

Nonconvulsive status epilepticus: Epilepsy Research Foundation Workshop Reports

Matthew Walker, Helen Cross, Shelagh Smith,
Camilla Young, Jean Aicardi, Richard Appleton, Sarah Aylett,
Frank Besag, Hannah Cock, Robert DeLorenzo,
Franck Drislane, John Duncan, Colin Ferrie,
Denson Fujikawa, William Gray, Peter Kaplan,
Micheal Koutroumanidis, Mary O'Regan, Perrine Plouin,
Josemir Sander, Rod Scott, Simon Shorvon, David Treiman,
Claude Wasterlain, Udo Wieshmann

Epilepsy Research Foundation, London, United Kingdom

ABSTRACT – In April 2004, a group of physicians with an interest in nonconvulsive status epilepticus representing a spectrum of opinion met in Oxford, sponsored by the Epilepsy Research Foundation (a charitable organization), to discuss and debate the definition, diagnosis and treatment of nonconvulsive status epilepticus. We felt that such a meeting would be useful, as nonconvulsive status epilepticus is a subject that provokes strong reactions, perhaps largely due to the relative lack of evidence and the surfeit of opinion. The meeting was arranged such that there were formal talks followed by a discussion led by one of the attendees. We present here the extended abstracts of the main talks with the points raised by the discussants.

Despite disagreements on certain issues there was much in the way of consensus. First, it was agreed that nonconvulsive status epilepticus is a term that covers a range of disparate conditions with varying prognoses and treatments. The agreed definition was thus suitably vague, «Nonconvulsive status epilepticus is a term used to denote a range of conditions in which electrographic seizure activity is prolonged and results in nonconvulsive clinical symptoms». Secondly, it was agreed that even within a specific condition (e.g. complex partial status epilepticus), the prognosis and treatment depends upon the context in which the condition occurs (e.g. in the critically ill, in coma, in the «walking wounded» and in people with prior epilepsy). Perhaps, most importantly it was agreed that we lacked good clinical data, and the challenge was to design good studies for a condition that is underrecognised and often difficult to diagnose.

Key words: nonconvulsive status epilepticus, status epilepticus, absence status, complex partial status, ring chromosome 20, Angelman syndrome

Correspondence:

D^r M. Walker
Epilepsy Research Foundation,
PO Box 3004,
London, W4 4XT
United Kingdom
Fax: (+ 00 44) 20 8995 4781
<info@erf.org.uk>

Contents

The definition, classification and frequency of NCSE	255
Simon Shorvon	
Diagnosis of NCSE in children	259
Mary O'Regan, Helen Cross	
Pitfalls of EEG interpretation of repetitive discharges	261
Peter Kaplan	
Prognosis of NCSE	265
Denson Fujikawa	
Experimental evidence of status-induced brain damage	267
Hannah Cock	
Can we extrapolate the animal data to humans – the influence of epilepsy, drugs and age?	270
Claude Wasterlain	
Neuroimaging of NCSE	273
John Duncan	
What is the evidence for treatment regimens in NCSE ?	277
Rod Scott	
Typical absence status epilepticus	279
Micheal Koutroumanidis	
Complex partial status epilepticus	282
David Treiman	
Status epilepticus in coma	284
Robert DeLorenzo	
NCSE in specific childhood epilepsy syndromes	289
<ul style="list-style-type: none"> • NCSE in Angelman syndrome Jean Aicardi • NCSE and Ring chromosome 20 syndrome Perrine Plouin, Mary O'Regan • NCSE in the benign focal epilepsies of childhood with particular reference to autonomic status epilepticus in Panayiotopoulos syndrome Colin Ferrie • NCSE in children with learning difficulties Frank Besag 	
NCSE in the elderly	295
Franck Drislane	

The definition, classification and frequency of NCSE

Simon Shorvon

Department of Clinical Neurology, Institute of Neurology, The National Hospital for Neurology and Neurosurgery, Queen Square, London, WC1N 3BG, UK

The definition of NCSE

For many purposes and for epidemiology, it is important to have a definition of nonconvulsive status epilepticus (NCSE). The question of definition was extensively discussed by the delegates at the ERF Workshop on Nonconvulsive Status in Oxford in March 2004. The definition proposed here is:

«Nonconvulsive status epilepticus is a term used to denote a range of conditions in which electrographic seizure activity is prolonged and results in nonconvulsive clinical symptoms.»

The clinical features are variable as are the pathophysiological, anatomical and aetiological bases. The clinical patterns vary with context (for instance, in coma, sleep, cerebral damage, epileptic encephalopathy). Boundary conditions also occur where it is not clear to what extent «electrographic activity» is resulting in the symptoms observed or is simply the result of underlying cerebral damage/dysfunction. For operational purposes in epidemiological studies, it is reasonable to specify a minimum time limit for defining «prolonged electrographic activity», and usually this is 30 minutes, but it should be recognised that this time limit is arbitrary.

The electrographic seizure activity can take several forms, some of which clearly denote NCSE (clear-cut criteria) and some of which are less easy to interpret and probably denote NCSE only in some cases (equivocal criteria). The clear-cut criteria include:

- (a) Frequent or continuous focal electrographic seizures, with ictal patterns that wax and wane with change in amplitude, frequency and/or spatial distribution.
- (b) Frequent or continuous generalised spike wave discharges in patients without a prior history of epileptic encephalopathy or epilepsy syndrome.
- (c) Frequent or continuous generalised spike wave discharges, which show significant changes in intensity or frequency (usually a faster frequency) when compared to baseline EEG, in patients with an epileptic encephalopathy/syndrome.
- (d) PLEDs (periodic lateralised epileptiform discharges) or biPEDs (bilateral periodic epileptiform discharges) occurring in patients in coma in the aftermath of a generalised tonic clonic SE (subtle SE).

EEG patterns which are less easy to interpret include:

(e) Frequent or continuous EEG abnormalities (spikes, sharp waves, rhythmic slow activity, PLEDs, BiPEDs, GPEDs, triphasic waves) in patients whose EEG showed no previous similar abnormalities, in the context of acute cerebral damage (e.g. anoxic brain damage, infection, trauma).

(f) Frequent or continuous generalised EEG abnormalities in patients with epileptic encephalopathies in whom similar interictal EEG patterns are seen, but in whom clinical symptoms are suggestive of NCSE.

Categories (c) and (f) reflect the problem of deciding the significance of spike wave discharges in the setting of epileptic encephalopathy (e.g. Lennox Gastaut syndrome) in which the ictal and interictal EEG patterns may be very similar. The differentiation of the two is problematic. Category (e) reflects the difficulty of differentiating ongoing epileptic discharges from abnormalities, which signify severely disturbed brain function in patients in coma following acute cerebral injury.

The classification of NCSE

The classification of NCSE is best subdivided by age, and further subdivided into the forms of NCSE seen in the epileptic encephalopathies, acute brain injury, and those with a prior history of epilepsy (without encephalopathy). A classification is shown in *table 1*.

Boundary syndromes are also included where it is unclear to what extent the clinical symptoms are due to NCSE or to underlying cerebral damage/dysfunction.

Recent epidemiologically-based studies of the frequency of NCSE

There are five, recent epidemiological studies of status epilepticus that provide some estimates of the population frequency (Coeytaux *et al.* 2000, De Lorenzo *et al.* 1995, Hersedorffer *et al.* 1998, Knake *et al.* 2001, Vignatelli *et al.* 2003). These are summarised in *tables 2-3*. The studies probably underestimate the true frequency of NCSE, for a number of reasons:

- (a) All the studies were hospital based, and thus cases of NCSE that did not reach hospital are not included. These include those with self-limiting NCSE, those with mild NCSE, those not seeking medical attention and those who were treated in the community. There are potentially many such cases – especially of complex and simple partial NCSE, of NCSE in epileptic encephalopathies/syndromes. The cases of NCSE in acute brain injury on the other hand are likely to be well ascertained.
- (b) Patients with post-anoxic encephalopathy were included in the Richmond, Rochester and Bologna studies but excluded from the Swiss study. The study from

Table 1. Classification scheme for NCSE.**NCSE in the neonatal period and infancy**

- Neonatal NCSE
- NCSE in neonatal and infantile epilepsy syndromes
 - West Syndrome
 - Ohtahara syndrome
 - Severe myoclonic encephalopathies of infancy
 - Benign neonatal seizures (and benign familial neonatal seizures)
 - NCSE in other early neonatal and infantile epilepsies

NCSE in childhood

- NCSE in benign focal childhood epilepsy syndromes
- NCSE (often specific forms) in severe childhood epileptic encephalopathies/syndromes
 - Electrical status epilepticus in sleep (ESES)
 - Landau Kleffner Syndrome
 - NCSE in Dravet's syndrome
 - NCSE in Ring Chromosome X
 - NCSE in myoclonic syndromes of childhood
 - NCSE in Angelman's syndrome
 - Severe myoclonic encephalopathies of childhood
 - Myoclonic-astatic epilepsy

NCSE in childhood and adult life

- NCSE in the severe epileptic encephalopathies/syndromes (atypical absence and other forms of NCSE)
 - Lennox Gastaut syndrome
 - Other childhood epileptic encephalopathies
- NCSE in acute cerebral injury
 - Acute confusional states (including acute symptomatic partial SE)
 - NCSE in coma (including myoclonic status epilepticus in coma)
- NCSE in patients with epilepsy but without encephalopathy
 - Simple partial NCSE
 - EPC and non-motor forms of simple partial NCSE
 - Complex partial status epilepticus
 - Absence status epilepticus in idiopathic generalised epilepsies
 - Panyotopoulos syndrome, EMA, JME
 - Myoclonic status epilepticus in idiopathic generalised epilepsy
 - NCSE in the postictal phase of tonic clonic seizures
 - NCSE inpatients without epileptic encephalopathy/acute cerebral injury, which take the form of cognitive impairment or confusion, and which do not conform to the categories of simple or complex partial SE

Status epilepticus confined to adult life

- *De novo* absence status epilepticus of late onset

Boundary syndromes

- Cases with epileptic encephalopathy in whom it is not clear to what extent electrographic seizure activity is contributing to the clinical impairment
- Cases with acute brain injury in whom it is not clear to what extent electrographic seizure activity is contributing to the clinical impairment
- Cases with behavioural disturbances/psychosis in whom it is not clear to what extent electrographic seizure activity is contributing the clinical impairment

Hessen does not state whether or not these patients were included. The importance of this in terms of estimating incidence is indicated by the fact that 10% of all ascertained cases in the Rochester study fell into this category.

(c) In many clinical situations, NCSE requires EEG for diagnostic confirmation, and if EEG is not available, case ascertainment will be incomplete.

(d) Patients in whom the duration of the status epilepticus was not recorded would have been excluded. In addition, some cases of convulsive SE evolve into NCSE and may not be classified as such.

(e) Patients treated in the A&E departments and not admitted will be excluded from those studies based on hospital admission data only.

(f) Patients whose seizures were terminated by acute therapy within 30 minutes but which, in the untreated state, would have endured.

The variation in rates, depending on the presence or absence of tertiary neurological centres, in the Swiss and the German studies emphasises the potential for ascertainment bias in hospital series. Finally, the exclusion of children in the Hessen and Bologna studies and of neonates in the Richmond study will also result in underesti-

Table 2. Five population-based studies of status epilepticus (convulsive and nonconvulsive)

	Richmond Virginia USA (De Lorenzo <i>et al.</i> 1995)	Rochester, Minn, USA (Hesdorffer <i>et al.</i> 1998)	French-speaking Switzerland (Coeytaux <i>et al.</i> 2000)	Hessen, Germany (Knake <i>et al.</i> 2001)	Bologna, Italy (Vignatelli <i>et al.</i> 2003)
<i>Year</i>	1989-1991	1965-1984	1997-1998	1997-1999	1999-2000
<i>Population (denominator)</i>	202,774	1,090,055 ⁺	1,735,420	743,285	336,876
<i>Number of cases</i>	166	199	172	150	44
<i>Incidence of SE (per 100,000 per year)</i>	41 (raw)	18.3 (adjusted)	9.9 (raw)	17.1	10.7
	61 (adjusted)		10.3 (adjusted)		
<i>Female: male ratio of cases</i>	1: 1.2*	1: 1.9**	1: 1.7***	1: 1.9***	1: 0.84**
<i>History of prior epilepsy</i>	42%	44%	32.8%	50%	39%
<i>Exclusions</i>	Patients one month of age or less	-	Patients with post-anoxic encephalopathy	Patients under the age of 18 years	Patients under the age of 20 years

+ = Patient years

* = Raw data

** = Adjusted ratio

*** = Adjusted figures, from the regions with the best case ascertainment (and least likely to selection bias)

mation of cases, as NCSE is common in children and neonates.

Estimates of frequency based on a literature review and secondary sources

Indirect estimates can also be made from secondary sources and a review of published case material, and this has been attempted by Shorvon and Walker (Shorvon and Walker 2004). The indirect estimates are based on extrapolation from such non-epidemiologically-based data, but avoid the underascertainment discussed above (in

table 3, a comparison is made with figures from the epidemiological studies).

(i) The following forms of SE are rare (frequency less than 1 per 100,000 persons per year)

- Neonatal SE and NCSE in neonatal epilepsy syndromes
- NCSE in benign focal childhood epilepsy syndromes
- NCSE in severe childhood epileptic encephalopathies
- Simple partial NCSE
- NCSE in absence epilepsy
- Myoclonic SE in idiopathic generalised epilepsy

Table 3. Seizure type and epilepsy classification in five population-based studies

	Richmond Virginia USA (De Lorenzo <i>et al.</i> 1995)	Rochester, Minn, USA (Hesdorffer <i>et al.</i> 1998)	French speaking Switzerland (Coeytaux <i>et al.</i> 2000)	Hessen, Germany (Knake <i>et al.</i> 2001)	Bologna, Italy (Vignatelli <i>et al.</i> 2003)
Seizure type:					
<i>Simple partial</i>	23%	39%	18.1%	13.3%	9%
<i>Complex partial</i>	3%		26.7%	43.3%	16%
<i>Tonic clonic</i>	70%	48%	33.1%	33.3%	50%
<i>Absence</i>	1%	3.5%	3.5%	6.0%	2%
<i>Myoclonic</i>	1%	9.5%			26%
<i>Other</i>	1% *		18.8%**		
<i>Not specified</i>				4.0%	7%
Epilepsy type:					
<i>Acute symptomatic</i>		50.3%	62.7%		34%
<i>Remote symptomatic</i>		19.6%	28.4%		34%
<i>Idiopathic</i>		13.6%			7%
<i>Other</i>		16.6%****			25%***
<i>Unknown</i>			8.7%		

* = electrographic

** = hemiconvulsive 8.1%, subtle status 1.2%, tonic 2.3%, clonic 0.6%, others 6.4%

*** = unprovoked progressive symptomatic 11% and multifactorial 14%

**** = Progressive symptomatic 8.5%, febrile status epilepticus 8.0%

Table 4. Frequency of certain types of NCSE: comparison of literature estimates and figures from the 5 epidemiological studies

Type of NCSE	5 epidemiological studies (cases/100,00/year)	Literature estimates (cases/100,000/year)
<i>Simple partial SE</i>	1.1-14.1	1
<i>Complex partial SE</i>	1.1-14.1	15-45
<i>Absence SE</i>	0.2-1.2	0.2-0.5
<i>Myoclonic SE</i>	0.2-1.2	0.2-1.2

(Figures from the epidemiological studies extrapolated with age adjustment)

– Other forms of NCSE in patients with epileptic encephalopathy

– *De novo* absence status epilepticus of late onset

Amalgamating all these forms, the frequency can be estimated to lie between 1-10 cases/100,000/year.

(ii) Complex partial status epilepticus is probably seriously underestimated in the epidemiological studies, as many cases are self-limiting or treated in the community and do not reach hospital. On the basis of literature estimates, the real frequency has been estimated to be between 15-45 cases/100,000/year.

(iii) NCSE in acute cerebral injury. The epidemiological studies are likely to have accurate ascertainment rates in relation to this form of NCSE, and data from these studies suggest a frequency of between 6-10 cases/100,000/year.

(iv) NCSE in the static epileptic encephalopathies of childhood and adult life (e.g. Lennox Gastaut syndrome) are also likely to be seriously underestimated in the epidemiological studies, as many cases are self-limiting or treated in the community and do not reach hospital. On the basis of literature estimates, the real frequency has been estimated to be between 10-20 cases/100,000/year.

(v) The frequency of the boundary syndromes is unknown, but these may also be relatively frequent.

The overall population incidence of NSCE in the published direct epidemiological studies can be estimated to lie between 5.6-18.3/100,000/year (without age adjustment, as the published data do not provide enough information). From secondary sources, an indirect estimate can be calculated of 32-85/100,000/year; and the difference between the direct and indirect estimates can be taken to reflect the underascertainment inherent in the epidemiologically-based studies.

References

- Coeytaux A, Jallon P, Galobardes B, *et al.* Incidence of Status Epilepticus in French-speaking Switzerland (EPISTAR). *Neurology* 2000;55, 693-7.
- DeLorenzo RJ, Pellock JM, Towne AR, *et al.* Epidemiology of status epilepticus. *J Clin Neurophysiol* 1995; 12(4) 316-25.
- Hesdorffer DC, Loroscino G, Cascina G, *et al.* Incidence of Status Epilepticus in Rochester, Minnesota 1965-1984. *Neurology* 1998; 50, 735-41.
- Knake S, Rosenow F, Vescovi M, *et al.* for the Status Epilepticus Study Group Hessen (SESGH), Incidence of Status Epilepticus in Adults in Germany: a prospective, Population-Based Study. *Epilepsia* 2001; 42 (6), 714-8.
- Shorvon SD and Walker MC. Status epilepticus: its clinical features and treatment in children and adults (2nd Edition). *Cambridge University Press* 2004 (in preparation).
- Vignatelli L, Tonon C, D'Alessandro, R. On behalf of the Bologna Group for the Study of Status Epilepticus Incidence and Short-term Prognosis of Status Epilepticus in Adults in Bologna, Italy. *Epilepsia* 2003; 44, 964-8.

Discussion by Ley Sander

The National Society for Epilepsy,
Chesham Lane, Chalfont St Peter, Bucks, SL9 0RJ, UK

Epidemiology is the study of the dynamics of a medical condition in a population. A *sine qua non* for epidemiology is that data are derived or collected from an unselected population. In addition, accurate diagnosis and case ascertainment methods are a prerequisite if accurate epidemiological data are to be derived. The epidemiology of nonconvulsive status epilepticus is fraught with methodological problems. One issue is that of definition, as different investigators tend to use different definitions. Diagnosis criteria can also be problematic, as these would always involve the use of EEG. Currently, case ascertainment is usually carried out through hospitals, and this in itself can present problems. If we are ever going to arrive at precise data on the incidence of nonconvulsive status epilepticus the above methodological problems have to be resolved. Simon Shorvon has provided us with a definition for nonconvulsive status, which if widely adopted and used in further epidemiological work to define the condition would be a step forward. This definition is quite broad and is open to interpretation, particularly with regard to diagnosis. The diagnosis of nonconvulsive status is heavily dependent on recording electrographic seizure activity, therefore, standardised criteria for recording EEGs are necessary.

Finally, case ascertainment realistically will have to be confined to hospital and clinic environments because of the need for EEG.

Despite all this, even if clear definitions and EEG diagnosis criteria are standardised and applied throughout, it is

unlikely that one will ever arrive at a magic number with regard to the incidence of this condition, in view of heterogeneity of epilepsy. One would however, hope to provide estimations of incidence of the condition in a much smaller range than the ones currently provided, and which Simon Shorvon has so very elegantly reviewed.

Diagnosis of NCSE in children

Mary O'Regan¹, Helen Cross²

¹ Fraser of Allander Neurosciences Unit, Royal Hospital for Sick Children, Yorkhill, Glasgow, G3 8SJ, UK

² Neurosciences Unit, Institute of Child Health, The Wolfson Centre, Mecklenburgh Square, London, WC1N 2AP, UK

The definition of NCSE, if clarified, should aid diagnosis. However, as can be seen in the difficulties in definition, considerable dilemmas arise within the diagnosis of NCSE. Existing definitions suggest a clinically evident change in mental status or behaviour from baseline, associated with seizure activity on EEG. However, we already run into certain difficulty here in view of what may be defined as such in either category. In addition, different clinical perspectives may be seen both from an adult and paediatric point of view. Kaplan has addressed criteria for a definition with regard to change in behaviour (Kaplan 1999), but the key issue is often a change from the baseline state, which may be unclear particularly in individuals with a pre-existent difficulty.

To diagnose nonconvulsive status epilepticus (NCSE), a continuous or virtually continuous dysrhythmia or paroxysmal activity on the EEG is necessary. A continuous, abnormal electrical dysrhythmia may occur on the EEG and be difficult to equate with the clinical state. This is, in part, because we expect a motor component to a seizure, so loss of learning, autistic switch-off, crying, salivating, swallowing or wobbliness often seen in children may not be appreciated as epileptic phenomena. Such electrical status that occurs every time the child goes to sleep is seen in the Landau Kleffner syndrome and some cases of Lennox Gastaut syndrome.

NCSE is not a single disease entity but a pattern of reactions depending on cortical maturation and the clinical situation. These continuous dysrhythmias may be acute or chronic.

Acute continuous dysrhythmias

These complicate acute diseases of the nervous system such as trauma, (birth trauma, accidental and non-accidental head injuries), acute asphyxia episodes, (neonatal asphyxia, cardiac arrest and complications of cardiac surgery, drowning and smothering), meningitis, encephalitis, metabolic upset such as hypocalcaemia or

hypoglycaemia, inborn errors of metabolism (e.g. glycine encephalopathy, hyperammonaemias, mitochondriopathies) and poisoning including bacterial toxins such as those produced by *Shigella*. The dysrhythmia is a consequence of the acute insult and the underlying condition; in addition, the dysrhythmias must be treated. The nonconvulsive status epilepticus does not usually recur once the acute encephalopathy has settled.

NCSE in an acutely ill child may have little in the way of clinical signs or symptoms as he/she may be ventilated and sedated and/or paralysed in an intensive care unit. It may present as an obtunded state with little reaction to any stimulus or as a change in behaviour, with visual hallucination, confusion or a fugue-like state.

Many drugs can cause NCSE; anticonvulsants, in particular carbamazepine, when used in particular epileptic syndromes such as juvenile myoclonic epilepsy, and tiagabine has also been implicated (Perruca *et al.* 1998). Withdrawal of benzodiazepines can also induce NCSE. Other drugs, which can cause NCSE, are the third generation cephalosporins, tacrolimus, ifosfamide, intravenous contrast medium, chloroquin, lithium, baclofen and lithium and this list is not exhaustive.

Chronic continuous dysrhythmias

In paediatric practice, these chronic discontinuous dysrhythmias occur in two broad categories of patients. The first group have a structural brain abnormality, either from a previous brain injury or a malformation of cortical development. The abnormalities may be diffuse or focal. The functional epilepsies comprise the second group and can occur in virtually any epilepsy syndrome. However, it is more common in the malignant epilepsies of childhood; early myoclonic encephalopathy, Ohtahara syndrome, West syndrome, Dravet syndrome, Lennox Gastaut syndrome, myoclonic astatic syndrome, Landau Kleffner syndrome, epilepsy with continuous spike waves during slow sleep and in Ring chromosome 20 epilepsy syndrome. There are different types of NCSE absence status, complex partial status, myoclonic status cognitive status and behavioural status. There is little correlation between the type of dysrhythmia on the EEG and the clinical phenotype.

Clinical features of NCSE in children

NCSE occurring relatively suddenly in a normal or near normal child attending mainstream school is usually fairly obvious, at least as a clinical event even if the correct diagnosis is not made immediately. However, if the child is intellectually disabled, has numerous daily seizures and is on multiple anticonvulsants as in typical Lennox Gastaut syndrome, then subtle alterations in behaviour are more difficult to detect. In this situation, careful clinical observation often can reveal that there has been a change in one of the following categories:

1. *Motor* symptoms may manifest as increasing ataxia, dystonia (Neville *et al.* 1998) dysarthria, constant drool-

ing, a marked delay in motor reaction times, akathisia and in some case as a polymyoclonia with frequent erratic twitching. In some cases, it may present as a motor dyspraxia (Neville and Boyd 1995) with loss of previously learnt skills. In Dravet's syndrome, NCSE may be accompanied by fragmentary and segmental myoclonia and an increase in muscle tone.

2. *Affective*. The child may show loss of non-verbal communication (O'Regan and Brown 1998), social interaction and eye contact (an acquired autistic state), irritability, bad temper or withdrawn.

3. *Arousal* is decreased in an episode with drowsiness, lethargy, sometimes progressing to stupor.

4. *Cognitive*. The child may show a pseudo-dementia, may lose their way in a familiar environment, may put their clothes on back to front, show cessation of learning, loss of speech and language.

5. *Memory*. A combined loss of both short- and long-term memory may occur so that the children may wander not knowing who or where they are, or what they are doing.

6. *Loss of visual function*. This may be a presenting symptom in West Syndrome and the spasms may be minimal.

The child may have more than one of the above clinical features. In one study of children with ESES, the clinical indication for considering the diagnosis were; a cognitive deterioration, behavioural regression, acquired dyspraxia, ataxia, deterioration in communication skills, which included loss of Sign language and regression in developmental milestones. In the children presenting with neuro-behavioural symptoms, these included an acquired autistic state, hyperactivity, loss of inhibitory control, inattentive behaviour attention and memory deficits.

Suggested criteria for the diagnosis of NCSE

From the above discussion, it is obvious that the concept of NCSE is wide and there is no single test that could make the diagnosis unequivocal. Nevertheless, in order to evaluate treatments, prognosticate and make comparisons between studies, some definitions must be arrived at. This ideally must consist of a combination of clinical and EEG features and thus we would suggest the following criteria for the diagnosis of NCSE:

1. Clear and persistent clinical change in behaviour (manifested as changes in cognition, memory, arousal affect, ataxia, motor learning and motor behaviour). The word «clear» in the context of NCSE would imply that an adequate description of behaviour before the onset of NCSE is available for comparison and the time of onset could be defined given that the onset can be gradual and the duration of the NCSE prolonged. «Persistent» is another arbitrary term but we would say that the episode must last at least 30 mins.

