ORIGINAL ARTICLE

New-Onset Refractory Status Epilepticus and Febrile Infection-Related Epilepsy Syndrome Cases in Children: A Retrospective Cohort Study in South of Iran

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ABSTRACT

Objectives

Epilepsy is one of the most common health problems in Iran. Considering this issue, the present study aimed to investigate New-Onset Refractory Status Epilepticus (NORSE) and Febrile Infection-Related Epilepsy Syndrome (FIRES) cases in children and evaluate the neurological outcome, referring to the special care department of Namazi Hospital, Shiraz, Iran.

Materials & Methods

Eight hundred seventy-three patients with status epilepticus (SE) referred to the medical centers of Shiraz Medical Sciences University were retrospectively examined from September 2021 to December 2022. After obtaining consent, the patients completed the questionnaire based on the literature review. Research data were collected and analyzed using SPSS version 23 software, t-test, Pearson correlation, and chi-square statistical methods.

Results

The obtained results revealed that out of 873 patients with SE, 140 patients had inclusion criteria for NORSE and FIRSE (63 had NORSE, and 30 had FIRSE). The developmental status of the patient was good in 26.4% of cases and had minimal complications in 21.4% of cases. Mortality in the studied subjects was 33.6% (47 patients), and seizures were controlled in 63 patients (64.9). Furthermore, the results showed that the cause of epilepsy in 47 people (33.6%) of the investigated people was infection/inflammation. Furthermore, no correlation was observed between the gender and age of the patients and the investigated outcomes (p-value>0.05). Only in seizure control, a significant difference was observed between the females and males (p-value<0.05).

Conclusion

This study concluded that the rate of NORSE and FIRES in the examined children is high. Moreover, one-third of these patients will not have a chance to survive. The results of the present study emphasize the need for more comprehensive studies in this field.

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Introduction

New-Onset Refractory Status Epilepticus (NORSE) is a rare and life-threatening neurological condition characterized by the sudden onset of prolonged and treatment-resistant seizures in individuals without a prior history of epilepsy (1). Children and adults can develop NORSE, and its etiology and pathophysiology are still poorly understood (2). This subgroup of refractory epilepsy in children presents a unique opportunity for investigation. By understanding the underlying mechanisms, clinical progression, and outcomes, we can gain valuable insights that may help optimize treatment strategies and improve patient outcomes (3).

Despite advancements in diagnostic tools, neuroimaging techniques, and treatment modalities, the etiology and pathophysiology of refractory epilepsy, especially in the pediatric population, remain complex and multifactorial (4,5). Genetic predisposition, structural brain abnormalities, neurotransmitter imbalances, and immune system dysregulation have all been implicated in developing refractory epilepsy. However, the specific interplay of these factors and their contribution to stable refractory epilepsy in children necessitate further exploration (6).

A crucial component of patient care for people with NORSE is to evaluate their neurological outcome since it offers important insights into the severity of their brain damage, their functional recovery, and any potential long-term disability (7). The evaluation of the neurological outcome in NORSE patients is complex and combines clinical assessment, neuroimaging, electroencephalography (EEG), and other pertinent tests. Some patients may recover completely, while others may experience varying neurological deficits and cognitive impairment (7). The prevalence of NORSE is challenging to determine accurately due to its heterogeneous nature and the absence of standardized diagnostic criteria. NORSE is considered a rare condition, and its occurrence is estimated to be around 1 in 500,000 individuals per year (8).

The cause of the catastrophic epileptic disease known as Febrile Infection-Related Epilepsy Syndrome (FIRES), affecting previously healthy children between the ages of 3 and 15, is unknown. Besides, few effective treatments are available. These children experience a nonspecific febrile illness that is followed by prolonged refractory status epilepticus (SE) (9). FIRES is extremely rare, and its prevalence is estimated to be less than 1 in 1,000,000 individuals (10). It primarily affects previously healthy children, typically between the ages of 3 and 15 (11).

