ORIGINAL ARTICLE

Acute Necrotizing Encephalopathy in Children: Insights and Outcomes from Iran

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ABSTRACT

Objectives

Acute necrotizing encephalopathy of childhood (ANEC) is a rare, potentially life-threatening condition. This study aimed to identify clinical profiles and outcomes of ANEC while assessing the accuracy of severity scoring in the Iranian population.

Materials & Methods

The present study collected demographic, clinical, laboratory, and radiological data from children diagnosed with ANEC. Severity was measured using the ANE-Severity Score (ANE-SS), while outcomes were assessed with the Glasgow Outcome Score (GOS). This research analyzed the relationship between these scores and various parameters for statistical significance.

Results

Seven patients were included over three years, with an average age of 4.4±2.7 years (5 males). ANE-SS varied from moderate to high, with most patients experiencing moderate to severe disabilities, as indicated by the GOS. Significant correlations were found with initial serum magnesium levels, pupil light reactivity, and initial GCS score (P-value < 0.05).

Conclusion

Controlling initial magnesium levels may improve ANEC outcomes. Additionally, intact pupil light reactivity at admission was associated with a better prognosis.

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Introduction

Acute necrotizing encephalopathy of childhood (ANEC) is a rare form of fulminant encephalopathy that primarily affects previously healthy Asian children. This condition is characterized by a rapid onset of encephalopathy, often accompanied by seizures and the presence of symmetrical brain lesions (1). Although the highest reported prevalence occurs in children between six and 18 months of age, it is typically observed in preschool-aged individuals (1). Although the etiology of ANEC remains elusive, it is commonly observed to occur after a viral infection, including influenza type A, herpes simplex, mycoplasma virus, and human herpes virus-6. The specific pathophysiological mechanisms underlying this condition are still not fully understood (2–4). However, believingly, dysregulated immune responses and the occurrence of a cytokine storm, along with pathogenic gene variants of *Ran-binding protein 2* (RANBP2), contribute to developing brain inflammation and necrosis (3,5). The clinical presentation of ANEC can be categorized into three distinct stages. The prodromal stage is characterized by gastrointestinal or respiratory symptoms such as fever, cough, and diarrhea (2,6). Subsequently, patients rapidly progress to the encephalopathy stage, which is characterized by progressive neurological deterioration, focal neurological deficits, altered consciousness, and seizures (2,6). This stage is considered critical for ANEC, with some studies reporting a short-term mortality rate as high as 50% (2,6). The clinical and laboratory characteristics in this phase exhibit a wide range of variations, and the diagnosis primarily relies on distinct neuro-radiological discoveries, along with the elimination of comparable imitating disorders (5,7,8). Even if the patient survives, the recovery process is often hindered by neurological complications, even with intensive therapies. These complications include white matter degeneration, motor dysfunction, cognitive deterioration, and necessitating prolonged care and rehabilitation (8). The objective of this study was to enhance the existing body of knowledge on ANEC by providing a comprehensive analysis of multiple clinical instances, encompassing the initial presentation, diagnostic evaluation, treatment approaches, radiological profiling, and long-term prognosis. Additionally, this study aimed to assess the accuracy of the previously defined severity scoring system in the Iranian population.

Materials & Methods

Patient Recruitment

In this retrospective study over three years, the medical records of seven patients exhibiting clinical and radiological signs suggestive of ANEC were thoroughly examined. The local board of ethics approved the study, including using the data in future studies. The primary authors obtained informed consent from the patients' parents. The study aimed to document the patients' initial clinical and laboratory profiles (Table 1) and imaging (Table 2 & Figure 1) findings, as well as their outcomes. The diagnosis of ANEC was established based on the presence of acute febrile encephalopathy accompanied by neuroimaging results revealing symmetrical lesions involving both Thalami. Notably, the patients did not exhibit any clinical features resembling other disorders associated with ANEC.

Severity and Outcome Scores

This study utilized the ANE-Severity Score (ANE-SS) to assess the severity of illness and scored patients as low risk (0–1 point), medium risk (2–4 points), or high risk (5–9 points) (9).

Additionally, patients' neurological scores at discharge were assessed using the Glasgow Outcome Scale (GOS) (10). The outcomes were categorized as follows: good outcomes (GOS 4 and 5), fair outcomes (GOS 3), and poor outcomes (GOS 1 and 2).

