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Should epileptiform discharges be treated? Invited Review: Epilepsia

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Abstract

Objective: To evaluate the impact of epileptiform discharges (EDs) that do not occur within seizure patterns, such as spikes, sharp waves or spike waves, on cognitive function and to discuss the circumstances under which treatment of EDs might be considered.

Methods: Review of the literature.

Results: EDs may disrupt short-term cognition in humans. Frequent EDs for a prolonged period of time can potentially impair long-term cognitive function in humans. However, there is conflicting evidence on the impact of EDs on long term cognitive outcome because this relationship may be confounded by multiple factors such as underlying etiology, seizures, and medication effects. Limitations of existing studies include the lack of standardized ED quantification methods and of widely accepted automated spike quantification methods. Although there is no solid evidence for or against treatment of EDs, a non-evidence based practical approach is suggested. EDs in otherwise asymptomatic individuals should not be treated as the risks of treatment probably outweigh its dubious benefits. A treatment trial for EDs may be considered when there is cognitive dysfunction or regression or neurological symptoms that are unexplained by the underlying etiology, comorbid conditions, or seizure severity. In patients with cognitive or

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neurological dysfunction with epilepsy or EDs, treatment may be warranted to control the underlying epileptic syndrome.

Significance: EDs may cause cognitive or neurological dysfunction in humans in the short term. There is conflicting evidence on the impact of EDs on long term cognitive outcome. There is no evidence for or against treatment of asymptomatic EDs.

Keywords

Antiepileptic drugs; Cognition; Epileptiform discharges; Memory; Sleep

I. INTRODUCTION

Approximately 1–5% of the population has epileptiform discharges (EDs) on EEG.^{1; 2} EDs are seen more commonly in people with epilepsy than in controls, and include spikes or polyspikes, sharp waves, or spike and slow wave complexes, occurring isolated or in brief runs, without obvious clinical correlates. EDs may acutely disrupt cognitive or neurological functions in humans^{3–5} and their duration and distribution influences the type of dysfunction.^{5–8} However, the exact long-term impact of chronic EDs on neuronal circuitry and on cognitive outcome has not been clarified. The benefits and risks of treatments to suppress EDs are not clear.

The purpose of this manuscript is to discuss the impact of EDs on cognition, focusing on EDs that do not occur within recognizable seizure patterns or states, and to provide recommendations on when treatment of EDs might be considered. We will specifically refer to situations in the ambulatory or non-acute settings, excluding states with impaired consciousness. We focused this review on clinical data as recent reviews discuss the animal studies^{9; 10}.

II. QUANTIFICATION OF EDs AND COGNITIVE FUNCTION

1. Attempts to objectively quantify EDs.

Most methods for quantification of EDs have been specifically designed for electrical status epilepticus in sleep (ESES), an EEG pattern with almost continuous epileptiform activity during sleep.^{11; 12}

a) Spike-Wave Index (SWI) and Spike-Wave Percentage (SWP).—SWI and SWP provide measures of the percentage of the duration of EEG tracings occupied by EDs. In the original reports on ESES, SWI was defined as percent of slow wave sleep with EDs.^{11; 12} Lack of methodological details and variable interpretations on how to calculate SWI limit reproducibility.¹³ One study proposed quantifying SWI as percentage of one-second bins occupied by at least one ED and this was subsequently adopted and renamed as SWP.^{14; 15} Advantages of SWP include reproducibility and being relatively non-resource-intensive. However, SWP is not able to discriminate severity between EEGs when EDs occur at rates higher than one ED per second (Figure 1).¹⁵

b) Spike frequency (SF)—is the total number of EDs per unit of time, typically 100 seconds¹⁵. This method – if not automated – is more time-consuming than SWP, may be liable to sampling errors, but may discriminate ED severity when spiking is very frequent.

c) Computerized methods.—Automated methods may achieve reproducible and faster ED quantification.¹⁶ However, they can identify only the EDs (or their components) with the predefined parameters, may require adaptations for different patients, screening for rejection of artifacts and do not always identify the different morphologies of EDs. Therefore, automated computerized methods are still not widely used in clinical practice.

