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Different types of suppression-burst patterns in patients with epilepsy of infancy with migrating focal seizures (EIMFS)

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ABSTRACT

Purpose: In rare cases, patients with epilepsy of infancy withmigrating focal seizures (EIMFS) exhibit suppression-burst (SB) patterns on electroencephalography (EEG), similar to the findings observed in patients with Ohtahara syndrome and early myoclonic encephalopathy. In this report, we discuss six cases of EIMFS in which patients exhibited two types of SB patterns.

Methods: We evaluated six patients with EIMFS who had been admitted to the NHO Shizuoka Institute of Epilepsy and Neurological Disorders between 2011 and 2018. We retrospectively examined clinical characteristics and EEG findings for each patient. In all patients, the first EEG was performed within 1 month after seizure onset. Afterwards, EEG examinations were performed at irregular intervals (ranging from 1 to 5 months).

Results: Age at seizure onset ranged from 2 days to 3 months. SB was first detected within 1 month of age in two patients, and within the range of 3–14 months in the remaining four patients. Among the latter four patients, SB patterns persisted at the final EEG recording in three patients (34–54 months). In all patients, SB patterns were observed during sleep only. Interhemispheric asynchrony in SB was observed in the two patients who exhibited SB within 1 month of age, while synchronous SB patterns were observed in the remaining four patients.

Conclusions: Our findings indicate that EIMFS may be associated with two types of SB patterns (early-onset and late-onset), which can be distinguished based on the stage of emergence and level of synchrony.

1. Introduction

Suppression-burst (SB) is an electroencephalographic finding characterized by the alternating appearance of depressed background activity and bursts of mixed-frequency paroxysmal activity [1]. SB patterns are typically recorded in patients with forms of early-onset epileptic encephalopathy, such as Ohtahara Syndrome (OS) and Early Myoclonic Encephalopathy (EME) [2]. In patients with epilepsy of infancy with migrating focal seizures (EIMFS), typical interictal electroencephalogram (EEG) features include multifocal spikes with slow background activity [3]. However, recent reports have suggested that SB patterns can occur in rare patients with EIMFS [4,5]. In the present report, we discuss six cases of EIMFS in which we observed both early and late onset SB patterns.

2. Methods

Six patients were diagnosed with EIMFS based on the presence of migrating ictal EEG findings and seizure symptoms. Both OS and EME as a differential diagnosis of epilepsy syndrome with suppression-burst pattern were ruled out by seizure type and seizure symptoms.

All patients were treated at National Epilepsy Center, NHO Shizuoka Institute of Epilepsy and Neurological Disorders between January 2011 and July 2018. Probable diagnoses of OS and EME were excluded in these 6 patients based on ictal EEG findings and seizure symptoms.

This study reviewed clinical characteristics and long-term video

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Table 1
Clinical features of patients.

Patient/Sex	Gestational age	Seizure onset	Seizure types, symptoms	Type of SB	Age at first EEG (including short-term EEG at referring hospital)	Age at first long-term EEG (> 16 h)	Frequency of EEG examination	Age at the last EEG examination
Pt 1/F	40w	2d	Focal tonic, cyanosis, oral automatism, oculoclonic	Early	1w	2w	Every month	7m (died at 8 m)
Pt 2/M	39w	3d	Focal tonic, cyanosis	Early	1w	1m	Only once	1m
Pt 3/M	39w	3m	Focal tonic, focal to bilateral tonic-clonic	Late	3m	3m	Every 3 months in the first year and every 3-5 months thereafter	7y7m
Pt 4/M	39w	1m	Focal tonic, cyanosis, oculoclonic	Late	1m	5m	Every 2 months for the first 8 months and every 2-4 months thereafter	2y11m
Pt 5/F	39w	2m	Focal tonic, cyanosis, oral automatism, apnea	Late	2m	6m	Every month for the first 22 months and every 2-4 months thereafter	4y6m
Pt 6/M	36w	2m	Focal tonic, cyanosis, oral automatism	Late	2m	5m	every month for the first year and every 3 months thereafter	2y10m
Selioutski O, et al. 2013, [5] DB13-002 / M	Full-term	2d	N/A	Early	39 weeks of gestational age	–	N/A	107d
Selioutski O, et al. 2013, [5] DB12-014 / F	Full-term	6d	N/A	Early	39 weeks of gestational age	–	N/A	67d

