

Benign infantile focal epilepsy with midline spikes and waves during sleep: a new epileptic syndrome or a variant of benign focal epilepsy?

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ABSTRACT – Objective. To analyze the electroclinical features and evolution of seven infants with benign infantile focal epilepsy with midline spikes and waves during sleep (BIMSE). **Material and methods.** Seven patients were examined at our department between February 2003 and February 2009, with onset of seizures between six and 13 months of age (mean, 10.2 months; median, 11 months). Patients with cryptogenic and symptomatic focal epilepsies were excluded. Sex, age, familial history, type of seizures and AED treatment were noted and EEG monitoring, MRI and CT scanning, and developmental and psychomotor evolution were investigated. **Results.** Patients included five males and two females. All patients suffered from seizures during wakefulness. Two of the patients (29%) did not have a recurrence. Five (71%) had sporadic seizures (ranging between two and five). One of the seven patients (14%) presented with seizures in clusters. During seizures, staring was observed in six (86%), motion arrest in five (71%), stiffening in five (71%), cyanosis in three (42%), automatisms in one (14%) and lateralizing signs in four (57%). Two patients (29%) had secondary generalisation. The duration of the seizures ranged between 30 seconds and five minutes. No status epilepticus was observed. The interictal EEG recording during sleep showed low-voltage unilateral or bilateral spikes located in the central and vertex regions, followed by slow waves in all patients. Outcome was excellent in all patients. **Conclusion.** We believe that BIMSE is a new syndrome rather than an early presentation of benign epilepsy of childhood with centrotemporal spikes, Panayiotopoulos syndrome, or a late presentation of benign focal infantile seizures.

Key words: benign, focal seizure, idiopathic, infantile seizures, midline, spikes, ILAE classification

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Cases of focal benign idiopathic epilepsies in infancy have been extensively described (Fukuyama, 1963). The 2001 ILAE Task Force on Classification recognized benign familial infantile seizures (BFIS) and

benign non-familial infantile seizures (BNFIS) as epileptic syndromes (Engel, 2008). Previously, familial and non-familial epilepsies in infancy were shown to have similar electroclinical features (Caraballo *et al.*, 1997, 2003).

In 2000, Capovilla and Beccaria (2000) described an electroclinical condition of focal benign seizures in infancy which was hypothesized to be a new syndrome characterized by the presence of EEG abnormalities in the vertex regions during the sleep stages called “benign partial epilepsy in infancy and early childhood with vertex spikes and waves during sleep” with excellent prognosis. The same EEG pattern had been previously described as a marker of benign nature in this age group by Bureau and Maton (1998). In 2002, Bureau *et al.* (2002) published an investigation of a series of ten patients with this disorder, and in 2006, Capovilla *et al.* (2006) proposed to change the name of the syndrome to “benign focal epilepsy in infancy with midline spikes and waves during sleep (BIMSE)”, to avoid a confusing terminology with physiologic vertex spikes (Capovilla and Beccaria, 2007).

BIMSE is characterized by age at onset between four and 30 months and partial seizures, consisting of motion arrest, staring, cyanosis, and less commonly automatisms and lateralizing signs. Seizures are sporadic. The interictal sleep EEG is the clue for diagnosis: a spike followed by a bell-shaped slow wave in the midline region. A family history of epilepsy is reported to be present in half of the patients with BIMSE (Engel, 2008). The evolution is benign with normal neurological status and psychomotor development (Capovilla and Beccaria, 2000; Bureau *et al.*, 2002; Capovilla *et al.*, 2006.).

In this study we have analyzed the electroclinical features and evolution of seven infants with BIMSE.

Patients and methods

We studied seven patients with typical electroclinical features of BIMSE (five males and two females) between

February 2003 and February 2009, with onset of seizures between six and 13 months (mean: 10.2 months; median: 11 months). All our patients had normal physical examination and normal developmental skills and behaviour. Patients with an abnormal neurological examination, symptomatic patients (with abnormal complementary studies), and cryptogenic patients (with incomplete response to treatment) were excluded. Sex, age, familial history, type of seizure, and AED treatment were noted and EEG monitoring, MRI and CT scanning, and developmental and psychomotor evolution were investigated. We used the International 10-20 system to monitor EEGs. The mean follow-up after seizure onset was 24.1 months.

Results

The male/female ratio was five males (71%) to two females (29%). All of the patients were previously healthy, including an unremarkable perinatal history. We found a positive family history of epilepsy in five patients (71%) and febrile seizures in two (29%). The age at seizure onset was between six and 13 months (mean: 10.2; median: 11). All patients had their last seizure one to four months after the onset of seizures (mean: 1.57 months). The electroclinical features, treatment, and outcome of our series of patients is described in *table 1*.

