

Treatment of non-convulsive status epilepticus

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Introduction

Seizures of any type can continue unabated and they are then considered as a separate entity, status epilepticus. This is of great importance, as in certain circumstances a persistent seizure can result in neuronal damage irrespective of any physiological compromise.

Among the diagnoses of status epilepticus are a number that can be considered as non-convulsive status epilepticus including absence status epilepticus, atypical absence status epilepticus, electrical status epilepticus during slow-wave sleep (including Landau-Kleffner syndrome), complex partial status epilepticus and status epilepticus in coma. Indirect estimates for the incidence of non-convulsive status epilepticus have been as high as 14–24 per 100,000 population per year (the majority of these are non-convulsive status epilepticus in the setting of learning difficulties). Although non-convulsive status epilepticus includes a number of very different conditions, these forms of status epilepticus share two important qualities: difficulty in making the diagnosis, and uncertainty about the best mode of treatment.

Diagnosis

The diagnosis of non-convulsive status epilepticus can be difficult, and is dependent on EEG. In patients with a previous diagnosis of epilepsy, any prolonged change in personality, prolonged post-ictal confusion (greater than 20 minutes) or recent onset psychosis should be investigated with EEG as these can all be presentations of non-convulsive status epilepticus. If new onset developmental delay occurs in the setting of epilepsy then a sleep EEG should be considered to look for status epilepticus during slow-wave sleep (see below). In non-comatose patients with no history of epilepsy, non-convulsive status epilepticus can present as confusion or personality change (almost invariably in the setting of a metabolic derangement, encephalitis or other acute precipitant). Rarely, non-convulsive status epilepticus can present as autism and if suspicions are raised (usually a fluctuating course) then EEG is indicated.

Non-convulsive status epilepticus can follow convulsive status epilepticus, and is an important treatable cause of persistent coma following convulsive status epilepticus. This and status epilepticus with subtle manifestations such as twitching of the limbs, or facial muscles or nystagmoid eye jerking, which can result from hypoxic brain damage, are often collectively referred to as subtle motor status epilepticus. Up to 8% of patients in coma who have no outward signs of seizure activity are in non-convulsive status epilepticus, thus emphasising the importance of EEG in the investigation of comatose patients. Similarly, non-convulsive status epilepticus is underdiagnosed in the confused elderly in whom the confusion is frequently blamed on other causes.

Although EEG interpretation is usually straightforward, with regular repetitive discharges occurring in some patients in a cyclical fashion, difficulties can occur in differentiating non-convulsive status epilepticus from an encephalopathy of other cause. Thus electrographic definitions of non-convulsive status epilepticus should include: unequivocal electrographic seizure activity; periodic epileptiform discharges or rhythmic discharge with clinical seizure activity; and rhythmic discharge with either clinical or electrographic response to treatment. There is uncertainty about the relevance of periodic lateralised epileptiform discharges (PLEDs). This is most notable following severe encephalitis or hypoxic injury in which discharges can occur with such periodicity so as to be confused with periodic discharges seen following prolonged status epilepticus. Some have argued that such discharges represent ongoing seizure activity, and should be treated thus. The general consensus, however, is that a multitude of aetiologies can underlie PLEDs, and that they should only be treated as epileptic if there is other evidence of ictal activity.

Neuronal damage and non-convulsive status epilepticus

It has long been recognised that ongoing electrographic seizure activity can result in neuronal damage, so-called excitotoxic neuronal damage. This damage occurs in animal models of non-convulsive status epilepticus. These animal models, however, involve the induction of status epilepticus in non-epileptic animals with either powerful chemoconvulsants or prolonged high frequency repetitive stimulation. This is very different from the human situation. Furthermore, non-convulsive status epilepticus in humans tends to have lower frequency discharges, which if reproduced in animal models produces substantially less neuronal damage.

Another important finding has been that epileptic animals, animals pretreated with antiepileptic drugs (AEDs) and young animals are all resistant to chemoconvulsant induced neuronal damage. Thus young age, AEDs and prior history of epilepsy probably all confer some degree of neuroprotection. Lastly, in humans non-convulsive status epilepticus often results from an acute precipitant such as an encephalitis and, in such circumstances, the status epilepticus only minimally contributes to any resultant pathology.

There have been reports of prolonged memory problems, hemiparesis and death occurring following complex partial status epilepticus although, in most of these cases, the outcome relates to the underlying aetiology. Indeed, the degree to which non-convulsive status epilepticus contributes to neuronal damage in humans is unclear. Since aggressive treatment is not entirely benign, and can lead to hypotension and respiratory arrest, then the best approach to treatment will only be determined in randomised studies of aggressive versus more conservative management.

Specific forms of non-convulsive status epilepticus

Typical absence status epilepticus

This entity needs to be distinguished from complex partial status epilepticus and atypical absences seen in mental retardation. This term should perhaps be reserved for prolonged absence attacks with continuous or discontinuous 3 Hz spike and wave occurring in patients with primary generalised epilepsy. The EEG, however, may also include irregular spike and wave, prolonged bursts of spike activity, sharp wave or polyspike and wave.

Although absence epilepsy has its peak in childhood and commonly remits in adolescence, absence status epilepticus commonly occurs in later life. Absence status epilepticus can be divided into childhood absence status epilepticus (those usually already receiving treatment), late-onset absence status epilepticus with a history of primary generalised

seizure (often a history of absences in childhood) and late-onset absence status epilepticus developing *de novo* (usually following drug or alcohol withdrawal).

