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CURRENT AWARENESS SERVICE

SUDEP communication – aspects affecting conversations around sudden unexpected death in epilepsy (SUDEP)

Prof Rohit Shankar MBE, professor in Neuropsychiatry at the University of Plymouth Medical School, published a paper in the European Journal of Neurology in which he discussed epilepsy professionals' views on speaking about SUDEP with patients, and this included a comparison between the UK and Norway. He spoke to Kami Kountcheva about their findings and the issues standing in the way of better communication.

The findings of the study are discussed generally, without breaking them down by speciality. Consequently, Prof Shankar's comments and answers in this interview relate to all specialities. However, of the UK clinicians who took part in the study, 7% were general paediatricians and 14% were paediatric neurologists. The results from Norway did not specify the speciality in detail, and referred only to 'neurologists' and 'nurses'.

Kami Kountcheva: Can you tell me a bit about your study?

Rohit Shankar: The preamble to our study is that there had been around 16 sudden unexpected death in epilepsy (SUDEP) surveys worldwide of clinicians – neurologists, epilepsy nurses, psychiatrists etc. The aims of these studies were to try to understand if the clinicians were communicating SUDEP risk and what the challenges or barriers are to communication.

A major step forward has been that every single guideline since the National Institute for Health and Care Excellence (NICE) [2004], and now the American Academy of Neurology (AAN) [AAN.com, 2017], makes the discussion of SUDEP mandatory; no longer is it just 'good practice'. At its most basic level, you have to tell people with epilepsy about SUDEP, but you also must continue to follow it up at subsequent appointments and over the course of treating the patient.

One of the big goals was that we wanted to consolidate all these surveys – and identify the top 10 questions – so that from now on, we could develop a validated tool to take forward. We published that research in Seizure in 2023 [Watkins et al, 2023].

The next step was to use that survey. In the UK, the most recent survey had been performed in 2015 and it showed significant gaps in SUDEP communication. We thought that now would be a good time to undertake new survey. In part this was because the AAN guidelines were published in 2017 and also it was post-pandemic.

Our initial study was in the UK with 197 responses from professionals working with people with epilepsy.

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Subsequently, a colleague in Norway, Dr Oliver Henning, showed an interest in undertaking the same survey in that country.

From the UK, we had 197 responses representing a total population of approximately 60 million, and from Norway, 110 responses representing a population of approximately five million. It is important to emphasise that in the UK, compared with Norway and most other European countries, there are fewer health professionals, including neurologists, who specialise in epilepsy.

The UK and Norway are both socio-economically advanced countries and consequently, it seemed reasonable to compare and contrast the responses of the countries.

The results were interesting. In the UK, only two professionals stated that they don't talk about SUDEP with their patients with epilepsy. It seems like awareness of SUDEP has become part of the larger culture of epilepsy management in the UK and that is very encouraging.

The concern for the UK is that there was a subjective inclination on the part of many professionals to decide who is at risk. So, clinicians would talk about SUDEP if they decide the risk in a particular patient is high. The question is, how do you know who is high risk? There is no scientific algorithm to determine who is at risk although clearly risk factors have been well-known for decades. The other thing is that it might be that at that time, seizures might be low, so if you are judging it only on seizure frequency, you might decide the risk is low. However, this might ignore potentially important psychological and social factors which might have a direct impact on some individuals and therefore change the level of risk. Consequently, it is best practice that we communicate the risk factors, and we hope that people will change their habits and lifestyle accordingly to help reduce the risk.

> *NOTE by Richard Appleton: Clearly, for children with epilepsy, the risk is also determined by the specific epilepsy syndrome; for example, children with Dravet syndrome and Lennox-Gastaut syndrome are well-recognised to be a high risk of SUDEP and particularly under the age of 10 years. More paediatric-specific discussions about SUDEP – and mortality in epilepsy in children – can be found in an article published in an earlier issue of PECAS, published in 2018 [Appleton 2018].*

RS: I think the sense that one can define risk, especially sitting in a clinic in a 20-minute appointment, and then decide whether they want to tell somebody about SUDEP or not, is a significant clinical blind spot. Patients might not even share what they're going through other than their seizure control and their medications. So, there might be other factors which clinicians might not be aware of or ask about and therefore make a judgement based on incomplete information. Also, if it's not part of your usual discussion framework and you're running late, or if you're busy with other things, you might skip discussing SUDEP.

Risk is a very dynamic issue and depends on the individual, their situation and their environment. From seeing someone once, you can't actually say how at risk they are. Five years later, you might be able to say if the risk has changed for them relative to their original presentation if, for instance, their seizure control has worsened, or their situation has changed and particularly if they now they live on their own.

Even when people are at a lower risk, we must still, talk to them about SUDEP, so that they can either introduce or continue with behaviours that help to reduce the risk.

Norway was quite some way behind the UK in that the epilepsy professionals there did not even feel, to some degree, that SUDEP needs to be communicated. I think that did take our Norwegian co-author by surprise.