Statistical Analysis

The obtained results for quantitative variables are expressed as the mean ± standard deviation (SD), and for categorical variables, they are presented as percentages. Numerical and categorical variables were examined using Pearson's correlation coefficient and Spearman's rank correlation tests. Statistical significance was set at a P-value of less than 0.05 using SPPS version 20.

Results

Demographic Profiles and Prodromal Symptoms

In this investigation, seven patients were enrolled, five males, with an average age of 4.4 years (± 2.7 years). None of the participants had a history of seizures, neurological deficits, developmental delays, or family members with neurological disorders. Moreover, all patients were born to non-consanguineous parents. Six patients experienced high-grade fever (≥38.5 °C) before admission, two

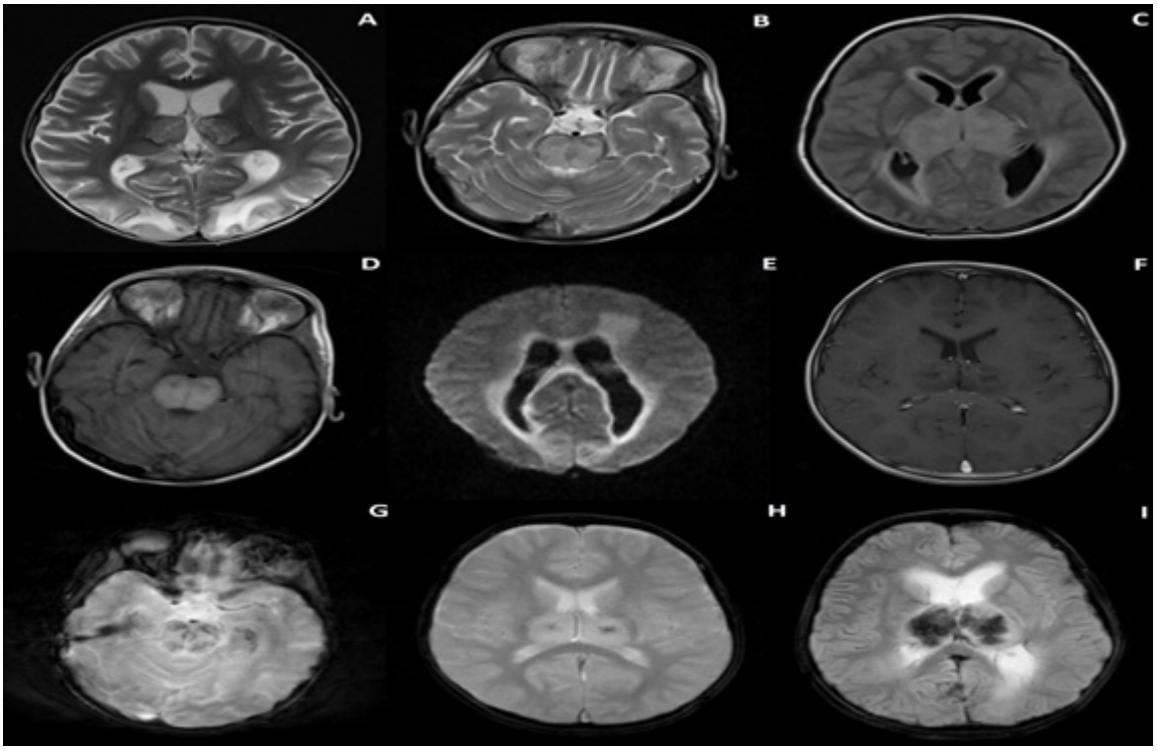

Figure 1. Showing some of the MRI findings

A. Axial T2 weighted image: symmetrical T2 hyperintense signal lesions in bilateral thalami and bilateral occipital lobes (Case 1)

B. Axial T2 weighted image: T2 hyperintense signal lesion in brainstem (Case 2)

C. Axial FLAIR image: symmetrical FLAIR hyperintense signal lesions in bilateral thalami and periventricular regions (Case 4)

D. Axial T1 weighted image: T1 hyperintense signal lesion in brainstem (Case 2)

E. Axial Diffusion–weighted image (DWI): symmetrical DWI hyperintense signal lesions in periventricular regions (Case 4)

F. Axial T1 plus contrast weighted image: symmetrical contrast enhancement in bilateral thalami (Case 3)

G. Axial GRE image: GRE hypointense signal lesions in brainstem and left hippocampus (Case 5)

H. Axial GRE image: symmetrical hyperintense signal lesions in bilateral thalami and bilateral central signal loss (Case 6)

