

Nonconvulsive (Dialeptic) Status Epilepticus in Children

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Abstract: Many issues regarding the definition, phenomenology, categorization and outcome of nonconvulsive (or dialeptic) status epilepticus are still unresolved. Management is often difficult, with highly variable response to treatment. This classically includes oral benzodiazepines or steroids. New insights into pathophysiological mechanisms involved in sustaining epileptic activity or deficits in seizure termination may lead to improved management programs. Relevant synaptic processes implicate functional alterations of GABA_B, GABA_A and NMDA receptor complexes. Early results with NMDA blockers (e.g. ketamine) in animal models and pediatric patients are encouraging. Metabolic approaches have included ketogenic diets. Dynamic approaches of electroencephalographic signals may open the way to neuromodulation through electrical resetting techniques applied at critical phases.

INTRODUCTION

Behavioral and cognitive disturbances are common but often challenging problems in pediatric practice. Their frequent occurrence in association with seizure disorders poses particularly difficult questions with regard to diagnosis and management. In recent years, there has been renewed interest in the relationships between cognitive dysfunction and epileptic activity. Patients with epilepsy often exhibit various neurocognitive deficits, which may be acute, subacute, progressive or chronic. Wider access to electroencephalography (EEG) has proved important in recognizing nonconvulsive status epilepticus as a significant cause of mental status impairment. This condition is conventionally distinguished from status epilepticus with a convulsive (usually tonic-clonic) element.

A variety of terms have been used to describe nonconvulsive status epilepticus, including minor status epilepticus, spike-wave stupor, epileptic twilight state, *epilepsia minores continua*, *petit mal status*, impulsive-petit-mal status and absence status epilepticus. However, all of these terms have been criticized [1] for either failing to encompass the range of clinical features or for implying unproven pathophysiology. For example, use of the term 'absence' to characterize possibly subtle alteration of conscious level is misleading, labels including 'petit-mal' incorrectly point to childhood absence epilepsy, and spike-wave stupor defines the situation by an EEG pattern. Nonconvulsive status epilepticus has remained a difficult topic as concerns nosologic definition, diagnosis and pathophysiology. There has been much confusion in all these domains, resulting in mixed messages with respect to management. While some authors reserve the concept for distinct episodes similar to other seizures, other authors

include in it a wide range of subtle behavioral alterations, some of them not clearly reversible. In clinical practice, nosology based on ictal semiology may appear more useful. In the context of semiological seizure classification, the term 'dialeptic' as been suggested for seizures with alteration of consciousness as main ictal feature [2]. Absence seizures are thus dialeptic seizures with generalized ictal EEG discharges, whereas complex partial seizures are dialeptic seizures with focal ictal EEG discharges.

Dialeptic status epilepticus may therefore represent a group of situations that are primarily characterized by nonconvulsive clinical epileptic activity (i.e. without marked positive motor signs). By analogy with convulsive status epilepticus (i.e. seizures lasting for more than 30 minutes or occurring so frequently that there is no recovery between attacks), this electroclinical activity persists for more than 30 minutes. Some authors have suggested a minimum duration of 60 minutes, but in clinical practice, dialeptic status epilepticus commonly persists for several days or weeks before coming to medical attention. Although this definition is often used, it may amalgamate various clinical settings with distinct diagnostic, therapeutic and prognostic implications. Prolonged focal seizures that have selected, well-defined clinical features as their main manifestation, such as blindness (i.e. amaurotic status epilepticus) or aphasia (i.e. aphasic status epilepticus), are usually not referred to as forms of dialeptic status epilepticus. Some authors would also include infantile spasms under this rubric, but although prolonged conscious impairment without obvious motor signs associated with continuous EEG discharges may rarely be seen in this condition, this generalization broadens the boundaries of dialeptic status epilepticus beyond phenomenology, and it may thereby invalidate it. More confusion exists between categories of situations that have been termed generic (or 'minor') nonconvulsive status epilepticus, comatose (or 'subtle') nonconvulsive status epilepticus and electric status epilepticus during sleep (or continuing spike-wave in sleep), although they are very easy to distinguish in clinical terms.

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Comatose nonconvulsive status epilepticus represents a late stage of the natural history of uncontrolled convulsive status epilepticus, whether untreated or refractory to treatment. It appears as part of a continuum of clinical expression of convulsive status epilepticus which ranges from generalized tonic-clonic seizures to progressively more subtle motor manifestations that may eventually disappear while electroencephalographic epileptiform activity remains continuous or nearly so and the patient's conscious level remains severely depressed.

Continuous spike-wave discharges during sleep appear as generalized slow (usually around 2/s) spike-wave complexes, sometimes with a frontal emphasis, that occupy more than 85 percent of slow wave sleep, while this activity is exceedingly rare in rapid eye movement sleep. The abnormalities often persist for several months or years. They may be associated with cognitive deterioration or behavioral disturbances, although seizures (usually drop attacks or atypical absences) are infrequent. In many cases, no structural abnormality can be found, although cerebral dysplasia may be a rare cause [3]. The lack of clinical alteration concomitant to the electrographic epileptiform activity excludes it from the context of dialeptic status epilepticus.

In this review, we have confined our attention to generic nonconvulsive status epilepticus, i.e. 'dialeptic' status epilepticus.