Due to the rarity of NORSE and FIRES, more information is needed on their epidemiology and ideal treatment (12). Even though NORSE has been better understood in recent years, more research is still required to fully understand the disorder, identify potential triggers, and develop effective treatment strategies (13). Therefore, the present study aimed to investigate NORSE and FIRES cases in children and evaluate the neurological outcome by referring them to the special care department of Namazi Hospital, Shiraz, Iran.

Materials & Methods

In the present retrospective study, all new cases of drug-resistant epilepsy in children were investigated by collecting data from Namazi Hospital, Shiraz, Iran, over the past ten years. Clinical characteristics, disease severity, and outcomes were collected.

The database was searched for epilepsy, SE,

and NORSE. Inclusion criteria for diagnosing NORSE patients, among other causes, include 1) absence of previous epilepsy diagnosis, 2) absence of neurologic disease, 3) seizures lasting more than one hour, and 4) use of at least two first-line antiepileptic treatments with the initiation of anesthesia. Exclusion criteria for NORSE include 1) lack of parental consent and 2) Criteria for diagnosing FIRES patients include: A) age between 3-15 years, B) presence of fever, C) resistance to treatment, D) seizures lasting more than one hour, and E) unidentified specific cause. The therapeutic methods used in the present study included IV Anti-seizure medication in the two first lines and anesthetic drugs used in the second line; if the seizure continued, according to the patient's condition, Methylprednisolone, immunosuppressors, and a ketogenic diet were used.

The studied outcomes encompassed intensive care unit (ICU) admission, duration of hospitalization, time of first seizure, administered drugs, observed side effects, patient mortality, progression towards malignancy, and patient developmental status. Child developmental status was categorized as follows:

- Neurologically Normal
- Mild Impairment: The patient can move and speak with minimal side effects.
- Moderate Impairment: The patient displays noticeable walking, movement, and cognition impairments.
- Severe Impairment: The patient experiences severe side effects (lack of environmental awareness, vegetative state, and inability to speak) and is deceased.

Statistical analysis

The chi-square test was utilized to compare qualitative variables. Pearson's correlation test was employed to identify the relationship between age and quantitative variables, with the Pearson coefficient indicating the extent of a linear relationship. A significance level of less than 0.05 was considered statistically significant. Statistical analysis was performed using SPSS software version 23.

Results

The obtained results revealed that out of 873 patients with status epilepticus, 140 patients had inclusion criteria for NORSE and FIRSE (63 had NORSE, and 30 had FIRSE), 82 individuals (58.6%) were male, and 64 individuals (45.7%) had a history of ICU hospitalization (Table 1).

The mean age of the study participants was 10.69 ± 5.87 years. Additionally, the mean time to the first seizure was 36.61 ± 16.52 months. The average duration of ICU hospitalization was 15.11 ± 11.64 days (Table 2).

Among all the examined individuals, only one patient (0.7%) showed positive autoimmune and onconeural antibodies. Furthermore, the Herpes Polymerase Chain Reaction (PCR) test was positive in six patients (4.3%). The results showed that six patients (4.3%) were using anesthetics, and 33 patients (23.6%) were using a ketogenic diet.

Moreover, the results showed that the cause of epilepsy in 47 people (33.6%) of the investigated people is infection (Figure 1).

The results indicated that 47 patients, accounting for 33.6%, had died, while seizures were controlled in 63 patients, which is 64.9%. Additionally, 19 patients, or 20.4%, experienced treatment-resistant epilepsy. The findings also showed that among the 93 patients with a fever, 63 were diagnosed with NORSE, and 30 had FIRSE.

Among the 93 people examined who were alive, 37 people (26.4%) were neurologically normal, and four subjects had severe impairment (2.9% of cases) (Table 3).

The results of Spearman's non-parametric correlation test showed a significant correlation (p-value<0.001) between age and the time of the first seizure (correlation coefficient: 0.659) (Table 4).

