Behavioral & Cognitive Comorbidities of Pediatric Epilepsy: a Focus on the Effects of Anti-Seizure Medications

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Abstract

Cognitive and emotional behavioral derangements are the most common comorbidities of epileptic disorders in children. The treatment of these comorbidities is challenging due to their heterogeneous etiologies that include among others, epilepsy-related underlying brain pathologies, seizure frequency, and anti-seizure medications. Compared to other factors, the contribution of medications to the psychiatric and cognitive comorbidities of the epilepsies is more likely to be controllable and may be reversed or even avoided. Despite the advent of multiple new generation anti-seizure medications, the lack of major differences in efficacy between drugs makes the side effects profile the most important factor in individualizing drug selection and potentially using "cognitive and emotional side effects" to the advantage of the child with epilepsy.

I. Introduction

Epilepsy is a very common neurological disorder affecting up to 1% of children, and is often accompanied by emotional behavioral and cognitive derangements. Indeed, children with epilepsy are at a high 60% risk of suffering from comorbidities such as depression, anxiety, attention deficits, learning disorders, aggression, and autism (1-3). These cognitive and behavioral impairments can result in social exclusion and isolation, as well as difficulties in accessing educational services, and they can thus negatively affect quality of life more than the seizures themselves (4). Cognitive abilities and discipline are essential factors in determining a child's progression towards independence. Moreover, adolescents experiencing epilepsy at early ages are at higher risk of suicide (5). Unfortunately, the etiologically heterogeneous nature of these comorbidities poses a therapeutic challenge. Indeed, the multiple potential contributory factors include the presence of an underlying pathology, the location and extent of a possible epileptogenic lesion, seizure frequency and duration, as well as the number and types of anti-seizure medications. Identification of contributory factors is necessary to optimize the therapeutic approach and to alleviate the burden of these comorbidities. The underlying pathology, its type and location are usually key contributors. Frontal lobe lesions, for example, are usually associated with rigidity, disinhibition and autistic-like features, while temporal lobe pathologies are associated with mood disturbances, and language and memory deficits. Environmental factors, such as family and social support systems as well as social stigmata associated with the diagnosis of epilepsy, should not be ignored as they are also likely to affect emotional and cognitive behaviors. In addition, adverse side effects of anti-seizure medication constitute potentially reversible contributors. Indeed, despite the advent of multiple relatively new FDA-approved anti-seizure medications, the choice of medications heavily relies on the side effect profile as effectiveness against seizures is often comparable. We will review the most common emotional behavioral comorbidities of the epilepsies followed by a discussion of commonly used anti-seizure medications and their cognitive and behavioral side effect profile.

II. Common emotional behavioral comorbidities

II. 1 Anxiety and Depression

Up to one third of children with epilepsy suffer from anxiety and depression. The symptoms are similar to those of peers without epilepsy, and may be different from those seen in adults. Depressive behaviors are characterized by tearfulness, irritability, sadness and moodiness while anxious behaviors are marked by excessive tantrums, clinginess, worrying, nervousness and negativity. Generalized anxiety, social phobia and depression are often tightly related to environmental factors such as the reaction to illness where children and adolescents often feel like they lose control over their bodies and hope for recovery, and usually have a particular fear of experiencing seizures in public places and during physical activities. Familial resilience, emotional support, coping strategies, communication or lack thereof, also profoundly influence the child's mood. In addition, paroxysmal emotional changes may themselves be seizures in children with temporal or frontal lobes epilepsy who can experience auras of anxiety and fear. Furthermore, there is growing research into potentially common predisposing genes and neurotransmitters deficits that may underlie both epilepsy and mood disorders (6). In addition to treatment strategies commonly employed in depression and anxiety, a special attention should be dedicated to potential anti-seizure medication adverse effects, and to environmental factors, specifically the fear of having seizures and capacity-related inability to cope with psychosocial or academic demands. These potentially reversible factors should be considered prior to initiating classical interventions and medication for depression and anxiety. Indeed, at times, optimizing anti-seizure medications, or the child's environment, may completely prevent the need for psychiatric medications.

II.2 Autism spectrum disorder

Epilepsy and autistic spectrum disorder can co-occur. Autistic features include language deficits, impaired socialization, as well as repetitive and restricted range of behaviors. The primary or classical form of autism which is believed to be mostly genetic in nature, is associated with a high risk of developing epilepsy in adolescence and adulthood (7). Epilepsy is also associated with the secondary forms of autism occurring in the context of genetic syndromes, frontal brain lesions or metabolic conditions. In addition, epileptiform features in the form of continuous spike-waves in sleep (CSWS) are known to be associated with autistic-like regressions in behaviors and language (Laundau-kleffner syndrome). This has triggered a growing research interest in investigating the contribution of seizures and epileptiform features in the emergence of autistic features in children with epilepsy.