I. Axial GRE image: symmetrical bilateral thalami signal loss (Case 7)

Table 1. The CBC, electrolytes, LFTs, and VBG parameters shown were the initial documented values upon admission. LDH, ESR, and CPR were the highest documented values throughout hospitalization. PCR testing was performed on oral and nasopharyngeal swabs

Parameter	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Units
WBC	13.7	10.9	4.9	14	7.2	6.4	4.7	10^3/mcl
PMN	77.9	71.6	80.5	61	72.9	79.7	78	%
Lymph	13.7	19.8	18.5	6	16.1	15.3	21	%
Hemoglobin	14.5	10.1	11.3	10.4	9.8	11.5	12.7	g/dl
Platelets	153	524	98	57	377	105	101	10^3/mcl
ESR	32	106	9	22	42	13	34	mm
CRP	98	15.1	26.4	77.8	2	8.1	11.1	mg/L
pH	7.5	7.5	7.43	7.36	7.5	7.34	7.4	-
CO2	30.8	35	33.8	22.4	31.3	35.2	26.6	mmHg
HCO3	23.8	24.6	22	12.3	22.2	18.6	15.9	mmol/L
Calcium	10	8.9	8.73	10	9.3	6.1	9.3	mg/dl
Phosphor	3.3	2.4	3.7	4.1	3.2	1.8	2.7	mg/dl
Magnesium	2.4	2.2	2.6	1.4	2.7	2.1	1.7	mg/dl
Sodium	138	137	137	165	135	147	145	mEq/L
Potassium	3.3	3.9	4.4	3.3	3.5	3.4	5.3	mEq/L
Blood Sugar	71	86	98	281	103	115	93	mg/dL
CSF WBC	0	0	0	0	0	0	0	/mm^2
CSF Sugar	60	58	71	76	110	65	86	mg/dl
CSF Protein	26	31	88	43	63	54	115	mg/dl
LDH	1487	726	8378	220	682	4972	1123	U/L
AST	34	32	74	43	102	5928	108	U/L
ALT	32	42	552	28	482	9632	28	U/L
SARS-CoV-2 PCR	COVID +	Neg	Neg	Neg	Neg	Neg	Neg	-
Influenza PCR	Neg	Neg	Type A +	Type A +	Neg	Neg	Neg	-
Pupil Miosis	Yes	Yes	No	Yes	Yes	Yes	Yes	-
PLR	No	No	Yes	No	Yes	No	No	-
Absent DTR*	Yes	Yes	No	No	No	No	No	-
Babinski Reflex	Flat	Flat	No	Yes	Yes	Yes	Flat	-
CC Lesion	Yes	Yes	No	No	No	No	No	-
Cerebellum Lesion	Yes	Yes	No	Yes	No	No	Yes	-
CCO Lesion	No	No	No	Yes	Yes	Yes	No	-
ANE-SS	2	4	4	6	5	6	6	-
GOS	2	3	4	1	4	1	2	-

* All others were reduced.

WBC: white blood cells, PMN: polymorphonuclear cells, Lymph: lymphocytes, ESR: erythrocyte sedimentation rate, CRP: c-reactive protein, CSF: cerebrospinal fluid, LDH: lactate dehydrogenase, AST: aspartate transaminase, ALT: alanine transaminase, PLR: pupillary light reactivity, CC: Corpus Callosum, CCO: Centrum Semiovale, ANE-SS: Acute necrotizing encephalopathy severity score, GOS: Glasgow Outcome Scale

Table 2. Patient MRI findings

LESION FINDING	NUMBER OF CASES SEEN (N)
CEREBELLUM	4
SUBCORTICAL	3
CORPUS CALLOSUM	2
CORTICOSPINAL TRACT	2
MIDBRAIN	4
PONS	4
MEDULLA OBLONGATA	1
DENTATE NUCLEUS	1
CENTRUM SEMI OVALE	3
TONSILAR HERNIATION/CEREBRAL EDEMA	2
GRE BLOOMING IN THALAMUS	3