2. Confirmation by clinical or neuropsychological examination that a clinical change has occurred.

3. The presence of continuous or virtually continuous paroxysmal episodes on the EEG

4. The absence of continuous major seizures either tonic, clonic, tonic.

It is suggested that all of the above criteria should be fulfilled before a diagnosis of NCSE is accepted. A clinical response to anticonvulsant medication such as intravenous/oral benzodiazepine with simultaneous improvement in the EEG and clinical symptoms would add further support to the diagnosis if positive, but does not exclude the diagnosis if negative (Livingston and Brown 1987). Sometimes, if the duration of the NCSE has been prolonged, there will not be an instantaneous clinical response, but there may be a slow and gradual improvement over months. When a trial of treatment is considered, clear clinical and/or electrical goals should be defined as to what will be classed as a response.

In summary, NCSE in children can be associated with many different EEG patterns and clinical features. The most frequent clinical signs and symptoms are changes in behaviour, awareness, loss of skills -motor or communication, cognitive and memory difficulties. These clinical features can be difficult to detect if the child has pre-existing learning and behavioural problems. A continuous dysrhythmia can complicate many acute diseases of the nervous system and requires treatment in its own right, whereas NCSE occurs frequently in some of the childhood epilepsy syndromes. A high index of suspicion is often required in order to make the diagnosis.

References

- Kaplan PW. Assessing the outcomes in patients with nonconvulsive status epilepticus: nonconvulsive status epilepticus is underdiagnosed, potentially undertreated and confounded by morbidity. *J Clin Neurophysiol* 1999; 16: 341-52.
- Livingston JH, Brown JK. Non-convulsive status epilepticus resistant to benzodiazepines. *Archives of Diseases in Childhood* 1987; 62: 41-4.
- Neville BG, Boyd SG. Selective epileptic gait disorder. *J Neurol Neurosurg Psychiatry* 1995; 58: 371-3.
- Neville BG, Besag FM, Marsden CD. Exercise induced dystonia, ataxia, alternating hemiplegia associated with epilepsy. *J Neurol Neurosurg Psychiatry* 1998; 65: 241-4.
- O'Regan ME, Brown JK. Serum neuron specific enolase: A marker for neuronal dysfunction in children with continuous EEG epileptiform activity. *Eur J Paediatr Neurol* 1998; 2: 193-7.
- Perruca E, Graw, L, Avanzini G, et al. Antiepileptic drugs as a cause for worsening seizures. *Epilepsia* 1998; 39: 5-17.

Pitfalls of EEG interpretation of repetitive discharges

Peter Kaplan

The John Hopkins Bayview Medical Centre, Dept of Neurology,
4940 Eastern Avenue, Baltimore, MD 21224, USA

Disorders that present with altered mental status and repetitive discharges on EEG may be mistaken for the clinically pleomorphic condition of nonconvulsive status epilepticus (NCSE). The EEG interpretation of what constitutes «seizure activity» is subjective, involving analysis of EEG morphology, frequency, rhythm and temporal evolution with clinical correlates usually taken into consideration. The literature on repetitive discharges and on NCSE reflects the ambiguity in the interpretation of these patterns.

Repetitive discharge patterns (RDPs), or periodic EEG patterns straddle the borderlands of epilepsy and encephalopathy, as well as between ictal and interictal states. RDPs include periodic lateralized epileptiform discharges (PLEDs), bilateral independent periodic lateralized epileptiform discharges (BiPLEDs), and periodic epileptiform discharges (PEDs, GPEDs), which can be focal or generalized (Chatrian *et al.* 1964, Westmoreland *et al.* 1986, Reiher *et al.* 1991, de la Paz *et al.* 1981, Hussain *et al.* 1999, Snodgrass *et al.* 1989, Kuroiwa and Clesia 1980). RDPs are usually of lower frequency, and show less variability than seizure patterns, but frequently occur with seizures in the same patient.

Definitions: PLEDs, PLEDs-plus, BiPLEDs and GPEDs

PLEDs may be acute or chronic. Chronic PLEDs occur with chronic structural brain abnormalities and chronic epilepsy (Westmoreland *et al.* 1986). PLEDs are discharges with sharp or sharp-and-slow waves; spike, spike-and-waves, or multiple spike-and-waves; or complex bursts of multiple spikes with slow waves (Chatrian *et al.* 1964). They occur at 3/sec to 12/min (Chatrian *et al.* 1964) [or even as few as 8/min (Snodgrass *et al.* 1989)]. They usually occur at about 1 Hz, and last up to 600 msec., and vary from 50 to 300 μ V. They should be present for at least a ten-minute epoch during a standard recording, or be present continuously during a specific behavioural state (Kuroiwa and Clesia 1980).

RDPs and seizures

Many studies note the association between PDs and electrographic seizures, but fail to define what constitutes the ES and how it was determined which of the two states was present at a particular time (Snodgrass *et al.* 1989). One description connecting the two is as «an evolution of PLEDs to a new discharge pattern, often consisting of faster rhythmic activity» (Brenner 2004). Others have determined that seizures are occurring in patients with PLEDs

when there are focal motor phenomena (either regular and continuous, or intermittent), or when other clinical seizure manifestations are present (head or eye deviation, vocalization, chewing, psychic phenomena including visual and auditory hallucinations, confusion or autistic behavior) (Chatrian *et al.* 1964). PLEDs with rhythmic discharges (RDs) known as *PLEDs plus* (figure 1) are highly associated with seizures, while PLEDs without RDs (*PLEDs proper*) are less so (Reiher *et al.* 1991). Some have concluded that PLEDs are thus part of status epilepticus because one-third of initial EEGs on patients with PLEDs show ES. (Snodgrass *et al.* 1989) The principal arguments regarding distinguishing BiPLEDs (figure 2), and GPEDs from ES are similar, even though the relative etiologies, association with clinical seizures, and outcome differ.

An argument can be made that because EEGs represent a temporal sampling of a patient's brain activity, and because of the high association of PLEDs with generalized seizures (74%-90%) (Chatrian *et al.* 1964, Westmoreland *et al.* 1986, Reiher *et al.* 1991, de la Paz *et al.* 1981, Hussain *et al.* 1999, Snodgrass *et al.* 1989, Kuroiwa and Clesia 1980, Brenner 2004), that unless ongoing EEG monitoring is available, it is highly probable that electrographic seizures will be missed, hence the need for their treatment as seizures. PLEDs would then become an indication for ES treatment to forestall the *probable* occurrence of seizures. Another study found that spiking rate is not predictive of when subsequent seizures might occur, whereas interictal spike activity may be increased for hours to days after seizures. (Gotman and Marciani 1985) Others postulate that in many cases RDPs are equivalent to the terminal phase of SE (Snodgrass *et al.* 1989), or because they may exhibit increased metabolic or cerebral blood flow demands as evidenced by SPECT (Handforth *et*

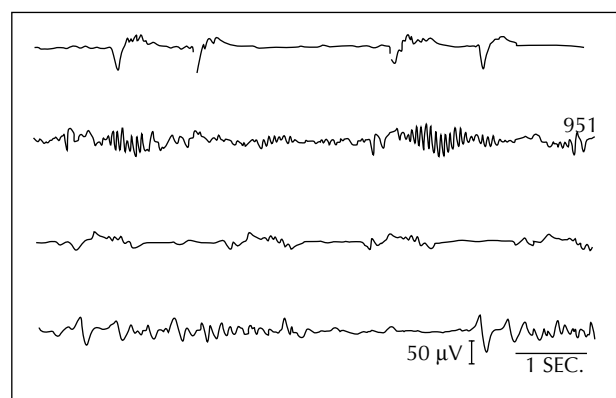


Figure 1. Illustrative samples of various RDPs in four patients with PLEDs Plus.

Reprinted from Reiher J, *et al.* Periodic lateralized epileptiform discharges with transitional rhythmic discharges: association with seizures. *Electroencephalogr Clin Neurophysiol* 1991; 78: 12-7, with permission from The International Federation of Clinical Neurophysiology.

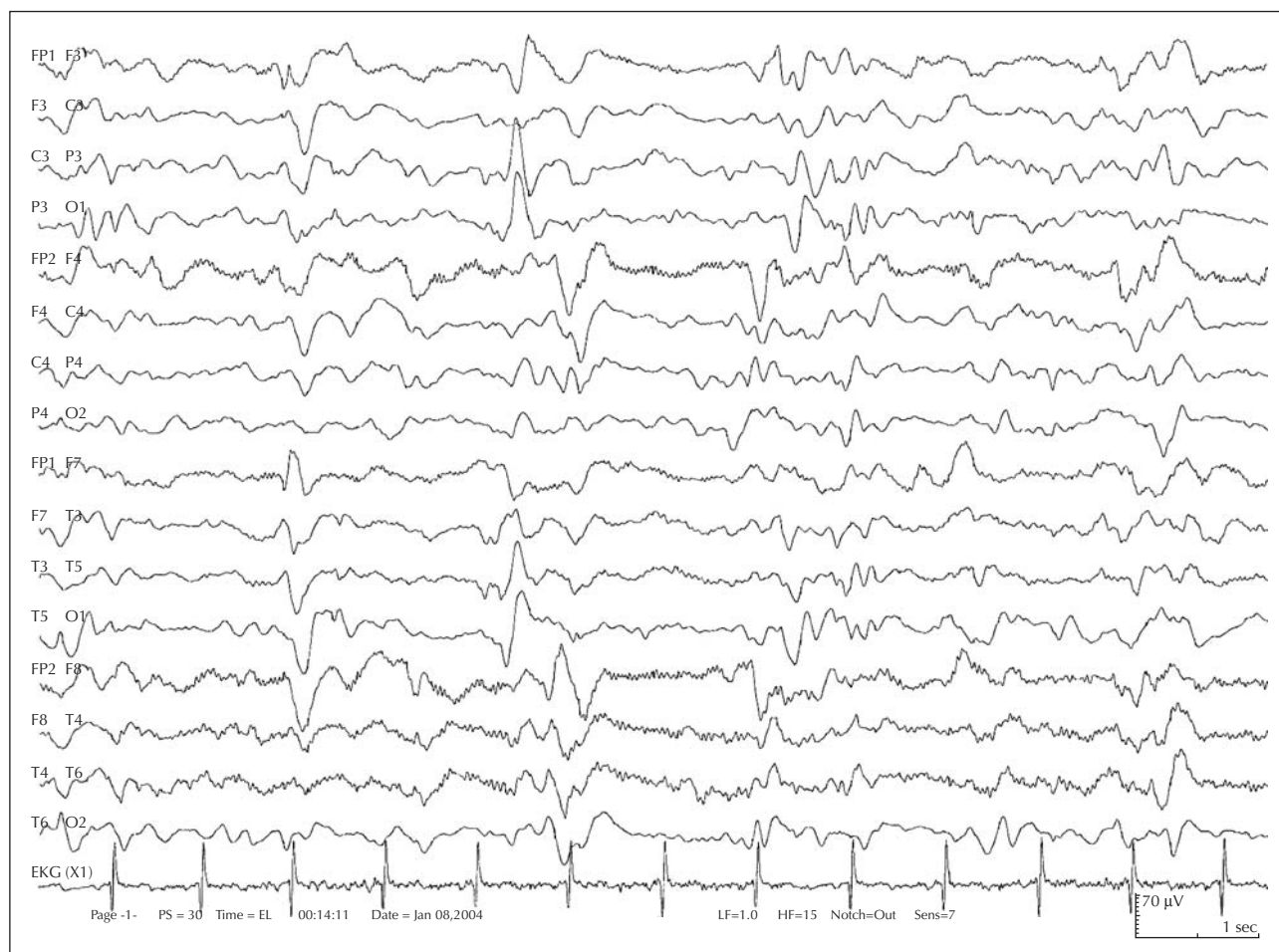


Figure 2. Bilateral, independent PLEDs occurring over the left and right frontal regions, without clinical correlate.

al. 1994) or PET imaging, that they warrant intensive AED or anesthetic management. Because RDPs are not actual seizures, but largely represent a post-ictal, «irritative», self-limited phenomenon, intensive therapy with propofol or coma-inducing doses of barbiturates or benzodiazepines tips the risk-benefit equation away from the patient. Thus, prophylaxis against seizures proper with agents such as phenytoin, along with moderate doses of diazepam or lorazepam would arguably be safer and sufficient therapy. Triphasic waves (TWs), which are blunted bi-or epileptic rhythmic complex are another periodic epileptiform pattern. They may increase with arousal (*figure 3 a and b*), disappear with sleep, and abate after intravenous benzodiazepines (BZPs). (Kaplan 1996, Fountain and Wladman 2001). Unlike NCSE, patients show no clinical improvement proximate to benzodiazepine administration. (Fountain and Waldman 2001).

Other conditions such as Lennox-Gastaut syndrome, often referred to as epileptic encephalopathy, exhibit «interictal» epileptiform discharges which when profuse are difficult to differentiate from seizures. Benign periodic dis-

charges (e.g. the psychomotor variant; subclinical rhythmic epileptiform discharges of adults [SREDA]) may resemble seizures on EEG, but lack visible clinical impairment.

RDPs and ES represent a continuum of EEG epileptiform activity, and a definition of what constitutes *interictal* RDPs *versus* ES or NCSE, largely depends on where one draws the line. The literature would suggest that patterns that represent seizures include (Brenner 2002, Young *et al.* 1996, Markland 2003, Shorvon 2004): (1) repetitive or continuous focal spikes, sharp-waves or monomorphic, rhythmic theta or delta waves, which wax and wane, usually at frequencies > 1 Hz with change in amplitude, frequency and/or spatial distribution; (2) repetitive focal spikes, sharp waves, spike-and-wave, sharp-and-slow wave complexes or rhythmic waves at fewer than one per second with decrementing voltage or frequency over less than 1-2 minutes; subsequent voltage attenuation; or improvement in clinical and EEG abnormality proximate to intravenous antiepileptic drug administration; (3) frequent or continuous generalised spike, sharp or rhythmic theta/

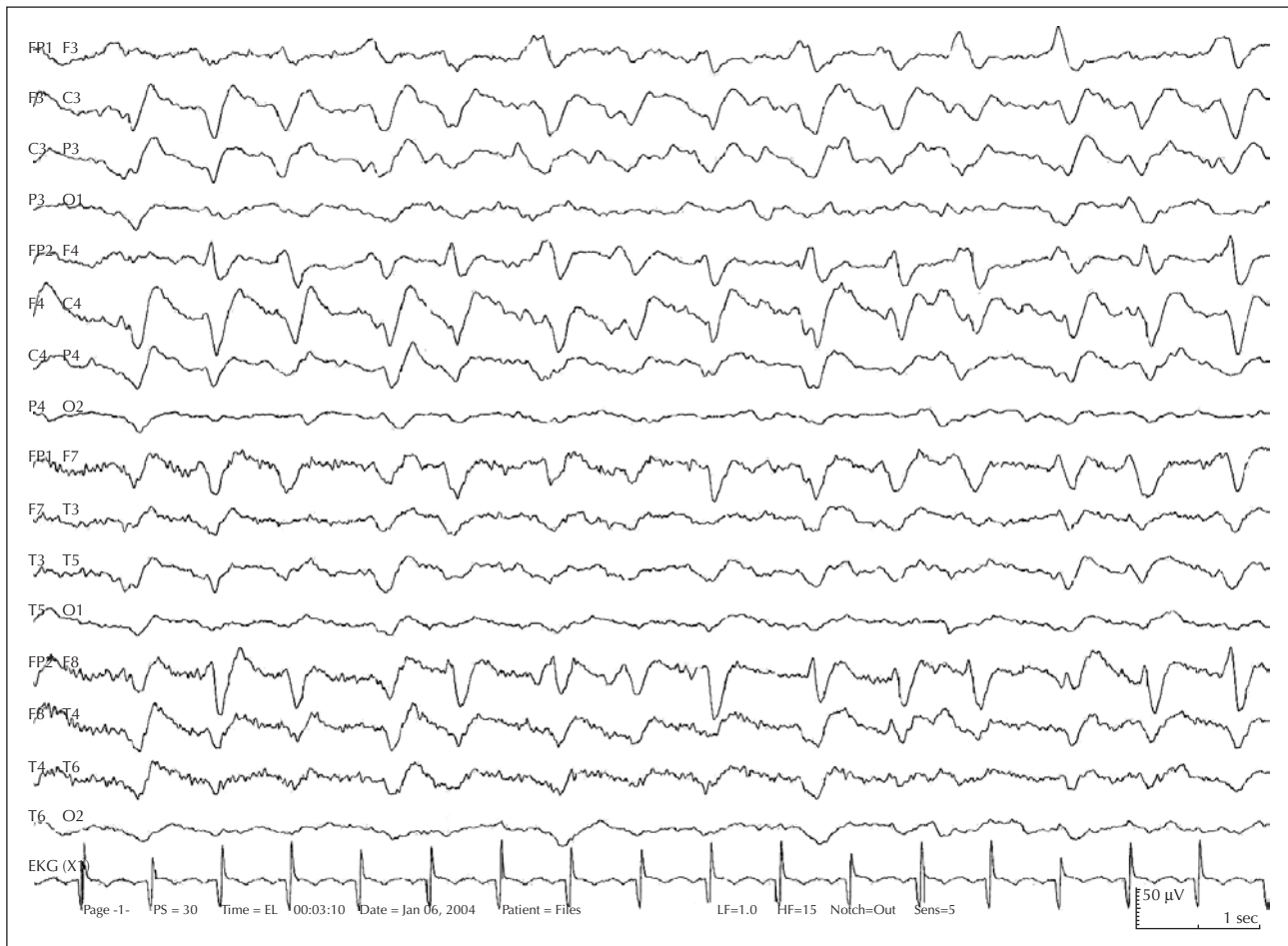


Figure 3a. Shows bi- and tri-phasic waves predominating over the anterior head regions at 0.5 to 1 Hz.

delta wave discharges in patients without a prior history of epileptic encephalopathy or epilepsy syndrome; (4) frequent or continuous generalised spike wave discharges, which show significant changes in profusion or frequency (usually a faster frequency) when compared to baseline EEG, in patients with an epileptic encephalopathy/syndrome; (5) PLEDs (periodic lateralised epileptiform discharges) or BIPEDs (bilateral periodic epileptiform discharges) occurring in patients in coma in the immediate aftermath of a generalised tonic clonic SE (subtle SE); (6) repetitive discharges with clinical correlates time-locked to discharge frequency (or resolving with EEG improvement).

EEG patterns, which are more difficult to interpret include: (7) frequent or continuous EEG abnormalities (spikes, sharp waves, rhythmic slow activity, PLEDs, BiPEDs, GPEDs) in patients without previous similar abnormalities, in the setting of acute cerebral damage (e.g. anoxia, infection, trauma); (8) frequent or continuous generalised EEG abnormalities in patients with epileptic encephalopathies

in whom similar interictal EEG patterns are seen, but in whom clinical symptoms are suggestive of NCSE.

Differentiation between ictal and interictal patterns in epileptic encephalopathies (e.g. Lennox-Gastaut syndrome) may be particularly difficult. (Young *et al.* 1996, Markland 2003) Similarly, distinguishing electrographic seizures from repetitive interictal discharges of damaged brain in coma is problematic.

Conversely, patterns exhibiting a monotonous rhythmicity of epileptiform discharges, or brief repetitive stereotyped salvos of discharges again lasting seconds, are an interictal pattern. Finally, RDPs and ES with coma represent a nosological and diagnostic dilemma: are they to be regarded as epiphenomena of damaged brain (and not as NCSE, but as electrographic status epilepticus), or as NCSE proper? Many of the same arguments apply.

EEG interpretation remains an art, with clinical correlation and response to therapy playing an important part in differentiating non-seizure repetitive discharges from ES and NCSE.

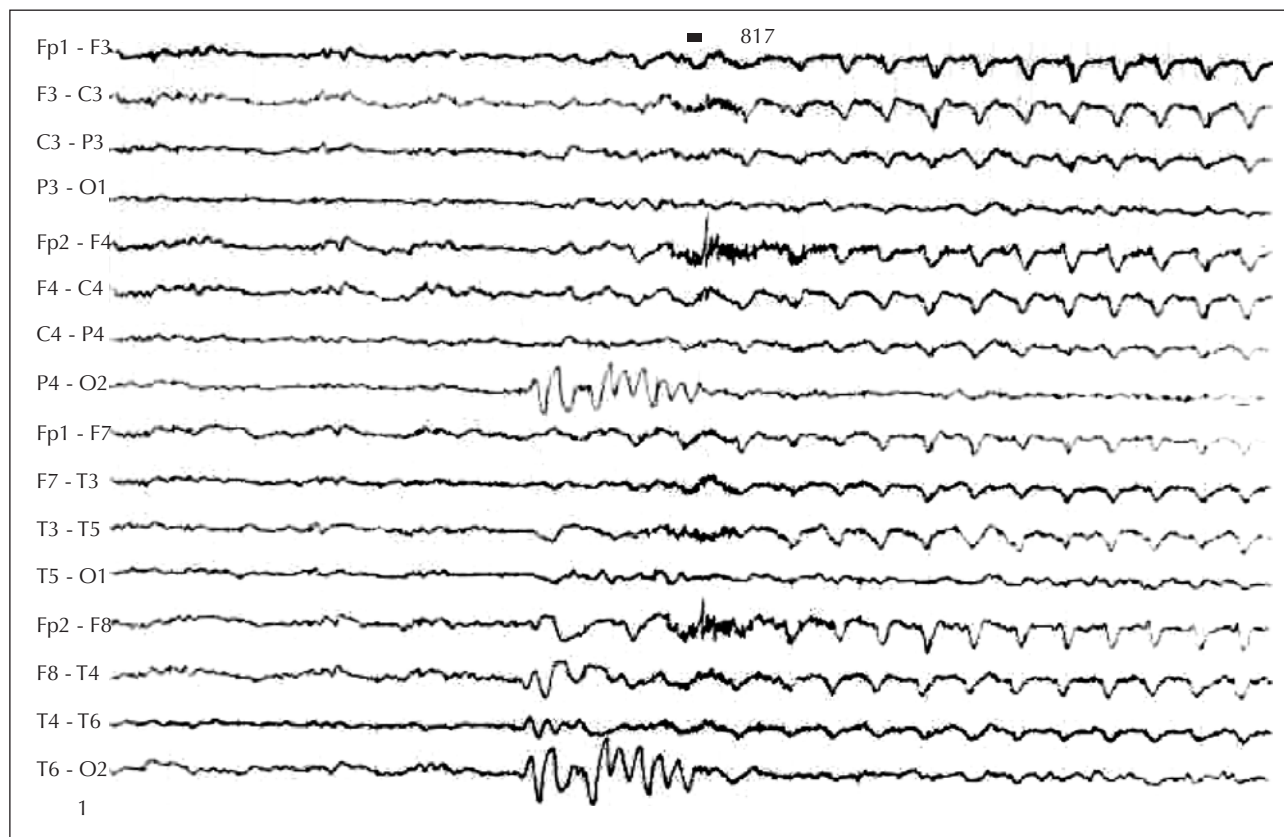


Figure 3b. The EEG shows triphasic waves that appear when the patient is aroused with noxious stimulation. The patient had anoxic encephalopathy.

References

- Brenner RP. Is it status? *Epilepsia* 2002; 43(Suppl 3): 103-13.
- Brenner RP. EEG in status epilepticus: convulsive and nonconvulsive. *J Clin Neurophysiol* 2004; in press.
- Chatrian GE, Cheng-Mei S, Leffman H. The significance of periodic lateralised epileptiform discharges in EEG: an electrographic, clinical and pathological study. *Electroenceph Clin Neurophysiol* 1964; 17: 177-93.
- de la Paz D, Brenner RP. Bilateral independent periodic lateralized epileptiform discharges. *Arch Neurol* 1981; 38, 713-5.
- Fountain NB, Waldman WA. Effects of benzodiazepines on triphasic waves: implications for nonconvulsive status epilepticus. *J Clin Neurophysiol* 2001; 18, 345-52.
- Gotman J, Marciani MG. Electroencephalographic spiking activity, drug levels, and seizure occurrence in epileptic patients. *Ann Neurol* 1985; 17, 597-603.
- Handforth A, Cheng JT, Mandelkern MA, et al. Markedly increased mesiotemporal lobe metabolism in a case with PLEDs: further evidence that PLEDs are a manifestation of partial status epilepticus. *Epilepsia* 1994; 35, 876-881.
- Hussain AM, Mebust KA, Radtke RA. Generalized periodic epileptiform discharges: etiologies, relationship to status epilepticus, and prognosis. *J Clin Neurophysiol* 1999; 16(1): 51-8.
- Kaplan PW. Nonconvulsive status epilepticus in the emergency room. *Epilepsia* 1996; 37: 643-50.
- Kuroiwa Y, Celesia GG. Clinical significance of periodic EEG patterns. *Arch Neurol* 1980; 37: 15-20.
- Markland ON. Pearls, perils, and pitfalls in the use of the electroencephalogram. *Semin Neurol* 2003; 23(1): 7-46.
- Reiher J, Rivest J, Grand-Maison F. et al. Periodic lateralised epileptiform discharges with transitional rhythmic discharges: association with seizures. *Electroenceph Clin Neurophysiol* 1991; 78: 12-7.
- Shorvon S. Epidemiology of NCSE. Presented at the Nonconvulsive Status Epilepticus Workshop 2004; Oxford, England: Worcester College. March 28-30.
- Snodgrass SM, Tsuburaya K, Ajmone-Marsan C. Clinical significance of periodic lateralized epileptiform discharges: relationship with status epilepticus. *J Clin Neurophysiol* 1989; 6: 159-72.
- Westmoreland BF, Klass DW, Sharbrough FW. Chronic periodic lateralized epileptiform discharges. *Arch Neurol* 1986; 43: 494-6.
- Young GB, Jordan KG, Doig GS. An assessment of nonconvulsive seizures in the intensive care unit using continuous EEG monitoring; an investigation of variables associated with mortality 1996; 47: 83-9.

Discussion by Shelagh Smith

Dept of Clinical Neurophysiology, National Hospital for Neurology and Neurosurgery, Queen Square, London, UK, WC1N 3BG

Periodic EEG phenomena, either focal, lateralised or generalised, are associated with widely diverse neurological disorders of varying severity and prognosis (Chatrian *et al.* 1964, Garcia-Morales *et al.* 2002). The underlying neuronal substrates of periodic discharges are uncertain, and attempts to draw unified hypotheses about their pathophysiological basis have been unsuccessful. The entity of periodic lateralised discharges (PED) presents particular challenges. These are relatively rare phenomena, with estimated incidence in unselected populations ranging from 0.4-1% (Pohlmann-Eden *et al.* 1996); they occur in all age groups, but may be less common in very young children. There is general agreement that PEDs are associated with acute or sub-acute cerebral lesions, with stroke, tumour and infection being the commonest underlying pathologies, and that patients with metabolic disturbance concomitant with such lesions are more likely to manifest PEDs (Neufeld *et al.* 1997). Studies of patients with PEDs mostly report a strong association with seizures, typically partial or focal motor in type. What is more controversial is whether PEDs represent an interictal or ictal pattern, and their relationship to non-convulsive and convulsive status epilepticus. Definitions of PEDs vary, and some have proposed that particular morphological characteristics (PLEDs plus) are more likely to be associated with overt seizures and status (Reiher *et al.* 1990). The dynamics of PEDs are unknown, as most series are retrospective, and intervals between the time of the initial EEG in which PEDs are identified, the onset of underlying pathology and the occurrence of acute seizures are highly variable. Furthermore, there are very few published data from continuous EEG monitoring to evaluate the time course of PEDs, particularly in relation to evolving ictal EEG patterns of status reported in humans. PEDs seem not to be a terminal manifestation of status, as the prognosis is not universally poor (Garzon *et al.* 2001).

