Epileptiform Discharges and cognition effects: do we need to treat?

Décharges épileptiformes et effets cognitifs : faut-il traiter ?

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Résumé

Des décharges épileptiformes survenant sans manifestations cliniques peuvent être observées dans différentes conditions cliniques. Leur démonstration chez des sujets asymptomatiques ou des patients présentant une déficience intellectuelle/comportementale ne conduit pas à des médicaments antiépileptiques (ASM) en raison de l'absence de bénéfice confirmé. Leur impact sur les fonctions cognitives dépend du moment et de la localisation de ces décharges. Dans les situations de régression cognitive/comportementale avec ou sans crises, les médicaments peuvent améliorer les fonctions cognitives ainsi qu'en cas d'encéphalopathies épileptiques. Chez les patients épileptiques, les ASM sont principalement utilisés pour réduire la récurrence des crises, mais peuvent également supprimer les décharges épileptiformes et provoquer des troubles cognitifs.

Mots-clés : Déficience cognitive- Décharges épileptiformes- Décharges interictales -Électroencéphalographie -Traitement

Abstract

Epileptiform discharges occurring without clinical manifestations can be observed in different clinical conditions. Their demonstration in asymptomatic subjects or patients with intellectual /behavior impairment don't lead to anti seizures medication (ASM) because of no confirmed benefit. Their impact on cognitive functions depends on time and location of these discharges. In situations of cognitive/behavior regression with or without seizures, medication can improve cognitive functions as well as in case of epileptic encephalopathies. In patients with epilepsy, ASM are used primarily to reduce seizures recurrence, but can also suppress epileptiform discharges and give cognitive impairments.

Keywords: Cognitive impairment- Epileptiform discharges- Electroencephalography -Interictal discharges- Treatment.

Introduction

Epileptiform discharges (EDs) include spikes-polyspikes, sharp waves and slow- wave complexes occurring isolated or in brief runs, without obvious clinical correlates (1). Interictal Epileptiform discharges (IEDs) are EDs unaccompanied by observable clinical epileptic manifestations (also called subclinical discharges), usually last 0.5–10 seconds since ictal discharge is defined conventionally by a minimal duration of 10 seconds (2).

Though not fully elucidated yet, the pathophysiological mechanisms of IED are well described in focal epilepsies during surgical evaluations. Interictal spikes occurring in the epileptogenic zone may be followed by either enhanced or depressed inhibition and can be abolished by using GABAA receptor antagonists (3). Also, studies on the relationship between IEDs topographic distribution and seizure patterns identified different types of IEDs and suggested that they may be mediated by distinct neurobiological mechanisms and that they play divergent functional roles (3). It follows that IEDs are not just signs of hypersynchronous excitatory neuron activity but an interaction between different neuron types with extended neuronal networks (3).

Though the exact long-term impact on neuronal circuitry and cognitive outcome has not been clarified yet. Different reports showed that two main factors, discharge duration and their distribution, might influence the type of dysfunction (1, 4, 5, 6, 7). In addition to causing transitory cognitive impairment, IED during early brain development may have long-term adverse effects on the developing neural circuits. According to documented animal models, these effects are cumulative over the time (8).

In clinical practice, it is important to balance the risk and the potential benefit of ASM use in suppressing IEDs.

EDs as a biomarker for seizures and epilepsy

In most cases, EDs are considered as the main EEG findings to support clinical diagnosis of epilepsy and to predict seizure recurrence in patients with single unprovoked seizure and in seizure-free patients under ASM withdrawal (9). In Benign Epilepsy with Centro-Temporal Spikes (BECTS), during patient's follow-up, the presence of IEDs on EEG does not impact subsequent seizure risk in the first four years of disease. However, while children without IEDs remained seizure-free, one-third of children with IEDs at this stage had a subsequent seizure (10). Consequently, IEDs have been often treated to reduce seizure recurrence and to increase seizure-free rate.

Neurophysiological and functional neuroimaging evidence suggest that IEDs may impact cognition either through transient effect on brain processing mechanisms (11) or through more long-lasting effects leading to prolonged inhibition of brain areas distant from, but connected to, the epileptic focus (12). The short-term impairment caused by IEDs is region-specific and may depend on when the IEDs occur to cause specific cognitive dysfunction. In other words, to cause short-term impairment, IEDs must occur in the right place and at the right time (11). However, there is controversy on the effect of IEDs suppression by treatment. Following ASM withdrawal, the spike rate decreased during long-term intracranial EEG monitoring and IEDs rate was not directly influenced, leading to the conclusion that seizures and IEDs might be generated by different networks (9). Intracranial EEG recordings often show that epileptiform activity is rather widespread and that the region generating most IEDs may not be the region of seizure onset (13), which means that IEDs and seizures have two different pathophysiological mechanisms.

