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CONCISE REPORT

Brain unidentified bright objects ("UBO") in systemic lupus erythematosus: sometimes they come back. A study of microembolism by cMRI and Transcranial Doppler ultrasound

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Objectives: The objectives of this report are to assess the occurrence of microembolic signals (MES) detected by transcranial Doppler ultrasound (TCD) in systemic lupus erythematosus (SLE) patients with (NPSLE) and without (SLE) neuropsychiatric involvement, and to verify the correlation between MES, clinical characteristics, especially the patent foramen ovale (PFO), and the presence of punctuate T2-hyperintense white matter lesions (WMHLs) detected by conventional magnetic resonance imaging (cMRI). **Methods:** A TCD registration to detect MES from the middle cerebral artery was carried out in SLE and NPSLE patients after exclusion of aortic and/or carotid atheromatous disease. In all patients conventional brain magnetic resonance imaging (cMRI) and transesophageal echocardiography were performed. Patients were stratified in two groups, with and without WMHLs, and compared. **Results:** Twenty-three SLE patients (16 NPSLE and seven SLE) were enrolled in the study. Overall MES were detected in 12 patients (52.1%), WHMLs were detectable in 15 patients (13 NPSLE and two SLE) while eight patients had normal cMRI (three NPSLE and five SLE). Matching TCD ultrasound and neuroimaging data, MES were detected in 10 (nine NPSLE and one SLE) out of 15 patients with WHMLs and in only two out of eight patients (two NPSLE and six SLE) with normal cMRI, both with NP involvement. A PFO was confirmed in all cases of MES detection. **Conclusion:** MES are frequent findings in SLE patients, especially in those with focal WMHLs detected by cMRI and correlating with PFO. These findings should be taken into account and suggest caution in the interpretation of cMRI pictures along with a careful evaluation of MES in patients with cMRI abnormalities that should be included in the workup of SLE patients. *Lupus* (2015) **0,** 1–6.

Key words: White matter hyperintense lesions (WMHLs); systemic lupus erythematosus (SLE); magnetic resonance imaging (MRI); transcranial Doppler ultrasound (TCD); microembolic signals (MES); patent foramen ovale (PFO)

Introduction

Central nervous system (CNS) involvement is a severe complication of systemic lupus erythematosus (SLE) with an estimated prevalence of 56.3%.[1] Clinical manifestations are heterogeneous and have been listed in the American College of Rheumatology (ACR) classification for neuropsychiatric lupus (NPSLE).[2] Pathogenesis is multifactorial including both ischemic/thrombotic and immune-mediated mechanisms.

Neuroimaging has an important role in diagnostic and prognostic assessment of patients with SLE and with suspected NP involvement.[3] Conventional magnetic resonance imaging (cMRI) is the technique of choice for CNS morphological evaluation,[4] and the most frequent MRI pathologic pattern consists of isolated or multiple T2-hyperintense small punctate lesions in subcortical and periventricular white matter (WMHLs) that in the past were often interpreted as the result of brain vasculitis or named as unidentified bright objects ("UBO").

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These lesions are very common in chronic NPSLE (25%–60%) and, even if they correlate with SLE clinical severity, past history of CNS involvement, cognitive dysfunction and presence of antiphospholipid antibodies (aPL), they are extremely not specific since they can also be found in SLE patients without NP symptoms (25%–50%) and in patients without SLE at all. In the general population, the prevalence of WMHL ranges from 11% to 21% and increases with aging, heart valvular disease and hypertension.[5]

Their pathogenesis is multifactorial including both ischemic/thrombotic and immune-mediated mechanisms being related to microinfarcts, demyelination or gliosis.[5] In the case of multiple small focal areas of ischemia, recurrent cerebral microembolism detectable through transcranial Doppler ultrasound (TCD) represents one of the hypothesized mechanisms.

The frequency of microembolic signals (MES) reported in the general population is around 15%.[12] A patent foramen ovale (PFO) is one of the more frequent etiologies; when associated with a heart right-to-left shunt (RLS) this condition is considered as an independent risk factor for cerebral embolism and stroke. Even if TCD and transesophageal echocardiography (TEE) are complementary diagnostic tests for PFO, TCD is recommended as the first choice for screening because of its simplicity, minimally-invasive character, low cost and high feasibility. Results of studies of WMHLs in patients with PFO are still controversial. A few studies have reported MES in SLE with or without NP involvement but, to our knowledge, no studies have investigated the occurrence of PFO in SLE patients as a potential risk factor for a higher rate of WMHLs in this disease.

We have planned this study to assess the correlations between MES, PFO and brain WMHL detected by cMRI in SLE patients.