Patient/Sex	Age at first SB detection	Age at SB disappearance	Interhemis-pheric asymmetry	State during which SB was observed	Effective treatment (> 50% reduction)	Ineffective treatment (< 50% reduction)	Psychomotor development	Brain MRI findings	Pathogenic genetic variants
Pt 1/F	2w	Persisted until final observation	+	Sleeping state	–	ZNS, PB, LEV, KBr	Profoundly delayed	Diffuse mild atrophy (0y3m)	*KCNT1* (c.1420C > A)
Pt 2/M	1m	Persisted until final observation	+	Sleeping state	–	PB, CBZ, CLB, KD	Profoundly delayed	Normal (0y5m)	Not performed
Pt 3/M	3m	7m	–	Sleeping state	KD	CBZ, LEV, CLB, ZNS, PHT, TPM, PB, PER, VPA	Profoundly delayed	Diffuse mild atrophy (5y9m)	Not performed
Pt 4/M	10m	Persisted until final observation	–	Sleeping state	Quinidine sulfate	KBr, LEV, PB, CZP, CLB	Profoundly delayed	Diffuse moderate atrophy, hypomyelination (2y7m)	*KCNT1* (c.1283 G > A)
Pt 5/F	1y2m	Persisted until final observation	–	Sleeping state	KD	Quinidine sulfate, PHT, VPA, ZNS, CLB, LEV, B6, CBZ, PER	Profoundly delayed	Diffuse mild atrophy, hypomyelination (2y3m)	*KCNT1* (c.2800 G > A)
Pt 6/M	1y2m	Persisted until final observation	–	Sleeping state	–	Quinidine sulfate, CBZ, CLB, PB, LEV, ZNS	Profoundly delayed	Bifrontal mild atrophy (0y6m)	*KCNT1* (c.862 G > A)
Selioutski O, et al. 2013, [5] DB13-002 / M	46d	3m (107d)	+	Waking and sleeping state	–	Multiple antiepileptic drugs, KD	N/A	Normal (10d)	*KCNT1* (c.1420C > T)
Selioutski O, et al. 2013, [5] DB12-014 / F	13d	2m (67d)	+	Waking and sleeping state	–	Multiple antiepileptic drugs, KD	Global developmental delay	Normal (17d)	*SCN2A* (c.4718 T > C)

EEG monitoring (> 16 consecutive hours) records for each patient. All EEG examinations performed at our institution consisted of long-term EEG monitoring, which was performed at irregular intervals amongst the patients. We also evaluated EEG findings obtained at referring hospitals, most of which consisted of short-term EEG recording obtained prior to the first admission to our hospital only. For both the long-term and short-term EEG, the first recording was performed within 1 month after seizure onset.

3. Results

Table 1 shows the characteristics of the 6 included patients. The gestational age of Patient 6 was 36 weeks, while the remaining 5 were born at full-term. Seizure onset occurred within 3 months after birth in all patients. Patients 1 and 2 developed seizures within a few days after birth, while seizure onset in the remaining patients (Patients 3–6) ranged from 1 to 3 months of age. All patients exhibited focal seizures characterized by asymmetric tonic posture, oral automatism, and cyanosis. Patient 3 alone developed focal-to-bilateral tonic-clonic seizures. In all patients, seizures were refractory to treatment with conventional antiepileptic drugs, although quinidine sulfate or ketogenic diets were partially effective in Patients 3, 4, and 5. Psychomotor development was profoundly delayed in all patients. Patient 1 died of pulmonary hemorrhage causally related to the major aortopulmonary collateral artery at the age of 8 months.