Disruptive cognitive effect of EDs

This deleterious effect on cognition and neurodevelopment is well known particularly in children and was showed by different studies. This effect is supported by the evaluation and the follow-up of patients with seizures and neurodevelopmental disorders particularly in children. In clinical practice, treatment of IEDs with ASM is widely thought to improve cognition and behavior due to the possible existence of transient cognitive impairment in patients with active epilepsies and the confirmed cognitive impairment in patients with some epileptic syndromes, particularly children with BECTS (5, 14, 15, 16, 17). Indeed, BECTS is an ideal model of epilepsy for a better understanding of the pathophysiology of IEDs in cognitive deficits since this syndrome is not related to a structural lesion and seizures are usually brief and infrequent, often making ASM unnecessary. Whereas EDs are usually very frequent, especially during non-REM (NREM) sleep (15).

In a study about 32 BECTS patients aged 6–11 years without any medication (14), they underwent all-night EEG monitoring and complex neuropsychological testing to diagnose the presence of core symptoms of attention-deficit/hyperactivity disorder (ADHD). The results were twofold: Firstly, a negative trend between spike-index on EEG and results of neuropsychological testing in Coding and in the Trail Making Test, which can be interpreted as higher rates of attention deficit and impulsivity in patients is associated with higher spike-index in the awake state and in total NREM sleep and secondly, a positive trend between the Test Observation Form results and spike-index in NREM stage I–II and NREM stage III sleep. Besides, other cognitive functions can be disrupted, particularly memory function. A literature review on memory function and impairment in children with BECTS (15) concluded that NREM sleep IEDs may interfere in the communication between temporal and frontal cortex, causing short-term and long-term declarative memory deficits (visual-spatial, auditory-verbal) in association with executive, linguistic and behavior difficulties.

Another recent study examining the whole-brain differences in cortical thickness in children with BECTS and normal developing children (16), demonstrated that IEDs can alter cortical morphology and, consequently, neuropsychological performances in specific regions. According to this study, a region of cortex where right centrotemporal spikes may originate was thinner in BECTS compared to children without BECTS. Also, typically developing children with faster processing speed had thicker cortices in regions supporting visuomotor integration, motor and executive function, and this relationship was not observed in children with BECTS. In children with ADHD, Rolandic spikes are more common in children with increased impulsivity and reduced inhibition of ongoing response. Also, there is a higher prevalence of EDs in sleep than awake EEG recording (50% vs 6%). Indeed, only 3.7% of those with EDs developed seizures in the follow-up (about 0.2% of all the population group) (18). Despite the high prevalence of EDs in this special population, epilepsy is rarely developed.

Furthermore, children with language disorders developed a higher incidence of EDs in studies using polysomnography or standard EEG recordings particularly in case of dysphasia (50% of children) and are in most cases left-sided (80%) vs in only 10% in age-matched controls (1, 12).

In other epileptic conditions, where some patients developed continuous spikes and waves during sleep (CSWS), there is evidence of cognitive regression related to EDs, defining the concept of epileptic encephalopathies. In the condition of epileptic encephalopathy, IEDs are the main cause of cognitive regression (12).

Do we need to treat EDs?

The hesitation to treating IEDs is perhaps since there is no strong evidence for or against the causal role of IEDs on long-term cognitive impairment (4). Therefore, we need to confirm the involvement of IEDs in cognitive impairment and to determine the types of IEDs that are more disruptive to cognitive functions (type, localization, frequency…). In practice, the impact of IEDs on cognition and on seizure occurrence/recurrence risk are evaluated in multiple conditions: asymptomatic individuals without epilepsy (with or without cognitive dysfunction / regression) and patients with epilepsy (1).

Asymptomatic individuals without epilepsy: the prevalence of EDs is about 0- 6% in children and 0- 7% in adults and the subsequent development of epilepsy is rare (6% in children and 2% in adults), suggesting that epilepsy is probably related to genetic traits and not to the presence of EDs (1). Over 1% of healthy school children who underwent awake EEG had EDs mostly located in centrotemporal regions (about 80%), probably linked to BECTS. Clinical symptoms including behavior, attention and learning abnormalities or hyperactivity were observed in only 15-30% of children (19). 12% of inpatients and outpatients without epilepsy history had EDs and more than 70% of them developed seizures in the follow-up. This evolution is probably related to the underlying progressive brain diseases rather than EDs (20). Those asymptomatic individuals without epilepsy showed some cognitive and behavioral disturbances that require prospective and well-controlled studies. Thus, IEDs should not be treated when effects are still unclear.

