■ Original article

Epileptic Disord 2022; 24 (5): 867-876

Epileptic Disorders

A retrospective cohort study of new-onset refractory status epilepticus (NORSE): clinical features, timing of immunotherapy and outcomes

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Epileptic Disorders

Highlights

- New-onset refractory status epilepticus (NORSE) is an uncommon entity with a high mortality rate.
- There is no established NORSE treatment protocol.
- Early immunotherapy is feasible: 81% of NORSE patients received a first-line agent within 7 days of presentation at our institution.
- There was no statistically significant effect of early immunotherapy on mRS outcomes.
- C-NORSE scores ≥5 were obtained in 12/18 (67%) cryptogenic cases and C-NORSE score < 5 was obtained in all 3 immune-mediated cases.

Epileptic Disorders

Background

- New-onset refractory status epilepticus (NORSE) is a clinical presentation in a patient without active epilepsy or pre-existing relevant neurological disorder without a clear, acute or active structural, toxic or metabolic cause [1].
- The outcome is generally poor in 62% of patients [2].
- A subset of patients with NORSE have autoimmune (19%) or paraneoplastic (18%) causes which are potentially treatable. However, the diagnostic workup and treatment of NORSE are not standardized and there are no published guidelines regarding the treatment options such as type or timing of immunotherapy [2,3].

[1] Hirsch LJ, Gaspard N, van Baalen A, Nabbout R, Demeret S, Loddenkemper T, et al. Proposed consensus definitions for new-onset refractory status epilepticus (NORSE), febrile infection–related epilepsy syndrome (FIRES), and related conditions. *Epilepsia*. 2018; 59:739–744.
[2] Gaspard N, Foreman BP, Alvarez V, Cabrera Kang C, Probasco JC, Jongeling AC et al. New-onset refractory status epilepticus: Etiology, clinical features and outcome. *Neurology*. 2015; 85(18):1604-1613.
[3] Cabrera Kang CM, Gaspard N, LaRoche SM, Foreman B. Survey of the diagnostic and therapeutic approach to new-onset refractory status epilepticus. *Seizure*. 2017;46:24-30.

Objectives

- Primary aim: to describe our retrospective cohort of NORSE (n=22) from Stanford University Hospital from 2004-2021 and assess the timing of immunotherapy and its effect on outcome at discharge and follow-up.
- Secondary aim: to apply the cryptogenic NORSE (C-NORSE) score to the subjects to evaluate its utility to identify C-NORSE [4]

[4] Iizuka T, Kanazawa N, Kaneko J, Tominaga N, Nonoda Y, Hara A, et al. Cryptogenic NORSE: Its distinctive clinical features and response to immunotherapy. *Neurol Neuroimmol Neuroinflam*. 2017;4(6):e396.

Results: Patient characteristics

	Cryptogenic NORSE	Immune-Mediated NORSE
Demographics (n=22)	n=18	n=3
age: median	25	27
female: n (%)	5 (28%)	2 (67%)
transferred from outside hospital: n (%)	10 (56%)	1 (33%)
time to hospital transfer (days): median	5	5
Presentation (n=22)		
fever: n (%)	11 (61%)	0
psychiatric prodrome: n (%)	7 (39%)	3 (100%)
psychosis: n (%)	1 (6%)	3 (100%)
agitation: n (%)	6 (33%)	0
Status Epilepticus (SE) classification (n=22)		
convulsive (prominent motor)	17 (94%)	3 (100%)
non-convulsive	1 (5%)	0
Number of ASMs to control SE, median	5.5	4
CSF (n=22)		
pleocytosis WBC >5: n (%)	9 (50%)	2 (67%)
CSF oligoclonal bands: n (%)	2/13 (15%)	2 (67%)
CSF Ab tested	7 (39%)	3 (100%)
CSF Ab positive	0	2 (67%)
Clinically significant serum Ab: n (%)	0	3 (100%)
LGI-1	0	1
NMDA-R Ab	0	2
MRI brain (n=22)		
abnormal: n (%)	14 (78%)	3 (100%)
symmetric DWI or T2 weighted FLAIR hyperintensities	11 (61%)	0

