www.jmscr.igmpublication.org
Index Copernicus Value: 79.54
ISSN (e)-2347-176x ISSN (p) 2455-0450
crossrefDOI: https://dx.doi.org/10.18535/jmscr/v7i3.60

IGM Publication
Journal Of Medical Science And Clinical Research
An Official Publication Of IGM Publication

Case Report

New onset Refractory status epilepticus: a case report

Authors
Dr Ganesan Vivek[1], Prof. Dr Lailu Mathews[2], Prof. Dr K. Subramaniyan[3]
Dr Sanjeev Kumar[4], Dr Maria Francis Roch.Y[5]
[1]MBBS, MD, PG Student, Department of Anaesthesiology and Critical Care, Chettinad Medical College & Research Institute
Mobile no: 7397361658, Email: *dr.vivekganesan@hotmail.com*
[2]MD Anesthesia, HOD, Department of Anesthesiology and Critical Care, Chettinad Medical College & Research Institute
Mobile no: 9443535910, Email: *lailu.mathews@gmail.com*
[3]MD;DM (Neuro), HOD, Department of Neurology, Chettinad Medical College & Research Institute
Mobile no: 9444079835, Email: *drsubra1234@yahoo.co.in*
[4]MD Anesthesiology, Asst. Professor, Department of Anesthesiology and Critical Care, Chettinad Medical College & Research Institute
Mobile no: 7358083921, Email: *carochess002@gmail.com*
[5]MD Anesthesiology, Asst. Professor, Department of Anesthesiology and Critical Care, Chettinad Medical College & Research Institute
Mobile no: 9710377660, Email: *ymfroch@gmail.com*

Abstract
Refractory status epilepticus is a neurological condition that follows a febrile illness. One variant of RSE is FIRES. Sequelae of FIRES include neuropsychological impairments occurring without latency. Clinical knowledge about FIRES is very scarce as it is rare manifestation. Patients usually present with prolonged period of refractive epileptic events which do not respond to first- and second-line anticonvulsant drugs. Though Few previously observed cases reported its association with autoantibodies, but no perticular antibody was found to be specific for the disease till now. Treatment of FIRES is difficult and it depends on the responsiveness of the patient to antiepileptic drugs along with anesthetics steroids and other supportive drugs. Mortality rate is high and few cases have reported relapses. early management is necessary in order to achieve control of the critically ill patient, control long term seizures and improve the quality of life of the patient.

Keywords: *Immunity, Refractory status epilepticus, Febrile infection-related epilepsy syndrome (FIRES), Epilepsy, Seizure, Fever, Antiepileptics, Infection*

Key Messages
FIRES is a serious neurological manifestation, that require early management of refractive seizures. Till now no specific diagnostic and management protocols were formalized. Aggressive treatment is required in the intensive care units to reduce the morbidity and mortality of the patient.

Introduction

Epilepsy is a common neurological disorder that affects approximately 65 million people worldwide. The principle characteristic of epilepsy is that itself terminates. Epileptic seizures terminate as a result of the refractory period that occurs following seizure activity. If the refractory period is disrupted the seizure will continue resulting in status epilepticus. On the other hand, refractory status epilepticus is a special type of SE, in which the seizures does not terminate or reoccur after 2-3 types of anti SE drugs and require special treatment to induce termination. Usually benzodiazapines are effective in the early treatment of status epilepticus. But they are ineffective to treat refractory status epilepticus. One important reason for this is, that the GABA receptors are internalised during status epilepticus and so treatment with benzodiazapines which target them remain ineffective. Nearly 40% of SE cases are refractory.[1]

New onset refractory status epilepticus (NORSE) is a relatively newly coined term for previously healthy adults who present with de novo refractory SE.[2] NORSE has a different distribution of etiologies with the most common being unknown, while a significant number (37%) tend to be secondary to paraneoplastic encephalitis or autoimmune pathologies or infectious causes. Those cases, where no cause is identified despite an extensive work-up, are referred to as cryptogenic NORSE or NORSE of unknown etiology. Febrile Infection-Related Epilepsy Syndrome (FIRES) is a subcategory of NORSE that has a prior febrile infection 2days- 2wks prior to onset of refractory status epilepticus, with or without fever at onset of seizure.[3] Various infectious and non-infectious causes have been considered to be responsible for this syndrome; however, many a times the exact cause is not identified.

FIRES was given many names that emphasize either the characteristics of acute refractory partial epilepsy or the presumed pathogenesis. Few names include “acute encephalitis with refractory, repetitive partial seizures” (AERRPS) (Sakuma et al., 2001), “severe refractory status epilepticus due to presumed encephalitis” (Sahin et al., 2001), “idiopathic catastrophic epileptic encephalopathy” (Baxter et al., 2003), “new- onset refractory status epilepticus” (NORSE) (Wilder- Smith et al., 2005)[4], “devastating epileptic encephalopathy in school- aged children” (DESC) (Mikaeloff et al., 2006), and FIRES (van Baalen et al., 2010)[5]. Japanese authors prefer the term AERRPS and European authors prefer FIRES.

