Echocardiographic features in antiphospholipid-negative Sneddon's syndrome and potential association with severity of neurological symptoms or recurrence of strokes: a longitudinal cohort study

Florence Assan, Dominique de Zuttere, Laure Bottin, Sebastian Tavolaro, Delphine S Courvoisier, Annick Barbaud, Sonia Alamowitch, Camille Francès, François Chasset

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Florence Assan, MD[1*], Dominique de Zuttere, MD[2*], Laure Bottin, MD[3], Sebastian Tavolaro, MD[4], Delphine S. Courvoisier, PhD[5], Annick Barbaud, MD, PhD[1], Sonia Alamowitch, MD[3], Camille Francès, MD[1], François Chasset, MD[1]

[1]Sorbonne Université, Faculté de Médecine Sorbonne Université, AP-HP, Service de Dermatologie et Allergologie, Hôpital Tenon, F-75020 Paris, France

[2]Service d'Explorations Fonctionnelles, Hôpital Franco-Britannique, Levallois-Perret, France

[3]Sorbonne Université, Faculté de Médecine Sorbonne Université, AP-HP, Service de Neurologie, Hôpital Saint-Antoine, F-75012, Paris, France

[4]Sorbonne Université, Faculté de Médecine Sorbonne Université, AP-HP, Service de Radiologie, Hôpital Tenon, F-75020, Paris, France

[5] Division of rheumatology, Department of Medicine, University of Geneva

Corresponding author & reprint requests:

François Chasset, MD, Sorbonne université, AP-HP, Service de Dermatologie et d'Allergologie, Hôpital Tenon, 4 rue de la Chine 75970 Paris CEDEX 20, France

Phone number: (+33156 01 75 47). Fax number: (+331 56 01 72 32)

Email: francois.chasset@gmail.com

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* contributed equally to the work and shared the first authorship

Introduction

Sneddon's syndrome (SS) is a rare non-inflammatory thrombotic vasculopathy characterized by the association of cerebrovascular thrombosis with livedo racemosa (LR) ([1]). SS has been described mostly in women between age 20 and 40 years ([1]), and its estimated incidence is about 4 per 1 million per year in the general population ([2]). SS can be classified in two subgroups: with antiphospholipid antibodies (aPL) (aPL^+ SS) and without aPL (aPL^- SS). Indeed, in about 50% of cases (0 to 85% depending on the series), SS is associated with aPL ([2,3]) and thus could be classified as antiphospholipid syndrome (APS) ([4–9]).

Heart valve disease (HVD) is frequently observed in both SS with and without aPL ([10,11]). Indeed, Francès et al. ([10]) found HVD or valve thickening in both aPL^+ and aPL^- SS patients, in more than 50% of cases. Of note, in aPL^+ patients (both systemic lupus erythematosus (SLE) and primary APS patients), an increased risk of stroke, transient ischemic attack (TIA) or neurocognitive dysfunction have been reported in patients with HVD, particularly those with Libman-Sacks (LS) endocarditis ([12–16]). A high prevalence of LS endocarditis (25%) has also been reported in a sample of 40 aPL^- SS patients ([17]), though there was no association between LS and the pattern of strokes (middle-size arteries, superficial perforating arteries, and deep perforating arteries). However, this study did not assess specifically the role of cardiac involvement in aPL^- SS, particularly the impact of LS endocarditis on the type and/or severity of neurological involvement. Moreover, the risk of recurrence of neurovascular events or the need to modify SS treatment in light of LS endocarditis development during-follow-up has not been assessed.

To address these questions, we analyzed echocardiographic data of a longitudinal cohort of aPL– SS patients with long-term follow-up. Specifically, we aimed to 1) describe the cardiac involvement of aPL^- SS patients, 2) assess the impact of LS endocarditis at baseline on the type and severity of neurological involvement, 3) describe the prevalence and type of cardiac

complications during long-term follow-up, and 4) assess the impact of LS endocarditis development during follow-up on risk of neurological relapse.

Patients and methods

Study design and setting

We analyzed echocardiographic data of a longitudinal cohort of aPL– SS patients followed in neurology and dermatology departments of French university hospitals between January 1991 and June 2018.

Participants and eligibility criteria

Patients were included if they were followed for aPL⁻ SS; did not have anticardiolipin antibodies, anti-beta2 glycoprotein 1 antibodies or lupus anticoagulant detected at a significant rate confirmed on at least 2 occasions and echocardiography at baseline.

Diagnosis of SS was based on the association of permanent LR (assessed by one expert senior dermatologist) and at least one stroke (cerebral infarct [CI], TIA, or a silent infarct, only visible as sequelae on brain imaging). Patients included in the previous study from our group describing strokes pattern were included if they had echocardiography at baseline ([17]). All patients had baseline transthoracic echocardiographic data, patients with unclear diagnosis (n=3), for example suspicion of infectious cause of endocarditis, were excluded.

Data collection and definitions

Clinical data collected were cardiovascular risk factors, clinical manifestations including first clinical manifestations and neurological manifestations, and first-line treatment for SS. Neurological relapse defined by a recurrence of CI, TIA or silent infarct were systematically assessed clinically and by brain imaging data during annual follow-up or in case of suggestive clinical symptoms.

Biological data collected were hemoglobin A1C, total cholesterol and triglycerides levels;

antinuclear antibodies and anti-native DNA antibodies by ELISA and Crithidia luciliae immunofluorescence; C3, C4 and CH50 activity; homocysteine level. aPL were tested annually during follow-up and negativity was defined according to 2006 Sydney criteria ([8]). Diagnosis of systemic lupus erythematosus (SLE) associated with SS was made according to the 2012 Systemic Lupus International Collaborating Clinics classification. ([18]) The reasons for antithrombotic treatment modifications during follow-up were assessed with focus on the potential association between the occurrence of LS endocarditis during follow-up and treatment escalation (switch from low-dose aspirin to vitamin-K antagonists).

Brain imaging data (MRI or CT) collected at diagnosis and during follow-up were reviewed, and neurological definitions were based on 2013 American Heart Association/American Stroke Association expert consensus ([19]). Silent infarction was defined by an imaging or neuropathological evidence of central nervous system infarction, without a history of acute neurological dysfunction attributable to the lesion. Hemorrhagic stroke was defined by a focal collection of chronic blood products within the brain parenchyma, subarachnoid space, or ventricular system on neuroimaging or neuropathological examination that was not caused by trauma. Carotid stenosis was evaluated either by carotid ultrasound or by aortic magnetic resonance imaging.