The results of the t-test showed that, among the investigated outcomes, gender has a significant relationship only with seizure control (p-value<0.05), so seizures are more controlled in males (Table 5).

Table 1. Demographic variables of the study population

Variable		Frequency	Percentage
ICU hospitalization	Yes	64	45.7
	No	72	51.4
	Missing	4	2.9
Ketogenic diet	Yes	33	23.6
	No	107	76.4
Fever	Yes	93	66.4
	No	47	33.6
VNS	Yes	29	20.7
	No	111	79.3
Callosotomy surgery	Yes	9	6.4
	No	131	93.6
Rituximab	Yes	3	2.1
	No	137	97.9
Total		140	100

Table 2. The mean of quantitative variables

Variable	Mean ± Standard Deviation	Minimum	Maximum
Age (years)	10.69±5.87	4	14
Duration of ICU hospitalization (days)	15.11±11.64	2	70
Time to First Seizure (months)	36.61±16.52	1	48
Duration of Intubation (days)	10.84±7.77	3	30

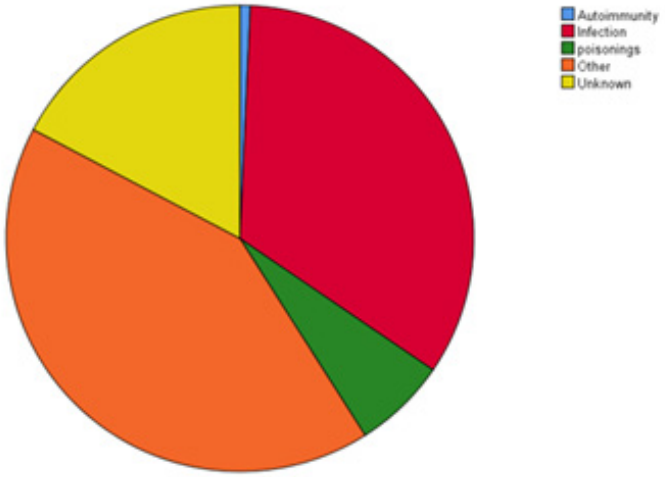

Figure 1. The final diagnosis of the cause of epilepsy in the subjects investigated

Table 3. The developmental status of the children investigated

	Frequency	Percentage
Neurologically normal	37	26.4
Mild impairment	38	27.1
Moderate impairment	14	10
Severe impairment	4	2.9
Dead	47	33.6
Total	140	100

Table 4. Correlation between age and outcomes investigated

			Age
Spearman's rho	Age	Correlation Coefficient	1.000
		Sig. (2-tailed)	.
		N	140
	Duration of ICU Hospitalization (days)	Correlation Coefficient	.045
		Sig. (2-tailed)	.728
		N	63
	Time to First Seizure (months)	Correlation Coefficient	.659
		Sig. (2-tailed)	.000
		N	118
	Duration of Intubation (days)	Correlation Coefficient	-.236
		Sig. (2-tailed)	.194
		N	32

Table 5. The relationship between gender and the outcomes investigated

Variable	Gender	N	Mean	SD	P-value
ICU Hospitalization (days)	Male	39			.508
	Female	25			
Duration of ICU Hospitalization (days)	Male		15.41	12.63	. 797
	Female		14.63	10.04	
Fever	Male	44			.582
	Female	49			
VNS	Male	14			.209
	Female	15			
Callosotomy surgery	Male	5			.230
	Female	4			
Duration of Intubation (days)	Male		10.63	7.26	.855
	Female		11.15	8.71	
Patient survival	Male	55			.967
	Female	38			
Controlled seizures	Male	42			.003
	Female	21			

Discussion

Approximately 50% of NORSE patients remain undiagnosed despite extensive workup. NORSE is identified as a distinct clinical manifestation with a new onset of drug-resistant epilepsy in a patient without prior active epilepsy or related neurological disorders (such as acute cerebral infarction, brain tumors, excessive drug use, and the like) and without an apparent structural, toxic, or metabolic cause (14). The FIRES, known as catastrophic epilepsy syndrome, is a severe variant of the condition that develops after a febrile episode. Most children (73%) who appear with this particular syndrome are between ages four and nine (15). In Iran, due to the severe outcomes and high mortality rate, no statistics exist on NORSE and FIRES (16).

