia and epilepsy has been reinforced by multiple studies showing that neonates with severe hypoglycemia are at increased risk of developing epilepsy during childhood (11). Specifically, neonates admitted to neonatal intensive care units (NICUs) with recurrent or prolonged episodes of hypoglycemia often exhibit a higher incidence of epilepsy and other neurodevelopmental disorders in later life (12). Furthermore, neonatal hypoglycemia is frequently accompanied by comorbidities such as intrauterine growth restriction (IUGR), low birth weight, prematurity, and maternal conditions like diabetes, all of which compound the risk of adverse neurological outcomes (13,14). Infants who experience neonatal seizures related to hypoglycemia are particularly susceptible to developing post-neonatal epilepsy, highlighting the need for early detection and aggressive management of hypoglycemia. Accordingly, a study identified symptomatic occipital lobe epilepsy as a common outcome in children who experienced neonatal hypoglycemia, with lesions primarily in the occipital region. Some cases of epilepsy following hypoglycemia have a favorable prognosis, while others involve persistent, hard-to-control seizures. This highlights the diverse outcomes associated with neonatal hypoglycemia (15). Moreover, it was pointed out that the injury patterns observed in imaging studies of hypoglycemic infants are often underrepresented, making it difficult to fully understand the role of hypoglycemia in the development of seizures (16). In a low-resource setting, Kapoor et al. reported the long-term neurological outcomes of children affected by neonatal hypoglycemic brain injury (NHBI). The study showed that NHBI leads to a broad spectrum of seizure types and neurodevelopmental comorbidities, with a significant portion of affected children developing medication-resistant epilepsy (17). The findings also highlight a high prevalence of global developmental delay and cerebral palsy among these patients (17). Further investigation on infants who experienced hypoglycemic seizures showed that the risk of epilepsy and other neurodevelopmental disorders was significantly higher in these children (18).

Additionally, a recent longitudinal study by Yalçın et al. on infants with severe neonatal hypoglycemic encephalopathy reported that 85.7% of the infant's developed epilepsy during follow-up, with the majority experiencing seizures in the neonatal period (19). This strengthens the high risk of long-term neurological complications following neonatal hypoglycemia. These studies highlight the importance of early detection and management of neonatal hypoglycemia to mitigate the risk of epilepsy and other neurodevelopmental disorders.

Accordingly, this study’s primary purpose is to pinpoint possible risk factors for epilepsy in children who experienced neonatal hypoglycemia by examining factors such as age at onset of hypoglycemia, duration of hypoglycemia, family history of epilepsy, and NICU admission to grasp better how metabolic issues in early life can impact the development of epilepsy in the future.

Materials & Methods

Study design, setting, and population

This case-control study, conducted between 2017 and 2021, aimed to determine the potential risk factors for epilepsy in children with a history of neonatal hypoglycemia at Bentolhoda Hospital in Bojnurd. The case group included children who had a history of hypoglycemia and subsequently developed epilepsy. In contrast, the control group consisted of children who also had a history of hypoglycemia but did not go on to develop epilepsy.

Inclusion and exclusion criteria

Medical records from 2017 to 2021 at Bentolhoda Hospital were reviewed, and children who met the criteria for neonatal hypoglycemia were selected as the study population. All of the participants in this study have a previous history of documented neonatal hypoglycemia and admission in nursery or neonatal or NICU wards. Accordingly, neonates with blood glucose levels below 25 mg/dL in the first 4 hours of life, below 35 mg/dL from 4 to 24 hours, and below 45 mg/dL after 24 hours were selected for inclusion in the study. These criteria were used to identify cases of hypoglycemia in newborns during the first 28 days of life. MRI data (for the case group) were extracted from their medical records at Emam Ali Hospital, and during

periodic follow-up visits with a child neurologist, the researchers completed the ages and stages questionnaire (ASQ) for children for both (case and control groups). Further exclusion criteria included incomplete documentation, difficulty reaching parents, lack of cooperation, gestational age <37 weeks, and the existence of conditions like low calcium levels, lack of oxygen, low sodium levels, high sodium levels, inherited metabolic disorders (IEM), and abnormalities in the brain's structure from birth (congenital anomaly) that are also shown in Figure 1.