Health professionals in both countries cited problems with time and resources, and some of the Norwegian clinicians used the old arguments that this might upset patients. And, of course, it might. No one would ever like to be told that they are at risk of dying suddenly. But that's the job that we've signed up to and needs to be done in a person-centred manner, providing a balanced view of mitigators, like being compliant with medication, while also discussing the factors that lower the threshold of harm, such as generalised seizures, seizures in sleep, etc. Clearly, there seems to be a significant gap between UK and Norwegian attitudes to SUDEP.

KK: What about countries that are not as socioeconomically advanced?

RS: Our group published a paper on this a few years ago [Kinney et al, 2019]. For this research we asked all 114 ILAE branches about SUDEP research, practice and diagnosis in the last 10 years. Seventy-seven (66%) branches responded . It was fascinating because we then realised that SUDEP is quite an 'economically developed country' concept. In many countries, autopsies are not performed, either because there are no resources or because religious practice bans them. Consequently, there is no learning and death in patients with epilepsy is a not a big issue. In many developing countries, there is also no proper recording of the cause of death, so you can't even find out if it was an epilepsy (SUDEP) death or not.

KK: What makes attitudes to SUDEP communication different between the UK and Norway?

RS: I think you can divide the reasons into patient reasons, clinician reasons and then the third sector.

The first thing is that the UK was way ahead in terms of developing guidelines, in part because of its focus on research into SUDEP. NICE 2004 was one of the seminal guidelines which introduced SUDEP communication into epilepsy care. The AAN, the American guidelines, were only published over a decade later. Professor Lina Nashef actually deduced sudden death in epilepsy in 1995 in residential homes [Nashef et al, 1995a; Nashef et al, 1995b]. The first classification of SUDEP came from Prof Nashef [Nashef 1997] and Dr Annegers [Annegers 1997] in 1997 which was tightened in 2012 [Nashef et al, 2012]. Crucially, epilepsy charities, particularly SUDEP Action I believe, played a significant role to keep the momentum going.

There is currently no debate in the UK about whether we should or shouldn't talk about SUDEP with patients with epilepsy; this is now well-established. Not discussing SUDEP goes against both best practice and NICE recommendations.

Another observation I have is that the NHS is a much more democratic health system than those in many other countries. Consequently, more patients are more aware and more knowledgeable about their condition. They want to know about it and clearly this encourages a culture of communication; there is always room for improvement.

The influence of epilepsy specialist nurses (ESNs) has been very positive and in all aspects of epilepsy care. The UK is one of the few places which has ESNs. In most other countries, there is a medical model for epilepsy which is led and delivered by neurologists. Clearly, neurologists (adult and paediatric) are essential but at grassroots, ESNs are the clinicians who actually undertake epilepsy awareness training, engage patient lobbies and, at a much more informal level, tend to be much closer to the patient needs. They are also much more receptive of the need to communicate and appear to do so, as our study showed.

Research has also been very important and the UK has been one of the key players in this area. The US is now doing more work on SUDEP, but the risk and communication aspects of SUDEP is still led by the UK. Our study also found that the use of the SUDEP and seizure safety checklist was important. Many professionals use it to understand risk. This too could have helped defuse the perceived tension of such sensitive conversations.

Consequently, all these factors create an ecosystem which is much more evolved for SUDEP communication.

KK: Is there any circumstance where it might be appropriate not to speak about SUDEP at all?

RS: None that I can think of. I speak about it with every person with epilepsy. Every patient is different, of course, but the main thing is that you can't just mention SUDEP and leave it hanging in the air and send the patient home. We have to follow the thread through and tailor the conversation to the individual. The patient must be given the opportunity to raise their views, express any anxieties and ask questions. Clearly, the patient might feel anxious and frightened. It is the clinician's role to know the evidence and risks for the individual patient. We have a responsibility to tell people what the risks are. One of the issues our study raised was that clinicians generally felt they did not have enough time to discuss SUDEP comprehensively in their clinics because of time constraints.

KK: What is needed to help facilitate more of these conversations?

RS: This is where something like EpSMon, the SUDEP Action app, comes in. This currently has approximately 5,000 users, which is the largest sample size of users. Every three months, they update their risk level based on any new information. Using these data, we undertook some research in women with epilepsy of childbearing age to assess whether they understood the risk of SUDEP and the harm that epilepsy may cause in pregnancy [Zhou et al, 2023].

A key finding was that a significant number of women were clearly unaware of SUDEP as a phenomenon. They were made aware of it during their assessment and the associated risks by EpSMon. However, three months later, when they repeated the questionnaire, many had forgotten about it. This showed that we cannot assume that discussing SUDEP only once will be enough for it to be 'registered'.

On their third attempt at repeating the questionnaire on the app, results suggested that awareness started to change. Clearly, the study has a number of limitations and probable biases, but it showed that the message has to be repeated a number of times before it is a person's consciousness.

In our most recent study, it was clear that a high number of clinicians had lost patients to SUDEP. I expect that that's quite a gut-wrenching moment. Consequently, having lost a patient to SUDEP, clinicians may be more likely to speak about SUDEP to their other patients. I wouldn't want to wish clinicians to have a SUDEP to become more receptive to discuss it, but I think there is something to be said about peer learning. I don't think we've done that enough, especially around SUDEP. For clinicians, a SUDEP death might induce a sense of failure or concern about their clinical judgements. But they shouldn't! I think we have to develop a therapeutic community or a community of practice, where clinicians can share their thoughts and experiences with others, who might be new to the field or sceptical of SUDEP risk, or both. I think a missing link is that regular clinician to

clinician learning, and it would be great to bring that change.

