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Review article

Neuropsychological impairment in childhood absence epilepsy: Review of the literature

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ABSTRACT

Aim: Childhood absence epilepsy (CAE) is a paediatric epilepsy syndrome characterized by typical absence seizures in school age children. Although it is commonly considered to have a good prognosis, with a good response to antiepileptic drugs, recent studies questioned this traditional view of a "benign" disorder, in particular regarding neuropsychological functioning. The aim of this study is to review the neuropsychological involvement in patients affected by CAE.
Methods: A literature search was carried out in PubMed's and Medline's databases for all relevant studies published between 1924 and 2014. The keywords used were neuropsychology, absence seizures, and CAE. Specific review articles, systematic reviews, textbooks and case reports were examined for any further publications.
Results: In intellectual functioning, CAE patients seem to perform worse than healthy children, even if their IQ scores fall within the normal range. Similarly, CAE seems to affect verbal skills and learning. Executive functions have been reported to be mildly impaired. Data regarding memory are still conflicting.
Discussion: Given the neuropsychological deficits in many CAE patients which significantly affect their quality of life, CAE should not be considered entirely "benign". An early identification of neuropsychological dysfunction in CAE children is essential for appropriate treatment.

Contents

Abbreviations: CAE, childhood absence epilepsy; TAS, typical absence seizures; IGE, idiopathic generalized epilepsies; AEDs, anti-epileptic drugs; IQ, intelligence quotient; WISC, Wechsler Intelligence Scale for Children; NIH, National Institutes of Health; NINDS, National Institute of Neurological Disorders and Stroke; FSIQ, Full Scale Intelligence Quotient; HCs, healthy controls; VIQ, verbal intelligence quotient; BECTS, benign epilepsy with centro-temporal spikes; PGE, primary generalized epilepsy; CPS, complex partial seizures; AERP, auditory event-related potential; MRI, magnetic resonance imaging; VPA, valproic acid; ADHD, attention deficit and hyperactivity disorder; ESX, ethosuximide; LTG, lamotrigine; CBCL, Childhood behaviour checklist test.

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1. Introduction

Childhood absence epilepsy (CAE) is a well-known paediatric epileptic syndrome, which generally responds to medical treatment. According to the proposed diagnostic scheme of the currently valid classification and terminology of the International League Against Epilepsy, [1] CAE is a syndrome within the Idiopathic Generalized Epilepsies (IGE) showing Typical Absence Seizures (TAS).

CAE accounts for 10–17% of all cases of childhood-onset epilepsy, and in children's cohorts the prevalence has been estimated to range from 0.4 to 0.7 per 1000 people and, with some exceptions, it is more frequent in girls than in boys (11.4% vs 2.5%) [2]. This syndrome is characterized by daily, frequent but brief staring spells which typically begin at 4–10 years of age in an otherwise apparently healthy child [3]. Absence seizures are clinically characterized by impairment of consciousness without major motor symptoms, and a typical EEG pattern of generalized, bilateral, synchronous, symmetrical spike–wave discharges of 3–4 Hz. Childhood absence epilepsy generally has a good prognosis as regards the disappearance of seizures and the possibility to discontinue therapy with antiepileptic drugs (AEDs) [4,5]. However, within this syndrome there are many variables that can significantly modify its clinical outcome as CAE is probably genetically heterogeneous, but the precise mode of inheritance and the genes involved are incompletely understood [6].

Children with epilepsy, particularly CAE, suffer from attention and executive functions problems and these impairments often persist even when seizures are treated [7]. Although CAE is historically believed to be a "benign" disorder, children affected by CAE may have a poor psychosocial adjustment. This theory disagrees with the traditional view of CAE as a "benign disorder" [8].

In order to summarize the current findings on neurocognitive impairment in CAE, this review examines the effects of this syndrome in seven main domains: intellectual functioning, language, learning disabilities, attention, motor skills, executive functions, memory functioning. Scientific knowledge regarding cognitive involvement in childhood epilepsies is rapidly expanding but it is in continuous need of further investigation and we outline areas of consensus as well as areas of uncertainty that may indicate directions for future research.

Data for this review were identified with Medline and PubMed surveys for studies dealing with absence seizures, references from relevant articles and research from authors' files. Research was performed including papers published from 1924 to 2015. We sought to identify evidence published in English; specific review articles, systematic reviews, textbooks and case reports were examined for any further publications, as were the reference sections of all articles identified by the literature search. Only publications containing the most relevant results for this investigation were included (Table 1).