2. Challenges quantifying the impact of EDs.

Several nuances in the evaluation of EDs do not lend themselves to a straightforward quantification of their impact on clinical findings.

a) Distribution and lateralization.—The clinical dysfunction may reflect the localization of EDs.³ EDs located in eloquent areas, multifocal EDs, or generalized EDs are expected to be more deleterious than EDs originating from regions that do not contribute to specific testable cognitive functions.

b) Voltage differences.—It is unknown whether high-voltage EDs have the same potentially deleterious effect on cognition than low-voltage EDs.

c) Morphology.—EDs include spikes, polyspikes, and sharp waves in different combinations, with or without an aftergoing slow wave, which has also been proposed to disrupt cortical functioning.¹⁷

d) Sleep-wakefulness stages.—ED severity is not always independent of the wakefulness-sleep stage. It is unclear how EDs at different stages affect the severity of the epileptic encephalopathy. Because most cognitive tests depend on the patient's response (i.e., are done in wakefulness) it is more feasible to test cognitive functions in wakefulness⁵. Conversely, it is more likely to interpret sleep-related deficits as related to information storage and plasticity when no active testing is done in sleep.¹⁸

3. Correlation of EDs to cognitive / functional outcomes

Evaluation of the short-term (acute) impact of EDs is limited to cognitive functions that can be assessed based on quick response times. Cognitive assessment could also modify EDs, further complicating the interpretation of results. Evaluation of long-term impact of EDs on cognitive function can be complicated by the possibility that the cognitive impact may be context and timing dependent. The temporal evolution of symptoms (cognitive, seizures) and EDs is often unclear because EEGs and specific cognitive tests are usually performed after symptom onset. Accurate evaluation of the pre-morbid cognitive function and EEG is therefore limited.

III. IMPACT OF EDs ON COGNITION

1. ASYMPTOMATIC INDIVIDUALS WITHOUT EPILEPSY WHO HAVE EDs

In asymptomatic individuals with no prior epilepsy, the prevalence of EDs ranges from 0 to 6% in children^{19; 20} and from 0 to 7% in adults²⁰ (Table 1). The significance of these incidentally found EDs in otherwise healthy individuals is not clear as subsequent development of epilepsy is rare (approximately 6% in children and 2% in adults²⁰) and the few cognitive and behavioral disturbances suggested in these individuals (Table 1) warrant better confirmation with prospective, well controlled and powered studies.²⁰

2. PATIENTS WITH EDs WHO PRESENT WITH NEUROLOGICAL DISORDERS OTHER THAN SEIZURES

Inpatient and outpatient populations with no history of seizures show a higher prevalence of EDs (2–14%) than in community based studies.^{20; 21} The cognitive significance of these EDs is unclear and may represent a biomarker of abnormal brain (Table 1).

Attention deficit hyperactivity disorder (ADHD)—In a series of 48 children with a mean (range) age of 9.4 (6.7–14.9) years, 16 children with ADHD and rolandic spikes were compared to 16 children with ADHD and no rolandic spikes, and with 16 healthy controls.²² Rolandic spikes were more common in ADHD children with increased impulsivity, reduced inhibition of ongoing response and interference control.²² In addition, overnight sleep recordings show a higher prevalence of EDs in ADHD. Among 42 children with ADHD studied with polysomnography, 53.1% showed EDs, three of whom also had seizures during polysomnography and others had other neurological comorbidities (language disorder, dyspraxia).²³ A series of 23 patients aged 4–17 years with Smith-Lemli-Opitz and serial EEGs showed abnormalities (usually EDs) in 51% of children.²⁴ Within the same individual the presence of EDs on a particular EEG predicted on average a 27% increase in ADHD symptom severity.²⁴ There is yet lack of evidence proving that EDs cause ADHD symptoms independent of any other underlying etiology.

Language disorders.—A higher incidence of EDs in children with language disorders has been demonstrated in studies using polysomnography or standard EEG recordings. EDs (left-sided in 84%) were detected in 50% of children with dysphasia (4–11 years old, n=52) compared to 10% of age-matched controls.²⁵ The type of dysphasia relates to the incidence and severity of EDs in few studies. Children with expressive developmental dysphasia were more likely to have EDs (37.5%) in polysomnography studies than controls (5.1%).²⁶ These included generalized EDs in NREM sleep, although in 2/9 children EDs were detected in wakefulness or REM sleep. Frequent EDs were detected in 56% of children with expressive dysphasia (SWI in sleep 2.5–66%). There is no evidence that these EDs have a causal role on language disorders other than reflecting the underlying etiology. Of interest, one of the two control children with EDs in the latter study had a sleep SWI of 21.6% but no evidence of language dysfunction.

Autism spectrum disorders (ASD) and Intellectual disability (ID).—Both ASD and ID populations demonstrate higher incidence of both epilepsy and EDs than controls.²⁷

Whether EDs in these patients contribute to cognitive impairment or are just a reflection of an underlying abnormal brain is unknown. Overall, 20–60% of children with ASD have epileptiform abnormalities.²⁷ When children with epilepsy are excluded, 8–20% of the remaining ASD patients have EDs.²⁷ Asperger's syndrome had lower rate of EDs and clinical seizures compared to other ASD patients, whereas history of aggression was linked with the presence of EDs but not of clinical seizures.²⁸

EDs are often more common in children with autistic regression even in the absence of history of epilepsy,²⁹ yet the temporal association of EDs and autistic regression is difficult to establish. Compared to pure language regression (LKS), autistic regression was less frequently associated with seizures (8% vs 33% in LKS) or EDs (28% vs 56% in LKS), occurred at younger ages, and was more commonly associated with developmental delay.³⁰ Therefore, EDs may either play a lesser role in the pathogenesis of or be a weaker surrogate marker for autistic regression than they are for pure language regression. An alternative possibility, also supported by existing experimental evidence,³¹ is that the developmental impact of the etiologies underlying these age-specific syndromes may be further modified by age, gender or region-specific factors.

