Clinical and neuroimaging features of new-onset refractory status epilepticus patients

Vo Hong Khoi[1,2,3], Phan Duy Phuc[1]✉

[1] Hanoi Medical University

[2] Neurology Center – Bach Mai hospital

[3] VNU University of Medicine and Pharmacy

Correspondence to

Phan Duy Phuc

Hanoi Medical University

Email: phucbkh37hmu@gmail.com

Manuscripts submission:

Peer Review:

Manuscripts accepted:

ABSTRACT

Objective: New-onset refractory status epilepticus (NORSE) is rare, clinical symptoms and characteristics on magnetic resonance imaging (MRI) are diverse, sometimes difficult to recognize, sometimes the cause cannot be determined and it is very difficult to treat. This article describes the clinical signs and MRI characteristics of patients presented with New-onset refractory status epilepticus at the Neurology Center of Bach Mai Hospital.

Subjects and Methods: A cross-sectional descriptive study in which data were retrospectively collected from 34 NORSE-patients treated in Neurology Center – Bach Mai Hospital from February 2023 to January 2025.

Results: 34 patients were presented with new-onset refractory status epilepticus, of which the male/female ratio was 15/19 (= 0.79). The average age is 38.29 ± 19.09 years (range from 16 - 73 years). Regarding the cause of NORSE, 18 patients (52.9%) were cryptogenic – NORSE, 13 patients (38.2%) were diagnosed autoimmune encephalitis. There were 20 patients with focal onset evolving into bilateral convulsive SE (58.8%), 9 patients with focal motor SE (26.5%), and 5 patients with generalized convulsive SE (14.7%). The prodrome symptoms are fever (32.4%), confuse (55.9%), fatigue (47.1%), sleep disorder (14.7%), headache (35.3%), memory disorders (29.4%), and upper respiratory tract infection (12.8%). All patients received magnetic resonance imaging (MRI) with an abnormality rate of 55.9% on MRI, including 12 patients with unilateral hemispheric lesions (35.3%) and 7 patients with bilateral lesions (20.6%).

Conclusion: The clinical signs and MRI characteristics manifestations of NORSE-patients is highly variable.

Keyword: NORSE, New-Onset Refractory Status Epilepticus.

DOI:10.62511/vjn.44.2025.047

I. INTRODUCTION

Status epilepticus (SE) is defined as continuous epileptic activity on clinical presentation and/or EEG, or recurrent seizures without regaining consciousness between episodes, lasting more than 5 minutes. Refractory Status Epilepticus (RSE) is a serious condition in which seizures do not respond to initial treatment with sufficient dose of intravenous benzodiazepines and intravenous longer-acting antiseizure medications. Among patients with status epilepticus, approximately 23-48% progress to RSE.[1]

New-Onset Refractory Status Epilepticus (NORSE) clinically characterized by new-onset refractory SE in patients without prior epilepsy, no pre-existing neurological injury (such as stroke, brain tumor,…), and no acute structural, toxic, or metabolic cause. Febrile Infection-Related Epilepsy Syndrome (FIRES) is a subset of NORSE associated with a prior febrile infection, with fever occurring within 24 hours to 2 weeks before the onset of refractory status epilepticus.[2]

The clinical course of NORSE includes two phases: acute phase and chronic phase (including refractory epilepsy and neurological deficits). The mortality rate is 12% in children and approximately 16-27% in adults and it can lead to severe neurological sequelae in survivors.3 Prodromal symptoms included confusion, fever, fatigue, headache, symptoms of gastrointestinal or upper respiratory tract infection, and behavioral changes. Seizures occurred before admission in 90% of cases.[4] Some abnormalities on MRI include persisting mesial temporal lobe signal abnormality, initial diffuse leptomeningeal enhancement, hippocampal atrophy, claustrum abnormalities.[5] SE tends to last longer in patients with NORSE of unknown origin, but there is no difference in ICU stay duration, outcomes, or mortality rate.[4]

This study aimed to describe the clinical and MRI characteristics of NORSE patients to help guide timely diagnosis and treatment.

II. SUBJECTS AND METHODS

1. Study Subjects

We selected 34 patients presented with NORSE from February 2023, to January 2025 at the Neurology Center of Bach Mai Hospital.

2. Study design

Cross-sectional descriptive study.

3. Data collection

Data were collected from medical records, information collected included patient demographic characteristics, clinical signs, magnetic resonance imaging, etiological diagnosis, and outcomes at discharge.

