Case Report

Super Refractory Status Epilepticus: A Case Report from Livingstone Central Hospital, Zambia

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ABSTRACT

***Background**:* Status Epilepticus (SE) is defined as more than five minutes of persistent seizure activity without full recovery of consciousness in between the seizures. If SE fails to respond to two antiepileptic drugs, it is called refractory status epilepticus (RSE) and if it continues or recurs 24 hours after anesthesia, it is called super refractory status epilepticus (SRSE). We present a case of 22 years old Zambian nursing student who presented with first episode of generalized tonic-clonic seizures which later turned out to be SRSE. This case has been presented due to the rarity of this condition. To the best of our knowledge this is the first documented case of SRSE in Zambia.

***Objective**:* To familiarize the clinicians through this case about SRSE and challenges in its diagnosis and the management in resource poor Zambian health settings.

Case History: A 22 years old male nursing student with first episode of generalized tonic clonic seizures brought into the medical emergency of Livingstone Central Hospital. He was treated with 60mg of diazepam but fits continued and patient was transferred to ICU, where he was treated with phenobarbitone infusion with no effect until he was intubated and given general anesthesia with thiopental infusion. After 36 hours, he was extubated, and fits returned soon. His fits finally came under control after treatment with sodium valproate, levitracetam and lorazepam His FBC, LFTs, RBS, electrolytes, CT scan of brain and MRI of brain did not show any abnormality.

Conclusion: Though SRSE is a rare condition but once it presents, it becomes difficult to manage. All cases of SE should be treated with urgency to prevent them from becoming RSE and SRSE.

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INTRODUCTION & LITERATURE REVIEW

Status epilepticus (SE) is defined as 5 minutes or more of continuous or intermittent seizure activity with incomplete recovery of consciousness.[1]This definition provides an appropriate time interval to initiate treatment for impending SE and prevent more prolonged SE. Because generalized tonic-clonic seizures usually last about 1 minute, longer seizure activity implies a failure of the physiologic factors that normally terminate a seizure.[1]SE becomes refractory status epilepticus (RSE) if it fails to respond to adequate doses of at least two antiepileptic medications and its treatment usually requires life-supporting interventions. RSE occurs in about 30% of SE cases and has a higher morbidity and mortality risk than non-refractory SE.[2, 3] Mayer et al did retrospective cohort study from 1st January 1994 to 31st March 1998 at Presbyterian Medical Centre in Columbia, to determine the frequency, risk factors and impact on the outcome of RSE. They found out that 69% of seizures recurred after

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treatment with a benzodiazepine and 31% of seizures recurred after treatment with a second-line anticonvulsant drug (usually phenytoin), fulfilling criteria for RSE. Although mortality was not increased, RSE was associated with prolonged hospital length of stay (P<.001) and more frequent functional deterioration at discharge (P=.02).[2] Anesthetic drugs like pentobarbital, propofol and midazolam are required to treat RSE. These drugs can cause severe respiratory depression so patients must be intubated and ventilated. Rossetti et al did a retrospectively assessed case series from 1st January 1997 to 31st March 2004 at two tertiary referral hospitals in Boston to investigate whether various coma inducing options were associated with different prognosis after RSE. They found out that RSE was more prevalent in incident than recurrent episodes of SE (P=.06). Mortality rate was higher in patients with RSE (23%) as compared to patients with non-RSE (8%) (P=.05). The clinical status was less likely to return to baseline for RSE than non-RSE. Outcome was independent of the specific coma inducing agents used and the extent of EEG burst suppression, suggesting that the underlying cause represents its main determinant.[3]

Super refractory SE is a stage of refractory SE characterized by unresponsiveness to initial anesthetic therapy.[4] It is a new concept that has been the focus of recent basic and therapeutic work and is defined as "SE that continues or recurs 24 hours after the onset of anesthesia, including those cases in which SE recurs on the reduction or withdrawal of anesthesia".[4] Super refractory SE is a well-recognized clinical problem which usually occurs in two quite distinct clinical situations[5]:

1. In patients with severe brain injury
2. In patients with no history of epilepsy in whom SE develop out of blue with no overt cause, which is called new- onset refractory SE (NORSE).[6]

Variety of treatments are used in SRSE, almost entirely based on open observational studies or case reports. Simon Shorvon at University College London in 2011, did a review of the therapies used for the control of SRSE.[5] Therapies included anesthesia, antiepileptic drug therapy, hypothermia and other medical, immunological and physical therapies. Marchi et al in a retrospective cohort study on the impact of therapeutic coma on SE outcome, found out that therapeutic coma was associated with poorer outcomeafter SE, furthermore it portends higher infection rates and longer hospitalisations.[9] Sanjay et al did a review article on the refractory SE and reported that treatment options for patients who progress to RSE and SRSE vary considerably though midazolam, propofol and pentobarbital are most frequently utilized. Use of each medicine includes a unique set of advantages and disadvantages, and such therapy should be individualized according to the seizure etiology (if known) and the individual patient's needs. Failure of one therapy doesn't predict the responses to other therapies and they should be given adequate trials sequentially unless contraindicated. There is no evidence on superiority of one approach to other as yet.[10]

We are reporting a case of new onset SRSE from Livingstone Central Hospital.

CASE PRESENTATION

A 22 year old male, Zambian nursing student was brought in the medical emergency of Livingstone Central Hospital with history of having a black out and falling down when he was about to deliver a speech in a ceremony. He soon developed generalized tonic-clonic seizures. This was with no prior history of seizures and any substance misuse. He was treated with intravenous diazepam but seizures continued and patient was referred to Intensive Care Unit (ICU) where he received about 60mg of intravenous diazepam during short period of about 30 minutes. He was put on phenobarbitone infusion but seizures continued. He was later intubated and general anesthesia with thiopental infusion was given for about 36 hours.

