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Childhood-only epilepsy with generalized tonic-clonic seizures: A well-defined epileptic syndrome

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ABSTRACT

Purpose: The aim of this study was to analyze patients whose only manifestation of epilepsy were generalized tonic-clonic seizures (GTCS) during childhood and discuss its validity as separate syndrome of childhood.
Methods: We included children with at least two unprovoked GTCS between 3 and 11 years of age, no other seizure types at diagnosis, normal psychomotor development and neurological examination, an EEG with normal background and paroxysms of generalized spikes and waves with a frequency 2.5 Hz or above, and an unknown cause for epilepsy. Only patients with a follow-up > 2 years were included.
Results: Over a 12-year period (2005–2017) 26 patients met the inclusion criteria of epilepsy with GTCS only. Mean age at onset was 5 years. The seizures occurred while awake in 16 patients, on awakening in two, and during sleep in eight patients. The duration of seizures was around 3 min. Generalized spike-and-wave discharges were observed in all patients when awake and during sleep in eight and 26 patients, respectively. Nineteen responded well to valproic acid or levetiracetam. Two patients who received clobazam initially did not respond well; however, a switch to valproic acid resulted in excellent seizure control. Antiepileptic treatment was discontinued in sixteen patients who remained seizure free over a period of 2–9 years of follow-up.
Conclusion: Epilepsy with GTCS alone in childhood is a type of epilepsy; however, it may be considered as a well-defined epileptic syndrome. Patients responded well to valproic acid or levetiracetam.

1. Introduction

Idiopathic generalized epilepsies (IGEs) are types of generalized epilepsies in which all the seizures have a generalized onset and the EEG typically shows generalized spike-wave discharges and a normal background (ILAE Commission on Classification and Terminology, 1989, Scheffer et al., 2017). Seizure types include absence, myoclonic, tonic, atonic, and tonic-clonic seizures (GTCS) (ILAE Commission on Classification and Terminology, 1989). IGEs may initiate in infancy, childhood, or adolescence, and more rarely during adulthood, and may be lifelong or age restricted (Scheffer et al., 2017; Unterberger et al., 2001; Caraballo and Dalla Bernardina, 2013; Engel, 2006). They present in otherwise healthy people with normal development, neurologic exam, and neuroimaging. As IGEs are genetically determined, the term genetic generalized epilepsies has been proposed, encompassing the IGE subgroup and also other types of generalized epilepsies (Scheffer et al., 2017). In the recent ILAE Classification proposal, the term "idiopathic" has been replaced by "genetic" (Scheffer et al., 2017); however, as the genetic marker in patients with IGE-GTCS is not well known, they may be considered as probably genetic. Here, we have maintained the term "idiopathic generalized epilepsy".

Four well-established IGEs are recognized: Childhood absence epilepsy (CAE), juvenile absence epilepsy, juvenile myoclonic epilepsy, and epilepsy with generalized tonic–clonic seizures alone (EGTCA) (Engel, 2006; Andermann and Berkovic, 2001; Gélisse et al., 2012). Although the age of onset of EGTCA is reported as broad, from 5 to 41 years, it is clearly more prevalent during adolescence, leaving CAE as the only IGE syndrome of onset in childhood (Unterberger et al., 2001). This immediately raises the question about the existence of other idiopathic generalized epilepsy syndromes starting in childhood, a frequent question in daily clinical practice.

It has been argued that EGTCA is not a well-defined epilepsy syndrome (Engel, 2006), but a constellation of different epilepsy subtypes (Andermann and Berkovic, 2001; Gélisse et al., 2012), encompassing GTCS alone on awakening, during sleep, and at random. Additional to these differences in circadian occurrence of GTCS, the factor of age at onset has also been noted, especially in patients starting in childhood (Andermann and Berkovic, 2001; Nieto-Barrera, 2001). Nevertheless, to

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our knowledge only two authors have specifically analyzed this issue (Oller-Daurelia & Oller, 1992; Camfield and Camfield, 2010).