Echocardiography

All patients underwent comprehensive echocardiography including standard transthoracic 2-D and Doppler echocardiography studies by the same senior cardiologist (DZ) at diagnosis and during follow-up annually when available. Speckle-tracking echocardiography was also systematically used from the moment this technique became available in our laboratory (2007). Echocardiography assessments were performed using Vivid 7 and Vivid e9 ultrasound machines with M3s, M5sc-D and 4V-D probes (GE Healthcare, Milwaukee, WI), in accordance with the American Society of Echocardiography successive guidelines ([20,21]). Left ventricular

(LV) internal dimensions and wall thickness, chamber volumes, and valvular morphology were assessed. LS vegetations were identified as described by Roldan et al. ([16]), as abnormal localized, protruding, and sessile echodensities >3 mm in diameter with well-defined borders as part of or adjacent to valve leaflets, annulus, subvalvular apparatus, or endocardial surfaces. LV ejection fraction (LVEF) was measured by the modified Teichholz method. Left atrial (LA) volume was calculated by the biplane method of disks and indexed to body surface area (BSA); left atrial volume index >34 ml/m^2 was used to define left atrial enlargement (LAE) ([20]). LV mass index (LVMi) was obtained from M-mode LV mass measurement with standard criteria and normalized for BSA ([20]). LV enlargement (LVE) was defined as end-diastolic diameter >56 mm (linear M-mode measurement) ([22]). LV hypertrophy (LVH) was defined as LVMi/BSA >115 g/m^2 for men and >95 g/m^2 for women. LV inflow was obtained by pulsed wave Doppler in the apical 4-chamber view; peak early (E) and late (A) diastolic velocities, deceleration time, and E/A ratio were obtained. Peak early diastolic medial and lateral mitral annular velocity (e^0) and ratio of mitral-inflow early diastolic velocity to average e' velocity were obtained from pulsed tissue Doppler; E/e' >13 was used as a cutoff of diastolic dysfunction (DD) ([21]). For deformation imaging, standard grayscale 2-D images were acquired in conventional 4-, 2-, and 3-chamber view. Global longitudinal strain (GLS) was calculated by the average of 3 apical views with standard software ([22, 23]). Cutoffs of -16% for abnormal GLS were used ([24]). Stage B heart failure (SBHF) was defined by 1) DD (E/e' >13), 2) LAE (>34 ml/m^2), 3) LVH (>115 g/m^2 for men, >95 g/m^2 for women), and 4) impaired GLS (cutoff -16%) ([24]). Pulmonary artery systolic pressure was calculated by adding an estimate of right atrial pressure (using inferior vena cava size and response to respiration) to the RV-RA gradient calculated using peak tricuspid regurgitation velocity. According to standard methods ([25]), aortic insufficiency was considered moderate to severe when two or more of the following semi-quantitative and quantitative criteria were present: vena contracta width ≥ 3 mm, pressure half-time ≤ 500 ms,

effective regurgitant orifice ≥ 10 mm^2, and regurgitant volume ≥ 30 mL. Other factors supporting lesion severity included the duration and eccentricity of the regurgitant jet. The final determination of severity by the interpreting cardiologist incorporated all aspects of the imaging and Doppler echocardiography study. The severity of aortic stenosis (AS) was evaluated according to standard methods ([26]). Peak aortic jet velocity was derived from transaortic flow, recorded with continuous wave Doppler using a multiwindow approach. Peak and mean gradients were calculated by using the simplified Bernoulli equation. The continuity equation was used to calculate aortic valve area (AVA). Moderate and severe AS were defined as AVA 1.0 to 1.5 cm^2 and < 1.0 cm^2, respectively. Mitral valve prolapse (MVP) was defined as superior displacement 2 mm of any part of the mitral leaflet beyond the mitral annulus according to the American Society of Echocardiography guidelines ([26]). According to standard methods ([25]), mitral regurgitation was considered moderate to severe with presence of two or more of the following semi-quantitative and quantitative criteria: vena contracta width ≥ 3 mm, effective regurgitant orifice ≥ 20 mm^2, regurgitant volume ≥ 30 mL. The conventional indices for assessment of the severity of mitral stenosis, such as mitral valve area (MVA) by planimetry and pressure half-time and the maximum and mean mitral valve pressure gradients, were measured as recommended ([27]).

Statistical analysis

Data are presented as median (range) or number (%). We used chi-square or Fisher's exact test (as appropriate) and Mann-Whitney test to compare categorical and unpaired non-normally distributed quantitative data, respectively. Two-tailed $P < 0.05$ was considered statistically significant. Kaplan-Meier survival curves were used to assess the risk of neurological relapses, considering the time from first transthoracic echocardiography or occurrence of LS endocarditis to last follow-up for censored individuals or to the occurrence of new stroke or TIA. Hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated by Cox regression and survival

curves were compared by the log-rank test. Analyses were performed with JMP v13 (SAS Inst. Inc., Cary, NC)

Results

Patient characteristics

We included 61 patients (52 women, median age at diagnosis 45 [range 24-60]). Demographic and disease characteristics of included patients are summarized in **Table 1**. Full data including individual clinical features, LS endocarditis status and treatment received of aPL- Sneddon, as well as presence of relapse are provided as **supplemental data**. CI and TIA were the most frequent initial clinical manifestations (n=48, 78.7%). The most common thrombotic neurological events were CI only (n=40, 65.6%), TIA only (n=8, 13%) and CI+TIA (n=8, 13%). Other neurological symptoms included migraine (n=22, 36%), epilepsy (n=13, 21%) and cognitive impairment (n=23, 44%). For cardiovascular risk factors, 34 (55.7%) patients had high blood pressure, 30 (49%) had BMI > 25 kg/m^2 and 35 (57.4%) previously or currently smoked tobacco. Only three patients presented a ≥ 50% carotid stenosis, and two patients with a < 50% carotid stenosis inferior. Only one patient fulfilled criteria for SLE. Most patients received low-dose aspirin as first-line treatment to prevent thrombotic neurological events (n=44, 72%).

Cardiac findings at baseline (Table 2)

For valvular involvement, 36 (59%) patients showed leaflet thickening, including isolated mitral valve thickening (n=16, 26%), isolated aortic valve thickening (n=14, 23%) and both mitral and aortic thickening (n=6, 10%). In total, 18 (29.5%) patients showed LS endocarditis (**Figure 1**) at baseline, including mitral LS endocarditis in 11 (18%) and aortic LS endocarditis in 9 (14.75%). Median thickness of mitral and aortic LS endocarditis was 5 mm (range 3.7–7.0) and 4 mm (range 3.0–5.3), respectively. Moreover, 25 (40.9%) patients showed aortic regurgitation (**Figure 1-D**), including 4 (6.6%) with moderate to severe aortic regurgitation.