KK: What's next?

RS: We now have data using the same survey on SUDEP communication from Spain and Sweden and we hope to collect similar data from Finland, Hungary and Italy. This will clearly provide a wider picture of how SUDEP is discussed in Europe and will also allow us to benchmark the UK within this wider community.

RS is the medical lead and partner of the EpSMon app (non-commercial)

Interview by Kami Kountcheva
Co-Editor

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Forthcoming courses and conferences

The following are details of forthcoming conferences and courses in epilepsy and general paediatric neurology.

2025

January
20-24
14th ILAE School on Pre-Surgical Evaluation for Epilepsy and Epilepsy Surgery
Brno, Czech Republic
ta-service.cz/epodes2025

March
20-22
19th World Congress on Controversies in Neurology
Prague, Czech Republic
cony.comtecmed.com

April
2-4
International Congress on Structural Epilepsy & Symptomatic Seizures 2025
Gothenburg, Sweden
bit.ly/3X8FlOt


Gothenburg


Lisbon

26-27
7th ILAE School on EEG in the First Year of Life
Haikou City, Hainan Province, China
ilae.org/files/dmfile/eeg2025-flyer.pdf

May
11-27
12th International Residential Course on Drug Resistant Epilepsies
Tagliacozzo, Italy
epilepsytagliacozzo.com

August-September
30-3
36th International Epilepsy Congress
Lisbon, Portugal
ilae.org/congresses/36th-international-epilepsy-congress

2026

May
3-6
18th Eilat Conference on New Antiepileptic Drugs and Devices
Madrid, Spain
bit.ly/3Wq6dcc

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Nonconvulsive status epilepticus in children

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Dr Amitav Parida, consultant paediatric neurologist, Birmingham Children's Hospital.
Professor Rajat Gupta, consultant paediatric neurologist, Birmingham Children's Hospital

Introduction

Nonconvulsive status epilepticus (NCSE) is an important epileptic phenomenon with a range of presentations. It is important that paediatricians have some understanding of NCSE.

NCSE typically presents with an alteration in behaviour such as reduced alertness, altered sensorium, catatonia, subtle motor manifestations (such as frequent eye twitching, automatisms, brief and often migrating myoclonic seizures, staring, chewing and swallowing), abnormal speech (including aphasia, dysphasia, dysarthria) and autonomic dysfunction (including facial flushing and pupillary dilatation).

NCSE most commonly occurs in a child with an underlying epilepsy, and usually an early-onset and severe epilepsy, in the context of an acquired or traumatic brain injury, in encephalitis and some rare genetic syndromes.

We will discuss the ILAE classification, the suggested EEG criteria for the diagnosis of NCSE and its treatment.

Definition and Classification

The ILAE guidelines published an updated definition for status epilepticus (SE) and classified this further depending on the presence or absence of prominent motor symptoms and the degree of impaired consciousness [Trinka et al, 2015]. Status epilepticus without prominent motor symptoms is non-convulsive status epilepticus (NCSE) and this can be further subclassified [Trinka et al, 2015] (*Figure 1*).

- B.1 NCSE with coma (including 'subtle' SE)
- B.2 NCSE without coma
  - B.2.a Generalised
    - B.2.a.a Typical absence status
    - B.2.a.b Atypical absence status
    - B.2.a.c Myoclonic absence status
  - B.2.b Focal
    - B.2.b.a Without impairment of consciousness (aura continua, with autonomic, sensory, visual, olfactory, gustatory, emotional/ psychic/experiential, or auditory symptoms)
    - B.2.b.b Aphasic status
    - B.2.b.c With impaired consciousness
  - B.2.c Unknown whether focal or generalised
    - B.2.c.a Autonomic SE

Figure 1. ILAE Classification of NCSE [Trinka et al, 2015].

As with most recent ILAE classifications, it is detailed, and for many (if not most) paediatricians with no or little interest in epilepsy, may be difficult to unravel. It may also be difficult to recognise in children even amongst some paediatric neurologists. Other definitions have also been suggested, for example, in 2004: 'a term used to denote a range of conditions in which electrographic seizure activity is prolonged (30 minutes) and results in nonconvulsive clinical symptoms' [Walker et al, 2005]. In 2015, a suggested definition was: 'Nonconvulsive seizures lasting 30 minutes or recurrent over 30 minutes without return to normal consciousness; continuous or recurrent NCS [non convulsing seizure] lasting more than 5 minutes, and continuous and recurrent NCS for more than 50% of an EEG epoch' [Herman et al, 2015]. The number of definitions reflects the variation in presentation and also the uncertainty of NCSE.

Both clinical features with a change in behaviour or reduced consciousness from baseline and EEG evidence of NCSE are required for a diagnosis of NCSE.