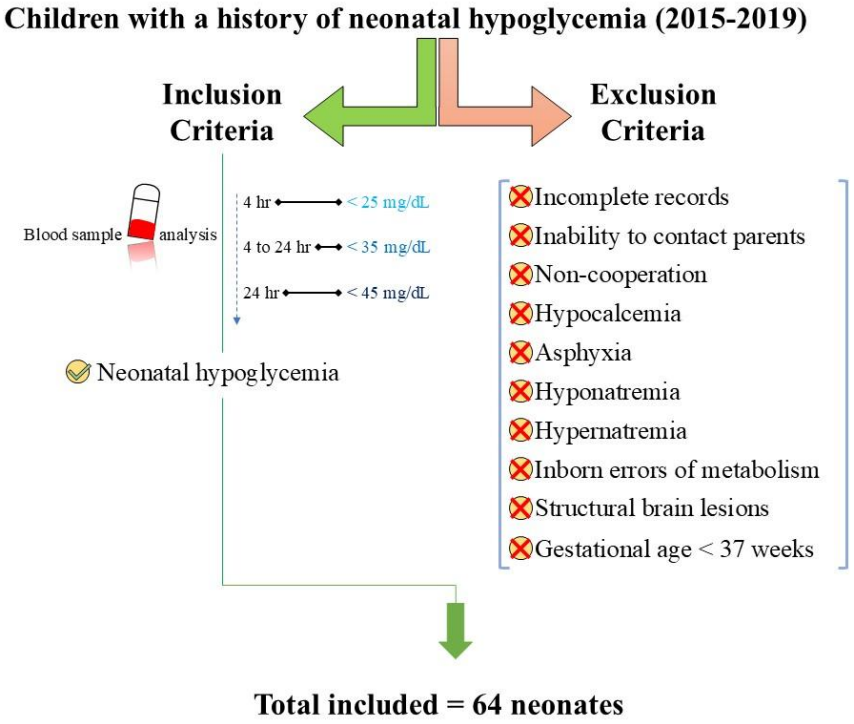

Figure 1: Inclusion and exclusion criteria flow diagram.

Data collection

The ASQ, tailored to each age group, is divided into five main areas to assess developmental status: 1) communication, 2) gross motor skills (movement of legs and arms), 3) fine motor skills (hand and finger movements), 4) problem-solving (conceptual understanding), and 5) personal-social skills. Nineteen children were assigned to the case group. For the control group, 45 children with a history of neonatal hypoglycemia were randomly selected, and their families were contacted. First, families were asked about their child's history of epilepsy. If no epilepsy was reported (control group), the families were invited to participate in the research at Imam Ali Hospital. If epilepsy was reported (case group), the patient's brain MRI was interpreted based on a standard checklist, and the result was divided into two categories: normal or abnormal (pathologic or non-pathologic). Besides, the ASQ was completed for both groups at follow-up. Pregnancy, delivery, and neonatal health data were collected using a designed checklist extracted from hospital records.

Data analysis

After data collection, accuracy was ensured, and data were coded and entered into SPSS version 20 for statistical analysis. Descriptive statistics, including frequency, mean, standard deviation, minimum, and maximum, were used to describe the characteristics of the samples. The normality of quantitative variables was assessed using the Kolmogorov-Smirnov test, and independent t-tests were applied for normally distributed variables. Non-parametric tests were used for variables that did not follow a normal distribution. The homogeneity of demographic variables between the two groups was analyzed using Chi-square, Fisher's exact test, and independent t-tests. Logistic regression was employed to control confounding variables.

