Childhood absence epilepsy and benign epilepsy with centro-temporal spikes: a narrative review analysis

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Review article

Background: **Recent studies have shown a possible coexistence of absence seizures with other forms of epilepsy. The purpose of this study was to ascertain the possible contemporary or subsequent presence of childhood absence epilepsy (CAE) and benign epilepsy with centro-temporal spikes (BECTS) in pediatric epileptic patients.**

Data sources: **A PubMed systematic search indexed for MEDLINE, PubMed and EMBASE was undertaken to identify studies in children including articles written between 1996 and 2015. Retrospective studies, meta-analysis and case reports were included. The list of references of all the relevant articles was also studied. The date of our last search was December 2015.**

Results: **Review of the literature revealed 19 cases, 8 females and 11 males, reporting a consecutive or contemporary coexistence of CAE and BECTS within the same patients. Patient's age ranged between 4 and 12 years. Three out of 19 patients presented concomitant features of both syndromes, whereas 16 patients experienced the two syndromes at different times.**

Conclusions: **BECTS and CAE may be pathophysiologically related, and the two epileptic phenotypes may indicate a neurobiological continuum. Further studies are needed to elucidate a probable genetic or functional link between partial and primarily generalized electro-clinical patterns in idiopathic childhood epilepsies.**

World J Pediatr 2017;13(2):106-111

Key words: **absence seizures; benign epilepsy with centro-temporal spikes; childhood abscence epilepsy**

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doi: 10.1007/s12519-017-0006-9
Online First, January 2017

Introduction

Typical absence seizures (TAS) can be defined as generalized seizures with an abrupt onset and ending of altered awareness which can vary in severity.[1] These episodes of altered consciousness are characterized by generalized spike-wave discharges at 3 Hz or more on electroencephalogram (EEG).[2] Memory for events during seizures is usually impaired and clonic movements of eyelids, head, eyebrows, chin or other facial parts may occur, while myoclonus of the limbs is rarely observed. Clinical manifestations typically last 9-10 seconds and are, at times, activated by hyperventilation and photic stimulation.[3]

Absence seizures can be divided into two main forms: childhood absence epilepsy (CAE), with an age of onset of approximate 6 years, and juvenile absence epilepsy (JAE), with an age of onset of approximate 12 years.[3] These idiopathic forms of generalized epilepsy affect 2%-10% of all pediatric epileptic patients.[4] CAE is characterized by seizures with a sudden onset and interruption of on-going activities lasting from a few seconds to half a minute, blank stare and possibly a brief upwards rotation of the eyes.[2]

JAE patients usually have a lower level of altered consciousness compared with CAE patients and they can present myoclonus. Women and men are equally affected and the prevalence of this form is approximately 0.2%-2.4% of all epilepsies.[5]

Recent studies have shown a possible coexistence of absence seizures with other forms of epilepsy such as panayiotopoulos syndrome, idiopathic occipital epilepsy, Gastaut-type idiopathic occipital epilepsy, West syndrome, myoclonic epilepsy of infancy, Juvenile myoclonic epilepsy and benign epilepsy with centro-temporal spikes (BECTS).[6-11]

BECTS represents 8%-20% of childhood epilepsies

and commonly afflicts children aged 1-14 years with a peak at 7-10 years of age. BECTS symptoms include hemi-facial or hemi-body motor involvement, mainly affecting the face and oropharynx with speech arrest and hyper-salivation. BECTS diagnosis is based on characteristic seizure manifestations and a typical EEG pattern with sharp waves located in the centro-temporal leads (centro-parietal, fronto-central and centro-occipital).[12]

Based on the recent increasing interest on CAE and BECTS, we performed this study in order to ascertain the possible contemporary or subsequent presence of CAE and BECTS in epileptic pediatric patients.

Methods

This article provides an overview on scientific literature concerning the possible coexistence of CAE with BECTS. A PubMed systematic search indexed for MEDLINE, PubMed and EMBASE was undertaken to identify studies of children including articles written between 1996 and December 2015. The keywords used were BECTS, JAE, CAE, Centro-temporal epilepsy, absence seizure, benign Rolandic epilepsy. Retrospective studies, meta-analyses, case series and individual case reports were included. The list of references of all the relevant articles was also studied to include all reports and reviews related to the subject. Only English language articles were reviewed. The date of our last search was December 2015. Exclusion criteria were: scientific papers written in languages different to English and papers dating before 1995.

