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Long Term outcomes after NORSE: Treatment with Vagus Nerve Stimulation

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Abstract: New-onset refractory status epilepticus (NORSE) is associated with high mortality, therapy resistant epilepsy (TRE) and poor cognitive and functional outcomes. Some patients develop multifocal TRE, for whom surgery with a curative intention, is not an option. In these patients, Vagus Nerve Stimulation (VNS) is performed as a palliative treatment. We report the long-term outcomes regarding seizure frequency, functional and cognitive outcome, and effectiveness of VNS in two patients with TRE as a consequence of NORSE. In the first patient with cryptogenic NORSE, VNS implantation occurred during the acute stage, probably contributing to the cessation of her status epilepticus. However, in the long-term follow-up, the patient persisted with daily multifocal seizures. In the second patient, VNS implantation was delayed to manage his epilepsy when the NORSE, ultimately due to autoimmune encephalitis, had resolved. During long-term follow-up, no reduction in seizure frequency was achieved. The current evidence supporting the use of VNS in patients with TRE after NORSE warrants further investigation.

Key words: Status epilepticus, autoimmune epilepsy, encephalitis, VNS, therapy resistant epilepsy.

1. Introduction

New-onset refractory status epilepticus (NORSE) is a clinical presentation of refractory status epilepticus (RSE) in previously healthy individuals, without an acute structural, toxic, or metabolic cause ¹. In approximately 50% of cases the etiology is unknown while in the other half, autoimmune encephalitis is the most common cause ². No specific therapy is currently available for those patients; therefore, combinations of antiseizure medications (ASMs), anesthetics, immunotherapy and ketogenic diet are prescribed in the attempt to stop NORSE ³. Furthermore, few cases of acute implantation of Vagus Nerve Stimulator (VNS) have been described ⁴. Most treatment recommendations are based on expert opinion.

NORSE is associated with high mortality and poor cognitive and functional outcomes ². Around 40% of patients with NORSE develop epilepsy afterwards ^{2,3}. Some patients can develop bitemporal or multifocal therapy resistant epilepsy (TRE), for whom surgery with a curative intention is not an option ⁵. In these patients the implantation of VNS is performed as a palliative treatment. Although the general effectiveness of VNS has been described ⁶, there is insufficient data regarding its long-term outcomes in patients after NORSE.

We describe two patients who had NORSE and developed TRE epilepsy. The VNS was implanted in the acute and chronic phase, respectively. The long-term outcomes will be reviewed.

2. Cases Presentation

Patient 1

A 37-year-old woman, with an unremarkable medical history, was found unconscious after a week of mild flu-like symptoms, including fever. She was

brought to the emergency department where a bilateral tonic-clonic seizure was witnessed. Her disease progressed to multifocal RSE. Different ASMs and anesthetics were prescribed without success. The initial work-up was done early and was negative for structural, toxic, metabolic, and infectious etiologies. Autoimmune encephalitis was proposed as a possible etiology and she completed a course of corticosteroids, intravenous immunoglobulin (IVIG) and rituximab weekly, while she was admitted to Intensive Care Unit (ICU). When the results arrived, her complete autoimmune panel was negative. After 30 days of NORSE, she had received two more doses of rituximab, but she persisted in Super-RSE (SRSE). At that time, VNS was implanted, and rapid upwards titration of output current was established, reaching 1.25mA in 48 hours and 1.75mA on the seventh day. On the same day the SRSE was aborted. Additionally, on the seventh day she completed three doses of rituximab without changes to her ASMs or anesthetics during the preceding days. Even though NORSE was aborted, focal seizures, some of which progressed to bilateral tonic-clonic seizures, persisted (**Table 1**). Six doses of rituximab were given, and immunotherapy was continued as an outpatient using azathioprine, without improvement of the seizure frequency. She never experienced a seizure-free period and daily seizures occurred despite different combinations of ASMs, VNS and azathioprine. After 1.5 years she was admitted to the Epilepsy Monitoring Unit (EMU). Immune work-up was repeated and was negative. Multifocal epilepsy due to NORSE of unknown etiology was the final diagnosis. At the last follow-up, two years after onset of NORSE, she persisted with daily focal seizure with impairment of awareness despite four ASMs and high VNS parameters. Neuropsychological evaluation showed

moderate global cognitive and mild emotional involvement, affecting her social life (**Table 1**).