III. RESULTS

There was a female predominance with the male/female ratio was 15/19 (= 0.79). Age ranged from 16 - 73 years, most patients are under 50 years old (61.8%). The average age is 38.29 ± 19.09 years.

***Table 1**. The causes of NORSE.*

Cause	Number of patients	%
Autoimmune encephalitis	13	38.2
Herpes Simplex encephalitis	3	8.8
Cryptogenic	18	53.0

Comments: In our Neurology Center, we treat many patients with autoimmune encephalitis, so the incidence of these patients is quite high (38,2%). Most patients were tested for a meningitis/encephalitis multiplex PCR panel in the cerebrospinal fluid, however the only infectious cause detected was herpes simplex virus, with a rate of 8.8%. Despite the expanding

diagnostic panel, the rate of cryptogenic-NORSE remains quite high, similar to other studies.

Among patients presented with NORSE, 24 patients (70.6%) presented with prodromal symptoms. This result is almost identical to the result in Gaspard's 2015 study (60%).[4]

***Table 2**. The prodromal symptoms of NORSE.*

Symptoms	Number of patients	%
Fever	11	32.4
Confuse	19	55.9
Fatigue	16	47.1
Sleep disorder	5	14.7
Headache	9	26.5
Behavior disorders	12	35.3
Memory disorders	10	29.4
Upper respiratory tract infection	4	12.8

Comments: NORSE-patients can have a wide variety of prodromal symptoms, commonly including confuse, fatigue, fever, behavior disorders or memory disorders. Other symptoms may also occur, such as headache, sleep disorder, upper respiratory tract infection,… which are easily confused with other diseases and difficult to recognize the association with later status epilepticus.

***Table 3**. Classification of status epilepticus according to ILAE 2015.*

Symptoms	Number of patients	%
Focal onset evolving into bilateral convulsive SE	20	58.8
Focal motor SE	9	26.5
Generalized convulsive SE	5	14.7

Comments: Most patients had focal onset evolving into bilateral convulsive SE (20 patients, 58.8%) based on ILAE 2015 classification. Focal motor SE occurred in 9 cases (26.5%), and generalized convulsive SE occurred in 5 cases (14.7%).

All status epilepticus patients in our Neurology Center underwent brain magnetic resonance imaging. Of the NORSE-patients, 55.9% had abnormal findings on MRI. This result is similar to that in Gaspard's 2015 study (62%) and Matthews's 2020 study (50%).[4,6]

***Table 4**. MRI lesion characteristics of the NORSE-patients*

MRI findings	Number of patients	%
Side of lesions		
No lesions	15	44.1
Unilateral hemispheric lesions	12	35.3
Bilateral lesions	7	20.6
Locations		
Temporal	16	47.1
Insular	9	26.5
Claustrum	5	14.7
Thalamus	5	14.7
Occipital	2	5.9

Comments: Most patients with MRI abnormalities had unilateral lesions (12 patients, 35.3%). 7 patients (20%) with bilateral lesions. Some common locations of abnormalities on MRI include temporal (47.1%), insular (26.5%), claustrum (14.7%), thalamus (14.7%) and occipital (5.9%).

DOI:10.62511/vjn.44.2025.047

***Table 5**. Some characteristics of cryptogenic-NORSE and other causes (autoimmune, infection)*

	Cryptogenic-NORSE	Other causes (autoimmune, infection)	p value
Prodromal symptoms	12 (50%)	12 (50%)	0.715
Fever	5 (45.5%)	6 (54.5%)	0.897
Confuse	8 (42.1%)	11 (57.9%)	0.515
Fatigue	7 (43.8%)	9 (56.3%)	0.716
Behavior disorder	4 (33.3%)	8 (66.7%)	0.236
MRI abnormalities	7 (36.8%)	12 (63.2%)	0.179

Comments: There is no significant difference in some prodromal symptoms and MRI abnormalities between the group with cryptogenic-NORSE and the group with other causes (p>0.05).

IV. DISCUSSION

In this study, we analyzed the clinical and neuroimaging characteristics of 34 patients with new onset refractory status epilepticus (NORSE) at the Neurology Center of Bach Mai Hospital. Our findings provide valuable insights into the demographic patterns, etiologies, prodromal symptoms, and neuroimaging abnormalities associated with NORSE, with several similarities and differences compared to previous studies.

