Could MRI be a diagnosis criteria in the seronegative antiphospholipid syndrome?

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Aims and objectives

Antiphospholipid syndrome (APS) is characterized by pregnancy complications, recurrent arterial and venous thrombosis affecting one or more organs and tissues and presence of circulating antiphospholipid antibodies (aPA). Central nervous system (CNS) involvement in APS is highly prevalent, and the most frequent radiological pattern described is the presence of white matter lesions in brain magnetic resonance imaging (MRI). Small vessel brain injury includes different clinical manifestations such as memory loss, progressive cognitive impairment and a history of migraine headache.

Presently, the diagnostic criteria for APS includes the fulfillment of both clinical and laboratory criteria. However, some routine laboratory tests to detect lupus anticoagulant (LA), anticardiolipin antibody (aCL) and anti-B2-glycoprotein-1 (anti-B2-GP1) come back negative in patients who present clinical signs suggestive of APS. Therefore, the term Seronegative Antiphospholipid Syndrome (SN-APS) was proposed, including patients with clinical manifestations suggestive of APS and persistent negative results for aPA.

Nowadays, the Sidney criteria classification includes three standardized laboratory tests, the determination of LA, aCL and anti-B2-GP1. Different antibodies directed against molecules such as posphatidylethanolamine, prothrombin, annexin V and vimetin/cardiolipin complex have been found in patients with APS. In patients with SN-APS these antibodies could play an important role in its diagnosis. In a recent study, the presence of these markers was analyzed in a group of 67 patients with SN-APS and it reached a sensibility of 23.5%. Unfortunately, these antibodies are not included in the Sidney criteria, and its determination is not available as a standardized technique in most institutions.

This entails a challenging situation for the physician, who must make a decision about the treatment of these patients, who behave as APS and eventually could benefit from the known therapies but do not match any of the routine screening tests. Efforts are being made to describe other criteria to increase the diagnostic yield in SN-APS, with the purpose of treating these patients the same way as if the routine screening laboratory tests came back positive. Regarding this, several investigations are being carried out, such as the new diagnostic criteria consensus development and the research and standardization of new markers. Its results will probably be included in future criteria.

The main purpose of this study is to define a MRI standardized pattern in APS, and its usefulness in the diagnosis of SN-APS with small vessel brain injury.
Methods and materials

We retrospectively reviewed MRI brain images of 23 patients: 13 patients with cerebral APS selected from a series of 60 APS patients in our Center, and 10 patients with SN-APS. The first group comprised 13 patients (77% women and 23% men, the mean age was 47.23 years old) who fulfilled the APS criteria, had CNS signs and had undergone a cerebral MRI. The second group included 10 patients (80% women and 20% men with a mean age of 50.1 years old) classified as SN-APS. These patients presented with clinical manifestations and similar lesions in the MRI than the ones seen in the group with confirmed APS, although they had several negative aPA measurements and their MRI lesions were firstly classified as ischemic. We have selected those MRI with lesions considered ischemic or thrombotic after ruling out other causes. A full laboratory panel was performed to discard known agents of vascular risk that could cause ischemia. Likewise, we discarded other diseases which cause similar cerebral lesions in the MRI such as degenerative or inflammatory diseases.

The MRI scans were conducted between 2004 and 2013. Fourteen MRI examinations were performed with a Siemens MAGNETOM Avanto 1.5T, four with a General Electric Optima MR360 1.5T, three with a General Electric Signa HDxt 3.0T Optima Edition and two with a General Electric Optima MR450w 1.5T with GEM. All the MRI studies included T1, T2, FLAIR and diffusion sequences. All the images were reviewed by two neuroradiologists with more than 10 years of experience. Clinical information relating which group each patient belonged to was blinded. The lesions were classified according to the distribution, anatomical location, number and size. The Fazekas scale was used to determine the degree of white matter involvement. This qualitative scale gives information related to the white matter affection across the brain. According to the scale, non-confluent white matter punctiform lesions are classified as Fazekas 1 (Fig. 1 on page 6). Incipient bridging lesions are Fazekas 2 (Fig. 2 on page 6), and when large, confluent and diffuse lesions appear they are graded as Fazekas 3 (Fig. 3 on page 7). We used FLAIR images to grade the studies.
**Fig. 1**: 54-year-old woman with history of a cerebral-vascular infarct and two positive LA results, so she was diagnosed of APS. Non-confluent white matter punctiform lesions were seen on MRI. (Fazekas 1).

**References**: HU Son Espases - Palma de Mallorca/ES

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**Fig. 2**: 57-year-old man diagnosed of SN-APS due to cognitive impairment, small vessel disease in the brain MRI and only one positive determination of LA. (Fazekas 2).
**Fig. 3:** 71-year-old woman. MRI showed large and confluent white matter lesions. (Fazekas 3).

