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Short communication

Infantile spasms followed by childhood absence epilepsy: A case series

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ABSTRACT

Purpose: Infantile spasms (IS) represent a severe seizure disorder of infancy and early childhood characterized by epileptic spasms along with hypsarrhythmia often accompanied by intellectual disability. According to the current classification and terminology (3) IS can be categorized as known etiology, formerly known as "symptomatic", when an underlying cause has been observed prior to the onset of spasms, or of "unknown cause" with "unfavorable" and "favorable" outcome (previously referred as "cryptogenic" or "idiopathic", respectively). Single reports described children with "unknown cause and favorable outcome" (UC/FO) IS who later developed childhood absence epilepsy (CAE). This study aims to determine the prevalence of CAE following IS.
Methods: a multicenter retrospective chart review was performed; children with UC/FO IS who subsequently developed CAE during follow-up were identified. Eight Italian pediatric epilepsy centers participated in this study.
Results: seven out of 24 (29 %) children (3 males) showing a favorable outcome (UC/FO) IS received a second diagnosis of CAE during follow-up. Mean age at IS presentation was 5.8 months (SD ± 0.9). All achieved seizure control of IS at a mean age of 8.5 months (SD ± 1.3) (3 monotherapy, 4 polytherapy). CAE was diagnosed at a mean age of 8.0 years (SD ± 3.0). Six children achieved sustained remission of CAE with valproic acid, whereas 1 child required dual therapy by adding ethosuximide.
Conclusion: although it is not possible to determine whether the association between UC/FO IS and CAE implies a causality relationship, the later occurrence of CAE in patients with UC/FO IS might support a possible role of thalamo-cortical dysfunction.

1. Introduction

Infantile spasms (IS) represent a unique form of age-specific epileptic disorder of infancy and early

childhood. IS are characterized by epileptic spasms along with a peculiar electroencephalographic (EEG) pattern (hypsarrhythmia) [1].

The former classification of epilepsies and epileptic syndromes edited by the ILAE (International League Against Epilepsy) in 1989, distinguished two groups of patients suffering from IS, on the basis of etiology: 1) symptomatic IS, when underlying disorders could be identified (~68 %); 2) cryptogenic IS, when a specific involvement of the brain could be suspected but not clearly identified (~24 %). Later, an additional group, called "idiopathic" (~8 %), was proposed; it included patients with IS, prior defined as "cryptogenic", who showed a normal psychomotor development before the onset of epilepsy, with no underlying disorders or definite presumptive causes, and no neurological or neuroradiological abnormalities [2].

Recent insights into genetics of epilepsies along with the

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improvement in imaging technologies contributed to the development of a new classification in 2017 (3). Accordingly, cryptogenic and idiopathic IS were included into the etiological category of "unknown cause". Thus, in our study, we re-named idiopathic IS as "unknown cause and favorable outcome" (UC/FO), which are believed to be caused by a genetic predisposition, and cryptogenic IS as "unknown cause and unfavorable outcome".

Although epileptic spasms usually resolve after 5 years of age, 50–70 % of affected patients develop other seizure types and 18–50 % of subjects with drug-resistant epilepsy evolve into Lennox-Gastaut syndrome or other forms of epileptic encephalopathy [4,5].

The clinical course of IS remains unpredictable, especially in cases with "unknown cause" IS. Indeed, the diagnosis of UC/FO IS can only be confirmed *"a posteriori"* depending on the evolution of the disease [1]. Hence, studying the natural history of patients with UC/FO IS can contribute to a better understanding of the underlying pathophysiological mechanisms and, possibly, to the identification of new predictive factors.

Specchio et al. firstly described two cases of children with unknow cause IS showing a favorable outcome and a later occurrence of childhood absence epilepsy (CAE), suggesting the hypothesis that the two syndromes could share some of the same physiopathogenetic mechanisms [6].