3. PEOPLE WITH EPILEPSY

Several studies have examined the short or long-term impact of EDs in certain syndromes with focal or generalized EDs: EDs affected central information processing, response times to stimuli or cognitive responses.³² In other studies comparing the effects of EDs or seizures on learning and cognitive aspects, EDs in the absence of seizures had either no effect or mild independent effect on attention and speed of information processing,⁶ especially when EDs occurred at high frequencies.

A. Short-term effects of EDs (Table 2).

Impact of EDs on neuropsychological tests.: Short-term cognitive impairment induced by EDs is not necessarily a consequence of a global attention impairment but it may reflect disruption of brain functions specifically located in the affected brain regions.³ In addition, the cognitive deficits may depend on when the EDs occur.⁵ To cause specific cognitive dysfunctions, EDs may have to occur in the right place^{3; 33} at the right time⁵ (Table 2).

Impact of EDs on daily activities.: Twenty children were evaluated for performance in scholastic tasks.³⁴ A higher rate of EDs was associated with low test performance, especially for arithmetic.³⁴ The driving performance of six individuals with EDs was monitored while driving at a constant speed of 90 km/h on a highway for a total of 420 km per patient.⁴ During periods with EDs, three individuals had impaired ability to maintain course and an additional individual showed trends towards impairment.⁴ The impairment in maintaining course during EDs occurred even in patients who had been seizure free for years.⁴ The results of standard laboratory tests such as Corsi block-tapping or short-term verbal memory test during EDs in these same patients did not predict the results of the driving test.⁴ While EDs may impair certain attention sensitive tasks, including in seizure-free individuals, this impairment may not be predictable by standard neuropsychological tests.

EDs versus transient cognitive impairment (TCI) and short non-convulsive seizures.:

If EDs lead to a measurable cognitive change these discharges may not be subclinical, but instead clinical (TCI) or ictal (“subtle seizures”).³ Various visual or auditory response tests have temporally correlated components of epochs with EDs to response delays.^{17; 35} It has been proposed that the ED effect begins just before the spike and ends with the termination of the after-coming slow wave.¹⁷ In another series, the cognitive performance of 188 children (6–18 years old) was evaluated during a two-hour-duration testing session with simultaneous EEG monitoring.³⁶ The study population was divided into: 1) children with epilepsy who had short non-convulsive seizures during the test (i.e., electro-clinical events of staring or subtle movements lasting for seconds), 2) children with epilepsy without short non-convulsive seizures during the test, and 3) controls without epilepsy.³⁶ Short non-convulsive seizures markedly impaired cognition.³⁶ These were shorter than 19 seconds and were usually focal seizures and less frequently absence or myoclonic seizures. EDs without seizures also impaired cognition but their effects were more subtle.³⁶ Are EDs a milder condition on the spectrum of non-convulsive seizures? Or are EDs an early marker of the underlying etiology / state that predisposes to either cognitive dysfunction and / or epileptic seizures? Resolving these questions may help decide on the optimal management of individuals with EDs.

Challenges in interpretation of results.: Study participants in short-term cognitive tests are an inherently biased population, because subjects with frequent EDs in the awake and alert state are typically preferred for these studies.³⁷ Therefore, these results may or may not apply to subjects with less frequent EDs or to subjects with EDs during sleep. Further, external stimuli and level of attention on a particular task may modify the frequency and characteristics of EDs.^{1; 4; 33}

B. Long-term effects of EDs.

Pediatric focal epilepsy syndromes.: Childhood epilepsy with centro-temporal spikes (CECTS), Panayiotopoulos syndrome, and late-onset childhood occipital epilepsy (Gastaut type) share common features such as relatively mild and infrequent seizures and frequent and sleep-potential EDs which persist for several years after seizure freedom.³⁸ In children with CECTS, abnormal neuropsychological development, especially in the verbal domain, was linked to more frequent EDs during sleep,³⁹ while, in another study, impairments in academic and familial functioning was reported in 29%.⁴⁰ Predictors of poor evolution were related to EDs and not to seizures.⁴⁰ No correlation between spike rates and cognitive performance was seen in a different study of CECTS.⁴¹ In a series of 26 children with focal EDs (19 with CECTS, 2 with Panayiotopoulos syndrome, 1 with focal seizures, 4 with no history of seizures) and learning difficulties, central information processing speed at baseline negatively correlated with frequency of EDs, without separating those without seizures.³² On follow-up, worsening central information processing speed correlated with increased EDs but also with ongoing seizures.³² It is unclear whether the seizures or EDs had independent impact on central processing. Among children with focal epilepsy syndromes, those with left centro-temporal EDs performed worse during complex language tasks, while children with occipital spikes performed worse in simultaneous information processing, especially in visual transformation tasks.⁴² In summary, the evidence, based on