Patient 2

A previously healthy 33-year-old man presented with RSE that progressed to SRSE over a few days. His NORSE presentation was preceded by flu-like symptoms, without fever, one week before the onset. The SRSE required management in ICU and an extensive work-up was completed after which structural, toxic, metabolic and infections causes were ruled out. Seventy-two hours later the cause of SRSE had not yet been identified and the presentation was consistent with NORSE. Simultaneously, seizure management was initiated using different ASMs and anesthetics. After six weeks, the SRSE was aborted. However, due to a persistent state of confusion an autoimmune encephalitis was considered, and immunotherapy was started. At that time, the autoimmune panel revealed a positive anti-N-methyl-D-aspartate receptor (NMDAR) antibody in CSF. Imaging studies and serum investigations were negative for a paraneoplastic syndrome. The patient improved and 1.5 months after he was discharged home with three ASMs, prednisone and azathioprine (**Table 1**). Eight months later, when a taper of ASMs was trialed, the patient developed focal non-motor seizures with impairment of awareness, which sometimes progressed to bilateral tonic-clonic seizures. Despite different ASMs and immunosuppressive treatments, the frequency of seizures worsened over time. Three years later, the patient was investigated in the EMU and multiple independent bi-temporal seizures were captured. Brain magnetic resonance imaging (MRI) showed bilateral mesial temporal sclerosis (MTS) and cortical atrophy mainly in the left posterior quadrant (**Figure 1**). A repeat autoimmune panel was negative. Azathioprine was

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discontinued and VNS was proposed, which the patient declined. Over the subsequent nine years, seizure frequency increased to up to twelve per month. At that time, the patient reconsidered VNS, which was implemented with the parameters increasing overtime. Eight months after the VNS implantation the frequency of seizures improved reaching 2-3 per month. However, this was not sustained. Two years after the implantation, the seizure frequency returned to 8-12 seizures per month. His neuropsychological assessment showed multifocal cognitive impairment, as well as poor quality of life (**Table 1**).

3. Discussion

We presented two patients with multifocal and bi-temporal TRE respectively, that developed as a consequence of NORSE. In Patient 1, the clinical presentation was compatible with febrile infection-related epilepsy syndrome (a subtype of NORSE) and the etiology was unknown despite an extensive work-up. In addition, there was no clear response to immune-based therapies over time, which potentially argues against an autoimmune etiology. For this patient, VNS was implanted during the SRSE in an attempt to resolve the SRSE. In Patient 2, the NORSE was eventually found to be caused by an anti-NMDAR antibody encephalitis. In this second patient, VNS was implanted in a delayed manner to manage escalating seizures, years after the NORSE had presented. In both patients, the NORSE led to prolonged admissions to ICU and resulting in TRE.

The effectiveness of VNS in patients during NORSE and with epilepsy after NORSE is unknown. A recent systematic review focused on the use of VNS in the acute management of RSE and included 9 patients with NORSE. The analysis reported that for 66% (6/9) of patients RSE ceased after the implantation of VNS

4. The systematic review included only case reports, which were the highest level of available evidence for this rare condition. There was a clear relationship between VNS and cessation of RSE in only two cases^{7,8}. A different report details a patient whose implantation was considered successful, seizures recurred, and the patient died⁹. In the other reports, it is unclear which of the multiple treatments or a combination thereof were responsible for ceasing the NORSE^{4,10}. In Patient 1 about whom we report, a rapid upwards titration of output current was completed without side effects reaching a stimulation intensity of 1.75mA by the seventh day, which coincided with cessation of status epilepticus. However, discrete seizures persisted daily, and the patient developed epilepsy without a latent period after NORSE. In this patient, no reduction in the frequency of seizures was achieved overtime despite the combination of different ASMs, immunotherapy and high parameters of VNS.

Even though in patient 2 the NORSE was due to autoimmune encephalitis, the immunological study was negative in the post-NORSE stage, which may explain the lack of response to chronic immunotherapy. At this stage, structural changes (such as MTS, focal or diffuse cortical atrophy) would be the main mediators in seizure production. In this patient the term "autoimmune-associated epilepsy", that was recently proposed by the International League Against Epilepsy (ILAE), is appropriate to highlight how other non-immune factors may play a role in post-autoimmune encephalitis epilepsy¹¹. In this patient, the implantation of VNS was late (nine years after NORSE) and although he experienced a significant reduction (75%) in the frequency of seizures, this was not sustained overtime.