CLINICAL EXAMPLES

Case#1 – A three year-old boy with Lennox-Gastaut syndrome associated with chromosome 4 translocation disrupting the *JNK* gene. Development was normal before 15 months of age, when myoclonic-atonic seizures, atypical absences and subsequent mainly axial tonic seizures appeared. Epilepsy proved difficult to control with multiple antiepileptic regimens. Interictal EEG showed frequent 2-2.5/s ill-formed diffuse discharges (150-300 μ V) predominating in the frontal regions. Progressive cognitive and motor deterioration led to severe mental retardation, hypotonia and ataxia. From age three, he presented episodes of decreased interaction, increased hypotonia, ataxia and myoclonic jerks, bradykinesia and drooling associated with continuous generalized 1.5-2.5/s spike-waves (300-500 μ V). These episodes of dialeptic status epilepticus could last for several weeks. They did not respond to dosage adaptation of current antiepileptic treatment. They responded poorly to benzodiazepines. Several episodes showed good response to oral corticosteroids, but others no response at all. From age four, oral ketamine trials were used effectively in these episodes.

Case#2 – A seven year-old boy with hemiplegic cerebral palsy due to widespread left-hemisphere necrosis caused by antenatal carotid thrombosis. He had mild specific learning difficulties. He had complex partial epilepsy since age 5, that was well controlled with valproic acid monotherapy. He presented with marked deterioration at school, with a drop in IQ from 100 to 67. Parents reported that he had become rude and opposing and that he showed compulsive and obsessive behavior. These behavioral changes had been noted for the last 4 months, though onset had been insidious, with some fluctuation and occasional resuming to the previous habitual

behavior. EEG showed continuous generalized 2/s spike-wave complexes with higher amplitude over the right (200 μ V) than the left (100 μ V) hemisphere. After 2 days, oral benzodiazepines led to resumption of interictal clinical state and electroencephalographic features. Dialeptic status epilepticus recurred 6 months later and was more readily recognized. Benzodiazepines had no effect, but the status was controlled after 2 weeks of oral corticosteroids.

Case#3 – An eight year-old girl with no past medical history. Since the birth of her younger sister, three years previously, her parents had noted that she was increasingly more absent-minded and that she started to say rude words with no apparent reason, whereas they described her as remarkably attentive and polite before her sister's birth. Progressively, she had more and more episodes of staring, sometimes "freezing" while she was active. She became clumsy, dropping objects and developed occasional tremor. In the last three months before presentation, she started to have episodes of repeating words or phrases. She was seen by a child psychiatrist, who sent her for an EEG. This showed nearly continuous generalized 2.5-3/s spike-wave activity (300 μ V), rarely interrupted by irregular slow (2-2.5/s, 100 μ V) background activity of high amplitude in the posterior regions. Oral benzodiazepines had no effect on the clinical features or on the EEG. A two-week course of corticosteroids was associated with periods of clinical improvement but failed to abort the status epilepticus, which was eventually controlled by a five-day course of oral ketamine.

Case#4 – A seven year-old girl with Angelman syndrome due to chromosome 15q11-q13 deletion. She had severe developmental delay with mental retardation, no speech, ataxia, typically happy behavior and characteristic EEG for Angelman syndrome. She started to have myoclonic and partial complex seizures at the age of four. These occurred in bouts, sometimes precipitated by mild febrile infections, with months-long seizure-free periods. Maintenance antiepileptic treatment included up to three different drugs. A few months after she started to walk independently, she stopped walking without any apparent precipitating factor, showed increased ataxia, became much less interested in her surrounding, laughed much less and had periods of agitation alternating with periods of placidity. EEG showed more or less continuous generalized 1-2/s sharp-slow complexes (200-300 μ V). Within 10 days of oral corticosteroids, she returned to her previous state, interacting happily and walking again, while the typical EEG patterns of Angelman syndrome re-emerged.

Case#5 – A 5 year-old girl with acute lymphoblastic leukemia. A few hours after completion of her first chemotherapy course, that included asparaginase, vincristin, daunorubicin and intravenous and intrathecal methotrexate, she presented with intense tiredness, hypotonia, confusion and staring with occasional tonic eye deviation toward the left. EEG showed continuous 1-1.5/s spike-wave complexes (300 μ V) over the left frontotemporal region while she was obtunded with undeviated eyes and showed no movements. Intravenous injection of 6 mg of diazepam was followed by disappearance of the discharges and emergence of high amplitude (400 μ V) 1.5-2/s rhythmic activity containing no

spikes over the left hemisphere, while derivations over the right side continued to show 50-75 μ V irregular 4-6/s activity. However, dialeptic status epilepticus recurred two hours later. It did not respond to another injection of benzodiazepines, but stopped after intravenous loading dose of phenytoin.

Case#6 – An eleven year-old girl with simple and complex partial seizures since age 9, related to left frontal cortical dysplasia. Cognition was normal prior to epilepsy onset but had been deteriorating since. Seizure control was difficult with several associations of multiple antiepileptic drugs. She had two episodes of secondarily generalized convulsive status epilepticus. She presented again with simple partial status epilepticus, characterized by gaze deviation toward the right and right facial twitching correlated with continuous left frontal discharges. Oral benzodiazepines and subsequent oral phenobarbital did not stop this activity. After 4 hours, she was in partial complex status epilepticus, which responded to oral corticosteroids within 2 weeks. However, when corticosteroids were withdrawn, simple partial status epilepticus recurred and evolved into complex partial status epilepticus. This only responded to reintroduction of corticosteroid therapy, which could be withdrawn gradually over a three-month period.