of whom were refractory to acetaminophen use. One patient was admitted to the hospital after one week of diarrhea and high-grade fever following Measles, Mumps, and Rubella (MMR) vaccine administration. Prodromal symptoms varied from nonspecific viral infections and fever to nausea, vomiting, diarrhea, cough, and rhinorrhea, with an average duration of 7.9 days (± 4.7 days) from symptom onset to admission. All patients were hospitalized immediately following seizures, with the majority experiencing generalized tonic-clonic seizures (observed in four patients), two of which were classified as status epilepticus. The average seizure duration reported by the parents was 15.6 minutes (± 11.5 minutes). Upon admission to the Pediatric Intensive Care Unit (PICU), the Glasgow Coma Scale (GCS) scores ranged from 5 to 10, with an average of 7.5 points (± 2.2 points), with four patients requiring intubation and nasogastric (NG) tube insertion.

Clinical and Laboratory Profiles

Upon admission, most patients presented with miotic pupils, with five showing nonreactive responses to light, while only one patient had mid-sized and reactive pupils. Deep tendon reflexes (DTRs) were absent in two patients and decreased in the remaining individuals, with three patients exhibiting positive bilateral Babinski signs during plantar reflex testing. PCR testing was conducted on oral and nasopharyngeal swabs from all patients, revealing two patients positive for influenza type A and one positive for severe-acute-respiratory-syndrome-related coronavirus (SARS-CoV-2). Initially, white blood cell (WBC) counts were within normal limits for most patients (mean of 8.8 ± 3.9 10^3/mcl), although Patient 6 later developed pancytopenia, with the WBC count decreasing to 1.5 (10^3/mcl). The average initial hemoglobin and platelet levels were 11.4 ± 1.6 g/dl and 202 ± 177 (10^3/mcl), respectively. The recorded erythrocyte sedimentation rate (ESR), c-reactive protein (CRP), and lactate dehydrogenase (LDH) levels ranged from 9 to 106 mm (mean of 36.8 ± 32.6 mm), 2 to 98 mg/L (mean of 34 ± 37.9 mg/L), and 220 to 8378 U/L (mean of 2512.5 ± 3034 U/L), respectively. Venous blood gas (VBG) analysis was performed

on all patients immediately after admission, with average blood pH, pCO2, and HCO3 levels documented as 7.4 ± 0.06, 30.7 ± 4.7 mmHg, and 19.9 ± 4.5 mmol/L, respectively. None of the patients had WBCs in their lumbar puncture (LP) samples, although three patients had elevated protein levels exceeding 60 mg/dl (mean of 60 ± 31.9 mg/dl). The initial serum levels of calcium, phosphorus, magnesium (Mg), sodium, and potassium were recorded as 8.9 ± 1.3 mg/dl, 3 ± 0.7 mg/dl, 2.1 ± 0.4 mg/dl, 143.4 ± 10.5 mEq/L, and 3 ± 0.7 mEq/L, respectively.

Radiological Profiles

Normal chest x-rays were recorded in all patients, except Case 4, who exhibited right para-hilar and para-cardiac opacities, as well as an increased prominence of the bronchovascular pattern, potentially attributed to influenza type A infection. This particular patient, in contrast to the others, presented with a reduced ejection fraction of 18% and severe left atrial and ventricular enlargement, suggestive of previously undiagnosed hypertrophic obstructive cardiomyopathy (HOCM). Abdominal sonography revealed no pathological findings in the studied patients. The MRI results are outlined in Table 2. Patients who succumbed to the illness displayed signs of severe cerebral edema and tonsillar herniation in their MRIs prior to death. One patient exhibited bilateral hydrocephalus, along with T2/FLAIR (fluid-attenuated inversion recovery) hyperintense and T1 hypointense signal lesions in the periventricular white matter and ependymal lining. Another patient showed signs of aneurysmal dilatation of the Torcular Herophili. The Dentate nucleus was affected in one patient, while Corpus Callosum lesions were observed in two patients. Involvement of the midbrain, pons, cerebellum, and Centrum Semiovale was all observed in three or more of the patients.

Outcomes and Neurological Sequelae

All the subjects received immediate and appropriate doses of methylprednisolone and intravenous immune globulin (IVIg) within a day of admission. According to Yamamoto et al.'s scoring system, all patients included in this study were classified as medium to high risk, with an average score of 4.7 ± 1.5. Among the seven individuals, two passed away following a generalized tonic-clonic seizure, subsequent apnea, and bilateral blown pupils, indicating brain herniation due to severe cerebral edema. Among the five survivors, the average length of hospital stay was 27.5 ± 9.4 days, and all patients were conscious upon discharge. However, two of these patients exhibited muscle weakness, while three had moderate to severe disability based on the GOS. These patients were predominantly bed-ridden and lacked independent functionality post-discharge (Table 1).