EEG

During the awake state, EEG background activity was normal in all patients with no paroxysmal abnormalities. During sleep, EEG showed physiological patterns according to age. We found low-voltage unilateral or bilateral

Table 1. Electroclinical features, treatment and evolution of patients.

Patient no.	1	2	3	4	5	6	7
Sex	M	M	F	F	M	M	M
Age (months)	45	36	39	48	26	15	32
Personal antecedents	No	No	No	No	No	No	No
Familial epilepsy	No	No	Yes	Yes	Yes	Yes	Yes
Familial febrile epilepsy	No	Yes	No	No	Yes	No	No
Age at onset (months)	13	11	10	12	9	6	11
Age at last seizure (months)	-	12	11	-	13	7	15
Imaging	MRI	CT	MRI	CT	CT	CT	CT
EEG	BVS-DSW	BVS-DSW	UVS-DSW	UVS-DSW	BVS-DSW	BVS-DSW	BVS-DSW
EEG normalization time	30	33	36	40	ABN	ABN	ABN
Treatment	CBZ	PB	VPA	CBZ	CBZ	PB	PB
Follow-up period (months)	32	25	29	36	17	9	21

M: male; F: female; BVS: bilateral vertex spikes; UVS: unilateral vertex spikes; DSW: diffuse slow waves; ABN: abnormal; CBZ: carbamazepine; PB: phenobarbital; VPA: valproic acid.



Figure 1. (Patient 1) EEG showing bilateral central spikes followed by high slow wave.



Figure 2. (Patient 3) EEG showing unilateral central spikes followed by a high slow wave.

spikes located in the central and vertex regions, followed by diffuse slow waves in sleep stages I-II (*figures 1, 2*). In five cases (71%) we observed bilateral spikes in the central regions followed by diffuse slow waves and in two cases (29%) unilateral, low-voltage spikes followed by diffuse slow waves. EEG normalization occurred in 57% of our patients (4/7) during follow-up. The mean time of normalization was 23.2 months (17-28). In 42% (3/7) the EEG remained abnormal.

CT and MRI

By definition, all of the patients had normal CNS images (CT scanning was performed for five patients and MRI for two).

Seizure semiology

All patients suffered from seizures during wakefulness. For two of our patients (29%) seizures were only reported

once. For other patients, sporadic seizures (varying from two to five) were reported. One of the patients (14%) presented a cluster of seizures.

During seizures, staring was observed in six (86%), motion arrest in five (71%), stiffening in five (71%), cyanosis in three (42%), automatisms in one (14%), and lateralizing signs in four (57%). Two of the seven patients (29%) had secondary generalisation. The duration of seizures ranged from 30 seconds to five minutes. None of the patients had status epilepticus. The clinical features of the patients are listed in *table 2*.

Follow-up

The mean follow-up after onset of seizures was 24.1 months. The outcome was excellent for all patients and all continued to be seizure free up to the present time. Physical examination and mental development was reported to be normal. All patients were treated

Table 2. Seizure semiology.

Patient no.	1	2	3	4	5	6	7
Frequency of seizures	Single episode	Sporadic episodes	Sporadic episodes	Single episode	Sporadic episodes	Sporadic episodes	Sporadic episodes
State during seizure	Awake	Awake	Awake	Awake	Awake	Awake	Awake
Staring	Yes	Yes	Yes	Yes	Yes	No	Yes
Motion arrest	Yes	No	Yes	Yes	Yes	No	Yes
Cyanosis	No	No	Yes	No	Yes	No	Yes
Stiffening	Yes	Yes	No	Yes	Yes	Yes	No
Automatisms	No	No	Yes	No	No	No	No
Lateralizing signs	Yes	Yes	No	Yes	No	Yes	No
Clusters	No	No	No	Yes	No	No	No

Table 3. Comparison of electroclinical features, treatment and evolution between BIMSE patients from different series.

Series	This study	Capovilla and Beccaria (2000)	Bureau et al. (2002)
No. of patients	7	19	10
Sex	5 M 2 F	12 M 7 F	3 M 7 F
Personal antecedents	No	No	1 febrile seizure 1 breath holding spell
Familial epilepsy	71%	47%	10%
Familial febrile epilepsy	29%	15%	20%
Age at onset (months)	6-13 (mean 10.2)	4-30	1-20 (mean 9.9)
Mean time between first and last seizure (months)	1.5	24-36	24.1
Imaging	100% normal (7/7)	100% normal (13/19)	67% normal (6/10)
EEG	BVS-DSW (5) UVS-DSW (2)	BVS-DSW	BVS-DSW (3) UVS-DSW (7)
Mean EEG normalization time (months)	23 (57%)	46.8	?
Treatment	(100% treated) CBZ (3) PB (3) VPA (1)	(15% treated) PB (2) VPA (1)	(90% treated) VPA + CBZ (1) CBZ (5) pyridoxine (1) PB (2)
Follow-up period (months)	24.1	66.3	79.2

M: male; F: female; BVS: bilateral vertex spikes; UVS: unilateral vertex spikes; DSW: diffuse slow waves; CBZ: carbamazepine; PB: phenobarbital; VPA: valproic acid.

with AEDs (three with carbamazepine, three with phenobarbital, and one with valproic acid); two patients were treated after the first seizure, three after the second seizure and the other two following the third episode. Three of the patients continue to take AEDs.