At present, PEDs are best considered as the consequence of a dynamic pathophysiological state in which unstable neurobiological processes create an ictal-interictal continuum (Pohlmann-Eden *et al.* 1996). Although it may be possible to agree definitions which delineate PEDs from other periodic or repetitive EEG phenomena, electrographic features alone will probably not determine which patients require aggressive antiepileptic therapy. Diagnosis of nonconvulsive status requires concurrence of EEG ictal patterns and clinical ictal features, including subtle alteration of consciousness and/or subtle motor activity. Definitions of EEG ictal patterns should include response or change following intervention with antiepileptic drug treatments.

References

- Chatrian GE, Cheng-Mei S, Leffman H. The significance of periodic lateralised epileptiform discharges in EEG: an electrographic, clinical and pathological study. *Electroenceph clin Neurophysiol* 1964; 17: 177-93.
- Garcia-Morales I, Garcia MT, Galan-Davila L. *et al.* Periodic lateralised epileptiform discharges. Etiology, clinical aspects, seizures and evolution in 130 patients. *J Clin Neurophysiol* 2002; 19: 172-7.
- Garzon E, Fernandes RMF, Sakamoto, AC. Serial EEG during human status epilepticus. Evidence for PLED as an ictal pattern. *Neurology* 2001; 57: 1175-83.
- Neufeld MY, Vishnevskaya S, Treves TA, *et al.* Periodic lateralised epileptiform discharges (PLEDS) following strokes are associated with metabolic abnormalities. *Electroenceph clin Neurophysiol* 1997; 102: 295-8.
- Pohlmann-Eden B, Hoch DB, Cochius G, *et al.* Periodic lateralised epileptiform discharges – a critical review. *J Clin Neurophysiol* 1996; 13: 519-30.

Prognosis of NCSE

Denson Fujikawa

UCLA Neurology, VA Greater Los Angeles Healthcare System, 1611 Plumner Street, Sepulveda, California, 91343, USA

With respect to prognosis of NCSE, one that is uniform cannot be proposed, because the term «nonconvulsive SE» encompasses a wide variety of epileptic conditions. Defining a minimal duration of NCSE is not as important as in GCSE; the difficulty lies in diagnosing unsuspected patients, who may have been in SE for days, months or even years. The current classification of NCSE does not reflect the wide variability in patient presentation, from the «walking wounded» to the «ictally comatose.» For purposes of prospective studies and treatment, unresponsive patients with electrographic SE should be separated into those in whom the cognitive deficit arises from the discharges themselves, and those in whom it is due to an underlying neurological abnormality, in which the discharges are an epiphenomenon. Before progress can be made in determining prognosis, a better classification is needed, one that takes into account the wide variability in presentation, and groups like patients with each other.

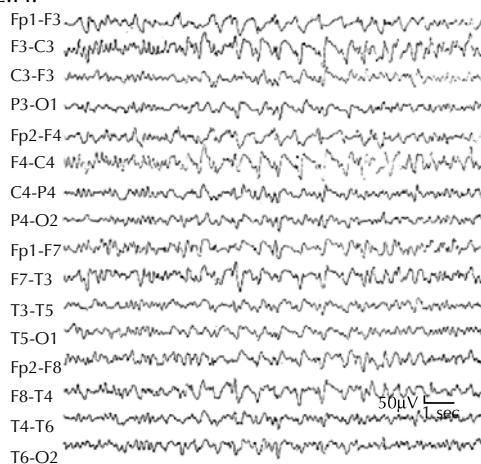
Two illustrative cases

Patients who exemplify the two extremes (the «walking wounded» versus the «ictally comatose») are described in figures 1 and 2 respectively. The first patient had three episodes of NCSE, with suppression of bilaterally synchronous 2-2.5-Hz frontotemporal spike and slow-wave discharges from 33%, down to less than 10% of total EEG time on random EEGs over a nine-year period (and down to 2-4% of total EEG time for two years), with progressive improvement in full-scale IQ from 102 to 125 (verbal IQ from 103 to 133), together with normalization of frontal executive function deficits (figure 1).

Generalized Nonconvulsive SE and Persistent EEG Bursts of Spike and Slow-Wave Discharges in an ambulatory patient, with marked cognitive improvement

- 64 y/o man with 3 episodes of generalized NCSE, the first two 3 weeks apart, and the last 7 years later.
 - EEGs during the third episode in 12/90 showed bilaterally synchronous 2-2.5-Hz spike and slow-wave discharges (SWDs) frontotemporally, occupying 33% of total EEG time, decreasing to 2-4% from 10/92-9/94 while on Depakote. His last EEG in 1996 showed <1% SWDs.
 - Neuropsychological testing from 5/87 to 6/96 showed a 23-point increase in full-scale IQ (from **102 to 125**), with increase in verbal IQ increase from **103 to 133**, and normalization of frontal executive function deficits, coincident with a reduction in the amount of SWDs on EEG.
 - The patient died in April, 1999 at age 64; no further Information is available.
- (From Licht EL *et al.* *Epilepsy Behav* 2002; 3: 96-100)

E.H.



33% of this EEG had bifrontal 2-2.5-Hz SWDs of 0.5-52 s duration; during the 52-s burst the patient appeared "normal," and subtracted from 100 to 0 by 1's, with 2 mistakes

Figure 1.

Ambulatory patients, especially those presenting with absence SE, are thought to do well, although follow-up with detailed neuropsychological and EEG testing is in general lacking. This patient provides dramatic evidence that chronic subclinical cognitive deficits may be uncovered with detailed evaluation and, with treatment, might be reversible. In this patient's case, it took years before maximal improvement was seen.

The second patient had end-stage renal disease requiring hemodialysis, and diabetes mellitus, with a history of disorientation for three months and with an EEG showing hyperventilation-induced, bilaterally synchronous 2.5-Hz frontotemporal spike and slow-wave discharges (*figure 2*).

Although he showed psychomotor retardation, he was alert and oriented, and was discharged on phenytoin. One week later, he was found comatose at home; an EEG showed bilaterally synchronous periodic (1 Hz) sharp-wave discharges (BiPEDs). He was treated with lorazepam, phenytoin and phenobarbital intravenously, the sharp-wave discharges were eliminated over several days, and he became responsive to verbal commands within one week and was discharged from the hospital. Two of three EEGs were normal awake and at stage I sleep studies more than one year later; the third showed mild slowing of the waking rhythm. Brain MR scanning showed mild cortical atrophy. However, neuropsychological testing done 1.3 years after his episode of electrographic SE revealed significant cognitive impairment: attention and

concentration were fair-to-poor, memory tasks were variably impaired, visuospatial skills and frontal lobe functioning were poor, and he was severely depressed. Full-scale IQ was 88, verbal IQ 95, performance IQ 78, well below what could be expected from someone with a B.S. degree in engineering. The patient was lost to follow-up and died five years after his episode of electrographic SE. This patient shows that although ictally comatose patients have a poor prognosis, those who are unresponsive because of the electrographic discharges can recover and be discharged from the hospital as ambulatory patients, a less likely possibility in those in whom unresponsiveness is the result of underlying medical and/or neurological conditions, with secondary electrographic discharges.

Discussion by Frank Besag

Beds and Luton Community NHS Trust, Twinwoods Health Resource Centre, Milton Road, Clapham, MK41, UK

The first question that needs to be asked when considering the prognosis of non-convulsive status epilepticus is: prognosis with regard to what? The prognosis with regard to ongoing NCSE, further bouts of NCSE, ongoing epilepsy, cognitive factors and behavioural disturbance are all-important. The prognosis with regard to each of these factors is very variable. Ongoing NCSE may respond to emergency treatment, may terminate spontaneously or, in some cases, may continue for years. Further bouts of NCSE may be prevented, in at least some cases, by appropriate continued antiepileptic medication. The control of obvious

An ambulatory patient who became ictally comatose but recovered with cognitive deficits

56 y/o man with type I diabetes mellitus, end-stage renal disease and sensory neuropathy, on hemodialysis 3 times a week for 2 years. Admission 12/7-12/12/93 for falling 3 times per day for one month and episodes of disorientation for 3 months. Alert and oriented, with psychomotor retardation, wide-based gait and decreased sensation of the distal lower extremities. EEG 12/10/93: mild slowing and hyperventilation-induced 1-2 sec bursts of bisynchronous 2.5-Hz spike and slow-wave discharges frontotemporally (**top EEG**). Readmitted 12/16/93 because he was found unresponsive to commands, with serum K⁺ 7.6, BUN 104, creatinine 13.3, glucose 43. On 12/20/93: Unresponsive, with spontaneous head and LLE movements, neutral plantar responses, and no response to painful stimuli. EEG 12/20/93: Continuous generalized bilaterally synchronous periodic 1-Hz SWDs (BPEDs) (**middle EEG**). Given lorazepam 6 mg i.v. and DPH 1400 mg i.v. with elimination of BPEDs. EEGs 12/21/93: Resumption of discontinuous BPEDs. 12/21/93: Loaded with 1 g of phenobarbital i.v. DPH level 7, phenobarbital 18 on 12/22. Turned head to voice and moved upper extremities and left lower extremity spontaneously. EEG 12/22/93: Intermittent lower-amplitude BiPEDs (**bottom EEG**). 12/23/93: DPH 12.2, PB 12.0. Withdrew extremities to painful stimulus. 12/26/93: Awake, looking around room, moving all extremities. 12/27/93: Responsive to verbal commands. 12/28/93: EEG: moderate slowing, with intermittent 2-8 sec FIRDA. DPH 13.5, PB 20. Followed 2-step commands. 3/2/95, 3/9/95: EEGs: two normal awake and stage I sleep studies. 5/15/95: Brain MR scan: mild cortical atrophy. 8/14/95: EEG: mild slowing of waking rhythm. 8/22/95: Neuropsychological assessment: B.S. in engineering; laid off 1982. MMSE 25/30. VIQ 95, PIQ 78, FSIQ 88. Attention and concentration fair-to-poor. Variable performance on memory tasks. Visuospatial skills, frontal lobe functioning poor. Severely depressed. 2/6-2/10/98: Psychiatric admission because of suicidal ideation. Angry at being admitted. At discharge, irritable but organized. 11/28/98: Died at age 60; no further information available.

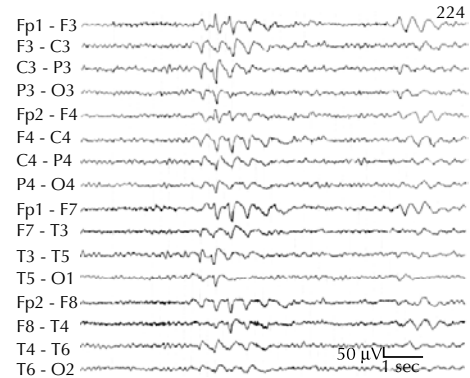


Figure 2.

seizures is not necessarily related to the control of NCSE, as in some cases both will be controlled with ongoing medication however in other cases, either the overt seizures or the NCSE may be controlled. Cognitive and behavioural outcomes are particularly important. Although it is difficult to collect hard evidence, it appears that the longer the duration of NCSE the more likely it is that permanent cognitive deficits will occur. In this context, it is very important to distinguish between the reversible cognitive impairment that resolves when the NCSE is treated and irreversible permanent damage that might result from longer-term NCSE. There are remarkably few data on behavioural outcome, although there is some evidence that NCSE might have a profound effect on behaviour. If continuous spike-wave in slow wave sleep (CSWS) is included in the definition of NCSE, then the Landau-Kleffner Syndrome and other specific, acquired cognitive deficits may result. These specific cognitive deficits are typically ac-

companied by marked behavioural deterioration. NCSE may often be difficult to detect and consequently to diagnose but, in at least some cases, may have serious consequences, particularly with regard to cognitive and behavioural outcome. Early recognition and prompt treatment almost certainly improve the prognosis greatly.

Experimental evidence of status-induced brain damage

Hannah Cock

St Georges Hospital Medical School, Clinical Neurosciences, Epilepsy Group, Dept of Cardiac and Vascular Sciences, Cranmer Terrace, London, SW17 0RE, UK

There are many well-characterized models of nonconvulsive status epilepticus (Hosford 1999, Stables *et al.* 2002) (*table 1*), which allow assessment of both cause and con-

Table 1. Models of nonconvulsive status epilepticus

Model	Details	Examples
<i>In vitro</i>	Hippocampal slice (± culture)	Bicuculline, low Mg ²⁺ , Electrical stimulation
Chemical <i>in vivo</i>	Bicuculline	Focal (i.v. = generalized)
	PTZ	i.p., low dose (absence SE)
	Kainate* NMDA	i.p., icv, focal (hippocampal, amygdala)
	Tetanus toxin *	Focal (hippocampal, amygdala) Focal (hippocampal, cortical)
Electrical <i>in vivo</i>	Stimulation *	Amygdala, hippocampal perforant path

sequences of NCSE in an intact preparation under controlled conditions.

Following initial experiments in the 1970s (Meldrum and Brierley 1973), there is now overwhelming evidence that *de novo* NCSE, as a result of chemical or electrical insults, commonly results in cell death, with a characteristic pattern of neuronal vulnerability, comparable to that seen in human epilepsy (surgical and post-mortem specimens).

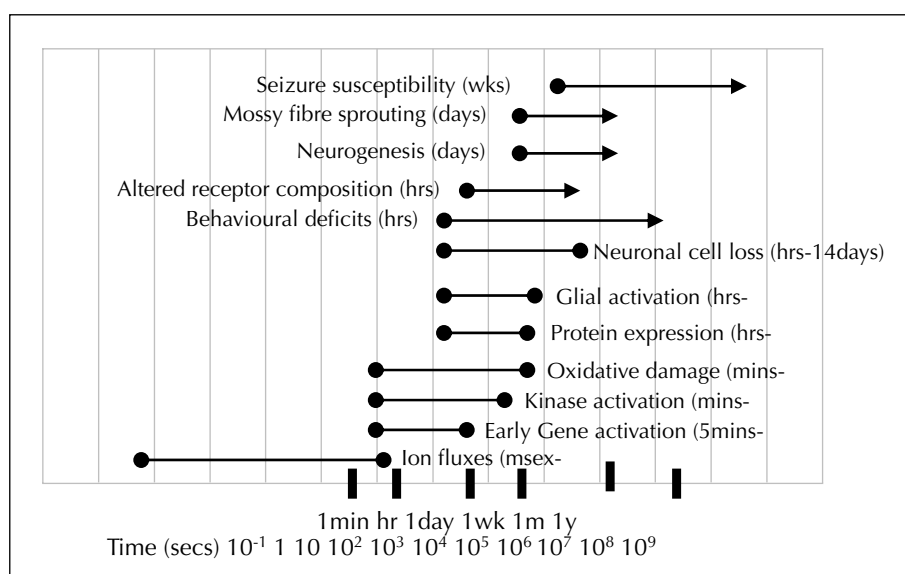
Several of the models also go on to develop spontaneous seizures, though it is important to recognize that the observations (from initially normal brains) may not be comparable with NCSE in the epileptic brain (Holmes 2002). Animal data also support the idea that seizures cause irreversible impairment in spatial and emotional learning and memory (Majak and Pitkanen 2004), though there are insufficient studies on NCSE alone to draw specific conclusions in this respect. The hippocampus has

been most studied, and several factors including age (Wasterlain *et al.* 2002), duration, type and spread of seizure (Tuunanen *et al.* 1999), genetic background (Schauwecker 2002) and environmental factors (Rutten *et al.* 2002) are known to influence the extent and severity of damage. In recent years, understanding of the mechanisms leading to cell death has also been greatly enhanced.

NMDA receptor activation is considered an early event, but impaired calcium handling (Pal *et al.* 1999), mitochondrial dysfunction, increased production of reactive oxygen and nitrogen species (Cock 2002), and caspase activation (Narkilahti 2003) have all been demonstrated following NCSE. A number of studies have demonstrated prevention of cell death associated with the prevention of both behavioural/memory deficits and the later development of epilepsy following NCSE (Rice and De Lorenzo 1998). However, this is not a consistent finding (Pitkanen, 2002), and it appears that cell death is neither necessary nor sufficient for epileptogenesis, nor for cognitive decline following NCSE. Nonetheless, this does not mean that where cell death does occur it is not relevant to either process.

Most of the animal literature equates «damage» with cell death, and neuroprotection with preventing cell death, despite the fact that cell death represents only one extreme endpoint of many identified processes following NCSE (figure 1).

A broader definition of damage, encompassing any injury/hurt that is disadvantageous, is almost certainly more appropriate in the context of epilepsy. Many of the activated cascades leading to cell death might have significant functional consequences in surviving neurons, and additional processes such as neurogenesis (Parent *et al.* 1999), altered connectivity and receptor composition;

**Figure 1.** Changes after NCS in experimental models

synaptic reorganization, and changes in intracellular signalling processes may be equally important to both epileptogenesis and cognitive changes following NCSE. If «damage» is considered in this broader context, it may be that all types of seizure at any stage of development are damaging to some extent. For example, in immature brains, traditionally considered relatively resistant to cell death, alterations in the expression of glutamate receptors and transporters (Zhang *et al.* 2004) have been demonstrated. Similarly, although models of absence status characteristically don't result in identifiable neuronal death, and initial learning deficits appear reversible, surviving animals do have a lowered seizure threshold (Wong *et al.* 2003). Thus, where studies have failed to identify «damage» it may be that we are just not looking hard enough. The primary challenge is separating that changes are damaging from those which might be compensatory, and/or crucial to normal functioning (Walker *et al.* 2002). This is not straightforward. For example, although neurogenesis, and aberrant connectivity of new neurons, may contribute to epileptogenesis (Scharfman *et al.* 2003), neurogenesis is also thought to be important for normal memory functions (Shors *et al.* 2001).

In conclusion, there is overwhelming evidence from *in vivo* studies that NCSE occurring *de novo* is damaging, contributing both to epileptogenesis and cognitive impairments. It seems likely that the same applies in at least some instances of NCSE in the epileptic brain. Work is required to identify reliable markers of damage that correlate to clinically meaningful endpoints, before neuroprotective studies can be properly evaluated.

References

- Cock HR. The role of mitochondria and oxidative stress in neuronal damage after brief and prolonged seizures. *Do Seizures Damage the Brain* 2002; 135: 187-96.
- Holmes GL. Seizure-induced neuronal injury - animal data. *Neurology* 2002; 59, S3-S6.
- Hosford DA. Animal models of nonconvulsive status epilepticus. *J Clin Neurophysiol* 1999; 16, 306-13.
- Majak K, Pitkanen A. Do seizures cause irreversible cognitive damage? Evidence from animal studies. *Epilepsy & Behaviour* 2004; 5: S35-S44.
- Meldrum BS, Brierley JB. Prolonged epileptic seizures in primates. Ischemic cell change and its relation to ictal physiological events. *Arch Neurol* 1973; 28: 10-7.
- Narkilahti S, Pirttilä TJ, Lukasiuk K, *et al.* Expression and activation of caspase 3 following status epilepticus in the rat. *Eur J of Neuro* 2003; 18: 1486-96.
- Pal S, Sombati S, Limbrick DD, DeLorenzo RJ. *In vitro* status epilepticus causes sustained elevation of intracellular calcium levels in hippocampal neurons. *Brain Res* 1999; 851: 20-31.
- Parent JM, Gage FH, Gray WP. Altered postnatal neurogenesis as a form of seizure-induced brain plasticity. *Epilepsia* 1999; 40: 1.

Pitkanen A. Drug-mediated neuroprotection and antiepileptogenesis - Animal data. *Neurology* 2002; 59, S27-S33.

Rutten A, van Albada M, Silveira DC, *et al.* Memory impairment following status epilepticus in immature rats: time-course and environmental effects. *Eur J Neurosci* 2002; 16: 501-3.

Scharfman HE, Sollas AE, Berger RE, Goodman *et al.* Perforant path activation of ectopic granule cells that are born after pilocarpine-induced seizures. *Neurosci* 2003; 121: 1017-29.

Schauwecker PE. Modulation of cell death by mouse genotype: Differential vulnerability to excitatory amino acid-induced lesions. *Exp Neurol* 2002; 178: 219-35.

Shors TJ, Miesegae G., Beylin A. *et al.* Neurogenesis in the adult is involved in the formation of trace memories. *Nature* 2001; 410: 372-6.

Stables JP, Bertram EH, White HS. *et al.* Models for epilepsy and epileptogenesis: report from the NIH workshop, Bethesda, Maryland. *Epilepsia* 2002; 43: 1410-20.

Tuunanen J, Lukasiuk K, Halonen T, *et al.* Status epilepticus-induced neuronal damage in the rat amygdaloid complex: Distribution, time-course and mechanisms. *Neurosci* 1999; 94: 473-95.

Walker MC, White HS, Sander JWAS. Disease modification in partial epilepsy. *Brain* 2002; 125: 1937-50.

Wasterlain CG, Niquet J, Thompson KW, *et al.* Seizure-induced neuronal death in the immature brain. *Prog Brain Res* 2002; 135: 335-53.

Wong M, Wozniak DF, Yamada KA. An animal model of generalized nonconvulsive status epilepticus: immediate characteristics and long-term effects. *Exp Neurol* 2003; 183: 87-99.

Zhang G, Rao YSH, Hsu FC, *et al.* Long-term alterations in glutamate receptor and transporter expression following early-life seizures are associated with increased seizure susceptibility. *J Neurochem* 2004; 88: 91-101.

Discussion by Liam Gray

Division of Clinical Neurosciences, Biomedical Sciences Building, Bassett Crescent East, Southampton, SO18 7PX, UK

Animal models of complex partial status show characteristic patterns of cell death, especially in the hippocampus, whilst models of absence status show little evidence of structural damage. Dr. Cock emphasises the important point that animal models have largely been used to examine the effect of NCSE on naïve brain. One of the critical clinical questions is whether NCSE damages an already epileptic brain, as this may inform strategies for protecting cognitive function in patients with epilepsy.

When considering brain damage after experimental complex partial status epilepticus, it is important to distinguish between cell death at the time of status, progressive cell loss afterwards and maladaptive responses to injury in surviving cells. The relative contribution of status-induced death and sub-lethal injury to epileptogenesis is unclear. Partial neuroprotection post-NCSE does not prevent epileptogenesis and the failure to protect hilar interneurons

may be particularly important in this regard. However, neuroprotection may have an important role in preserving cognitive function and in preventing progressive decline. Dr Cock's assertion to broaden our definition of damage beyond that of cell death is of fundamental importance to the use of animal models for understanding the consequences of NCSE. There is increasing evidence that NCSE induces a train of responses in the injured brain, which sometimes become maladaptive, resulting in spontaneous seizures, cognitive decline and alterations in behaviour that characterise the epileptic state. The delineation of these responses, as well as mechanisms by which they become maladaptive, is one of the major challenges in epilepsy research.

Can we extrapolate the animal data to humans – the influence of epilepsy, drugs and age?

Claude Wasterlain

VA Medical Centre (127), 11301 Wilshire Boulevard,
West Los Angeles, CA 90073, USA

The best model of a cat is another cat, and preferably the same cat. However, the usefulness of models depends on their specific purpose. When studying therapeutic responses, it would seem highly desirable to use a disease

model that reproduces all features of the human disease as closely as possible. However, appearances can be deceiving: the response of low dose pentylentetrazol seizures to drugs is an excellent predictor of these drugs' effects on childhood absence seizures, yet the clinical and behavioral appearance of pentylentetrazol seizures does not mimic those of childhood absences at all. For most purposes, there is no need to reproduce fully a human illness too complex to be understood. We must reproduce an isolated component of the illness that can be approached experimentally in reductionist fashion, and this is what most animal models of nonconvulsive SE have done. If we ask, to what extent we can extrapolate the experimental results to clinical situations, little evidence is currently available to answer that question in the case of nonconvulsive status epilepticus (NCSE).

Can we extrapolate the behavioral or electrographic features of experimental SE to humans?

Behaviorally, the animal models of NCSE produce clonic seizures, and therefore are not truly nonconvulsive. Electrographically and clinically, however, the evolution of SE induced by electrical or chemical stimulation closely resembles that described by Treiman first in rats, then in human SE (*figure 1*).

Metabolically, both complex partial SE and the commonly used experimental models activate primarily the limbic brain. Thus, experimental SE has many features in com-

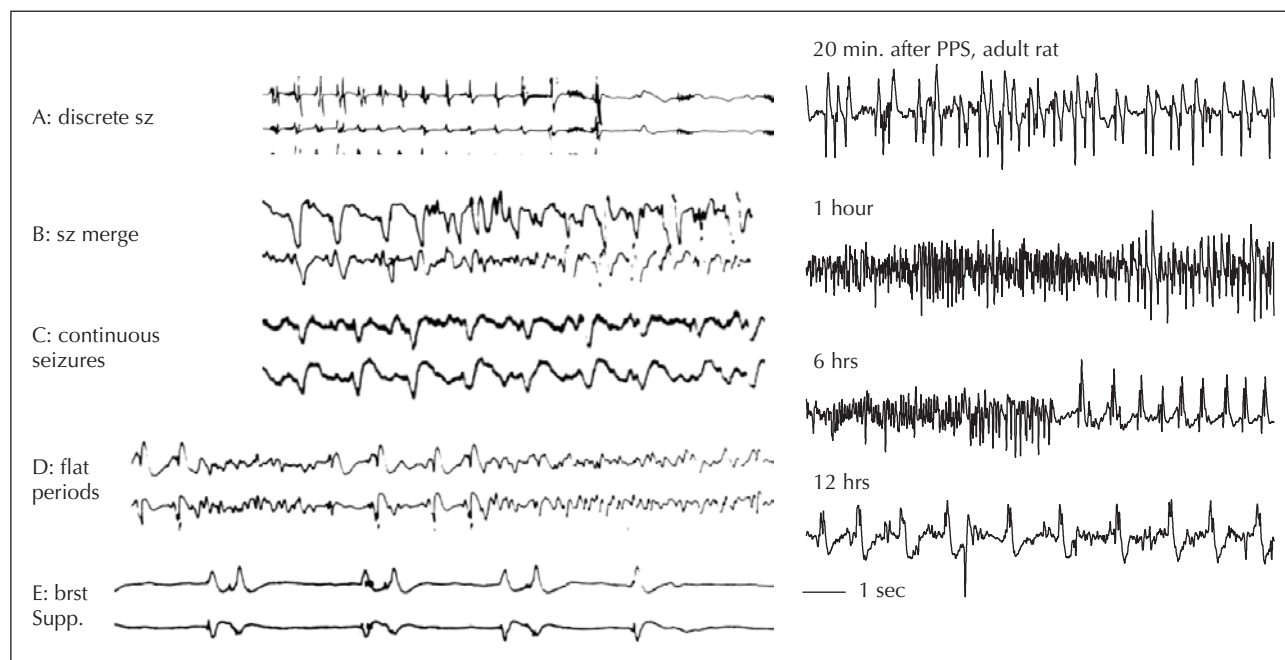


Figure 1. The electrographic evolution of human SE (Treiman et al., 1990, on the left) goes through five stages which parallel the evolution of SE induced in rats by stimulation of the perforant path (on the right, Mazarati et al., 1998). Behavioral seizures differ in their motor expression, but follow a similar progression

mon with complex partial SE, and differs substantially from other NCSE syndromes.