We performed a retrospective multicenter study to investigate the possible relationship between UC/FO IS and the subsequent occurrence of CAE.

2. Material and methods

We performed a multicenter retrospective chart review of patients with UC/FO IS who developed CAE during follow-up. Patients with IS were recruited from 8 Italian pediatric epilepsy centers and were followed-up for at least 5 years between January 1998 and November 2018.

Overall, 212 charts of patients with IS were reviewed, 24 (11.3 %) out of them were identified as having UC/FO IS according to the following criteria: 1) history of epileptic spasms with onset before the age of 12 months; 2) hypsarrhythmia at EEG recording; 3) normal development prior to disease onset; 4) absence of genetic causes (a customized 121 genes NGS panel for epilepsy syndromes was performed in all subjects); 5) absence of structural abnormalities at brain magnetic resonance imaging (MRI).

Three patients with insufficient medical documentation were excluded from the study.

Demographic data, EEG and MRI features, epileptic family history and clinical presentation were collected and analyzed.

Positive family history for epilepsy and/or febrile seizures was found in 8 out of 24 patients. Mean age at IS onset was 5.1 months (SD ± 1.8 months).

Nine patients underwent monotherapy treatment: 5 adrenocorticotropic hormone (ACTH) and 4 vigabatrin (VGB). Fifteen children received antiepileptic polytherapy treatment with up to 4 AEDs: 12 patients received 2 AEDs (11 patients ACTH and valproic acid [VPA]; 1 patient VGB and ACTH), 2 patients received 3 AEDs (ACTH, VPA, and carbamazepine [CBZ]; ACTH, VGB, VPA), 1 patient received 4 AEDs (ACTH, VGB, VPA, topiramate [TPM]).

All patients achieved seizure control, defined as the absence of clinical spasms and normalization of EEG pattern. Mean age at seizure control was 8.2 moths (SD ± 2 months).

All children had a favorable outcome defined as sustained remission of clinical spasms for at least 6 months from the beginning of antiepileptic therapy without reappearance of spasms, nor need for further medications, the absence of developmental delay- as measured by standardized age-referenced developmental testing (Griffiths Mental Development Scale (Griffiths-II, [1996]) or Bayley Scales of Infant Development (BSID-II, [1993]) - after IS and an intellectual quotient (IQ, Wechsler scale) > 85 within range limits in the neuropsychological testing.

Two patients were later diagnosed with CTS (Centro-temporal Spikes Epilepsy, previously defined as an Idiopathic Focal Epilepsy, currently considered as genetic or possibly genetic form) and achieved seizure control with VPA treatment. Seven patients developed CAE. The remaining 15 patients did not experience any other type of epilepsy once recovered from IS.

In this study, we analyzed 7 children with UC/FO IS who presented CAE.

CAE, belonging to the group of the Generalized Genetic/possibly Genetic Epilepsies (GGE) [3], previously known as Idiopathic Epilepsies (IGE), was diagnosed according to the ILAE classification of epilepsy syndromes criteria: (1) onset between 4–12 years of age; (2) no neurologic abnormalities and an age-appropriate development; (3) short duration of absence seizures (4–20 seconds) with abrupt and severe impairment of awareness; (4) electroclinical correlation between absence seizures and 3 Hz spikes (or polyspikes)-and-waves discharges, with a normal background EEG activity.

3. Results

Seven (3 males, 4 females) out of 24 (29 %) children with UC/FO IS received a diagnosis of CAE during the follow-up (Table 1). Clinical course and history of patients with UC/FO IS did not significantly differ from the other 17 patients and no defined predictive factors distinguished patients with CAE from the ones with CTS. Notably, at the time of diagnosis of IS, EEG features of both CAE and CTS patients were consistent with hysparrhythmia during wakefulness and sleep, with normal age-related EEG findings in sleep and wakefulness after IS resolution. At the time of diagnosis of CAE and CTS, the typical epileptiform discharges increased during the transition phase to sleep.

