

Review Article

Executive dysfunction in idiopathic epilepsy: the journey so far

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ABSTRACT

Epilepsy is one of the most common neurological disorders known to man with a high global prevalence. This disease process affects the overall quality of life. In recent times the concept of executive dysfunction in patients with epilepsy has emerged. This phenomenon has widespread therapeutic implications. This review hence aims to summarize our current understanding of the topic, highlighting the results of benchmark studies and outlining the aspects that require further research. The keywords epilepsy, executive dysfunction and cognitive retraining were used in the search engines of Pubmed and Google scholar and articles identified were extensively reviewed. The consensus of this review is that executive dysfunction is a phenomenon that occurs in patients with epilepsy irrespective of epilepsy type, however the magnitude varies with contributory factors which include poor seizure control. Furthermore, patients with cognitive dysfunction have a further decline over the course of the disease process, however longitudinal studies in regard to the same are lacking and there is a need for additional research in this regard.

Keywords: Cognitive retraining, Epilepsy, Executive dysfunction

INTRODUCTION

Epilepsy is one of the most common neurological disorders known to man with a global prevalence of 50-70 million and an annual prevalence of 2.4 million per year.^{1,2} This disease process affects the overall quality of life due to its psychosocial and cognitive outcomes. Several studies have analysed the incidence of executive dysfunction in patients with epilepsy. New data is emerging about the same with every additional study. This review aims to summarize the existing data on the topic focusing on the therapeutic implications of seizure control on cognitive outcomes.

DEFINITION AND CLASSIFICATION OF SEIZURE AND EPILEPSY

A 'seizure' is a paroxysmal alteration of neurologic function caused by the excessive, hypersynchronous discharge of neurons in the brain while 'epilepsy' is the

condition of recurrent, unprovoked seizures.⁴ The definition of epilepsy has evolved over the years. Seizure and epilepsy classification has evolved over the years and in 2017 International league against epilepsy (ILAE) has published the operational classification of seizure types and epilepsies.⁵

Executive functions

Executive functions (EF) reflect a constellation of higher order cognitive processes that are markedly vulnerable to the aging process.⁶ Executive function tasks are as 'frontal' neuropsychological measures and is an umbrella term for functions such as planning, working memory, inhibition, mental flexibility, as well as the initiation and monitoring of action.⁷

Executive functions are related to goal-directed behavior. This complex system has different skills; attention, planning, receiving and manipulating information in a

proper way allowing individuals to behave in an integrated manner.⁶ Executive functions are mediated by complex neural circuits or feedback loops that connect discrete regions in the prefrontal lobes with other cortical regions in the brain and sub cortical structures and it constitutes three basic functions working memory operations such as the maintenance and updating of relevant information ('updating'), inhibition of prepotent impulses ('inhibition'), and mental set shifting ('shifting').⁸

SEARCH METHODOLOGY

This article is intended to be a review of our current understanding of executive dysfunction in idiopathic epilepsy based on recent research. Literature searches were conducted in PubMed, Google scholar combining the terms 'epilepsy' with 'executive dysfunction'. The identified articles were then extensively reviewed.

IDIOPATHIC EPILEPSY AND EXECUTIVE DYSFUNCTION

It was in the early 1900s that the first studies exploring the relationship between cognition and epilepsy emerged.^{9,10} This study threw light on the possibility of cognitive impairment in the setting of epilepsy, a possibility that was previously unexplored. While these studies assessed basic intelligence, an interest in this topic was sparked and further researched have expanded on this idea, focusing on specific aspects of cognition. Additionally effects of epilepsy surgeries further fortified the research into the cognitive aspects of epilepsy.¹¹

In 1942 performed by Lennox established a drop in cognition which he termed 'mental decay' in patients with epilepsy and analyzed the various causative factors.¹²

While most studies conducted found a definite impairment in cognition, a prospective study performed by Bourgeois et al challenged this relationship by finding normal cognitive parameters among children with epilepsy.¹³ However this was not supported by other studies and has largely been discarded.

A study performed by Farwel et al (in 1985) assessing the neuropsychological functions among children with epilepsy found definite cognitive dysfunction and documented a linear relationship between increasing seizure frequency and magnitude of this impairment.¹⁴

Other studies further elaborated on the same and explored the role of various seizure attributes like etiology, type, age at onset, localization, severity and duration of seizure in reducing the cognitive ability.

In 1992, Singhi et al examined the profile of intelligence quotient (IQ) scores of children with generalized idiopathic epilepsy, their siblings and compared them with matched controls. They attempted to determine the influence of various epilepsy related variables on (IQ).¹⁵

This study aimed to address the methodological problems in the previous studies which included inconsistency in diagnosis and classification of seizures, inclusion of populations with different types of seizures, highly variable individual differences among patients, use of normative data provided in the intelligence tests, and an analytic framework that did not control for confounding effects of various epilepsy-related variables.¹²⁻¹⁴ This study also found a definite cognitive impairment among children with epilepsy and concluded that age of onset and seizure duration were significant factors in developing cognitive impairment. It however did not explore the effect of anti-epileptic drugs on the cognitive process.

