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Neurocognitive Comorbidities in Pediatric Epilepsy

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Abstract

Epilepsy is categorized as a prevalent misunderstood chronic neurologic disorder. Epilepsy episodes occur as a result of abnormal neuronal excitability that was reported to occur due to a disruption depolarization and repolarization mechanisms. In addition to that, currently there are numerous studies that attribute idiopathic epilepsy to a genetic factor as it was found that there is an increased familial incidence of epilepsy. Several studies estimated that around 69 million people worldwide are diagnosed with epilepsy and it is one of the most common neurological disorders occurs to children where approximately 150,000 children experience unprovoked seizure every year, and about 30,000 of them develop epilepsy. Many of these cases demonstrated some neuropsychiatric comorbidity, which consequently affects the quality of their lives in a significant manner. Cognitive impairments might be represented as memory problems, mental defects, and attention impairment, analyzed as the most common comorbid disorders in epilepsy. Thus, it is important to analyze the factors that contribute to cognitive difficulties. Many agents was shown to have a debilitating effect on cognitive function in epilepsy such as the degree of epileptic activity and epilepsy causative factors, psychosocial status of patients in addition to surgical or therapeutic treatment of seizures.

1. Effect of neurotransmitter systems on epilepsy and cognition

Several neurotransmitters and genes were analyzed for their association with epilepsy-related cognitive outcomes[1]. A summary of this relation is shown in **figure.1**

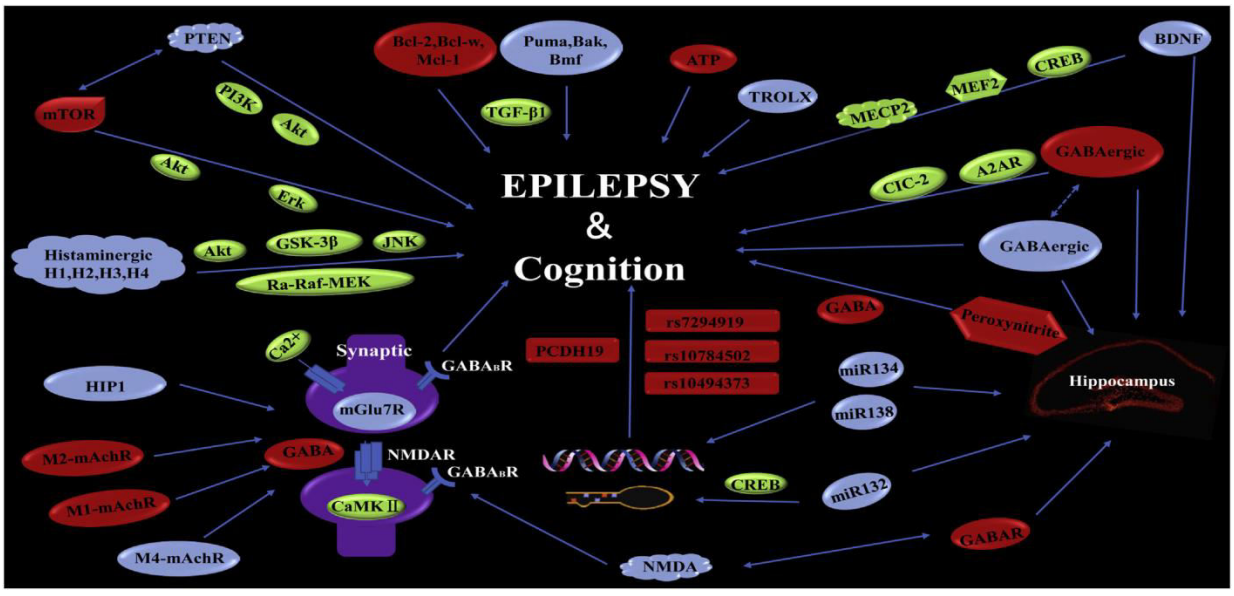

Figure.1 the Red parts show genes or molecules witha negative effect on epilepsy-related cognitive outcomes; blueparts demonstrate genes ormolecules with a positive effect on epilepsy-related cognitive outcome

2.Comorbidity of childhood Epilepsy

Epilepsy is the most prevalent neurologic condition in children, affecting around 0.5–1.0% of children under the age of 16 years. Additionally, around 70%–76% of the individuals stated above have a disability or handicap that has a negative impact on their everyday lives. Childhood epilepsy has been connected to additional comorbidities in affected individuals [2].