Overall, 45 (73.8%) patients showed mitral regurgitation (**Figure 1-I**), with moderate to severe mitral regurgitation in 3 (4.9%). For LV parameters, median EF at baseline was 69% (range 52–86%); only 1 (2%) patient had EF < 53%. Relaxation impairment was the most frequent LV abnormality, observed in 24 (39%) patients, and median peak longitudinal strain was -20.95 (range -26.2 – -14.2); 1 (1.7%) patients had initial peak longitudinal strain > -16%. For SBHF criteria, 47 (80%) patients had at least one criterion, but none fulfilled all four criteria ([24]). Median systolic pulmonary arterial pressure was 26.5 mmHg (range 18–42); 3 (4.9%) patients had systolic pulmonary arterial pressure > 35 mmHg.

Comparison of demographic, clinical, biological and radiological features with and without LS endocarditis at baseline (Table 3)

Patients with and without LS endocarditis at baseline did not differ in socio-demographic or neurological features, including number of CI and TIA events at baseline or prevalence of migraine, epilepsy and cognitive impairment. At baseline, the number of TIA events was marginally greater among patients with versus without LS endocarditis: median 2 (range 1–6) versus 1 (1–2) p=0.06.

The frequency of Raynaud phenomenon was higher with than without LS endocarditis at baseline [13 (72%) vs 16 (37%), p=0.01]. LS endocarditis was marginally associated with prevalence of antinuclear antibodies [≥1/160: 8 (46%) vs 10 (24%), p=0.079]. No significant differences for baseline characteristics were observed between patients with and without echocardiographic data (data not shown).

To note, SLE patient did not have LS endocarditis at baseline and was lost to follow-up.

Transthoracic echocardiography follow-up data and occurrence of new LS (Table 4)

During follow-up, 46 (75.4%) patients underwent transthoracic echocardiography at least once (14 lost to follow-up, one death). Median follow-up between the first and last transthoracic echocardiography was 72 months (range 12–252). Among the 46 patients, LS endocarditis developed in 8 (17.4%) during follow-up, and 26 (42.6%) had LS endocarditis at the last echocardiography. After 5 years of follow-up, 3 (6%) had a new LS and the median follow-up between baseline and the occurrence of LS endocarditis was 8 years (range 1–16). In total, 13 (28.3%) patients showed significant worsening of cardiac status after a median follow-up of 13 years (range 1–16); worsening of valvular lesions was most frequently observed. Three patients needed surgery: two valvular replacements (mitral and aortic respectively) and one ascending aortic aneurysm operation. None of these patients had LS endocarditis. Among 33 patients without LS endocarditis at baseline, neurological, cardiovascular and radiological features did not differ between those with and without LS endocarditis during follow-up (**Table 5)**. Of note, no patient showing LS endocarditis during follow-up had a modification of the antithrombotic treatment because of LS endocarditis.

Risk of neurological relapse by LS endocarditis status

Risk of neurological relapse during follow-up was not associated with presence of LS endocarditis at baseline (HR: 1.20 [95% CI: 0.35 to 4.01] p=0.90) (**Figure 2A)**. Moreover, among patients without LS endocarditis at baseline, risk of neurological relapse was not associated with incidence of LS endocarditis during follow-up (HR: 0.38 [95% CI: 0.09 to 1.60], p=0.19) **(Figure 2B)**.

After adjusting for antithrombotic treatment regimen (low-dose aspirin versus other treatments), similar results were observed (HR: 1.06 [95% CI: 0.33 to 4.74] p=0.92) for LS endocarditis at baseline and (HR: 0.38 [95% CI: 0.02 to 1.89], p=0.31) for LS endocarditis occurring during follow-up.

Among the 18 patients with LS endocarditis at baseline, 3 (17%) had neurological relapse compared with 11 (26%) in patients without LS endocarditis at baseline (Odds ratio (OR): 0.62 [IC 95% 0.15 to 2.58], p=0.50). Moreover, among the 8 patients who developed LS endocarditis during follow-up 1 (12.50%) had relapse versus 8 (32%) in patients who did not develop LS endocarditis (OR: 0.30 [IC 95% 0.03-2.90], p=0.25)

Discussion

In this study, we describe the echocardiographic features of cardiac involvement in aPL⁻SS patients, with a long-term follow-up up to 27 years. We found a high prevalence of cardiac involvement, including HVD, LV diastolic dysfunction, left atrium dilatation or increased systolic pulmonary arterial pressure. HVD was the most frequent cardiac involvement, with a high frequency of valvular thickening and regurgitation: 32.8% and 40.9% for the aortic valve and 36.0% and 73.8% for the mitral valve, respectively.

The most common non-valvular alterations were LV relaxation impairment and left atrium dilatation, with a prevalence of 39.0% for both. Although other causes of LV relaxation impairment cannot be excluded (such as endomyocardial fibrosis), this finding is consistent with a study focusing on echocardiography assessment of LV diastolic function in primary APS[29].

During follow-up, 13 (28.3%) patients showed significant cardiac worsening other than LS endocarditis, including 2 (4%) who required cardiac surgery for valvular replacement, which is notable. This result is equivalent to that reported in a meta-analysis ([29]), finding that 3% of APS

patients underwent valve replacement. Importantly, valvular replacement by mechanical prosthesis or bioprosthesis has been widely described APS with or without SLE ([30-35]) but never in aPL- SS. One patient underwent ascending aortic aneurysm surgery, even if the association between SS and aortic aneurysm occurrence is unclear. Moreover, patients presenting significant cardiac complications in our cohort had longer follow-up, which suggests that regular and long-term cardiac follow-up is needed to detect complications, especially since valvular degeneration may have a long period of being silent ([36]).

We observed a high prevalence of LS endocarditis in aPL$^-$ SS patients. Indeed, we found LS endocarditis in 18 (29.5%) patients at baseline. These results suggest that the prevalence of LS endocarditis in aPL$^-$ SS may be higher than that reported in aPL$^+$ SS, ranging from 6 to 10% in several cohort studies including APS and/or SLE patients ([12-14]), to 23% in a meta-analysis including aPL+ SLE patients ([37]).