Can we extrapolate the animal data on brain damage to humans with complex partial SE?

Meldrum in 1973, proved that seizures in paralyzed, ventilated monkeys caused neuronal loss, and Sloviter and Damiona in 1981, showed that cell death is the direct result of excessive neuronal firing. In the immature brain, Thompson *et al.* 1997, 1998 and Sankar *et al.* 1998, demonstrated that neuronal death results from severe, prolonged seizures (*figure 2B, C*).

Human evidence is largely anecdotal: brain damage is often seen in children or adults who died from SE (*figure 2D, F*), although epidemiologic evidence is lacking (Camfield 1997). DeGiorgio *et al.* 1996, found decreased hippocampal neuronal densities in five patients who died after SE, compared to epileptics without SE and to controls. Rabinowicz *et al.* 1995, and O'Regan and Brown 1998, found increased neuron-specific enolase, a marker of neuronal injury, in the serum of patients with NCSE. A number of imaging studies found cerebral edema acutely, and atrophy chronically, after NCSE (Chu *et al.* 2001, Lansberg *et al.* 1999, Lazeyras *et al.* 2000), but others did not (Salmepera *et al.* 2000). One five year-old patient had a normal brain MRI before NCSE, atrophy after NCSE (Pascual-Castroviejo *et al.* 1999), and neuronal loss was

found at autopsy in areas that became atrophic after NCSE (Nixon *et al.* 2001). Atrophy was reported in areas of intense seizure activity (Freeman *et al.* 2002, Men *et al.* 2000, Morimoto *et al.* 2002), supporting a mechanistic explanation.

Can we extrapolate experimental evidence of seizure-induced epileptogenesis to humans?

SE-induced epileptogenesis is common, and easily induced in many (but not all) animal models, at all ages (Sanakar *et al.* 2000). Human evidence is remarkably sparse, and subject to diverging interpretations: for example, in population-based statistics in Rochester, Minnesota, USA, the risk of unprovoked seizure is 3.3-fold higher after acute symptomatic SE (41%), than after single seizures (Hesdorffer *et al.* 1998). In a population-based cohort study in UK, the risk of developing afebrile seizures was vastly increased after SE, compared to simple febrile convulsions (Verity *et al.* 1993). Of course, these differences might reflect a more severe illness in patients with SE, rather than SE-induced epileptogenesis. A patient who survived domoic acid SE developed chronic epilepsy, but of course no treated controls were available to separate toxin-induced from seizure-induced epileptogenesis (Cendes *et al.* 1995).

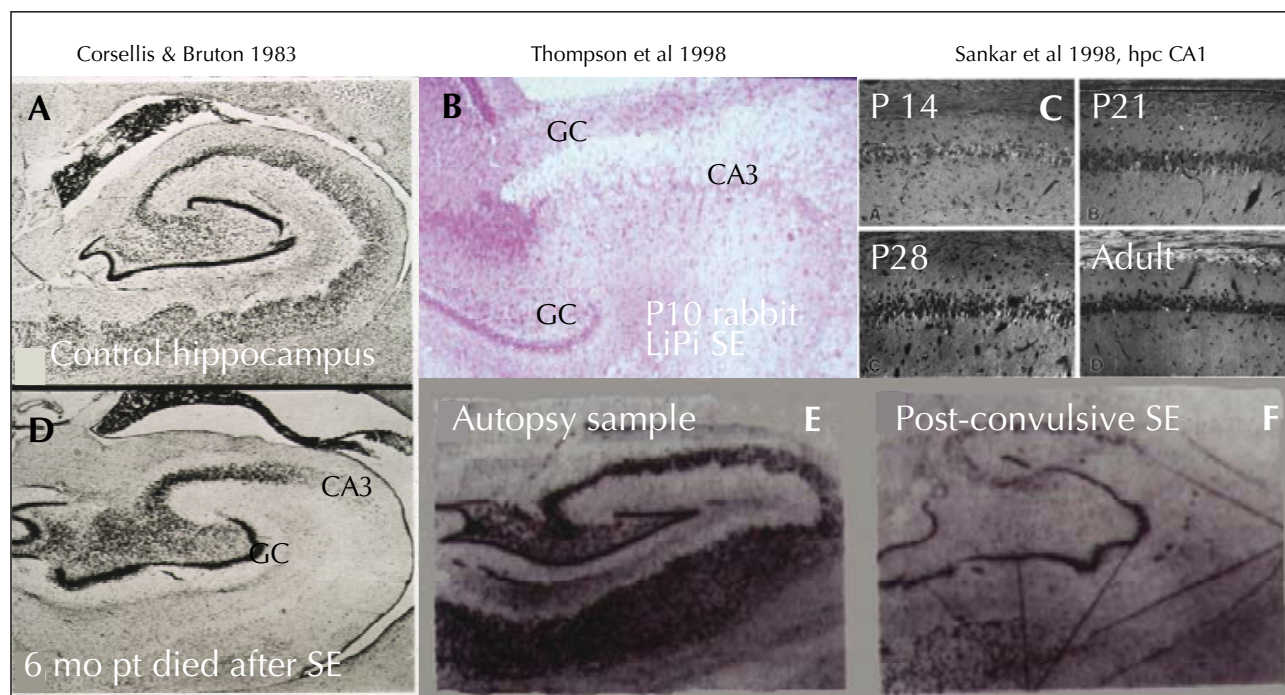


Figure 2. The hippocampus of humans who died after status epilepticus shows extensive neuronal injury in CA1, CA3 and hilus, both in a 5-year-old child (D) and in an adult (F). The distribution of damage is very similar to that seen in a 10-day-old rabbit after SE induced by lithium and pilocarpine (B). A study of the ontogeny of neuronal injury shows that it is both age- and model-dependent, since in 14-day-old rats CA1 damage is maximal in this model (C) and absent in the perforant path stimulation model (not shown).

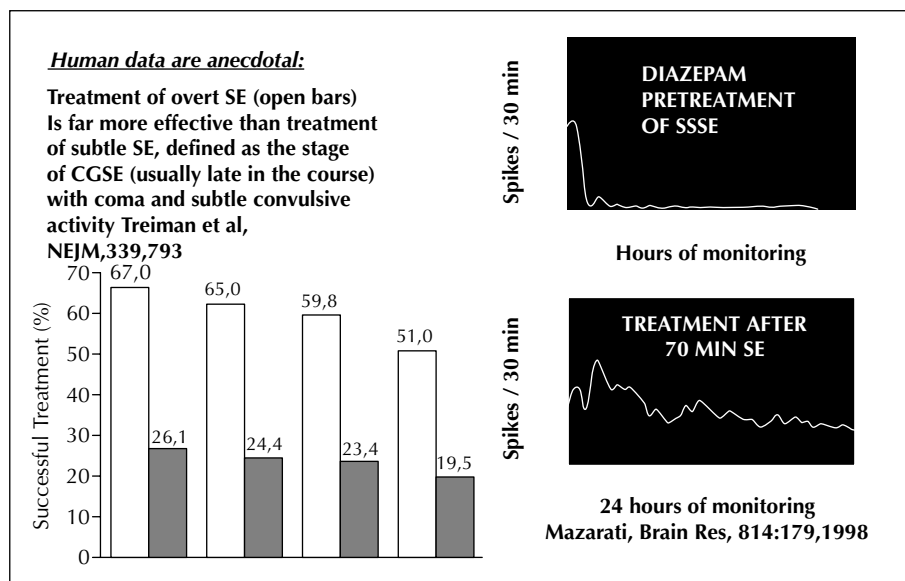


Figure 3. Early injection of diazepam stops spikes in perioral path stimulation SE (top right). This very effective therapeutic response is largely lost when injection of the same agent is delayed (bottom right), possibly due to SE-induced internalization of GABAA receptors.

Can we extrapolate animal data on SE-induced pharmacoresistance to humans?

The time-dependent development of pharmacoresistance to benzodiazepines and other anticonvulsants has been documented in animal models (Mazarati *et al.* 1998). In human SE, (as shown in figure 3) early treatment is much more efficacious than late treatment (Treiman *et al.* 1990), but pharmacoresistance is only one of several possible explanations for that phenomenon.

References

- Camfield PR. Recurrent seizures in the developing brain are not harmful. *Epilepsia* 1997; 38: 735-7.
- Cendes F, Andermann F, Carpenter S. *et al.* Temporal lobe epilepsy caused by domoic acid intoxication: evidence for glutamate receptor-mediated excitotoxicity in humans. *Ann Neurol* 1995; 37,123-6.
- Chu K, Kang DW, Kim JY. *et al.* Diffusion-weighted magnetic resonance imaging in nonconvulsive status epilepticus. *Arch Neurol* 2001; 58(6), 993-8.
- DeGiorgio CM, Gott PS, Rabinowicz AL. *et al.* Neuron-specific enolase, a marker of acute neuronal injury, is increased in complex partial status epilepticus. *Epilepsia* 1996; 37(7), 606-9.
- Freeman JL, Coleman LT, Smith LJ. *et al.* Hemiconvulsion-hemiplegia-epilepsy syndrome: characteristic early magnetic resonance imaging findings. *J Child Neurol* 2002; 17(1), 10-6.
- Hesdorffer DC, Loroscino G, Cascina G. *et al.* Incidence of Status Epilepticus in Rochester, Minnesota 1965-1984. *Neurology* 1998; 50, 735-41.
- Lansberg MG, O'Brien MW, Norbash AM. *et al.* MRI abnormalities associated with partial status epilepticus. *Neurology* 1999; 52(5), 1021-7.
- Lazeyras F, Blanke O, Zimine I. *et al.* MRI, (1)H-MRS, and functional MRI during and after prolonged nonconvulsive seizure activity. *Neurology* 2000; 55(11), 1677-82.
- Mazarati AM, Baldwin RA, Sankar R. *et al.* Time-dependent decrease in the effectiveness of antiepileptic drugs during the course of self-sustaining status epilepticus. *Brain Res* 1998; 814,179-185.
- Meldrum BS, Brierley JB. Prolonged epileptic seizures in primates. Ischemic cell change and its relation to ictal physiological events. *Arch Neurol* 1973; 28, 10-17.
- Meldrum BS, Vigoroux RA, Brierley J.B. Systemic factors and epileptic brain damage. Prolonged seizures in paralysed artificially ventilated baboons. *Arch Neurol* 1973; 29, 82-7.
- Men S, Lee DH, Barron JR. *et al.* Selective neuronal necrosis associated with status epilepticus: MR findings. *Am J Neuroradiol* 2000; 21, 1837-40.
- Morimoto T, Fukuda M, Suzuki Y. *et al.* Sequential changes of brain CT and MRI after febrile status epilepticus in a 6 year-old girl. *Brain Develop* 2002; 24, 190-3.
- Nixon J, Bateman D, Moss T. An MRI and neuropathological study of a case of fatal status epilepticus. *Seizure* 2001; 10(8), 588-91.
- O'Regan ME, Brown JK. Serum neuron specific enolase: A marker for neuronal dysfunction in children with continuous EEG epileptiform activity. *European Journal of Paediatric Neurology* 1998; 2, 193-197.
- Pascual-Castroviejo I, Pascual-Pascual SI, Pena W. *et al.* Status epilepticus-induced brain damage and opercular syndrome in childhood. *Dev Med Child Neurol* 1999; 41(6), 420-3.
- Rabinowicz AL, Correale JD, Bracht KA. *et al.* Neuron-specific enolase is increased after nonconvulsive status epilepticus. *Epilepsia* 1995; 36, 475-479.

Salmenpera T, Kalviainen R, Partanen K. *et al.* MRI volumetry of the hippocampus, amygdala, entorhina MRI volumetry of the hippocampus, amygdala, entorhinal cortex, and perirhinal cortex after status epilepticus. *Epilepsy Res* 2000; 40(2-3), 155-70.

Sankar R, Shin DH, Liu H. *et al.* Patterns of Status Epilepticus-induced neuronal injury during development and long-term consequences. *J Neurosci* 1998; 18, 8382-8393.

Sankar R, Shin D, Mazarati AM. *et al.* Epileptogenesis after status epilepticus reflects age- and model-dependent plasticity. *Ann Neurol* 2000; 48(4), 580-9

Sloviter RS, Damiano BP, Sustained electrical stimulation of the perforant path duplicates kainate-induced electrophysiological effects and hippocampal damage in rats. *Neurosci Lett* 1981; 24, 279-284.

Thompson KW, Wasterlain CG. Lithium-pilocarpine status epilepticus in the immature rabbit. *Brain Research* 1997; 100, 1-4.

Thompson K, Holm AM, Schousboe A. *et al.* Hippocampal stimulation produces neuronal death in the immature brain. *Neuroscience* 1998; 82, 337-48.

Treiman DM, Walton NY, Kendrick C. A progressive sequence of electroencephalographic changes during generalized convulsive status epilepticus. *Epilepsy Res* 1990; 5, 49-60.

Verity CM, Ross EM, Golding J. Outcome of childhood status epilepticus and lengthy febrile convulsions: findings of national cohort study. *BMJ* 1993; 307(6898), 225-8.

Discussion by Matthew Walker

Dept of Clinical and Experimental Epilepsy,
Institute of Neurology, Queen Square, London, WC1N 3BG, UK

Professor Wasterlain has eloquently made the point that there is overwhelming animal evidence of neuronal damage, epileptogenesis and pharmacoresistance with non-convulsive status epilepticus, further emphasising Dr Cock's argument that neuronal damage is only one part of a host of changes that occur following status epilepticus. He also provides evidence that there are similar findings in humans, but that the evidence is indirect. Perhaps his most important contention is at the beginning, when he quotes Norbert Wiener... «The best model of a cat is another cat, and preferably the same cat». This is where the problem lies in extrapolating the data. There is growing animal evidence that there are a number of factors that can influence the response of animal models to status epilepticus, including age, history of previous epilepsy and exposure to antiepileptic drugs, all of which are relevant to the human condition. Most conclusions from animal models are however, achieved in models induced in naïve animals using powerful stimuli. Thus, there is little doubt of the possible consequences of nonconvulsive status epilepticus, but these consequences are not necessarily inevitable, and we should take care in extrapolating the animal data to humans. In particular, we should take note of Professor Wasterlain's comment that the animal models «reproduce an isolated component of the illness». Thus when using the animal data to inform us about the human condition, we should take care to bear in mind the limitations of the experiments.

Neuroimaging in NCSE

John Duncan

National Society for Epilepsy, Chalfont St Peter,
Gerrards Cross, SL9 0RJ, UK

There is not a large or systematic literature on this topic, but there are many anecdotal human studies and the topic features in parts of other papers. The definitions used are important, and studies may encompass partial and absence status, and also epilepsy partialis continua.

Partial status

Aetiologies identified by neuroimaging

The aetiology of nonconvulsive status epilepticus (NCSE) may be identified by MRI, but there may be no evident abnormality (Thomas *et al.* 1998). Common underlying aetiologies include focal cortical dysplasia (Yoshimura 2003), alcohol abuse, vascular disease, tumours, hippocampal sclerosis, neurosyphilis and nonketotic hyperglycemia, and other metabolic derangements (Fujiwara *et al.* 1991; Thomas *et al.* 1999; Kumpfel *et al.* 2000; Chang *et al.* 2001). Polymicrogyria may underlie electrical status epilepticus during sleep (Guerrini *et al.* 1998).

Cerebral atrophy, in Alzheimer's disease, may be the pathology underlying NCSE and be demonstrated with MRI (Armon *et al.* 2000). Focal cortical dysplasia, that underlies NCSE, may not be evident preoperatively, despite detailed imaging, and only shown pathologically if resective surgery is carried out (Ng *et al.* 2003). Initial imaging abnormalities in NCSE may suggest a progressive cerebral pathology, such as a neoplasm, and follow-up after resolution of NCSE may indicate the transient nature of abnormalities (Murchison *et al.* 1995).

Diagnosis

Imaging techniques may be useful in diagnosing NCSE. NCSE may be caused by focal seizure activity, which may not be evident on scalp EEG. In a case report, the sodium amyltal test was used to make the diagnosis (Burneo *et al.* 2003).

MRI changes with NCSE

Focal nonconvulsive status may be associated with cerebral swelling, increased signal on T2-weighted and fluid attenuated inversion recovery images, with gyral swelling. Hyperintensity on diffusion-weighted imaging reflects cytotoxic intracellular oedema due to excitotoxicity that leads to neuronal death. The apparent diffusion coefficient is decreased acutely in the corresponding areas. The MRI abnormalities may indicate the presence of cytotoxic and vasogenic edema, hyperperfusion of the epileptic region, and alteration of the leptomeningeal blood-brain barrier

(Juhász *et al.* 1998, Lansberg *et al.* 1999). In some cases, the absence of diffusion-weighted imaging (DWI) changes may infer an absence of cytotoxic oedema (Hattori *et al.* 2003). There may be increased signal in feeding arteries on MRA, and leptomeningeal enhancement on postcontrast MRI (Lansberg *et al.* 1999). On follow-up, abnormalities resolve, and there may be atrophy and hypointensity on DWI (Kumpfel *et al.* 2000, Matsuoka *et al.* 2003, Chu *et al.* 2001, Hattori *et al.* 2003).

Perfusion imaging with dynamic contrast enhancement with gadolinium shows increased local blood delivery in focal status (Warach *et al.* 1994). NCSE may be associated with increased perfusion, demonstrated with perfusion imaging and high signal on DWI that resolved after cessation of the status (Flacke *et al.* 2000). In a case of epilepsy partialis continua, serial diffusion and perfusion MR imaging followed the changes in haemodynamic and cell membrane permeability (Calistri *et al.* 2003).

Subcortical T2 hypointensity in the vicinity of the epileptic focus has been reported in partial status epilepticus in the context of nonketotic hyperglycemia. The explanation was not clear, and the accumulation of free radicals was suggested (Seo *et al.* 2003).

In focal motor status epilepticus investigated with DWI, decreased diffusion of water (increase of apparent diffusion coefficients (ADC)) have been reported, with return to normal afterwards, and with, in some cases, the development of atrophy (Wiesmann *et al.* 1997, Diehl *et al.* 1999, Senn *et al.* 2003). Transient focal hyperperfusion may also be identified (El-Koussy *et al.* 2002).

MR spectroscopy

In a case of focal status, with increased signal at the focus shown with FLAIR imaging, (Aghakhani *et al.* 2004) H-MRS showed elevated lactate, decreased N-acetylaspartate (NAA), and elevated choline (Cho). EEG-fMRI revealed an area of increased BOLD signal. After seizure control, lactate and Cho returned to normal, whereas the NAA level may remain reduced, implying neuronal loss or persistent dysfunction (Lazeyras *et al.* 2000).

Using proton magnetic resonance spectroscopic imaging there was an increase in lactate to creatine plus phosphocreatine (lactate/creatine) values, following complex partial seizures. This reflected an imbalance in energy supply and demand, during and soon after complex partial seizures, but this was not seen during or after absence seizures. There was no change in the N-acetylaspartate/creatine ratio following seizures, inferring that there was no subsequent neuronal dysfunction, but this was not NCSE (Cendes *et al.* 1997).

During frontal partial status epilepticus, on the basis of a focal cortical malformation, N-acetyl-aspartate concentration in the focal dysgenic cortex was decreased interictally, and further reduced during episodes of status. The

creatine plus phosphocreatine concentration was normal ictally and interictally. Lactate was evident during status, but not interictally. The inference was of transient metabolic derangement consequent to the status, superimposed on the abnormalities associated with the malformation (Mueller *et al.* 2001).

SPECT changes with NCSE

Single-photon emission computed tomography study using 99mTc-ECD often demonstrates focal hyperperfusion in NCSE, particularly of frontal origin (Fujiwara *et al.* 1991; Ichiseki *et al.* 1995; Juhász *et al.* 1998; Thomas *et al.* 1999; Matsuoka *et al.* 2003; Hattori *et al.* 2003) and in epilepsy partialis continua (Sztriha *et al.* 1994). Increased focal signal on SPECT studies of rCBF may persist for many hours after focal status appears to have stopped (Tatum *et al.* 1994).

It has been debated whether periodic lateralized epileptiform discharges (PLEDs) represent a form of seizure discharge, even status epilepticus. In a case report (Ali *et al.* 2001) and in a series of 18 patients with PLEDs, SPECT showed increased focal cerebral blood flow, suggesting that this may represent a form of partial status epilepticus (Assal *et al.* 2001).

FDG PET changes with NCSE

Focal hypermetabolism and concordant focal increase in T2-weighted signal images in MRI have been reported in epilepsy partialis continua (Yoshida *et al.* 1995). Nonconvulsive status epilepticus may however, be associated with focal hypometabolism, rather than hypermetabolism (Chung *et al.* 2002). Hypometabolism in the right parietal lobe has been reported in a case of electrical status epilepticus in sleep (ESES) (Mariotti *et al.* 2000).

Studies of partial non-convulsive status in animal models

Limbic status epilepticus, produced in baboons by injection of kainic acid into the amygdala, was associated with increased glucose metabolism in the ipsilateral frontal and temporal lobes, as shown with 18F-FDG PET (Cepeda *et al.* 1982).

Kainic acid was injected into the amygdala of dogs to induce complex partial status epilepticus (Hasegawa *et al.* 2003). MRI studies comprising T2 weighted (T2W) imaging, fluid attenuated inversion recovery (FLAIR) and DWI were carried out at 3, 6, 12, 24 and 48 h after onset of complex partial status epilepticus, and the animals were killed immediately after the MRI, to obtain histological correlation. At 3 and 6 h, DWI hyperintensity and low ADC were found in the injected amygdala, without any T2W and FLAIR imaging changes. At 12 and 24 h, all imaging showed hyperintensity with higher ADC in the amygdala and the hippocampus. At 48 h, all imaging

techniques showed continued hyperintensity, but ADC was returning to normal.

This study suggests that DWI may be a useful imaging method for localizing the epileptic focus and for identifying brain damage in status epilepticus.

Increased Lactate, and a sustained decrease in N-acetyl aspartate have been noted in the hippocampal region with the KA model (Ebisu *et al.* 1996, Najm *et al.* 1998).

By way of comparison, in rats, pilocarpine induced status epilepticus has been marked by increased T2-weighted signal, and increased regional blood volume, reflecting hyperperfusion, principally in the amygdale, piriform and entorhinal cortices (Yu *et al.* 2002, Roch *et al.* 2002a, Fabene *et al.* 2003). Chronically, these features resolved and were replaced by those of atrophy and gliosis (Roch *et al.* 2002b). Status epilepticus, induced by electroshocks, caused decrease of the apparent diffusion coefficient of brain water, thought to be due to cell swelling (Prichard *et al.* 1995).

Absence status

Glucose metabolism was measured in six adults with typical absences (Theodore *et al.* 1984). Interictally, glucose metabolism was normal. Two were studied again during absences. In one, generalized spike wave activity occupied 38% of the scanning time and this was associated with a 60% increase in glucose consumption. The other was in absence status and a global reduction of glucose consumption was seen.

Serial atypical absences, with generalized 3- to 3.3-Hz spike-and-wave discharges on EEG, were shown to be of right frontal origin, associated with focally increased glucose metabolism on 18F-fluorodeoxyglucose PET (Millan *et al.* 2001).

Serial absences, but not true absence status was associated with a global increase in cerebral blood flow, and a particular increase in the thalamus, measured with H₂¹⁵O PET (Prevett *et al.* 1995). Using fMRI, a prolonged absence was associated with reduction of BOLD signal in the association areas of the neocortex and an increase in the thalamus (Salek-Haddadi *et al.* 2003). Other workers have found both increases and decreases of BOLD signal in the neocortex with absences and increases in the thalamus have been a more consistent finding (Aghakhani *et al.* 2004).