Whole-exome sequencing in Patients 1, 4, 5, and 6 revealed pathogenic variants in *KCNT1* (potassium sodium-activated channel subfamily T member 1). A genetic examination was not performed in the remaining two patients.

At the first EEG examination, SB patterns were observed in Patients 1–3 only. EEG findings in Patients 4–6 at the first examination consisted of multifocal spikes or sharp waves with slow background activity. However, SB patterns were observed at the last EEG recording in Patients 4–6, at the ages of 35 months, 58 months, and 34 months, respectively. SB patterns were observed only during sleep in all 6 patients.

Interhemispheric asynchrony in SB patterns was observed in Patients 1 and 2, persisting until the final examination, whereas SB patterns in Patients 3–6 were invariably synchronous. Figs. 1 and 2 shows the representative EEG recordings for each patient.

4. Discussion

In the present report, we discussed the cases of 6 patients presenting with 2 different types of SB patterns. While emergence during the early infantile stage was associated with asymmetrical SB patterns, emergence during the later infantile period was associated with symmetrical features. As observed in Patients 1 and 2, Patient 3 presented with SB at the first EEG examination at the age of 3 months, although such findings disappeared by the age of 7 months. Previous authors have reported that, among 4 patients with EIMFS who began to exhibit SB patterns within 6 weeks after birth, SB patterns disappeared in 2 patients by the age of 6 months, evolving into other types of abnormal EEG findings such as hypsarrhythmia [4–6].