The occurrence of LS endocarditis during follow-up was not uncommon in our series n=8 (17.4%). Neither the presence of LS endocarditis at baseline nor the development of new LS during follow-up was associated with any clinical features or disease severity at baseline or neurological relapse during follow-up. These results contrast with those observed in aPL$^+$ SS. Indeed, in a study assessing the association between ischemic cerebrovascular events and HVD in patients presenting SLE, cerebrovascular events were associated with aPL positivity/APS, and left-sided HVD ([38]). Consistent with these results, four other studies found a significant association between valvular involvement including LS endocarditis and cerebrovascular events in APS patients with or without SLE ([13,15,39,40]) with HR ranging from 3.88 ([13]) to 5.6 ([15]). No study has assessed the risk of neurological relapse with LS development during follow-up in APS patients. We did not observe any change in the neurological outcomes in patients with the occurrence of LS endocarditis during follow-up suggesting that a new LS endocarditis seemed not to increase the risk of neurological relapse in aPL$^-$ SS patients. This result is in

accordance with recent pathological autopsy findings showing that strokes are caused by "*in-situ*" vasculopathy of cerebral arteries rather than an embolic etiology associated with LS endocarditis ([11]).

However, the main limitation of this study is the relatively low number of included patients as well as the low number of neurological relapses. Therefore, the absence of difference observed may be related to the small sample size. Indeed, to detect as significant a HR of 4 (respectively 3), in line with estimated association in APS ([13, 15]), with a risk alpha of 5% and a power of 80% would require 50 (respectively 67) aPL-SS patients including 13 (respectively 17) with new LS endocarditis. Interestingly, in this study, the risk of neurological relapse was lower in the population of patients with new LS (HR=0.38), and the higher boundary of the HR confidence interval (1.89) was lower than all HR found between LS and cerebrovascular events in APS, which may be a signal that this association is different in aPL- SS disease. Moreover, aPL- SS is a rare disease and this is the first study assessing the relationship between occurrence of LS endocarditis and neurological relapses with a long-term follow-up. In order to improve knowledge on this potential association, individual data of our patients are provided in a supplemental file and may be used for individual meta-analysis. Moreover, the age of patients may have affected results, particularly for patients in whom LS endocarditis developed during follow-up. Indeed, after age 50 years, it may be difficult to differentiate degenerative abnormalities and calcifications from LS endocarditis. Indeed, in patients in whom LS endocarditis developed during follow-up, the median age was 53.9 (range 39–66.9) including 2 patients who were > 60 years old. Therefore, the prevalence of LS may have been overestimated. However, we used the validated criteria from Roldan et al. ([16]) and doubtful cases were excluded. Finally, the shorter follow-up duration between LS+ compared with LS- endocarditis at baseline (147.2 months [12.4-386.7] vs 55.5 [3.6-221.5], p=0.004) may have impacted our results. However, no specific reasons were identified to explain this difference.

In particular, only one death occurred in the LS+ endocarditis group. Moreover, in the new LS+ group similar follow-up duration was noted compared with no new LS endocarditis (177.4 months [63.8-239.4] vs. 147.2 [12.4-386.7], p=0.9). A strength of this study is the stability of antithrombotic treatment, thus avoiding time-varying confounding effect. Indeed, the modification of antithrombotic treatment because of the occurrence of a new LS endocarditis would have been an important confounding factor. However, in our cohort, treatment was never modified by the occurrence of LS endocarditis during follow-up. In particular, low-dose aspirin was not changed to a vitamin-K antagonist in these patients. From the available data regarding aPL^+ SS, a switch to a vitamin-K antagonist may have been discussed. Indeed, the preventive treatment of ischemic stroke or TIA in patients meeting the criteria for APS is based on long-term vitamin-K antagonist therapy ([40]). In addition, although no study has specifically assessed the risk of stroke in aPL^+ SS with LS occurring during follow-up, as discussed earlier, the risk of stroke seems increased in aPL^+ SS with LS endocarditis ([13,38,39,41]). There is no current recommendation for the treatment of aPL^- SS. In the study of Francès et al., the number of cerebrovascular events per year did not differ in aPL^- SS patients with low-dose aspirin or vitamin-K antagonist treatment. Thus, although no conclusion can be drawn based on our limited sample size, our data raise the hypothesis that LS endocarditis occurrence during follow-up should not lead to antithrombotic treatment escalation.

Conclusion

Cardiac involvement is frequent in aPL^- SS. Long-term follow-up is needed to detect complications after several years. No change in neurological relapse was observed in patients presenting LS endocarditis occurrence during follow-up without any modification in antithrombotic treatment. Further research is necessary to assess the usefulness of treatment escalation in these patients.

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Authors contributions

- Research design: SA, CF, FC
- Data acquisition: FA, DZ, LB, CF, FC
- Data analysis/interpretation: FA, DZ, ST, AB, FC, DC
- Manuscript preparation: FA
- Final approval: FA, DZ, LB, ST, AB, SA, CF, FC, DC

References

1. Sneddon, I. B. CEREBRO-VASCULAR LESIONS AND LIVEDO RETICULARIS. *Br. J. Dermatol.* 1965; **77**: 180–185
2. Zelger, B. Sepp N, Stockhammer G, Dosch E, Hilty E, Ofner D, *et al*. Sneddon's syndrome. A long-term follow-up of 21 patients. *Arch Dermatol* 1993; **129**: 437–447
3. Wu, S., Xu, Z. & Liang, H. Sneddon's syndrome: a comprehensive review of the literature. *Orphanet J Rare Dis* 2014; **9**: 215
4. Kalashnikova LA, Nasonov EL, Borisenko VV, Usman VB, Prudnikova LZ, Kovaljov VU, *et al*. Sneddon's syndrome: cardiac pathology and antiphospholipid antibodies. *Clin. Exp. Rheumatol.* 1991; **9**: 357–361

5. Levine, S. R., Langer, S. L., Albers, J. W. & Welch, K. M. Sneddon's syndrome: an antiphospholipid antibody syndrome? *Neurology* 1988; **38**: 798–800
6. Asherson, R. A. & Cervera, R. Unusual manifestations of the antiphospholipid syndrome. *Clin Rev Allergy Immunol* 2003; **25**: 61–78
7. Sanna, G., D'Cruz, D. & Cuadrado, M. J. Cerebral manifestations in the antiphospholipid (Hughes) syndrome. *Rheum. Dis. Clin. North Am.* 2006; **32**: 465–490
8. Miyakis S, Lockshin MD, Atsumi T, Branch DW, Brey RL, Cervera R, *et al*. International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (APS). *J Thromb Haemost*. 2006; **2**: 295-306
9. Schellong, SM, Weissenborn K, Niedermeyer J, Wollenhaupt J, Sosada M, Ehrenheim C, Lubach D. Classification of Sneddon's syndrome. *VASA* 1997; **26**: 215–221
10. Francès C, Papo T, Wechsler B, Laporte JL, Biousse V, Piette JC Sneddon syndrome with or without antiphospholipid antibodies. A comparative study in 46 patients. *Medicine (Baltimore)* 1999; **78**: 209–219
11. Berciano J, Terán-Villagrá N. . J Neurol. sept 2018;265(9):2143-5.
12. Krause I, Lev S, Fraser A, Blank M, Lorber M, Stojanovich L, *et al*. Close association between valvar heart disease and central nervous system manifestations in the antiphospholipid syndrome. *Ann. Rheum. Dis.* 2005; **64**: 1490–1493
13. Moyssakis I, Tektonidou MG, Vasilliou VA, Samarkos M, Votteas V, Moutsopoulos HM. Libman-Sacks endocarditis in systemic lupus erythematosus: prevalence, associations, and evolution. *Am. J. Med.* 2007; **120**: 636–642 (2007).
14. Roldan, C. A., Shively, B. K. & Crawford, M. H. An echocardiographic study of valvular heart disease associated with systemic lupus erythematosus. *N. Engl. J. Med.* 1996; **335**: 1424–1430