Investigation

EEG is required to confirm or exclude the diagnosis of NCSE. The Salzburg criteria (*Figure 2*) are utilised alongside the 2021 American Clinical Neurophysiology Society Standards (*Figure 3*) to help make a diagnosis of NCSE. EEG interpretation to look for NCSE in patients with epileptic encephalopathy can be difficult due to an abnormal background EEG at baseline. The Salzburg criteria have specific guidance for this situation [Beniczky et al, 2013]. In addition, a recent publication has suggested that the response to intravenous (IV) anti-seizure medication (ASM) may also assist in the diagnosis of NCSE [Leitinger et al, 2023].

Aetiology

NCSE is a common feature in a number of specific epilepsy syndromes, the most common being:

1. **Lennox-Gastaut Syndrome (LGS)**
   An electroclinical diagnosis with many structural and genetic causes. The cardinal clinical features include a child with multiple seizure types, developmental impairment / intellectual disability and a characteristic inter-ictal and ictal EEG pattern. Nocturnal tonic seizures are the predominant seizure type but other seizures include atonic, atypical absences, focal, and generalised tonic-clonic seizures. EEG features include slow spike and wave (1.5-2.5Hz) discharges and paroxysms of fast activity (10-20 Hz).

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Patient without known epileptic encephalopathy:
Epileptiform discharges >2.5Hz OR
Epileptiform discharges ≤ 2.5Hz or rhythmic delta/theta activity (>0.5Hx) AND
EEG and clinical improvement after IV ASM
Subtle clinical ictal phenomena during the EEG pattern
Typical spatiotemporal evolution

Patient with a known epileptic encephalopathy:
Increase in prominence or frequency of features when compared to baseline with observable change in clinical state
Improvement of clinical and EEG features after IV ASM
If there is only EEG improvement and no clinical improvement – possible NCSE

Figure 2: Salzburg criteria for NCSE [Beniczky et al, 2013]

Electrical Status Epilepticus (ESE):
Electrical seizure for ≥10 continuous minutes
OR for a total duration of ≥ 20% of any 60-minute period of recording.

Electroclinical Status Epilepticus (ECSE):
Electroclinical seizure for ≥10 continuous minutes
OR for a total duration of ≥ 20% of any 60-minute period of recording.
AND a seizure with bilateral tonic-clonic manifestations present for ≥ 5 minutes

Figure 3: 2021 American Clinical Neurophysiology Society's Standards: Both Electrical Status epilepticus (ESE) or Electroclinical Status Epilepticus (ECSE) can be classified as NCSE [Hirsch et al, 2021]

2. **Epilepsy with myoclonic atonic seizures (EMAtS) previously known as Doose Syndrome**
   This epilepsy is characterised by the abrupt onset of myoclonic atonic seizures, and many children also develop absence and generalised tonic-clonic seizures. Development impairment often becomes apparent after the onset of the seizures.
3. **Dravet syndrome**
   This syndrome is well-characterised [Lagae 2021]. Its onset is in the first year or life and may include prolonged episodes of convulsive status epilepticus (CSE). Episodes of NCSE become more common beyond the age of five years. One of the characteristic manifestations of NCSE in Dravet syndrome is a period of 'obtundation' in which the child is minimally responsive and often with excessive salivation and irregular myoclonus or subtle and brief myoclonic seizures. The EEG may only show rhythmic slow wave activity and not always the expected slow spike and slow wave activity that characterises NCSE. Episodes may last many hours, and occasionally days.

NCSE is also associated with a few specific genetic disorders, most of which are also associated with epilepsy. The three most common are:

1. **Ring Chromosome 20 syndrome**
   Recurrent episodes of NCSE and/or an abrupt and severe onset of seizures, including prolonged absences, in a previously well child should prompt consideration of targeted Ring Chromosome 20 testing by karyotype analysis. Ring Chromosome 20 might be missed on microarray and whole genome/exome sequencing platforms.
2. **Angelman Syndrome**
   Early developmental impairment, ataxia, stereotypical behaviours and a tendency to sudden and un-provoked laughter or excitability should raise suspicion of this condition. DNA methylation studies should be considered as this condition can be missed on microarray or even whole genome sequencing analysis.
3. **Rett syndrome**
   Epilepsy develops in at least 90% of children (predominantly girls) with this syndrome. The prevalence of NCSE is unknown but electrical status of slow wave sleep (ESESS) is probably more common than has been appreciated. Although the ILAE classification of NCSE does not include ESESS, this may be entirely inappropriate. Although is cannot be regarded as a phenomenon that requires early management (as in NCSE), ESESS may have a detrimental effect on the child's level of alertness and even motor function [Nissenkorn, 2010].

NCSE may occur due to acquired brain injury resulting from a number of causes, such as:

1. Hypoxic brain injury following a cardiac arrest or near-drowning
2. Metabolic and toxic encephalopathies (such as hypoglycaemia)
3. Traumatic brain injury (usually severe)
4. Autoimmune encephalitis (such as NMDA receptor or MOG-antibody associated encephalitis)
5. Infectious encephalitis, typically herpes simplex encephalitis

A detailed search for the underlying cause of NCSE is important, and particularly if there is no obvious cause. This is because an underlying cause (such as hypoglycaemia or a genetically-determined metabolic disorder such as GLUT1 deficiency) might be readily

amenable to treatment and may improve the short- and long-term outcome.