The existence of IGE-GTCS in childhood with GTCS as the only seizure type has been discussed. The neurological history and examination as well as brain imaging are normal, but the interictal EEG shows bursts of generalized spikes and waves with a normal background. Few authors have recognized it as a well-defined epileptic syndrome, others have manifested doubt. In 1992, Oller-Daurella and Oller published 80 children with IGE-GTCS wondering if it exists as syndrome. Recently, the ILAE (Scheffer et al., 2017) proposal has considered this clinical-EEG pattern as a type of epilepsy with GTCS rather than an epilepsy syndrome.

The aim of this study was to analyze patients whose only manifestation of epilepsy were GTCS during childhood and discuss its validity as a subtype of EGTCSA or even as a separate syndrome of childhood.

2. Patients and methods

We retrospectively evaluated patients selected from our pediatric epilepsy cohort consisting of 26 children with idiopathic generalized epilepsy of childhood, who met the following inclusion criteria at the time of diagnosis:

1) At least two unprovoked GTCS between 3 and 11 years of age
2) No other seizure types at diagnosis
3) Normal psychomotor development and neurological examination
4) An EEG with normal background and paroxysms of generalized spikes and waves (regular or irregular with a frequency 2.5 Hz or above) followed or not by slow waves
5) No evidence of focal abnormalities
6) Unknown cause for epilepsy
7) At least 2 years of follow-up

No ictal EEG or Video-EEG were registered; the seizures were defined as GTCS based on detailed analysis of the interview conducted by the main author in which no characteristics of focal onset were determined and on the absence of focal abnormalities on the EEG.

Patients with intellectual disability, brain lesion, absence epilepsy of childhood with GTCS, myoclonic epilepsy of childhood with GTCS, generalized idiopathic epilepsy of adolescence with variable phenotypes and isolated GTCS, epilepsy with focal seizures to GTCS, or acute symptomatic seizures were excluded.

We analyzed sex, age at onset, personal and family history of epilepsy, seizure duration and manifestations, circadian distribution, seizure frequency, response to therapy, and outcome.

EEGs were performed while awake and asleep. Electrodes were placed according to the international 10–20 system. Brain CT scan and MRI were performed in all patients.

Between February 2005 and February 2016, 26 patients who met the inclusion criteria of IGE-GTCS were identified and have been followed up to the present time. All patients were evaluated longitudinally, clinically, and with EEGs for 2–12 years (mean: 6.5 years). A mean of 10 ± 3 EEGs were obtained for each patient. We evaluated the charts reviewing clinical and EEG details of all patients that were unanimously agreed upon by all authors. School performance and social relationships were evaluated based on parent and teacher report.

Chi-squared or Fisher exact tests were used for non-parametric comparisons and the *t*-test for continuous variables.

The study was approved by the Ethical Review Board of the Juan P. Garrahan Hospital, Buenos Aires.

3. Results

3.1. Number of patients and gender

Twenty-six children, 16 boys and 10 girls, met the inclusion criteria of epilepsy with GTCS only over a 12-year period (2005–2017).

3.2. Age at onset

Age at first afebrile seizure ranged from 3 to 11 years, with a mean age of 5 and a median of 5.8 years.

3.3. Personal and family history of febrile convulsions, and epilepsy

There was a family history of epilepsy in seven cases (26.9%), and personal history of epilepsy compatible with idiopathic focal epilepsy in infancy in one (3.8%). Febrile seizures were reported in 10 (38.4%).

3.4. Ictal manifestations

By definition the ictal manifestation was GTCS in all 26 children (100%). The seizures occurred while awake in sixteen patients (61.5%), on awakening in two (7.6%), and during sleep in eight patients (30.7%). Sixteen patients (61.5%) had two seizures, six (29.1%) had three seizures, three (11.5%) had four seizures, and one patient (3.8%) had five seizures.