3. Neurological comorbidities

Numerous reasons have been linked to the development of neurological morbidity in children with epilepsy. To demonstrate, one of the primary contributors is the harmful effect of persistent seizures on brain development and the medicines used to treat seizures, as well as the physiological changes that predispose the brain to seizures. These neurological comorbidities express themselves in a variety of ways, including cognitive or linguistic impairment, migraine, and sleep issues [3].

3.1. Cognitive impairment

In compared to control instances, children with epilepsy achieved grade retention and placement in special education. Numerous population-based investigations of children with epilepsy indicated that intellectual function impairment (full-scale IQ quotient 70) was the most often seen comorbidity, occurring in more than a quarter of cases [4].

Additionally, it was discovered that the kind of epilepsy can have a significant influence on the incidence of cognitive impairment. Numerous studies have established that children with symptomatic generalised epilepsy have a lower full-scale intelligence quotient than children with idiopathic generalised epilepsy or focal epilepsy. Additionally, patients with temporal lobe epilepsy show much poorer memory recognition than those with frontal lobe epilepsy or childhood absence epilepsy [5].

Another key element that increases to the extent of cognitive impairment is the antiepileptic medication (AED) selection, with some AEDs, such as phenobarbital, causing increased cognitive impairment. Additionally, among the new AEDs, topiramate was found to produce memory and cognitive impairments in a dose-dependent way. Other treatment drugs studied, such as oxcarbazepine, lamotrigine, and levetiracetam, were found to have minor cognitive adverse effects. These findings concluded that carefully selecting AEDs and administering the lowest effective dose were critical variables in minimising the cognitive adverse effects of AEDs in epileptic patients [6].

3.2. Language impairment

Numerous causes may lead to linguistic impairment in epilepsy patients. Such aspects include underlying neuropathology, the effect of induced seizures on the developing brain of a kid, cognitive development, and finally, the degree and potency of epilepsy. Speech impairment was found in around 27.5 percent of children with epilepsy. A comparison of normal and epileptic

children demonstrated that the epileptic child typically achieves a lower language score in the recognition of learned words, category fluency, as well as response to complicated sentences with a high degree of complexity, with the latter observations occurring in cases of epilepsy onset occurring at an earlier age. Consequently, careful treatment must always be related to epilepsy [7].

3.3. Migraine

Numerous research examining the relationship between epilepsy and migraine development in children have revealed a positive link between these two phenomena. Both epilepsy and migraine have been linked to increased brain excitability, and as a result, the optimal medicine for treating both conditions may overlap. The percentage of migraines occurring in epileptic children compared normal children was 14.7 percent To 2.7 percent. Finally, epileptic children have a 4.5-fold increased risk of developing migraine headaches compared to children who do not have epilepsy [8].

The headaches typically begin within a year of the diagnosis of epilepsy or shortly thereafter and occur in patients who have been diagnosed with idiopathic epilepsy for at least ten years. Regarding the occurrence of migraine in diverse kinds of epilepsy, a recent investigation indicated that migraine was prevalent in children with benign epilepsy with centrotemporal spikes and juvenile myoclonic epilepsy [9].

3.4. Sleep issues

Numerous studies have revealed that epileptic patients experience a variety of sleep issues, including parasomnias, parent/child contact throughout the night, sleep deprivation, daytime tiredness, as well as bedtime sleeping fragmentation [10].

Seizures associated with epilepsy exacerbate the occurrence of these sleeping disorders, as studies have established that epileptic children with seizures experience greater sleep problems than seizure-free children. Additional research suggested that AEDs had the same effect on sleep patterns as seizures did. Continuous sleepiness in patients may be attributed to not just the harmful effect of AEDs, but also to sleep fragmentation, which may contribute significantly to that drowsiness. Finally, epilepsy patients have a higher percentage of stage one sleep and a longer latency to rapid eye movement sleep than control subjects [11].