Case#7 – A thirteen year-old girl with right frontal epilepsy since the age of 6 years. Seizure control was very good with valproic acid and lamotrigin bitherapy. The patient stopped lamotrigin because she did not have any more tablets. Forty-eight hours later, she presented with blank staring, little reactivity to external stimuli, head and gaze deviation toward the right and she had an urge to walk in circles. When she was held, she had disorganized, purposeless movements of the limbs. EEG showed continuous *en arceaux* 14/s activity more marked anteriorly (150-250 μ V) with no asymmetry, and occasional spike-waves in the right frontal region. Following 10 mg of intravenous diazepam, the clinical state normalized and EEG showed diffuse irregular slow (delta) activity and occasional right frontal spike-waves. Lamotrigin was reintroduced and there were no further episodes.

DIALEPTIC STATUS EPILEPTICUS

Many authors have attempted to differentiate generic nonconvulsive status epilepticus as being either generalized or complex partial. Because of electroencephalographic and, to a lesser extent, clinical similarities, the former is regarded as a prolonged form of absence seizure, hence the term 'absence status'. However, genuine absence status (i.e. long-duration typical absence seizure) appears to be very rare in otherwise well-characterized childhood absence epilepsy. It may be less infrequent in association with other epileptic syndromes, such as juvenile myoclonic epilepsy. It has been reported to occur frequently in a few less common pediatric epileptic syndromes, including epilepsy with eyelid myoclonia and absences [4]. Although absences have been documented in many forms of epilepsy [5] and absence status has been reported in 3 % of patients who have absence seizures [6], the term is often overused to characterize phenomena that are not absences. It has also been applied to patients with very frequent but discrete typical absences

correlated to 3/s spike-wave complexes in the EEG. This has led to some confusion with regard to management and outcome of dialeptic status epilepticus.

In contrast, in complex partial nonconvulsive status epilepticus, epileptic activity has a focal origin and it may spread to involve both hemispheres. This condition was originally described by Gastaut *et al.* [7] in temporal lobe epilepsy. It also occurs in association with other foci, particularly in the frontal lobes, where dialeptic status epilepticus can be categorized in different types including simple partial, complex partial and forms showing overlap with absence status epilepticus [8]. The episodes of status are often heralded by preceding discrete complex partial seizures. Progression from simple to complex partial nonconvulsive status epilepticus has also been described (Case#6) [9]. However, in many cases of possible complex partial status epilepticus, it is difficult to ascertain the origin of the ictal activity at the time of diagnosis. Careful clinical examination may reveal evidence of focal origin. However, clinical distinction between generalized and focal origin is often difficult or impossible to make. Some authors have noted that many cases of dialeptic status epilepticus do not fit the International League Against Epilepsy classification scheme [10]. As noted above, the term 'dialeptic status epilepticus' might appear more appropriate in this context [11].

CLINICAL MANIFESTATIONS

The clinical manifestations of dialeptic status epilepticus in children typically include cognitive or behavioral impairments. The symptoms characteristically fluctuate in intensity over time. Sometimes, the presentation mimics dementia. The alteration of the conscious level can range from slowing of ideation to complete loss of awareness. Patients are usually able to carry out simple and even complex daily life activities to some extent, so that the diagnosis of dialeptic status epilepticus is generally difficult to make at onset. Speech may be slurred, incoherent, sometimes with echolalia (i.e. parrot-like repetition of heard syllables, words or phrases) and palilalia (i.e. iterative repetition of words or of a statement). Parents often describe their child as not being 'their usual self'. Children may show behavioral regression. There may be mood or even personality changes. In a series of nine children (aged 3-16, mean 11) with predominantly psychiatric manifestations of complex partial nonconvulsive status epilepticus, presenting symptoms included sexual disinhibition in two children with a unilateral frontal epileptic focus (left or right), depressive affect in two with a left temporal focus, emotional lability in two with a bifrontal focus, visual and complex auditory hallucinations in one with a right temporal focus, coprolalia (i.e. uttering of rude words) in one with a left hemispheric focus and emotional blunting and abulia (i.e. low impulsivity) in one with a left paracentral focus [12].

Additional clinical features may include ataxia, bradykinesia, myoclonic jerks, mild hypotonia, mild dystonic posturing, automatisms (e.g. lip licking, fumbling with clothes, touching body parts, mumbling or humming), blinking, gaze deviation, nystagmus and autonomic signs (e.g. changes in pupil size, pallor, flushing, heart rate and