According to parent report, the duration of seizures was around 3 min. Status epilepticus was not registered in any of the patients. No other seizure type was observed during their evolution. The GTCS was triggered by sleep deprivation in four patients, and in two of these four cases, GTCS were associated with sudden arousal.

Four patients (15.3%) had a language disorder -consisting of a mild expressive language disorder in three and a moderate mixed expressive-receptive language disorder in one-, four patients had poor school performance (15.3%), and three (11.5%) presented with attention deficit disorder with or without hyperactivity.

3.5. Electroencephalographic findings

Generalized spike-and-wave discharges were observed in all patients when awake and during sleep in eight (30.7%) and 26 patients (100%), respectively (Figs. 1 and 2). In five children polyspike-and-wave paroxysms were also observed. In the patients with generalized discharges while awake, these paroxysms were activated during sleep. In seven patients the discharges occurred predominantly in anterior regions (26.9%) and the voltage of generalized discharges was asymmetric in five patients (19.2%). Later in the course of the syndrome, focal spikes during sleep and while awake were not observed. The occipital spikes were not activated by eye opening. In all patients response to intermittent photic stimulation, hyperventilation, and eye closure were normal. No ictal EEG recordings were registered in any of the patients (Fig. 3).

3.6. Treatment

Antiepileptic treatment with a single drug was started in all patients: Valproic acid (VPA) in 15, levetiracetam (LVT) in six, and clobazam in five cases. Two patients who received clobazam initially did not respond well; however, a switch to valproic acid resulted in excellent seizure control.

3.7. Evolution

All 26 patients except four had a good response to AEDs. Seizures remitted within three years after onset despite persistent EEG abnormalities in 19 (73%). In three children with four, five, and six seizures, respectively, the episodes remitted within 4–5 years.

AEDs were discontinued in 16 patients who remained seizure free over a follow-up period of 1–9 years. Four patients continue with yearly seizures. Two of these patients had a language disorder and the other two learning disabilities.

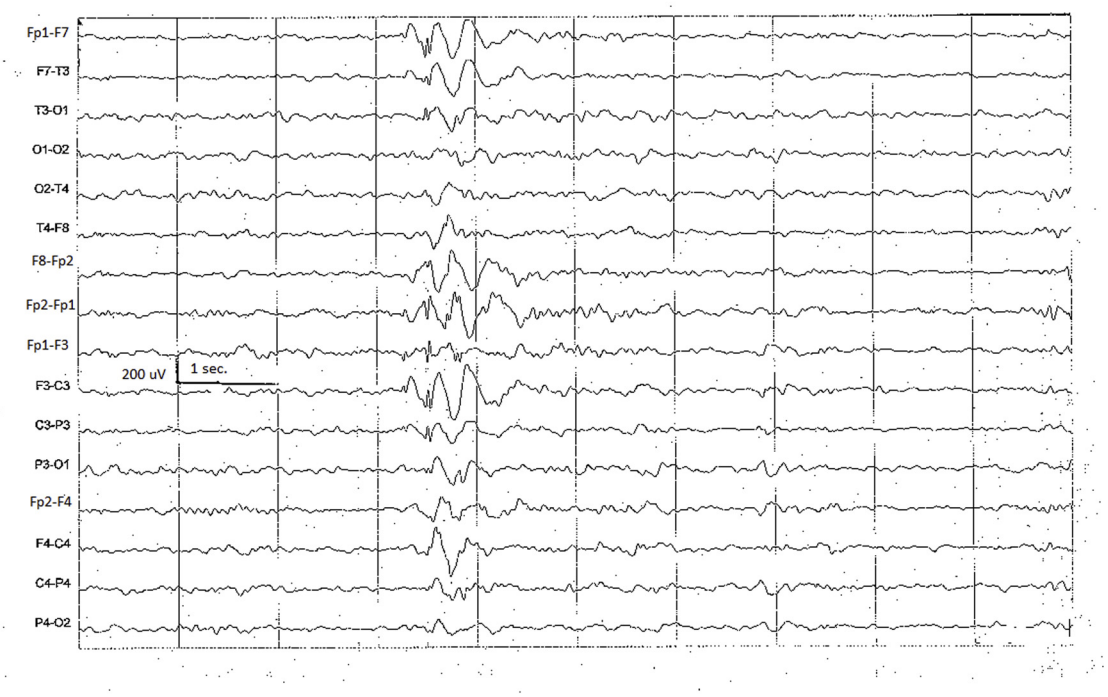

Fig. 1. In a 10-year-old boy the sleep EEG recording shows generalized spikes and waves predominantly in anterior regions.