The present study aimed to investigate and determine new cases of drug-resistant epilepsy in children, accompanied by an assessment of neurological outcomes.

The data analysis revealed that 26.4% of patients had normal neurological outcomes, while 27.1% had minimal adverse effects. Mortality occurred in 33.6% of the study participants (47 patients), and 64.9% (63 patients) had controlled seizures. Furthermore, the results showed that inflammation/infection was the main etiology of epilepsy in 33.6% (47 individuals) of the examined cases. In 20.4% (19 patients), drug-resistant epilepsy was observed. A significant relationship between gender and seizure control was observed. Among the 93 feverish patients, 63 had NORSE, and 30 had FIRES. In the current study, no significant association between age and gender and mortality was found.

In a retrospective cohort study by rt al. in 2021, forty (87%) patients had NORSE of unknown etiology. Nineteen (48%) presented with fever at SE onset, 16 (40%) had a previous fever, and five (12%) had no fever. The patients with preceding fever had more prolonged SE and worse outcomes, and 25% recovered baseline neurological function. The patients with fever at onset were younger, had shorter SE episodes, and 89% recovered baseline function (17).

In the study by Mehuri Habibabadi et al. (18), a significant relationship was observed between mortality and gender, while no significant relationship was found between mortality and age. Similarly, no significant relationship was found between the gender of the examined individuals and patient mortality. Notably, the number of deceased cases in the current study was 33.6% (47 patients).

Husari et al. (19) identified 40 patients with NORSE out of 672 cases of SE over 3.5 years (6% of cases). None of the patients had positive neuronal antibodies. Various treatments, including immunotherapy, were attempted, with immunotherapy used in half of the patients. Five patients (12.5%) died during the acute phase of their illness, and four patients were lost to follow-up. Among the remaining 31 patients, 65% experienced seizures, and 58% had ongoing neurocognitive impairments. In the present study, out of 140 patients, 13% (19 patients) had drug-resistant epilepsy. Additionally, the mortality rate among the studied individuals was 33.6% (47 patients), higher than that reported by Husari et al. Of the 47 deceased patients, 27 were male and 20 were female. In this study, out of the 63 NORSE patients, 47 individuals had abnormal inflammatory tests and had an inflammation/ infection cause, with one case testing positive for autoantibodies. In the present study, 26% of patients (37 individuals) had normal neurological development, 27.1% (38 patients) had mild neurological sequelae, 10.7% (14 patients) had moderate neurological sequelae, and 2.9% (4 patients) had severe developmental impairments.

In Gaspard et al.'s study, viral causes were the most identified cause of NORSE and accounted for 20% of cases. In the current study, the cause of epilepsy was infection in 33.6% of cases (20).

Strengths and limitations

The present study is the first report of NORSE and FIRES cases from Iran. However, it has limitations, including being retrospective and a single-center study.

In Conclusion

The results of the present study showed that the prevalence of NORSE and FIRES in the examined children was high, and the mortality rate was high in these people. Considering that a significant part of epilepsy cases can be controlled, post-discharge care should be taken into consideration.

Acknowledgment

This study received approval from the Ethics Committee of Shiraz University of Medical Sciences with the ethics code IR.SUMS.MED.REC.1401.156.

Authors' Contribution

Hamid Nemati[1]interpreted the findings, finalized the text, and supervised the project Atena Modanlou collected the patients' information, analyzed the data, , Eslam Shorafae, Razie Taghizade, Soroor Inaloo prepared the manuscript draft.

Conflict of Interest

None.

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