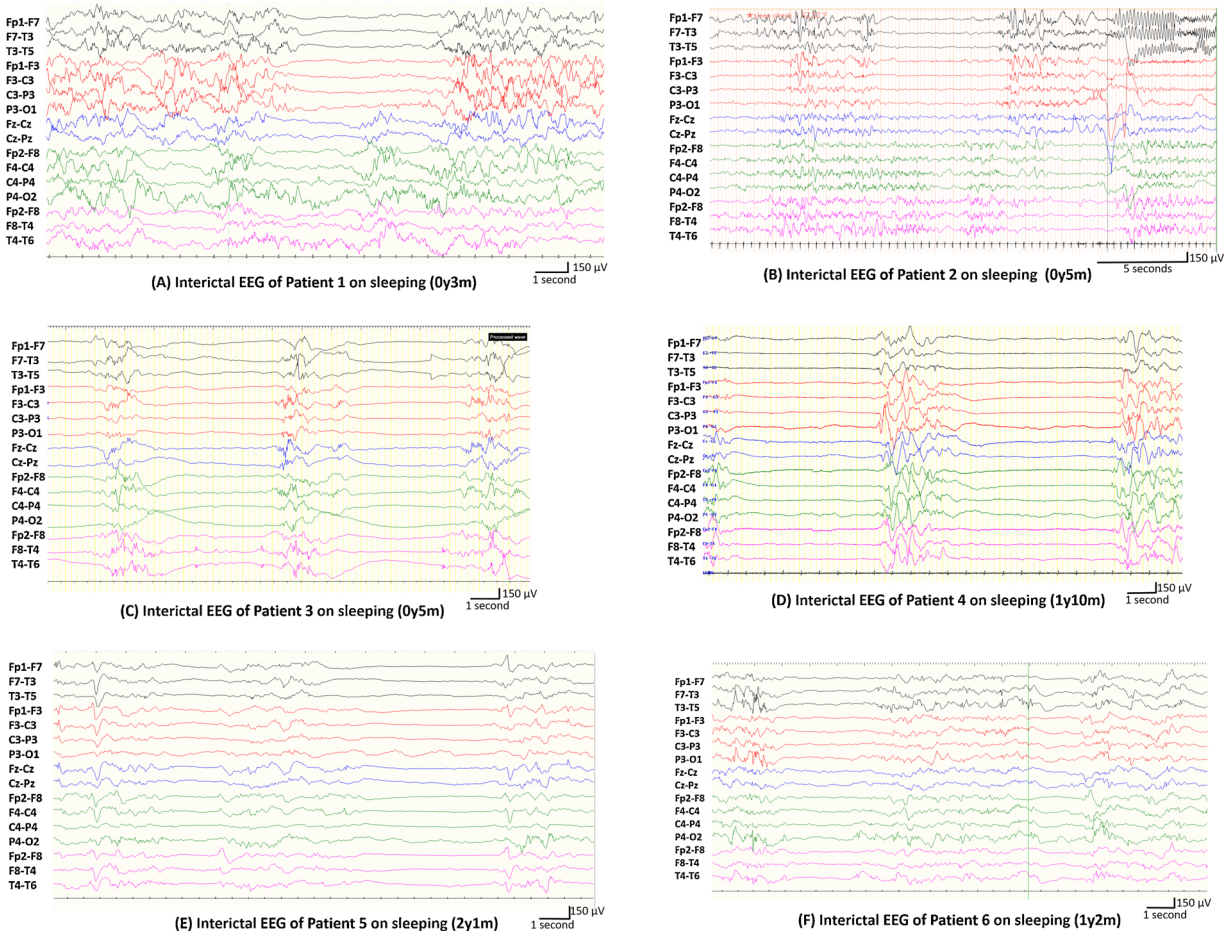

Fig. 1. (A)–(F) Alternating periods of mixed-frequency discharge and slow waves of high amplitude (bursts) and suppression are observed with interhemispheric asynchrony.

Although previous reports have documented SB patterns during both sleep and wakefulness [5], SB was observed only during sleep in our 6 patients. Although SB has been reported to occur in patients with OS during both sleep and wakefulness [7], it is typically observed during sleep only in patients with EME [2]. In this sense, EIMFS with late SB may be more similar to EME than to OS, while EIMFS with early SB may differ from both OS and EME.

In contrast to previous findings, we observed different degrees of SB asynchrony in Patients 1 and 2 [4]. Such asynchrony may be characteristic of EIMFS with early-onset SB, given the immaturity of the central nervous system at this stage. Symmetrical and continuous EEG activity is observed in healthy newborns [8]; however, in preterm newborns, EEG activity is asymmetrical and discontinuous, depending on the level of development. SB patterns also develop during the early infantile stages in patients with OS, exhibiting asymmetry in approximately two-thirds of patients [7]. Thus, the asymmetrical pattern observed in patients with early-onset SB may derive from the immaturity or dysfunction of interhemispheric connections. Indeed, asymmetrical