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Results

In the APS group, all patients had more than six supratentorial lesions in the white matter, and 38% presented with Fazekas 2 or higher (Fig. 4 on page 16 and Fig. 5 on page 16). 46% of the patients had infratentorial lesions (Fig. 6 on page 17). The corpus callosum was affected in 30% of the studies. 69% of the patients had cerebral atrophy signs, and 44% of these had parietal atrophy predominantly (Fig. 7 on page 17). Grey matter lesions were seen in two patients (15%), acute/subacute infarcts in two patients (15%) and old geographic infarcts in one patient (7%).

Fig. 4: 46-year-old woman with systemic lupus erythematosus (SLE). She was diagnosed of APS due to migraine, sensory motor syndrome and positive aPA in two occasions (LA, aCL and anti-B2-GP1). MRI showed incipient bridging white matter lesions. (Fazekas 2).

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Fig. 5: 46-year-old man with APS diagnosed by the combination of an atypical akinetic-tremoric syndrome with small vessel disease lesions seen in the MRI, and two positive aPA (LA and anti-B2-GP1) determinations. MRI showed large and confluent white matter lesions. (Fazekas 3).

References: HU Son Espases - Palma de Mallorca/ES
Fig. 6: 51-year-old woman diagnosed with SLE and APS with several aCL and LA positive determinations and small vessel disease in the MRI. In the image, the infratentorial area may be affected due to the presence of bilateral cerebellar white matter lesions.

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Fig. 7: 52-year-old woman with SLE. She suffered from lack of concentration, memory loss and difficulty carrying out daily tasks. She was diagnosed of APS after two positive determinations for aPA. MRI showed cerebral atrophy, specially significant in the parietal lobe.

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In the SN-APS group, at least one white matter lesion was present in all patients and more than six lesions were seen in 80% of them (Fig. 8 on page 18). 50% of the patients were graded 2 or more in the Fazekas scale (Fig. 9 on page 19). 20% had infratentorial lesions (Fig. 10 on page 20), and the corpus callosum was not affected in any of the studies. 30% of the patients had cerebral atrophy signs (Fig. 11 on page 20), with no parietal atrophy present. One patient (10%) had grey matter lesions and another one (10%) had acute/subacute infarcts. None of the patients presented old geographic infarcts.
Fig. 8: 54-year-old woman diagnosed of SN-APS by the combination of migraine and one positive determination of aCL. In the image, multiple non-confluent white matter punctiform lesions (Fazekas 1) can be observed.

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Fig. 9: 59-year-old man with a clinical diagnosis of SN-APS due to Parkinson clinical signs, cognitive impairment and a history of deep vein thrombosis and pulmonary
thromboembolism, with persistently negative aPA. MRI showed incipient bridging white matter lesions. (Fazekas 2).

References: HU Son Espases - Palma de Mallorca/ES

Fig. 10: 54-year-old woman diagnosed of SN-APS by the combination of migraine and one positive determination of aCL. (Same patient as in Figure 8). In this image the infratentorial area is affected, with the presence of a lesion in the left cerebellar white matter.

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Fig. 11: 59-year-old man diagnosed of SN-APS due to Parkinson clinical signs, cognitive impairment and a history of deep vein thrombosis and pulmonary thromboembolism, with persistent negative aPA (same patient as in Figure 9). In this image we see an enlarged subarachnoid space, related to diffuse cerebral atrophy signs.

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When comparing both groups, the results showed that all patients had white matter lesions and a high percentage of those patients had more than six lesions (100% in APS group, 80% in SN-APS group). Furthermore, the Fazekas scale was equal or greater than two in 38% of the APS group patients and 50% of the SN-APS. When we selected
MRI exams with six or more white matter lesions and Fazekas scale graded 2 or more, we were not able to differentiate by radiological pattern the APS patients from the SN-APS patients.
Fig. 4: 46-year-old woman with systemic lupus erythematosus (SLE). She was diagnosed of APS due to migraine, sensory motor syndrome and positive aPA in two occasions (LA, aCL and anti-B2-GP1). MRI showed incipient bridging white matter lesions. (Fazekas 2).

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**Fig. 5:** 46-year-old man with APS diagnosed by the combination of an atypical akinetic-tremoric syndrome with small vessel disease lesions seen in the MRI, and two positive aPA (LA and anti-B2-GP1) determinations. MRI showed large and confluent white matter lesions. (Fazekas 3).

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Conclusion

Cerebral involvement in APS can manifest in different ways, and the small vessel injury may be the only finding in MRI. We have identified a MRI pattern strongly associated with both APS and SN-APS groups, defined by more than 6 supratentorial lesions and Fazekas scale graded as 2 or more. These findings are not common in healthy patients within the studied age group; therefore we strongly believe that this pattern could be useful for the diagnosis of SN-APS cases but further studies should be carried out to reinforce it.
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