15. Roldan CA, Sibbitt WL Jr, Qualls CR, Jung RE, Greene ER, Gasparovic CM, *et al.* Libman-Sacks endocarditis and embolic cerebrovascular disease. *JACC Cardiovasc Imaging* 2013; **6**: 973–983

16. Roldan CA, Tolstrup K, Macias L, Qualls CR, Maynard D, Charlton G, *et al*. Libman-Sacks Endocarditis: Detection, Characterization, and Clinical Correlates by Three-Dimensional Transesophageal Echocardiography. *J Am Soc Echocardiogr* 2015; **28**: 770–779

17. Bottin L., Francès C, de Zuttere D, Boëlle PY, Muresan IP, Alamowitch S., Strokes in Sneddon syndrome without antiphospholipid antibodies. *Ann. Neurol.* 2015; **77**: 817–829

18. Petri M, Orbai A-M, Alarcón GS, Gordon C, Merrill JT, Fortin PR, et al. Derivation and validation of the Systemic Lupus International Collaborating Clinics classification criteria for systemic lupus erythematosus. Arthritis Rheum. août 2012;64(8):2677-86.

19. Sacco RL, Kasner SE, Broderick JP, Caplan LR, Connors JJ, Culebras A, *et al*. An updated definition of stroke for the 21st century: a statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 2013; **44**: 2064–2089

20. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr. janv 2015;28(1):1-39.e14.

21. Nagueh SF, Smiseth OA, Appleton CP, Byrd BF, Dokainish H, Edvardsen T, et al. Recommendations for the Evaluation of Left Ventricular Diastolic Function by Echocardiography: An Update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging. 2016;17(12):1321-60.

448 22. Marwick TH, Leano RL, Brown J, Sun JP, Hoffmann R, Lysyansky P, Becker M *et al.*
449 Myocardial strain measurement with 2-dimensional speckle-tracking echocardiography:
450 definition of normal range. *JACC Cardiovasc Imaging* 2009; **2**: 80–84
451 23. Yingchoncharoen, T., Agarwal, S., Popović, Z. B. & Marwick, T. H. Normal ranges of left
452 ventricular strain: a meta-analysis. *J Am Soc Echocardiogr* 2013; **26**: 185–191
453 24. Wang Y, Yang H, Huynh Q, Nolan M, Negishi K, Marwick TH. Diagnosis of Nonischemic
454 Stage B Heart Failure in Type 2 Diabetes Mellitus: Optimal Parameters for Prediction of
455 Heart Failure. *JACC Cardiovasc Imaging* 2018; **11**: 1390–1400
456 25. Lancellotti P, Tribouilloy C, Hagendorff A, Moura L, Popescu BA, Agricola E, *et al.*
457 European Association of Echocardiography recommendations for the assessment of
458 valvular regurgitation. Part 1: aortic and pulmonary regurgitation (native valve disease).
459 *Eur J Echocardiogr* 2010; **11**: 223–244
460 26. Baumgartner H, Falk V, Bax JJ, De Bonis M, Hamm C, Holm PJ, Iung B *et al.* 2017
461 ESC/EACTS Guidelines for the Management of Valvular Heart Disease. *Rev Esp Cardiol*
462 *(Engl Ed)* 2018; **71**: 110
463 27. Baumgartner H, Hung J, Bermejo J, Chambers JB, Evangelista A, Griffin BP, Iung B *et al.*
464 Echocardiographic assessment of valve stenosis: EAE/ASE recommendations for clinical
465 practice. *J Am Soc Echocardiogr* 2009; **22**: 1–23; quiz 101–102
466 28. Coudray N, de Zuttere D, Blétry O, Piette JC, Wechsler B, Godeau P, Pourny JC, *et al.* M
467 mode and Doppler echocardiographic assessment of left ventricular diastolic function in
468 primary antiphospholipid syndrome. *Br Heart J* 1995; **74**: 531–535
469 29. Nesher, G., Ilany, J., Rosenmann, D. & Abraham, A. S. Valvular dysfunction in
470 antiphospholipid syndrome: prevalence, clinical features, and treatment. *Semin. Arthritis*
471 *Rheum.* 1997; **27**: 27–35

30. Bouma W, Klinkenberg TJ, van der Horst IC, Wijdh-den Hamer IJ, Erasmus ME, Bijl M, *et al.* Mitral valve surgery for mitral regurgitation caused by Libman-Sacks endocarditis: a report of four cases and a systematic review of the literature. *J Cardiothorac Surg* 2010; **5**: 13

31. Bai, Z., Hou, J., Ren, W. & Guo, Y. Diagnosis and surgical treatment for isolated tricuspid Libman-Sacks endocarditis: a rare case report and literatures review. *J Cardiothorac Surg* 2015; **10**: 93

32. Hachiya K, Wakami K, Tani T, Yoshida A, Suzuki S, Suda H, Ohte N. Double-valve replacement for mitral and aortic regurgitation in a Patient with Libman-Sacks endocarditis. *Intern. Med.* 2014; **53**: 1769–1773

33. Samejima Y, Kodaka M, Ichikawa J, Mori T, Ando K, Nishiyama K, Komori M. Management of a Patient With Antiphospholipid Syndrome Undergoing Aortic Valve Replacement Using the Hepcon Hemostasis Management System Plus and Rotational Thromboelastometry: A Case Report. *A A Case Rep* 2017; **8**: 100–104

34. Keenan, J. B., Rajab, T. K., Janardhanan, R., Larsen, B. T. & Khalpey, Z. Aortic valve replacement for Libman-Sacks endocarditis. *BMJ Case Rep* **2016**, (2016).