small case series of children with EDs and focal epilepsy, suggests worse cognitive outcome in the long term and this impairment may reflect the location of EDs.

Generalized epilepsies.: Spike wave discharges seen in children with childhood absence epilepsy may disrupt attention, consciousness, and information processing in the short term⁴³ There is also some evidence of long-term cognitive deficits. In a study comparing 16 children with childhood absence epilepsy, 14 children with type I diabetes, and 15 healthy children, the children with childhood absence epilepsy did not perform differently on measures of intellectual function, memory, academic achievement, fine motor speed, or processing speed⁴⁴. However, they performed worse on problem solving, letter fluency, complex motor control, attention/behavioral inhibition, and psychosocial functioning.⁴⁴ Children with childhood absence epilepsy may have worse long-term psychosocial outcomes than patients with non-epileptic chronic diseases, such as juvenile rheumatoid arthritis.⁴⁵ Juvenile myoclonic epilepsy may also show long-term subtle frontal processing dysfunction^{46; 47}. It is possible that EDs progressively disrupt thalamo-frontal neuronal networks leading to deficits in functions subserved by these networks. However, both functional deficits and EDs may represent just biomarkers of genetically determined abnormal thalamo-frontal neuronal networks.⁴⁷

Epileptic encephalopathies with language or cognitive regression.: ESES is characterized by almost continuous spiking during non-rapid eye movement sleep frequently associated with different degrees of cognitive regression.^{11; 48} Long duration of the ESES pattern has been classically considered as a marker of poor cognitive outcome.⁴⁸ In a literature review of 209 cases, an ESES duration longer than 2 years was associated with poor cognitive outcomes.⁴⁹ In a series of 30 patients with ESES who responded to treatment, there was a correlation between duration of the ESES pattern and return to cognitive baseline at follow-up. Fifty percent of children with ESES lasting less than 13 months return to baseline but none of those with ESES lasting longer than 18 months.⁵⁰ Objective measures of cognitive function before and after epilepsy surgery suggest that stopping ESES improves cognition (Table 3).^{51–53} However, relatively small series and potential confounders such as underlying etiology, seizure burden, and AED treatment may warrant caution when attributing improvement exclusively to ED reduction. Further, in a series of seven patients, no association was found between duration of ESES and cognitive outcome.⁵⁴

Common pathophysiological mechanisms.: Some genetic mutations present different degrees of ASD, EDs, epilepsy, and ID in the same patients,^{55–59} suggesting a common etio-pathogenesis probably mediated by abnormal synaptic plasticity and excitatory/inhibitory imbalance mechanisms.⁶⁰ This opens a new approach to potentially treat these disorders,⁵⁹ but also suggests that EDs may be just a manifestation of the underlying pathologic process, not the cause of cognitive regression (Table 4). Different underlying mechanisms lead to ESES, an EEG pattern with prominent epileptiform activity. Both mutations in GRIN2A^{55; 61} and early thalamic lesions have been associated with the development of prominent EDs and ESES later in life,^{62–64} further emphasizing the idea of common pathways which lead to similar clinical phenotypes.

How to assess the impact of EDs on cognition.: The question of whether long-term exposure to EDs impairs cognition and whether treatment of EDs can reverse this potential impairment remains unresolved. The short-term impact of EDs on cognition is tested with individuals in two different conditions: with and without EDs. Experiments are completed within a few hours of wakefulness and individuals act as their own controls. Patients with ESES or with CECTS lend themselves to this approach as they can be tested with a formal neuropsychological exam at baseline, their EDs can be reduced with AEDs for a period of time, and a post-intervention formal neuropsychological exam can be repeated. Comparisons before and after treatment then can be corrected only for a limited number of confounders such as seizure burden, but not for factors that define the individual, such as gender or genetic substrate. Although such studies may be useful for short-term outcomes, interpretation of long-term outcomes may be challenged by the difficulty in dissociating the putative treatment-related improvement from the relative improvement in cognitive skills due to natural development or changes in educational system or life situations. Promising results may then justify larger scale studies on relative homogeneous populations (e.g., same syndrome or genetic background) designed to compare the developmental trajectories of individuals with EDs, as a function of treatment, while accounting for the multiple known confounders. Careful assessment of ED burden, types, and location would be important for both types of studies.