Results

Among the 64 studied children, 68.4% of the case group and 51.1% of the control group were male. The mean age in the case and control groups was 4.1 and

4.6 years, respectively. Approximately 58% of children in the case group had a family history of epilepsy in first- or second-degree relatives, compared to only 4.4% in the control group. Most children in both groups had no history of maternal diabetes, hypertension before or during pregnancy, eclampsia, or substance abuse during pregnancy. In contrast to the control group, more than half of the children in the case group had parental consanguinity and a history of NICU admission. Of the children in the case group, 62.3% were admitted to the NICU due to hypoglycemia. The most crucial clinical symptoms during the neonatal period include lethargy, poor feeding, jaundice, and seizures. Additionally, 53% of the case group had ocular diseases (e.g., strabismus or vision impairment) at follow-up, while no visual impairment was observed in the control group.

Table 1: Results of independent t-test for demographic findings in the case and control groups

Variable	Groups (Mean±Std.dev)		t-value	p-value
	Case	Control		
Mother's age at birth (years)	27.44±6.76	27.78±6.6	0.18	0.858
Height at birth (cm)	47.72±3.84	48.32±3.89	0.55	0.580
Birth weight (gr)	2594.4±537.9	2546.6±765.7	-0.24	0.810
Head circumference at birth (cm)	33.97±0.99	32.92±2.24	-2.57	**0.013**
Current height (cm)	118.5±23.99	108.17±6.28	-1.80	0.089
Current weight (kg)	25.94±16.18	16.96±2.87	2.50	0.019
Current head circumference (cm)	49.23±4	49.49±2.12	0.18	0.860
Apgar score 1	9.00±0	8.93±0.25	1.399	0.250
Apgar score 2	10.00±0.00	9.96±0.20	1.408	0.350
Blood glucose drop (mg/dL)	28.38±6.34	26.89±7.83	-0.63	0.530
Age at hypoglycemia (days)	43.05±31.42	10.9±12.57	-4.31	**< 0.001**
Duration of hypoglycemia (hours)	6.39±1.68	2.67±1.88	-7.26	**< 0.001**
Number of seizures due to hypoglycemia	1.37±0.76	0.07±0.25	21.00	**< 0.001**
Duration of NICU stay (hours)	8.32±7.86	0.33±1.33	-4.40	**< 0.001**
Seizure-to-epilepsy interval (years)	3.23±2.24	N/A	N/A	N/A

N/A: Not applicable

Table 1 shows significant differences in head circumference at birth, age at hypoglycemia onset, duration of hypoglycemia, NICU stay, and number of seizures ($P < 0.05$). The mean interval between the first seizure and epilepsy onset in the case group was approximately three years. According to the results of the student's t-test, no significant difference was found between the two groups regarding maternal age at birth, birth height, birth weight, Apgar scores in 1 and 5 min, blood glucose levels during hypoglycemia, current head circumference, or current height ($P > 0.05$).

Table 2: Comparison of demographic and clinical characteristics between the case group (children with epilepsy) and control group (children without epilepsy)

Variable	Case Group	Control Group	χ^2	p-value
Gender				
Male	13 (68.4%)	23 (51.1%)	1.62	0.200
Female	6 (31.6%)	22 (48.9%)		
Family history of epilepsy				
Yes	11 (57.9%)	2 (4.4%)	23.57	**<0.001**
No	8 (42.1%)	43 (95.6%)		
History of diabetes and hypertension before				
Yes	0 (0%)	5 (11.1%)	2.29	0.130
No	19 (100%)	40 (88.9%)		
History of diabetes and hypertension during				
Yes	6 (31.6%)	18 (40%)	0.4	0.520
No	13 (68.4%)	27 (60%)		
History of eclampsia/pre-eclampsia				
Yes	4 (21.1%)	7 (15.6%)	0.28	0.590
No	15 (78.9%)	38 (84.4%)		
Parental consanguinity				
Yes	10 (52.6%)	13 (28.9%)	3.27	0.071
No	9 (47.4%)	32 (71.1%)		