Mean age at IS presentation was 5.8 months (SD ± 0.9). Three children received monotherapy (2 ACTH, 1 VGB) while 4 needed polytherapy with the combination of ACTH and VPA. All of them achieved seizure control at a mean age of 8.5 months (SD ± 1.3).

Mean age at CAE onset was 8.0 years (SD ± 3.0). All of them received VPA as first-line treatment. Six children achieved sustained remission of CAE during the first 2 months of AED therapy, while 1 patient who continued to have absence seizures after 4 months of VPA monotherapy, achieved definitive seizure control with the addition of ethosuximide.

The mean age at the last visit was 11.5 years (SD ± 3.9).

From a neurological point of view all patients remained stable without specific neurological impairment and age-appropriate cognitive development.

4. Discussion

It is commonly thought that children with IS of "unknown cause" can develop other seizure types during their lives [7]. However, to the best of our knowledge, only isolated cases of transition from IS to a GGE/IGE have been reported. *Specchio* et al. described two patients who experienced CAE later in life [6], while *Mangano* et al. reported a child who later developed juvenile myoclonic epilepsy [8].

The coexistence of two epilepsy syndromes formerly referred as "*idiopathic*" and currently considered to have no other presumable cause than genetic predisposition, appears to be extremely rare.

Indeed, only few reports described the occurrence of the two different epilepsy syndromes of unknown cause, in the same patient [9].

Over the past decades strenuous efforts have been made to understand the pathophysiologic basis of IS. However, although the current knowledge about this disorder is gradually increased, no consistent pathologic feature or process has been so far identified. Assuming that different epilepsy syndromes experienced by the same patient are mechanistically linked, studying the relationship between UC/FO IS and

Table 1
Disease characteristics of patients with "*unknown cause and favorable outcome*" of IS (in bold patients with subsequent CAE).

	Gender	Family history	Age at IS onset (months)	AED for IS	Age at IS control (months)	GDQ or BCSb at IS control	Epilepsy	Age at epilepsy onset (years)	AED for epilepsy	Age at last visit (years)	Wechsler scales type and IQ
1	**Male**	**None**	**4**	**VGB**	**8**	**GDQ 97**	**CAE**	**4.8**	**VPA**	**8.2**	**WPPSI 103**
2	**Male**	**None**	**6**	**ACTH**	**10**	**BCSb 105**	**CAE**	**13.9**	**VPA**	**18.7**	**WISC IV 104**
3	**Female**	**FSs**	**6.5**	**ACTH, VPA**	**10**	**BCSb 95**	**CAE**	**7.8**	**VPA**	**12.8**	**WISC IV 92**
4	**Female**	**None**	**5.6**	**ACTH, VPA**	**7**	**GDQ 99**	**CAE**	**8.7**	**VPA**	**12.2**	**WISC IV 101**
5	**Female**	**FSs, JME**	**6.5**	**ACTH, VPA**	**8**	**BCSb 105**	**CAE**	**7.5**	**VPA**	**11.3**	**WISC IV 108**
6	**Male**	**None**	**7**	**ACTH**	**10**	**BCSb 98**	**CAE**	**4.9**	**VPA**	**6.2**	**WIPPSI 97**
7	**Female**	**None**	**5.5**	**ACTH, VPA**	**7**	**GDQ 103**	**CAE**	**8.7**	**VPA**	**11.6**	**WISC 4 96**
8	Male	None	6	ACTH	9		/	/	/	18.7	
9	Male	CTS	4.5	ACTH, VPA	6.5		/	/	/	16.3	
10	Male	None	6	VGB	8		/	/	/	15.8	
11	Male	None	5	ACTH	9		/	/	/	17.4	
12	Male	None	2.5	VGB, ACTH	6		CTS	12.5	VPA	17.6	
13	Female	FSs	3	ACTH, VPA, CBZ	10		/	/	/	12.8	
14	Female	None	5	ACTH, VPA	7		/	/	/	12.2	
15	Male	FSs	8	ACTH	10		/	/	/	13.7	
16	Female	FSs	7.5	ACTH, VPA	10		/	/	/	11.3	
17	Male	None	2.5	ACTH, VPA	4		/	/	/	12.1	
18	Male	FSs, FLE	3	VGB	6		/	/	/	18	
19	Male	None	6.5	ACTH, VPA, CBZ	8		/	/	/	5.1	
20	Male	None	7	ACTH, VPA	11		/	/	/	6.2	
21	Female	None	7	ACTH, VPA	9		/	/	/	11.6	
22	Male	None	5	VGB	12		/	/	/	11.4	
23	Male	None	2	ACTH, VGB, VPA, TPM	7		/	/	/	20	
24	Male	JME	2	ACTH, VPA	5		CTS	14.5	VPA	20.4	