For each study, the number of patients assessed, the type of study and comparisons made, and all clinical characteristics of the analyzed patients were examined. Only publications containing the most relevant results for this investigation were included. The following data were recorded: age, gender, epileptic features, EEG features, therapy and contemporary or consecutive clinical semiology.

Results

Review of the literature revealed 19 cases, 8 females and 11 males, reporting a consecutive or contemporary coexistence of CAE and BECTS within the same patients (Table). Patients age ranged between 4.1 and 12.0 years (mean age 8.37 years with standard deviation 2.41).

Three out of 19 patients presented concomitant features of both syndromes whereas 16 patients experienced the two syndromes at different times. In particular, the clinical onset of 3 patients was characterized by absence seizures, while rolandic features were initially reported in the remaining 13 patients.

On the whole, 17 patients were treated with antiepileptic drugs (AEDs); there are no available data regarding the treatment of two subjects.

Considering the three patients with a contemporary presence of BECTS and CAE at onset, two of these were treated with valproic acid (VPA) and became seizure free but there are no available data regarding the third patient. EEG features were all characterized by 3 Hz generalized spike waves (SW) paroxysms and two patients also presented respectively bilateral centrotemporal spikes and frontal or temporal bilateral interictal discharges.[18,19] Among subjects with a consecutive presentation of the two epileptic syndromes, 3 patients initially presented absence seizures: one of these experienced one single episode of BECTS treated with VPA that resolved after increase of therapy whereas another patient manifested rolandic symptoms during VPA and lamotrigine (LTG) treatment that was continued for 2 years and 6 months until the patient became seizure free.[4] Only one patient included in this clinical subgroup exhibited BECTS after 5 years of phenobarbital (PHB) and clonazepam (CLZ) therapy obtaining freedom from seizures after introducing VPA.[16] The two subjects described by Cerminara et al[4] initially manifested on EEG bilateral SW complexes 3 Hz followed by bilateral centrotemporal spikes increased in frequency during sleep whereas the other patient's EEG revealed 3 Hz SW paroxysms and a right centrotemporal focus at onset, with the persistence of the latter EEG features during Rolandic seizures. On the other hand, 13 patients initially presented BECTS; two of these were not treated and manifested typical absence seizures respectively after 2 years and 6 months from onset, achieving clinical improvement with the introduction of VPA.[18,20] The first subject exhibited on EEG a typical BECTS pattern followed by the appearance of 3 Hz generalized SW activity; the second patient initially presented delta waves in the right temporal-occipital region followed by a persisting typical absence pattern. One patient with the same initial symptoms started VPA therapy and suffered from absence seizures during treatment. His manifestations improved with the addition of CLZ.[16] Another 2 patients presenting absence seizures after BECTS onset and respectively treated with VPA and VPA+LTG clinically improved with the introduction of CLZ and with the withdrawal of VPA.[16,17] Three patients treated with carbamazepine (CBZ) for the same initial symptoms exhibited absence seizures after a few months of therapy.[16] All obtained seizure freedom interrupting CBZ and beginning therapy respectively with VPA+ ethosuximide (ETX),