IV. TO TREAT OR NOT TO TREAT

While better evidence becomes available, treatment decisions have to be made. The hesitancy in treatment of EDs comes from the fact that there is no strong evidence for or against the causal role of EDs on long-term cognitive impairment. We suggest a non-evidence-based practical approach to manage EDs in different clinical scenarios (Figure 2).

Asymptomatic subjects.

The cognitive impact of EDs in asymptomatic persons without epilepsy is unclear, while the risk for subsequent epilepsy is low and probably related to genetic traits. Therefore, incidentally detected EDs in asymptomatic subjects without epilepsy should not be treated because the treatment benefit is unclear.

Patients with EDs and cognitive dysfunction/regression without epilepsy.

There are reports of some cognitive improvement with AEDs in patients in this category.^{3; 8; 65} However, larger series demonstrate mixed results. In a double-blind, single-crossover trial, eight children (6–12 years old) with learning and behavior problems and EDs were randomized to receive valproate or placebo.⁶⁶ Increased distractibility, increased response time, lower memory scores, and no clinical improvement were found in children on valproate.⁶⁶ In a prospective, open-label study, six children (7–15 years old) with focal EDs and learning difficulties were treated with levetiracetam.⁶⁷ At ten weeks follow-up, four participants showed improvement in the Wide Range Assessment of Memory and Learning but not on the Wechsler Individual Achievement Test.⁶⁷ In summary, although some patients may achieve some cognitive improvements on AEDs, this may reflect natural fluctuations in the course of the disease, and there is currently insufficient evidence to recommend AEDs in

patients with cognitive dysfunction/regression without epilepsy. There may also be worsening of cognitive function with AEDs.⁶⁸

Patients with EDs, cognitive dysfunction/regression in epileptic encephalopathies

In epileptic encephalopathies with regression, administration of ACTH, high dose steroids or immunotherapy has been reportedly effective in improving the EEG and treating regression.¹¹ Reduction of EDs in patients with ESES with high-dose benzodiazepines is associated with improved cognitive function in some cases.^{69–71} In a series of 32 children with ESES, reduction of EDs with valproate or ethosuximide was associated with cognitive improvement.⁷² Epilepsy surgery for identified epileptogenic lesions in patients with ESES halted cognitive deterioration or even improved cognition in at least half of the patients.^{52; 53} Results need to be interpreted in the setting of uncontrolled data acquisition, in a naturally fluctuating condition with other factors potentially influencing outcome.⁴⁸ In summary, in patients with epileptic encephalopathies and cognitive dysfunction/regression, which can be related to EDs, a treatment trial might be justified.

Patients with EDs, cognitive dysfunction/regression and well-controlled seizures.

In a double-blind, placebo-controlled, single-crossover study, 61 children (7–17 years) with well-controlled seizures and behavioral and/or cognitive problems were randomized to lamotrigine or placebo.⁷³ Well controlled seizures were defined as no or infrequent focal or generalized seizures. Behavior (assessed with the Conners ratings scales for parents and teachers) improved in patients with reduced EDs while on lamotrigine.⁷³ No significant effect on seizure frequency was noted. Therefore, a trial with AEDs may be considered in some patients in this category, especially when the cognitive dysfunction is progressive.

Patients with cognitive dysfunction/regression and ongoing seizures.

In patients with cognitive dysfunction/regression, or ongoing seizures, treatment may be warranted to control seizures. There is insufficient evidence to support that cessation of EDs is a better therapy endpoint for the currently available treatments.

Treatment options for EDs.

Few studies evaluate AEDs for EDs and their results should be interpreted in the context of natural fluctuations in EDs.⁷⁴ A large pediatric series compared EDs in 213 EEG pairs before and after introduction of AEDs.⁷⁵ The EDs suppression rate (complete disappearance of EDs of all types in the EEG tracing after treatment) was 22% for phenobarbital, 33% for carbamazepine, and 46% for valproate,⁷⁵ and these values remain stable for focal or generalized EDs, time elapsed between EEGs, and neonatal or non-neonatal EEGs.⁷⁵ In a double-blind single-crossover study, 12 patients (4–21 years old) with generalized drug-resistant epilepsy were treated with add-on lamotrigine and placebo, with EDs markedly reduced (duration and density of EDs) on lamotrigine.⁷⁶ In a double-blind placebo-controlled randomized cross-over study low-dose intramuscular clonazepam markedly decreased EDs in children.⁷⁷ For patients with ESES, high-dose benzodiazepines have been shown to decrease epileptiform activity in some patients.^{69–71} In a placebo-controlled double-blind crossover study in 18 children (5–10 years) with ESES, levetiracetam showed

moderate reduction of nocturnal EDs.⁷⁸ In a series of 44 patients with ESES treated with long-term hydrocortisone, the EEG normalized in 21 patients (48%), although relapse occurred in 14 of them.⁷⁹ In summary, valproate, lamotrigine, levetiracetam, benzodiazepines, and steroids potentially among others, may have an effect on EDs, although it is unclear if that effect is independent of the effect on seizures and therefore the effect of seizures on EDs. However, certain AEDs can also exacerbate EDs or certain negative behaviors (e.g., hyperactivity) (reviewed in¹¹).