Abbreviations: ACTH, adrenocorticotropic hormone; CAE, childhood absence epilepsy; CTS, centro-temporal spikes epilepsy; FLE, frontal lobe epilepsy; FSs febrile seizures; IS, infantile spasms; TPM, topiramate; VGB, vigabatrin; VPA, valproic acid; neuropsychological testing: Griffith developmental quotient (GDQ) and BAYLEY cognitive sub-quotient (BCSb).

later occurrence of CAE might provide insights into their pathophysiology and etiology.

We are aware that it is not possible to determine whether the association between UC/FO IS and CAE implies a causal relationship. Besides the genetic predisposition hypothesized by *Specchio et al.* [6], the later occurrence of CAE in patients with UC/FO IS might support a possible role of thalamo-coritcal dysfunction. *Lado* and *Moshé* emphasized a role of cortex-subcortical regions interaction in IS development, suggesting that pro-convulsant changes should be necessary in both cortical and brainstem regions [10]. Notably, absence seizures are thought to involve abnormally functioning of thalamo-coritcal networks. In fact, spike-wave discharges occur through repetitive cyclic activity between the cortex and thalamus. Furthermore, thalamo-cortical dysfunction seems to play a pivotal role also in IS development as supported by *Myers et al.* throughout the demonstration that infra-slow EEG activity (ISA) was highly frequent in IS [11]. There is a growing evidence about a crucial role of a possible thalamic dysfunction in the generation of ISA in patients suffering from IS. Generally (and also in our patients), hypsarrythmia tends to be more evident during sleep, suggesting a thalamic involvement. This involvement may represent the link with the thalamic and the cortico-thalamic network dysfunction leading to the occurrence of CAE.

Indeed, ictal ISA recorded in association with the spasms may partly be due to abnormal G-coupled inward rectifying potassium channel (GIRK) expression in the thalamus among other regions of the brain. It is conceivable that IS originate from abnormal interactions between cortical and subcortical circuits rather than in any other region alone. It has been postulated that loss of GABAergic inhibition caused by abnormal GIRK subunit 2 expression in the thalamus plays a major role in the genesis of IS and might be a possible link with the subsequent CAE development. The efficacy of ethosuximide in the animal model of IS described by Cortez et al. supports this link [12].

Moreover, the finding that 2 patients with UC/FO IS later developed CTS might further suggest a possible genetic overlapping between these three electroclinical syndromes.

5. Conclusions

This retrospective study involving a small cohort of pediatric patients with IS who showed an excellent long-term follow-up outcome confirms the possibility of sequential appearance of CAE in children who have suffered from IS. The small number of patients does not clearly support that the two syndromes can be considered as a neurological continuum. Further efforts should be made in order to report larger case series which might confirm this possible association. Finally, our study suggests that the long-term prognosis of CAE in these patients seems to be good, with an excellent response to anticonvulsant drugs.

Transparency document

The Transparency document associated with this article can be found in the online version.

Declaration of Competing Interest

None.

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