References

- Aghakhani Y, Bagshaw AP, Benar CG, *et al.* fMRI activation during spike and wave discharges in idiopathic generalized epilepsy. *Brain* 2004; in press.
- Ali II, Pirzada NA, Vaughn BV. Periodic lateralized epileptiform discharges after complex partial status epilepticus associated with increased focal cerebral blood flow. *J Clin Neurophysiol* 2001; 18: 565-9.
- Armon C, Peterson GW, Liwnicz BH. Alzheimer's disease underlies some cases of complex partial status epilepticus. *J Clin Neurophysiol* 2000; 17: 511-8.
- Assal F, Papazyan JP, Slosman DO, *et al.* SPECT in periodic lateralized epileptiform discharges (PLEDs): a form of partial status epilepticus? *Seizure* 2001; 10: 260-5.
- Burneo JG, Knowlton RC, Gomez C *et al.* Confirmation of non-convulsive limbic status epilepticus with the sodium amytal test. *Epilepsia* 2003; 44: 1122-6.
- Calistri V, Caramia F, Bianco F, *et al.* Visualization of evolving status epilepticus with diffusion and perfusion MR imaging. *AJNR Am J Neuroradiol* 2003; 24: 671-3.
- Cendes F, Stanley JA, Dubeau F, *et al.* Proton magnetic resonance spectroscopic imaging for discrimination of absence and complex partial seizures. *Ann Neurol* 1997; 41: 74-81.
- Cepeda C, Menini C, Naquet R, *et al.* Positron emission tomography in a case of experimental focal epilepsy in the baboon. *Electroencephalogr Clin Neurophysiol* 1982; 54: 87-90.
- Chang JW, Chang JH, Park SC, *et al.* Radiologically confirmed de novo glioblastoma multiforme and hippocampal sclerosis associated with the first onset of nonconvulsive simple partial status epilepticus. *Acta Neurochir (Wien)* 2001; 143: 297-300.
- Chu K, Kang DW, Kim JY, *et al.* Diffusion-weighted magnetic resonance imaging in nonconvulsive status epilepticus. *Arch Neurol* 2001; 58: 993-8.
- Chung PW, Seo DW, Kwon JC, *et al.* Nonconvulsive status epilepticus presenting as a subacute progressive aphasia. *Seizure* 2002; 11: 449-54.
- Diehl B, Najm I, Ruggieri P, Foldvary N, *et al.* Periictal diffusion-weighted imaging in a case of lesional epilepsy. *Epilepsia* 1999; 40: 1667-71.
- Ebisu T, Rooney WD, Graham SH, *et al.* MR spectroscopic imaging and diffusion-weighted MRI for early detection of kainate-induced status epilepticus in the rat. *Magn Reson Med* 1996; 36: 821-8.
- El-Koussy M, Mathis J, Lovblad KO, *et al.* Focal status epilepticus: follow-up by perfusion- and diffusion MRI. *Eur Radiol* 2002; 12: 568-74.
- Fabene PF, Marzola P, Sbarbati A, *et al.* Magnetic resonance imaging of changes elicited by status epilepticus in the rat brain: diffusion-weighted and T2-weighted images, regional blood volume maps, and direct correlation with tissue and cell damage. *Neuroimag* 2003; 18: 375-89.
- Flacke S, Wullner U, Keller E, *et al.* Reversible changes in echo planar perfusion- and diffusion-weighted MRI in status epilepticus. *Neuroradiol* 2000; 42: 92-5.
- Fujiwara T, Watanabe M, Matsuda K, *et al.* Complex partial status epilepticus provoked by ingestion of alcohol: a case report. *Epilepsia* 1991; 32: 650-6.
- Guerrini R, Genton P, Bureau M, *et al.* Multilobar polymicrogyria, intractable drop attack seizures, and sleep-related electrical status epilepticus. *Neurology* 1998; 51: 504-12.
- Hasegawa D, Orima H, Fujita M, *et al.* Diffusion-weighted imaging in kainic acid-induced complex partial status epilepticus in dogs. *Brain Res* 2003; 983(1-2): 115-27.

- Hattori H, Matsuoka O, Ishida H, *et al.* Magnetic resonance imaging in occipital lobe epilepsy with frequent seizures. *Pediatr Neurol* 2003; 28: 216-8.
- Ichiseki H, Hamamoto M, Miyazaki T. *et al.* Regional cerebral blood flow in status epilepticus measured by single photon emission computed tomography (SPECT). *Nippon Ika Daigaku Zasshi* 1995; 62: 605-14.
- Juhász C, Scheidl E, Szirmai I. Reversible focal MRI abnormalities due to status epilepticus. An EEG, single photon emission computed tomography, transcranial Doppler follow-up study. *Electroencephalogr Clin Neurophysiol* 1998; 107: 402-7.
- Kumpfel T, Lechner C, Auer D, *et al.* Non-convulsive status epilepticus with marked neuropsychiatric manifestations and MRI changes after treatment of hypercalcaemia. *Acta Neurol Scand* 2000; 102: 337-9.
- Lansberg MG, O'Brien MW, Norbash AM, *et al.* MRI abnormalities associated with partial status epilepticus. *Neurology* 1999; 52: 1021-7.
- Lazeyras F, Blanke O, Zimine I, *et al.* MRI, H-MRS, and functional MRI during and after prolonged nonconvulsive seizure activity. *Neurology* 2000; 55: 1677-82.
- Mariotti P, Della Marca G, Iuvone L, *et al.* Is ESES/CSWS a strictly age-related disorder? *Clin Neurophysiol* 2000; 111: 452-6.
- Matsuoka O, Ishida H, Hisatsune S, *et al.* Magnetic resonance imaging in occipital lobe epilepsy with frequent seizures. *Pediatr Neurol* 2003; 28: 216-8.
- Millan E, Abou-Khalil B, Delbeke D, *et al.* Frontal Localization of Absence Seizures Demonstrated by Ictal Positron Emission Tomography. *Epilepsy Behav* 2001; 2: 54-60.
- Mueller SG, Kollias SS, Trabesinger AH, *et al.* Proton magnetic resonance spectroscopy characteristics of a focal cortical dysgenesis during status epilepticus and in the interictal state. *Seizure* 2001; 10: 518-24.
- Murchison JT, Sellar RJ, Steers AJ. Status epilepticus presenting as progressive dysphasia. *Neuroradiol* 1995; 37: 438-9.
- Najm IM, Wang Y, Shedid D, *et al.* MRS metabolic markers of seizures and seizure-induced neuronal damage. *Epilepsia* 1998; 39: 244-50.
- Ng YT, Kim HL, Wheless JW. Successful neurosurgical treatment of childhood complex partial status epilepticus with focal resection. *Epilepsia* 2003; 44: 468-71.
- Prevett MC, Duncan JS, Fish DR, *et al.* Demonstration of thalamic activation during absence seizures using H215O and PET. *Neurology* 1995; 45: 1396-402.
- Prichard JW, Zhong J, Petroff OA, *et al.* Diffusion-weighted NMR imaging changes caused by electrical activation of the brain. *NMR Biomed* 1995; 8: 359-64.
- Roch C, Leroy C, Nehlig A, *et al.* Predictive value of cortical injury for the development of temporal lobe epilepsy in 21-day-old rats: an MRI approach using the lithium-pilocarpine model. *Epilepsia* 2002a; 43: 1129-36.
- Roch C, Leroy C, Nehlig A. *et al.* Magnetic resonance imaging in the study of the lithium-pilocarpine model of temporal lobe epilepsy in adult rats. *Epilepsia* 2002b; 43: 325-35.
- Salek-Haddadi A, Lemieux L, Merschhemke M, *et al.* Functional magnetic resonance imaging of human absence seizures. *Ann Neurol* 2003; 53: 663-667.
- Senn P, Lovblad KO, Zutter D, *et al.* Changes on diffusion-weighted MRI with focal motor status epilepticus: case report. *Neuroradiol* 2003; 45: 246-9.
- Seo DW, Na DG, Na DL, *et al.* Subcortical hypointensity in partial status epilepticus associated with nonketotic hyperglycemia. *J Neuroimaging* 2003; 13: 259-63.
- Sztriha L, Pavics L, Ambrus E. Epilepsia partialis continua: follow-up with 99mTc-HMPAO-SPECT. *Neuropediatrics* 1994; 25: 250-4.
- Tatum WO, Alavi A, Stecker MM. Technetium-99m-HMPAO SPECT in partial status epilepticus. *J Nucl Med* 1994; 35: 1087-94.
- Theodore WH, Brooks R, Sato S *et al.* The role of positron emission tomography in the evaluation of seizure disorders. *Ann Neurol* 1984; 15 (suppl): S176-179.
- Thomas P, Giraud K, Alchaar H, *et al.* Ictal asomatognosia with hemiparesis. *Neurology* 1998; 51: 280-2.
- Thomas P, Zifkin B, Migneco O, *et al.* Nonconvulsive status epilepticus of frontal origin. *Neurology* 1999; 52: 1174-83.
- Warach S, Levin JM, Schomer DL, *et al.* Hyperperfusion of ictal seizure focus demonstrated by MR perfusion imaging. *AJNR Am J Neuroradiol* 1994; 15: 965-8.
- Wieshmann UC, Symms MR, Shorvon SD. Diffusion changes in status epilepticus. *Lancet* 1997; 350: 493-4.
- Yoshida T, Tanaka M, Masuda T, *et al.* Epilepsia partialis continua with an epileptic focus demonstrated by PET and unique MRI findings: report of a case. *Rinsho Shinkeigaku* 1995; 35: 1021-4.
- Yoshimura K. A case of nonconvulsive status epilepticus associated with focal cortical dysplasia. *Brain Dev* 2003; 25: 207-10.
- Yu O, Roch C, Namer IJ, *et al.* Detection of late epilepsy by the texture analysis of MR brain images in the lithium-pilocarpine rat model. *Magn Reson Imaging* 2002; 20: 771-5.

Discussion by Udo Wieshmann

The Walton Centre for Neurology and Neurosurgery, Lower Lane, Fazakerley, Liverpool, L9 7LJ UK,

The main role of neuroimaging in nonconvulsive status epilepticus (NCSE) is to identify structural abnormalities in selected patients using conventional X-ray computed tomography (CT) or magnetic resonance imaging (MRI).

Novel imaging tools including positron emission tomography (PET), single-photon emission computed tomography (SPECT), functional magnetic resonance imaging (fMRI) and perfusion and diffusion Imaging provided an interesting insight in some of the underlying changes in highly selected patients but are, overall, not practical. PET and SPECT have a low temporal resolution and expose the patient to ionizing radiation. fMRI and perfusion MRI have a low signal-to-noise ratio, diffusion MRI appears to be of limited sensitivity. The use of the above techniques is further limited by the necessity to transfer acutely ill patients to the X-ray department for lengthy investigations. Near infrared spectroscopy and transcranial doppler ultrasound can be used at the bedside, but have inherent technical limitations including very limited sampling.

An ideal neuro-imaging tool should detect neuronal changes associated with NCSE, should provide insight in the underlying mechanisms and should have no side effects.

More than 70 years after the introduction of the EEG, this tool is still awaited.

Clinical neuroimaging in NCSE

EEG remains the main diagnostic tool in non-convulsive status epilepticus (NCSE). Standard radiology textbooks make no specific reference to NCSE (Grainger and Allison, 1998). There is no clinical use of neuroimaging in patients with typical absence status. Neuroimaging does have a clinical role, in adjunction to EEG, in patients with complex partial NCSE. CT and, if feasible, MRI, are useful clinical tools in complex partial status epilepticus with which to exclude underlying structural abnormalities. CT would also be used in most patients prior to a lumbar puncture, for example in a patient with NCSE and suspected Herpes encephalitis.

Experimental neuroimaging in NCSE

Taken together, the results of positron emission tomography, single-photon emission computed tomography (SPECT), functional magnetic resonance imaging (fMRI), magnetic resonance spectroscopy and perfusion and diffusion weighted imaging (DWI) in status, suggest a focal increase in flow and metabolism with oedema, increased lactate and reduced NAA in partial status and a possible increase in flow in the thalamus in absence status (Warach *et al.* 1994 and John Duncan for review). DWI has been reported as normal in some patients with status, raising doubts about the sensitivity of the technique (Diehl *et al.* 2001). Only anecdotal evidence is available despite the fact that some techniques have been available for many years (PET for example since 1975). A possible explanation is that such studies are usually not feasible in acutely ill patients.

Two bedside methods, near infra-red spectroscopy (NIRS) and transcranial Doppler (TCD) ultrasound are worth mentioning in this context. Neither NIRS nor TCD generate images (at least at this stage). NIRS provides measurements of cerebral oxygenation and TCD of blood flow. Both methods demonstrated changes during seizures (Haginoya *et al.* 2002; Buchheim *et al.* 2004; Niehaus *et al.* 2000). The main problem is that both techniques sample only small areas. Whether electrical impedance tomography is useful in NCS remains to be seen (Bagshaw *et al.* 2003). There is clearly a need for new, inexpensive and non-invasive bedside tools.

References

Bagshaw AP, Liston AD, Bayford RH, *et al.* Electrical impedance tomography of human brain function using reconstruction algorithms based on the finite element method. *Neuroimage* 2003;

20: 752-64.

Buchheim K, Obrig H, v Pannwitz W, *et al.* Decrease in haemoglobin oxygenation during absence seizures in adult humans. *Neurosci Lett* 2004; 354: 119-22.

Diehl B, Najm I, Ruggieri P, *et al.* Postictal diffusion-weighted imaging for the localization of focal epileptic areas in temporal lobe epilepsy. *Epilepsia* 2000; 42: 21-8.

Grainger RG, Allison DJ, *Diagnostic radiology* 1998; 3rd ed. Churchill Livingstone.

Haginoya K, Munakata M, Kato R, *et al.* Ictal cerebral haemodynamics of childhood epilepsy measured with near-infrared spectrophotometry. *Brain* 2002; 125: 1960-71.

Niehaus L, Wiesmann UC, Meyer BU, Changes in cerebral hemodynamics during simple partial motor seizures. *Eur Neurol* 2000; 44: 8-11.

Warach S, Levin JM, Schomer DL, *et al.* Hyperperfusion of ictal seizure focus demonstrated by MR perfusion imaging. *AJNR Am J Neuroradiol* 1994; 15: 965-8.

What is the evidence for treatment regimens in NCSE?

Rod Scott

The Wolfson Centre, Mecklenburgh Square,
London, WC1N 2AP, UK

The diagnosis, classification and outcomes of nonconvulsive status epilepticus are not generally agreed, and therefore there is no foundation on which to build appropriate treatment strategies. This has led to a difficult and confusing literature from which no clear guidelines can be derived. I will however, consider three related situations;

1. subtle generalised convulsive status epilepticus
2. 'generic' NCSE comprising absence and complex partial NCSE
3. epileptic encephalopathies

Important aspects of the management of NCSE include treatment of epileptic discharges, identification of pharmacological precipitants, treatment of underlying or associated encephalopathy, and the management of behavioural and educational difficulties.

Subtle generalised convulsive status epilepticus (sGCSE)

This clinical situation is otherwise known as status epilepticus in coma, and manifests as subtle motor activity associated with ongoing epileptic discharges. The outcome is poor with a high mortality. It seems likely that sGCSE is more similar to refractory convulsive status epilepticus (CSE) than to NCSE, given the natural history (*i.e.* may begin as an episode of convulsive status epilepticus) and observed poor outcome. Thus, guidelines appropriate for CSE are appropriate for sGCSE. Although many guidelines exist, it is only the early aspects that are based on evidence from a randomised controlled trial, and the

evidence is that benzodiazepines are relatively ineffective in the treatment of sGCSE with a response rate no greater than 25% (Treiman *et al.* 1998). There are few data assessing later therapies for sGCSE and therefore the guidelines at this stage are largely practice- and experience-based.

Generic NCSE

The main goal of therapy for absence and complex partial status epilepticus is to clear the EEG of epileptic discharges with the aim of improving an individual's function. There are no randomised controlled trials comparing active ingredients with placebo, or comparing therapies. A study comparing the treatment approaches by neurologists and intensive care physicians revealed a broad spectrum of recommended agents and differing views on how aggressively to treat NCSE, including whether, or when, to admit to intensive care unit (Holtkamp *et al.* 2003). Benzodiazepines are the most widely recommended agents, although there continues to be debate on which route is the most effective. Intravenous and oral benzodiazepines (Gastaut *et al.* 1984) have been used successfully. Other recommended first-line agents include, phenytoin (Camacho *et al.* 2001) and sodium valproate (Kaplan 1999). The evidence to support any of these recommendations is largely anecdotal. In addition, there remains uncertainty about how aggressive treatment needs to be. If NCSE can be shown to cause brain injury then aggressive treatment can be justified; if not, then the treatment may cause more morbidity than the NCSE.

NCSE can be provoked by a variety of agents and these should be identified. Drugs that have been implicated in the provocation of NCSE include antiepileptic drugs (e.g. phenytoin, tiagabine, carbamazepine, vigabatrin, phenobarbitone), antiepileptic drug withdrawal (e.g. benzodiazepines, lamotrigine, sodium valproate), antidepressants (e.g. fluoxetine), antibiotics (e.g. cephalosporins), anti-asthma drugs (e.g. theophylline), and chemotherapeutic agents (e.g. ifosfamide).

Epileptic encephalopathies

The relationships between epileptic discharges, learning disability, behavioural disorders and underlying encephalopathy remain unclear. However, treatment is based on the hypothesis that epileptic discharges are causally related to the encephalopathy, and therefore treatment of discharges may improve outcome. Conventional AEDs including benzodiazepines, sodium valproate and ethosuximide have been recommended although there are no rigorous trials supporting the recommendations. Other agents include sulthiame and ketamine. There is increasing evidence that steroids may be helpful in certain circumstances, particularly in Landau-Kleffner syndrome. Multiple sub-pial transections may be a useful surgical intervention. Although there appears to be a return towards normality in some children treated with steroids, the steroids seldom return the child to complete normality. Therefore, in addition to pharmacological or surgical

therapy, behavioural and educational interventions may be required.

In conclusion, there are no clear guidelines on the management of NCSE. This is because there is no clear definition of NCSE, very few randomised controlled trials, and those that exist are not carried out in the most typical patients. Unfortunately, at the current time there does not appear to be a clear strategy for rectifying these weaknesses

References

- Camacho A, Perez-Martinez DA, Villarejo A, *et al.* Nonconvulsive status epilepticus: experience in 33 patients. [Spanish]. *Neurologia* 2001; 16: 394-8.
- Gastaut H, Tinuper P, Aguglia U, *et al.* Treatment of certain forms of status epilepticus by means of a single oral dose of clobazam. [French]. *Rev Electroencephalogr Neurophysiol Clin* 1984; 14: 203-6.
- Holtkamp M, Masuhr F, Harms L, *et al.* The management of refractory generalised convulsive and complex partial status epilepticus in three European countries: a survey among epileptologists and critical care neurologists. *J Neurol Neurosurg Psychiatry* 2003; 74: 1095-9.
- Kaplan PW. Assessing the outcomes in patients with nonconvulsive status epilepticus: nonconvulsive status epilepticus is underdiagnosed, potentially overtreated, and confounded by comorbidity. *J Clin Neurophysiol* 1999; 16: 341-52.
- Treiman DM, Meyers PD, Walton NY, *et al.* A comparison of four treatments for generalized convulsive status epilepticus. Veterans Affairs Status Epilepticus Cooperative Study Group. *N Engl J Med* 1998; 339: 792-8.

Discussion by Richard Appleton

The Roald Dahl EEG Unit, Alder Hey Children's Hospital, Eaton Road, Liverpool, L12 2AP, UK

The evaluation of the effectiveness of any treatment - and specifically when comparing different treatments - must take into account many factors. Firstly, there must be an agreed definition of what constitutes nonconvulsive status epilepticus (NCSE) and an accurate electro-clinical classification of the different (NCSE) syndromes. Secondly, there must be the correct identification and study of 'pure' populations of patients with the same NCSE syndrome and same underlying aetiology. Finally, there must be clearly defined and practicable outcome measures by which different treatment regimes can be evaluated.

In terms of classification, the NCSE syndromes of hypsarrhythmia, generalised slow, spike and slow wave activity in Lennox-Gastaut syndrome (LGS), the Landau-Kleffner/electrical status epilepticus of slow sleep (ECESS) syndrome complex and complex partial (focal) status epilepticus are quite separate and relatively well-recognised. However, it is also important to classify further the NCSE

syndromes by aetiology – as these syndromes may result from a range of different causes – and, not surprisingly may show differential responses to the same treatment regimes. Perhaps somewhat surprisingly, only within the last few years has there been any attempt to assess different treatment options in specific causes of arguably the most common NCSE syndrome – West syndrome (hypsarrhythmia defining the NCSE) and specifically tuberous sclerosis (Ciron *et al.* 1997) and Down's syndrome (Eisermann *et al.* 2003). This type of assessment (by aetiology) has not been evaluated (or at least, not reported) for the other commonly identified NCSE syndromes. The reports published of different treatment regimes in these other, non-West, NCSE syndromes have tended to group or 'lump' together all causes and, as a consequence, the results are difficult to interpret. Any conclusions are at best of uncertain and at worst, of dubious clinical significance.

Finally, the outcome measures used to assess the response to any individual, but more importantly, comparative treatments, are clearly important and must include:

- Clinical criteria; these should encompass clinically identified seizure activity and non-seizure activity (e.g. awareness, short-term memory, processing of information) – which may be difficult to evaluate in view of the fact that the children may be young and may have accompanying moderate, severe or even profound learning difficulties.
- EEG criteria
- Short- and long-term follow-up data; it is clearly important to identify one or more treatment regimes that may be effective in terminating an episode of NCSE. However, it is equally (if not more) important to obtain information on how effective a specific treatment may be, firstly in ensuring that any initial termination of an episode of NCSE is sustained and secondly in preventing a recurrence – as

recurrences are a frustratingly common and persistent phenomenon in most NCSE syndromes. This is reflected by the fact that so many different (and still expanding [e.g.: ketamine (Mewasingh *et al.* 2003)]) treatments are used in the management of NCSE.

With these pre-requisites for assessing treatment regimes, it is not surprising that there are extraordinarily limited published scientific data that can be used to decide how and with what NCSE can and should be most appropriately treated.

References

- Chiron C, Dumas J, Jambaque I, *et al.* Randomised trial comparing vigabatrin and hydrocortisone in infantile spasms due to tuberous sclerosis. *Epilepsy Research* 1997; 26, 389-95.
- Eisermann MM, DeLaRaillere A, Dellatolas G, *et al.* Infantile spasms in Down syndrome – effects of delayed anticonvulsant treatment. *Epilepsy Res* 2003; 55: 21-7.
- Mewasingh LD, Sekhara T, Aeby A, *et al.* Oral ketamine in paediatric non-convulsive status epilepticus. *Seizure* 2003; 12: 483-9.

Typical absence status epilepticus

Micheal Koutroumanidis

Dept of Clinical Neurophysiology and Epilepsy,
Guy's and St Thomas's NHS Trust, London, SE1 7EH, UK

Absence status epilepticus (ASE) is a prolonged state of altered consciousness, associated with generalised 3Hz spike-wave EEG activity. A history of typical absences (TA) or generalised tonic-clonic seizures GTCS is usually dis-

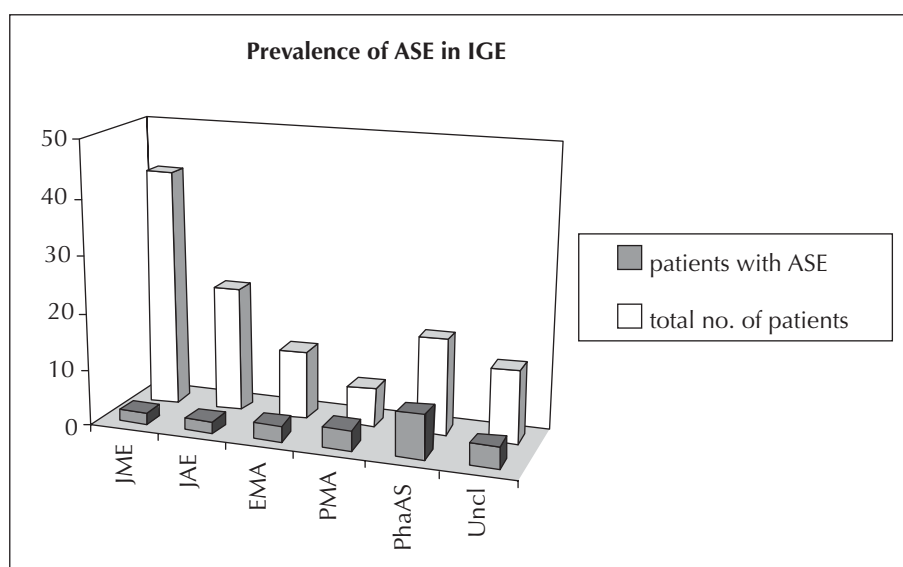


Table 1. Prevalence of absence status epilepticus (ASE) in IGE.

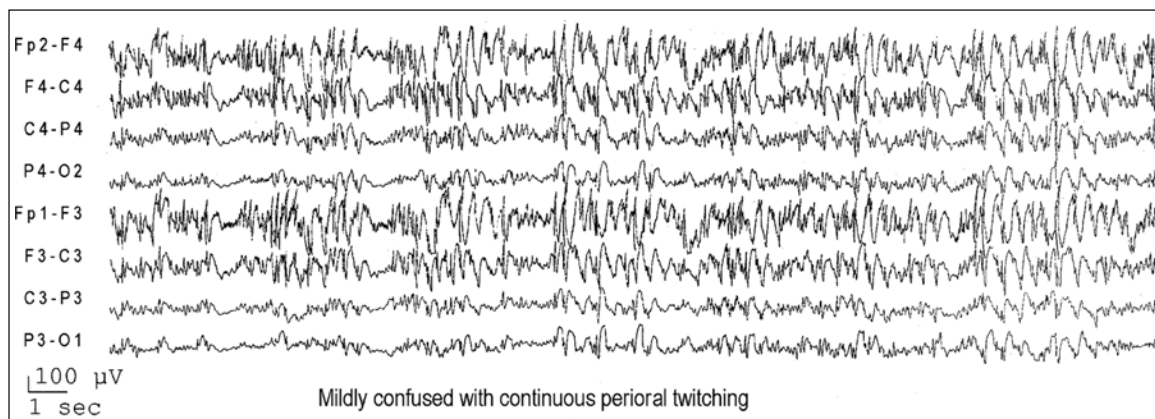


Figure 1. ASE in a 23-year-old woman with perioral myoclonia with absences (PMA). She started with typical absences and GTCS at the age of 11 years, and the first episode of ASE occurred when she was 14 years old. She had four episodes of ASE in total, all ending in GTCS. No precipitants were identified. Ictal EEG shows a continuous arrhythmic pattern of generalized spike/polyspike-and-wave discharges.