Four patients (57%) had a normal EEG (with a mean normalization time of 23.2 months). Three patients (43%) continued to have an abnormal EEG which revealed the same pattern as the diagnostic EEG (bilateral central spikes in all cases).

Discussion

In this study we have described seven patients presenting with focal seizures and an EEG pattern consisting of low-voltage spikes in the midline region followed by high-voltage diffuse slow waves. All of the patients had a normal perinatal and developmental history, and a normal physical examination. Most of the patients in this cohort were male. The median age at onset was 11 months. All patients had a normal CT or MRI and excellent response to AEDs.

The disease evolution in our series presented similar characteristics to those previously reported (Capovilla and Beccaria, 2000; Capovilla *et al.*, 2006; Bureau *et al.*, 2002). A comparison of the results reported here with those of Capovilla and Beccaria (2000) and Bureau *et al.* (2002) are summarised in *tables 3 and 4*, and are discussed below.

In accordance with the series of Capovilla and Beccaria (2000), a male predominance was observed, however, this is different from the findings of Bureau *et al.* (2002), where the main gender group was female (70%).

None of our patients had any prior medical history, as was the case in the series of Capovilla and Beccaria (2000). In the series of Bureau *et al.* (2002) 20% of the patients had a history of prior neurological abnormalities (one patient with febrile seizure and another with breath-holding spells). A family history of epilepsy was identified in 71% of patients reported here, compared to 47% of the series of Capovilla and Beccaria (2000) and 10% of Bureau *et al.* (2002). A family history of febrile seizures was identified in 29% of our population, similar to 15% of those of Capovilla and Beccaria (2000) and 20% of the series of Bureau *et al.* (2002).

The age at seizure onset was 6-13 months (mean: 10.2) in our series, compared to 4-30 months reported by Capovilla and Beccaria (2000) and 1-20 months reported by Bureau *et al.* (2002). Five of the patients presented here had recurrent seizures (ranging from 2-5 seizures), and the mean time between the first and last seizure was 1.5 months, compared to 2-3 years in the other series (Capovilla and Beccaria, 2000; Bureau *et al.*, 2002).

Neuroimaging studies (CT scanning or MRI) were performed for all of our patients with normal results. In the series of Capovilla and Beccaria (2000) 13/19 of the patients had normal CNS imaging. In the series of Bureau *et al.* (2002), 6/10 patients underwent imaging studies revealing four patients to be normal and two to have non-specific posterior white matter T2 hyperintensity, based on MRI.

EEG monitoring for our patients showed bilateral vertex spikes (BVS) in five patients and unilateral vertex spikes (UVS) in two. In the series of Bureau *et al.* (2002) three had BVS and seven UVS. EEG normalization time was 23 months in our series and 3.9 years in the series of Capovilla and Beccaria (2000).

With regards to seizure occurrence, of the patients reported here, two had a single seizure episode and five had sporadic seizures, similar to the series of Capovilla and Beccaria (2000), of which two patients had a single seizure and 17 sporadic seizures. Repeated seizures (up to 20 for one particular patient) were reported in the series of Bureau *et al.* (2002).

All of the patients in our series had seizures only during wakefulness, similar to those of Bureau *et al.* (2002) but in contrast to Capovilla and Beccaria (2000) who reported 5/19 (26%) patients with seizures during sleep and 19/19 (100%) with seizures during wakefulness.

The semiology of the seizures was characterised by staring in 86% of patients, similar to 90% reported by Capovilla and Beccaria (2000); motion arrest in 71%, compared to 84% by Capovilla and Beccaria (2000) and 50-70% by Bureau *et al.* (2002); stiffening in 71%, compared to 47% by Capovilla and Beccaria (2000) and 50-70% by Bureau *et al.* (2002); automatisms in 14%, similar to 10.5% by Capovilla and Beccaria (2000); lateralizing signs in 57%, compared to 15% by Capovilla and Beccaria (2000) and 10-30% by Bureau *et al.* (2002) and clustered seizures in 14%, compared to 31% by Capovilla and Beccaria (2000) and none by Bureau *et al.* (2002).