Epidemiology of NCSE

Studies on the epidemiology for NCSE have limitations because of the different definitions of NCSE. There is also acknowledgement that NCSE may be under-represented due to under- recognition of the condition and out-patient management of patients may fail to capture patients in epidemiological studies [Walker et al, 2005]. Consequently, most reported data are likely to be selected, and particularly from adult patients on intensive care units.

In one region of Japan, retrospective data collected over two years (2003-2005) identified 14 cases of NCSE amongst 120 children (aged between one month and just under fifteen years) with a first episode of status epilepticus. The calculated annual incidence for NCSE for this cohort was 4.9/100,000 population. No deaths were reported from NCSE [Nishiyama et al, 2011].

However, the population studied may impact on the epidemiological figures with higher incidences reported in unwell children in an intensive care setting. A multicentre retrospective study from paediatric intensive care units (PICU) throughout the US investigated 98 children (aged one month to under 21 years but with only three patients aged over 18 years). All had presented with convulsive status epilepticus (CSE) and had continuous EEG monitoring performed. The results showed that 15% (15/98) had electrographic status epilepticus [Sánchez Fernández et al, 2014]. A prospective study from one PICU in Philadelphia (USA), showed that 19/100 critically ill paediatric patients with an acute encephalopathy who underwent continuous EEG had non-convulsive status [Abend et al, 2011].

Prognosis

In a prospective observation study looking at children treated for acute encephalopathy in one PICU in Philadelphia (USA) over a 2.5-year period, 21.5% (43/200) of children had electrical status epilepticus which was associated with increased odds of mortality (5.1) and worse scores on the Paediatric Cerebral Performance Scale at discharge [Topjian et al, 2013]. Long-term prospective data (with a mean follow up of 2.7 years) from the same group looking at children in one PICU setting showed that 14 children diagnosed as having electrical status epilepticus had a worse Glasgow Outcome Scale category, lower quality of life (measured on the Paediatric Quality of Life inventory score) and higher risk of developing epilepsy than children who had electrical seizures only [Wagenman et al, 2014] .

Prospective data from Toronto, Canada, that assessed 259 children who were admitted to PICU and had continuous EEG monitoring, showed that a seizure burden over 12 minutes per hour was associated with a greater neurological decline as measured on the Paediatric Cerebral Performance Category score [Payne et al, 2014]. This correlates closely with NCSE EEG diagnosis criteria established by the American Clinical Neurophysiology Society which used at least 20% seizure burden in a 60-minute period of recording as being associated with a poorer outcome [Hirsch et al, 2021].

Management

There are no consensus guidelines for the management of NCSE in children. This reflects the absence of any reliable data on its epidemiology, as well as the variation in its definition.

In adults, the 2010 European Federation of Neurological Societies guidelines suggested that adult NCSE (which was also defined as subtle SE) should be treated like CSE [Meierkord et al, 2010]. However, the very limited studies of the management of NCSE precludes the absence of clear guidelines. An updated treatment pathway has recently been suggested for adult patients [Bravo et al, 2021].

The ILAE guidelines [Trinka et al, 2015] suggest that absence status epilepticus should be treated at 10-15 minutes from seizure onset, as this is felt to be the timepoint when the seizure will be prolonged if not treated (t1). However, the guidelines acknowledge that the evidence for this timeframe is limited (and therefore arbitrary) and that the time for the seizure to cause any irreversible long-term consequences (t2) is unknown. There is no guidance on what timepoint treatment should commence for other types of NCSE.

Another question in the management of NCSE is how aggressive any treatment should be. A study by Ruijter et al [2022] of adult patients with NCSE following a cardiac arrest found that the prognosis was no different if they received a step-wise and ASM approach to seizure management (with phenytoin, sodium valproate or levetiracetam, in any order) or no ASM.

Furthermore, when interpreting reported studies, it is important to remember that most are derived from case series meaning that the age of the patient, the aetiology of the NCSE, the type of NCSE and how treatment is delivered varies considerably. Multiple drugs are often used in the treatment, making it difficult to understand which medication (if any) or combination of medications was most effective. Publications have generally combined populations of both adults and children, underlying aetiologies and even those with CSE as well as NCSE. Clearly, this precludes any meaningful comment and certainly conclusion as to the most effective treatment of NCSE.

Adult NCSE management pathway

A recent NCSE management pathway for adults has been

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suggested and categorises treatment choices into Tiers based on efficiency and tolerability [Bravo et al, 2021]. The first choice in NCSE is the use of any of the six commonly-used intravenous (IV) medications: a benzodiazepine, levetiracetam, sodium valproate, fosphenytoin, lacosamide or brivaracetam (Tier I). Phenobarbital is in Tier II. These drugs are also used if NCSE is found on the EEG [Leitinger et al, 2023] (it may be relevant that is a common author to both publications). If there is no improvement with the first medication, this should be replaced 'rapidly' with another Tier I option [Bravo et al, 2021] before then considering phenobarbital.