In our first patient, the VNS titration was fast, reaching 1.75 mA in one week; in the second patient it was slow, reaching 2 mA in 8 months. The safety of rapid

titration is currently unknown, and several factors need to be considered to avoid complications and reduce adverse effects. Notably, in the acute stages of NORSE patients are sedated and unconscious and therefore less likely to experience side effects.

The VNS implantation in TRE post NORSE has been described in three patients; two patients with FIRES⁵, one with acute encephalitis with refractory repetitive partial seizures (AERRPS)¹² and only the last patient experienced a decrease in the number of seizures of more than 50% in follow-up. The mechanisms how VNS can improve NORSE are still unknown. An anti-inflammatory theory has been proposed. Brain inflammation may play a role in increasing the hyperexcitability during NORSE and VNS has shown to reduce levels in interleukins in patients with TRE^{4,5}. The lack of response to VNS in the chronic stage for both of our patients, could be explained by a lack of immunological role in the chronic stages of their disease course. However, we do not know if our first patient would be worse without VNS.

Furthermore, we have described the poor cognitive, emotional, and social outcomes that developed our patients. Our findings show that the long-term effect of NORSE leads to multifocal impairments across different cognitive domains, which is likely to have a direct impact on quality of life.

4. Conclusion

NORSE has significant long-term morbidity, including therapy resistant epilepsy and cognitive, emotional, and social consequences. Available treatments lack effectiveness. We describe two cases with TRE after NORSE, who underwent VNS implantation. Although the VNS implantation was done at different points

in the illness trajectory (acute and chronic phase of NORSE), we show the long-term outcomes after the implantation of VNS, which is still unknown and warrants further investigation. Our case description also adds to the literature with respect to the effect of VNS during the acute phase of NORSE. In fact, in the first case VNS likely contributed controlling status epilepticus acutely, however, the current evidence supporting its use is poor.

5. Disclosure of Conflicts of Interest

Dr JG Burneo is the Jack Cowin Endowed Chair in Epilepsy Research at Western Ontario. The remaining authors have no conflict of interest.

6. Ethical Publication Statement

We confirm that we have read the Journal's position on issues involved in ethical publications and affirm that this report is consistent with those guidelines.

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Table 1. Clinical features, diagnostic investigations, and treatment during NORSE and Epilepsy after NORSE

PHASE I: NORSE	Patient 1	Patient 2
Current Age / Age at onset (years)	39 / 37	44 / 33
Etiology	Unknown	Encephalitis anti-NMDAR no tumor associated
NORSE duration	37 days	42 days
Serum and CSF studies		
- Infectious	CSF (a): Encephalitis panel, bacterial and fungal culture: Negative Serum: Hepatitis, HIV, VDRL, CMV: Negative	CSF (b): Encephalitis panel, bacterial and fungal culture, VDRL: Negative Serum: Hepatitis, HIV, VDRL, Lyme, CMV: Negative
- Inflammatory/immune	CSF: Autoimmune panel: negative. Serum: Autoimmune panel, ANA, Anti dsDNA, anti-nucleosomes, anti-histones, anti DFS70, ANCA, anti-tiroglobuline, Rheumatoid factor: Negative	CSF: Autoimmune panel: anti-NMDA positive. Serum: ANA, anti dsDNA, anti-ENA, ANCA, Rheumatoid factor: Negative
- Paraneoplastic	CSF (Neoplastic cytology): Negative CT (Thorax-Abdomen-Pelvis) and Ultrasound (abdomen, pelvis) were negative for tumor	CSF (Neoplastic cytology): Negative. CT (Thorax-Abdomen-Pelvis) and Ultrasound (scrotum, thyroid, abdomen) were negative for tumor.
- MRI findings	-At onset: Negative -During NORSE: Hypersignal in FLAIR in the left mesial temporal lobe and left insular white matter - 1.5 Years after, the abnormal signal disappeared	-At onset: Negative -During NORSE: Hypersignal in FLAIR in bilateral mesial temporal lobe, left occipital and splenium -At discharge from hospital: Subtle signal change in the left hippocampus and small residual signal in splenium
EEG findings	Continuous multifocal spikes and polyspikes (maximum right posterior temporal region)	Burst suppression pattern with multifocal spikes (left temporal, left frontal, right frontocentral and bifrontal)
Treatment		
- ASM	PHT, LEV, LCM, CLB, PB, VPA, PER, LZP	PHT, PB, LEV
- Anesthetics	Midazolam, Ketamine, Propofol	Midazolam, Fentanyl, Ketamine, Propofol
- Antimicrobials	Acyclovir, Ceftriaxone, Vancomycin, Piperacilin/tazobactam (partial treatment)	Acyclovir, Vancomycin, Piperacilin/tazobactam (Partial course)
- Immunomodulatory agents	Methylprednisolone, IVIG, Rituximab (6 doses-weekly), azathioprine (maintenance therapy)	Methylprednisolone (followed by Prednisone), azathioprine (maintenance therapy)
- VNS	Cessation of NORSE was 7 days after VNS was implanted: Day 0: OC=0.25 mA, F=20Hz, PW= 250µsec, ON=30s, OFF=30 min Day 1: OC=1.0 mA, F=20Hz, PW= 250µsec, ON=30s, OFF=30 min Day 2: OC=1.25 mA, F=20Hz, PW= 250µsec, ON=30s, OFF=30 min Day 7: OC=1.75 mA, F=20Hz, PW= 250µsec, ON=30s, OFF=30 min	Implanted after NORSE was controlled.
PHASE II: Epilepsy after NORSE	Patient 1	Patient 2
Current Age / Age at onset (years)	39 / 37	44 / 33
Latent period after NORSE	No	8 months
Seizure Classification	Type 1: focal impair awareness non-motor seizures to bilateral tonic clonic seizures: déjà vu/hear voices and sounds → behavioral arrest → eyes deviation to the left → left facial asymmetry → left arm dystonia → head and eyes deviation to the right → sometimes bilateral clonic movements. Type 2: strange sensation → touches her head → smiling → whistling → speak some words with a bit delayed in reacting.	Type 1: focal impair awareness non-motor seizures: behavioral arrest → staring → loss of awareness → right hand automatisms /dystonic posture of the left hand. (Type 1 sometime progress to bilateral tonic-clonic).
EEG findings	Interictal: Multifocal independent spikes augmented during sleep (almost 2 years after NORSE).	Inter Ictal: Independent bitemporal spikes, maximum right (8 years after NORSE)

