Lidocaine Treatment in Refractory Status Epilepticus Resulting from Febrile Infection-Related Epilepsy Syndrome: A Case Report and Follow-Up

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Abstract

We report the management of refractory status epilepticus (SE) by using continuous intravenous infusions of lidocaine in a previously healthy 15-year-old girl with a "catastrophic encephalopathy" in whom a diagnosis of febrile infection-related epilepsy syndrome was supposed. One week after a banal pharyngitis and fever, the patient presented confusion and intractable clusters of seizures. Although she underwent multiple examinations investigating all possible etiologies (intracranial infection, autoimmune disease, or toxic and metabolic illness), all results were negative except a feeble positivity to *Mycoplasma pneumoniae* serum antibodies. SE was initially treated with benzodiazepine followed by administration of barbiturates and subsequent induction of coma because of refractory SE; different antiepileptic drugs (AEDs) were given at different times in a period of 6 weeks but clinical and electroencephalographic improvements were achieved only after continuous infusion of lidocaine. When she recovered from SE, the patient developed severe psychomotor and cognitive impairment associated with cerebral atrophy. Treatment with lidocaine or other alternative drugs in cases of prolonged SE should be taken into account as soon as it becomes clear that the clinical condition is refractory to common AEDs included in available guidelines for SE treatment, to improve the bad outcome of this severe condition, at least limiting the negative effects of prolonged high metabolic demand due to continuous epileptiform activity and/or the possible negative effects of prolonged burst-suppression coma.

Keywords
- FIRES
- children
- epilepsy
- lidocaine
- status epilepticus

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Introduction

Febrile infection-related epilepsy syndrome (FIRES) is an infection-related epileptic encephalopathy described by many authors with different names[1]: new-onset refractory status epilepticus (NORSE), devastating epileptic encephalopathy in school age children (DESC), acute encephalitis with refractory repetitive partial seizures (AERRPS), fever-induced refractory epileptic encephalopathy in school age children, and FIRES. Common features are the acute onset of refractory seizures occurring in previously healthy children after a banal febrile infection of different origins and progressive mental deterioration with bad outcome. The pathogenesis of this entity is still unknown even if immune-mediated mechanisms have been suggested[2,3] and all extensive treatment efforts, including intensive care, are fruitless leading to a severe outcome. The severe acute presumed symptomatic refractory status epilepticus (SE) that develops at onset is associated with a high morbidity rate in terms of seizures and cognition at follow-up. It is still unclear if this condition represents a specific nosologic entity per se or a particularly severe refractory SE due to specific etiologies, even if some series have been published to define this entity.[4,5] Recently published articles focus their attention on therapy, proposing ketogenic diet,[6,7] and suggest a role of inflammation processes in determining SE.[3]

Our report aims to discuss the treatment and follow-up of prolonged super refractory SE, as defined by Shorvon, as SE that continues or recurs 24 hours or more after the onset of anesthetic therapy, with lidocaine, a possible alternative drug in SE[8] in a 15-year-old girl whose clinical picture was suggestive of FIRES.

Case Report

A 15-year-old girl was admitted to our emergency department for altered mental status, confusion, physical agitation, and light neck stiffness. The previous week she experienced fever, asthenia, and upper respiratory tract infection treated with paracetamol and antibiotics. On admission, Glasgow Coma Scale was 8 and she presented mild increase in body temperature (37.9°C). She subsequently presented intractable SE with clusters of seizures clinically characterized by generalized tonic–clonic jerks, focal myoclonic seizures involving both sides alternatively and lasting from few seconds to several minutes. Initial electroencephalography (EEG) showed diffuse slow delta activity. In the hypothesis of infectious meningoencephalitis, antibiotic and antiviral reatment was initially started, without clinical improvement. SE was treated initially with diazepam, midazolam, and phenobarbital at weight-appropriate dosages without efficacy. Barbiturate coma with thiopental sodium in the intensive care unit (ICU) was then induced. EEG showed suppression burst features with suppression periods lasting 3 to 4 seconds and persistent electroclinical seizures, characterized by diffuse bilateral clonia. Initial improvement of EEG pattern led to reduction of barbiturate coma with reappraisal of SE so phenytoin (PHE), sodium valproate (VPA), adrenocorticotropic hormone, pyridoxine, and levetiracetam (LEV) at appropriate dosage were introduced at different times in a period of 6 weeks, without significant electroclinical improvement (►**Fig. 1A**). Lidocaine was then started at a dose of 1.25 mg/kg/h resulting in a progressive resolution of SE and EEG improvement from the 1st day of administration (►**Fig. 1B**), allowing the barbiturate coma to be completely removed in the subsequent days. She was discharged from the ICU with intravenous lidocaine, VPA, and LEV. Lidocaine was tapered off 6 months after and her latest treatment is a polytherapy with Carbamazepine, Clobazam, and Lacosamide with persisting seizures (►**Fig. 2**). Even in absence of a clear immunological etiology, a trial with intravenous immunoglobulin G was subsequently tried after SE, without clinical improvement on seizures. At 18 months follow-up she presented moderate cognitive disability (intelligence quotient [IQ]: 55), emotional instability, and a significant psychomotor deterioration. At clinical examination, she was able to walk with partial weight bearing, showed tendon retraction and signs of peripheral neuropathy due to nerve compression from prolonged lying. Partial seizures with secondary generalization persisted with visual sensation, scotoma, gaze deviation, overflow of saliva, loss of consciousness, chewing automatism, generalized clonia, sometimes followed by vomiting; seizure frequency reduced over time without seizure-free periods longer than 15 to 20 days. Her EEG