If coma or stupor persists together with a high seizure frequency, management is escalated to an IV anaesthetic medication with midazolam or propofol (Tier I medication) or ketamine or phenobarbital (Tier II medications) (Bravo et al., 2021). Enteral or IV ASM (e.g. phenytoin, fosphenytoin, sodium valproate etc.) should continue alongside any anaesthetic agent (Bravo et al., 2021).

However, if coma or stupor resolves and the seizure frequency lessens, it is recommended that an enteral ASM also be given: these are perampanel or pregabalin (Tier I), clobazam or topiramate (Tier II), oxcarbazepine, carbamazepine, clonazepam or vigabatrin (Tier III) [Bravo et al, 2021].

It is again important to emphasise that the evidence underpinning the above recommendations is very limited. It is equally important to emphasise that an increasingly aggressive approach to the management of what seems to be refractive NCSE carries a correspondingly increased risk (and actual incidence) of significant adverse side-effects.

Implications for paediatric NCSE management

It is unclear if this adult pathway can be extrapolated in treating paediatric patients, but most guidelines highlight the role of benzodiazepines, levetiracetam, sodium valproate, phenytoin and phenobarbital and these are medications that are commonly used in the management of seizures, including CSE and NCSE in children. However, adopting a more aggressive approach with IV anaesthetic drugs may not always be appropriate and particularly in young children. Drugs such as thiopentone and ketamine may cause severe metabolic acidosis and multi-organ failure, with a significant risk of death, and would have to be used with great caution. The initial approach as to the level of treatment must be on a case-by-case basis and take account of the child's age, underlying cause of the NCSE and the realistic goals of treatment. Aggressive treatment to quickly resolve NCSE needs to be carefully balanced against the side effects caused by often multiple ASMs and/or the need for IV anaesthetic drugs. This demands close discussion between the paediatrician, paediatric neurologist and paediatric intensivist. It is important to acknowledge that there is a lack of robust evidence to suggest that aggressive treatment improves the longer-term neurodevelopment outcome of children with NCSE.

For specific acquired aetiologies the emphasis should be to treat the underlying cause of the NCSE; a specific example is the aggressive immunomodulation in autoimmune encephalitis as well as the use of appropriate ASMs.

In children with Developmental and Epileptic Encephalopathies (DEE), pragmatic outpatient-based management should be considered particularly if a child's hydration and nutrition can be adequately provided at home and where the child has a background of a pattern of recurrent episodes of NCSE, as in children with Dravet syndrome and Lennox-Gastaut syndrome.

Drugs used in Paediatric NCSE

Benzodiazepines

The role of benzodiazepines as the first-line treatment of convulsive status epilepticus is established in emergency seizure pathways including in the Advanced Paediatric Life Support (APLS) guidelines used in the UK. The European Federation of Neurological Society guidelines for adults would suggest benzodiazepines are the first-line management for adults with NCSE (or subtle SE) [Meierkord et al, 2010] and a survey of adult neurologists in South Korea showed 97.6% agreement for the use of benzodiazepine as first-line treatment and 66.7% agreement for further dose as second-line treatment for NCSE treatment [Byun et al, 2020].

Data in six paediatric patients shows that a variety of benzodiazepines (diazepam, clonazepam, clobazam) can be utilised in NCSE and the effect even within benzodiazepines can vary depending on the patient and the NCSE subtype [Manning and Rosenbloom, 1987]. Clearly, this was a very small study and midazolam has now replaced clonazepam but it broadly reflects what is seen in current clinical practice.

However, it is recognised that benzodiazepines may not stop NCSE [Livingston and Brown, 1987] which is why there is interest in other types of ASM. Similarly, more recent data for 31 paediatric patients with focal NCSE showed 15 patients did not respond to benzodiazepines, demonstrating that other treatment options will be necessary [Maltoni et al, 2021].

The use of short courses of benzodiazepines in specific syndromes (myoclonic atonic seizures, Lennox-Gastaut Syndrome, Angelman syndrome and Ring Chromosome 20) will be discussed in detail below.

Levetiracetam

Levetiracetam was used in 8/17 (47%) of cases of paediatric NCSE as second-line treatment after benzodiazepine in a retrospective observational study of patients treated in an emergency department in Melbourne, Australia [Pfeiffer et al, 2022]. However, specific data relating to seizure outcome with levetiracetam is not available in the publication.

Outcome data with the use of levetiracetam in NCSE is limited within the literature but data for five patients with NCSE treated in a PICU in Philadelphia (USA) showed that two of the five had NCSE termination with IV levetiracetam and the remaining three had a temporary termination but the doses used were lower at 6.5-31mg/kg [Abend et al, 2009] than loading doses commonly used in UK paediatric practice (typically 40mg/kg of levetiracetam).

Sodium Valproate

Uberall et al, [2000] showed that IV sodium valproate had an 80% success rate (4/5 children) in seizure cessation in absence status after benzodiazepine, phenytoin and phenobarbitone had failed. Aldenkamp et al, [2006] emphasised that sodium valproate is used in clinical practice as it seems to be effective in treating NCSE; this was reflected in an expert opinion in 2005 which showed that sodium valproate was effective in treating in absence SE in children [Wheless et al, 2005]. Mitchell [1996] also reported that the rapid initiation of enteral (oral) sodium valproate may help with recurrent absence status epilepticus but they gave no patient data.