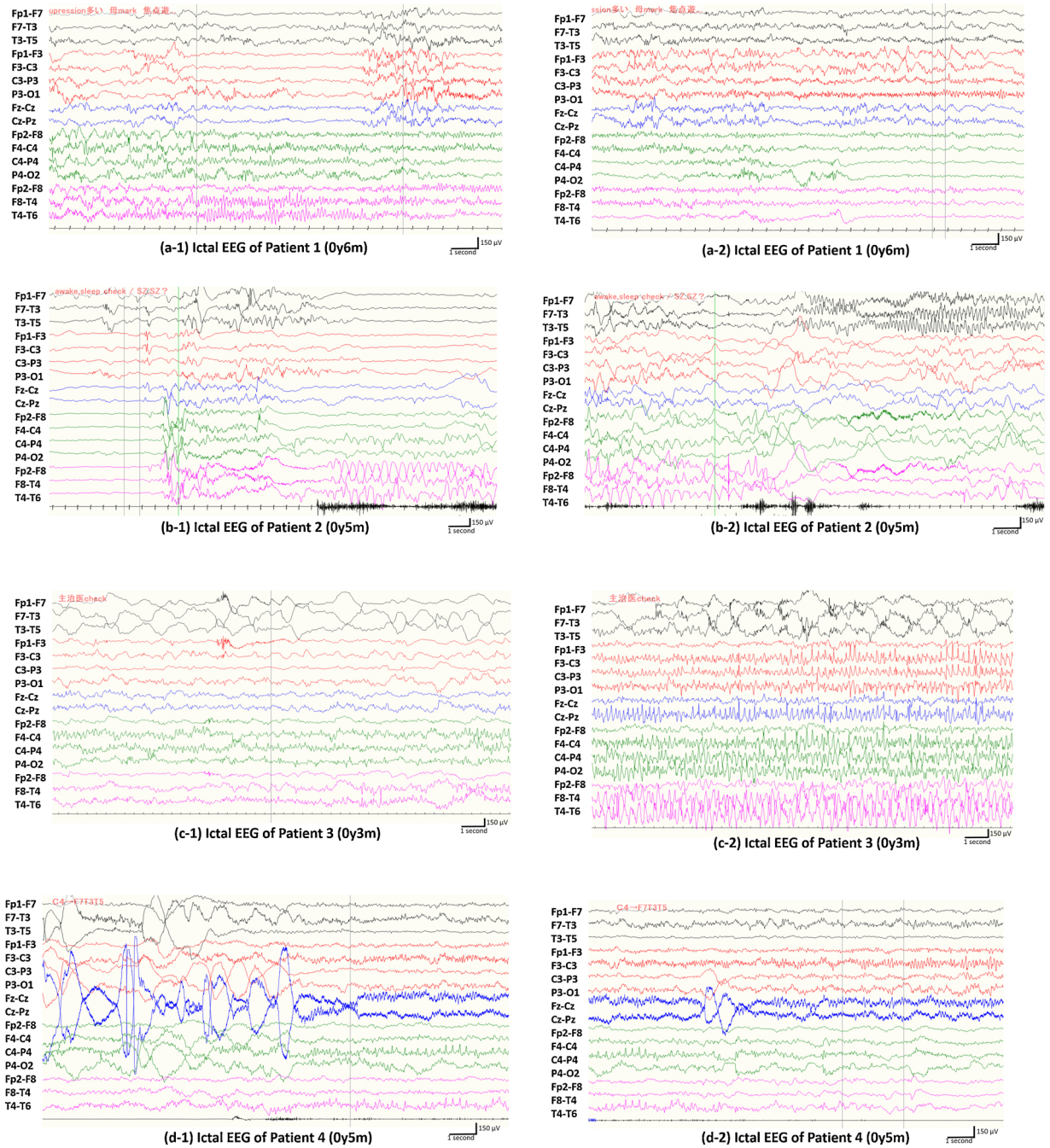

Fig. 2. (a)–(f) Alternating periods of mixed-frequency discharge and slow waves of high amplitude (bursts) and suppression are observed with interhemispheric synchrony. **(a)** Clusters of fast waves appeared at T4 (a-1), then gradually migrated to P3 (a-2). **(b)** Clusters of sharp waves appeared at F8 (b-1), then migrated to T3 (b-2). **(c)** Clusters of fast waves appeared at C4, then spread to T4 (c-1), and finally spread diffusely (c-2). **(d)** Clusters of fast waves appeared at C4 and T4 (d-1), then migrated to F3 (d-2). **(e)** Clusters of fast waves appeared at P3 (e-1), then migrated to T3 (e-2), and finally migrated to T4 (e-3). **(f)** Clusters of fast waves appeared at T4 (f-1), then migrated to T3 (f-2).

