Case Report

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Immunotherapy in NORSE- A Case Report

Anjani Bala[1], **Manoj Kumar Singh**[2], **Abhishek Kumar**[3], **Munish Kumar**[4]

[1]Junior Resident, Department of Pediatrics, Patna Medical College, Patna, Bihar, India, [2]Associate Professor, Department of Pediatrics, Patna Medical College, Patna, Bihar, India, [3]Senior Resident, Department of Pediatrics, Patna Medical College, Patna, Bihar, India, [4]Assistant Professor, Department of Neurology, Patna Medical College, Patna, Bihar, India.

Abstract

We present the case of a healthy five-year-old girl who presented with fever followed by refractory status epilepticus. Admitted to the intensive care unit, was managed with intravenous midazolam and first line antiepileptic drugs in loading doses. Seizure continued even then, so other antiepileptic medications were titrated to therapeutic doses. Intravenous acyclovir added in view of possibility of viral encephalitis. She also received high dose intravenous methyl prednisolone. Complete remission of seizure can't be achieved in spite of several antiepileptic drugs. Lastly Intravenous immunoglobulin administered which caused dramatic improvement in clinical condition and complete seizure control. Laboratory investigation including autoimmune and paraneoplastic studies, CSF analysis yielded negative results. MRI brain nothing significant. Our case fulfils the definition of new-onset refractory status epilepticus (NORSE).

Keywords: Refractory status epilepticus, NORSE, Immunotherapy.

Corresponding Author: Munish Kumar, Assistant Professor, Department of Neurology, Patna Medical College, Patna, Bihar, India.
E-mail: munishpmch@gmail.com

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Introduction

Status epilepticus defined as a continuous, generalized, convulsive seizure lasting > 5 min,or two or more seizures during which the patient does not returnto baseline consciousness.[1] Refractory status epilepticus (RSE) is defined as continuous or repetitive seizures lasting longer than 60 min despite treatment with intravenous benzodiazepine (lorazepam) and another standard anticonvulsant (usually phenytoin/ fosphenytoin) in adequate loading dose.[2] New-onset refractory status epilepticus (NORSE) is defined as a condition, not a specific diagnosis, with new onset of refractory status epilepticus without a clear acute or active structural, toxic or metabolic cause in a patient with no prior history of epilepsy.[3] It includes patients with viral or autoimmune causes. If no cause is found after extensive evaluation, this is considered "cryptogenic NORSE" or "NORSE of unknown cause." NORSE is rare usually occur in previously healthy children and young adults. Similar conditions have also been described under various names in children, one of them is febrile infection-related epilepsy syndrome (FIRES), which is defined as a sub- group of NORSE preceded by a febrile illness between 2 weeks and 24 h prior to the onset of refractory status epilepticus, and removing any age criteria.[3] There are reports on approximately 200 NORSE and more than 200 FIRES cases.[4] A prodromal phase with flu-like symptoms precedes the refractory status epilepticus onset in NORSE cases, with short-term mortality of 12-27%, long-term disability and epilepsy. An early diagnosis can't be made, as no specific imaging or laboratory abnormalities have been identified. Autoimmune encephalitis is the most frequently identified. In the absence of specific diagnosis, immunotherapy could be tried in addition to antiepileptic treatment with good results.[4] We report an unusual case of a child with NORSE who ultimately responded with immunotherapy.

Case report

A five year old previously normal female child presented to our pediatric emergency with status epilepticus. She had complex focal as well as generalized tonic-clonic seizures. Three days prior to presentation had history of one episode of fever and vomiting. On presentation, the patient was unconscious, her pulse was 114/min, respiratory rate 30/min, blood pressure 90/60mmHg, oxygen saturation 98% on room air, pupils were bilaterally dilated and sluggish reacting to light, neck was soft, hypertonia in all four limbs, deep tendon reflexes were brisk, plantar response bilaterally extensor. Cardiovascular, respiratory and abdominal examinations were normal. Patient was managed with intravenous midazolam and first