Correlations between Profiles and Outcomes

Table 3 presents this study's statistical findings, revealing that most parameters assessed had no significant correlation with either ANE-SS or GOS. However, there was a notable association between serum magnesium levels and both the ANE-SS and GOS. Specifically, lower initial serum magnesium levels were strongly correlated with increased disease severity, as indicated by a P-value of 0.008 and a correlation coefficient (cc) of -0.88. Conversely, higher initial serum magnesium levels were significantly correlated with improved patient outcomes, with a P-value of 0.036 and a cc of 0.78. These results suggest that lower magnesium levels at disease onset are associated with increased disease severity

and poorer outcomes. On the other hand, initial sodium levels were significantly (P-value = 0.0008) and inversely (cc of -0.95) correlated to disease outcome; however, it did not significantly affect disease severity scores. Increased sodium levels were observed only in the two patients who died, suggesting a potential correlation with poor outcomes. However, due to the possibility of this being an incidental finding, no definitive conclusions can be drawn regarding its impact on disease severity. Additionally, initial acidosis characterized as low pH and serum bicarbonate levels were correlated with higher disease severity scores. A lower pH was borderline statistically related to higher severity scores (P-value of 0.052 and CC of -0.74), in comparison with disease outcome (P-value of 0.08 and CC of 0.68). The same was noted for lower initial bicarbonate levels, although in this case, the analysis did reach statistical significance for disease severity

Table 3. Correlations between various profiles and the ANE-SS score and GOS. Correlations between the initial platelet and CSF protein levels and the ANE-SS score were not analyzed as these parameters are included in the scoring system

	Variable	Against ANE-SS		Against GOS	
		CC	P-value	CC	P-value
Laboratory	WBC	-0.39	0.38	-0.38	0.39
	NLR	0.14	0.74	-0.5	0.18
	Hemoglobin	-0.49	0.26	-0.31	0.48
	Platelets	-	-	0.38	0.39
	ESR	-0.14	0.74	0.27	0.55
	CRP	-0.46	0.28	-0.22	0.63
	LDH	-0.29	0.51	0.12	0.78
	AST	0.69	0.084	-0.2	0.66
	ALT	-0.15	0.74	0.29	0.51
	Sodium	0.62	0.135	-0.95	0.0008
	pH	-0.74	0.052	0.68	0.08
	CO2	-0.36	0.41	0.42	0.33
	HCO3	-0.77	0.041	0.64	0.11
	Calcium	-0.11	0.8	-0.18	0.68
	Magnesium	-0.88	0.0089	0.78	0.036
	Blood Sugar	0.74	0.52	-0.36	0.41
	Phosphor	-0.19	0.68	0.2	0.66
	Potassium	0.23	0.61	0.24	0.59
	CSF Sugar	0.41	0.34	0.38	0.39
	CSF Protein	-	-	0.22	0.62
Clinical	GCS	0.007	0.98	0.8	0.01
	Pupil Miosis	0.32	0.48	-0.52	0.22
	Pupil Reactivity	-0.24	0.59	0.81	0.026
	Non-Absent DTR	-0.7	0.054	0.08	0.86
	Plantar Reflex	0.6	0.14	-0.49	0.25

Continued Table 3.

MRI	Corpus Callosum	-0.745	0.054	0.08	0.86
	Cerebellum	-0.075	0.87	-0.37	0.41
	Centrum Semiovale	0.6	0.15	-0.3	0.4
	Subcortical	-0.37	0.4	0.29	0.51
	Corticospinal Tract	-0.24	0.59	0.56	0.18
	Midbrain	-0.07	0.87	-0.44	0.31
	Pons	0.37	0.4	0.29	0.51
	Medulla Oblongata	-0.32	0.48	0.52	0.22
	Dentate Nucleus	-0.32	0.482	0.2	0.65
	Bloom in Thalamus	-0.15	0.74	0.14	0.75

CC: Correlation Coefficient, WBC: white blood cells, NLR: Neutrophil-Lymphocyte Ratio, ESR: erythrocyte sedimentation rate, CRP: c-reactive protein, LDH: lactate dehydrogenase, AST: aspartate transaminase, ALT: alanine transaminase, CSF: cerebrospinal fluid, GCS: glasgow coma scale, ANE-SS: Acute necrotizing encephalopathy severity score, GOS: Glasgow Outcome Scale.