During his stay in ICU, lab tests like full blood count, ESR, random blood sugar, urea, creatinine

&electrolytes, liver function tests were carried out but no abnormality was found on all these investigations. His CT scan of brain and MRI brain was done and it did not show any abnormality.

Patient was extubated after 36 hours and soon seizures recurred. He was now started on about 1.8g/day in divided doses of sodium valproate by nasogastric tube, which was increased to 2.4g/day in divided doses about 24hours later. Patient's seizures reduced in frequency and now he was having about 8-10 very brief clonic seizures lasting 8-10 seconds. He was given 2mg intravenous lorazepam PRN whenever he had seizures. During his treatment with sodium valproate his liver enzymes like ALT and AST started rising and he developed a generalized maculopapular rash with raised eosinophils.

On his 5th day in ICU, it was decided to introduce levitracetam tablets and to taper down sodium valproate due to rash and raised liver enzymes. Soon after the introduction of levitracetam the seizures stopped. About 3 days later sodium valproate was completely stopped and he continued on 1g twice a day of levitracetam. Soon after stopping of sodium valproate, the rash cleared and his liver enzymes came back to normal. Patient was discharged from ICU after 12 days. At the time of discharge, the patient was free of seizures and no cognitive deficits were observed despite having persistent seizures.

DISCUSSION

Our patient was 22years old male who presented with new onset generalized tonic-clonic seizures which were treated with intravenous diazepam and phenobarbital infusion. In ICU he was treated with general anesthesia but his seizures returned when patient came out of anesthesia. He presented as new-onset refractory SE (NORSE).Despite doing the basic laboratory investigations available in our setting and neuroimaging like CT scan and MRI of brain, no cause of his seizures was found and his seizures came out to be cryptogenic. Gaspard et al did a retrospective review of the patients with refractory SE without etiology identified within 48 hours of admission between 1st January 2008 and 31st December 2013 at 13 academic medical centers and reported that in 52% of the patients, the etiology remained cryptogenic.[10] Autoimmune encephalitis was the most common identifiable cause of NORSE.Outcome of these patients at discharge was poorer but improved at follow-up. Epilepsy developed in most cases.[10] Our patient in contrast to this study had better outcome at discharge but it remains to be seen whether he will develop epilepsy in future.Onceour patient went into SRSE, it posed challenges in the management. Literature shows that management of RSE and SRSE is challenging, it requires balancing the benefits and risks of treatments used to rapidly control seizures.[7]Some studies suggested that drug-induced coma may be associated with poorer outcome, [8, 9]however other studies challenge this view, considering that delayed treatment could represent high risk of mortality.[10]Our patient responded well to drug induced coma though his seizures returned once he was out of coma.

Different treatments have been used to control seizures in cases of RSE and SRSE, but no treatment has shown superiority over the other.[11]In an emergency situation, the first priority should be the management of airway, breathing and circulation. In addition the continuous EEG monitoring should be done to monitor the seizure activity. Unfortunately it is not yet available in Zambia. For SE-specific management lorazepam is the first line drug.[11]If lorazepam is not available then diazepam is the 2nd choice which was the case in our patient's situation. If initial management with benzodiazepines fail to control the seizures then phenytoin infusion should be initiated at the dose of 20mg/kg body weight at a rate of not more than 50mg/minute however in our Zambian setup due to unavailability of phenytoin in injectable form, phenobarbitone infusion should be given at a dose of 10-20mg/kg body weight. When all these measures fail to control the seizures then patient should be intubated and given general anesthesia. Propofol, midazolam and thiopental can be used to anesthetize the patient. In our patient we

used thiopental. Once the patient has gone to SRSE there are different options which have been tried by different clinicians.

1. Intravenous magnesium has been tried by some clinicians even in the absence of evidence of its deficiency.[12]
2. Immunotherapy has been tried even in the absence of any evident immunologic cause of SRSE. The rationale is that many of the episodes without known cause might be due to overt immunologic disease. Emergency treatment is usually tried with high dose methylprednisolone (1g prednisolone per day), and then followed if there is no response, by one or two courses of intravenous immunoglobulin (IVIG). If there is a response, longer term treatment with steroids or IVIG can be used.[5]
3. Some people have tried other therapies like electroconvulsive therapy (ECT) and Transcranial magnetic stimulation.

After developing SRSE our patient was put on sodium valproate but due to hepatic damage and rash, the treatment was changed to levitracetam which worked well for the patient and he came out free of seizures. The patient is currently doing fine on 2g/day of oral levitracetam. The patient has not manifested any cognitive decline despite having prolonged seizures.

CONCLUSION

Though SRSE is a rare condition but once it presents, it becomes difficult to manage. All cases of SE should be treated with urgency to prevent them from becoming RSE and SRSE.

ABBREVIATIONS

SE: Status Epilepticus, RSE: Refractory Status Epilepticus, SRSE: Super Refractory Status Epilepticus, NORSE: New Onset Refractory Status Epilepticus, FBC: Full Blood Count, RBS: Random Blood Sugar, LFTs: Liver Function Tests, IVIG: Intravenous Immunoglobulin

DECLARATIONS

Ethical Approval

Not applicable in case report.

Consent

Informed consent to publish the case report was obtained from the patient.

Competing Interest

The authors declare that they have no competing interests.

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Authors Contribution

All three authors contributed in management of patient and revision and approval of the final manuscript.

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