Patients and methods

SLE patients of age less than 50 years consecutively observed at our institution in a period of six months were enrolled and, apart from age, no other exclusion criteria have been defined. All patients fulfilled the 1997 revised ACR classification criteria for the disease.[6] This study was approved by the local ethics committee and was performed according to the Declaration of Helsinki; written consent was obtained before investigation. In all patients clinical and demographic data were assessed. Relevant comorbidities and related concomitant medication were recorded: hypertension, diabetes, dyslipidemia, smoking, carotid atherosclerosis and valvular heart disease. Sero-immunologic tests included aPL (anticardiolipin and anti-beta2 glycoprotein I measured by standardized enzyme-linked immunosorbent assay (ELISA) kit) and lupus anticoagulant (LA, by kaolin clotting time and Russel viper venom test). Titers of aPL were determined and deemed as significant for values above 40 GPL/MPL units. Systemic Lupus Erythematosus Disease Activity Index-2000 (SLEDAI-2000) score was calculated in order to assess disease activity at the time of the study. All patients underwent a neurologic examination and NP events (i.e. NPSLE) were identified according to the diagnostic workup indicated for the various NP syndromes as advised by the formal case definition nomenclature of the 1999 ACR classification criteria, after exclusion of secondary causes.[2] Ongoing anti-aggregate and or anticoagulant therapy was also recorded.

TCD

All patients were evaluated using a TCD system with a 5 MHz pulsed-wave machine by an expert, blinded to the patient's clinical history and according to a local standardized protocol, based on international expert consensus. The patients, in the supine position, were prepared with an 18-gauge needle inserted into the cubital vein. At least one middle cerebral artery (MCA) was insonated using TCD. The contrast agent was prepared using 9 ml isotonic saline solution and 1 ml air mixed with a three-way stopcock by exchange of saline/air mixture between the syringes and injected as a bolus. The test was performed twice with the patient at rest and after Valsalva maneuver with intravenous injection of contrast agent injected, and with the Valsalva maneuver started 3 s after injection. Then a sequential monitoring to detect microbubbles (MB) was performed and the registration of more than two bubbles in a time of up to 15″ was counted as positive test according to recommendations to standardize the examination procedure from the "ad hoc" International Consensus Meeting.[7] A four-level categorization according to the MB count was applied: 1) 0 MB (negative result); 2) 1–10 MB (mild positive); 3) >10 MB and no curtain (moderate positive), and 4) curtain (severe positive).

A transthoracic echocardiography (TTE) and a transesophageal echocardiography (TEE) were carried out in all patients with a positive TCD test.

cMRI

cMRI was performed within two weeks of the TCD examination, using a conventional 1.5 Tesla whole-body MT imaging Magnetom SP 4000 (Siemens), using a standard circular polarized head coil T1 (500 ms repetition time (TR), 14 ms echo time (TE)), and T2 (2002 ms TR, 90 ms TE) sequence-weighted images, diffusion-weighted imaging (DWI) sequences (10,000 ms TR; TE 109 ms; 5 mm thickness; 96×96 matrix) and fluid-attenuated inversion recovery (FLAIR) sequences (8002 ms TR, 104 ms TE, 2000 ms T1, 6.0 mm thickness, 1.0 mm gap, 256×192 matrix) were acquired. Because of the aim of the study, cMRI was considered abnormal if one or more white matter T2-hyperintense small (<10 mm) punctate lesions located in the subcortical and/or in the periventricular regions (WMHL) and/or if one or more T2-hyperintense small (<10 mm) punctate lesions located in the gray matter of the cortex or basal ganglia (GMHLs) were observed. Cortical atrophy, defined as an area of brain parenchyma characterized by volume loss and major infarcts (>10 mm), were also taken into account.

Results

A total of 23 patients, 22 female (F) and one male (M), were enrolled, 16 with and seven without history of neurological involvement. The patients were comparable for age (average 42.2 years; range 32–50), disease duration (average 98 months; range 43–220), and disease activity (average SLEDAI-2000 score 3.5; range 0–8). Comorbidities and thrombophilic state are shown in Table 1.

NP history, TCD evaluation and cMRI

All patients were jointly examined by the same team composed of two rheumatologists (MP, AB) and two neurologists (CA, ADV). Based on their history, clinical picture and neurologic examination, 16 patients (69.6%) were classified as NPSLE and seven patients (30.4%) as without NP involvement (SLE). Among patients with NP involvement, this complication has been reported after 37 months (range 0–52 months) from SLE onset. A single NP event was recorded in four cases and multiple events in the remaining 12 cases, for a total of 30 NP events, seven focal (four cerebrovascular accident, two seizures, one demyelinating syndrome) and 23 diffuse (10 headache, five mood disorder, five cognitive dysfunction, two psychosis, one acute confused state). No patient had ongoing or overt acute NP manifestations at the time of TCD examination (average 57 months after the onset of the NP event, range 11–98).