The seizure types at the onset of the disease are mainly partial or secondarily generalized. The partial seizures are often complex partial seizures, at times with facial myoclonia. Results of the initial magnetic resonance imaging (MRI) are usually normal. Hyperintensities are detectable in some patients, predominantly in the temporal regions, but also in the insula and the basal ganglia[6], probably secondary to long- lasting epileptic activity.

The management of NORSE is challenging. Seizures are typically resistant to conventional antiepileptic drugs. The risk of iatrogenic injury is substantially increased in affected patients. Additionally, the patient’s internal environment is disrupted. Electrolyte disorders, coma associated malnutrition and combined infections that result from refractory status epilepticus can endanger the lives of affected patients. Correcting disorders in internal environment is therefore a challenging task in the management of refractory status epilepticus. Most of the existing studies of FIRES deal with case series of patients receiving a single coma-inducing agent, which may not accurately reflect clinical practice, in which treatments may be combined. Few studies have investigated FIRES and its treatment, but technical difficulties are different in each patient. There is also uncertainty about the optimal extent of electroencephalographic (EEG) suppression.

The onset of FIRES is acute and, usual have prior febrile symptoms. Initially, isolated seizures, which quickly evolve to SE, may be observed. The outcome of FIRES is poor, with a death rate

of up to 30%[6]. This paper presents a case of FIRES that describes the diagnostic and therapeutic challenges posed by this condition, evaluating the role of EEG burst suppression and investigating the effect of various pharmacologic options as well as discussing its management difficulties. Despite the aggressive efforts that were taken, the patient succumbed to the complications of the illness and side effects of the treatment strategies adopted. This shows that the treatment options currently available are in adequate, so an intensive research in the area of pathogenesis of status epilepticus is required for the better outcome.

FIRES is a rare neurological disorder with an estimated annual incidence of 1/1,000,000.[5] till now etiology remained unknown. This paper presents a FIRES case that describes the diagnostic and therapeutic challenges posed by this condition. Recent literature review showed an apparent clustering of reported cases of FIRES all over the world. Comparison is also attempted with the previously reported clinical series.

Case History

A previously healthy 24-year-old female was conducted at our Hospital with the complaint of 5 episodes of seizures in a span of 9 days. Symptoms first appeared 14 days before the admission of the patient, with high grade fever associated with intermittent cough and cold. Fever was not associated with chills and rigors. She was first admitted in local hospital and was treated for fever and got discharged.

Later she experienced 1st episode of self-limited tonic-clonic seizure 9 days ago, which lasted for 2-3 minutes.

- A/W uprolling of eyeballs
- A/W tongue bite
- A/W clenching of teeth
- Not A/W sphincter incontinence

Post ictal LOC+, lasted for 2 minutes after which she recovered on her own. Patient then had 2 more episodes of seizures at home, interval between episodes >20 minutes, following which she was brought here; on her way to hospital, she had one more episode of seizure. Patient was admitted in the ICU. She had no family history for neurological or autoimmune pathologies.

On examination, patient was drowsy but arousable. She was treated with IV fluids, anti-epileptic medications, anti-viral medications, vitamin supplements, PPI and other supportive medications. The MRI brain was negative. Lumbar puncture and CSF analysis showed TC-15 of which neutrophils 46%, monocytes: 12%, basophils: 2%, protein- 27.9 and glucose -69. Despite being treated with 3 anti-epileptic medication for 2 days, patient continued to have seizures (GTCS + Left Myoclonic Jerks) and hence patient was intubated with informed consent from patient's attendants and started on midazolam + phenobarbitone infusion. Continuous EEG monitoring was done which showed burst suppression pattern. (figure 1)

For 2 days, patient showed slow improvement, but when phenobarbitone infusion was weaned off, patient developed left focal seizure with B/L peri-orbital and peri-oral twitching, associated with fever spikes. So, Phenobarbitone infusion was restarted and antibiotic escalation was done.

On further deterioration of the condition, tracheostomy was performed and ventilatory support was provided. EEG continued to show epileptiform discharges and so phenobarbitone infusion was continued. Autoimmune encephalitis panel was found to be negative. Patient went into septic shock and was placed on inotropic support. ET culture showed growth of highly resistant Acenitobacter species, urine culture showed growth of candida species and catheter venous tip culture showed growth of klebseilla species. Patient was kept on appropriate IV antibiotics as per available culture sensitivity report. Routine blood investigation revealed the development of AKI (with creatinine 2.07) and medications were changed accordingly. Patient continued to have fever spikes.

With the medication changed, Patient developed rashes on face and upper limbs. Suspecting drug

induced erythema multiforme, carbamazepine was stopped. Cardiologist opinion was obtained and ECHO was done which showed no RWMA, EF:60% and normal valves and chambers. With ongoing antibiotic treatment, when repeat cultures showed no growth, antibiotics were gradually stopped. Her sensorium gradually improved, and so she was weaned off from the ventilatory support and was placed on CPAP. Chest physiotherapy was given daily. Patient's general condition seemed to improve much and hence patient was shifted to the ward. Later patient was discharged with intact tracheostomy tube with T piece and was asked to continue steroid treatment with oral prednisone along with antiepileptic drug (phenobarbital, levetiracetam, Perampanel) and other less conventional agents.