All of our patients were administered a single AED (three with carbamazepine, three with phenobarbital, and one with valproic acid). In the series of Capovilla and Beccaria (2000) 15% were treated and in the series of Bureau *et al.* (2002) 90% were treated (one patient was administered two AEDs).

For infants with focal seizures, with or without secondary generalisation which have normal medical and developmental history, physical examination and imaging, and

Table 4. Comparison of seizure semiology between BIMSE patients from different series.

Series	This study	Capovilla and Beccaria (2000)	Bureau <i>et al.</i> (2002)
Frequency of seizures	Single (2) Sporadic (5) (2-5 seizures)	Single (2) sporadic (17)	Several
State during seizure	Awake (100%)	Awake 17/19 (89%) Awake and asleep 2/19 (11%)	Awake (100%)
Staring	6/7 (86%)	17/19 (90%)	?
Motion arrest	5/7 (71%)	16/19 (84%)	50-70%
Cyanosis	3/7 (42%)	17/19 (90%)	50-70%
Stiffening	5/7 (71%)	9/19 (47%)	50-70%
Automatisms	1/7 (14%)	2/19 (10.5%)	?
Lateralizing signs	4/7 (57%)	3/19 (15%)	10-30%
Clusters	1/7 (14%)	6/19 (31%)	None

Table 5. Comparison of clinical features between BIMSE (benign infantile focal epilepsy with midline spikes and waves during sleep), BIS (benign infantile seizures), BCECTS (benign childhood epilepsy with centrotemporal spikes) and PS (Panayiotopoulos Syndrome) (modified from Capovilla *et al.*, 2006).

	BIMSE	BIS	BCECTS	PS
Age at onset	4-30 months	3-18 months	> 36 months	> 24 months
Seizure frequency	+	+++	+	+
Cluster	+	+++	-	-
Cyanosis	+++	+	-	+
Loss of consciousness	+	+++	-	++
Lateralizing signs	+	++	+++	+++
Automatisms	+	++	+	+
Secondary generalisation	-	+++	+	++
Ictal vomiting	+	+	-	+++
Status epilepticus	-	-	+	+++
EEG	Midline spikes	normal	C-T spikes	OFT spikes

BFIS: benign familial infantile seizures; BNFIS: benign non-familial infantile seizures; CT: centrotemporal; OFT: occipito-fronto-temporal.

evolution, EEG monitoring should be performed to investigate the presence of EEG abnormalities described here. The presence of such EEG findings may represent an electroencephalographic marker for benign infantile seizures, but may alternatively represent a discrete epileptic syndrome. Such specific EEG abnormalities may also confirm the benign nature of the disorder thus limiting unnecessary further diagnostic studies and aggressive treatments.

At present, the existence of focal benign epilepsy during infancy is undeniable. We confirm the existence of the electroclinical syndrome previously described by Capovilla and Beccaria (2000) and Bureau *et al.* (2002), which is characterised by stereotyped seizures, a distinctive EEG interictal pattern, a lack of clustered seizures, and a positive family history, which together support the recommendation as a new idiopathic syndrome.

A distinction should be made between BIMSE and BFIS or BNFIS, based on the specific characteristics of BIMSE: a late onset, no clusters, decreased seizure frequency, and an abnormal interictal typical EEG pattern (Caraballo *et al.*, 1997, 2003; Vigeveno *et al.*, 1992; Capovilla and Beccaria, 2000; Bureau *et al.*, 2002; Capovilla *et al.*, 2006; Capovilla and Beccaria, 2007).

The distinction between BIMSE and Benign Childhood Epilepsy with Centrottemporal Spikes (BCECTS) and Panayiotopoulos Syndrome (PS) should be made based on the seizure semiology and EEG. In BCECTS, seizures often occur during sleep, and focal clonic activity of the face and arms is typical, cyanosis is absent, and there is no impairment of consciousness. In BIMSE, seizures occur during wakefulness and the EEG shows spikes with a lower voltage in the midline region. For PS, patients often have longer seizures with focal signs, ictal vomiting, and occipital spikes (Engel, 2008; Capovilla and Beccaria, 2007; Dalla Bernardina *et al.*, 2002). The differential diagnosis of benign infantile epilepsy with midline spikes and waves during sleep (BIMSE) is listed in *table 5*.

Conclusion

We believe that BIMSE is a new syndrome rather than an early presentation of BCECTS or PS, or a late presentation of BFIS or BNFIS.

It is important to consider this syndrome as a benign entity. Thus, therapeutic decisions should not be excessive and prolonged or expensive treatments should be avoided.

Future prospective studies with flexible and broad inclusion criteria should be conducted to confirm the existence and nosology of this syndrome. □

Disclosure.

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