II.3 Attention deficit and hyperactivity disorder (ADHD)

ADHD is the most common behavioral disorder in school-age children and manifests with hyperactivity, impulsivity, impatience, and inability to sustain attention. It develops in about 30% of children who suffer from epilepsy. Children with ADHD are also at a higher risk of later developing epilepsy (8). While it is reasonable to believe that ADHD-like clinical features in children with epilepsy are potentially related to the underlying brain dysfunction at the origin of the seizures or to adverse effects from anti-seizure medications, other causative factors may be involved. These include among others, the co-occurrence of classical ADHD, frequent epileptiform discharges, and postictal mood changes. While these factors may be difficult to sort out, it is important from a practical end to rule out reversible anti-seizure drug-related side effects before using ADHD medications.

III. Specific anti-seizure medications

Despite the advent of multiple new medications for seizure

control, the relatively newer drugs are comparable to the older generation medications in their efficacy against seizures. In general, new medications have a lower rate of adverse side effects, specifically less life-threatening ones such as organ failure and bone marrow suppression. However, cognitive and emotional derangements, which constitute the most common drug adverse effects, occur with both old and new generation medications. Cognitive disturbances include decreased mental processing speed, motor speed, as well as attention, learning, and memory impairment, while emotional derangements commonly include mood lability, hyperactivity, and aggressivity. These may end up being more detrimental on quality of life than seizures themselves. Indeed, in addition to poor seizure control, prominent adverse effects also qualify for drug failure. In cases where more than two medications fail due to lack of efficacy against seizures or due to prominent adverse effects, alternative non-pharmacological interventions should be considered, including epilepsy surgery, the ketogenic diet and the vagal nerve stimulator (9,10). The anti-seizure medications are broadly tailored to the types of seizures (focal or generalized) but only rarely to more specific factors such as specific epilepsy syndromes. Indeed, there is a paucity of solid high quality evidence for etiology-specific drug use and efficacy in the epilepsy literature. Since medications are generally considered to be comparable in efficacy, refining the selection and individualizing it heavily relies on the side effect profile. While all anti-seizure medications may cause mental dulling and sedation, especially with polytherapy and at toxic levels, below is a discussion of commonly used medications available in Lebanon and their cognitive and emotional behavioral adverse effects at non-toxic levels.

III.1 Older anti-seizure medications

Phenobarbital is one of the oldest and most mental-dulling anti-seizure medications, yet it is still widely prescribed for both partial and generalized seizures except absence seizures mainly due to its low cost. Cognition, memory, attention and intelligence as measured by IQ scoring, can be seriously impaired in children (11). Behavioral disturbances are numerous and include hyperactivity, withdrawal, and sedation (12).

Phenytoin is another relatively "broad-spectrum" anti-seizure medication. **Carbamazepine** is used for complex partial seizures with or without secondary generalization, but not in primarily generalized epilepsy. The use of these drugs in children has not been associated with major identifiable cognitive or behavioral issues (13). Unlike newer generation medications, they tend to be associated with more adverse effects in general, and similarly to the other old generation drugs, they often require close blood work, and serum drug level monitoring.

Valproate is one of the most effective drugs against both partial and generalized epilepsies. It is associated with rare yet potentially fatal adverse effects, especially in the first two years of life (liver failure), but remains a first line treatment for benign genetic non-lesional generalized epilepsies (idiopathic) in adolescent boys though not in girls due to the risk of teratogenicity and polycystic ovary syndrome. From a cognitive and behavioral endpoint, its use is not associated with absolute cognitive issues when compared to nondrug conditions in children. It can also have impulse control properties and it is worth using this to the advantage of the child with autism and epilepsy. However, on occasions, in our experience, it can paradoxically lead to hyperactivity and agitation.

Ethosuximide is the drug of choice in the initial treatment of the childhood absence epilepsy syndrome. Despite its widespread use, there is little data on its potential cognitive and behavioral side effects. In one study, it was found to be associated with fewer adverse attentional deficits compared to valproate and lamotrigine (14).

III.2 New generation anti-seizure medications

Oxcarbazepine is considered a first line therapy for focal seizure types. Studies have not revealed any consistent cognitive or behavioral adverse effects associated with its use in children when compared to carbamazepine or valproate (15).