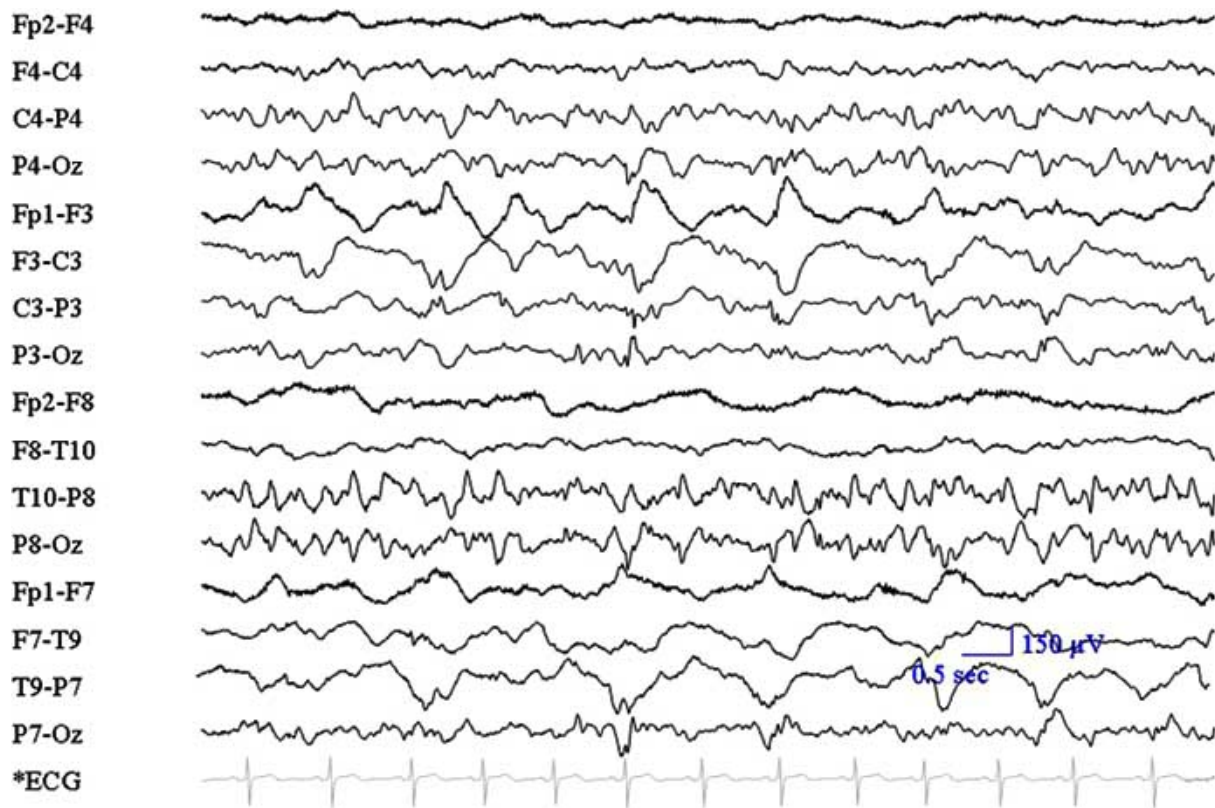


Fig. (1a). There is focal spiking over the right temporal and posterior temporal region in this 9 year-old boy who became mute and appeared confused following chemotherapy with methotrexate for acute lymphoblastic leukemia. There is in addition an excess of slow (delta) activity over a wide area of the left hemisphere.

blood pressure changes). These clinical signs also tend to fluctuate with time.

ELECTROENCEPHALOGRAPHIC FEATURES

The diagnosis of dialeptic status epilepticus is made on a clinical basis and confirmed by EEG.

Complex partial status epilepticus can manifest with widely variable EEG patterns, including spike-waves, spikes (sometime fast spiking) or other discharge activities (Fig. 1). The discharges are often continuous or very frequent. They may be focal and persistently confined to one region or widespread. Sometimes, the discharges switch from one hemisphere to the other, without necessary clinical correlation. At times, EEG is less specific, mostly showing irregular or rhythmic slow activity and isolated discharges, making confirmation of diagnosis more difficult. Fluctuation may be seen, not always correlated with clinical fluctuation, though some of the less specific EEG findings may represent postictal changes. As noted above, it may be difficult to identify a focal origin to the activity, and some recordings are indistinguishable from those obtained in generalized dialeptic status epilepticus.

Generalized forms tend to show continuous or near-continuous 1-2/s spike-wave or sharp-slow complexes (Fig. 2). These complexes are often less distinct, well-formed and stereotyped than the typical 3/s spike-wave pattern seen in

childhood absence epilepsy. This is also true in patients who have status in the context of childhood absence epilepsy. However, the EEG features of dialeptic status epilepticus are better defined and more sustained than the interictal electroencephalographic findings in Lennox-Gastaut syndrome, which is important in view of the prevalence of dialeptic status epilepticus in this epileptic syndrome. This appearance of more clearly defined generalized sharp-slow complexes contrasting with the interictal findings is also found in other conditions. In particular, characteristic rhythmic EEG patterns may be seen in other conditions where dialeptic status epilepticus may occur, such as Rett syndrome or Angelman syndrome [13]. These nonepileptic patterns must be distinguished from dialeptic status epilepticus as they do not constitute an indication for treatment.

The EEG features of dialeptic status epilepticus do not seem to correlate with the degree of conscious level alteration and behavioral disturbances. Although the EEG characteristics are often present and they often alert clinician to the diagnosis, it is not uncommon that children suspected of having dialeptic status epilepticus on the basis of good clinical evidence only show slow EEG activity or intermittent spiking that does not appear sufficiently continuous to suggest dialeptic status epilepticus. In such cases, careful reappraisal of the clinical circumstances may be helpful and it remains the clinician's difficult task to assess

