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NEW ONSET REFRACTORY STATUS EPILEPTICUS (NORSE): A CASE REPORT

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ABSTRACT

New-onset refractory status epilepticus (NORSE) is rare and potential life-threatening neurological state where one develops status epilepticus without apparent aetiology. In the following case report, we see the management of NORSE (new onset of refractory status epilepticus) through standard guidelines in a patient with a history of CAD (coronary artery disease) with the risk-benefit ratio. The management had a major risk of respiratory depression and heart failure and/or heart block, been given the age factor and the medical history of the patient and no known aetiology. Initiation of benzodiazepines and antiepileptic medication had a major impact on the patient, where the risk of heart block was high. The recovery of the patient was thoroughly monitored for 7 complete days. upon no further complaints the patient was then discharged. But the patient was stabilized by first managing the NORSE and then treating the cardiac conditions.

KEYWORDS : New-onset refractory status epilepticus, respiratory depression, heart failure, coronary artery disease, benzodiazepines.

INTRODUCTION

The International League Against Epilepsy (ILAE) defines status epilepticus (SE) as continuous clinical and/or electrographic seizure activity, or recurrent seizure activity without recovery to baseline, lasting for ≥ 5 minutes. [1-2]

Due to unknown aetiology and the rareness of the condition and lack of studies, there is no optimal treatment for NORSE.

Signs and symptoms

In 2/3 of NORSE cases, the initiation of the condition is marked by mild febrile illness, associated with malaise and/or fatigue and symptoms of respiratory tract or gastro-intestinal infections.

Behavioural and cognitive symptoms, more like apathy or agitation, amnesia and sometimes hallucinations can be presented. Hallucinations may indicate an autoimmune aetiology. Initial phase may last for a few days or a week or two and is generally followed by progressive onset of seizures. Both focal and bilateral tonic-clonic seizures may or may not occur. They may be irregular in the beginning but become increasingly more frequent, Later the patient's consciousness declines as he/she converse into status epilepticus.

This acute phase usually lasts up till a few days or maybe several weeks and in some cases can even last for several months. Throughout this phase, the patient remains comatose as the result of seizures and anaesthetic treatment and may develop any complications cognate with prolonged unconsciousness and mechanical ventilation.

Once SE is managed and anaesthetic treatment is suspended, the patients progressively retrieve consciousness and can be discharged from the ICU.

The surviving patients usually suffer long term cognitive and functional impairment and many have epilepsy, which would require prolonged treatment with anti-seizure medications.

Causes:

The most found causes of NORSE are autoimmune such as encephalitis associated with anti-neuronal anti bodies, followed by viral encephalitis. Studies found that genetic polymorphism in SCN2A gene (gene involved in dravet syndrome) and in IL1RN gene (a gene coding for an immunomodulatory protein), however further studies are required to fully explore the hypothesis of genetic predisposition.[3]

Diagnosis:

Brain CT and MRI scans are essential to rule out stroke and other conditions with the characteristic changes on imaging. In some of the cases, brain CT can reveal leptomeningeal enhancement, bilateral claustrum hyperintensity.[4]

To rule out infections and known metabolic, infection, inflammatory and autoimmune conditions CSF studies and blood tests should be performed.

Electroencephalography (EEG) and continuous EEG monitoring are usually required to detect seizures, as they frequently become increasingly subtler clinically, then undetectable, during the course of disease.

stimulus-induced rhythmic changes are seen with or without periodic or ictal discharges (SIRPIDS) as reported in similar intensive care units.[5]

Case Report

we present a case of NORSE in an 85year old female patient. The patient was bought to the ER with the chief complaints of jerky movements with stiffness of all four limbs associated with frothing of mouth and up rolling of eyes. And have had 6 such episodes, 1 episode 4 days ago which lasted for 10 minutes and 4 episodes on the same day of hospitalisation at home since 1am and 1 episode in the ER lasting for 5 minutes. After which the patient had postictal drowsiness, arousable to deep stimuli and bladder imbalance.