Table 1 List of comorbidities and thrombophilic state of our NPSLE and SLE patients

	NPSLE (no. of patients)	*SLE (no. of patients)*
	16	7
Comorbidities		
Hypertension	2	2
Dyslipidemia	1	1
Carotid atherosclerosis	1	–
Valvular heart disease[a]	1	–
Smoking	1	1
Thrombophilic antibodies		
aPL	4	–
LA	1	–
aPL and LA	2	2

[a]Including mitral valve prolapse.
NPSLE: systemic lupus erythematosus with neuropsychiatric involvement; SLE: systemic lupus erythematosus; aPL: antiphospholipid antibodies; LA: Lupus anticoagulant.

All 23 patients underwent cMRI. Single or multiple WMHLs were found in 15 patients (65.2%). The WMHLs ranged in size from 3 mm to 10 mm. WMHLs occurred exclusively in supratentorial areas. When multiple and bilateral, WMHLs were asymmetrically distributed mainly in subcortical and periventricular regions. Local atrophy of the cortex, consisting of gyral atrophy and widening of sulci, was seen in two patients; no abnormalities in DWI, GM lesions or major infarcts were detected.

Two out of seven (28.5%) SLE patients and 13 out of 16 (81.2%) NPSLE patients had an abnormal cMRI with one or more detectable small WMHLs, mostly point shaped.

All patients underwent TCD and the presence of MES was documented in 12 (52.1%), of whom 11 were NPSLE (68.7%) and one was SLE (Table 2). When neuroimaging data were matched with TCD ultrasound, MES were detected in nine out of 13 NPSLE-WHML-positive (69.2%) individuals and in only one NPSLE case with normal cMRI. Among the seven patients without NP events, the combined evaluation by cMRI and TCD showed the presence of WHMLs and MES + in one case (Table 2).

Prevalence of MES and PFO

MES were detected in a total of 12 patients (52.1%). In three patients there were mild MES

Table 2 Correlation between the presence of MES, PFO and WMHL in NPSLE and SLE patients

Type first NP event	*NPSLE[a] no. of pts (%) 16*	*SLE no of pts (%) 7*	p *value*
TCD evaluation			
MES +	11/16 (68.7)	1/7 (14.2)	0.027
TTE evaluation			
PFO +	11/16 (68.7)	1/7 (14.2)	0.027
cMRI			
WMHL +	13/16 (81.2)	2/7 (28.5)	
WMHL + MES +	9/16 (56.2)	1/7 (14.2)	Ns
WMHL + MES −	4/16 (25)	1/7 (14.2)	Ns
WMHL − MES +	1/16 (6.25)	0 (0)	Ns
WMHL − MES −	2/16 (12.5)	5/7 (71.4)	Ns

[a]Fifteen diffuse, one focal.
TCD: transcranic Doppler ultrasound; MES: microembolic signals; PFO: patent foramen ovale; cMRI: conventional magnetic resonance imaging; WMHL: white matter T2-hyperintense small punctuate lesions; NPSLE: systemic lupus erythematosus with neuropsychiatric involvement; SLE: systemic lupus erythematosus.

(1–10 MB), in three cases moderate MES (>10 MB) and in the remaining six cases a curtain (severe MES). No significant correlation was found between MES intensity and severity of MRI findings, expressed as size and number of WMHLs (data not shown). Noticeably, all patients with MES had a PFO documented by a TEE. No correlation between MES and aPL or LA status was found, and no significant correlations were documented among the distribution of comorbidity, neuroimaging or TCD abnormalities.

Discussion

The aim of our study was to assess the occurrence of MES detected by TCD in a select group of SLE patients, age less than 50 years, with and without NP involvement, consecutively seen at our clinic, extensively evaluated in terms of cardiovascular profile. Compared with the general population, in SLE patients MES were found in similar proportion, with an estimated prevalence of 14.9% (range 9%–23%) irrespective of their previous history of NP involvement or aPL status.[8] On the contrary, MES was clearly demonstrated to be more frequent in patients with MRI abnormalities compared with patients with normal MRI, and multiple acute infarcts, especially those that are bilateral and affect various networks of cerebral circulation, are strong indicators of a proximal embolic source or a systemic cause.[9] The origin of MES in SLE is still a debated issue. No clear association with carotid plaques or heart-valve disease has been demonstrated. Pooled data coming from three studies in SLE patients, assessing carotid lesions from small plaques to high-degree stenosis, have not shown significant differences between patients with positive and negative MES,[9,10] although an increased frequency of mitral valve prolapse and artificial valves has been observed in SLE patients with MES. Some of these studies speculated that the source of the microemboli could be cardiac, but confirmatory data by TTE or TEE are lacking.