V. CONCLUSIONS

EDs may impair cognition in the short-term in a location-specific fashion. In contrast, there is conflicting evidence on the impact of EDs on long term cognitive outcome. Currently, there is not sufficient evidence to support treatment of EDs alone, although treatment trials may be considered if EDs are suspected to contribute to cognitive disability and behavioral problems.

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KEY POINTS

- There is evidence supporting that epileptiform discharges disrupt short-term cognitive processes in humans.
- Disruption of short-term cognitive processes is location-specific as it reflects the area of cortex affected by epileptiform discharges.
- The impact of epileptiform discharges on long-term learning and cognition is unclear.
- At present, there is no evidence for or against treatment of epileptiform discharges alone.

Figure 1. Comparison of spike percentage and spike frequency for epileptiform discharge quantification.

The spike percentage considers that both tracings are equally severe with 100% of one-second bins occupied by, at least, one spike-wave in them. In contrast, the spike frequency considers that the upper tracing would be more severe as there is a higher number of spikes per unit of time.

Figure 2. Suggested management of patients with EDs and different clinical conditions.

When EDs appear in otherwise asymptomatic subjects, treatment is usually not recommended. In patients with cognitive dysfunction or regression and no ongoing seizures there is insufficient evidence to recommend treatment although treatment may be justified in individual cases when suspicion that cognitive dysfunction relates to EDs exists. When EDs occur in the setting of cognitive dysfunction or regression and ongoing seizures, treatment is warranted. Treatment in this case may address the entire syndrome. Therapies targeting the EDs may be considered if EDs are suspected to underlie the cognitive dysfunction and if risk is lower than benefit. **Legend:** **B:** Benefits. **EDs:** epileptiform discharges. **R:** Risks.

Table 1.

Frequency of EDs in different populations.

Study and year	Study population	Incidence of EDs	Findings
Asymptomatic individuals			
Cavazzuti et al, 1980 ⁸⁰	3726 school children (6–13y) with no history of epilepsy, no neurological or psychological deficits who underwent EEG in wakefulness, rest, and hyperventilation	131 children (3.5%) Location: Generalized or temporal or rolandic/parietal	Emotional disturbances in 44/131 children (33.6%) Hyperactivity in 23/131 children (17.6%)
Capdevila et al, 2008 ¹⁹	970 “healthy” volunteer children (5–8y) who underwent an 8-lead polysomnography	14 children (1.45%) Localization: Centro-temporal (79%) Temporo-occipital (14%) Fronto-central (7%)	Behavioral, attention, and learning abnormalities or hyperactivity in 50% of children with EDs.
Inpatients or outpatients with no history of seizures			
Borusiak et al, 2010 ⁸¹	382 children (6–13y) with EEG including hyperventilation and photic stimulation performed for minor head trauma	25 children (6.6%) Localization: Rolandic (48%) Multifocal (36%) Generalized or bifrontal (16%)	3/25 (12%) children developed at least one afebrile seizure at a median (range) follow-up of 4.2 (1.2–7.1) years.
Sam & So, 2001 ²¹	521 inpatients and outpatients who underwent an EEG.	64 patients (12.3%) had EDs	47/64 (73.4%) patients had an acute or progressive cerebral disorder. Seizures provoked by the underlying disorder developed in 3/64 (4.7%) patients but in none of the 17 patients without acute or progressive cerebral disorders.
Attention deficit hyperactivity disorder			
Holtman et al, 2003 ⁸²	483 children (2–16y) with ADHD evaluated with routine EEGs	27 children (5.6%) had right-sided or bilateral rolandic spikes	1/27 (3.7%) had seizures on follow-up.

Legend: ADHD: Attention deficit hyperactivity disorder. **ED:** Epileptiform discharges. **EEG:** Electroencephalogram. **y:** year.

Table 2.

Summary of studies evaluating the short-term influence of EDs on cognition.