(P-value of 0.041 and CC of -0.77), and similar to that of sodium, as pH did not reach statistical significance, it is possible that this is also another incidental finding. Additionally, initial blood sugar correlates non-significantly with disease severity but not with outcome. Given the variations in the time from symptom onset to hospital admission and the differences in their symptoms, this could easily be just another incidental finding. Other laboratory tests, such as LDH, ESR, and CRP elevations, were not statistically significant and were only weakly correlated with disease severity and outcomes. The initial levels of Aspartate Transferase (AST) and Alanine Transaminase (ALT) showed some correlation with the ANE-SS, particularly AST, but were ultimately non-significant (P-value > 0.05). Regarding physical examination findings, except for pupil reactivity and GCS, none of the other factors significantly correlated disease severity or outcome. Interestingly, a reactive pupil and higher GCS upon admission were associated with a better outcome, as indicated by a P-value of 0.02 and 0.01, respectively. Among the radiological profiles examined, none of the three peculiar findings were significantly correlated with either study parameter. When comparing the severity score and disease outcome, the ANE-SS score was correlated with mortality, with a Spearman's rho of 0.66. However, this correlation was not statistically significant (P-value = 0.1).

Discussion

Study Summary and Key Notes

ANEC is an uncommon and potentially life-threatening neurological disorder that affects the central nervous system (CNS). This study examined the diverse clinical, laboratory, and radiological characteristics of children diagnosed with ANE and compared them to the severity of the disease and its outcome. The data gathered from the seven ANEC patients included in this study offer valuable insights into the different profiles associated with this rare condition. The majority of participants were young boys who did not have any significant medical history or family history of neurological disorders. The prodromal symptoms exhibited by the patients varied, although a high-grade fever was a common feature, and seizures were the presenting symptom in all

patients. Interestingly, one patient was diagnosed with ANEC after receiving the MMR vaccine. Treatment involving Methylprednisolone and IVIg was initiated for all patients, resulting in varying outcomes. Unfortunately, two patients died from severe cerebral edema complications, while the remaining patients survived with different degrees of neurological sequelae.

Magnesium as a Potential Neuroprotective Agent

A significant association was observed in this study between the initial serum magnesium (Mg) concentration and the severity of the disease, as well as the outcome. The data indicates that patients with higher serum Mg levels upon admission tended to have a lower severity score and better outcomes upon discharge. Although both disease severity and GOS showed a significant correlation, it was more potent concerning the former. Previous research has suggested that magnesium ions possess neuroprotective effects within CNS tissue, particularly in the white matter (11). One of its functions is to regulate CNS homeostasis and maintain the integrity of the blood-brain barrier (BBB). Supraphysiological concentrations of magnesium have been found to prevent lipopolysaccharide-induced injury. Additionally, magnesium has been observed to inhibit the glutamate N-methyl-D-aspartate receptor (NMDA-R), thereby preventing neuronal death, and serves as a source for various neurotrophins. Low levels of magnesium have been associated with increased activation of microglia and the release of Nitric Oxide (NO) and proinflammatory mediators such as prostaglandin E2 (PGE2) (12). Animal models have demonstrated that supplementation with magnesium reduces the severity of cerebral edema, including that observed in traumatic brain injury (TBI) and vasogenic edema, by downregulating aquaporin-4 (12). Furthermore, loss-of-function mutation of the *Mitochondrial Magnesium Homeostasis Factor* gene (MRS2) in demyelination mutant rats (*dmy*) resulted in cell death and myelin dysfunction (13–15). Studies have also shown that magnesium sulfate (MgS) therapy can protect the brain's white matter, particularly in neonates (16), and prevent injury from hypoxic-ischemic stress (HIS). Antenatal administration of MgS has significantly reduced the risk of cerebral palsy (17). Magnesium has also been implicated in stroke, with some studies indicating that lower levels are associated with a greater risk of ischemic stroke, mortality, and increased intracerebral hemorrhage scores (18). The findings of this investigation align with prior research that emphasized the possible neuroprotective characteristics of magnesium. However, serum magnesium has not been researched within ANEC patients, and while this research noted a distinct correlation, more studies need to be performed to validate these findings.