Levetiracetam is a new generation drug commonly used as first line for unspecified seizure types (focal or generalized). When compared to carbamazepine in adults, it was found to improve executive function. In children, when used as add-on therapy, no cognitive side-effects have been observed (16). In addition, this drug has a very benign organ system side effect profile. However, its use has been associated with behavioral changes such as hyperactivity, irritability, hostility, as well as depression in adolescents (17). In cases where we occasionally had to discontinue it in our practice, the reason was drug-related hyperactivity, aggressivity, or impulsivity.

Lamotrigine is a new generation broad spectrum medication against most seizure types, however due to potential allergic reactions, its initiation necessitates a very slow titration schedule over months. In some but not all studies it has been shown to have a positive effect on behavior and cognition in children with epilepsy (18). In our experience, when a slow medication up-titration can be performed (when seizures are infrequent, or when switching from one medication to another), we use it as a first line medication, especially in children with impulsivity or autistic-features.

Topiramate is another relatively new anti-seizure medication. Despite its equal efficacy to valproate in the idiopathic generalized epilepsies, it is much less tolerable due to adverse effects. Indeed, its use is associated with mental dullness, attentional deficits, speech problems and memory difficulties in adults. In children, it has also been associated with similar cognitive and behavioral disturbances (19), even more so in children with underlying intellectual disabilities (20). In our experience, similarly to phenobarbital, topiramate should be reserved to select cases of seizures resistant to other drugs.

Clobazam is often used as an adjunctive treatment option for focal or generalized seizures. It is also recommended in Lennox-Gastaut syndrome. The neuropsychological side-effect profile of clobazam is not well studied. However, despite being a benzodiazepine, its use is associated with agitation, self-injurious behavior, insomnia, irritability, and increased motor activity (21).

Vigabatrin is mainly used in the treatment of infantile spasms. This condition is often complicated by neurodevelopmental deficits and thus solid data on its cognitive and emotional behavioral side effects are difficult to obtain.

IV. Conclusions and remarks

Psychiatric and cognitive disturbances are the most common comorbidities of epileptic disorders in children. This review highlights the importance of considering drug-related cognitive and emotional behavioral side effects when selecting anti-seizure medications. Along those same lines, the baseline cognitive and emotional behavioral functioning of the child with epilepsy should be thoroughly characterized and factored in when choosing a medication. This is important in order to avoid behavioral and cognitive disturbances that may worsen quality of life even more than seizures. In addition, with an educated drug selection, side effect profiles may be used to the advantage of the child with epilepsy. For instance, a child with baseline impulsivity, ADHD or autistic features would likely benefit from lamotrigine or valproate in the presence of focal or generalized seizures, or from carbamazepine or oxcarbazepine in the context of confirmed focal seizures. Levetiracetam should be avoided in children with impulsivity, anxiety, depression, or autistic features.

In order to minimize anti-seizure medication related adverse effects and improve tolerability, drug titration should be slow and gradual. If one anti-seizure medication fails at seizure control, it is recommended to replace it using sequential and not additive drug trials in order to prevent polypharmacy when possible. Indeed polypharmacy has been associated with higher rates of intellectual decline (22). The number of prescribed medications should be dropped to a minimum (usually not more than 2-3 drugs) at the earliest opportunity, for instance when a child enters a period of stability. In addition, any child who is seizure free for more than two years qualifies for a medication discontinuation trial irrespective of the risk of recurrence.

V. Future directions

In our translational epilepsy laboratory at the American University of Beirut, neurobehavioral research in age-tailored and clinically-relevant rodent seizure models is employed to investigate emotional and cognitive behavioral disturbances, their causative factors, and novel treatment interventions. These rodent seizure models recapitulate common clinical scenarios such as neonatal hypoxic ischemic encephalopathy and adolescent temporal lobe epilepsy. Measurable behavioral disturbances are studied through objective neurobehavioral testing panels such as the Morris water maze, conditioning experiments, the open field test, and forced swim testing. These are correlated with long-term rat electroencephalography (EEG), and with histological and proteomic brain assays. In addition to dissecting the underlying mechanisms of epilepsy-related cognitive and emotional behavioral disturbances, this line of research also allows the evaluation of potential side effects of novel antiepileptic drugs developed in our laboratory.

References

(1) Piazzini A, Canevini MP, Maggiori G, Canger R. Depression and anxiety in patients with epilepsy. Epilepsy & Behavior. 2001 2:481-9.

(2) Davis SM, Katusic SK, Barbaresi WJ, Killian J, Weaver AL, Ottman R, Wirrell EC. Epilepsy in children with attention-deficit/hyperactivity disorder. Pediatric neurology. 2010 42:325-30.