	Ictal: onset changes among seizures with the majority over right posterior temporal region and a few over left temporal region (almost 2 years after NORSE).	Ictal: Onset over left temporal region mostly and over right temporal region in a lesser degree (3 years after NORSE).
MRI findings	Slightly increased T2 signal is present in both hippocampi. The abnormal signal in left insular region disappeared (almost 2 years after NORSE).	Bilateral hippocampal atrophy and T2 hyperintense signal abnormality. Resolution of signal abnormality in splenium (9 years after NORSE).
Epilepsy Classification	Multi Focal Epilepsy	Independent Bi Temporal Epilepsy
Etiology	Unknown	Structural (Bilateral MTS) / "Autoimmune-associated"
Past ASM	PHT, LEV, LCM, CLB, PB, VPA, PER, LZP	LCS, ESL, PER, PHT, BRV
Current ASM	LEV, LCM, PER, ESL	PB, VPA, TPM, LTG
Other treatment	Immunotherapy: Azathioprine 150 mg/d since NORSE	None
VNS	Implanted at 30 days after NORSE (cessation of SRSE occurred 7 days after VNS was implanted)	Implanted 9 years after NORSE
Frequency of seizures before VNS	N.A.	12 per month
Frequency of seizures after VNS (Output current mA)	1 month: Up to 5 (2.5) 3 months: 1-2 per day (2) 6 months: 1-2 per day (2) 12 months: 1-3 per day (2) 18 months: 1-3 per day (2.25) 22 months: 1-3 per day (3) 24 months: 1-3 per day (3)	3 months: 15 per month (0.85) 6 months: 10 per month (1.75) 8 months: 2-3 months (2) 12 months: 2 months (2) 18 months: 2-3 month (2) 21 months: 12 per month (2.75) 24 months: 8-12 per month (3)
Cognitive Outcome	Mild to severe generalized impairments across all cognitive domains (Neuropsychological evaluation).	Multifocal Cognitive Impairment. Probably non-dominant (more likely right) mesial temporal impairment and frontal dysfunction (not clearly lateralized). Dominant temporal impairment (more likely left) not ruled out.
Emotional Outcome	Mild symptoms of depression and anxiety (She took antidepressants when symptoms were severe)	No evidence of depression or any other mood disturbance.
Social Outcome	She is unable to carry out all of her previous activities but is able to take care of her own affairs without help. She works from home as a writer of educational material.	Not currently working as truck driver. He is on a disability support program