The average age of the patients is 38.29 ± 19.09, which is consistent with the findings of Gaspard and Matthews.[4,6] However, unlike the bimodal age distribution observed in these studies (peaks at 28.5 and 65 years for Gaspard, and 27 and 63 years for Matthews), our study predominantly involved younger patients (61.8% patients were under 50 years old). This disparity may be attributed to the high prevalence of autoimmune encephalitis in our Neurology Center, a condition more common in younger populations. In contrast, etiologies more frequently seen in older adults, such as infections, were less common in our center. There was a female predominance, similar to other studies.[4,6]

The majority of cases in our study were classified as cryptogenic NORSE, with a notable proportion of antibody-positive cases identified. The incidence of autoimmune encephalitis was higher in studies of Gaspard 2015 and Matthews 2020. This difference could be explained by the fact that our center is a specialized referral facility for severe autoimmune encephalitis, leading to a higher concentration of such cases. The rate of cryptogenic NORSE according to out study is 53%, similar to Gaspard (52%) but lower than that reported by Matthews (73%).[4,6]

It can be observed that there are many prodomal symptoms of NORSE. Compared to the study of Matthews et al, our study had less frequent prodrome (70.6% vs 96%), but more frequent than the study of Gaspard et al (70.6% vs 60%).[4,6] This variation may be due to differences in study populations, data collection methods, and cultural perceptions of prodromal manifestations.

Notably, we did not find significant differences in the frequency of prodromal symptoms between patients with cryptogenic NORSE and those with other etiologies. This finding contrasts with Iizuka et al., who reported

a higher incidence of prodromal symptoms in cryptogenic NORSE.[7] The inconsistency across studies suggests that prodromal symptoms may not reliably distinguish between etiologies, emphasizing the need for further research to elucidate their diagnostic significance

Abnormal brain MRI findings were detected in 55.9% of our patients, comparable to Matthews (50%) and Gaspard (62%), but lower than the 82.1% reported by HJ Kim et al. This discrepancy may be attributed to differences in imaging protocols and timing, as most of our patients underwent MRI on admission using a 1.5 Tesla scanner. Since MRI abnormalities in NORSE may evolve over time, a follow-up imaging strategy could provide a more comprehensive understanding of neuroimaging patterns in this condition.[4–6]

Our study has some limitations as it is a single-center, retrospective, small-group study, and diagnostic and laboratory updates change over time, some prodromal symptoms are also easily overlooked. However, this study also provides an overview of the clinical and neuroimaging features of NORSE-patients, helping to guide physicians in approaching and diagnosing them promptly.

V. CONCLUSION

In our study, NORSE-patients had a wide range of clinical and MRI manifestations. Common prodromal symptoms included fever, confusion, headache, behavioral disturbances, and fatigue. The most common classification of status epilepticus was focal onset evolving into bilateral convulsive status epilepticus. Many NORSE patients had no abnormalities on MRI. Among patients with abnormalities on MRI, the location was varied, and could be unilateral or bilateral.

REFERENCES

1. Dubey D, Kalita J, Misra UK. Status epilepticus: Refractory and super-refractory. *Neurol India*. 2017;65(Supplement):S12-S17. doi:10.4103/neuroindia.NI_958_16
2. Bhatia K, De Jesus O. New Onset Refractory Status Epilepticus. In: *StatPearls*. StatPearls Publishing; 2024. Accessed March 8, 2024. http://www.ncbi.nlm.nih.gov/books/NBK567765/
3. Gaspard N, Hirsch LJ, Sculier C, et al. New-onset refractory status epilepticus (NORSE) and febrile infection–related epilepsy syndrome (FIRES): State of the art and perspectives. *Epilepsia*. 2018;59(4):745-752. doi:10.1111/epi.14022
4. Gaspard N, Foreman BP, Alvarez V, et al. New-onset refractory status epilepticus: Etiology, clinical features, and outcome. *Neurology*. 2015;85(18):1604-1613. doi:10.1212/WNL.0000000000001940
5. Kim HJ, Lee SA, Kim HW, Kim SJ, Jeon SB, Koo YS. The timelines of MRI findings related to outcomes in adult patients with new-onset refractory status epilepticus. *Epilepsia*. 2020;61(8):1735-1748. doi:10.1111/epi.16620
6. Matthews E, Alkhachroum A, Massad N, et al. New-onset super-refractory status epilepticus. *Neurology*. 2020;95(16):e2280-e2285. doi:10.1212/WNL.0000000000010787
7. Iizuka T, Kanazawa N, Kaneko J, et al. Cryptogenic NORSE. *Neurol Neuroimmunol Neuroinflammation*. 2017;4(6):e396. doi:10.1212/NXI.0000000000000396