None of the children had typical absences, myoclonus, or focal seizures compatible with idiopathic focal epilepsies of childhood and none of the patients evolved to another type of epileptic syndrome. At the last control, four patients had learning disabilities, four had language disorders, consisting of a mild expressive language disorder in three and a moderate mixed expressive-receptive language disorder in one, and two had behavioral disturbances consisting of attention deficit disorder associated with hyperactivity.

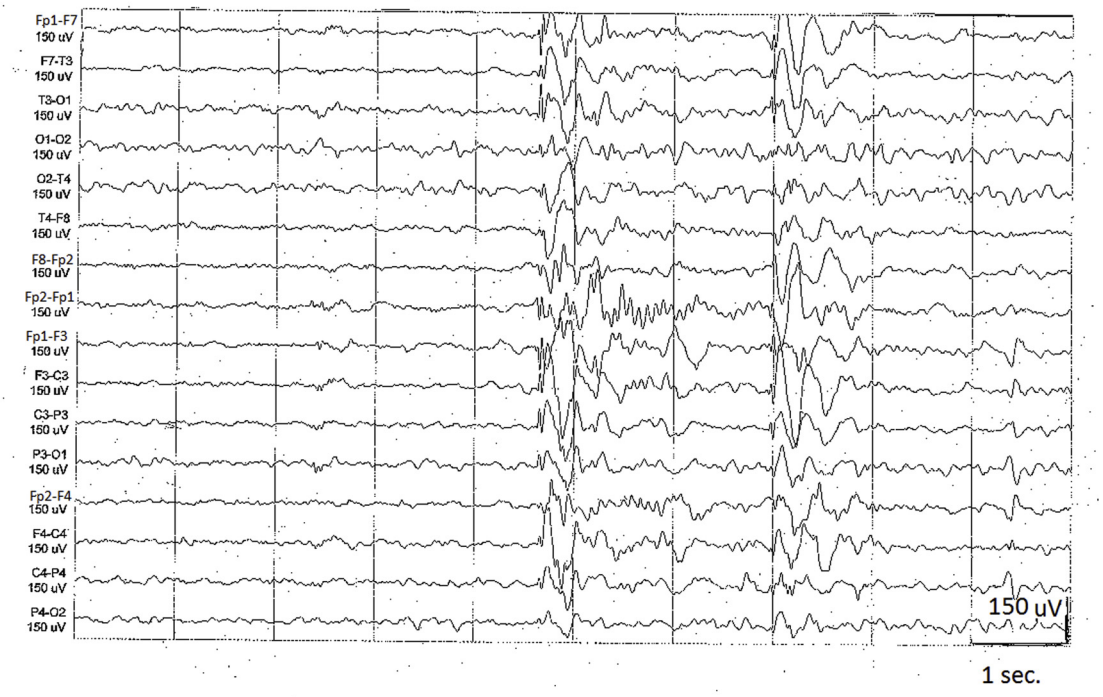

Fig. 2. In a 9-year-old girl the sleep EEG recording shows paroxysms of generalized spikes and waves and slow waves predominantly in anterior regions.