Table. Pertinent data of the patients reported in literature

Case	Age/Sex	Type of seizure or syndrome	EEG	AEDS	Contemporary or consecutive clinical semeiology	References
1	10 y	At 3.1 y, typical AS;	SW complex 3 Hz;	VPA+LTG	Consecutive	Cerminara, 2012[4]
	M	At 4.4 y, BECTS	Bilateral centro-temporal spikes during sleep			
2	8 y	Complex FS;		VPA+LTG	Consecutive	Cerminara, 2012[4]
	F	At 7.0 y, typical AS;	Bilateral SW complex 3 Hz;			
		At 7.4 y, BECTS	Bilateral centro-temporal spikes increase in frequency during sleep			
3	9 y M	At 4.8 y, BECTS;	Right centro-temporal spike and SW complexes;	OCBZ;	Consecutive	Grosso, 2006[13]
		At 4.9 y, atypical AS	2.5 Hz generalized SW complexes	VPA		
4	8 y	At 5.2 y, BECTS;	Right centro-temporal SW paroxysm;	OCBZ;	Consecutive	Grosso, 2006[13]
	M	At 5.7 y Atypical AS+eye fluttering	3-4 Hz diffuse epileptiform discharges	VPA		
5	9 y	BECTS;	Generalized SW;	VPA	Contemporary	Montenegro, 2006[14]
	F	Typical AS	Complex 3 Hz			
6	11 y F	At 7.0 y, BECTS;	Bilateral centro-temporal spikes increase in frequency during sleep;	VPA;	Consecutive	Hamano, 2002[15]
		At 10.0 y, atypical AS	Diffuse iregular SW bursts (1-4 seconds)	VPA+PHB		
7	6 y F	BECTS (orofacial right seizure and GTCS);	Centrotempoparietal focus left;	CBZ;	Consecutive	Dimova, 2002[16]
		Simple AS	Irregular SW paroxysm	CBZ+VPA		
8	9 y	BECTS (GTCS while asleep);	Temporal focus right;	CBZ;	Consecutive	Dimova, 2002[16]
	M	Atonic absences	Irregular about 3 Hz SW paroxysm	VPA, +ETX		
9	6 y	BECTS (orofacial right seizure);	Central and centrotemporal focus left>right;	VPA;	Consecutive	Dimova, 2002[16]
	F	Simple AS	Bilateral 3 Hz SW paroxysm	VPA+CBZ, CLZ		
10	10 y M	BECTS (GTCS and left-side orofacial);	Centroparietal focus right;	VPA;	Consecutive	Dimova, 2002[16]
		AS with eyelid myoclonia	Parietal focus on the midline, 3.5 Hz SW paroxysm	VPA+CLZ;		
11	12 y M	BECTS (GTCS in sleep with motor faciobrachia onset on left);	Central-precentral focus right and brief irregular SW discharges;	VPA (ended due to hepatitis), CBZ;	Consecutive	Dimova, 2002[16]
		AS with eyelid myoclonia	Tempoparietal focus left, irregular SW paroxysm	CLZ		
12	6 y M	BECTS (orofacial left seizure while asleep);	Tempoparietal focus right;	CBZ;	Consecutive	Dimova, 2002[16]
		Simple AS	3-3.5 Hz generalized SW paroxysm	VPA, +CLZ		
13	12 y M	At 5.0 y, GTCS and simple AS;	3 Hz SW paroxysm and right centro- temporal focus;	PHB+CLZ;	Consecutive	Dimova, 2002[16]
		At 11.0 y, BECTS (orofacial left seizure)	Centro-temporal focus right	CLZ, CLZ+CBZ, VPA		
14	5 y	At 5.0 y, BECTS;	Anterior-predominant 3/s SW complexes	VPA+LTG;	Consecutive	Catania, 1999[17]
	F	At 5.4 y, typical AS+eyelids flickered	with bilateral rolandic discharges interictally	VPA		
15	7 y M	At 7.0 y, BECTS (left side focal motor seizure with secondary generalization);	Delta waves in the right temporal-occipital region	VPA	Consecutive	Ramelli, 1998[18]
		At 7.6 y, typical AS;	3 Hz generalized SW paroxysm;			
		At 7.9 y, lateral focal motor seizures with jerks on the left half of the face	Right centro-temporal spikes and 3 Hz generalized SW paroxysm			
16	11 y	BECTS	Bilateral centrotemoral spikes and	VPA	Contemporary	Ramelli, 1998[18]
	F	Typical AS	3 Hz generalized SW paroxysm			
17	6 y M	Typical AS;	3 Hz generalized SW paroxysm with frontal or temporal right or left interictal discharges	-	Contemporary	Echenne, 1997[19]
		Partial facial motor seizures occuring in cluster on awaking				
18	4 y M	Partial and secondary generalised seizures on awakening;	3 Hz generalized SW paroxysm and rhythmic focalised spikes and SW predominating on frontal	-	Consecutive	Echenne, 1997[19]
		Typical AS				
19	10 y	At 6.4 y, BECTS;	Right centro-temporal spikes;	No	Consecutive	Gambardella, 1996[20]
	F	At 8.1 y, typical AS	3 Hz generalized SW activity	VPA		

M: male; F: female; Y: year; EEG: electroencephalogram; HZ: hertz; S: seconds; AS: absence seizure; SW: spike and wave; BECTS: benign epilepsy of childhood with centrotemporal spikes; FS: febrile seizure; GTCS: generalized tonic-clonic seizure; AEDS: anti-epileptic drugs; VPA: valproic acid; LTG: lamotrigine; OCBZ: oxcarbamazepine; PHB: phenobarbital; CBZ: carbamazepine; ETX: ethosuximide; CLZ: clonazepam.