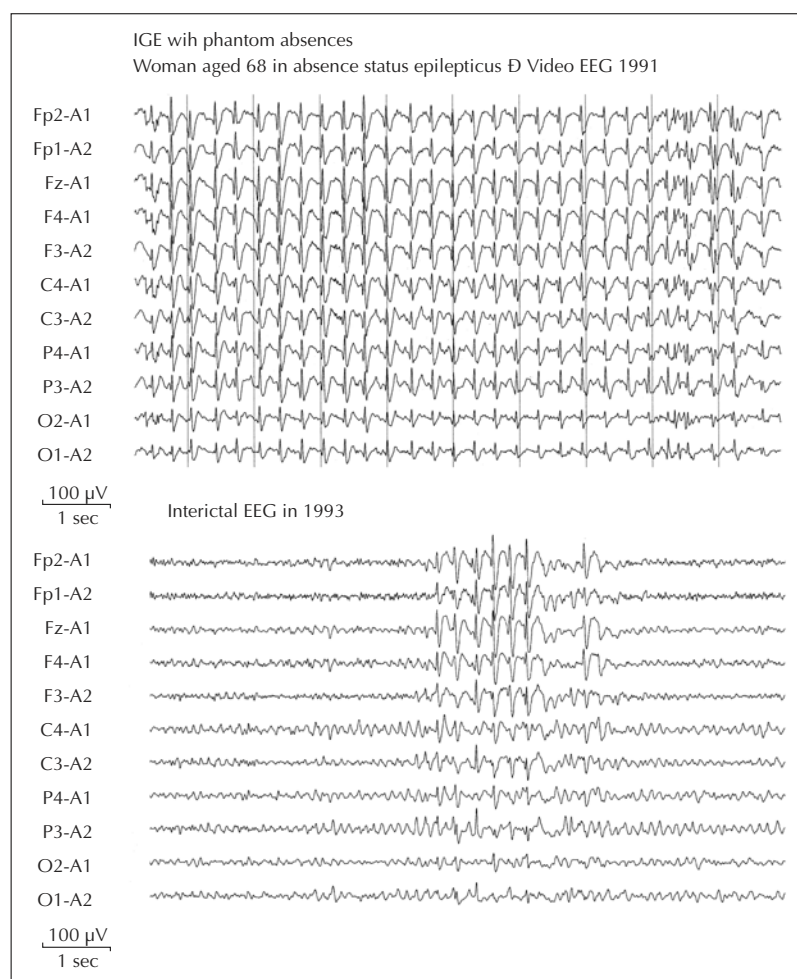


Figure 2. ASE in a 68-year-old woman with phantom absences and late onset GTCS. Her first ASE occurred at age 30 years, and she had had more than 35 episodes of ASE, invariably ending with GTCS. There were no precipitating factors. Despite a continuous regular EEG pattern of spike-and-wave at 3 Hz, impairment of cognition was minimal.

cernible. Because there are no generalised convulsions, ASE is classified as a form of nonconvulsive status epilepticus (NCSE), of which lobar NCSE is thought to be the main representative. However, any similarities between the two conditions end here. Impairment of consciousness is milder in ASE than in lobar NCSE, and lacks the characteristic latter's cycling changes between unresponsiveness and partial responsiveness. Speech and memory are also less severely disturbed (Shorvon, 1994, Treiman, 1995). Abnormal movements, if present, consist of regional bilateral (eyelid, perioral, or upper limb) myoclonia in sharp contrast to the lateralised focal motor activity in lobar NCSE. Aetiology, EEG and imaging findings and response to treatment also differ markedly. Although some debate exists as to whether lobar NCSE can induce brain damage, there is no clinical evidence of ensuing morbidity irrespective of the number of ASE episodes in the individual patient. Despite these fundamental differences, most large studies have included all patients with NCSE, without trying to separate those with possible ASE. Thus, our knowledge on ASE is still limited, and relies on few small series and case reports.

ASE is not rare. Andermann and Robb (1972) found ASE in 10% of their adult patients with TA, whereas we diagnosed ASE in 25% of our adults with TA (15.5% of IGE), using video-EEG (Agathonikou *et al.* 1998). The first episode usually occurs well after the onset of TA and GTCS (mean onset of ASE: 29.5 years; TA: 9 years; GTCS: 21 years (Agathonikou *et al.* 1998)), but it may be the first ever

clinical manifestation of IGE in up to 1/3 of patients. It recurs in up to 85% of patients, (Agathonikou *et al.* 1998) sometimes up to 100 times, (Baykan *et al.* 2002) and consistently terminates with GTCS in up to 50% of patients. Early childhood appears strangely immune to ASE, and the two youngest patients in the literature were 10 years old (Baykan *et al.* 2002, Panayiotopoulos *et al.* 2001). The prevalence of ASE seems to be syndrome related, and occurs more often in conditions associated with brief and mild TA (*figure 1*).

Its typical onset at an age period when the severity of TA has lessened may also explain the apparent paradoxical discrepancy between the profound impairment of cognition of the «archetypical» sporadic absence and the relatively preserved responsiveness of memory and speech during the prolonged ASE. Minor regional motor phenomena during ASE are usually similar to those during the sporadic TA, conforming to the profile of the specific sub-syndrome (*figure 1*).

Ictal EEG may be continuous or discontinuous at 3 Hz, but may be slower if recorded late into the state (D'Agostino *et al.* 1999) (*figures 1, 2 and 3*). Precipitating factors include sleep deprivation, alcohol, stress or relaxation, withdrawal of AED for IGE or administration of inappropriate AED for IGE, but may be consistently absent in up to 30% of patients (Agathonikou *et al.* 1998).

Diagnosis is frequently missed, as patients' relatively composed appearance may be deceptive. Characteristically, patients with recurrent episodes have attended A&E claim-

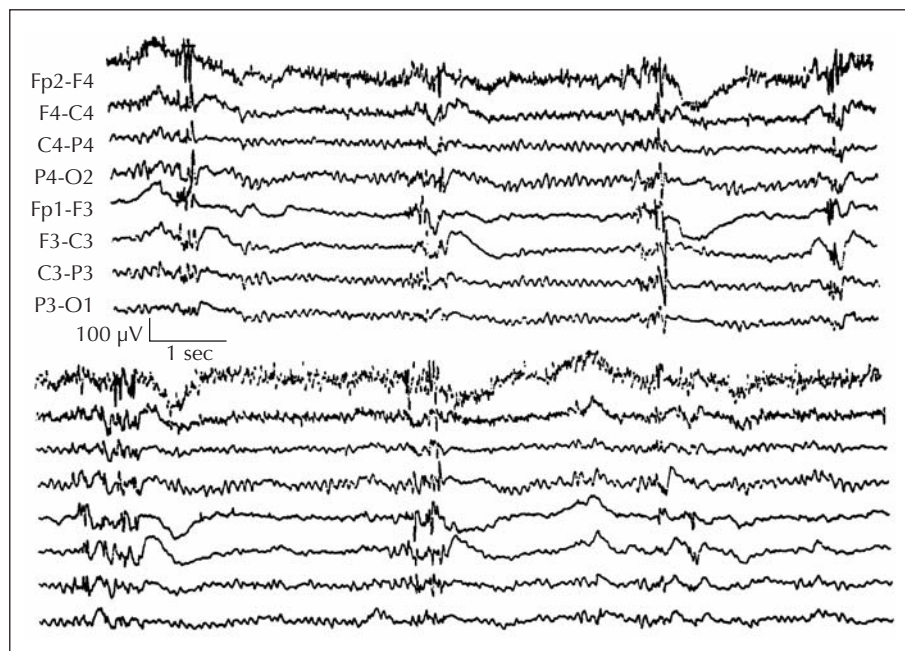


Figure 3. ASE associated with discontinuous, pseudorhythmic, generalised 3Hz spike-and-wave pattern in a 66-year-old patient with typical absences since the age of 9 years, and GTCS since the age of 48 years. He has had more than 30 episodes of ASE, usually ending with GTCS. There are no precipitating factors.

ing that they are in ASE, only to be believed after EEG confirmation a few hours later. If NCSE is clinically suspected, differentiation from lobar NCSE requires EEG and is usually straightforward with the possible exception of the frontal lobe NCSE (Thomas *et al.* 1999). Particular attention is needed when the EEG is discontinuous (figure 3).

De novo, late onset ASE (Thomas *et al.* 1992) has been described in elderly patients without previous epileptic seizures, but with diverse pathological conditions, including metabolic disturbances, toxic and pharmacologic agents, benzodiazepine withdrawal, angiography etc. Although there might be some overlap, this is probably a distinct condition that should not be confused with ASE when the latter occurs as a first IGE manifestation in otherwise healthy patients, not least because of different management.

ASE is certainly easier to treat than lobar NCSE, and most patients appear to respond to a currently «liberal» approach that includes any benzodiazepine IV until the EEG improves and the patient feels better. However, there are no data on the risk of early recurrence, and no EEG criteria to unequivocally define the offset of the episode. The high rate of recurrence and termination with a GTCS, the long duration and the possible life-threatening risks (typically a patient driving during ASE until a GTCS occurred), suggest the need for a standard, rigorous protocol. Lorazepam IV is equally effective but longer acting than diazepam, while Clonazepam IV may have a place if there is prominent myoclonus. As some patients may be aware of their recurrent ASE, treatment may start outside hospital with buccal Midazolam (Scott *et al.* 1999). A 24-hour admission will ensure clinical and EEG clearance, and enable topping up of sodium valproate (SV) levels if needed. Persistence is best dealt with SV i.v. (D'Agostino *et al.* 1999, Alehan *et al.* 1999), and early reassessment is important.

References

- Aghakhani Y, Bagshaw AP, Benar CG, *et al.* fMRI activation during spike and wave discharges in idiopathic generalized epilepsy. *Brain* 2004; in press.
- Alehan FK, Morton LD, Pellock JM. Treatment of absence status with intravenous valproate. *Neurology* 1999; 52: 889-90.
- Andermann F, Robb JP. Absence status. A reappraisal following review of thirty-eight patients. *Epilepsia* 1972; 13: 177-87.
- Baykan B, Gokyigit A, Gurses C, *et al.* Recurrent absence status epilepticus: clinical and EEG characteristics. *Seizure* 2002; 11: 310-9.
- D'Agostino MD, Andermann F, Dubeau F, *et al.* Exceptionally long absence status: multifactorial etiology, drug interactions and complications. *Epileptic Disord* 1999; 1: 229-32.
- Panayiotopoulos CP, Ferrie CD, Koutroumanidis M, *et al.* Idiopathic generalised epilepsy with phantom absences and absence status in a child. *Epileptic Disord* 2001; 3: 63-6.
- Scott RC, Besag FM, Neville BG. Buccal midazolam and rectal diazepam for treatment of prolonged seizures in childhood and adolescence: a randomised trial. *Lancet* 1999; 353: 623-6.
- Shorvon S. The concept of status epilepticus and its history. Chap 1 in: Shorvon S ed. *Status epilepticus: its clinical features and treatment in children and adults*. 1994; Cambridge: Cambridge University Press, 1-20.
- Shorvon S. *Status Epilepticus: its Clinical Features and Treatment in Children and Adults*. Cambridge: Cambridge University Press 1994; 382.
- Thomas P, Zifkin B, Migneco O, *et al.* Nonconvulsive status epilepticus of frontal origin. *Neurology* 1999; 52: 1174-83.
- Treiman DM. Electroclinical features of status epilepticus. *J Clin Neurophysiol* 1995; 12: 343-62.

Complex partial status epilepticus

David Treiman

Barrow Neurological Institute, 350 West Thames Road, Phoenix, AZ 85013, USA

There are many definitions of status epilepticus and its various subtypes, which depend on duration and frequency of ictal activity, and extent of recovery and duration between ictal events. However, (Treiman 1996), suggested a unifying physiologic definition of status epilepticus as a situation where seizure-induced, acute impairment of neurological function or alteration of brain physiology does not fully recover to the pre-seizure state before another seizure occurs. This fits nicely with the definition of complex partial status epilepticus provided by Shorvon 1994: a prolonged epileptic episode in which fluctuating or frequently recurring focal electrographic epileptic discharges, arising in temporal or extratemporal regions, result in a confusional state with variable clinical symptoms.

Complex partial status epilepticus (CPSE) was first described independently by Hughlings-Jackson, and perhaps by Charcot, (Goetz 1987) in 1888, although there were earlier isolated reports of cases that likely were episodes of CPSE. The first case verified by EEG was described by Gastaut and colleagues in 1956. We now recognize CPSE as the epileptic twilight confusional state caused by prolonged focal epileptic discharges from temporal or extratemporal regions of the brain. Although once considered rare, there was an explosion of interest in this entity starting about 20 years ago, perhaps due to the advent of CCTV/EEG epilepsy monitoring (Delgado-Escueta and Treiman 1987) and by 1990 more than 200 cases had been reported. Current thinking is that CPSE may account for as many as one quarter of all episodes of SE.

Two clinical presentations have been suggested - discontinuous (complex partial seizures separated by confusion)

and continuous (epileptic twilight state). (Gastaut and Tassinari 1975) These two presentations probably represent a continuum in a spectrum of electroclinical changes that approximate, albeit in a much milder way, to those of generalized convulsive status epilepticus (GCSE) described by Treiman *et al.* 1990. A frequent, but not essential, clinical feature of CPSE is cycling between a continuous twilight state with partial and amnesic responsiveness and an arrest reaction with motionless stare, complete unresponsiveness and stereotyped automatisms, (Treiman and Delgado-Escueta 1983, Delgado-Escueta and Treiman 1987).

Diagnosis of CPSE is based on a clinical presentation of a confusional state (sometimes punctuated by periods of less responsiveness and stereotyped automatisms), an ictal EEG with focal discharges like those of isolated CP seizures on an abnormal background, prompt response of the behavior and EEG to intravenous AEDs, and an interictal epileptiform focus in one or more temporal or frontal lobes. Differential diagnosis includes absence SE, other 'epileptiform' causes of confusion, and a variety of organic encephalopathies and psychiatric syndromes. (Treiman and Delgado-Escueta 1983). Thus, EEG is essential for differentiating CPSE from other causes of confusional states, although, in the absence of readily available EEG, rapid recovery after intravenous treatment with an antiepileptic drug is convincing.

Progressive neuronal damage occurs the longer experimental CPSE continues (Fujikawa 1996), and profound memory deficits have been reported after prolonged episodes of human CPSE (Engel Jr. *et al.* 1978, Treiman *et al.* 1981, Krumholz *et al.* 1995). The EEG may progress through the five stages (discrete, merging, continuous, continuous with flat periods, periodic epileptiform discharges) reported by Treiman *et al.* (1990) in GCSE, but probably requires much longer to do so, and thus the later EEG stages are rarely observed in CPSE. However, there have been two reports of these EEG changes in human CPSE, (Reiher *et al.* 1992, Nowack and Shaikh 1999) A unifying conceptualization of the relationship between different types and clinical presentations of cortical (localization related) SE is proposed: the electroclinical presentation of cortical SE is the result of an interaction between the extent of cortical spread (SP? CP? SG), impairment of transmission down the neuroaxis (overt? subtle? electrical), and «severity» of the episode (EEG stage I? V). This concept will need to be validated by further clinical data and comparative experimental studies.

References

Delgado-Escueta AV, Treiman D.M. Focal status epilepticus: Modern concepts. In: Luders H, Lesser RP, editors. *Epilepsy: Electroclinical syndromes*. Berlin: Springer-Verlag 1987; 347-91.

Engel J, Ludwig BI, Fetell M. Prolonged partial complex status epilepticus: EEG and behavioral observations. *Neurology* 1978; 28: 863-9.

Fujikawa DG. The temporal evolution of neuronal damage from pilocarpine-induced status epilepticus. *Brain Res* 1996; 725: 11-22.

Gastaut H, Roger J, Roger A. Sur la signification de certaines fugues épileptiques: état de mal temporal. *Rev Neurol* 1956; 94: 298-301.

Gastaut H, Tassinari CA. In: Redmond A, editor. *Status epilepticus. Handbook of Electroencephalography and Clinical Neurophysiology*. Amsterdam: Elsevier, 1975.

Goetz CG. Charcot at the Salpêtrière: ambulatory automatisms. *Neurology* 1987; 37: 1084-8.

Krumholz A, Sung GY, Fisher RS, *et al.* Complex partial status epilepticus accompanied by serious morbidity and mortality. *Neurology* 1995; 45, 1499-504.

Nowack WJ, Shaikh IA. Progression of electroclinical changes in complex partial status epilepticus: filling in the blanks. *Clin Electroencephal* 1999; 30: 5-8.

Reiher J, Grand'Maison F, Leduc CP. Partial status epilepticus: short-term prediction of seizure outcome from on-line EEG analysis. *Electroencephalogr Clin Neurophysiol* 1992; 82: 17-22.

Shorvon S. The concept of status epilepticus and its history. Chap 1 in: Shorvon S ed. *Status epilepticus: its clinical features and treatment in children and adults*. Cambridge: Cambridge University Press, 1994: 1-20.

Shorvon S, *Status Epilepticus: its Clinical Features and Treatment in Children and Adults*. Cambridge: Cambridge University Press, 1994: 382.

Treiman DM, Delgado-Escueta AV. Complex partial status epilepticus. In: Delgado-Escueta AV, Wasterlain CG, Treiman DM, Porter RJ, editors. *Status Epilepticus: Mechanisms of Brain Damage and Treatment (Adv Neurol, Vol 34)*. New York: Raven Press 1983; 69-81.

Treiman DM, Delgado-Escueta AV, Clark M. Impairment of memory following complex partial status epilepticus. *Epilepsy International Congress Abstracts* 1981; 57.

Treiman DM, Walton NY, Kendrick C. A progressive sequence of electroencephalographic changes during generalized convulsive status epilepticus. *Epilepsy Res* 1990; 5: 49-60.

Treiman DM. Status epilepticus. *Bailliere's Clinical Neurology* 1996; 5: 821-39.

Discussion by Matthew Walker

Dept of Clinical and Experimental Epilepsy, Institute of Neurology, Queens Square, London, WC1N 3BG, UK

There have been case reports of acute neurological deficit and poor outcome in patients with complex partial status epilepticus (Treiman and Delgado, 1983, Engel *et al.* 1978, Krumholz *et al.* 1995). Yet these have been selected case reports and the true incidence of morbidity and mortality following complex partial status epilepticus remains largely unknown. A recent study in 100 unselected patients with nonconvulsive status epilepticus suggests that the mortality may be as high as 18% (Shneker and Fountain 2003). This study raised an important issue in that those with a prior diagnosis of epilepsy had a much

lower mortality than those with nonconvulsive status epilepticus in the setting of an acute medical illness. Indeed, considering just patients with epilepsy in unselected case series of complex partial status epilepticus reveals a low mortality with only 2 out of 101 patients dying, one of which was probably secondary to treatment (Shneker and Fountain 2003, Scholtes *et al.* 1996, Tomson *et al.* 1992, Cockerell *et al.* 1994, Williamson *et al.* 1985). Furthermore, in none of these studies was any serious morbidity reported in patients with epilepsy who develop nonconvulsive status epilepticus. Acutely precipitated complex partial status epilepticus, and complex partial status epilepticus in the setting of a person with epilepsy should thus be considered as two separate conditions. Complex partial status epilepticus in someone with epilepsy is probably, for the most part, a relatively benign condition; patients commonly have repeated episodes which may respond to oral benzodiazepines (Cockerell *et al.* 1994).

Complex partial status epilepticus in the setting of an acute medical illness has, on the other hand, a high mortality and morbidity (Shneker and Fountain 2003). The mortality probably relates to the underlying cause (see figure). Aggressive treatment in such patients can, in some circumstances (e.g. the acutely ill elderly), increase mortality (Litt *et al.* 1998), and the treatment decisions have to be based upon the balance of benefit and adverse effects of the drugs given.

References

- Cockerell OC, Walker MC, Sander J W, *et al.* Complex partial status epilepticus: a recurrent problem. *J. Neurol. Neurosurg. Psychiatry* 1994; 57: 835-7.
- Engel J, Ludwig BI, Fetell M. Prolonged partial complex status epilepticus: EEG and behavioral observations. *Neurology* 1978; 28: 863-9.
- Krumholz A, Sung GY, Fisher RS, *et al.* Complex partial status epilepticus accompanied by serious morbidity and mortality. *Neurology* 1995; 45: 1499-504.
- Litt B, Wityk RJ, Hertz SH, Mullen, *et al.* Nonconvulsive status epilepticus in the critically ill elderly. *Epilepsia* 1998; 39: 1194-202.
- Scholtes FB, Renier WO, Meinardi H. Non-convulsive status epilepticus: causes, treatment, and outcome in 65 patients. *J Neurol Neurosurg Psychiatry* 1996; 61: 93-5.
- Shneker BF, Fountain NB. Assessment of acute morbidity and mortality in nonconvulsive status epilepticus. *Neurology* 2003; 61: 1066-73.
- Tomson T, Lindbom U, Nilsson BY. Nonconvulsive status epilepticus in adults: thirty-two consecutive patients from a general hospital population. *Epilepsia* 1992; 33: 829-35.
- Treiman DM, Delgado-Escueta AV. Complex partial status epilepticus. In: Delgado-Escueta AV, Wasterlain CG, Treiman DM, Porter RJ, editors. *Status Epilepticus: Mechanisms of Brain Damage and Treatment* (Adv Neurol, Vol 34). New York: Raven Press, 1983: 69-81.
- Williamson PD, Spencer DD, Spencer SS, *et al.* Complex partial status epilepticus: a depth-electrode study. *Ann Neurol* 1985; 18: 647-54.

Status epilepticus in coma

Robert DeLorenzo

Dept Neurology, Virginia Commonwealth University, School of Medicine, PO Box 980599, Richmond, Virginia, VA 23298, USA

Status epilepticus (SE) is a major medical and neurological emergency that is associated with significant morbidity and mortality (Aicardi and Chevrie 1970, Bleck 1991, DeLorenzo *et al.* 1995, DeLorenzo *et al.* 1996, De Lorenzo *et al.* 1997, Hauser 1990, Logroscino *et al.* 2002, Shinnar *et al.* 2001, Shorvon 2002, Towne *et al.* 1994, Treiman *et al.* 1998, Treiman 1999, Waterhouse *et al.* 1999). Considerable interest has been directed towards understanding the presentation of SE in coma. Studies from the VCU SE study have demonstrated that SE is a major cause of coma (DeLorenzo *et al.* 1998) and that a significant fraction of comatose patients manifest SE (Towne *et al.* 2000). Thus, it is important to recognize the importance of conducting EEG monitoring on all comatose patients and all SE patients that are treated successfully for clinical seizure activity but still remain in coma.

SE as a cause of coma

Studies from our research effort (DeLorenzo *et al.* 1998) have demonstrated that following the treatment of convulsive SE, 67% of cases were in coma 1 hour after the successful treatment of convulsive SE (CSE), either due to medication effects or underlying medical problems. Continuous EEG monitoring, for a minimum of 24 hours, of 164 prospectively evaluated patients in coma for more than 2 hours after the successful treatment of clinical CSE demonstrated that 52% of the cases had no epileptiform discharges after treatment of CSE. Thus, 52% of the comatose cases with no clinical seizure activity in CSE had no further epileptiform discharges after treatment (*figure 1A*). However, 48% of the cases that remained in coma after treatment of CSE had after SE ictal discharges (ASIDS) (*figure 1A*). The patients that manifested ASIDS were found to manifest two distinct EEG patterns: delayed ictal discharges (DIDS) and non-convulsive SE (NCSE). DIDS were defined as electrographic seizure discharges that occurred as single events or as multiple episodes, but that did fit the definition of NCSE (DeLorenzo *et al.* 1998). Thirty four per cent of all comatose cases after the control of clinical CSE manifested DIDS (*figure 1A*). In addition, 14% of the comatose cases following the successful control of clinical CSE were still in NCSE and would not have been clinically recognized unless EEG monitoring was performed (*figure 1A*). NCSE is a severe form of SE that is more difficult to identify, and has been associated with a

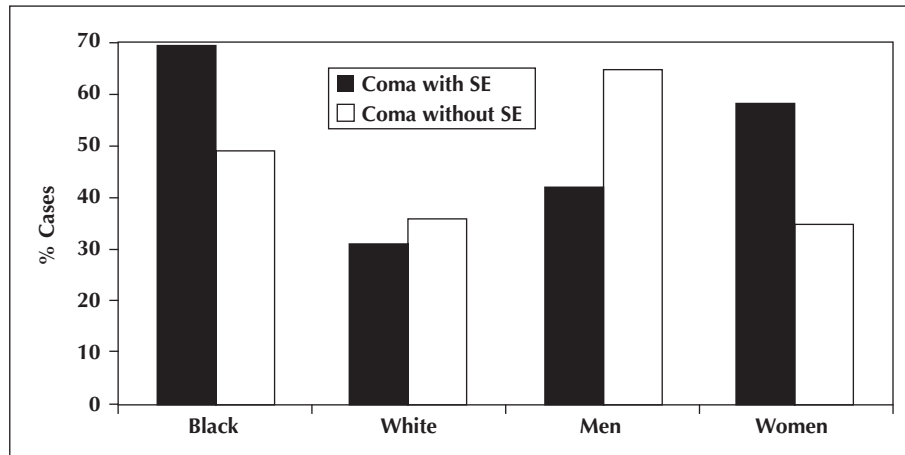


Figure 1. A) Percentage of patients with EEG patterns of ASIDS, NCSE and DIDS in comatose patients after the control of CSE with standard SE treatment; 164 patients were EEG monitored for at least 24 hours after control of CSE. **B)** Mortality (white) and poor outcome (black) for the no ASIDS, NCSE and DIDS EEG pattern. * $p < 0.001$, ** $p < 0.02$. Modified from DeLorenzo *et al.* 1998

higher morbidity and mortality (DeLorenzo *et al.* 1998, Tomson *et al.* 1986, Treiman *et al.* 1984). It is important to determine if the different EEG patterns observed after the clinical control of clinical CSE had any effect on outcome, since this would determine the need for EEG monitoring or further treatment efforts. *Figure 1B* presents data demonstrating that the mortality and morbidity were much higher for patients with the EEG patterns containing DIDS and NCSE compared to cases where the EEG did not manifest ASIDS. Thus, the presence of ASIDS and especially NCSE EEG patterns after the control of clinical seizure activity in CSE, were significantly associated with a much higher mortality and poor outcome (mortality plus morbidity, DeLorenzo *et al.* 1998) (*figure 1B*).

The etiologies for the patients with no ASIDS, DIDS, and NCSE are presented in *table 1*.

The data represent the total number of patients in each etiology for each EEG type. The number of patients in the

no ASIDS, DIDS, and NCSE groups was 84, 56, and 24 respectively. The DIDS and NCSE cases did not manifest the drug overdose etiology and had a lower number of AED discontinuations and ETOH withdrawal. These findings suggest that etiology may be contributing to the morbidity and mortality associated with these EEG patterns, since the etiologies with the higher mortalities were associated with the patients with DIDS and NCSE. To evaluate risk factors for mortality and poor outcome (morbidity plus mortality, DeLorenzo *et al.* 1998), multivariate logistic regression analysis with age, etiologies, and EEG patterns as covariates was conducted to evaluate whether the EEG patterns were still predictors of outcome when controlling for etiology and age. The etiologies shown in *table 1* were grouped into high, moderate and low mortality groups to increase the power of the analysis, as described previously (DeLorenzo *et al.* 1998). The results demonstrated that the NCSE EEG pattern was a predictor

Table 1. Etiologies for each EEG pattern

Etiology	No ASIDS	NCSE	DIDS
AED discontinuation	33	13	9
ETOH	11	8	2
CVA	24	21	36
Head trauma	2	0	2
Hypoxia/anoxia	7	21	11
Systemic infection	1	17	7
Metabolic	5	8	16
Remote symptomatic	12	0	3
Drug overdose	2	0	0
Subdural hematoma	1	4	5
Tumor	1	8	9

The data represent the percentage of patients with each etiology for each EEG type. The total number of patients with ASIDS, NCSE and DIDS were 84, 24 and 56. Modified from DeLorenzo *et al.* 1998.