Substance abuse during pregnancy				
Yes	0 (0%)	1 (2.2%)	0.429	0.513
No	19 (100%)	44 (97.8%)		
Verbal developmental disorders				
Yes	8 (42.1%)	1 (2.2%)	17.58	**<0.001**
No	11 (57.9%)	44 (97.8%)		
Motor developmental disorders				
Yes	10 (52.6%)	1 (2.2%)	23.85	**<0.001**
No	9 (47.4%)	44 (97.8%)		
Cognitive developmental disorders				
Yes	9 (47.4%)	2 (4.4%)	17.29	**<0.001**
No	10 (52.6%)	43 (95.6%)		
NICU admission history				
Yes	14 (73.7%)	4 (8.9%)	27.74	**<0.001**
No	5 (26.3%)	41 (91.1%)		

Table 2 highlights the significant differences between the two groups, as determined by the Chi-square test. These differences include factors such as a family history of epilepsy, developmental disorders (verbal, motor, and cognitive), history of NICU admission, reasons for NICU admission, and underlying diseases ($P < 0.05$).

Initially, the relationship between variables and the development of epilepsy was assessed through univariate analysis. The logistic regression model included variables such as family history, length of NICU admission, neonatal age at hypoglycemia onset, head circumference at birth, gestational age, and duration of hypoglycemia to control for confounding factors. In the final model, neonatal age at the time of hypoglycemia, duration of NICU admission, and family history of epilepsy were significantly associated with epilepsy.

Table 3: Logistic regression analysis of risk factors for epilepsy in children with neonatal hypoglycemia

Variable	Coefficient	Std.ere	Significance level (p-value)	Odds Ratio	Lower bound	Upper bound
Constant	-5.102	1.409	0.000	0.06	-	-
Neonatal age at hypoglycemia	0.075	0.026	**0.004**	1.078	1.025	1.134
Duration of NICU stay (hours)	0.736	0.285	**0.010**	2.088	1.194	3.654
Family history of epilepsy	3.761	1.574	**0.017**	43.006	1.966	940.960

Table 3 reveals that, even after accounting for other variables, the risk of developing epilepsy increases eightfold with each additional day of age at the time of hypoglycemia. Additionally, for each additional hour of NICU stay, the risk of epilepsy doubled. The risk of developing epilepsy in children with a family history of epilepsy was 43 times higher than in others.

In the group of individuals with epilepsy, seizure symptoms ranged from feelings of fear and staring episodes to hemiconvulsive movements or generalized tonic-clonic convulsions. The most commonly used medication was carbamazepine, used by 48% of the patients, followed by sodium valproate, levetiracetam, and acetazolamide. Electroencephalography (EEG) most frequently revealed abnormal sharp or spike waves in the parieto-occipital region, occurring in 63% of cases. Additionally, 36% of patients with epilepsy were resistant to medication. MRI changes were observed in all but one of the epileptic children (18 total), as there was no access to the brain MRI of one patient. These changes were found in the occipital region and the posterior periventricular area. Among these children, 82% (14 out of 18) showed gliosis and encephalomalacia, which are pathological findings. Meanwhile, 18% (3 out of 18) exhibited nonspecific signal changes in these regions, which are considered non-pathological findings. The MRI results for one patient (5%) came back normal. It is unclear whether the control group had any abnormal MRIs, as none of the children in this group required neuroimaging. Additionally, some of these children may experience epileptic seizures in the future. Figure 2. MRI findings in children with neonatal hypoglycemia and epilepsy. (The case group).