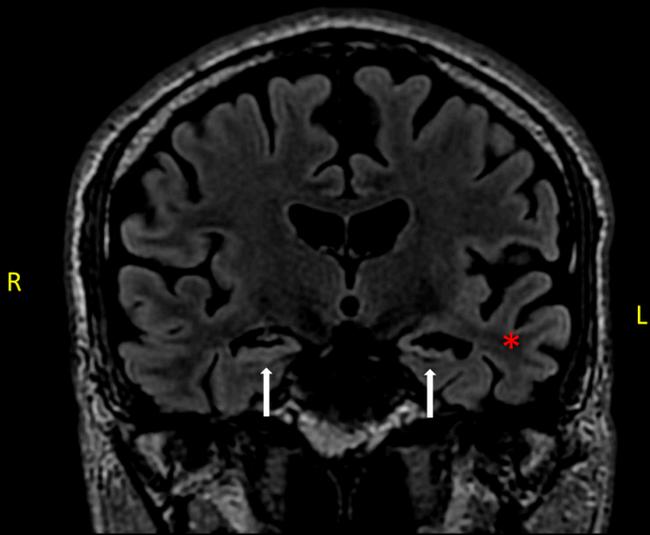
Cytochemical study in CSF showed mild pleocytosis: a: 14 cel; b: 20 cel (lymphocyte predominance)

Encephalitis panel: Herpes Simple Virus I-II, varicella zoster, and enterovirus RNA

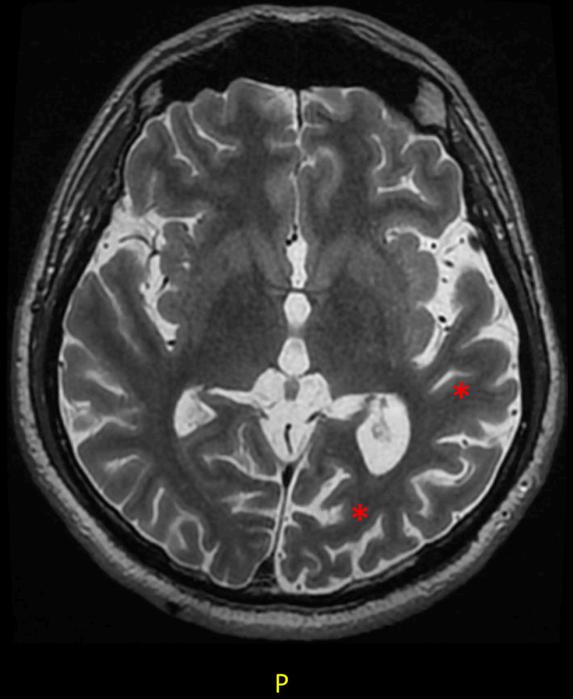
Autoimmune panel: Anti-AMPA, anti-CASPR, anti DPPX, anti-GABA antibody, anti-LGI1, anti-NMDA, anti-GAD65, anti IgLON5
 NMDAR: N-methyl-D-aspartate receptor; CSF: cerebrospinal fluid; HIV: human immunodeficiency virus; VDRL: test for syphilis;
 CMV: Cytomegalovirus; ANA: Antinuclear antibodies; dsDNA: double stranded DNA; ANA: Nuclear Antigen Antibodies, ANCA: Antineutrophil cytoplasmic antibody; CT: Computerized tomography; MRI: magnetic resonance imaging; EEG: electroencephalogram; ASM: anti-seizure medication; PHT: phenytoin; LEV: Levetiracetam; LCM: lacosamide; CLB: clobazam; PB: phenobarbital; VPA: valproic acid; PER: perampanel; LZP: Lorazepam; ESL: eslicarbazepine; BRV: brivaracetam; TPM: topiramate, LTG: lamotrigine; IVIG: Intravenous Immunoglobulin; MTS: mesial temporal sclerosis; VNS: Vagus nerve stimulator; SRSE: super refractory status epilepticus; N.A: not applicable.

Figure 1. Bilateral mesial temporal sclerosis and left temporo-occipital cortical atrophy were seen in Patient 2. Coronal FLAIR MRI showing bilateral atrophy and hyper signal in both hippocampi (white arrows) (A). Axial T2 MRI shows important cortical atrophy especially in the left posterior quadrant (red asterisks) (B). R (right); L (left); P (posterior).

A



B



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