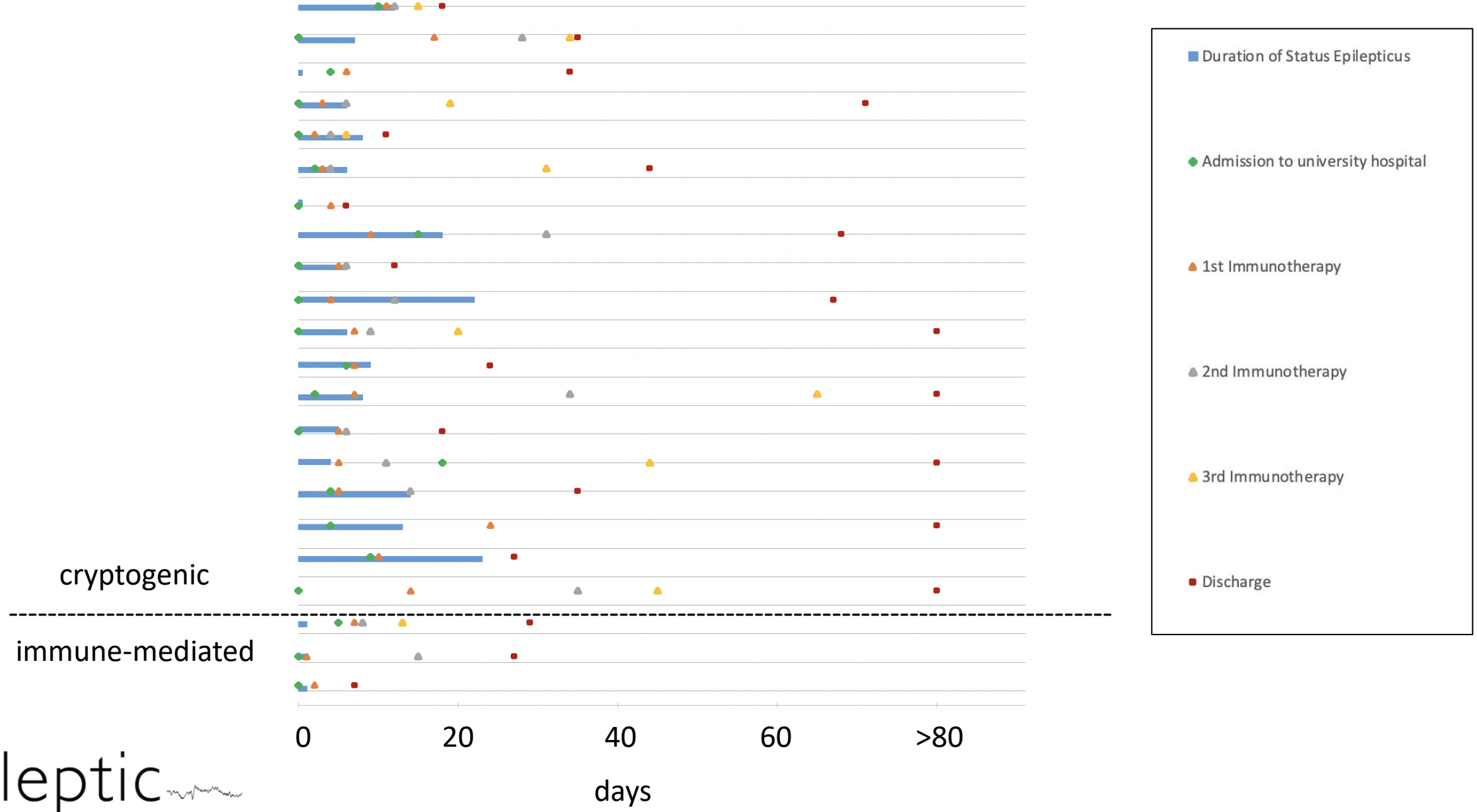
Results: C-NORSE scores with respect to diagnosis and antibody status