CLZ and VPA+CLZ. Another subject treated with CBZ for BECTS experienced absences after a few months achieving remission of seizures with the introduction of VPA.[16]

All patients described by Dimova et al with rolandic features at epilepsy onset, presented on EEG centro-temporal or temporal, right or left focuses followed by the appearance of regular or irregular 3 Hz SW paroxysms. Some of these patients continued to manifest mild EEG alterations during treatment, in absence of clinical seizures.

A particular correlation was observed in three patients of which two were treated with oxcarbamazepine and one with VPA+PHB.[13,15] All patients (patients number 3, 4 and 6 in the Table) manifested absence seizures after a brief period of therapy suggesting a possible drug-induced pathogenesis that disappeared with the suspension of previous therapy and with the introduction of VPA monotherapy. There are no available data regarding the therapy of one patient who initially presented BECTS followed by absence seizures.[19]

Discussion

The relationship between CAE and BECTS is still a matter of extensive debate. The concomitant or consecutive presence of BECTS and CAE has been reported by few authors in literature. Although these clinical conditions are both rather frequent epilepsies of childhood, the concomitance of both syndromes in the same patient has been rarely observed.[18] In fact, the incidence rate of CAE 15 years of age has been estimated ranging from 6.3/100 000/year from 8.0/100 000/year, while BECTS incidence is estimated at 21/100 000.

The aim of our review was to investigate the coexistence of both syndromes in pediatric patients, based on clinical features. It is important to underline that we have analyzed in depth the clinical and EEG characteristics of the patients reported in literature in order to exclude the possibility that the association of CAE and BECTS could correspond to a variant. In fact, CAE has an age of onset between 4 and 10 years and it is characterized by brief (4-20 sec) and frequent absence seizures with an abrupt and complete impairment of consciousness. Moreover, at EEG recording, 3 Hz ictal discharges of high-amplitude spike and double spike- and slow-wave complexes are present.

We therefore identified 19 patients of which 16 with consecutive and 3 with contemporary clinical manifestations. In particular, these three patients described by Montenegro, Ramelli and Echenne,[14,18,19] respectively presented similar clinical features during day-time (TAS) and night-time or on awakening (focal motor seizures involving the oro-facial district). Two of these patients were treated with VPA,[14,21] obtaining complete clinical remission. The Authors conclude that although both entities tend to have a number of common features, including an early age of onset, good outcome, and an autosomal dominant inheritance with incomplete penetrance and age-dependent expression, the coexistence (concomitant occurrence) of two idiopathic epilepsy syndromes remains controversial and has been rarely observed. However, the clinical expression of both syndromes is defined as multifactorial, resulting from interactions between genetic and environmental factors, so a genetic link between partial and primarily generalized epilepsies can be contemplated.[14,18,21] By exploring the underlying mechanisms of spike-wave discharges and the pathophysiology of benign focal epilepsy, some investigators studied the modifications of EEG during sleep: the activation of rolandic spikes during slow-wave synchronized EEG activity (REM sleep) suggested that sleep-regulating thalamic nuclei may play a role in their generation. Nobili et al[22] found a high positive correlation between BECTS discharges during sleep and delta (0.5-4.0 Hz) and spindle activity (12.0-16.0 Hz). These findings suggest that the thalamic networks have a role in pacing sleep spindles. It may also be involved in focal discharges responsible for rolandic spike generation, as they are known to be in the case of absence epilepsy. The most recent data seem to emphasize the role of the thalamus more strongly; the neural activity may be simultaneous in the thalamus and cortex, without any primacy of the two structures, in a "unified" theory.[25,26]

In the remaining 16 reviewed cases a consecutive occurrence of BECTS and CAE was reported in the same patient. Dimova et al[16] considered the possibility of coincident benign epilepsy with Centro-temporal spikes and absence features as a rarity, one that requires further detailed genetic and electrophysiological studies to elucidate the carriers of inheritance and liability and the basic mechanisms in these common forms of childhood epilepsy. Focusing on electro-clinical features, rolandic foci have been observed in childhood absence sometimes prior to the treatment, so the authors concluded that crossover phenomena may occur between BECTS and CAE. Although clinical absences were reported, generalized spike-wave discharges in this BECTS population were not combined with other atypical EEG patterns; a full suppression of both clinical and EEG absence features, as well as a normal neuropsychological development were observed after discontinuation of AEDs.