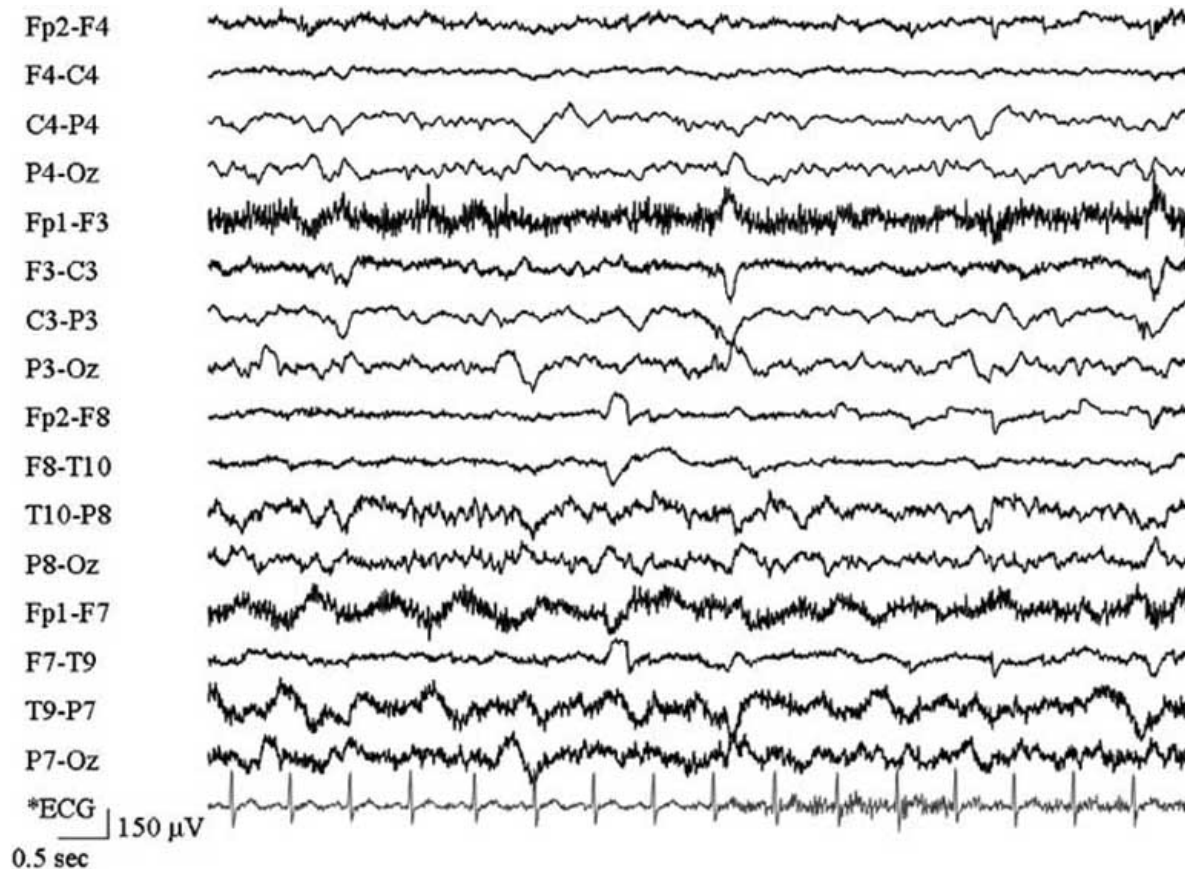


Fig. (1b). Electroencephalogram recorded following clinical neurological improvement. There has been resolution of the focal spiking and improvement in the widespread slowing.

the possibility of continuing but fluctuating activity as opposed to a postictal phase.

Rarely, patients present with atypical EEG features, such as generalized fast activity (Case#7) [14]. This situation may be mistaken for other conditions where a similar electroclinical picture that appears to be nonepileptic in origin is related to impairment of fronto-motor control (as in one personal child with a tumor close to the motor cortex or one adult with multiple sclerosis [15]), or precipitated by medication, such as levetiracetam [15] or methylphenidate (in one other pediatric personal case).

EPIDEMIOLOGY

Epidemiological data concerning dialeptic status epilepticus in children are scarce because of the lack of consensus on diagnosis and, above all, because of the probably high rate of non-recognition of the symptoms as being pathological, or their misinterpretation as essentially behavioral problems. In adults, dialeptic status epilepticus is estimated to represent about one quarter of all cases of status epilepticus [16]. In children, it appears to be more frequent beyond infancy than earlier. It is expected to be more frequent in children with brain lesion (Case#2). There is almost always a history of seizures, though the lack thereof does not exclude the diagnosis (Cases#3 and 5). Complex partial status epilepticus is more common in patients with

complex partial seizures, with an estimated prevalence of 15%. In Lennox-Gastaut syndrome, that is characterized by tonic seizures, atonic seizures and atypical absences, interictal with diffuse, variably defined electroencephalographic complexes of slow (around 2/s) and sharp waves, and mental retardation, dialeptic status epilepticus is even more common (Case#1), affecting up to two-thirds of patients [17]. As mentioned above, dialeptic status epilepticus is also common in Angelman syndrome (Case#4).

Very rarely, dialeptic status epilepticus is the main manifestation of encephalitis [18]. Such cases, which are self-resolving, have been regarded as 'limbic encephalitis', though no evidence of viral infection was found.

