Refractory Status Epilepticus In Intensive Care Unit: A Case Of Lafora Body Disease
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Citation

Abstract
Status epilepticus is a medical emergency that requires rapid and vigorous treatment to prevent neuronal damage and systemic complications. Refractory status epilepticus refers to sustained seizures that do not respond to initial drug therapy and persist longer than 60 minutes. Admission of such patients to an intensive care unit setting and meticulous hemodynamic monitoring is mandatory. We describe a case of Lafora body disease, an autosomal recessive form of progressive myoclonus epilepsy characterized by seizures and cumulative neurological deterioration.

INTRODUCTION
Status epilepticus (SE) is a situation with high morbidity and mortality, causing transient or consistent brain damage, lasting for half an hour or more resistance [1]. SE can be caused by a stroke, hypoxic injury, toxic, metabolic, infectious, traumatic, tumoral and genetic reason, or idiopathic [2]. Patients in status epilepticus present a clinical emergency. On one hand, the clinician's objective is to control the seizures quickly and to prevent recurrences; on the other hand, to determine true etiologic factor by laboratory and neuroimaging and EEG studies [2,3,4,5].

Arterial blood gas analysis may reveal a metabolic acidosis [6,7]. Cardiac and other hemodynamic monitoring should be established urgently. Aggressive supportive care and prompt termination of electrical seizure activity are the goals for generalized status epilepticus. An intravenous line is mandatory. Preparation for possible intubation and respiratory support should be made [8]. Various combinations of anticonvulsant agents have been used to manage this condition. Correction for metabolic disturbance, if present, is clearly indicated. Low serum Na⁺, glucose, Ca++ or Mg++ can result in recurrent seizure activity. Drug or alcohol withdrawal, or certain drug intoxication, can be precipitating factors [9]. Complications of status epilepticus are many. The abnormal electrical discharges themselves may cause neuronal damage. Systemic complications include hyperthermia, acidosis, hypotension, respiratory failure, rhabdomyolysis and aspiration [1]. Prognosis is related most strongly to the underlying process causing status epilepticus [1,3,5]. Admission of the patients to an intensive care unit setting and meticulous hemodynamic monitoring is mandatory [10].

Lafora body disease is a disorder of progressive myoclonic epilepsy syndrome which is caused by a mutation in EPM2A genus [11]. Biopsy of various tissues, including brain, muscle, skin and bone reveals characteristic polyglucosan inclusions called Lafora bodies [3,11]. The disease begins with myoclonic seizures in childhood and progresses with tonic–clonic seizures, ataxia, visual seizures and dementia in the adolescence. The patients generally die 2-10 years after onset. [3,11].

The purpose of this report is to review management of refractory status epilepticus in a patient with Lafora disease, who had repeated attacks of severe myoclonus, tonic-clonic convulsions, and refractory status epilepticus.

CASE REPORT
A 19 years old male patient had his first convulsion at 9 years old. His seizures repeated with a rapid onset three years later and carbamazepin and valproat was begun. However his seizures continued once a month for the next two years, clonozepam and vigabatrin was added to the treatment. Progressive worsening in memory, increased frequency in seizures, myoclonus and ataxia were followed until he was sixteen. Lafora body disease was diagnosed on
skin biopsy at that time. Seizure frequency had increased as 2-3 times in a week for the next three years. The patient admitted to emergency service with status epilepticus was accepted unconsciously in our intensive care unit. Valproat, clonozepam and phenytoin were administered in the intensive care unit. Unfortunately this regimen failed to stop generalized tonic-clonic seizures so that midazolam and thiopental infusions were added to the therapy. But the seizures in his face and eyelids continued. The respiration was maintained with mechanical ventilation, and hemodynamic and nutritional supportive treatments were performed. Also, electrolyte and metabolic disturbances were eliminated and managed as the patients’ need. Thiopental infusion therapy could not be ceased because when infusion rate decreased generalized seizures repeated. Against all these therapeutic interventions the patient was lost with the complication of sepsis at the 68th day.

**DISCUSSION**

We have reported long-term clinical follow-up of a case with Lafora disease, who had repeated attacks of severe myoclonus, tonic-clonic convulsions, ataxia, dementia, and refractory status epilepticus.