35. Nakasu, A., Ishimine, T., Yasumoto, H., Tengan, T. & Mototake, H. Mitral valve replacement for Libman-Sacks endocarditis in a patient with antiphospholipid syndrome secondary to systemic lupus erythematosus. *J Surg Case Rep* **2018**; rjy069

36. Diosteanu R, Schuler G, Müller U. Cardiac valve degeneration in a patient with Sneddon syndrome. Clin Res Cardiol. juin 2015;104(6):453-5.

37. Zuily S, Regnault V, Selton-Suty C, Eschwège V, Bruntz JF, Bode-Dotto E *et al.* Increased risk for heart valve disease associated with antiphospholipid antibodies in patients with systemic lupus erythematosus: meta-analysis of echocardiographic studies. *Circulation* 2011; **124**: 215–224 (2011).

38. Morelli S, Bernardo ML, Viganego F, Sgreccia A, De Marzio P, Conti F *et al.* Left-sided heart valve abnormalities and risk of ischemic cerebrovascular accidents in patients with systemic lupus erythematosus. *Lupus* 2003; **12**: 805–812

39. Roldan, C. A., Gelgand, E. A., Qualls, C. R. & Sibbitt, W. L. Valvular heart disease as a cause of cerebrovascular disease in patients with systemic lupus erythematosus. *Am. J. Cardiol.* 2005; **95**: 1441–1447 (2005).

40. Sacco RL, Adams R, Albers G, Alberts MJ, Benavente O, Furie K *et al.* Guidelines for prevention of stroke in patients with ischemic stroke or transient ischemic attack: a statement for healthcare professionals from the American Heart Association/American Stroke Association Council on Stroke: co-sponsored by the Council on Cardiovascular Radiology and Intervention: the American Academy of Neurology affirms the value of this guideline. *Stroke* 2006; **37**: 577–617

41. Djokovic A, Stojanovich L, Stanisavljevic N, Banicevic S, Smiljanic D, Milovanovic B *et al.* Relationship between cerebrovascular and valvular manifestations in a Serbian cohort of patients with antiphospholipid syndrome. *Clin. Exp. Rheumatol.* 2018; **36**: 850–855 (2018).

Table

Table 1. Baseline characteristics of the aPL$^-$SS included patients (n=61)

Follow-up (months), median (range)	119 (3.63-386.7)
Female, n (%)	52 (85%)
Age at diagnosis (years), median(range)	45 (24-60)
Neurological manifestation, n(%) - Cerebral infarct (CI) - Transient ischemic attack (TIA) - Silent infarct - Hemorrhagic stroke (HS) - TIA+CI - TIA+CI+HS	 41 (67.2%) 8 (13.1%) 2 (3.3%) 1 (1.6%) 8 (13.1%) 1 (1.6%)
Initial clinical manifestation, n (%) - TIA/CI - Epilepsy - HS - Livedo - Neuropsychiatric - Thrombosis	 48 (78.7%) 1 (1.6%) 2 (3.3%) 6 (9.8%) 3 (4.9%) 1 (1.6%)
Other neurological symptoms/complications, n (%) - Epilepsy - Migraine - Cognitive impairment	 13 (21%) 22 (36%) 23 (44%)
Cardiovascular risk factors, n (%) - High blood pressure - BMI> 25 - Diabetes mellitus - Tobacco smoking (current or former) - Dyslipidemia	 34 (55.7%) 30 (49%) 2 (3.3%) 35 (57.4%) 23 (37.7%)
Positive antinuclear autoantibodies >1/80, n (%) Positive anti-DNA autoantibodies, n (%)	18 (30%) 1 (2%)
First-line treatment for Sneddon, (%) - Low-dose aspirin - Antiplatelet clopidogrel - Vitamin K antagonist - No antithrombotic treatment	 44 (72%) 9 (15%) 4 (6%) 4 (6%)

BMI: body mass index; NA: non available data; MTHFR: Methylenetatrahydrofolate Reductase;

Table 2. Baseline results of transthoracic echocardiography of the aPL-SS patients (n=61)

Aortic valve	
-Bicuspidia, n (%)	5 (14.7%)
-Valvular thickening, n (%)	20 (32.8%)
-Calcification, n (%)	4 (6.6%)
-Aortic stenosis, n (%)	9 (14.7%)
-Moderate to severe aortic stenosis, n (%)	2 (3.3%)
-Aortic regurgitation, n (%)	25 (40.9%)
-Moderate to severe aortic regurgitation, n (%)	4 (6.6%)
-LS, n (%)	9 (14.75%)
-LS thickness (mm), median (range)	4 (3 - 5.3)
Mitral valve	
-Valvular thickening, n (%)	22 (36%)
-Prolapse, n (%)	4 (6.6%)
-Mitral regurgitation, n (%)	45 (73.8%)
-Moderate to severe mitral regurgitation, n (%)	3 (4.9%)
-Mitral stenosis, n (%)	5 (14.7%)
-Moderate to severe mitral stenosis, n (%)	0 (0%)
-LS, n (%)	11 (18%)
-LS thickness (mm), median (range)	5 (3.7 - 7)
Left Ventricular Parameters	
-EF%, median (range)	69 (52-86)
-LVDD (mm), median (range)	48.7 (38.4-59)
-Interventricular septal wall thickness (mm), median (range)	10.4 (7.1-19.8)
-Posterior wall thickness (mm), median (range)	9 (6.7-15.4)
-LV mass (g/m2), median (range)	96.5 (63-189)
-LV mass index, median (range)	0.37 (0.27-0.57)
-LV dysfunction*, n (%)	1 (1.6%)
-LV relaxation dysfunction	24 (39%)
-LV dilatation**, n (%)	7 (11%)
-LV hypertrophy***, n (%)	26 (42%)
-Peak longitudinal strain, median (range)	-20.95 (-26.2 / -14.2)
- SBHF criteria ****	
at least one criteria, n (%)	47 (80%)
all four criteria, n (%)	0 (0%)
Left atrium dilatation *****, n (%)	16 (39%)
Left atrium volume (mm), median (range)	33.5 (25-56)
Systolic pulmonary arterial pressure (mmHg), median (range)	26.5 (18-42)
Overall LS, n (%)******	18 (29.5%)
Age at LS diagnosis (years), median (range)	46.9 (28-64)
Patients with at least one follow-up echocardiography, n(%)	46 (75.4%)

EF% : left ventricular ejection fraction, LVDD: left ventricular end diastolic diameter; *LV dysfunction defined by FE%<55%; LS: Libman–Sacks endocarditis; ** Left ventricular enlargement: end-diastolic diameter >56 mm; *** Left ventricular hypertrophy: LVMi/BSA >115 g/m^2 for men and >95 g/m^2 for women; **** Stage B heart failure, defined by by 1) DD (E/e' >13), 2) LAE (>34 ml/m^2), 3) LVH (>115 g/m^2 for men, >95 g/m^2 for women),

and 4) impaired GLS (cutoff -16%) ***** Left atrial dilatation: left atrial index >34 ml/m^2; ****** two patients had both aortic and mitral LS