Patients with cognitive dysfunction or regression without seizures: there is a higher prevalence of focal EDs (2–14%), though the cognitive significance is unclear, and may represent a biomarker of abnormal brain function (19, 20). Non-epileptic children (6-12 years) with developmental disorders of behavior or cognition (aged from 6 to 12 years) who were randomized to receive valproate or placebo, showed increased distractibility and response time, lower memory scores, and no clinical improvement was noted in children on valproate (21). Other neurodevelopmental disorders like autism spectrum disorders (ASD) and intellectual disability have a higher incidence of both epilepsy and EDs particularly in ASD with autistic regression even in the absence of a history of epilepsy (20 to 60% have EDs vs 8 to 20% if epilepsy is excluded) (22). It is still unknown whether EDs contribute to cognitive impairment or they are just a reflection of an underlying brain abnormality. Some reports found a high correlation between the presence of EDs and lower intellectual quotient and some patients may achieve some cognitive improvements on ASM. This effect may reflect the natural fluctuations in the course of the disease. Also, ASM may worsen the cognitive function impairment particularly in children and the elderly, especially when using old generation ASM and with higher dosages and/or on polytherapy (more than 2 drugs) (23). It should be concluded that evidence is too insufficient to recommend ASM for EDs in patients with cognitive dysfunction without epilepsy.

Patients with epilepsy: Though the literature reports a negative impact of IEDs on behavior and cognition and randomized placebo-controlled studies showed that treatment of IEDs can im-

prove behavior in epileptic children, further controlled-study designs are needed to evaluate the effect of ASM in reducing IEDs. There seems to be no final answer as to whether or not ASM can suppress IEDs. It depends upon the drug type and on IEDs pattern. For spike-wave activities with epilepsy, ASM can be effective against IEDs in some cases such as patients with Childhood Absence Epilepsy or in BECTS (24). While ASM can be effective against IEDs such as Levetiracetam, Topiramate, and Lamotrigine, no effect or controversial data are reported for other drugs such as Vigabatrin, Gabapentin, and Carbamazepine (25, 26). ASM is prescribed to prevent seizure recurrences and not to treat IEDs, except in special situations such as epileptic encephalopathies. Classically, in case of epileptic encephalopathies with CSWS, the long duration of the CSWS pattern is a marker of poor cognitive outcome. About 50% of children with less than 13- month-long CSWS return to baseline, but none of those with over 18-month-long CSWS supported the negative effect of IEDs on cognition and sidestepped the need for treatment. Also, the objective measurements of cognitive function before and after epilepsy surgery suggests that stopping IEDs improves cognition (22, 27). The FDG-PET imaging provides a way to study long-lasting effects of IEDs on brain functioning at rest (11). Comparative studies of children having epileptic encephalopathy with CSWS and normal MRI and children with BECTS showed a deeply abnormal pattern of regional glucose metabolism in children with epileptic encephalopathy that is anatomically related with EEG foci and type of neuropsychological defect. There is also evidence that reduction of IEDs in patients with CSWS is associated with improved cognitive functions in some case treated with high-dose of steroids, immunotherapy, high-dose of benzodiazepines, Valproate or Ethosuximide or also by surgery for epileptogenic lesion (27, 28, 29). For all these reasons, treatment trials might be justified for IEDs in case of epileptic encephalopathies even in the absence of clinical seizures. The improvement of IEDs is associated with clinical improvement of cognitive deficit and clinical seizures.

In other clinical conditions such as patients with cognitive dysfunction or regression and well-controlled seizures, patients can be evaluated for treating IEDs. The ASM may be considered in some patients, especially when the cognitive dysfunction is progressive. Treatment may be warranted to control seizures in cases of cognitive dysfunction or regression and ongoing seizures, though there is insufficient evidence to support that cessation of IEDs is a better therapy endpoint (1).

In summary, there are multiple literature reports on negative effects of IEDs on specific cognitive functions, seizure recurrence and postsurgical prognosis while other reports associate ASM with potential beneficial effect in suppressing IEDs and improved cognitive functions.

Since IEDs impair performance acutely, and probably chronically, there are good theoretical reasons for suppressing them. Yet, no consensus has been reached. Many ASMs which are effective in controlling clinical seizures have little effect on IEDs. Better methods of measuring outcomes may allow the selection of individual patients for whom IEDs treatment is worthwhile (26).

Meanwhile, randomized trials are needed to develop specific recommendations on timing of treatment, ASM choice, treatment duration, and withdrawal of medication in specific patient conditions.

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