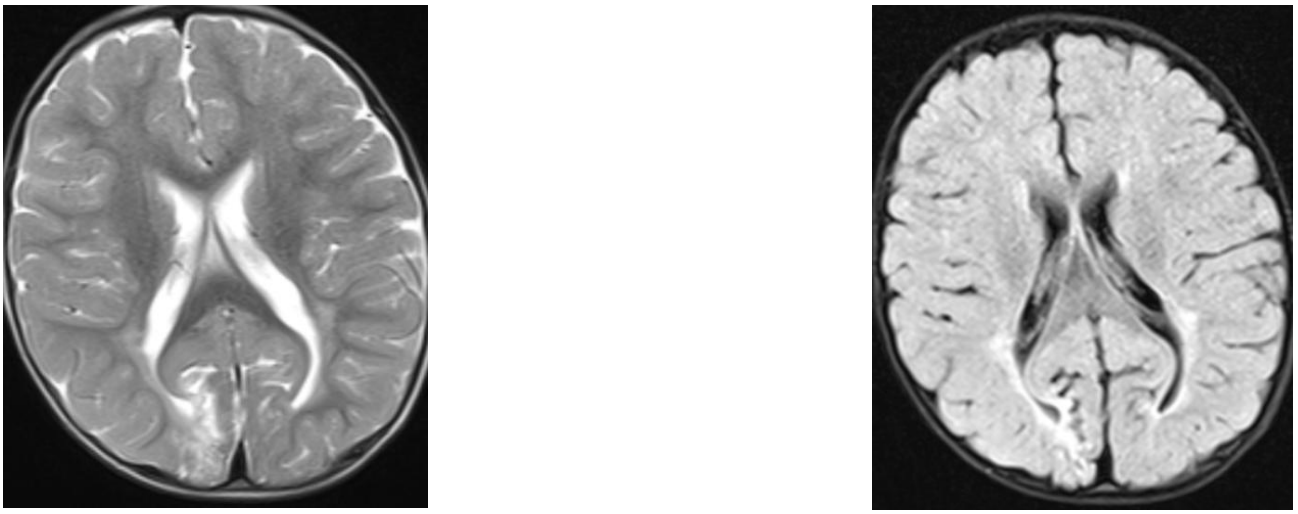

Figure 1: A1: 4-year-old-boy with epilepsy, axial T2 and FLAIR showed increase signal intensity (gliosis) and malacia in posterior periventricular in occipital lobe particularly in right hemisphere. (Abnormal- pathologic)

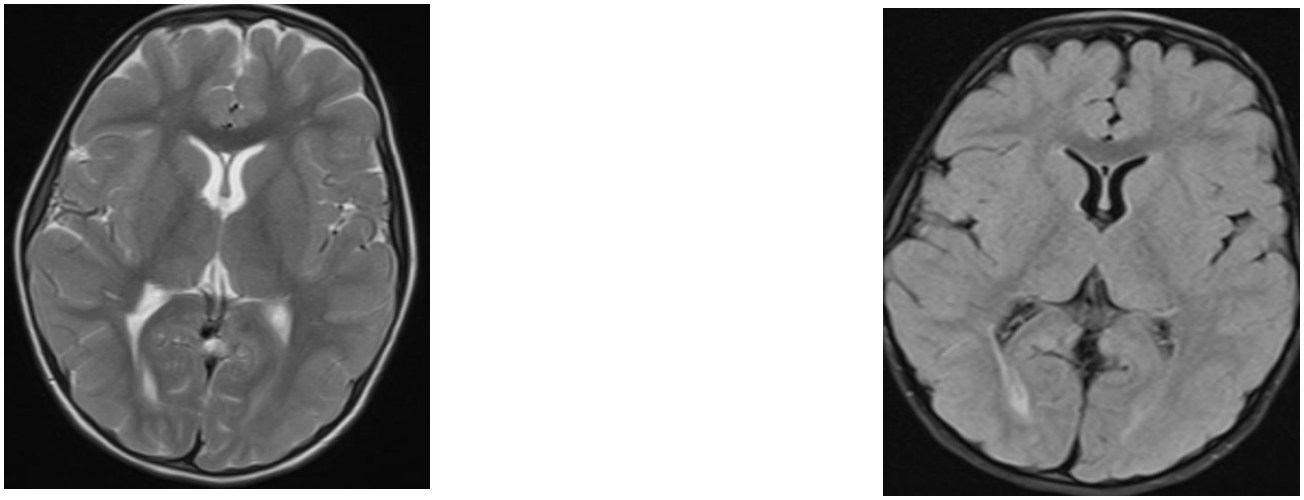

Figure 2: A2: 3/5-year-old-girl with epilepsy, axial T2 and FLAIR showed mild increase signal intensity in posterior zone without gliosis and malacia. (Abnormal- non-pathologic)