The patient had no history of similar complaints in the past. Had no history of hypertension, type 1 or 2 diabetes.

Patient had a year long history of CAD (on medication tablet lasilactone) and anaemia (on medication tablet orofex-XT).

The vitals of patient in the ER were temperature 98.6*F, blood pressure 190/70 mmHg, pulse 48 bpm, GRBS 164 mg/dL, s1s2(+), bilateral airway entry (+) with occasional crepts, GIT soft, nontender, GCS E1V2M5.

Treatment given in the ER:

Inj.midazolam 2cc/IV/stat, inj. Levetiracetam 1.5gm/IV/stat, inj. Optineuron (Pyridoxine (Vitamin B6), Cyanocobalamin (Vitamin B12), Nicotinamide, D-Panthenol, Riboflavin (Vitamin B2), Thiamine (Vitamin B1). 1amp(30ml)/IV/stat, inj. paracetamol 1gm/IV/stat, inj. Pantoprazole 40 mg/IV/stat, inj. Ondansetron 4mg/IV/stat.

Later in the ER inj. piperacillin+tazobactum 4.5 gm/IV/TID was given with IVF NS @30ml/hour. Medications prescribed if GTCS repeat: inj. lacosamide 10 mg/IV/stat, SOS intubation,

inj. 20 mfq Kcl+ 1 gm mgso4+ 200 ml NS over 3 hours. Lacosamide was administered later the same day in dose of 10 mg/IV/stat.

The patient had bradycardia, cardiac arrest, CPR given. As the patient was anaemic, the patient was given 3 packets of PRBCs.

Later the same day, the patient was shifted to the NSICU, where the vitals were temperature 98.6*F, B.P 170/100 mmHg, pulse 48 bpm and was evaluated for complete heart block. On observation the patient was drowsy, arousable, not oriented and moving bilateral upper and lower limbs.

Medications prescribed: inj. Levetiracetam 1 gm/IV/BD, inj. Pantoprazole 40 mg/IV/stat, inj. piperacillin+tazobactum 4.5 gm/IV/TID, inj. Ondansetron 4 mg/IV/TID, IVF NS @ 30ml/hr, inj. Thiamine (vitaminB1) 100mg/IV/OD, tab. aspirin 75 mg/PO/OD, tab. clonidine hydrochloride 100mcg+ hydrochlorothiazide 20mg.

Day 2 in NSICU, vitals: temperature normal, B.P 130/80 mmHg, pulse 81 bpm GRBS 148 mg/dL. On observation patient is conscious, occasionally obeying commands.

Medications prescribed: continue the same treatment with addition of inj. isoprenaline 15 ml/hr and tab. Osedrate 500 mg/PO/BD.

Laboratory reports:

Table 1: haematology report

Haematology	Day1	Day 2	Normal values
Haemoglobin	8.8	8	11-15 mg/dl
RBC	3.7	3.3	3.8-5 m/cumm
HCT	28.1	26	38-50%
MCV	74.5	77	83-101 fl
MCH	23.3	23	27-32 pg
MCHC	31.3	33	32-36 g/dl
WBC	11700	8400	4000-11000 /cumm
Neutrophils	74	66	40-80%
Lymphocytes	20	22	20-40%
Monocytes	6	7	2-10%
Eosinophils	-	5	1-6%
Basophils	-	-	0-5%
Platelets	3.7	3.2	1.5-4.5 lakh/cumm

Table 2: urine analysis

Urine	Day 1	Normal values
Epithelial cells	3-4	0-1/hpf
puss cells	15-20	-
RBC	6-8	-

Table 3: biochemistry report

Biochemistry	Day 1	Normal values
Urea	27	10-45 mg/dl
Creatinine	0.8	0.6-1.5 mg/dl
Uric acid	4.4	3.5-7.0 mg/dl