In the global approach to cerebral microembolism in SLE, we have taken into account that TCD is an important screening method for the diagnosis of PFO, a cardiovascular risk factor missed or overlooked in previous studies and that has been implicated in the pathogenesis of several detrimental conditions such as stroke, migraine and cognitive dysfunction.[11,12] The correlation between NP disorders and TCD abnormalities has been frequently reported, and the published European League Against Rheumatism (EULAR) recommendations for the management of SLE with NP manifestations suggest including TCD in the diagnostic workup of SLE patients who present with NP signs or symptoms, especially in the presence of cerebrovascular clinical pictures.[13]

Moreover, the observation of increased number of MES could support the hypothesis that multiple small or large emboli may be a missed cause of cognitive dysfunction or other diffuse NP syndromes commonly found in SLE that could have their counterpart in WMHL on cMRI.[9,12] As MES, also WMHL are observed in a considerable proportion of patients with SLE and a vascular origin have been proposed. WMHL are a common incidental finding also in asymptomatic healthy individuals with a 10-fold increase in prevalence in those older than 55 years.[5,12] Therefore, we chose to analyze a younger population (younger than 50 years) to overcome a potential bias.

With this restriction and similar to previous studies, we characterized our patients considering the prevalence of common cardiovascular risk factors to investigate if these would affect the occurrence of MES. However, in our patients, we did not find any significant correlation between MES and comorbidities, nor with aPL status, since the distribution of these conditions was similar between those patients who had MES and those who did not. We also characterized patients according to the presence of NP involvement. In our series TCD abnormalities were associated with a history of NP disorders, especially diffuse manifestations. This finding is consistent with previous reports.[8,9,14]

In the study by Cantú Brito et al., cognitive involvement was statistically more frequent in patients with positive MES with a statistical significant trend both in stroke and seizures. Dahl et al. found an association between positive MES and cognitive impairment in SLE patients.[10] Other studies have shown that SLE patients with positive MES were more frequently associated with a history of stroke.[8] An interesting result of the present study is that in 56.2% (9/16) of the patients with NP events, the combined presence of MRI abnormalities and MES had been found, while only one patient (14.2%) among SLE patients, without NP involvement, had a similar pattern of combined MES and MRI involvement.

Our study also confirmed what had already been demonstrated in previous reports[5] about the observation that in SLE the TCD can be considered a sensitive imaging modality to detect right-to-left shunt and to establish the diagnosis of PFO.[15] Indeed, all patients with MES had a PFO demonstrated by TEE. To the best of our knowledge, for the first time, we observed an association among PFO, WHML and NP involvement (especially diffuse).

In keeping with these results, mild, minor and indolent NP manifestations, with a slow and insidious onset, so frequently observed in SLE patients, especially when observed in the context of a non-active disease, can indicate a similar pathogenic mechanism.

Furthermore, if we consider that the probability of finding positive MES (and consequently a PFO) increases in the presence of an abnormal MRI, and that an abnormal MRI is a frequent and not specific finding in SLE patients, in our opinion it should be advised that all SLE patients, especially if they are young people with abnormal MRI (i.e. WHMLs), should be investigated for MES by TCD (and eventually for PFO too), this information being relevant not only in terms of interpretation of neuroimaging findings (i.e. UBO) and for correct attribution of antecedent, current or future NP events, but also in view of a more appropriate therapeutic approach, when other risk factors are lacking or ruled out.

There are some limitations to our study. The first one is represented by the small sample examined. The second one is that the distribution of different patterns (diffuse and focal) of NP involvement was not balanced and therefore any conclusion about correlations with instrumental findings should be considered with caution. In summary, MES—which can be related to PFO—are a frequent finding in SLE patients and its frequency has increased in patients with MRI abnormalities (i.e. WMHLs or UBO) and history of NP events.

These findings suggest caution in the interpretation of cMRI pictures (so-called UBO) in SLE patients and reinforce the determination that a careful evaluation of MES by TCD, and a possible PFO in patients with MRI abnormalities, with or without NP symptoms, should be part of the routine workup. If confirmed in larger prospective longitudinal studies, the detection of MES using noninvasive transcranial Doppler could aid clinicians in identifying a subset of lupus patients with PFO at risk for WHML appearance.

Declaration of Conflicting Interests

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