Phenytoin

Phenytoin was used as second-line treatment for paediatric NCSE after benzodiazepine in 53% of cases (9/17 patients) in a retrospective observational study of Australian patients treated in an emergency department; there were no data on seizure outcome [Pfeiffer et al, 2022]. Data on adult NCSE showed 50% seizure cessation with phenytoin in the TRENdS study, a randomised controlled trial that compared the initial use of lacosamide or fosphenytoin with 37 patients in each arm [Husain et al, 2018]. However, there is a theoretical risk of phenytoin potentially worsening seizure control in a number of electroclinical syndromes such as Dravet syndrome and epilepsy with myoclonic-atonic seizures.

Lacosamide

Two of five children treated with IV lacosamide for NCSE after, on average, 2.8 anti-seizure medications, achieved NCSE termination [Grosso et al, 2014]. In the TRENdS study, lacosamide demonstrated seizure cessation in 63.3% of patients compared with 50% seizure cessation with fosphenytoin [Husain et al, 2018].

Brivaracetam

Data for brivaracetam use in adults is very limited and there are no(?) data in children. Retrospective multicentre registry data from Spain, which included 19 adult patients with NCSE, showed a response rate similar to CSE while the combined response rate (for both CSE and NCSE) was 53% [Santamarina et al, 2019].

Phenobarbital

Phenobarbital has been used to treat atypical absence SE for decades [Cascino, 1993] but there does not seem to be any published data on its effectiveness in NCSE. Adult data from a retrospective, multicentre study from Germany showed that in 17 of 31 patients with super-refractory status epilepticus secondary to NCSE with coma, seizure termination was achieved with phenobarbital. For focal NCSE leading to super-refractory CSE, seizure termination occurred in 10 of 20 patients [Kunst et al, 2023].

Midazolam infusions

Continuous midazolam infusions were used in five children [Koul et al, 1997]. Fatema et al reported that one of 18 children with NCSE had complete remission during EEG monitoring with midazolam bolus followed by infusion; another six showed an 80% response and five showed a 50-80% response during EEG monitoring [Fatema et al, 2018]. The authors did not give any definition of what constituted a clinical response.

Ketamine

A case series of five patients treated with enteral ketamine showed resolution clinically and on EEG; three patients had ketamine as first-line treatment and two patients had received prior treatments. One patient had a relapse of NCSE but again responded to ketamine [Mewasingh et al, 2003].

A recent systematic review of super refractory status epilepticus (both CSE and NCSE) in adults and children and which included 197 patients with NCSE showed that seizure resolution was 53-91% in one large case series and 40-100% in a small case series with the use of either enteral or IV ketamine [Adhikari et al, 2024].

Perampanel

Adult data from a retrospective observational study from a neurological ICU in Taiwan showed that perampanel led to clinical and EEG resolution of NCSE within 72 hours in 47% (eight of 17 patients); seven of 16 responded with NCSE without coma and a single patients responded with NCSE with coma. Patients had received a median of three ASMs prior to the use of perampanel [Lim et al, 2021].

Pregabalin

In a retrospective study, two of 10 adult patients had seizure cessation with oral or nasogastric administered pregabalin given as either a second- or fourth-line treatment [Swisher et al, 2013].

Topiramate

Topiramate was used as first-line treatment in paediatric NCSE in Belgium [Aldenkamp et al, 2006] but the data on

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effectiveness is not available. In 106 adult patients with refractory and super refractory SE, including 17 with NCSE, 27% showed seizure cessation, although the authors did not specify how many patients with NCSE improved [Fechner et al, 2019].

Carbamazepine and oxcarbazepine

There are no clear data for the use of carbamazepine and oxcarbazepine in children. The third-line use of enteral oxcarbazepine in 10 adult patients (which also included three with CSE) reported that 79% showed resolution of NCSE or CSE (or both) [Kellinghaus et al, 2014]. It must be noted that carbamazepine can often induce NCSE and particularly absence NCSE in the genetic epilepsies, juvenile absence and juvenile myoclonic epilepsy.

Vigabatrin

Despite being listed as a Tier III antiseizure medication to be used as maintenance therapy for NCSE [Bravo et al, 2021], there seems to be no data to support this recommendation.

Steroids

Steroids are available in various forms including: ACTH (or its synthetic equivalent, tetracosactide), prednisolone and methylprednisolone, dexamethasone and ganaxolone.

ACTH was used in three children with atypical absences, who had clinical remission and EEG improvement, but relapses occurred with withdrawal and repeated courses were needed [Manning and Rosenbloom, 1987]. Fatema et al showed that two of 13 children with NCSE had seizure resolution on EEG following a five-day course of IV methylprednisolone in a dose of 30mg/kg. Four patients showed an 80% remission and another four a 50-80% remission based only on the EEG. Clinical seizure data were not reported [Fatema et al, 2018].