Over the next two decades there were several studies that analyzed the concept of cognition in epilepsies and exploring various facets of this entity. An analysis of the major studies show that on an average, subjects with idiopathic generalized epilepsy (IGE) performed significantly below control in all cognitive factors except visual-spatial thinking ability, which showed a non-significant effect.¹⁶⁻²⁰ A meta-analysis of the various studies performed on the sub-syndromes of IGE showed that many areas of cognitive functioning are affected in these patients. In the studies reviewed, most cognitive abilities examined displayed medium to large disease effects.¹⁶

Some of the studies performed have tried to analyze the role of anti-epileptic drugs (AEDs) on cognitive impairment with disparate results. Phenobarbitone has been found to have maximal effect on cognitive impairment followed by carbamazepine while lamotrigine and levetiracetam have the least effect on cognition.²¹ The major cognitive effects of AEDs are impaired attention, vigilance, and psychomotor speed with secondary effects on other cognitive functions.²²

Taylor et al showed that at least part of the cognitive impairment may be the result of epileptogenesis and is not just caused by the accumulating effects of seizures and medication.²³ This study was performed on newly diagnosed patients with epilepsy prior to initiation of AEDs and age and sex matched controls were involved. This study noted that the domains most affected were memory and psychomotor speed with more than one-half of the patients having at least one abnormal test score across the test battery. There were no differences in epilepsy-related or mood variables between those who demonstrated dysfunction and those that did not.

In the study by Borai et al, impaired executive function among adult patients with idiopathic epilepsy was demonstrated.²⁴ The impairment was seen in domains of cognitive flexibility, set shifting and consequently goal maintenance. Higher seizure frequency was noted to be associated with greater cognitive deficiency in some parameters of the Wisconsin card sorting test.

The underlying pathophysiology between the development of cognitive dysfunction and epilepsy has been attributed in part to epileptogenesis and to in part to the other determinants like seizure duration, frequency and presence of status epilepticus.^{16,23} Additionally recent studies have attempted to elucidate the underlying molecular and genetic basis for the cognitive dysfunction in epilepsy. Gamma aminobutyric acid (GABA) receptors have been demonstrated to be involved in causing somatosensory disturbances, learning functions impairment, cognitive deficit in addition to reducing seizure threshold.²⁴ Additionally involvement of the glutaminergic system has been implicated both in causing cognitive impairment and behavioural changes.²⁵ Furthermore the acetyl cholinergic system and the central histaminergic system has also been found to be contributory.²⁶ The most recent study analyzing the molecular and genetic background of cognitive dysfunction in epilepsy listed several contributory factors including genes like protocadherin and the B-cell lymphoma 2 (BCL2) gene family, oxidative stress and specific molecules such as the brain derived neurotrophic factor.²⁶ Despite extensive research done however, the exact molecular mechanisms remain uncertain.

The course and progression of cognitive dysfunction in epileptics has not been studied in depth. A study has identified three different cognitive phenotypes in patients with temporal lobe epilepsy, and has suggested that these three subgroups follow a different cognitive course over a 4-year period.²³ It has also been suggested that those with cognitive dysfunction at the time of diagnosis are at risk to develop intractable chronic epilepsy.²⁸ Taylor et al hypothesized that patients of epilepsy with or without cognitive dysfunction at the time of diagnosis may behave differently. Those with cognitive impairment at baseline were more likely to have severe intractable epilepsy and greater cognitive decline. Results from other studies are awaited. The group of patients who demonstrated cognitive dysfunction at the time of diagnosis may also have cognitive trajectories different from those who did not demonstrate dysfunction, would experience greater cognitive decline, and may be at risk of developing more severe intractable epilepsy.²³

It is known that poorly controlled seizures leads to cognitive impairment. However overenthusiastic treatment of seizures may result in the cognitive side effects of medications to appear. Hence the clinician needs to keep a balance between the two poles.

CONCLUSION

This review aimed to summarize our current understanding on the aspect of executive dysfunction in epilepsy. The studies included in this review were the major landmark ones that paved the way for a better conceptualization of the subject. The consensus of this review is that executive dysfunction is phenomenon that occurs in patients with epilepsy irrespective of epilepsy

type, however the magnitude varies with contributory factors. This aspect highlights the therapeutic role of modifying their contributory factors to reduce the burden on cognitive dysfunction.

To summarize the etiological factors contributing to cognitive dysfunction include presence of underlying brain damage, epilepsy-related factors like nature of epilepsy syndrome, duration of epilepsy, localization of epileptogenic focus, age at onset and seizure-related factors like seizure type, seizure frequency and status epilepticus. Additional contributory factors are treatment-related factors including type of antiepileptic drug, dose and drug interactions.

There is a need to identify those patients already at risk of cognitive impairments so they can be referred for appropriate intervention and management to try and prevent further decline. Therefore, future research needs to focus on the characteristics of those patients who appear to be more susceptible to cognitive impairments, examine the mechanisms that may underlie their increased susceptibility, and assess the impact of seizures and treatment on an already compromised brain.

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