Table 4: serum electrolytes report

Electrolytes	Day 1	Normal values
Serum Na +	138	136-145 mmol/Dl
Serum K+	4.4	3.5-5.0 mmol/dL
Serum cl-	97	95-105 mmol/dL
Serum Mg++	4.6	2.5-4.5 mg/dL
Serum po4	4.6	2.4-4.5 mg/dL
Serum ca++	9.1	8.8-10.8 mg/dL

Table 5: LFT reports

LFT	Day 1	Normal values
Total protein	6.5	6-7.5 mg/dL
Serum albumin	3.5	3.5-5.0 mg/Dl
Total bilirubin	0.7	0.3-1.2 mg/dL
Conjugated bilirubin	0.2	Up to 0.25 mg/dL
SGOT	93	5-45 mg/dL
SGPT	61	5-45 mg/dL
Serum alkaline phosphatase	33	30-120 mg/dL

PT/INR:
Test: 14 seconds (12-14)
Control: 13 seconds
PR: 1.1
INR: 1.1

APTT:
Test: 35 seconds (30-35)
Control: 34 seconds

Viral markers:
HBsAg: negative
HIV I&II: nonreactive
HCV: nonreactive
Aerobic culture and sensitivity urine: interpretation: no bacterial growth after 24 hours of aerobic incubation.

2D echo: conclusion
- Normal cardiac output
- No LV RWMA
- Good LV function
- Severe MR, No AR
- Severe TR/ severe PAH (80 mmHg)
- IVC- normal
- No PE/Clot/vegetation
- EF= 60%

CT brain: impression:
- Few tiny hypodense areas noted in the bilateral capsuloganglionic regions and periventricular white matter regions.
- An irregular calcification of size 10x5mm noted in the posterolateral part of left tentorial leaflet region superiorly-s/o likely physiological calcification DD calcified granuloma.
- Age related cerebral and cerebellar atrophic changes noted I the form of mild dilated ventricular system, cisternal sulcal spaces and cerebellar folia.
- Patchy mucosal thickening noted in bilateral maxillary ethmoid and sphenoid sinuses.

3D CT chest plain:
- Fibro calcific granulomatous lesion noted in the right lung upper lobe apical region-s/o old pulmonary TB lesions.
- Parenchyma of both lungs show hyperinflation with accentuated broncho vascular markings-s/o COPD/age related.
- Mild bronchiectasis changes noted in all lobes of both lungs.
- Few thin scattered parenchymal and interstitial fibrotic strands noted in all lobes of both lungs.
- Ill-defined faint ground glass opacities noted in all lobes of both lungs-s/o likely alveolitis.
- No signs of covid corads-2.
- Bilateral mild plural effusion noted with adjacent lung atelectasis noted.
- Ryle's tube in situ.
- Trachea oesophagus normal.
- Carina, main bronchi and both hilar appear normal.
- Mild cardiomegaly.
- Few mediastinal nodes noted (largest 15mm in the sub cranial region).
- Generalised osteoporotic changes noted.

ABG:
Ph: 7.2 (7.35-7.45), Pco2: 37.1mmHg (32.0-45.0), pO2: 33 mmHg (83-108), Hct: 31% (45-55),

Day 3:
on observation, conscious coherent, no fresh seizure activity, post CPR status normal.

Vitals: bp: 110/80 mmHg, PR: 77 b/min, spo2: 98% @ RA, GRBS: 106 mg/dL, cvs: s1s2+, resp: BAE+, GCS: E4V5M6. Medication prescribed: continue the same treatment and add tab orciprenaline 10 mg/PO/TID.

Day 4:
chief complaints, chest pain with difficulty in breathing. On observation, patient is conscious, coherent and co-operative. Vitals: BP:130/80 mmHg, PR:92 bpm, temperature: 98.6*F. Medication prescribed: continue the same treatment.

Day 5:
no fresh complaints from the patient, on observation: patient is conscious, coherent and cooperative Cvs: s1s2+, R/s: BAE+ Vitals: BP: 140/90 mmHg, PR: 82 bpm, spo2: 99% on RA, temperature: afebrile Medication prescribed: continue the same treatment.