Ganaxalone is a relatively new neuroactive steroid which has been investigated as a treatment for epilepsy, particularly in epilepsy with the CDKL5 mutation. In a phase 2 trial investigating the use of an IV ganaxalone bolus followed by an infusion, 11 adult patients who had failed a median of three ASMs (including benzodiazepine, levetiracetam or lacosamide) were included. Seizure cessation occurred in a median time period of five minutes with 94% of patients (which also included six patients with CSE) and which lasted for 24 hours. No patients required escalation of treatment to general anaesthesia within 24hrs of starting ganaxalone, which was the study's primary outcome [Vaitkevicius et al, 2022].

Ketogenic diet

Case reports of two children treated with a modified Atkins diet showed cessation of NCSE after five and 10 days respectively [Kumada et al, 2010]. The international guideline on ketogenic diet highlights its potential use in super-refractory CSE [Kossoff et al, 2018]. Its early initiation has been suggested as a treatment option for new onset refractory status epilepticus (NORSE) and also febrile infection-related epilepsy syndrome (FIRES) [Wickstrom et al, 2022].

Management of NCSE in specific conditions

Dravet Syndrome:

The international consensus guidelines for Dravet syndrome indicate that nonconvulsive (obtundation) status epilepticus is seen in 10-49% of cases and when these occur, the child's medication should be reviewed [Wirrell et al, 2022]. There is a case report of fenfluramine use in nonconvulsive status in Dravet syndrome in one patient [Specchio et al, 2020].

Epilepsy with myoclonic atonic seizures (EMAtS) (previously known as Doose syndrome):

The international Delphi consensus guideline for myoclonic atonic seizures states that approximately 50% of patients will develop NCSE in the first year. There was a strong consensus for the use of the ketogenic diet, sodium valproate or benzodiazepine (clonazepam) which could be used in combination if required. There was moderate consensus for the role of steroids (usually enteral prednisolone or occasionally IV) [Joshi et al, 2021]. An epilepsy consensus guideline from Egypt places steroids as first-line treatment for NCSE [Kishk et al, 2024].

Lennox-Gastaut Syndrome:

NCSE, specifically atypical absence NCSE, occurs in 50-75% of patients with LGS. These are often punctuated by brief tonic seizures [Riva et al, 2022]. Expert opinion recommends the use of either a three to five day course of clobazam, a short course of steroids or high dose IV sodium valproate with the objective of restoring the EEG to a baseline pattern [Cross et al, 2017].

Angelman syndrome:

Around 20% of patients with Angelman syndrome develop NCSE and one recommended first-line treatment is a short course of diazepam (taken two or three times a day) and a second-line treatment of steroids [Duis et al, 2022]. In one study, 80% of patients responded to outpatient oral diazepam [Worden et al, 2018]. Adjunct therapies include clobazam, ethosuximide, lamotrigine and topiramate, but if NCSE is not controlled, IV methylprednisolone, levetiracetam, lacosamide, sodium valproate or acetazolamide may be used [Duis et al, 2022]. It was suggested that phenytoin and phenobarbitone should be avoided [Duis et al, 2022].

Ring chromosome 20

Frequent episodes of NCSE are a common feature in ring chromosome 20 but its management is less clear, in part because of its rarity. Sodium valproate and lamotrigine tend to be the preferred treatments but options could be lacosamide, zonisamide, the ketogenic diet and possibly

vagus nerve stimulation (VNS) [Peron et al, 2020]. There is a single case report of IV methylprednisolone being very effective [Kishore et al, 2022].

Personalised plans

Emergency seizure plans should be in place for all patients with epilepsy. For relevant patients, this should also include a personalised plan to treat CSE and also NCSE. This is a specific recommendation in the recently-revised National Institute for Health and Care Excellence (NICE) 2022 epilepsy guideline.

Future Studies

The FAST-trial (NCT05263674) is a randomised open label multicentre trial which is enrolling adults with NCSE to investigate its management and specifically if sedation in ITU or high-dose ASM is the better option (University of Southern Denmark, 2023). Its results may have implications for children, particularly those aged 12 years and above.

Conclusion

We have outlined the diagnosis, classification, aetiology and treatment of NCSE in clinical practice. However, it is important to emphasise that the evidence base for its management and particularly the choice and use of ASMs is very limited and has often been extrapolated from adult data, which itself are also limited. Some of this extrapolation may be appropriate for older children (aged 12 years and above) because the pharmacokinetic and pharmacodynamic processes are similar to most adults. However, the extrapolations may not be appropriate for younger children and particularly those under five years of age. In view of the limited evidence-base, management of NCSE in children should be on a case-by-case basis, with consideration of the cause and the epilepsy syndrome, the clinical impact and risk-benefit balance of any treatment. It also mandates early discussion of the child with a specialist in paediatric epilepsy based in a tertiary care centre whenever there is the possibility of a child being in NCSE; it may also require transfer of the child to a PICU in a tertiary epilepsy centre for optimal management.

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Recently published papers

This section highlights recently published papers. There are many (often more than 300) epilepsy papers published every three months, so what follows has been edited. All animal papers have been excluded.

We hope you find the papers of interest in your pursuit to keep abreast of the very latest knowledge.

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