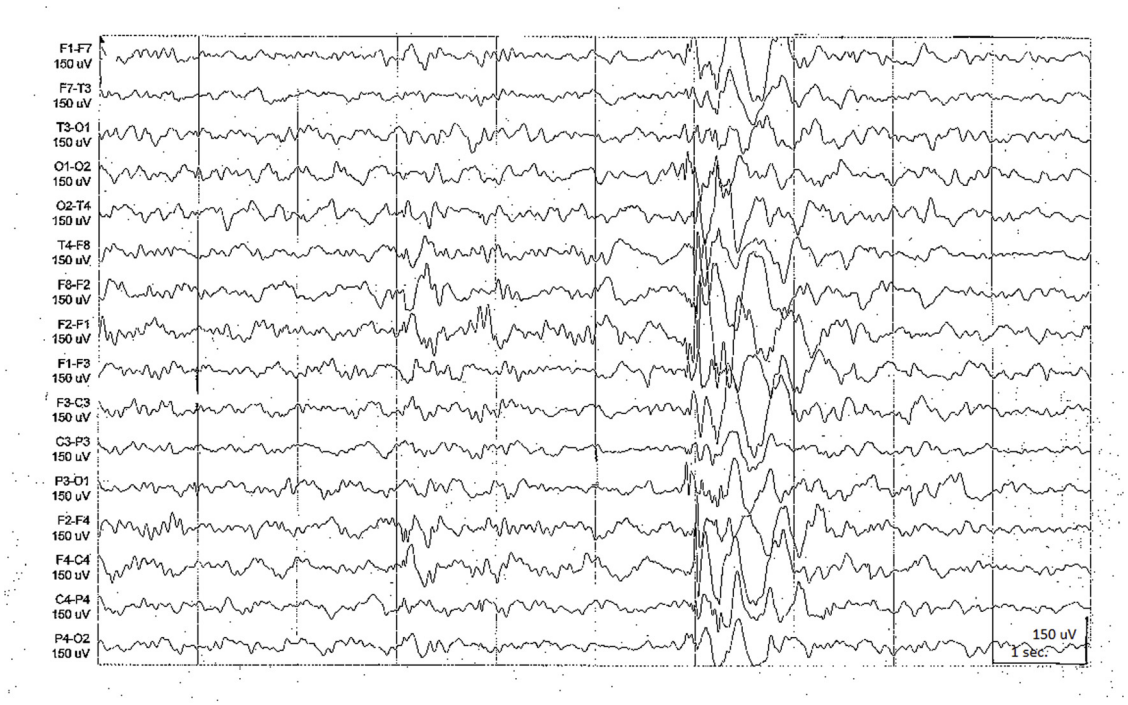

Fig. 3. In an 8-year-old boy the sleep EEG recording shows paroxysms of generalized spike-polyspike waves and slow waves.

No significant differences were found in response to treatment, electroclinical features, and comorbidities were found when comparing age at onset, sex, and personal and family history.

In Table 1, the electroclinical features, neuroradiological findings, treatment, and outcome are shown.

4. Discussion

Here we report children with GTCS associated with generalized paroxysms in the EEG recording compatible with idiopathic generalized epilepsy. The outcome of this group of patients is good, both in terms of seizure freedom and from the neuropsychological point of view. Most of the patients responded well to monotherapy and in sixteen patients the AED was discontinued and they remained seizure free after 1–9 years of follow-up. In a multilevel evaluation according to the new classification of the epilepsies, our group of patients with GTCS and generalized EEG paroxysms may be considered a generalized type of epilepsy (Scheffer et al., 2017; Fisher et al., 2017; Falco-Walter et al., 2018). However, taking into account the age at onset, the electroclinical features, the good response to the AEDs, and the outcome we could consider this group of patients to have an age-dependent and responsive well-defined epilepsy syndrome as well. The age-dependent onset and good response to AEDs may be features to differentiate this condition from adolescent-onset epilepsy with GTCS alone.

Another interesting point is that over time, the patients have not evolved to another type of idiopathic generalized epilepsy or epilepsy syndrome. Our findings are very important in the counselling of parents regarding the good seizure outcome and cognitive prognosis. A longer time of follow-up and genetic studies comparing this group of children with patients with adolescent-onset epilepsy with GTCS alone would be necessary to draw more robust conclusions.