4. Psychiatric Comorbidities

Several children with epilepsy develop psychiatric comorbidities, which pose a fundamental challenge for the children and their families. Numerous investigations revealed that individuals may develop a psychological condition early in the course of their illness and also prior to the onset of seizures.

Attention deficit/hyperactivity disorder (ADHD) and anxiety disorders are the most prevalent psychiatric disorders in epileptic children. Psychosis, oppositional defiant disorder, and tic disorders may also occur in epileptic patients on a less frequent basis [12].

4.1.ADHD

ADHD was shown to affect between 12% and 39% of epileptic children, which was much greater than the 3–7% of children who were not diagnosed with epilepsy [13].

Additionally, ADHD is substantially more prevalent in children initially diagnosed with epilepsy than in healthy controls (31% vs. 6%, respectively), with the inattentive type being the most frequently found. According to a recent analysis, epileptic patients had a 2.54-fold greater risk of developing ADHD compared to normal patients. Additionally, a link between age and risk indicated that it increased with age, increasing 2.26-, 3.53-, and 5.30-fold for patients aged 0–6 years, 6–12 years, and 12–18 years, respectively [14].

Specific psychiatric diseases, such as main mood disorders, significantly increase the risk of suicide in individuals with epilepsy. On the other hand, fewer studies have examined the proclivity of children to commit suicide as a result of epilepsy, where it was reported that [15] suicidal ideation occurred in 17% and 18% of complex partial seizure and childhood absence epilepsy patients, respectively, and suicidal intent occurred in 8% and 11% of complex partial seizure patients, respectively, but these rates were not significantly higher than those observed in normal children (9 percent ideation, 1 percent intent).

Depression or psychological discomfort is the most significant factor affecting a person's quality of life [16]. Not only epileptic children, but also their families suffer as a result of their disease. Furthermore, a research of the psychological health of family members of epileptic children discovered an elevated risk of mental problems in mothers of chronically epileptic children, but not in dads or siblings[17].

5.Physical comorbidities

Children with epilepsy may develop physical comorbid disorders as a result of the disease or as a side effect of medication. Numerous adverse effects of AED use, including allergic response, cytopenia, electrolyte imbalance, and renal or hepatic impairment, occur and are usually reversible if the AED is discontinued. On the other hand, certain physical comorbidities **(Table.1)** associated with AEDs, such as hormonal imbalance, may have an effect on the medical health and quality of life of epileptic children [6].

Table.1 Examples on physical of comorbidity as a result of AEDs usage in epileptic children

Physical comorbidity	Antiepileptic drug
Bone loss	Topiramate-valproic acid-lamotrigine-phenobarbital
Immunological disturbances	Carbamazepine- valproic acid
Hypothyroidism	Carbamazepine- valproic acid
Polycystic ovary syndrome	valproic acid
Weight gain	valproic acid-pregabalin-gabapentin-vigabatrin
Weight loss	Topiramate-felbamate-zonisamide
Dyslipidemia	Carbamazepine- phenobarbital
Carnitine deficiency	Carbamazepine- phenobarbital- valproic acid

6. Treatment

Numerous therapeutic agents are approved for the management of epilepsy occurrences in affected children, but caution should be exercised since certain medicines should be avoided because they can treat seizures while also increasing the prevalence of comorbidity [18].

Table.2 Preferred and avoided drugs in the treatment of epilepsy

Epilepsy+comorbidity	Preferred drug	Avoided drug
Epilepsy+Migraine	Valproate, Topiramate	Phenobarbitone
Epilepsy+Cognitive impairment	Gabapentin, Lamotrigine	Phenobarbitone,Topiramate
Epilepsy+Depression	Citalopram, Venlafaxine	Topiramate, Gabapentin
Epilepsy+Psycosis	Quitapine	Risperidone, Topiramate

7. Conclusion

Epilepsy has been confirmed to influence a large number of children each year, and the life-threatening impact is not limited to the epilepsy itself; numerous studies and reports have established that those children also suffer from a variety of neurological, psychiatric, as well as physical disorders as a consequence of the epilepsy or as a side effect of the treatment. As a result, caution is needed in selecting the medicine with the lowest initial dose able to prevent any associated side effects.

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