Discussion

Our patient was a young female, presented with refractory status epilepticus, after an initial nonspecific febrile illness, with no relevant history of neurological disorder. The evolution into SE was not limited by the induction of pharmacological coma and different antiepileptic agents and reappeared at the weaning of the anaesthetics fulfilling the criteria for Super-Refractory Status Epilepticus. On the other hand, SRSE is often present in FIRES.[7] Van Baalen et al.[5] and Kramer et al.[6] published the most important series emphasising the information available till date and outlined the clinical profile of FIRES.

Febrile infection–related epilepsy syndrome (FIRES) is a catastrophic epileptic encephalopathy with a yet undefined etiology. The pathogenesis underlying the cascade leading to such severe epilepsy is still enigmatic. FIRES is often a diagnosis of exclusion as it lacks specific clinical criteria and/or confirmatory tests. The temporary correlation between fever and the onset of SE has led to consider an autoimmune origin for this syndrome, although current evidence does not confirm this suspicion. Other hypothetical causes of FIRES as described by the previous studies suggest genetic predisposition, and presence of pro inflammatory markers triggered by infectious agents. In this patient, total counts were found to rise in CSF, indicating an underlying infection.

Treatment of FIRES is difficult and it is typically unresponsive to conventional antiepileptic therapy. Though few studies have suggested a patient responsive treatment, however there are no clear guidelines about dose, duration of therapy and evaluation of effectiveness. Generally, IV antiepileptics are preferred in established status epilepticus. If seizures continue to persist for 2 hrs, then general anesthesia is recommended where dosing is based on EEG burst suppression approach (thiopental/pentobarbital/midazolam). Anesthesia is recommended to prevent excitotoxicity. The disadvantage of anesthesia is hypotension, cardiorespiratory depression, and development of acute tolerance. Pentobarbital follows zero order kinetics, so it has a tendency to accumulate and prolong recovery phase. Although the effectiveness of AEDs has not been clearly established in super refractory status epilepticus, it is a conventional practice to administer antiepileptics along with anesthesia. The AEDs conventionally used are carbamazepine, lacosamide, levetiracetam, phenobarbital, phenytoin, topiramate, and valproate. However, there is no evidence that any of these is more or less effective than other. Inflammation plays an important role in epileptogenesis, so potential use of steroid is advised. In some cases, early ketogenic diet, was suggested to optimise seizure control and cognitive outcomes in FIRES. Clear knowledge about the underlying pathophysiology is required to frame treatment strategies. Several hypotheses have been put forward and the scope for future research in this area is huge.

To conclude, refractory status epilepticus should be suspected when a patient presents with acute onset refractory seizures following a simple febrile illness with no previous history. Each case of refractory status epilepticus with a good recovery should be reported as the course of illness and response to treatment is variable. The

accumulated experience will help to provide clinicians with some guidelines regarding management.

References

1. Gaspard N, Hirsch LJ, Sculier C, Loddenkemper T, van Baalen A, Lancrenon J, et al. New-onset refractory status epilepticus (NORSE) and febrile infection-related epilepsy syndrome (FIRES): State of the art and perspectives. Epilepsia. 2018;59(4):745-52.
2. Verma R, Raut TP, Giri P, Praharaj HN. New onset refractory status epilepticus (NORSE) as the heralding manifestation of herpes simplex encephalitis. BMJ Case Reports. 2013;2013:bcr2013009466.
3. Nicolas Gaspard LJH. New-Onset Refractory Status Epilepticus (NORSE) and Febrile Infection-Related Epilepsy Syndrome (FIRES) national organisation for rare disorders. [Available from: https://rarediseases.org/rare-diseases/new-onset-refractory-status-epilepticus-norse/.
4. Wilder-Smith EP, Lim EC, Teoh HL, Sharma VK, Tan JJ, Chan BP, et al. The NORSE (new-onset refractory status epilepticus) syndrome: defining a disease entity. Ann Acad Med Singapore. 2005;34(7):417-20.
5. van Baalen A, Vezzani A, Hausler M, Kluger G. Febrile Infection-Related Epilepsy Syndrome: Clinical Review and Hypotheses of Epileptogenesis. Neuropediatrics. 2017;48(1):5-18.
6. Kramer U, Shorer Z, Ben-Zeev B, Lerman-Sagie T, Goldberg-Stern H, Lahat E. Severe refractory status epilepticus owing to presumed encephalitis. J Child Neurol. 2005;20(3):184-7.
7. Nabbout R, Mazzuca M, Hubert P, Peudennier S, Allaire C, Flurin V, et al. Efficacy of ketogenic diet in severe refractory status epilepticus initiating fever induced refractory epileptic encephalopathy in school age children (FIRES). Epilepsia. 2010;51(10):2033-7.