A number of precipitating factors can trigger an episode of dialeptic status epilepticus. These include (even mild) infection, sleep deprivation, and various drugs. Among these, administration of several antiepileptic are paradoxically associated with an increased risk of dialeptic status epilepticus, namely carbamazepine, vigabatrin, tiagabin, oxcarbazepine, and to a lesser extent, lamotrigin, phenobarbital and phenytoin. Withdrawal of antiepileptic drug, particularly benzodiazepines and lamotrigin, can also precipitate dialeptic status epilepticus (Case#7). Administration of other drugs can induce dialeptic status epilepticus, including amitriptyline, theophylline,

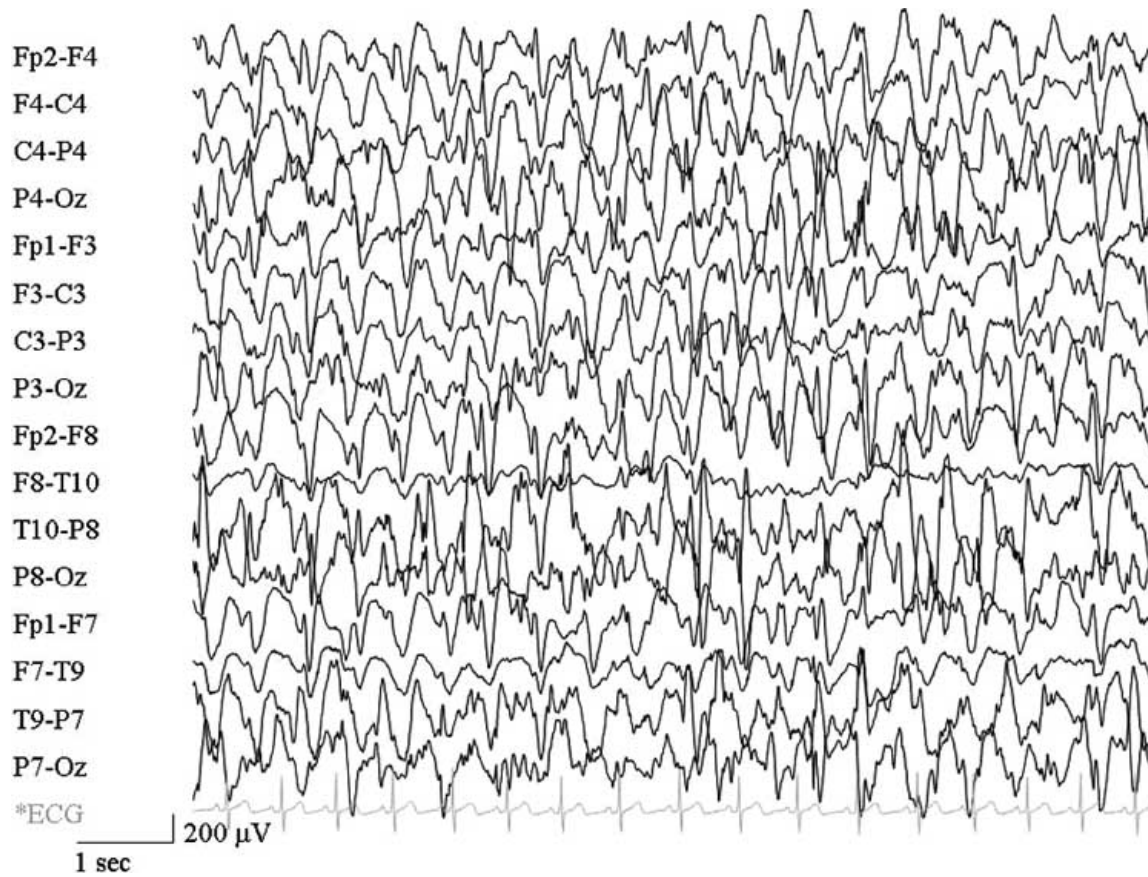


Fig. (2). Generalized spike-wave complexes are seen continuously in this 7 year-old girl who has become behaviorally withdrawn over the past 2-3 weeks.

cephalosporins (with a risk increase by renal failure) and some chemotherapeutic agents (Case#5), such as methotrexate, ifosfamide, cyclophosphamide, cyclosporin, vinblastin and cisplatin.

IMAGING

Brain imaging is not necessary for the diagnosis of dialeptic status epilepticus. It may be indicated, but rarely acutely, in situations where the etiology of the seizure disorder is unknown or for more general work-up. A few reports have described the effect of dialeptic status epilepticus on brain imaging, mostly in adults. Magnetic resonance imaging is more commonly normal during the episode [10]. It may, however, demonstrate reversible cortical swelling, associated with increased T2 signal and decreased water diffusion. Subsequently, it may show increased diffusion and atrophy. During dialeptic status epilepticus, magnetic resonance spectroscopy may show a decreased peak of N-acetyl aspartate (reflecting loss of functioning neurons) and increased peaks of lactate (reflecting anaerobic metabolism) and choline, with increased mobility of choline [19]. Ictal single photon emission computed tomography (SPECT) with hexamethylpropylene-amine-oxim (HMPAO) may document generalized [10] or focal increase in cerebral blood flow as compared to interictal findings. Ictal positron emission tomography (PET) using

^{18}F -fluorodeoxyglucose (FDG) may document increased regional glucose metabolism, contrasting with interictal hypometabolism.

PATHOPHYSIOLOGY

Insights into the pathophysiological mechanisms that underlie dialeptic status epilepticus could have important implications for management. In this context, several processes should be considered. The mechanisms of seizure initiation have not been studied in this particular condition, but they are likely to be similar to other seizure models, whether generalized or focal [20]. In cortical structures, most if not all epileptic activities derive from imbalance between depolarizing and hyperpolarizing influences in large interconnected networks of neurons. These influences can concern synaptic or intrinsic membrane properties as well as regulation of ion distribution. More topical to dialeptic status epilepticus are the mechanisms that promote continuation of epileptic activity, failure of mechanisms that stop this activity, and mechanisms that permit a number of cerebral functions to be preserved despite the ongoing the epileptic activity.