Discussion

The present study aimed to investigate potential risk factors for epilepsy in newborns with a history of hypoglycemia. It compared two groups: one consisting of neonates with hypoglycemia who developed epilepsy and the other of those who did not develop epilepsy. This research observed significant variations in the developmental progress of children who had neonatal hypoglycemia, depending on whether they had epilepsy, as assessed using the ASQ. In particular, children with epilepsy displayed significant developmental delay in comparison to those without, indicating that epilepsy could potentially impact or coincide with hindered neurodevelopment. Prior studies have shown that even mild neonatal hypoglycemia significantly raises the chances of neurodevelopmental issues (20–22). Wickström et al. reported that children who had experienced moderate hypoglycemia in the past faced double the risk of neurological and developmental delay and triple the risk of cognitive developmental delay compared to children with normal blood sugar levels (23). These results are in agreement with the present findings, emphasizing the importance of early detection and intervention in addressing possible developmental delays linked to neonatal hypoglycemia and epilepsy.

The results indicated that maternal medical conditions during pregnancy, including diabetes, hypertension, eclampsia, substance abuse, gender, and parental consanguinity, were not significantly different among the groups, indicating that they were not involved in the development of epilepsy. Moreover, these findings demonstrated a significant difference in the duration of hypoglycemia in neonates in case and control groups, potentially leading to the subsequent development of epilepsy. The significant occurrence of unusual MRI results suggests that neonatal hypoglycemia can lead to brain damage, specifically in the occipital lobe, which may increase the risk of

epilepsy in the future. The MRI abnormalities found in this study, like gliosis and encephalomalacia, mirror the usual damage seen in hypoglycemic brain injuries and indicate a link between the severity of brain lesions and the onset of epilepsy (24). A similar conclusion was drawn by Gu et al., who found that the number of days neonates experienced hypoglycemia was significantly associated with abnormal MRI findings. Correspondingly, those with abnormal MRI results did not have lower glucose levels than those with normal MRI findings (25). Prolonged hypoglycemia leads to greater brain damage, which can establish a foundation for epilepsy. Here, this study has exclusively assessed epileptic neonates who had MRI results (19 children in the case group). Accordingly, most neonates (14 of 18 with MRI results) had abnormal (pathologic) presentations.

Furthermore, significant differences in the developmental domain were observed between the two groups. According to a cohort study, neonates with hypoglycemia face a doubled risk of any neurological or developmental complications and a threefold increased risk of cognitive developmental delay when compared to neonates with normal glucose levels. This study highlighted that moderate hypoglycemia in neonates correlates with an increased risk of neurodevelopmental disorders in the case group (23). Additionally, the findings of the present study revealed a higher incidence of epilepsy among patients with a positive family history of epilepsy. This was consistent with a study conducted in Saudi Arabia, which retrospectively assessed the medical records of 420 patients to evaluate the impact of family history on epilepsy risk factors, causes, and diagnoses (26). The study concluded that a prior family history of epilepsy significantly affects its classification and may indicate a genetic predisposition (26).