(3) Steffenburg S, Gillberg C, Steffenburg U. Psychiatric disorders in children and adolescents with mental retardation and active epilepsy. Archives of Neurology. 1996 53:904-12.

(4) Boylan LS, Flint LA, Labovitz DL, Jackson SC, Starner K, Devinsky O. Depression but not seizure frequency predicts quality of life in treatment-resistant epilepsy. Neurology. 2004 62:258-61.

(5) Nilsson L, Ahlbom A, Farahmand BY, Åsberg M, Tomson T. Risk factors for suicide in epilepsy: a case control study. Epilepsia. 2002 43:644-51.

(6) Kanner AM. Depression in epilepsy: a neurobiologic perspective. Epilepsy Currents. 2005 5:21-7.

(7) Bolton PF, Carcani-Rathwell I, Hutton J, Goode S, Howlin P, Rutter M. Epilepsy in autism: features and correlates. The British Journal of Psychiatry. 2011 198:289-94.

(8) Davis SM, Katusic SK, Barbaresi WJ, Killian J, Weaver AL, Ottman R, Wirrell EC. Epilepsy in children with attention-deficit/hyperactivity disorder. Pediatric neurology. 2010 42:325-30.

(9) Obeid M, Wyllie E, Rahi AC, Mikati MA. Approach to pediatric epilepsy surgery: State of the art, Part I: General principles and presurgical workup. european journal of paediatric neurology. 2009 13:102-14.

(10) Obeid M, Wyllie E, Rahi AC, Mikati MA. Approach to pediatric epilepsy surgery: State of the art, Part II: Approach to specific epilepsy syndromes and etiologies. european journal of paediatric neurology. 2009 13:115-27.

(11) Schubert R. Attention deficit disorder and epilepsy. Pediatric neurology. 2005 32:1-0.

(12) Wolf SM, Forsythe A. Behavior disturbance, phenobarbital, and febrile seizures. Pediatrics. 1978 61:728-31.

(13) Aldenkamp AP, Alpherts WC, Diepman L, Van't Slot B, Overweg J, Vermeulen J. Cognitive side-effects of phenytoin compared with carbamazepine in patients with localization-related epilepsy. Epilepsy research. 1994 19:37-43.

(14) Glauser TA, Cnaan A, Shinnar S, Hirtz DG, Dlugos D, Masur D, Clark PO, Adamson PC. Ethosuximide, valproic acid, and lamotrigine in childhood absence epilepsy: initial monotherapy outcomes at 12 months. Epilepsia. 2013 54:141-55.

(15) Donati F, Gobbi G, Campistol J, Rapatz G, Daehler M, Sturm Y, Aldenkamp AP. The cognitive effects of oxcarbazepine versus carbamazepine or valproate in newly diagnosed children with partial seizures. Seizure-European Journal of Epilepsy. 2007 16:670-9.

(16) Levisohn PM, Mintz M, Hunter SJ, Yang H, Jones J. Neurocognitive effects of adjunctive levetiracetam in children with partial-onset seizures: A randomized, double-blind, placebo-controlled, noninferiority trial. Epilepsia. 2009 50:2377-89.

(17) Schiemann-Delgado J, Yang H, Loge CD, Stalvey TJ, Jones J, LeGoff D, Mintz M. A long-term open-label extension study assessing cognition and behavior, tolerability, safety, and efficacy of adjunctive levetiracetam in children aged 4 to 16 years with partial-onset seizures. Journal of child neurology. 2012 27:80-9.

(18) Pressler RM, Binnie CD, Coleshill SG, Chorley GA, Robinson RO. Effect of lamotrigine on cognition in children with epilepsy. Neurology. 2006 66:1495-9.

(19) Kang HC, Eun BL, Wu Lee C, Ku Moon H, Kim JS, Wook Kim D, Soo Lee J, Young Chae K, Ho Cha B, Sook Suh E, Chae Park J. The effects on cognitive function and behavioral problems of topiramate compared to carbamazepine as monotherapy for children with benign rolandic epilepsy. Epilepsia. 2007 48:1716-23.

(20) Coppola G, Verrotti A, Resicato G, Ferrarelli S, Auricchio G, Operto FF, Pascotto A. Topiramate in children and adolescents with epilepsy and mental retardation: a prospective study on behavior and cognitive effects. Epilepsy & Behavior. 2008 12:253-6.

(21) Sheth RD, Goulden KJ, Ronen GM. Aggression in children treated with clobazam for epilepsy. Clinical neuropharmacology. 1994 17:332-7.

(22) Bourgeois BF. Antiepileptic drugs, learning, and behavior in childhood epilepsy. Epilepsia. 1998 39:913-21.