Cerminara et al[4] recently described two patients affected by idiopathic generalized epileptic syndrome

with CAE, who experienced BECTS after remission of seizures and normalization of EEG recordings. Although recent interesting observations in animal models suggest that BECTS and CAE could be pathophysiologically and genetically linked, the authors concluded that the occurrence of CAE and BECTS in the same child appeared to be an extraordinary event.

A similar explanation was hypothesized by Gambardella et al,[20] who described two extraordinary cases of absence development after recovery from benign epilepsy with centro-temporal spikes, thus favouring the hypothesis that both epileptic forms are distinct entities.

By speculating on the evolving concepts concerning the pathophysiology of absence seizures, such as the "cortical focus" theory, it is known that they could originate from restricted regions of the cortex. Studies in animal models suggest that a cortical focus initiates a cascade of events that results in bilateral generalized spike-wave complexes and leads to a paroxysmal oscillation within the corticothalamic loops: these mechanisms may constitute the basis for a hypothesis concerning the pathophysiology of human absence. In fact, the role of the thalamus probably consists in providing a resonant circuitry to amplify and sustain the discharges.[23] Specific brain development during life might determine a greater susceptibility to changes in cortico-subcortical networks by influencing the local recurrent oscillatory activity of the corticothalamic circuitry. This could induce the appearance of different epileptic phenomena that could become evident either simultaneously or subsequently.[23,24]

It is interesting to underline that CAE can be associated to other forms of epilepsy, for example Caraballo et al,[25] previously described three patients who presented electroclinical features compatible with "Gastaut type" childhood occipital epilepsy, with seizures starting mainly with visual symptoms (occipital seizures), immediately followed by typical absences. One of the patients had been reported in detail earlier.[28]

Several authors have also reported children with BECTS developing absence features after initiation of AEDs.[13,15,17] In particular, patients with BECTS treated with LTG, OCBZ and PHB+VPA who experienced a seizure deterioration have been reported. The insidious worsening is usually attributed to the introduction of an antiepileptic drug or to an atypical course of the disease, although it may reflect the susceptibility of an underlying syndrome (especially with some atypical electro-clinical features), to certain anticonvulsants.

Finally, although CAE and BECTS are probably genetically determined, in spite of many large family studies and linkage analyses, the precise mode of inheritance and the genes involved remain largely unidentified. Family studies of idiopathic generalized and focal epilepsies suggest that CAE and BECTS are polygenic disorders and the individual phenotypes can be due to a peculiar grouping of genes.[27]

In conclusion, BECTS and CAE could be pathophysiologically related, possibly with an underlying genetic contribution. The coexistence of the two epileptic phenotypes with similar hereditary patterns may indicate a neurobiological continuum. On the other hand, the rarity of the coexistence or the later occurrence of the two different epileptic syndromes in the same patient weakens this hypothesis. However, as for most types of epilepsy, the clinical expression of both syndromes is likely to be multifactorial. Although it might be coincidental, genetic contribution shared by partial and primarily generalized epilepsies cannot be excluded. Further studies are necessary to elucidate a probable genetic or functional link between partial and primarily generalized electro-clinical patterns in idiopathic childhood epilepsies; in particular, animal research on mutant mice (to study the hypersynchronous thalamo-cortical activity) and careful and repeated neurological and neurophysiological monitoring throughout a long term follow-up of the patients with BECTS and CAE can be helpful in understanding better the pathophysiological limits of these two types of epilepsy.

Acknowledgements

We thank Federico Mecarini for his valuable contribution in the research for this paper.

Funding: The authors have no financial relationships relevant to this article to disclose.
Ethical approval: None.
Competing interest: The authors report no conflicts of interests and have no relevant disclosures.
Contributors: All authors equally contributed to the study design, study conduct, data collection, and manuscript preparation. Everybody contributed to the study design, study conduct, data collection and manuscript preparation. All authors contributed to the study conduct and data analysis and interpretation and manuscript preparation.

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Received January 14, 2016
Accepted after revision June 1, 2016