2. Intellectual functioning

Many study groups have focused on searching for a possible biological basis to explain CAE comorbidities in terms of abnormalities in brain regions implicated in behaviour, emotions, cognition and language.

Intelligence tests are considered the first-line tool for assessing cognitive problems in children. Results from intelligence quotient (IQ) tests help guide diagnosis, treatment, and educational planning, and are used by clinicians and researchers alike. The Wechsler Intelligence Scale for Children — Fourth Edition (WISC-IV, Wechsler, 2003a) is a sensitive tool for the evaluation of epilepsy-related cognitive impairments in clinically referred children with a high seizure burden [9].

Most of the available data show that although presenting an average IQ, roughly one fourth of all children affected by CAE have subtle cognitive difficulties. A significantly lower mean Full Scale Intelligence Quotient (FSIQ) score in CAE patients compared to healthy controls (HCs) was reported in Caplan's et al.'s studies [8,10–13]. The normal control group in Caplan et al.'s studies had a high mean FSIQ. Similarly Vega et al. [14] and Pavone et al. [15] observed lower FSIQ scores in CAE patients compared to controls, although the scores were within the normal range, and these studies both included a small number of patients. According to Jones et al. [16], eight out of 25 cases of CAE patients had a FSIQ below the average whereas the remaining CAE children had a lower FSIQ than HCs. Jones et al. however, used the same subjects already studied by Caplan et al. in previous studies; it is therefore possible to consider these results redundant. Similar results were seen during follow-up in each of the three groups, even though IQ appeared to be significantly related to baseline seizure variables in the group with an average IQ.

Frequent seizures were documented in a prospective consecutive study by Nolan et al. [17] as a negative prognostic factor for cognitive functioning. Significant associations were also seen between lower FSIQ and younger age of epilepsy onset [17], poor seizure control [10,18] and formal thought disorder [10], supporting the hypothesis that IQ might reflect the impact of epilepsy on cognition and language abilities.

Moreover, Caplan et al. [12] pointed out that CAE children with a lower IQ had significantly more social difficulties. The correlation between poorer IQ performances and behavioural problems was also highlighted by Hermann et al. [19] These authors pointed out that the presence of behavioural comorbidities might be associated with a significantly worse cognitive development.

General cognition in CAE children has often been related to that of other epileptic syndromes, generally resulting in higher IQ scores in comparison to children with complex partial seizures (CPS) [11,20] or with symptomatic epilepsy [18], but lower than in syndromes like benign epilepsy with centro-temporal spikes (BECTS) [21].

In a study by Mandelbaum et al. [22] a cognitive composite score elaborated after the administration of a battery of tests, detected that at baseline, children with CAE performed worse than subjects with partial or generalized convulsive seizures. Analysis of the subjects' performance after 6 and 12 months of antiepileptic therapy showed no significant deterioration attributable to medication.

Sirén et al. in a small prospective clinical study [23] hypothesized a positive role of AEDs on cognitive functions: cessation of seizures induced by antiepileptic medication positively influenced neurocognitive functioning in children with newly diagnosed CAE. The IQ score was within the normal range in both CAE patients and in the control group. During the follow-up after AED introduction, a significantly beneficial effect was reported in the study group in terms of motor fluency, memory and attention. However, in 2003, Nolan et al. [17] reported that the use of more than two anticonvulsant drugs was associated with lower IQ scores in a population of 169 children of whom 17 had CAE with a median of 1 antiepileptic drug. Similar data were obtained the following year [18] by assessing neuropsychological skills in 13 children with CAE of whom 5 were treated with one and 8 with two AEDS. However, because of the small size of these study groups it is not possible generalize these findings to all children with CAE.

A smaller number of papers did not find any significant differences in general cognition between CAE children, HCs, and CPS patients, even though patients mean IQ scores were often lower than normal mean values [7,17,24,25,26]. However several authors only recruited children with an IQ score > 70, a choice that might have limited the generalization of these studies.

3. Language

Although literature data are conflicting, most studies investigating verbal IQ (VIQ, a component of FSIQ) and language skills, found worse performances in CAE children than in normal children [26]. In particular, Caplan et al. detected lower VIQ and language mean scores in a CAE sample [11] and in a group of children and adolescents with CAE or CPS epilepsy [27], compared to HCs. Similar findings were reported by Jones et al. [16] and Henkin et al. [28].