Table 3. Univariate analysis between patients with or without Libman-Sacks endocarditis at Baseline (n=61)

Features	Baseline LS+ (n=18)	Baseline LS- (n=43)	p-value
Socio-demographic features			
-Female sex, n (%)	17 (94%)	35 (81%)	0.26
-Age at diagnosis, median (range)	41.5 (28-56)	46 (24-60)	0.10
-Age at livedo development, median (range)	29 (10-48)	34 (10-57)	0.13
-Age at first stroke, median (range)	40 (23-56)	55 (24-58)	0.23
Cardiovascular risk factors			
-BMI > 25, n (%)	6 (33%)	24 (56%)	0.11
-HBP, n (%)	10 (55%)	24 (56%)	0.99
-Dyslipidemia, (%)	5 (28%)	18 (42%)	0.30
-Diabetes mellitus, n(%)	0 (0%)	2 (5%)	1
-Smokers (current or former), n (%)	10 (56%)	25 (58%)	0.85
Neurological features			
- Number of CI, median (range)	1 (1-2)	1 (1-4)	0.11
- Number of TIA, median (range)	2 (1-6)	1 (1-2)	0.06
- Epilepsy, n (%)	3 (16.7%)	10 (23.3%)	0.73
- Migraine, n (%)	8 (44.4%)	14 (32.6%)	0.38
- Cognitive impairment, n (%)	7 (43.7%)	16 (44.4%)	0.96
Cardiovascular features			
- Coronary heart disease, n (%)	0 (0%)	5 (11.6%)	0.31
- Atrial fibrillation, n (%)	0 (0%)	3 (7.0%)	0.55
- Deep venous thrombosis/pulmonary embolism, n (%)	2 (11.8%)	4 (9.3%)	1.00
Kidney dysfunction, n (%)	2 (11.8%)	7 (16.3%)	1.00
Radiological features			
- Number of radiological CI, median (range)	2 (1-4)	2 (1-6)	0.54
- Number of radiological lacunar stroke, median (range)	2 (1-14)	1 (1-3)	0.19
- White matter changes*, median (range)	9 (4-18)	8 (0-23)	0.70
Raynaud phenomenon, n (%)	13 (72%)	16 (37%)	0.0125**
ANA ≥ 1/160, n (%)	8 (46%)	10 (24%)	0.079
Complement deficiency, n (%)	4 (24%)	3 (7%)	0.18
First received treatment			
-LDA, n (%)	14 (78%)	30 (70%)	0.76
-Antiplatelet clopidogrel, n (%)	2 (12%)	7 (16%)	1
-Vitamin K antagonist, n (%)	2 (12%)	4 (9%)	1
Follow-up months, median (range)	55.5 (3.6-221.5)	147.2 (12.4-386.7)	0.004**

LS: Libman-Sacks endocarditis; BMI: body mass index; HBP: high blood pressure; ANA: antinuclear autoantibodies; LDA: low dose aspirin; CI: cerebral infarct; TIA: transient ischemic attack; * White matter changes assessed by Scheltens score; ** Statistically significant in exploratory analysis but not after Bonferroni correction

Table 4. Characteristics of the aPL-SS patients with at least one transthoracic echography during follow-up (n=46)

Features	**N (%)**
Time between first and last transthoracic echocardiography (months), median (range)	72 (12-252)
New LS development, n (%)	8 (17.4%)
LS on last transthoracic echocardiography, n(%) Age at new LS development (years), median (range)	26 (42.6%) 53.8 (39-66.9)
Significant worsening (other than LS), n patients (%) New mitral regurgitation Mitral regurgitation worsening New aortic regurgitation Aortic stenosis worsening Ascending aortic aneurysm New LV dysfunction LV hypertrophy worsening LV relaxation dysfunction worsening	13 (28.3%) * 2 (4%) 2 (4%) 3 (6%) 2 (4%) 2** (4%) 1 (2%) 2 (4%) 2 (4%)
Cardiac surgery, n(%) - Valvular replacement - Ascending aortic aneurysm	3 (6.5%) 2 (4%) 1 (2%)

Features	**Significant worsening**	**No significant worsening**	**p-value**
Follow-up, months median (range)	156 (21-252)	60 (21-252)	0.03
Features	**LS occurence**	**No LS occurence**	**p-value**
Follow-up, months median (range)	177.4 (63.8-239.4)	147.2 (12.4-386.7)	0.9

* Some patients had more than one significant worsening, ** one patient needed surgery

Table 5. Univariate analysis between patients with or without occurence of Libman-Sacks endocarditis during follow-up among patients without LS at baseline and available follow-up data (n=33)

Features	New LS +	No New LS	p-value
Neurological features			
- Number of CI, median (range)	1 (1-2)	1 (1-4)	0.21
- Number of TIA, median (range)	1 (1-1)	1 (0-2)	1.00
- Epilepsy, n (%)	3 (37.5%)	5 (20%)	0.37
- Migraine, n (%)	4 (50%)	8 (32%)	0.42
- Cognitive impairment, n (%)	2 (28.6%)	10 (47.6%)	0.66
Cardiovascular features			
- Coronary heart disease n (%)	0 (0%)	4 (16%)	0.55
- Atrial fibrillation, n (%)	0 (0%)	2 (8%)	1.00
- Deep venous thrombosis/pulmonary embolism, n (%)	2 (25%)	2 (8%)	0.24
Kidney dysfunction, n (%)	1 (12.5%)	4 (16%)	1.00
Radiological features			
- Number of radiological CI, median (range)	3.5 (1-6)	2.5 (1-5)	0.43
- Number of radiological lacunar stroke, median (range)	1.5 (1-2)	1 (1-10.5)	0.82
- White matter changes*, median (range)	12 (1-21)	7 (0-18.8)	0.39
- Significant worsening, n (%)	1 (12.5%)	10 (40%)	0.22

LS: Libman-Sacks endocarditis; CI: cerebral infarct; TIA: transient ischemic attack * White matter changes assessed by Scheltens score