line antiepileptic drugs in loading doses. Seizure continued even then, so other antiepileptic medications were titrated to therapeutic doses (e.g. valproic acid, phenytoin, phenobarbital, carbamazepine, levetiracetam, lacosamide and lamotrigine). Antiviral drug, intravenous acyclovir added in view of possibility of viral encephalitis. She also received high dose intravenous methyl prednisolone (500mg for 5 days). Complete remission of seizure can't be achieved in spite of several antiepileptic drugs. Lastly Intravenous immunoglobulin (2g/Kg divided over 5 days) administered which caused dramatic improvement in clinical condition with complete seizure control. Laboratory investigation of complete blood count, liver and kidney function tests, electrolytes and urine analysis were normal. Viral markers were negative for hepatitis B and C, human immunodeficiency virus, cytomegalovirus and Epstein-Barr virus. The serological study for anti-nuclear antibody (ANA), cytoplasmic anti-neutrophil cytoplasmic antibodies (c-ANCA), and perinuclear anti-neutrophil cytoplasmic antibodies (p-ANCA), antiphospholipid and anticardiolipin antibodies were negative. Cerebrospinal fluid examination was normal except herpes simplex virus (HSV) I and II IgM reactive. Serum assays for antibodies to voltage-gated potassium channel (VGKC), glutamate decarboxylase (GAD), NMDA glutamate receptors and paraneoplastic neuronal antigens were negative. Thyroid function tests were normal. MRI brain showed generalized cortical atrophy.

Discussion

The term NORSE was used for the first time by Wilder-Smith et al,[5] to describe cases of super refractory status epilepticus (SRSE) without a previous history of epilepsy and with no identifiable underlying cause. Our patient, a healthy girl child with no history of epilepsy, developed refractory status epilepticus following one day history of mild fever. In spite of extensive lab investigations, CSF examination and MRI brain, we were unable to identify the exact cause. It seems to show remarkable clinical similarity to most NORSE cases reported in the literature, i.e. the presence of febrile illness with no preceding medical condition, negative laboratory studies including CSF analysis, status epilepticus refractory to most of the antiepileptics in adequate and tolerated doses. Initial MRI brain of NORSE usually discloses no specific abnormalities except for occasional T2/FLAIR hyperintense signal of the mesial temporal lobe, and often reveals generalized atrophy and bilateral hippocampus enhancement in follow-up studies.[6] In some studies leptomeningeal enhancements, basal ganglia involvement and signal hyperintensities in the peri-insular region noted.[7,8] Our case showing generalized cortical atrophy on MRI brain. The question arises as what could be the etiopathogenic basis of such changes on MRI brain? At first glance, just looking at the MRI, the picture seems strongly to suggest hypoxic ischemic encephalopathy. The problem is that this kind of working diagnosis is generally made on the basis of history of antenatal insult, perinatal insult, delayed cry and global developmental delay. All of these component were absent in our case. On the other hand CSF viral study showed HSV I and II IgM, but patient neither responded to acyclovir nor MRI brain changes are suggestive of herpes encephalitis. On further investigation the autoimmune and paraneoplastic antibody panel tests were negative. Our patient ultimately responded to Intravenous immunoglobuline. Treatment with anti-seizure drugs is often disappointing. At least 75% of patients require multiple antiepileptic medications along with anesthetics in continuous infusion.[9] Some studies have suggested better outcome with immunotherapies. This hypothesis is supported by the fact that 50 % of NORSE cases are caused by auto-immune encephalitis.[10] Several case reports have described antibodies to NMDA glutamate receptors and voltage gated potassium channel antibodies in patients with refractory status epilepticus.[11,12] In the management scheme proposed by Shorvon and Ferlisi, it has been suggested that early immunotherapy should be instituted in cases of super refractory status epilepticus where no cause has been identified.[13] Our case fulfills the definition of NORSE syndrome with unusual finding of generalized cerebral atrophy on MRI brain at presentation, hence reported.

Conclusion

New-onset refractory status epilepticus (NORSE) is a condition and not a specific diagnosis. It can be diagnosed after excluding other causes of refractory status epilepticus. Increased awareness of the entity "NORSE" may help determine the prevalence and etiology of the condition. Getting lesion from our case early immunotherapy advised to patients presenting with refractory status epilepticus not responding to standard anti-seizure drugs which may help improve prognosis.

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