Lafora body disease is one of the progressive myoclonus epilepsy syndromes, inherited as an autosomal recessive disorder, begin in childhood or adolescence [18,19]. The patient in this report had his first convulsion when he was in 9 years old. Lafora body disease is characterized by myoclonus, epileptic seizures, and dementia (progressive loss of memory and other intellectual functions) [13]. In our patient, progressive worsening in memory, increased frequency in seizures, myoclonus and ataxia were seen. Inclusions (polyglucosan bodies) in cells within the brain, skin, liver, bone, skeletal and cardiac muscle caused by mutations in the EPM2A gene is pathognomonic for Lafora’s disease [12,13]. Definitive diagnosis can be established with identification of periodic acid-Schiff (PAS) positive inclusions in eccrine sweat gland ducts on skin biopsy. CT/MRI, EEG may help to diagnosis [14,15]. In our patient, the diagnosis of Lafora disease had been proved by skin biopsy at 16 years old.

Refractory status epilepticus refers to sustained seizures that do not respond to initial drug therapy and persist longer than 60 minutes. Refractory status epilepticus is a major medical and neurological emergency that requires immediate treatment to avoid significant morbidity and mortality. The use of two or, sometimes, three first-line antiepileptics is often required to meet the criteria for refractory status epilepticus. Therapy should proceed simultaneously on four fronts: termination of seizures; prevention of seizure recurrence; management of precipitating causes of status epilepticus; management of the complications [13,14].

Initially, control of generalized seizure activity can often be obtained with either intravenous lorazepam 0.1 mg/kg, or diazepam 0.2 mg/kg. If these first line drugs fail parenteral phenytoin or fosphenytoin can be used as second line drugs. The loading dose of phenytoin in status epilepticus is 15 to 20 mg/kg at a maximum intravenous infusion rate of 150 mg/min [17]. However it should be considered that high-dose phenytoin has potential life-threatening cardiotoxic side effects [18-19].

Failure to respond to optimal benzodiazepine and phenytoin loading operationally defines refractory status epilepticus No data support a best third-line drug, and recommendations vary greatly. The list of third-line drugs includes phenobarbital, midazolam, propofol, pentobarbital, and lidocaine. Phenobarbital is given 20 mg/kg intravenously, with an infusion rate of no more than 1.5 mg/kg/min, in adults. If this is unsuccessful, barbiturate coma has been the most commonly used modality. Thiopental is given 3 to 4 mg/kg over two minutes intravenously followed by a continuous infusion rate of 0.2 mg/kg/min. The dose is then adjusted upward, every 3 to 5 minutes by 0.1 mg/kg/min, until the EEG becomes isoelectric. A general principle is to maximize the dosage of each drug before adding an additional agent [18,19]. However, adverse hemodynamic effects, including vasodilatation, hypotension, and decreased myocardial contractility, have been frequently encountered. Inotropic agents and, occasionally, pulmonary artery catheters are often required to support patients’ blood pressure and cardiac output during induction and maintenance of barbiturate coma. [1,4]. Recent experience with midazolam was found to be effective in controlling seizures and relatively free of significant side effects [16-21].

Treatment of Lafora disease is essentially supportive because no definitive therapy available. The myoclonic jerks are difficult to control, but a combination of valproic acid and a benzodiazepine is effective in controlling the generalized seizure. Group of phenytoin and barbiturates may require for the refractory status epilepticus [12]. Initially our patient was treated with carbamazepin and valproat, later clonazepam and vigabatrin, followed by midazolam and thiopental infusion in our intensive care unit. Also respiratory, hemodynamic and nutritional treatments were
administered. It was reported that these patients dies 2-10 years after onset of the disease \[15\]. Our patient had died in 9 \[^{th}\] year of the onset of the disease.

**CONCLUSIONS**

As a conclusion, these kinds of refractory status epilepticus disorders must be treated rapidly and aggressively. Management of seizures, rhabdomyolysis, oxygenation, hemodynamic stability, electrolytes and metabolic disturbances, and nutritional support should be carried in an intensive care unit.

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