Figures

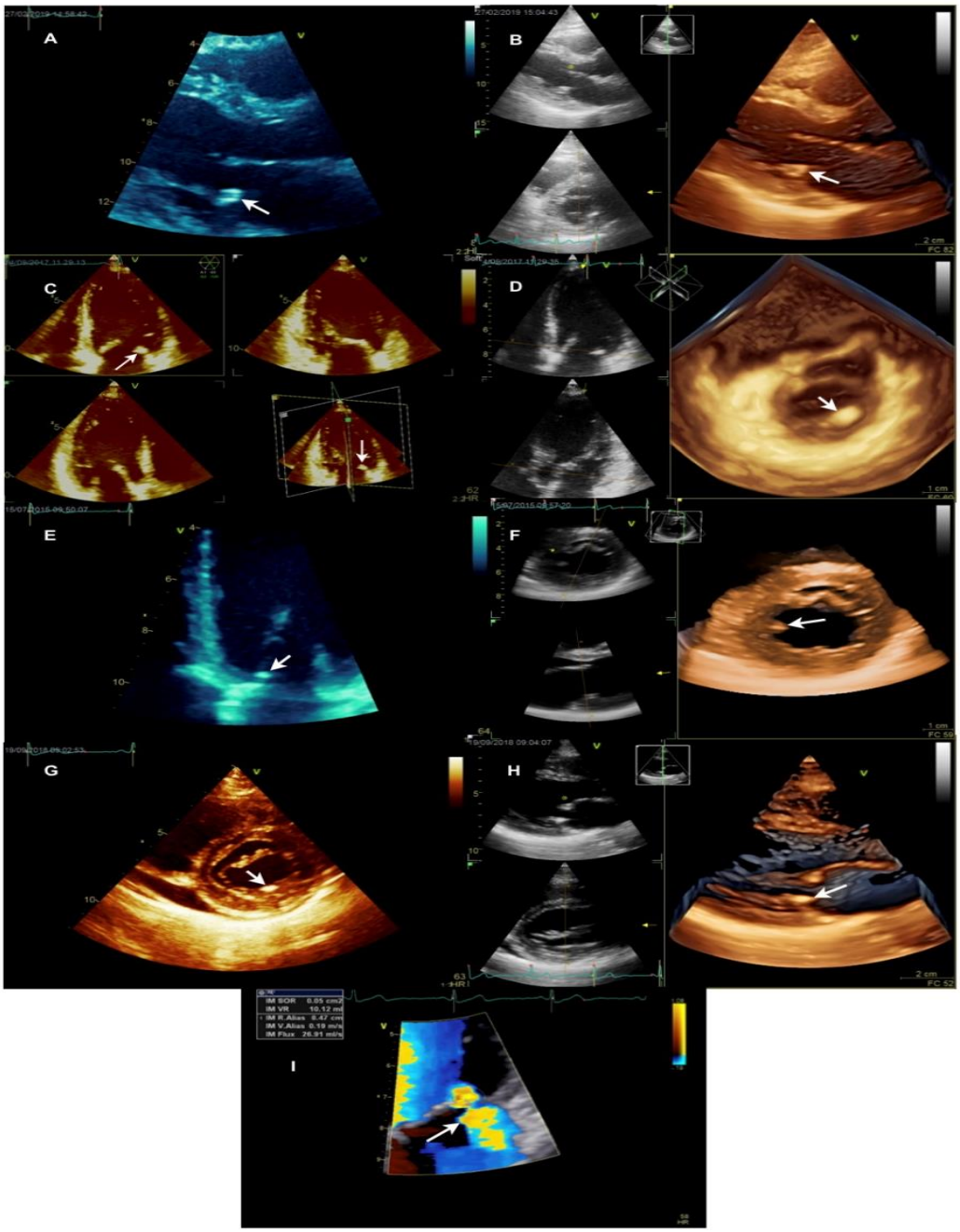

Figure 1 – Typical mitral abnormalities in Sneddon syndrome without antiphospholipid antibodies
A and B: patient PC, female, 53 years; (A) two-dimensional transthoracic echocardiography (2DTTE), parasternal long-axis view, zoomed image of the mitral valve with a Libman-Sacks vegetation (LSV) at the root, atrial side, of the posterior leaflet (arrow); (B) the same vegetative lesion (arrow) displayed with real-time three-dimensional transthoracic echocardiography (3DTTE).
C and D: patient AB, female, 31 years; (C) triplane (real-time 3DTTE-derived) two-dimensional apical views (4-chamber, 2-chamber and 2-chamber with aorta), mitral valve with a LSV (arrow) at the root, atrial side, of the posterior leaflet; (D) the same vegetative lesion (arrow) displayed with 3DTTE, parasternal short-axis view (arrow).
E and F: patient CC, female, 43 years; (E) 2DTTE, apical 4-chamber view, zoomed image of the mitral valve with a LSV attached to the posterior commissure (arrow); (F) the same vegetative lesion (arrow) displayed with real-time 3DTTE, parasternal short-axis view (arrow).
G to I: patient MG, male 54 years; (G) 2DTTE, parasternal short-axis view, showing a LSV (arrow) attached to the root, left atrial side, of the mitral valve posterior leaflet; (H) real-time 3DTTE, parasternal long-axis view showing a LSV attached to the root, atrial side, of the mitral valve posterior leaflet; (I) transthoracic two-dimensional color Doppler flow recording of a small volume mitral regurgitation (arrow); radius of the proximal isovelocity convergence region = 4.7 mm.

Figure 2

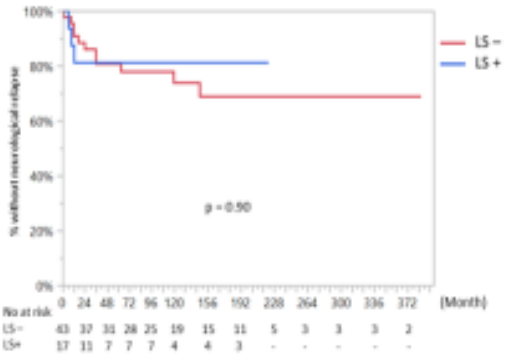

Figure 2A

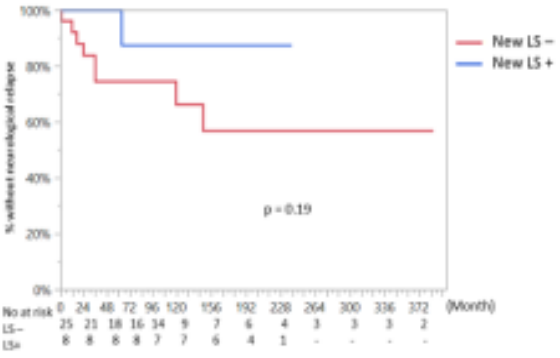

Figure 2B

Figure 2 legends:

Figure 2. 2.A: Kaplan-Meier curves for probability of neurological relapse over time stratified by presence or absence of LS at baseline. 2.B: Kaplan-Meier curves for probability of neurological relapse over time stratified by the occurrence or not of a new LS during follow-up