Day 6: NORSE recovered
Complaints of decreased responsiveness since an hour, no headache /vomit, difficulty breathing.

On observation: conscious, not oriented, pupil: dolls eye intact, moving both upper limbs and lower limbs

Medication prescribed: inj. Levetiracetam 1 gm/IV/BD (in 100ml NS), inj. Clexane 40 mg/SC/OD.

Day 7: NORSE recovered
Complaints of difficulty in breathing.
On observation: conscious, coherent and co-operative.
The patient was discharged on day 7 with the following discharge medications,

- Tab. Levetiracetam 500 mg/PO/BD
- Tab. lacosamide 100mg/PO/BD
- Cap. Atorvastatin + aspirin 75mg/PO/OD
- Tab. Orciprenaline10 mg/PO/TID

DISCUSSION

In NORSE with cryptogenic aetiology and given the rarity of the condition and lack of systemic studies, there is no optimal treatment for NORSE.

standard therapies for status epilepticus are often not very successful and various additional treatment plans reported in the literature, includes immunotherapy, hypothermia, brain stimulation and surgery.[6]

In the case above, concurrent treatment for three of the conditions that developed in the patient, Tab osedrate 500 mg (calcium aspartate +calcium orotate +elemental zinc +folic acid +hydroxycobalamine +magnesium hydroxide +vitamin D3) is given for the treatment of generalised osteoporotic changes noted in 3D CT chest plain.

Tab. orceprenaline is prescribed for, Mild bronchiectasis changes in all lobes of both lungs and Ill-defined faint ground glass opacities in all lobes of both lungs-s/o likely alveolitis noted in the 3D CT chest plain.Inj. Clexane is advised to prevent coagulation, as the 2D echo suggests increase in TR velocity and RVSP which is a mark for PAH.

As studies suggests that epilepsy and use of antiepileptics may contribute to the risk of osteoporosis. Chemicals released by antiepileptics may increase the levels of enzymes from the liver which destroy vitamin D and reduces its levels in the body.[7] More than half the cases of reported NORSE remain cryptogenic in spite of extensive workup. Status epilepticus is a neurological condition that requires the immediate cessation of seizures to prevent permanent neurological damage. Initial management should be as per the currently available guidelines.[8] NORSE to stand out as a diagnosis, early investigations like the blood tests, brain imaging, CSF analysis and EEG (within 24-48 hours), can rapidly rule out or manage the condition. Besides the use of ASMs and anaesthetics other approaches are,

Neuromodulation:
A very few cases in the literature support the use of neuromodulation, where desynchronising networks by deep brain stimulation may improve seizure control.[9] limited evident data restricts application of neuromodulation. Other than this, therapeutic hypothermia is applied for neuroprotective and anti-inflammatory effects and after cardiac arrest.[10] Another treatment approach, electro convulsive therapy.[11]

Immunomodulatory treatment:
Only about 100 cases of cryptogenic NORSE are treated with immune suppression.[12-13]

Immunosuppressive treatment:
Rituximab: small case series included a few patients with cryptogenic NORSE showing positive response to intravenous rituximab.[14]

CONCLUSION

Given the extreme refractory nature of status epilepticus, its diagnostic features play a major role in early management with intensive immunotherapy, although this needs confirmation in future studies. In the literature and as well as in the case mentioned above immune therapies were less frequently prescribed in cryptogenic cases. This hesitation to prescribe immune suppressing treatments is due to unknown aetiology of NORSE and in absence of a well-established inflammatory cause. Many multi centres are established to help with registering the cases for networking of all reported cases.[15-16]

In the case reported above the patient was bought with the case of cryptogenic NORSE, its management did involve the treatment with standard protocol and the systemic complications were managed. It took 7 days for the patient to recover and with no fresh complaints the patient was then discharged from the NSICU.

Working together, we hope to share the experience to gain knowledge and share the management strategies also in supporting patients and their families, and stead further in understanding of and cure of this critical devastating condition.

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