Mechanisms that can ensure repetitive, epileptiform firing involve cells that can generate bursts of several slow action potentials mediated by Na^+ and Ca^{++} currents upon activation, particularly by strong or prolonged depolarization

(such as during a seizure), thus promoting repetitive firing. Excitation of other burst-generating neurons through axonal collaterals gives rise to a network of neurons that can generate powerful recurrent excitation. In addition to synaptic factors, nonsynaptic mechanisms appear to play an important role in continuation of epileptic activity. The ion fluxes related to the activity of the involved neurons generate currents that circulate in the extracellular space, inducing the excitability of the membrane of neighboring neurons through an electrical field effect [21]. Moreover, intense neuronal activity creates fluctuation in extracellular ions, particularly K^+ , that also tends to depolarize neighboring neurons [22].

Epileptic activity is known to induce a physiological cascade of intrinsic neuronal and synaptic mechanisms that tend to reverse this activity. As a result, most seizures are self-resolving. Failure of these mechanisms of seizure termination lead to seizure prolongation, eventually into status epilepticus. These events include intrinsic neuronal mechanisms, such as K^+ currents and ion pumps, which tend to hyperpolarize the neurons through their electrogenic activity. Synaptic mechanisms mostly involve γ -aminobutyric acid (GABA) and its receptors. Pharmacological treatment of seizures, including dialeptic status epilepticus, is therefore often directed at potentiating GABAergic inhibition. This is thought to be the mechanism of action of benzodiazepines. Corticosteroids may also act through modulation of GABA_A receptor activity. The efficacy in the treatment of dialeptic status epilepticus might be related to receptor gating with slow kinetics due to a non-aqueous reservoir mechanism, possibly involving the plasma membrane [23]. Peptides, such as opioids, and adenosine also likely play a role in seizure termination. However, functional modification of GABA_A receptors occurs in the course of status epilepticus [24]. While slow inhibitory postsynaptic potentials (IPSPs) mediated by GABA_B receptors still play a role after prolonged activity, fast IPSPs mediated by GABA_A receptors fade with repeated use [25]. This may account for increasing resistance to GABAergic antiepileptic drugs, such as benzodiazepines [26], phenobarbital [27] and vigabatrin [28], as status epilepticus persists. Concomitantly, there is increased sensitivity to N-methyl-D-aspartate (NMDA) receptor antagonists [27]. This suggests that prolonged status epilepticus is associated with excessive glutamatergic excitatory transmission, although the latter can also modulate GABAergic inhibition [26, 29]. While these experimental findings concern convulsive status epilepticus, treatment of pediatric dialeptic status epilepticus with oral ketamine, an NMDA-receptor antagonist, has been encouraging [30].

One of the most challenging aspects of dialeptic status epilepticus is the discrepancy between dramatic EEG features and relatively mild clinical manifestations. Patients in ongoing dialeptic status epilepticus can often carry out with many daily life activities for several weeks, months or sometimes years. This implies (at least) partial preservation of neural sensorimotor and cognitive processing. The processes involved in effective segregation between the neurons actively involved in the epileptic activity and the other neurons is currently poorly understood. Recent studies of neuronal circuits have used several approaches. Among them, nonlinear dynamic modeling seems particularly

promising. The search for broad-band spectra or rapid decaying autocorrelation functions can show areas of loss of complexity during ictal states with adjacent focal areas with less pronounced reduced complexity [31]. Several modes of population activities have been demonstrated in cortical neuronal networks, including oscillations, synchrony and waves. Neuronal networks have also been shown to produce 'avalanches' of spatial and temporal distribution of neuronal activity that comply with physical theories of critical systems [32]. Network stimulations and pharmacological experiments suggest that a critical branching process can optimize information transmission while preserving stability in cortical networks [32, 33].

CURRENT MANAGEMENT

Although dialeptic status epilepticus can be self-resolving, it is associated with short-term morbidity [34] and possible long-term cognitive sequelae [35], so that pharmacological intervention is often considered. However, although some authors have proposed to use response to benzodiazepines as a diagnostic test, response to treatment is highly variable. While very encouraging results were reported following a single oral dose of clobazam (average 1.0 mg/kg), benzodiazepines are commonly ineffective. They may even deteriorate or precipitate dialeptic status epilepticus, particularly in the context of Lennox-Gastaut syndrome [37]. The risk of iatrogenic morbidity associated with intravenous anticonvulsant therapy arguably contraindicates its use in dialeptic status epilepticus. In adult practice, it has been stressed that "the cure may be worse than the disease" [38]. However, the pediatric setting calls for specific reappraisal of this view, with particular reference to brain development and learning. Experience with epileptic encephalopathies suggest that dialeptic status epilepticus could have long-term effect on brain functioning through continuing epileptic activity. Furthermore, prolonged periods of impaired cognition has a deleterious effect on learning. A multivariate analysis conducted in 101 children with Lennox-Gastaut syndrome identified dialeptic status epilepticus as the main independent risk factors for severe mental retardation [39].

In addition to the lack of consensus on diagnosis of dialeptic status epilepticus in children, there is a marked lack of controlled trials to evaluate the effect of management. Most reports are anecdotal, and current attitudes are chiefly based on empirical experience. An example of a general protocol is outlined in Table 1.