Study (Author and year)	Population	Epilepsy	Tests for cognitive assessment	Compared groups	Results
Siebelink et al, 1988 ⁸³	21 children (age: mean: 9.25 years, standard deviation: 1.21 years)	Patients with suspected or proven epilepsy	One-hour long neuropsychological test battery (6 subtests of the revised Amsterdamse Kinder Intelligentie test, a Dutch test on intelligence)	Children with frequent EDs during neuropsychological testing (N=15) or no or infrequent EDs (N=6)	Most of the abnormal neuropsychological profiles were found in the group with EDs during the test. This study suggests short-term cognitive impairment due to EDs.
Fonseca et al, 2007 ⁸⁴	13 children (age range: 7 to 12 years) with rolandic spikes	Patients with CECTS	Visual discrimination task between words and pseudo-words	Periods of EDs compared to EDs-free periods	Only two patients (15.4%) made a significantly greater proportion of errors during periods of EDs than during EDs-free periods and there was no statistically significant difference in reaction times. This study suggests no short-term cognitive impairment due to EDs.
Aldenkamp et al, 2005 ³⁵	9 children (38 EEG epochs with epileptiform discharges of at least 3 seconds duration and no apparent clinical correlate)	Not specified	Visual and auditory reaction time	Generalized EDs compared to focal EDs	Only generalized EDs caused prolonged reaction times. Focal EDs, even when long lasting, were not associated with prolonged reaction times. This study suggests short-term cognitive impairment only for generalized EDs.
Aarts et al, 1984 ³	46 patients (age: mean: 25 years, range: 10 to 46 years)	Patients studied for epilepsy	Error rate for verbal and non-verbal attention tasks	Generalized compared to focal EDs and left focal compared to right focal	Abnormally high error rate in 9/24 (37.5%) patients with symmetrical generalized EDs. Abnormally high error rate in 7/22 (31.8%) patients with focal or bilateral asymmetrical EDs. Left-predominant EDs were mainly associated with errors in the verbal task while right-predominant EDs were mainly associated with errors in the non-verbal task. This study suggests short-term cognitive impairment both for generalized and focal EDs and the impairment is region-specific.
Binnie et al, 1987 ³³	91 patients (age: median: 20 years, range: 8–62 years)	Patients referred for known or suspected epilepsy	Short-term memory test of verbal and non-verbal material	Right focal EDs compared to left focal EDs	Impairment in the verbal, non-verbal, or both tasks was found in half of the patients. In patients with lateralized EDs, left EDs impaired the verbal task and right-sided EDs impaired the non-verbal task. One of the patients had independent right and left-sided EDs and showed impairment of the verbal task with left-sided EDs and impairment in the non-verbal task with right-

Study (Author and year)	Population	Epilepsy	Tests for cognitive assessment	Compared groups	Results
					sided EDs. This study suggests short-term cognitive impairment with cognitive impairment reflecting the localization of EDs.
Kleen et al, 2013 ⁵	10 adult patients with temporal lobe epilepsy who had depth electrodes implanted in the hippocampus	Patients with presurgical evaluation for refractory epilepsy	Short-term memory task		During the memory retrieval period, hippocampal EDs contralateral to the seizure focus or bilateral doubled the chances of an incorrect response. Bilateral EDs during the memory maintenance period also had a similar effect. In contrast, EDs during the memory encoding period had no effect. This study suggests short-term cognitive impairment dependent on the task and the timing of the EDs.

Short-term in this context refers to cognitive effects of EDs in the range of hours to days, not to cumulative effects of EDs over months or years.

Legend: **CECTS:** Childhood epilepsy with centro-temporal spikes. **EDs:** Epileptiform discharges. **N:** Number of patients in each study.

Table 3.

Comparison of objective measures of cognitive function before and after treatment in patients with CSWS, the most severe clinical correlate of ESES.