A further study involving 83 neonates with epilepsy linked to hypoglycemic brain injury found that epilepsy manifested with various degrees of severity and symptoms, including severe intellectual disability, microcephaly, visual impairments, behavioral issues, and autism spectrum disorders (16). This study emphasized the necessity of investigating evidence of neonatal hypoglycemia in infants presenting with epilepsy during early childhood (16). The results corroborate the current findings, indicating that cognitive issues and developmental disorders significantly correlate with the onset of epilepsy in neonates with hypoglycemia. In the present study, out of 18 patients with epilepsy who underwent MRI, 17 patients (94.5%) exhibited abnormal (pathologic and non-pathologic) MRI findings. Among these, 14 patients (82%) demonstrated changes characterized by gliosis and encephalomalacia (abnormal pathologic findings), while three patients (18%) had nonspecific signal increases in the occipital region (non- pathologic findings). Only one patient (5%) had a normal MRI result. These findings support previous research conducted from 1996 to 2012, aiming to evaluate the consequences of hypoglycemia on epilepsy in neonates. The studies found bilateral gliosis in the occipital white matter of all patients and documented cortical atrophy in nine cases. Gliosis in the parietal white matter and cortical atrophy in 6 cases were also observed (27).

The present study also found that neonatal hypoglycemia can be linked to various comorbid disorders, including epilepsy, visual impairments, and developmental disorders. This aligns with a study comparing findings of 27 patients with seizures and a history of neonatal hypoglycemia to 28 children with idiopathic occipital epilepsy, demonstrating that neonatal hypoglycemia could lead to a specific clinical syndrome encompassing epilepsy, visual disorders, and intellectual-motor disabilities (28). Additionally, neonates with hypoglycemia who are diagnosed early and treated appropriately may remain asymptomatic, while those with severe developmental delay may present seizures as part of their neonatal manifestations (28). Various studies have indicated that at-risk patients and those exhibiting hypoglycemic symptoms should undergo rigorous screening and treatment to prevent neurological disorders, including cerebral palsy, epilepsy, and visual impairments (19). The significance of hypoglycemia in the early days of life is underscored by the potential for irreversible complications, including persistent brain tissue loss, visual disorders, microcephaly, and developmental delays (ranging from mild to severe), as well as medication-resistant epilepsy. Therefore, it is recommended that the importance of breastfeeding, particularly in the early days of neonatal life, be consistently emphasized by health centers, healthcare providers, and nurses in inpatient settings.

Although this research offers significant findings on the connection between neonatal hypoglycemia and the risk of epilepsy in Northern Iran, it is essential to acknowledge the crucial limitations. Initially, the sample size was relatively limited. Another significant restriction was the dependence on medical records and questionnaires filled out by parents, which could result in inaccurate data collection, specifically regarding the exact timing and severity of hypoglycemia episodes and the potential risk of recall bias due to the study's retrospective nature. The research also does not consider possible variables like genes not linked to epilepsy in the family or environmental influences

affecting brain development. In future studies, these gaps should be addressed by updating the number of participants and examining genetic predispositions, environmental factors, and family history.

In Conclusion

This study's results highlight the important influence of neonatal hypoglycemia on the onset of epilepsy and related neurodevelopmental conditions. In particular, children who have experienced neonatal hypoglycemia are more likely to develop epilepsy, mainly if they had delayed onset of hypoglycemia, extended NICU stays, and a family history of epilepsy. These individual risk factors increase the chance of negative neurological results. MRI results continue to support the lasting impact of neonatal hypoglycemia, as the majority of children exhibit brain anomalies, particularly in the occipital area. This study highlights the significant importance of identifying and treating neonatal hypoglycemia promptly to effectively address its lasting neurological consequences, such as the potential development of epilepsy. Prioritizing thorough monitoring and personalized treatment plans for newborns with these known risk factors is important to prevent serious neurodevelopmental outcomes.

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Authors' Contribution

Shima Hosseinzadeh contributed to the study's design, data collection, and manuscript drafting.

Dorsa Vagharmousavi was involved in study's design, data collection, and manuscript drafting.

Ghasem Bayani assisted in the study design.

Rezvan Rajabzadeh participated in data analysis and writing results.

Meisam Babaei (corresponding author) supervised the entire research process, ensuring data accuracy, and provided critical revisions to the manuscript.

All authors reviewed and approved the final version of the manuscript.

Conflict of Interest

The authors declare that they have no conflicts of interest. No funding was received for this study, and the authors do not hold any stocks or shares in any organization that may gain or lose financially from the publication of this paper.

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