As in adults, phenytoin can be effective. Valproic acid has also been proposed as an alternative to benzodiazepines, and one study conducted in adults found that it prevents recurrence of dialeptic status epilepticus in 'primary generalized epilepsies' [40]. In our pediatric experience, we found that pyridoxine (30 mg/kg/day) could decrease the discharges by up to 50 % but did not abort dialeptic status epilepticus by itself. In some case, it might be useful as adjuvant therapy. We also found very good response to felbamate in the few patients in whom it was used. Several mechanisms might underlie this effect, including NMDA receptor antagonism. Felbamate may otherwise be effective in Lennox-Gastaut syndrome, a condition where dialeptic

Table 1. Suggested protocol for management of dialeptic status epilepticus.

<p>To review at presentation: clinical history; drug history, including recent addition of any antiepileptic drug; any known diagnosis of epilepsy syndrome/classification; previous episode(s) of dialeptic status epilepticus and response (clinical and EEG) to drug(s) used; current dialeptic status epilepticus: presentation, duration, drug(s), EEG features.</p> <p>If a drug regime proved useful in previous dialeptic status epilepticus, it should be used as first line. If not:</p> <p>First line: Benzodiazepine (e.g. lorazepam 0.05 mg/kg [orally if possible, or] intravenously, maximum two doses). If this fails second line.</p> <p>Second line: Ketamine (1.5 mg/kg/day orally in two divided doses for 3 days). Monitor possible side effects of ketamine. If this fails ketamine (1.5 mg/kg/day orally in two divided doses for 2 more days). If this fails third line.</p> <p>Third line: Review clinical situation and consider corticosteroids (e.g. prednisolone 2 mg/kg/day orally for 7-14 days according to clinical and EEG response) and discuss other options (valproic acid, phenobarbital, phenytoin).</p>

status epilepticus is prevalent. However, the use of this agent is limited by its potential severe side effects, the thorough follow-up of side effects with iterative blood tests and the slow increase in doses before maintenance levels can be achieved. Despite these limitations, sustained effect in patients who have milder conditions than Lennox-Gastaut syndrome may make felbamate a promising avenue in refractory dialeptic status epilepticus.

In addition to the antiepileptic treatment, in prolonged and/or frequently recurrent episodes, the behavioral and educational problems that characterize dialeptic status epilepticus need specific management which often requires a multidisciplinary approach.

PERSPECTIVES FOR MANAGEMENT

Current management of dialeptic status epilepticus is still disappointing in many cases. There is an urgent need to perform well-designed controlled studies of dialeptic status epilepticus management in children. This requires clear definitions of the condition and of its subclasses as well as of outcome measures. Preclinical research is also still much need. Animal models have been developed to mimic different forms of dialeptic status epilepticus. Prolonged complex partial seizures can be experimentally induced by low doses of kainic acid or pilocarpine [41, 42]. Generalized nonconvulsive status epilepticus can be experimentally induced by repetitive timed-injections of low doses of pentylenetetrazol [43].

Better understanding of the pathophysiology of dialeptic status epilepticus may open the way to optimized treatment. The decrease in GABA_A receptor activity as epileptic activity persists may reduce the emphasis currently placed on GABA_A receptor modulation. In contrast, the increasingly recognized role of GABA_B receptors, may lead to envisage the use of GABA_B receptor agonists, such as baclofen. Although the latter can occasionally provoke dialeptic status epilepticus in some clinical situations, it has also been shown to have a protective effect in several animal models of status epilepticus. The important role of NMDA

transmission in sustaining epileptic activity has led to early trials with ketamine [30], that need to be confirmed. Metabolic approaches may include ketogenic diets. These, which are currently used in severe epilepsies with great liability to dialeptic status epilepticus, such as Lennox-Gastaut syndrome, may act through several pathways, including GABA influences, as recently proposed to explain resistance to bicuculline and picrotoxin induced seizures [44]. Finally, dynamic approaches based on models of nonconvulsive epileptic activity as bistable systems [45] or neuronal avalanche models [32] may open the way to resetting techniques applied at critical phases. Based on EEG signal analysis, the activity associated with dialeptic status epilepticus may be seen as a stable pattern of neural circuit activity in the sense that it persists under various neural input that reflect various environmental conditions. This stable pattern contrasts with another stable pattern, which represents interictal activity. Pattern selection leading to a switch from one to another pattern depends on a number of parameters that can be termed 'control parameters'. When these reach a certain 'critical' value, the system becomes instable and may change to another pattern. Bistable systems models show coexistence of a limit cycle and a steady state. This should offer the possibility to terminate paroxysmal oscillation by an appropriate stimulus at a specific phase of the oscillation [46]. The advent of neurostimulation in human disease, including in pediatrics, should allow such developments.

CONCLUSION

Dialeptic status epilepticus is a heterogeneous group where distinction between generalized and focal origin is often difficult. Clinical recognition of dialeptic status epilepticus is important. EEG plays a major role in confirmation of diagnosis and is follow-up. EEG should therefore be performed in all patients presenting altered consciousness without obvious cause. Response to treatment is variable and management may be difficult. Oral benzodiazepines, ketamine and corticosteroids may be early options, but there has been a marked lack of well-designed

controlled studies of dialeptic status epilepticus management in children. There are animal models for focal and generalized forms of dialeptic status epilepticus. Recent advances in the understanding of pathophysiological mechanisms underlying seizure continuation and deficits in seizure termination may contribute to designing improved management programs. These will likely include modulation of GABA_B, GABA_A and NMDA receptor complexes as well as neuromodulation through electrical resetting techniques.

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