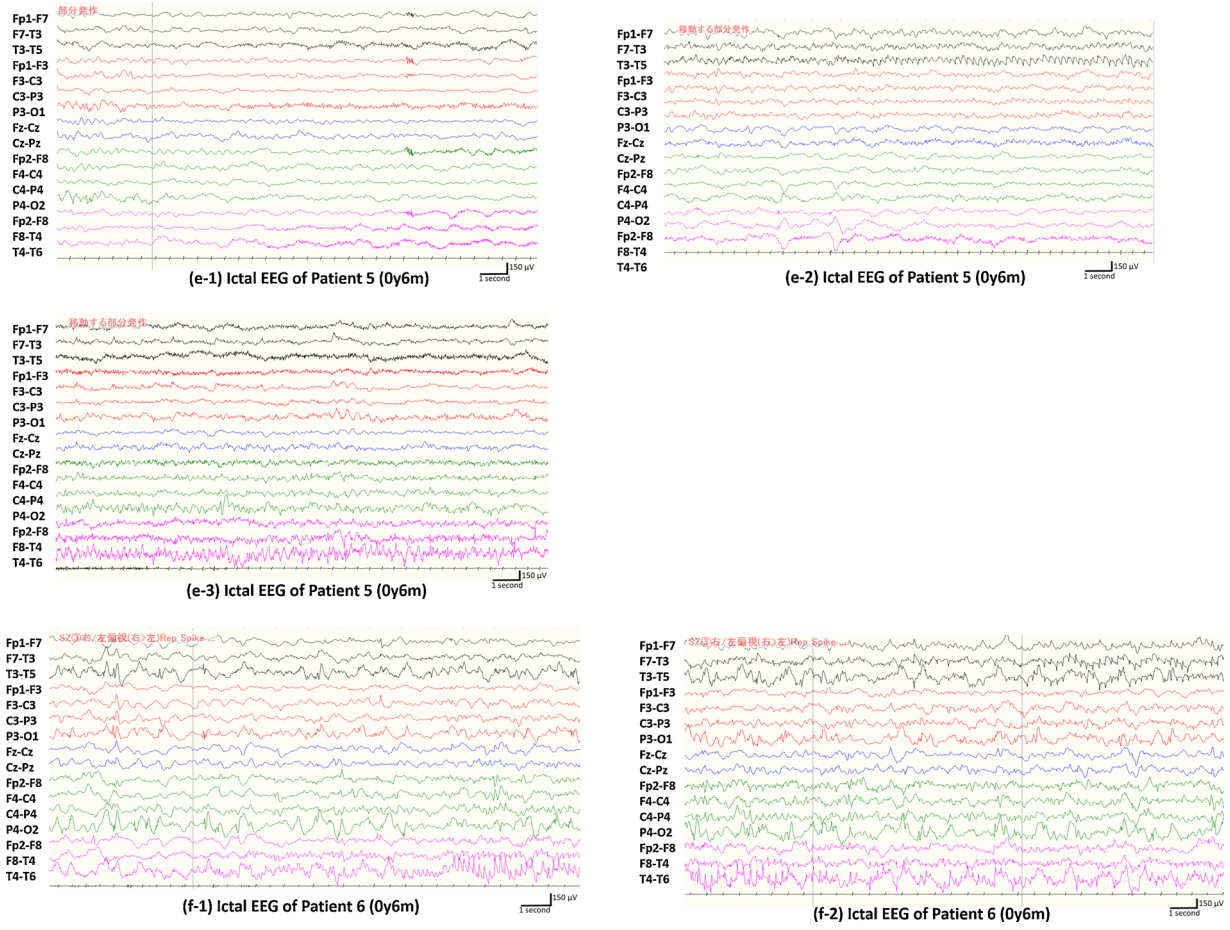

Fig. 2. (*continued*)

SB patterns have been observed in a few patients with epilepsy with corpus callosum hemorrhage or lesions [9,10], suggesting that immaturity or dysfunction of the corpus callosum plays an important structural or functional role in SB symmetry. Differences in the synchrony of SB patterns among patients with EIMFS may also be explained by the maturity or recovery of normal function of the corpus callosum.

In conclusion, findings in these 6 patients suggest that there are apparent differences between patients with EIMFS based on the stage of SB emergence and that early-onset and late-onset SB are each associated with different patterns of EEG activity, persistence, and synchronization. However, it remains to be determined whether 2 distinct types of SB can be observed in patients with EIMFS. Indeed, it is possible that such findings represent only a few alternatives along a spectrum of EEG findings in patients with EIMFS.

The present study possesses some noteworthy limitations, including the small sample size of 8 patients (6 from the present study and 2 previous cases). Furthermore, as this was a retrospective study, EEG examinations for each patient were performed at arbitrary intervals. Therefore, our findings should be interpreted with caution, and further studies are required to elucidate the clinical significance of SB patterns in patients with EIMFS.

Disclosures

None of the authors has any conflict of interest to disclose.

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