To our knowledge, pediatric patients with similar electroclinical features, age at onset, response to AEDs, and outcome were described by Oller-Daurella and Oller (1992) and Camfield and Camfield (2010). In the former series of 80 cases, 11 (14.2%) had mental disorders; seven patients had intellectual disability and the remaining four patients had unspecified cognitive disturbances. In the latter study of 40 patients with IGE-GTC, on the other hand, among those > 21 years of age at follow up (N = 30), major adverse social outcomes were described, i.e. a psychiatric diagnosis (27%), no high school graduation (40%), pregnancy outside a stable relationship (38%), living alone (23%), unemployment (33%), and criminal conviction (7%). Satisfaction with their social life was reported by 55–65% of the patients. The authors concluded that IGE-GTC is a recognizable, relatively benign syndrome with complete remission in 75%, but associated with a high rate of learning problems and unsatisfactory social outcome.

So far primarily generalized GTCS have never been observed in infancy; however, in adolescents GTCS has been described in the literature (Hamer et al., 1999; Korff and Nordli, 2005). The best known IGE with GTCS is EGTCA occurring in adolescents and adults and classified in the group of IGE with variable phenotypes in adolescents (Engel, 2006; Gélisse et al., 2012). Another IGE to consider is phantom absences with GTCS. In these patients, very subtle interruptions in activity with generalized spike-wave EEG paroxysms are observed. Episodes of absence status have been reported as well (Koutroumanidis et al., 2008).

It is crucial to be strict in the inclusion criteria to recognize this type of epilepsy. For example, normal children with an isolated pure form of GTCS or those with this type of seizure associated with a normal EEG recording may correspond to focal epilepsy or represent isolated seizures (Fernandez Baca Vaca et al., 2018). On the other hand, children with another epileptic syndrome, such CAE or childhood myoclonic epileptic syndrome, may have GTCS as the first manifestation (Caraballo and Dalla Bernardina, 2013).

Cases with typical clinical manifestations of benign rolandic epilepsy only associated with generalized paroxysms on the EEG at onset have been published (Vargas et al., 2018). Patients with apparently GTCS during sleep associated with generalized EEG paroxysms may

Table 1
Electroclinical features, neuroradiological findings, treatment, and outcome in our series of patients.

Patient number	Sex	First unprovoked GTCS: age (awake/sleep)	Total unprovoked GTCS	Age at last control (years)	Family history of epilepsy	Development	Febrile seizures	EEG	Neuroimaging Normal	Treatment
1	M	9y (awake)	3	16	+	ADD	–	GSWD GPSWD	MRI	LVT
2	F	10y (awake)	3	14	–	ADHD	+	GSWD	CT	VPA
3	M	10y (awake/sleep)	2	13	+	N	–	GPSWD	MRI	VPA
4	M	8y (awake)	4	12	+	N	–	IGSWD	MRI	LVT
5	F	8y (sleep)	2	11	–	N	+	GSWD GPSWD	CT	LVT
6	M	7y (awake)	2	9	+	Hyperactivity		GPSWD	MRI	VPA
7	F	7y (awake)	2	11	+	N	+	IGSWD	MRI	LVT
*8	F	5y (awake)	4	16	–	N	–	IGSWD	MRI	VPA
9	M	3y1m (awake)	2	14	–	**Language disorder**	+	I-GSWD	MRI	VPA
10	M	3y1m (sleep)	2	5.3	–	N	–	R-GSWD	CT	CLB
11	F	3y2m (awake)	2	12	–	Learning **disability**	–	I-GSWD	MRI	**VPA**
12	M	3y2m (awake)	4	6.5	+	N	–	I-GSWD	MRI	CLB, change to VPA
13	M	3y6m (awake)	2	7	–	**Language disorder**	–	R-GSWD GPSWD	CT	VPA
14	M	3y8m (awake)	2	7	–	N	+	R-GSWD	MRI	VPA
15	M	3y10 m (sleep)	2	6	–	**Language disorder**	+	I-GSWD	MRI	CLB
16	F	4y1m (awake)	3	10	–	N	–	I-GSWD	MRI	LVT
17	M	4y2m (sleep)	2	7	+	Learning **disability**	+	I-GSWD	CT	CLB
18	M	4y4m (awake)	2	6.5	–	N	+	I-GSWD GPSWD	MRI	CLB
19	M	4y7m (awake)	2	8	–	N	+	R-GSWD	CT	VPA
20	F	5y (awakening)	3	9	–	**Language disorder**	+	I-GSWD	MRI	VPA
21	F	4y9m (sleep)	5	8	–	N	–	I-GSWD	MRI	CLB, changed to VPA
22	M	5y11 m (awake)	2	17	–	N	–	R-GSWD	MRI	VPA
23	F	6y (sleep)	2	8	–	Learning **disability**	–	R-GSWD	MRI	LVT
24	F	6y6m (awake)	3	9	–	N	–	R-GSWD	CT	VPA
25	M	10y11 m (awakening)	2	15	–	Learning **disabilities**	–	I-GSWD	MRI	VPA
26	M	11y2m (sleep)	3	14	–	N	–	R-GSWD GPSWD	MRI	VPA