Initial Pupil Reactivity, GCS, and Patient Outcome

The correlation between the patients' GCS scores and pupillary light reactivity (PLR) upon admission was significantly linked to patient outcomes. While the GCS model is commonly used to assess the neurological status of post-TBI patients, examining pupillary reactivity and size is standard practice for all neurological emergencies. A study involving adult TBI patients revealed that assessing the GCS score in the field and the PLR upon admission accurately predicted 6-month post-TBI mortality (19). However, the motor score substantially contributes to the predictive

ability of the GCS, with this dynamic neurological assessment requiring thorough training for accurate documentation. Another study indicated that the absence of PLR upon admission was associated with a worse outcome in patients with out-of-hospital cardiac arrest (20). In children with hypoxic-ischemic encephalopathy (HIE), the absence of PLR during examination is a strong predictor of poorer outcomes (21). This study's findings highlight the prognostic importance of various neurological assessments, specifically the Pupillary Light Reflex (PLR). While these results align with previous research, they also open a new avenue for investigating ANEC patients that has not been explored before.

Limitations and Similarity

This research comprehensively analyzes the initial clinical, laboratory, and radiological characteristics of children diagnosed with ANEC. The study also investigated the significance and correlation of these profiles with disease severity and outcomes upon discharge or death. Most of the patients included in the study were male, with an average age of 4.4 years. The mortality rate was recorded as 28%, and a high rate of poor outcomes was reported, aligning with previous publications on the subject (2,22). Notably, the study findings suggest that serum magnesium levels may have a potential neuroprotective effect in this particular population. Furthermore, this study highlights the significant impact of an intact PLR on patient outcomes. To our knowledge, these findings have yet to be reported and analyzed in this population, although they are consistent with previous studies conducted in pediatric neurology. However, the main limitation of this study is the small sample size. Due to the rarity of ANEC and the fact that many patients are misdiagnosed or died before reaching primary pediatric neurology centers, possibly, some patients were not included in the study. Thus, further research is necessary to confirm or refute these results.

In Conclusion

By analyzing the associations between various initial characteristics and outcomes in patients with ANEC, it was discovered that most parameters exhibited a lack of significant correlation with both the ANE-SS and GOS. However, serum magnesium levels emerged as a noteworthy factor, as lower initial levels were linked to increased severity and poorer outcomes. These findings underscore the importance of monitoring and maintaining adequate magnesium levels in ANEC patients to potentially improve patient prognosis. This is likely due to magnesium's ability to maintain the BBB and reduce edema. Physicians should take note of these laboratory results early in the admission process of ANEC patients. With the exception of pupil reactivity and GCS, physical examination findings did not significantly impact the examined parameters. Interestingly, a reactive pupil and higher GCS upon admission were associated with a better outcome, highlighting the significance of neurological assessment in the early management and prognosis of ANEC. Furthermore, although a trend exists toward a correlation between the ANE-SS score and mortality, it did not reach statistical significance, likely due to the limited sample size. Overall, this study's findings offer valuable insights into the relationships between different clinical, laboratory, and radiological characteristics and disease severity and outcomes in ANEC patients and highlight the potential for magnesium supplementation to improve patient outcomes. Further research is necessary

to elucidate the underlying mechanisms and optimize treatment strategies for this rare and potentially life-threatening condition.

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Authors' Contribution

All authors meet the ICMJE criteria for authorship. Seilanian Toosi: Conceptualization, Methodology, Validation Hashemi: Conceptualization, Data curation, Investigation, Methodology, Supervision, Validation, Writing – review & editing Nejad Shahrokh Abadi: Data curation, Investigation, Writing – original draft, Writing – review & editing Arbastan: Methodology Akhoondian: Investigation Ashrafzadeh: Writing – review & editing Beiraghi Toosi Writing – original draft, Writing – review & editing Imannezhad: Investigation, Project administration Sara Maddahpour: Investigation, Writing - review & editing Naseri: Project administration
Saeidinia: Investigation, Methodology, Validation Kamali: Data curation, Writing - review & editing Shekari: Data curation, Writing - review & editing

Conflict of Interest

The authors declared no conflicts of interest regarding the publication of this paper.

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