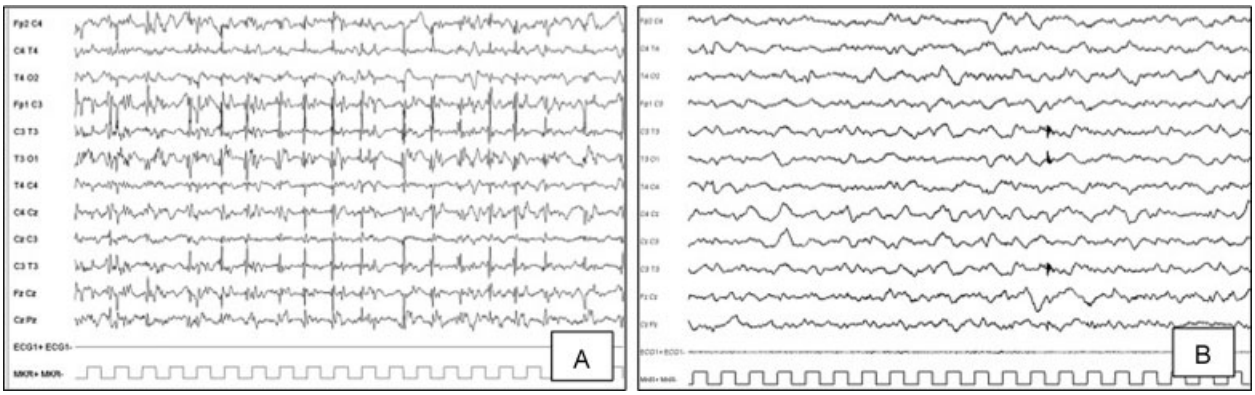

Fig. 1 (A) Electroencephalography (EEG) during status epilepticus: high pass filter: 0.530 Hz; low pass filter: 30 Hz; and gain: 150 microV/cm; (B) EEG during lidocaine infusion: high pass filter: 0.530 Hz; low pass filter: 30 Hz; and gain: 150 microV/cm.

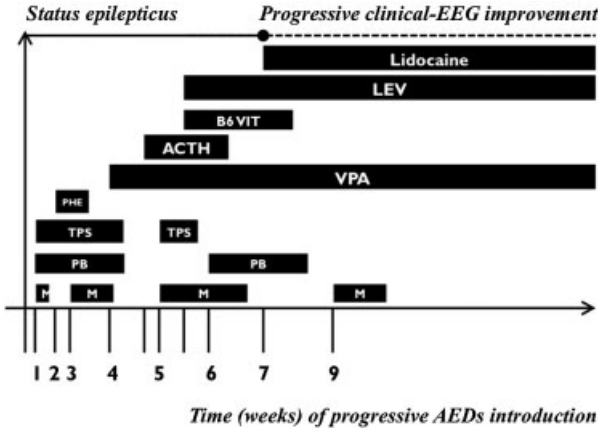

Fig. 2 Clinical course of the patient: timing of AEDs introduction and subsequent variations. AED, antiepileptic drugs; ACTH, adrenocorticotropic hormone; B6VIT, B6 vitamin; LEV, levetiracetam; M, Midazolam; PB, phenobarbital; PHE, phenytoin; TPS, sodium thiopental; VPA, sodium valproate.

pattern showed diffuse slow activity with multifocal epileptiform discharges.