Table 2. Multivariate logistic regression analysis of mortality with post-CSE EEG patterns, age and etiologies.

Factors	Mortality (%)	OR ^a (CI)	p-Value
Etiology			
Mid-mortality	25.7	1	
High mortality	62.9	2.58 (1.53, 4.35)	<0.001 ^b
Low mortality	6.2	0.50 (0.33, 0.74)	<0.001 ^b
Nonelderly	14.7	1	
Elderly	40.0	2.02 (1.2, 3.21)	0.003 ^b
CSE to no ASIDS	13.1	1	
CSE to NCSE	50.0	1.90 (1.10, 3.26)	0.027 ^c
CSE to DIDS	30.4	0.96 (0.76, 1.23)	0.608

^a OR (Odds Ratio) of the given factor *versus* the factor with OR = 1 after adjustment was made for other factors.

^b Statistically significant result of test of OR = 1 after adjustment was made for other factors.

^c Statistically significant result of test of OR < 1 after adjustment was made for the effect of etiology and age.

Modified from DeLorenzo *et al.* 1998.

of both increased mortality (*table 2*) and poor outcome (*table 3*) when compared to no ASIDS and DIDS and when controlled for age and etiology.

Thus, the presence of the NCSE EEG pattern after the control of clinical CSE was a predictor of mortality and poor outcome independent of etiology and age. Previous

studies have demonstrated that SE can have synergistic effects on mortality for some etiologies (Waterhouse *et al.* 1998). These results indicate that NCSE as a predictor, is independent in causing and increased morbidity and mortality due to this seizure type and not merely the result of more severe etiologies. The increased mortality and poor outcome associated with DIDS using univariate analysis

Table 3. Multivariate logistic regression analysis for poor outcome with post-CSE EEG patterns, age and etiologies

EEG pattern	Poor outcome (%)	OR ^a + (CI)	p-Value
Etiology			
Mid-mortality	38.3	1	
High mortality	68.8	2.05 (1.30, 3.25)	0.002 ^b
Low mortality	12.3	0.58 (0.42, 0.79)	<0.001 ^b
Nonelderly	26.3	1	
Elderly	49.3	1.65 (1.11, 2.46)	0.01 ^b
CSE to no ASIDS	20.2	1	
CSE to NCSE	58.3	1.66 (1.07, 2.59)	0.030 ^c
CSE to DIDS	44.6	1.00 (0.90, 1.27)	0.487

^a OR (*odds ratio*) of the given factor *versus* the factor with OR = 1 after adjustment was made for other factors.

^b Statistically significant result of test of OR = 1 after adjustment was made for other factors.

^c Statistically significant result of test of OR < 1 after adjustment was made for the effect of etiology and age.

Modified from DeLorenzo *et al.* 1998.

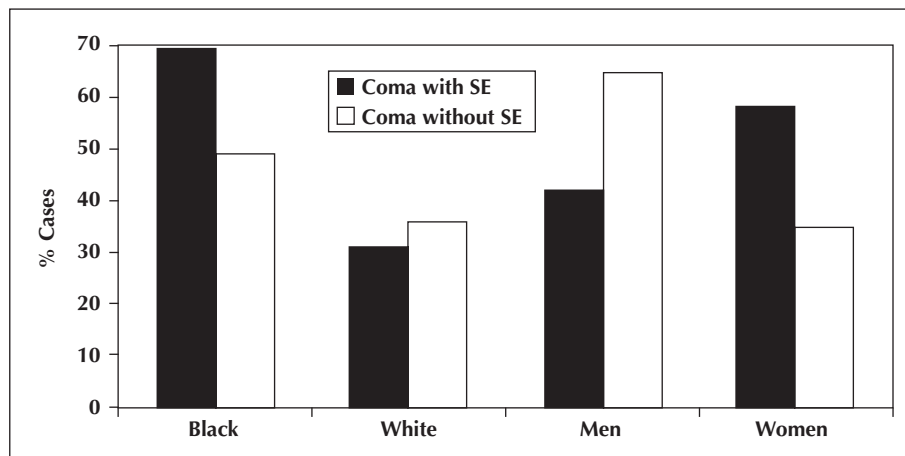


Figure 2. Distribution of race and gender for coma with and without SE. The data represents the percentage of white and black and men and women patients in coma with and without SE. The total for each race and gender was 100%. Modified from Towne et al. 2000.

(figure 1B) was no longer significant when controlled for age and etiology (tables 2 and 3). This multiregression logistic analysis also demonstrated that the high and low mortality etiology groups were significantly associated with poor and good outcomes, respectively, in comparison to the moderate etiology group (tables 2 and 3). In addition, increased age also demonstrated a statistically significant effect on mortality and poor outcome (tables 2 and 3). NCSE has been recognized as an important form of SE that can be more difficult to diagnosis without proper EEG monitoring, and recognition of NCSE after treatment of CSE in comatose patients is essential in the treatment protocol for SE. These results demonstrate the importance of EEG monitoring in coma following SE. In addition, the presence or absence of ASIDS on the EEG of comatose patients following the control of clinical seizures in CSE will serve as a useful test to predict outcome and guide treatment protocols.

Recognition of SE in comatose patients

In monitoring with EEG as part of the coma evaluation at VCU for patients that were in coma without overt signs of seizure activity, it was found that 8% of comatose patients met the criteria for the diagnosis of NCSE (Towne et al. 2000). NCSE was found to be a significant cause of coma in all age groups in this group of 217 cases of coma without signs of clinical seizure activity. In this group of comatose patients, EEG monitoring revealed 19 cases that had NCSE (8%). Since these cases were not continuously monitored, and monitoring after the onset of coma varied, this 8% value is probably a considerable underestimate of the true frequency of NCSE in coma. These results indicate that NCSE is a major, underrecognized cause of coma. The age distribution demonstrated that children (1 month to up to 16 years of age) comprised 11% of the patients and the remaining 89% of the patient were 16 years of age or older. There was no significant difference in the develop-

ment of NCSE in the coma patients across the age spectrum. Thus, both paediatric and adult neurologists should be aware of the importance of EEG monitoring in coma. The distribution of gender and race in comatose patients with and without SE is presented in figure 2. The data demonstrate that there were more women than men in the SE versus non-SE coma groups, but no statistically significant differences were observed in the racial distribution between coma with and without SE.

The immediate precipitating cause of the patient's coma was evaluated as a cause of coma with and without SE. The etiologies of coma with and without SE are shown in figure 3.

Hypoxia/anoxia was the most common etiology for the comatose patients in the study, occurring in 42% of the comatose patients. The distribution of other etiologies for coma is shown in figure 3. There was no significant difference in the distribution of etiologies for coma patients with or without SE. Further investigation into the causes and predictors of SE in coma is needed to more fully identify the comatose patients at greatest risk of developing SE.

Conclusions

Understanding the role of SE in coma is an important area for further research and may offer important insights into the treatment and care of comatose patients. The use of EEG monitoring is necessary to diagnose SE in coma and should be an essential diagnostic test in the work-up and evaluation of all comatose patients. In addition, patients that remain in coma after the successful treatment of clinical CSE need EEG monitoring to evaluate the presence of NCSE and DIDS. In many hospitals, this type of EEG evaluation is often not available at the weekends or at night. It is essential to provide 24 hour a day, 7 days a week EEG services to help in the treatment of SE and to detect the presence of NCSE in coma. These studies

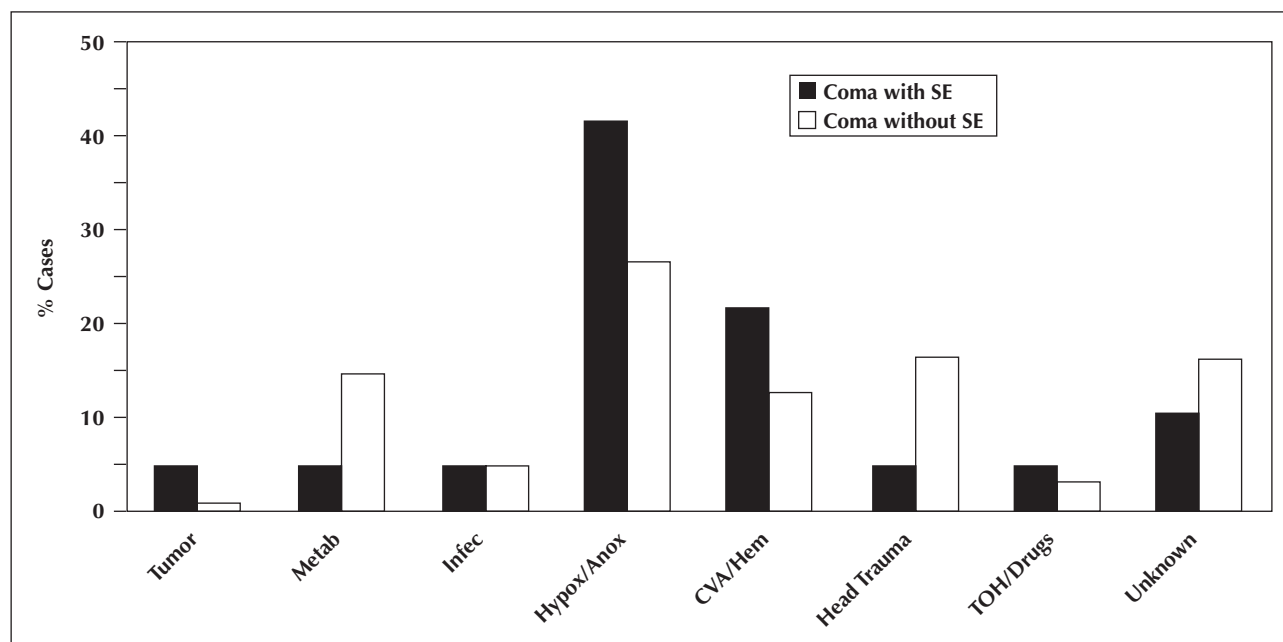


Figure 3. Distribution of etiologies for patients in coma with and without SE. Metab = metabolic; Infec = infection; hypox/anox = hypoxia and anoxia; CVA/Hem = cerebral vascular accidents and hemorrhages, ETOH/Drugs = alcohol or drug related. Data are represented as percentage of cases. Modified from Towne et al. 2000.

should provide the necessary research evidence to motivate hospital administrators to recognize the importance of EEG monitoring to improve outcome, and provide adequate quality control for the care of comatose and SE patients.

References

- Aicardi J, Chevrie JJ. Convulsive status epilepticus in infants and children: a study of 239 cases. *Epilepsia* 1970; 11: 187-97.
- Bleck T. Convulsive disorders: status epilepticus. *Clin. Neuropharm* 1991; 14: 191-8.
- DeLorenzo RJ, Ko D, Towne A, et al. Prediction of outcome in status epilepticus. *Epilepsia* 1997; 38: 210.
- DeLorenzo RJ, Pellock JM, Towne AR, et al. Epidemiology of status epilepticus. *J Clin Neurophysiol* 1995; 12: 316-25.
- DeLorenzo RJ, Towne AR, Ko D, et al. Prospective population-based epidemiological study of status epilepticus in Richmond, VA. *Neurology* 1996; 46: 1029-32.
- DeLorenzo RJ, Waterhouse EJ, Towne AR, et al. Persistent non-convulsive status epilepticus following the control of convulsive status epilepticus. *Epilepsia* 1998; 39: 833-40.
- Hauser WA. Status Epilepticus: Epidemiology considerations. *Neurol* 1990; 40(Suppl.2): 9-12.
- Kaplan PW. Assessing the outcomes in patients with non-convulsive status epilepticus. *J Clin Neurophysiol* 1999; 16: 341-52.
- Logroscino G, Hesdorffer DC, Cascino G, et al. Long-term mortality after a first episode of status epilepticus. *Neurol* 2002; 58: 537-41.
- Privitera M, Hoffman M, Moore JL, et al. EEG detection of nontonic-clonic status epilepticus in patients with altered consciousness. *Epilepsy Res* 1994; 18: 155-66.
- Shinnar S, Pellock JM, Berg AT, et al. Short-term outcomes of children with febrile status epilepticus. *Epilepsia* 2001; 42: 47-53.
- Shorvon S. Does convulsive status epilepticus result in cerebral damage or affect the course of epilepsy- the epidemiological and clinical evidence? *Pro Brain Res* 2002; 135: 85-93.
- Tomson T, Swanborg E, Wedlund JE. Nonconvulsive status epilepticus: high incidence of complex partial status. *Epilepsia* 1986; 27: 276-85.
- Towne AR, Pellock JM, Ko D, et al. Determinants of mortality in status epilepticus. *Epilepsia* 1994; 5: 27-36.
- Towne AR, Waterhouse EJ, Boggs JG, et al. Prevalence of non-convulsive status epilepticus in comatose patients. *Neurol* 2000; 25(54): 340-5.
- Treiman DM, DeGiorgio CMA, Salisbury SM, et al. Subtle generalized convulsive status epilepticus. *Epilepsia* 1984; 25: 653.
- Treiman DM, Meyers PD, Walton NY, et al. A comparison of four treatments for generalized convulsive status epilepticus. Veterans Affairs Status Epilepticus Cooperative Study Group. *N Engl J Med* 1998; 399: 792-8.
- Treiman DM. Convulsive status epilepticus. *Curr Treat Options Neurol* 1999; 1: 359-69.
- Waterhouse EJ, Garnett LK, Towne AR, et al. Prospective population-based study of intermittent and continuous convulsive status epilepticus in Richmond, Virginia. *Epilepsia* 1999; 40: 752-8.

Waterhouse EJ, Vaughan JK, Barnes TY, *et al.* Synergistic effect of status epilepticus and ischemic brain injury on mortality. *Epilepsy Research* 1998; 31: 199-209.

NCSE in specific childhood epilepsy syndromes

NCSE in Angelman Syndrome

Jean Aicardi

Child Neurology and Metabolic Diseases Dept, Hopital Robert Debré, 48 Boulevard Serurier, 75019, Paris, France

Angelman syndrome (AS), first described in 1965 (Angelman, 1965), is characterized by a constellation of learning disability, ataxia, epilepsy and motor abnormalities including spasticity with coactivation of agonist-antagonist muscles, increased muscle tone in limbs and truncal hypotonia with pyramidal tract signs (Zori *et al.* 1992). A dysmorphic facial appearance of the skull and face may appear only after several years, but often long remains inconspicuous. AS occurs in 1 out of 2,000-12,000 in the general population and may account for up to 6% of cases of severe mental retardation and epilepsy.

A deletion involving the maternally inherited chromosome 15, which encompasses a cluster of GABA receptor subunit genes is found in 70% of cases: about 5-10% of patients have uniparental paternal disomy for chromosome 15; 5% harbour a mutation of the imprinting centre, a key regulatory element of the gene expression; about 10% may have an intragenic mutation of the *UBA3A* gene. In only a few cases, is no genetic abnormality found (Saitoh *et al.* 1994). The vast majority of cases are sporadic. The few cases of familial recurrence are due to mutations of the imprinting centre or the *UBA3* gene. Individuals with chromosome 15q11-13 deletions usually have a more severe clinical picture, while uniparental disomy and *UBA3A* mutations seem to be associated with a milder phenotype (Lossie *et al.* 2001).

Learning disability is often severe and profound in about one third of cases (Lossie *et al.* 2001). It is associated with a cheerful mood. Some children also have bursts of unmotivated laughter, hence the name of «happy puppet syndrome» initially given to the condition. Most patients have delayed ambulation. Ataxia of mainly static type is constant and often severe. It is the major cause of delayed standing and ambulation, and cerebellar signs are common. Hand tremor during fine motor activities is frequent. A fine, almost continuous rhythmical myoclonus (of cortical origin as shown by back averaging studies) at about 11 Hz is often diagnosed as tremor (Guerrini *et al.* 1996). It is often associated with hand flapping.

Ninety per cent of patients suffer from epilepsy (Viani *et al.* 1995), which can present with any type of seizures, especially atypical absences and myoclonic attacks. More than half the patients suffer from episodes of decreased alertness and hypotonia, termed nonconvulsive status epilepticus, which can last for hours, days or weeks but become rare after age 6 years. Similar episodes have been previously reported as myoclonic status in nonprogressive encephalopathies (Dalla Bernardina *et al.* 1992). It seems that AS is the cause of most of these episodes even though some may be observed in the course of other chronic encephalopathies e.g. of perinatal hypoxic-ischaemic origin.

The EEG anomalies are of great diagnostic value; they include high amplitude slow waves sometimes associated with abortive spikes and/or 4Hz rhythmic activity often predominating posteriorly. These EEG findings are highly suggestive of AS. During episodes of status, irregular spikes-wave complexes at 2 Hz may be present (Matsumoto *et al.* 1992).

The diagnosis of AS has been defined by international consensus criteria (Williams *et al.* 1995) that include four major clinical features: learning disability, speech impairment, movement-balance disorder and behavioural peculiarity. It is often first suggested by the EEG anomalies. Imaging does not show any specific findings and metabolic investigations are negative. In about 80% of cases, the diagnosis can be confirmed by the methylation test that allows detection of deletion, uniparental disomy and intragenic mutations (Beckung *et al.* 2004). When the test is negative, mutation analysis of the *UBA3* gene is indicated.

Treatment of the epilepsy of AS is difficult especially in infancy and early childhood, and complete remission is rare. Benzodiazepines are effective for controlling myoclonus and may be combined with VP. Myoclonia may be made worse by carbamazepine and vigabatrin (Kuenzle *et al.* 1998). Prominent myoclonia may benefit from large doses of piracetam. The overall outcome is severe because of the combination of severe learning difficulties and motor disturbances.

References

- Angelman H. Puppet children: a report of three children. *Dev Med Child Neurol* 1965; 7: 681-8.
- Beckung E, Steffenburg S, Kyllerman M. Motor impairments, neurological signs, and developmental level in individuals with Angelman syndrome. *Dev Med Child Neurol* 2004; 46: 239-43.
- Dalla Bernardina B, Fontana E, Sgro V, *et al.* Myoclonic epilepsy ('myoclonic status') in non-progressive encephalopathies. In: Roger J, Bureau M, Dravet C *et al.* (eds). *Epileptic syndromes in infancy, childhood and adolescence*, 2nd Edn London, John Libbey 1992: 89-96.
- Guerrini R, De Lorey TM, Bonanni P, *et al.* Cortical myoclonus in Angelman syndrome. *Ann Neurol* 1996; 40: 39-48.

Kuenzle CH, Steinlin M, Wohlrab G, *et al.* Adverse effects of vigabatrin in Angelman syndrome. *Epilepsia* 1998; 39: 1213-5.

Lossie AC, Whitney MM, Amidon D, Dong HJ, *et al.* Distinct phenotypes distinguish the molecular classes of Angelman syndrome. *J Med Gene* 2001; 38: 834-45.

Matsumoto A, Kumagai T, Miura K, *et al.* Epilepsy in Angelman syndrome associated with chromosome 15q deletion. *Epilepsia* 1992; 33: 1083-90.

Viani F, Romeo A, Viri M, *et al.* Seizure and EEG patterns in Angelman syndrome. *J Child Neurol* 1995; 10: 467-71.

Williams CA, Angelman H, Clayton-Smith J, *et al.* Angelman syndrome: consensus for diagnostic criteria. *Am J Med Genet* 1995; 56: 237-8.

Zori RT, Hendrickson J, Woolven S, *et al.* Angelman syndrome: clinical profile. *J Child Neurol* 1992; 7: 270-80.

NCSE and Ring chromosome 20 syndrome

Perrine Plouin¹, Mary O'Regan²

¹Explorations Fonctionnelles Neurologiques, Hopital Necker Enfants Malades, 149 rue de Serres, F 75743, Paris, France, Cedex 5

²Fraser of Allander Neurosciences Unit, Royal Hospital for Sick Children, Yorkhill, Glasgow, G3 8SJ, UK

Ring chromosome 20, described in 1997 (Inoue *et al.*), is a rare chromosomal disorder with a characteristic epilepsy profile, since the initial description, the number of reported cases (for a review see Battaglia and Guerrini 2005 in this issue) highlighted further the uniqueness of the electro-clinical presentation. Other publications discussed the pathophysiological mechanisms eventually involved (Biraben *et al.* 2004).

Since 1997, more cases have been published and, among them an Italian population (Inoue *et al.* 1997); French cases (46 collected patients) are to be soon reported (Biraben *et al.* 2004).

In all reported patients, the first seizure occurred before the age of 16 years. In half of them, the first seizure occurred before 6 years of age, and in a few children before the age of one year. The majority of children have no dysmorphic features and if dysmorphism is present, it is very mild. Different types of seizures may occur: complex partial seizures with fear, often with visual symptoms, hallucinations and illusions, generalized tonic, clonic or tonic clonic seizures, nocturnal tonic seizures or arousals with frontal lobe semiology and nonconvulsive status epilepticus. Unusual duration of the seizures, as well as the unusual presentation of the seizures with fear may lead to false, psychiatric diagnosis. Nonconvulsive status epilepticus occurred in all cases, with a duration from 2 minutes to 4 hours. Ictal EEG was recorded in all cases (figures 1 and 2). EEG may manifest as continuous, bifrontal rhythmic theta/delta with accompanying spikes or sharp waves or may show continuous, diffuse abnormalities.

Cognitive evaluation during NCSE may show no or only minor deficits.

Twenty of our patients underwent neuropsychological evaluation: IQ <70 for 5 patients, IQ 70-90 for 7 patients, IQ 90-100 for 4 patients and IQ > 100 for 4 patients. These results are comparable to those already reported. Concerning behaviour, the most frequent symptoms were: poor attention and concentration, impulsivity, disinhibition, obsessive behaviours, aggressive outbursts. The majority of French children had seen a psychiatrist before a neurologist

All patients had refractory epilepsy. No single medication or combination proved to be helpful. (carbamazepine, sodiumvalproate, phenytoin, lamotrigine, clobazam, topiramate, gabapentin, levetiracetam, primidone, midazolam, clonazepam, phenobarbitone, pyridoxine IV, immunoglobulin, vagal nerve stimulator). Vigabatrin exacerbated seizures in one case. Several cases had surgical evaluations prior to diagnosis.

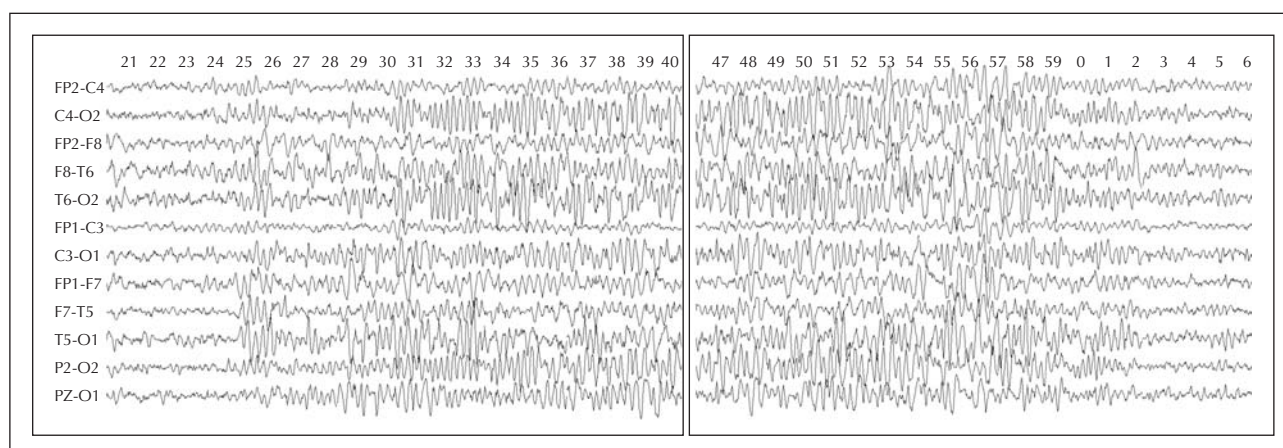


Figure 1. Seizure recorded in a 15-month-old patient with ring chromosome 20.

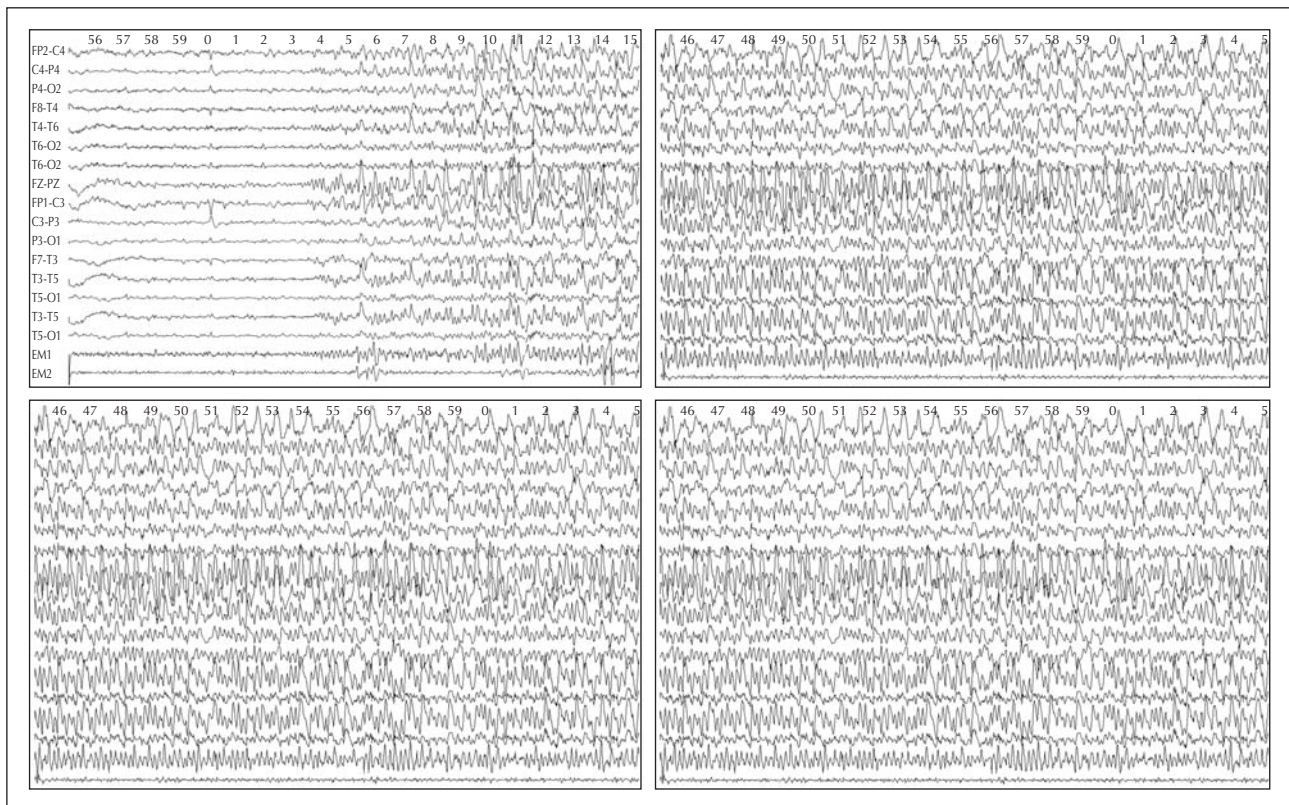


Figure 2. Seizure recorded in a 12-year-old patient with ring chromosome 20

Karyotype analysis was performed in 43 patients: the percentage mosaicism in peripheral blood lymphocytes varied from 0.5% to 100% and no relation was found between percentage mosaicism and cognitive outcome; one child was diagnosed *post mortem* on skin biopsy (7% r(20)), one mother was found to have 2% r(20) mosaicism with no symptoms.