There is no evidence that absence status induces neuronal damage, and thus aggressive treatment is not warranted. Treatment can either be intravenous or oral. Absence status epilepticus is often precipitated by the prescription of inappropriate antiepileptic drugs in idiopathic generalised epilepsy (e.g. carbamazepine). Absence status epilepticus responds rapidly to intravenous benzodiazepines, and these are so effective that the response is diagnostic. Lorazepam at 0.05–0.1 mg/kg is the benzodiazepine of choice. The effect may only be transient and a longer acting AED may need to be given. If intravenous treatment is required, but either benzodiazepines are ineffective or contraindicated then intravenous valproate (20–40 mg/kg) can be given. In cases of primary generalised epilepsy treatment should be continued with a suitable AED. If a precipitating factor can be identified in late-onset *de novo* cases, then long-term therapy is not usually indicated.

Complex partial status epilepticus

Complex partial status epilepticus has to be differentiated not only from other forms of non-convulsive status epilepticus, but also from post-ictal states, and other neurological and psychiatric conditions. EEG can be helpful, but often the scalp EEG changes are non-specific and the diagnosis is very much clinical in nature. The definition as ‘a prolonged epileptic episode in which focal fluctuating or frequently recurring electrographic epileptic discharges, arising in temporal or extratemporal regions, result in a confusional state with variable clinical symptoms’ is suitably vague and is necessary to emphasise that complex partial status epilepticus can originate in any cortical region and can fluctuate in a cyclical fashion. A further factor is importantly included in this definition, and that is the absence of coma; electrographic status epilepticus in coma is considered separately, partly because of its poor prognosis.

How aggressively complex partial status epilepticus should be treated depends upon: the prognosis of the condition; and if treatment improves the prognosis. As in all epilepsies the prognosis relates partly to the prognosis of the underlying aetiology and any concomitant medical conditions. Complex partial status epilepticus in someone with epilepsy is probably a more benign condition than acute precipitated status epilepticus, and should perhaps be treated thus. The medication used to treat status epilepticus is not without adverse effects and can result in hypotension, respiratory depression and, sometimes, cardio-respiratory arrest. This is more so with intravenous administration with its resultant rapid, high serum levels. At present, early recognition of the condition and treatment with oral or rectal benzodiazepines is recommended; oral clobazam has proven to be an effective treatment. In patients who have repetitive attacks of complex partial status epilepticus, oral clobazam (10–20 mg/day) over a period of 2–3 days given early at home can usually abort the status epilepticus, and such strategies should be discussed with patient and carers.

Early recognition is a critical goal, as the delay in treatment comes not from therapeutic strategy, but from failure to diagnose the condition in the first place. For more persistent or resistant complex partial status epilepticus intravenous therapy should be used, and lorazepam followed by phenytoin are the drugs of choice. In contrast to absence status epilepticus, the response to benzodiazepines can be disappointing, and often there is a resolution of the electrographic status epilepticus without concomitant clinical improvement (possibly due to post-ictal effects). Whether general anaesthesia is ever justified remains a matter for speculation; since most complex partial status epilepticus is self-terminating often without any serious neurological sequelae, then such aggressive therapy should, in most instances, be avoided. Treatment of the underlying cause (e.g.

encephalitis or metabolic derangement) is of course paramount, and can often lead to resolution of the status epilepticus.

Atypical absence status epilepticus

Atypical absence status epilepticus is associated with the epileptic encephalopathies such as Lennox-Gastaut syndrome. This entity can be difficult to diagnose, but should be considered if there is change in personality, decrease in cognition or increased confusion in a patient with one of these epilepsies. The EEG characteristics are usually that of continuous or frequent slow (< 2.5 Hz) spike and wave. This condition is usually poorly responsive to intravenous benzodiazepines, which should, in any case, be given cautiously, as they can induce tonic status epilepticus in these patients. Oral rather than intravenous treatment is usually more appropriate, and the drugs of choice are valproate, lamotrigine, topiramate, clonazepam and clobazam. Sedating medication, carbamazepine and vigabatrin have been reported to worsen atypical absences.

Non-convulsive status epilepticus in coma

Electrographic status epilepticus in coma is not uncommon and is seen in up to 8% of patients in coma with no clinical evidence of seizure activity. The diagnosis is often debatable as in many instances burst-suppression patterns, periodic discharges and encephalopathic triphasic patterns have been proposed to represent electrographic status epilepticus, while these mostly indicate underlying widespread cortical damage or dysfunction. Non-convulsive status epilepticus in coma consists of three groups: those who had convulsive status epilepticus, those who have subtle clinical signs of seizure activity and those with no clinical signs. Convulsive status epilepticus has, as part of its evolution, subtle status epilepticus in which there is minimal or no motor activity but ongoing electrical activity. This condition should be treated aggressively with deep anaesthesia and concomitant AEDs. The association of electrographic status epilepticus with subtle motor activity often follows hypoxic brain activity and has a poor prognosis, but aggressive therapy with benzodiazepines, phenytoin and increased anaesthesia is perhaps justified, since the little evidence available indicates that such treatment improves prognosis.

Lastly electrographic status epilepticus with no overt clinical signs is difficult to interpret – does it represent status epilepticus or widespread cortical damage? Since these patients have a poor prognosis, aggressive treatment is recommended in the hope that it may improve outcome. Lastly there is a group of patients in whom there are clinical signs of repetitive movements, but no electrographic seizure activity, and in these patients antiepileptic treatment and aggressive sedation is not recommended.

Conclusion

Non-convulsive status epilepticus is an all-encompassing term that covers a variety of conditions with very different prognoses from the entirely benign to the fatal (although this is mainly due to the underlying aetiology). These conditions are poorly replicated by available animal models, and this together with the lack of randomised treatment trials has meant that the best treatment options are unknown. It is important to remember that aggressive AED treatment is not benign especially when deep anaesthesia is proposed.

Further reading

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