Neuroimaging and laboratory investigations: brain magnetic resonance imaging (MRI) was initially normal except from bilateral mastoiditis; 1 month after vasogenic edema in external capsule, amygdalae, putamen, and lingual gyrus was evident; 2 months after edema was reduced in putamen and insulae but a concomitant worsening of signal alteration in subcortical white matter was observed. Brain MRIs performed after 6 and 12 months then showed diffuse cerebral atrophy. An extensive infectious, metabolic, and immunological work up was performed: cerebrospinal fluid (CSF), cutis, urine, feces, and blood were tested for infectious, metabolic, and immunological etiologies, resulting in a feeble positivity to *Mycoplasma pneumoniae* serum antibodies, not confirmed by polymerase chain reaction on the CSF.

Discussion

We report a case in which a diagnosis of FIRES was supposed as the patient, a previously healthy girl, after a banal upper respiratory tract infection, developed refractory SE, for which extensive diagnostic work up was negative. In our patient, a feeble positivity to *Mycoplasma pneumoniae* serum antibodies was found and only subsequent MRI showed progressive anomalies, such as diffuse cerebral atrophy, probably due to prolonged SE. At follow-up, cognitive level was poor associated with psychiatric problems. Our patient presented a super refractory SE lasting approximately 2 months that, despite several antiepileptic drugs (AEDs), achieved full control in a short time only after lidocaine was given, even at lower doses than reported in literature. Like ours, some studies in the literature report the use of lidocaine in FIRES: recently some positive outcome in terms of seizure control has been described:[9] these authors administered lidocaine at high dose in association with high dose phenobarbital and topiramate, with good seizure control.

Lidocaine is a local anesthetic drug that exerts its action blocking ionic currents on voltage-gated sodium channels in nerve cells during abnormal membrane depolarizations, currently used as an antiarrhythmic drug (class IB). The mechanism of action is unclear, it may have membrane-stabilizing effects and a central local anesthetic action on the inhibitory pathway fibers involved in direct cortical stimulation.

To date, no controlled trial for lidocaine in SE has been published. Despite many reports in literature since 1955 on the use of lidocaine in SE, this drug is not included in many current available protocols of SE treatment, probably because of its not well-defined efficacy on SE and its potentially serious adverse effects, in particular, in pediatric population.

In Italian guidelines for SE treatment in adults,[8] lidocaine is mentioned, with a grade C, level 4 of evidence, as an alternative treatment in refractory SE when other therapeutic options have failed; in guidelines for treatment of SE in children, this drug is cited even if its use is not recommended due to scarce literature data on its use in pediatric population.

In addition, no standardized procedures for lidocaine in SE have ever been reported in literature. Its use must be carefully evaluated in any single case, considering all prognostic factors, and must be done by expert physicians as, among other possible adverse events, at blood concentration exceeding 10 ug/mL it may be proconvulsant.[8]

As reported by many studies on pediatric series,[10] it seems that lidocaine may be particularly effective in those situations where first line AEDs (benzodiazepine, PHT, and barbiturates) for SE have been ineffective, exerting its action with some advantages, as the lower risk of respiratory depression and subsequent need of intubation. In addition, it is effective in a short time (distribution half-time: 8–17 minutes) even if this last one may also represent a disadvantage as, to maintain its effectiveness, it has to be administered in continuous infusion at a reported dosage of 2 to 3.5 mg/kg/h after a bolus of 1.5 to 2 mg/kg, given at a maximum rate of 50 mg/min.[8,10]

FIRES is a "catastrophic" and "devastating" encephalopathy that leads to a super refractory SE with a bad outcome as in the case reported, a previously healthy girl who developed severe psychomotor deterioration, cognitive impairment,[1,5] and emotional instability. Given to the quick effective response achieved with lidocaine we presume that, if this drug was introduced earlier, probably the duration of SE could have been shorter with a better long-term outcome.

Conclusions

To date, treatment algorithms in childhood refractory SE are characterized by the lack of randomized controlled trials and remain mostly empirical with different therapeutic approaches, mainly derived from adult guidelines for SE. In our experience, the use of lidocaine, based on many reports or case series available in the literature, has been effective in controlling SE.[8,10] In cases of super refractory SE, we suggest considering a therapeutic approach with other "alternative" drugs as soon as it becomes clear that the clinical condition is refractory to conventional AEDs included in available

guidelines for SE treatment, to reduce the worsening of long-term outcome due to cerebral sufferance subsequent to prolonged epileptic discharges and/or the possible negative effects of prolonged burst-suppression coma.

Disclosure

None of the authors has any conflicts of interest to disclosure. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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