Dopamin (DA) metabolism is significantly lower in pallidum and striatum in patients presenting with epilepsy linked to ring Ch 20. This low DA level is not associated with Parkinsonism at this age in these patients (Biraben *et al.* 2004). It may reflect a dysfunction of subcortical control loop. Confirmation of such results could have therapeutic consequences

In conclusion, epilepsy may start at any time from birth throughout childhood and adolescence and remains drug-resistant. There is a characteristic epilepsy and EEG phenotype. The percentage mosaicism may be very low, and enough cells (>100) have to be examined. Psychiatric and/or behavioural problems are common and cognitive outcome is variable. Ring (20) may be more common than previously thought but it is possible to have r(20) without any symptom. It is absolutely necessary to perform a long-lasting video-EEG to assess NCSE.

References

- Biraben A, Semah F, Ribeiro MJ, *et al.* PET evidence for a role of the basal ganglia in patients with ring chromosome 20 epilepsy. *Neurology* 2004; 63: 73-7.
- Inoue Y, Fujiwara T, Matsuda K, *et al.* Ring chromosome 20 and nonconvulsive status epilepticus. A new syndrome. *Brain* 1997; 120: 939-53.

NCSE in the benign focal epilepsies of childhood with particular reference to autonomic status epilepticus in Panayiotopoulos syndrome

Colin Ferrie

Dept of Paediatric Neurology, Clarendon Wing,
Leeds General Infirmary, Leeds, LS2 9NS, UK

The core benign focal epilepsies of childhood recognised by the International League Against Epilepsy (ILAE), are benign childhood epilepsy with centro-temporal spikes (BECTS), also known as Rolandic epilepsy, late-onset childhood occipital epilepsy (Gastaut type) (LOCOE) and Panayiotopoulos syndrome (PS). The latter is currently

classified by the ILAE as «early-onset benign childhood occipital epilepsy (Panayiotopoulos type)» (Engel 2001). However, many authorities no longer consider its designation as an occipital epilepsy secure, and in recognition that its symptoms are predominantly autonomic, prefer to classify it as an autonomic epilepsy (Ferrie *et al.* 2003). This practice will be followed here.

Nonconvulsive autonomic status epilepticus is a core feature of PS (Panayiotopoulos, in press). Indeed, since PS is one of the commonest epilepsies of childhood, probably accounting for 6-8% of children aged 1-13 years with seizures, and autonomic status epilepticus is reported in a little over half of all children with the syndrome (Panayiotopoulos 2002), it is one of the commonest causes of nonconvulsive status epilepticus overall, and may be the commonest cause in children without other neurological impairments.

PS occurs throughout childhood, but its peak age-at-onset is 4-5 years. Girls and boys are equally affected. Total seizure count appears to be low, with only 5-10% of those affected having more than 10 seizures. Remission is expected within a few years of onset. Seizure manifestations are dominated by autonomic, mainly emetic (nausea, retching, vomiting) symptoms, often with unilateral deviation of the eyes. Other autonomic features include colour changes, pupillary abnormalities, cardio-respiratory and thermo-regulatory alterations, and incontinence. Two thirds of seizures begin in sleep, often with the child waking up at the start of the seizure. Consciousness is preserved at the start, and sometimes, throughout the seizure. Seizures often (one third) end in hemi- or generalised tonic-clonic seizures (Panayiotopoulos 2002, Ferrie *et al.* 1997, Panayiotopoulos 1999, Caraballo *et al.* 2000, Kivity *et al.* 2000, Ferrie and Grunewald 2001, Panayiotopoulos 2001, Koutroumanidis 2002, Lada *et al.* 2003, Ohtsu *et al.* 2003). Recently, it has been recognised that syncopal-like episodes may be a manifestation of PS (ictal syncope) (Ferrie *et al.* 2003). The EEG in PS was initially thought to be identical to that in LOCOE, with occipital paroxysms being characteristic (Panayiotopoulos 1999). However, recent work has established that the interictal EEG findings are more varied, and consequently it can best be thought of as being multifocal (Panayiotopoulos in press; Panayiotopoulos 2002).

The seizures in PS are characteristically long. In a study of 86 seizures in 47 children with PS, the median duration of seizures was 15 minutes (range 1 minute – 7 hours). Over two thirds of seizures lasted over 10 minutes. Forty four percent of seizures lasted over 30 minutes, constituting status epilepticus. The median duration of such seizures was 2 hours (range 30 minutes – 7 hours) (Panayiotopoulos 2002). These seizures are, like the shorter seizures, dominated by autonomic symptoms, although many end in hemi- or generalised tonic-clonic seizures. They are therefore appropriately designated as nonconvulsive sta-

tus epilepticus. Such prolonged seizures occur both whilst awake (43%) and asleep (45%).

Many of the features of autonomic non-convulsive status epilepticus in PS are not obviously recognisable as being epileptic in nature. Consequently, children with such events are frequently misdiagnosed. Not infrequently, they are admitted to intensive care units with, for example, suspected encephalitis or strokes. By the next day, they are usually fully recovered, to everyone's surprise. Why this should be is perhaps best illustrated by describing an episode that occurred in a 4-year-old boy travelling by train at the start of his holidays:

«He was happily playing and asking questions when he started complaining that he was feeling sick, became very pale and quiet. He did not want to eat or drink. Gradually he was getting more and more pale, kept complaining that he felt sick and became restless and frightened. Ten minutes from the onset, his head and eyes slowly turned to the left. The eyes were opened but fixed to the left upper corner. We called his name but he was unresponsive. He had completely gone. We tried to move his head but this was fixed to the left. There were no convulsions. This lasted for another 15 minutes when his head and eyes returned to normal and he looked better although he was droopy and really not there. At this stage, he vomited once. In the ambulance, approximately 35 minutes from the onset, still he was not aware of what was going on although he was able to answer simple questions with yes or no. In the hospital he slept for 3/4h and gradually came around but it took him another ¼-1h before he became normal again.» (Courtesy of Panayiotopoulos, case 28)

A number of episodes of autonomic status epilepticus in PS have now been recorded on EEG (Beamanoir 1993, Oguni *et al.* 1999, Vigeveno *et al.* 2000). The discharge is characterised mainly by rhythmic theta or delta activity intermixed usually with small spikes. Recorded discharges have started both in the posterior and the anterior head regions, left or right, emphasising that it is inappropriate to designate PS as an occipital epilepsy (Koutroumanidis personal communication).

PS has an excellent prognosis and this is independent of whether episodes of nonconvulsive status occur. There has been no systematic study of treatment in PS. If recognised, most authorities would probably terminate prolonged seizures using a benzodiazepine, which could be administered as oral midazolam, rectal diazepam or IV lorazepam/diazepam. Our experience suggests this will almost certainly be successful. Many authorities do not recommend regular antiepileptic drug treatment in PS. There seems no reason to modify this policy in children who have had an episode of nonconvulsive status. However, rescue medication may be appropriately given to the family for acute treatment of seizures.

Nonconvulsive status epilepticus is not a characteristic feature of the other benign focal epilepsies of childhood.

Status is reported as occurring in younger children with BECTS (Dalla Bernardina *et al.*). However, these are usually hemiconvulsive in nature and some others may be mis-diagnosed cases of PS. In addition to this, a number of 'atypical syndromes related to BECTS' or 'atypical evolutions of BECTS' have been described, in some of which, various types of nonconvulsive status epilepticus occur. These all appear to have an inconstant relationship to continuous spike-wave during sleep (CSWS). In atypical benign partial epilepsy, seizures typical of BECTS occur along with other seizure types, such as atonic and atypical absence seizures. These can occasionally be in the form of nonconvulsive status (Aicardi and Chevrie 1982). Landau-Kleffner syndrome, accompanied by CSWS, is reported as exceptionally evolving from BECT (Tassinari *et al.* 2002). Finally, the syndrome of opercular (nonconvulsive) status consists of recurrent episodes of pseudobulbar palsy lasting hours, days, weeks or even months and accompanied by continuous or frequent EEG discharges in the opercular regions and sometimes by CSWS. It has been described as exceptionally occurring in children with otherwise typical BECTS (Salas-Puig *et al.* 2002).

The seizures of LOCOE are characterised by positive (hallucinations and illusions) and negative (blindness) visual symptoms, and often headache (Panayiotopoulos 1999). The seizures are usually, but not always, short. The characteristic interictal EEG, features occipital paroxysms consisting of runs of high amplitude sharp and slow wave complexes in the posterior head regions. These characteristically attenuate on fixation (Panayiotopoulos 1981). Some children will have continuous occipital paroxysms when fixation is eliminated, (e.g. when the eyes are closed or when in complete darkness). Although not usually classified as such, this might be considered a form of electrical status epilepticus. However, it should be noted that it is nearly always unaccompanied by any discernable clinical manifestation, although I have seen children with this pattern who complain of a diffuse headache, which is unresponsive to analgesics.

References

- Aicardi J, Chevrie JJ. Atypical benign partial epilepsy of childhood. *Dev Med Child Neurol* 1982; 24: 281-92.
- Beaumanoir A. Semiology of occipital seizures in infants and children. In: Andermann F, Beaumanoir A, Mira L, Roger J, Tassinari CA, eds. *Occipital seizures and epilepsies in children*. London: John Libbey & Co Ltd. 1993: 71-86.
- Carballo R, Cersosimo R, Medina C, *et al.* Panayiotopoulos – type benign childhood occipital epilepsy: A prospective study. *Neurology* 2000; 55: 1096-100.
- Dalla Bernardina B, Sgro V, Fejerman N. Epilepsy with centro-temporal spikes and related syndromes. In: Roger J, Bureau M, Dravet Ch (eds). *Epileptic syndromes in infancy, childhood and adolescence*. London: John Libbey & Co Ltd.: 181-202.
- Engel J. A proposed diagnostic scheme for people with epileptic seizures and with epilepsy: report of the ILAE task force on classification and terminology. *Epilepsia* 2001; 42: 796-803.
- Ferrie CD, Beaumanoir A, Guerrini R, *et al.* Early-onset benign occipital seizure susceptibility syndrome. *Epilepsia* 1997; 38: 285-93.
- Kivity S, Ephraim T, Weitz R, *et al.* Childhood epilepsy with occipital paroxysms: clinical variants in 134 patients. *Epilepsia* 2000; 41: 1522-3.
- Koutroumanidis M. Panayiotopoulos syndrome. *BMJ* 2002; 324: 1228-9.
- Oguni H, Hayashi K, Imai K, *et al.* Study on the early-onset variant of benign childhood epilepsy with occipital paroxysms otherwise described as early-onset benign occipital seizure susceptibility syndrome. *Epilepsia* 1999; 40: 1020-30.
- Panayiotopoulos CP. Inhibitory affect of central vision on occipital lobe seizures. *Neurology* 1981; 31: 1330-3.
- Panayiotopoulos CP. *Benign childhood partial seizures and related epileptic syndromes*. London: John Libbey, 1999.
- Panayiotopoulos CP. Panayiotopoulos syndrome. *Lancet* 2001; 358: 68-9.
- Panayiotopoulos CP, Ferrie CD, Koutroumanidis M, *et al.* Idiopathic generalised epilepsy with phantom absences and absence status in a child. *Epileptic Disord* 2001; 3: 63-6.
- Panayiotopoulos CP. *Panayiotopoulos syndrome: a common and benign childhood epileptic syndrome*. London: John Libbey, 2002.
- Salas-Puig J, Perez-Jimenez A, Thomas P, *et al.* Opercular epilepsies with oromotor dysfunction. In: Guerrini R, Aicardi J, Andermann F, *et al.* (eds). *Epilepsy and Movement Disorders*. London: Cambridge University Press 2002: 251-68.
- Tassinari CA, Rubboli G, Volpi L, *et al.* Electrical status epilepticus during slow sleep (ESES or CSWS) including acquired epileptic aphasia (Landau-Kleffner syndrome). In: Roger J, Bureau M, Dravet Ch (eds). *Epileptic syndromes in infancy, childhood and adolescence*. London: John Libbey & Co Ltd. 2002: 265-83.
- Vigevano F, Lispi ML, Ricci S. Early onset benign occipital susceptibility syndrome: video-EEG documentation of an illustrative case. *Clin Neurophysiol* 2000; 111(suppl 2): S81-6.

NCSE in children with learning difficulties

Frank Besag

Beds and Luton Community NHS Trust, Twinwoods Health Resource Centre, Milton Road, Clapham, MK41 6AT, UK

Nonconvulsive status epilepticus is of particular importance in children with learning disabilities because it may cause further cognitive and behavioural handicaps in those who already have limited intellectual reserves and who are at high risk of having behavioural problems. NCSE may be particularly difficult to diagnose in children with learning disabilities. Although the clinical changes are profound in some children, in others they may be very

subtle. The withdrawn state that can result from NCSE sometimes manifests as autistic features. During acute attacks of NCSE, the cognitive and behavioural effects may be reversed by intravenous injection of a benzodiazepine. If the child is liable to repeated bouts of NCSE, or is drifting in and out of the condition, then alteration of the regular antiepileptic medication regime will be required. NCSE can clearly cause state-dependent, potentially treatable and reversible cognitive and behavioural change. Can NCSE also cause permanent, irreversible cognitive and behavioural change? There seems to be growing evidence that it can. In addition to the poor cognitive development that occurs in some children who have NCSE for long periods, it seems that children who have very frequent epileptiform discharges during a critical developmental period of their lives may evolve an Asperger-like syndrome in their teenage years, which persists even though the epileptiform discharges are no longer present. These observations underline the importance of making an early diagnosis and providing prompt, effective treatment, which may prevent permanent cognitive and behavioural changes.

Discussion by Sarah Aylett

National Centre for Young People with Epilepsy, Lingfield, Surrey & Great Ormond Street Hospital for Children NHS Trust, London, UK.

Population studies suggest that the prevalence of epilepsy in children with learning disability (LD) is 20% (Mariani *et al.* 1993), with an estimate of 48% (Hauser *et al.* 1987) for those with concurrent cerebral palsy. There is a lack of information regarding the prevalence of nonconvulsive status epilepticus (NCSE) in these children. It is suggested that generalised epilepsies are more commonly associated with LD.

NCSE is seen in a number of epileptic encephalopathies in children with LD. These include infantile spasms, severe myoclonic epilepsy of infancy, Landau Kleffner syndrome (LKS), myoclonic astatic epilepsy, Lennox-Gastaut syndrome, Ring chromosome 20 and Angelman's syndrome. Rather than a separate entity, NCSE can be regarded as a feature of these syndromes, such as infantile spasms, in which there is frequently high voltage, chaotic spike wave (hypsarrythmia). However, it is difficult to assess the relative contribution of the underlying disorder, other seizures and NCSE to the developmental and cognitive difficulties in these children. This requires studies assessing outcome, and the possible underlying mechanisms in these specific syndromes. In myoclonic astatic epilepsy (MAE), it is considered that those with frequent episodes of myoclonic status have a less favourable cognitive outcome (Guerrini and Aicardi 2003).

The effect of NCSE on developmental outcome is limited to case series or reports. These suggest that recurrent episodes of NCSE in children are associated with an

impact on developmental progress, even with treatment (Manning and Rosenbloom 1987, Stores *et al.* 1995). In infantile spasms, the absence of hypsarrythmia in tuberous sclerosis is associated with an improved developmental outcome (Jambaque *et al.* 2000). The early onset of high rates of subclinical epileptic activity may be associated with regression of language and social communication skills, such as in LKS.

There are specific issues in relation to NCSE in children with LD. NCSE may go unrecognised in this group and a potentially reversible component of the LD not sought. Children with epilepsy and LD frequently have associated psychiatric co-morbidity such as attention deficit hyperactivity disorder and autistic spectrum disorder. There may be additional physical disability. This may have both implications for the manifestation of NCSE in this group and for potential adverse effects of treatment with antiepileptic drugs or steroids. In addition, NCSE in association with these encephalopathies is frequently resistant to treatment.

There is the issue of, to what extent the deficits associated with NCSE are potentially reversible or not. There may be irreversible effects of NCSE occurring in the context of brain maturation in relation to neuronal connections and pruning (O'Leary 1992). However, clinical observation of improvements memory, attention and processing with control of NCSE suggests there may be a reversible component. In LKS, improvement in language function may occur with treatment, however, the persistence of aphasia and dysfunction of the superior temporal gyrus (Majerus *et al.* 2003) suggests that NCSE occurring in the developing brain may be associated with residual deficits.

References

- Hauser WA, Shinnard S, Cohen H. Clinical predictors of epilepsy among children with cerebral palsy and/or mental retardation. *Neurology* 1987; 37 (Suppl 1): 150.
- Jambaque I, Chiron C, Dumas C, *et al.* Mental and behavioural outcome of infantile epilepsy treated with vigabatrin in tuberous sclerosis patients. *Epilepsy Res* 2000; 38: 151-60.
- Majerus S, Laureys S, Collette F, *et al.* Phonological short-term memory networks following recovery from Landau and Kleffner syndrome. *Hum Brain Mapp* 2003; 19: 133-44.
- Manning DJ, Rosenbloom L. *Arch Dis Child* 1987; 62: 37-40.
- Mariani E, Ferini-Strambi I, Sala M, *et al.* Epilepsy in institutionalized patients with encephalopathy: clinical aspects and nosological considerations. *Am J Ment Retardation* 1993; (Suppl): 27-33.
- O'Leary DM. Development of connectional diversity and specificity in the mammalian brain by pruning of collateral projections. *Curr Opin in neurobiol* 1992; 2: 70-77.
- Stores G, Zaiwalla Z, Styles E, Hoshika A. Non-Convulsive status epilepticus. *Arch Dis Child* 1995; 73: 106-11.

NCSE in the elderly

Frank Drislane

Comprehensive Epilepsy Centre, Beth Israel Deaconess Medical Centre, Harvard Medical School, Boston, MA, 02215, USA

Nonconvulsive status epilepticus (NCSE) may constitute one quarter of all status epilepticus (SE) (Celesia 1974, DeLorenzo *et al.* 1992, Shorvon 1994), and up to 40% of all SE occurs in the elderly (DeLorenzo 1997), especially when defined as those over 60. Overall, NCSE in the elderly may represent 10% of all SE across all ages.

Unfortunately, NCSE is often difficult to diagnose (at any age), and many elderly people have medical illnesses that can cause similar clinical deficits. Syncope, episodes of memory loss, confusion, or delirium may all be confused with NCSE. NCSE may be diagnosed incorrectly as metabolic abnormalities or psychiatric conditions (Kaplan 1996). This produces not only difficulties in epidemiologic ascertainment but also clinical problems in individual patients. It is difficult to treat NCSE appropriately if the diagnosis does not come to mind.

Cerebrovascular disease is the most commonly identified cause of SE in the elderly and accounts for the majority of NCSE. About 7% of acute strokes provoke at least one epileptic seizure (Rumbach *et al.* 2000), and about one fifth of these go on to SE, some of it nonconvulsive. Thus, about 1% of all strokes are associated with status; later epilepsy causes more. In the elderly, 60% of all SE may be due to acute or remote vascular disease (DeLorenzo 1997). Tumors and trauma may each account for another 5 to 10% of NCSE (Sung and Chu 1989). Many of the remainder are multifactorial, with contributions from acute metabolic or infectious precipitants (or medications or medication changes) superimposed upon an already impaired brain, affected by vascular or «degenerative» diseases (Shneker and Fountain 2003, Litt *et al.* 1998).

Less frequently, NCSE in the elderly represents an exacerbation of earlier epilepsy. Primary generalized «absence» seizures occur in the elderly, usually after an earlier epilepsy diagnosis (Agathonikou *et al.* 1998), or with *de novo* absence SE of late onset – often following benzodiazepine or other medication withdrawal, even without earlier epilepsy (Thomas *et al.* 1992).

Most NCSE in the elderly is not primarily generalized but of focal onset, complex partial status (CPSE), with possible secondary generalization (DeLorenzo 1997, Sung and Chu 1989, Granner and Lee 1994). Finally, ongoing, rapid, rhythmic epileptiform discharges strongly indicative of SE and seen in the very sick ICU patients with several neurological or medical illnesses (or after apparent generalized convulsions) are also common in the elderly. These are referred to alternately as electrographic status epilepticus, epileptic encephalopathies, and status in coma.

In perhaps the best study of the EEG in NCSE, Granner and Lee (1994) evaluated NCSE patients who responded well to antiepileptic drugs. EEG discharges were often generalized, but many became focal once medication was initiated. Waveform morphologies were remarkably variable; discharge frequencies were generally from 1.0 to 3.5Hz (mean 2.2). Older patients were more likely to have focal discharges, again indicating that NCSE in the elderly tends to be «symptomatic» or arise from a focal lesion.

NCSE in the elderly carries major morbidity and mortality. Among all patients with SE, mortality is generally about 25%, but it is over 50% in patients over age 80 and over 90% in patients over 60 with anoxia (DeLorenzo *et al.* 1992). NCSE in the elderly is no less lethal. CPSE has a mortality of approx. 30% in the elderly, simple partial SE 40%, and generalized status 90% (DeLorenzo 1997); many of the patients with generalized NCSE are those mentioned earlier with severe medical and neurological illnesses and prolonged electrographic SE.

The markedly elevated mortality among elderly patients with NCSE is almost always attributable primarily to the etiology (Towne *et al.* 1994). The elderly have more ischemic and hemorrhagic strokes, tumors, anoxia, and severe infections, but it is unclear whether age confers an independent risk for mortality. Considering the primary etiology of the SE and the very frequent co-morbidities in the elderly, it appears unlikely that there will be studies powerful enough to dissect out an independent risk of age alone.

Electrographic or ongoing SE in medically sick patients is often lethal, but it is not always diagnosed readily. Among our 42 elderly patients with electrographic status, the diagnosis was unsuspected for days in three quarters of them (Drislane and Schomer 1994). Often, electrographic status indicates an illness so severe that treatment of the ongoing rhythmic electrical activity will not be sufficient to save the patient. Nevertheless, some patients do improve on antiepileptic drugs.

Treatment of NCSE in the elderly is strikingly easy in some and impressively difficult in others. Patients with primary generalized, absence SE usually respond to modest doses of benzodiazepines and often do not need long-term AED maintenance. CPSE is typically due to some underlying lesion and often requires long-term medication. The response to AEDs is frequently delayed (sometimes up to days) and the diagnosis may be missed or discounted. Comatose ICU patients with severe underlying illnesses have a high mortality, whatever the treatment.

Treatment must cover concomitant medical illnesses such as cardiac and respiratory failure, as well as metabolic abnormalities and infections. These conditions all conspire to increase the incidence of confusion and medication side effects such as hypotension, as well as troublesome drug interactions. Most elderly patients with NCSE can be treated successfully, but there is a major need for

good clinical judgement balancing the severity of the seizures with the difficulties or complications of treatment.

References

- Agathonikou A, Panayiotopoulos CP, Giannakodimos S, *et al*. Typical absence status in adults: diagnostic and syndromic considerations. *Epilepsia* 1998; 39: 1265-76.
- Celesia GG. Modern concepts of status epilepticus. *JAMA* 1976; 235: 1571-4.
- DeLorenzo RJ, Towne AR, Pellock JM, Ko D. Status epilepticus in children, adults and the elderly. *Epilepsia* 1992; 33(suppl 4): S15-25.
- DeLorenzo RJ. Clinical and epidemiologic study of status epilepticus in the elderly (Chap 15). In: Rowan AJ, Ramsay RE, eds. *Seizures and epilepsy in the elderly*. Boston: Butterworth-Heinemann 1997: 191-205.
- Drislane FW, Schomer DL. Clinical implications of generalized electrographic status epilepticus. *Epilepsy Res* 1994; 19: 111-21.
- Granner MA, Lee SI. Nonconvulsive status epilepticus: EEG analysis in a large series. *Epilepsia* 1994; 35: 42-7.
- Kaplan PW. Nonconvulsive status epilepticus in the emergency room. *Epilepsia* 1996; 37: 643-50.
- Litt B, Wityk RJ, Hertz SH, *et al*. Nonconvulsive status epilepticus in the critically ill elderly. *Epilepsia* 1998; 39: 1194-202.
- Rumbach L, Sablot D, Berger E, *et al*. Status epilepticus in stroke. Report on a hospital-based stroke cohort. *Neurology* 2000; 54: 350-4.
- Shneker BF, Fountain NB. Assessment of acute morbidity and mortality in nonconvulsive status epilepticus. *Neurology* 2003; 61: 1066-73.
- Shorvon S. The concept of status epilepticus and its history (Chap. 1). In: Shorvon S, ed. *Status epilepticus: its clinical features and treatment in children and adults*. Cambridge: Cambridge University Press 1994: 1-20.
- Sung CY, Chu NS. Status epilepticus in the elderly: etiology, seizure type and outcome. *Acta Neurol Scand* 1989; 80: 51-6.
- Thomas P, Beaumanoir A, Genton P, *et al*. *De novo* absence status of late onset: report of 11 cases. *Neurology* 1992; 42: 104-10.
- Towne AR, Pellock JM, Ko D, DeLorenzo, RJ. Determinants of mortality in status epilepticus. *Epilepsia* 1994; 35: 27-34.