Abbreviations: Mmale; Ffemale; (+)present; (-)absent; Nnormal; FSFebrile seizures; R/I-GSWDregular/irregular generalized spike-wave discharge; GPSWDgeneralized polyspike-and-wave discharge; CTComputed tomography; MRMagnetic resonance; VPAValproic acid; CLBClobazam; LVTLevetiracetam. *Patient had benign infantile epilepsy during first year of life.

correspond to rolandic epilepsy. In these latter cases, the presence of typical rolandic seizures and/or the typical focal EEG pattern typical of idiopathic focal epilepsy rules out idiopathic generalized epilepsy with GTCS.

Regarding treatment, our series of patients responded well to AEDs, particularly VPA, but LVT was a very good option as well. It is interesting to comment that 15 patients in a series of 40 patients were treated successfully with carbamazepine, phenobarbital, and phenytoin, AEDs that epileptogists do not consider a good alternative and may even be contraindicated (Camfield and Camfield, 2010). The AED of choice for IGE with GTCS should be investigated.

It is well known that in adolescent patients generalized epilepsy may present with variable phenotypes (Engel, 2006; Zhang et al., 2017). Thus, we may consider the same concept in children with GTCS and absence and myoclonic seizures. IGEs in childhood may be caused by hyperexcitability of a particular functional area or system of the brain. However, these conditions are probably related to the same dysfunctional process of brain maturation which is generally mild and reversible and has a genetic predisposition. The coexistence of these types of seizure in the same patient may suggest a close genetic relationship between IGEs in children. Perhaps, in this group of patients exome or whole genome sequencing may show a different pattern of gene variants.

As to the neuropsychological aspect, in our group of patients only some of the children presented with mild language and behavioral disturbances without an important impact on the school performance. However, patients with epilepsy with GTCS were previously found to have school troubles and important social difficulties (Camfield and Camfield, 2010).

We consider it important to reopen in the pediatric epilepsy community the discussion on epilepsy in childhood with GTCS alone, especially regarding whether it is a type of epilepsy or a well-defined epileptic syndrome.

5. Conclusion

IGE with GTCS in childhood is a type of epilepsy, however it may be considered as a very well-defined epileptic syndrome.

The patients responded well to AEDs, especially VPA, and LVT may be considered as a good treatment option.

No important cognitive and behavioral changes were observed in our series of patients.

The differentiation of this entity is important for counselling of the parents and families of these children.

Future prospective and collaborative studies including genetic investigations are necessary to confirm if this group of patients represents

a well-defined epilepsy syndrome.

Disclosure

All co-authors have read and agreed to the content of the manuscript. None of the authors has any conflict of interest to disclose. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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