C-NORSE score	Diagnosis	Age	Sex	Ab Status	First-line immunotherapy (IV steroids, IVIg, PLEX)	Second-line immunotherapy
2	immune	28	male	LGI-1	steroids, IVIg	none
2	immune	20	female	NMDA-R	steroids, IVIg	rituximab
3	cryptogenic	25	male	negative	steroids, PLEX	none
4	immune	33	female	NMDA-R	steroids, IVIg, PLEX	none
4	cryptogenic	18	male	thyroglobulin*	steroids, IVIg	none
4	cryptogenic	20	male	negative	steroids, PLEX	none
4	cryptogenic	30	female	thyroglobulin*	steroids	none
4	cryptogenic	31	male	negative	steroids, IVIg, PLEX	none
4	cryptogenic	53	female	negative	steroids, IVIg, PLEX	none
5	cryptogenic	15	female	low titer GAD-65	steroids, IVIg, PLEX	none
5	cryptogenic	19	male	negative	steroids, IVIg, PLEX	rituximab
5	cryptogenic	42	female	negative	steroids, IVIg, PLEX	none
5	cryptogenic	58	male	low titer GAD-65	steroids, IVIg, PLEX	none
5	cryptogenic	60	male	negative	steroids, IVIg	mycophenolate mofetil, azathioprine
5	cryptogenic	71	male	negative	steroids, IVIg	none
6	cryptogenic	6	male	negative	steroids, IVIg	cyclophosphamide
6	cryptogenic	6	male	negative	steroids, IVIg	none
6	cryptogenic	9	male	negative	steroids, IVIg, PLEX	cyclophosphamide
6	cryptogenic	10	male	low titer GAD-65	steroids, IVIg, PLEX	rituximab
6	cryptogenic	25	male	negative	steroids, IVIg, PLEX	none
6	cryptogenic	46	female	negative	steroids	none

**Patients did not meet clinical criteria for Hashimoto's encephalitis. All GAD-65 levels were clinically insignificant <20nmol/L.*

Epileptic Disorders

Figure 1: Timeline of immunotherapy with respect to NORSE etiology



Epileptic Disorders

Outcomes

	Cryptogenic NORSE	Immune-Mediated NORSE
Hospital characteristics		
length of stay: (days), median	33	24
discharge destination: n (%)		
home	1 (6%)	2 (67%)
rehabilitation	10 (56%)	0
outside hospital	5 (26%)	1 (33%)
deceased	2 (11%)	0
Modified Rankin Scale (mRS) at discharge: n (%)		
mRS 6 death	2 (11%)	0
mRS 5	4 (22%)	1 (33%)
mRS 4	8 (44%)	0
mRS 3	2 (11%)	1 (33%)
mRS 2	2 (11%)	1 (33%)
mRS 0-1	0	0
favorable outcome (mRS 0-2)	2 (11%)	1 (33%)
mRS at follow up		
mRS 0-2 at 6 month follow up	7/11 (64%)	3/3 (100%)
mRS 0-2 at 12 month follow up	9/11 (82%)	2/2 (100%)
mRS 0-2 at last follow up (>13 months)	8/10 (80%)	2/2 (100%)

Conclusions

- The majority of our NORSE patients (81%) received early first-line immunotherapy within 7 days of presentation.
- There was no significant difference between early and late immunotherapy and a good outcome (mRS 0-2).
- C-NORSE score ≥ 5 was obtained in 12/18 (67%) cryptogenic cases and C-NORSE score <5 was obtained in all 3 immune-mediated cases.
- More studies are needed to assess the effects of various treatments such as timing of immunotherapies and their effects on outcome in different subsets of NORSE patients.

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