Author and year	Study characteristics	Cognitive function at baseline*	Cognitive function pre-treatment	Cognitive function post-treatment	Cognitive function 2 years post-treatment
Loddenkemper et al, 2009 ⁵²	N=8 Patients with CSWS treated with epilepsy surgery. Age range at surgery: 3 to 14 years. Cognitive measure: developmental quotient (DQ) calculated with the Vineland Adaptive Behavior Scale. One patient underwent pre- and post-operative visual motor integration (VMI) testing. Comparison: pre- and post-surgery	NA	DQ=19/94 (20%)	DQ=57/147 (39%)	NA
		NA	DQ=36/99 (36%)	DQ=40/123 (33%)	NA
		NA	DQ=52/100 (52%)	DQ=83/122 (68%)	NA
		NA	DQ=15/38 (38%)	NA	NA
		NA	DQ=26/194 (13%)	NA	NA
		NA	NA	NA	NA
		NA	DQ=12/59 (20%)	DQ=16/65 (24%)	NA
		NA	DQ=95/174 (55%) VMI=46.4%	DQ=135/198 (68%) VMI=9.8%	NA
Caraballo et al, 2008 ⁵¹	N=9 Patients with early-onset hydrocephalus, ESES and different clinical presentations. Age range: 9 to 16 years. Cognitive measure: Intelligence quotient using Wechsler Intelligence Scale for Children or Terman Merrill Scale. Comparison: Before, during and after ESES in the EEG	IQ=65	IQ=50	IQ=60	NA
		NA	IQ=55	IQ=65	NA
		IQ=65	IQ=55	IQ=62	NA
		NA	IQ=60	IQ=70	NA
		IQ=70	IQ=60	IQ=68	NA
		IQ=69	IQ=61	IQ=68	NA
		NA	IQ=58	IQ=69	NA
		NA	IQ=61	IQ=70	NA
Peltola et al, 2011 ⁵³	N=13 Patients with CSWS treated with epilepsy surgery. Age range at surgery: 3.6 to 9 years Cognitive measure: Intelligence quotient using age-appropriate Wechsler Intelligence Scale or Bayley-R for severely impaired patients Comparison: First measured IQ/DQ, preoperative IQ/DQ, and 6 months after surgery, and 2 years after surgery	VIQ=85 PIQ=69	VIQ=55 PIQ=58	VIQ=62 PIQ=65	VIQ=70 PIQ=66
		IQ=30	IQ=30	IQ=27	IQ=27
		IQ=43	IQ=26	IQ=28	IQ=20
		VIQ=105 PIQ=63	VIQ=68 PIQ=42	VIQ=65 PIQ=46	VIQ=60 PIQ=47
		IQ=93	VIQ=64	VIQ=64	VIQ=69
			PIQ=56	PIQ=62	PIQ=66
		IQ=50	IQ=20	IQ=24	IQ=25
		DQ<20	DQ<20	DQ<20	DQ<20
		VIQ=61 PIQ=67	IQ=40	IQ=40	IQ=21
		IQ=66	IQ=50	IQ=43	IQ=52
		IQ=50	IQ=46	IQ=47	IQ=45
		VIQ=90 PIQ=81	VIQ=56 PIQ=50	VIQ=60 PIQ=50	VIQ=64 PIQ=55
		IQ=100	IQ=45	IQ=30	IQ=42

Author and year	Study characteristics	Cognitive function at baseline*	Cognitive function pre-treatment	Cognitive function post-treatment	Cognitive function 2 years post-treatment
		IQ=90	IQ=28	IQ=39	IQ=44

Cognitive function improves in some but not all patients with CSWS after an effective treatment for EDs, although the effect on seizures and the underlying etiology may confound the association.

Legend: **CSWS:** Continuous spikes and waves during sleep. **DQ:** Developmental quotient. **ESES:** Electrical status epilepticus in sleep. **IQ:** Intelligence quotient. **N:** Number of patients in each study. **NA:** Not available. **PIQ:** Performance intelligence quotient. **VIQ:** Verbal intelligence quotient. **VMI:** Visual.

Baseline refers to the period of ESES in the EEG for the study by Caraballo et al⁵¹ and to the first measured IQ/DQ for the study by Peltola et al.⁵³

Table 4.

Several genetic defects which present with ASD, epilepsy, and ID in different combinations and degrees of severity.

Author and year	Genetic defect	Genetic product	Association between ASD, epilepsy, and intellectual disability
Lesca et al, 2012 and 2013 ^{55, 56}	Mutations in the GRIN2A gene	NMDA glutamate receptor alpha-2 subunit	Approximately 20% of cases with atypical CECTS, Landau-Kleffner syndrome, and CSWS have mutations in GRIN2A. These patients present with epilepsy, ID, and autistic features in different combinations and degrees of severity.
Novarino et al, 2012 ⁵⁸	Mutations in the gene BCKDK	Branched chain ketoacid dehydrogenase kinase	This mutation was detected in consanguineous families presenting with ASD, epilepsy, and ID.
Sahin et al, 2012 ⁵⁹	Mutations in TSC1 and TSC2 genes	Hamartin (TSC1) and Tuberlin (TSC2)	Patients with TSC have epilepsy (80–90%), ASD (50%), and ID (45%).
Mefford et al, 2012 ⁵⁷	Copy number changes in different chromosome regions: 1q21.1 15q11.2 15q13.3 15q24 16p11.2 16p13.11 17q12	Different genetic products	Copy number changes in chromosome regions are associated with ASD, epilepsy, and ID in different combinations and degrees of severity.

Legend: **ASD:** Autism spectrum disorder. **CECTS:** Childhood epilepsy with centro-temporal spikes. **CSWS:** Continuous spikes and waves during slow sleep. **ID:** Intellectual disability. **TSC:** Tuberous sclerosis complex.