Dementia associated with the antiphospholipid syndrome: clinical and radiological characteristics of 30 patients


Objective. To analyse the clinical and radiological characteristics of patients with dementia associated with the antiphospholipid syndrome (APS).

Methods. Twenty-five patients were identified by a computer-assisted (MEDLINE, National Library of Medicine, Bethesda, MD) search of the literature to locate all cases of dementia associated with APS published in English, Spanish and French from 1983 to 2003. Additionally, we included five patients from our clinics.

Results. There were 21 (70%) females and 9 (30%) males. The mean age of patients was 49±15 yr (range 16–79 yr). Fourteen (47%) of the patients suffered from primary APS, 9 (30%) had systemic lupus erythematosus and 7 (23%) had ‘lupus-like’ syndrome. Ten (33%) patients had Sneddon’s syndrome and 2 (7%) had cerebral lesions described as Binswanger’s disease. Other APS-related manifestations included thrombocytopenia in 12 (40%) patients, cerebrovascular accidents in 11 (37%), heart valve lesions in 8 (27%), deep vein thrombosis in 7 (28%), migraine in 7 (23%), seizures in 4 (13%); five of the 21 (24%) female patients had nine spontaneous abortions. Lupus anticoagulant was present in 21/29 (72%) patients and anticardiolipin antibodies were present in 24/29 (83%) patients. Cortical infarcts were found in 19 (63%) patients, subcortical infarcts in 9 (30%), basal ganglia infarcts in 7 (23%) and signs of cerebral atrophy in 11 (37%). Anticoagulation was used in 14/25 (56%) patients, steroids in 12/25 (48%), aspirin in 6/25 (24%) and dipyridamole in 5/25 (20%).

Conclusions. Dementia is an unusual manifestation of APS but one which has a high disability impact in a patient’s daily life. In order to prevent these consequences, an echocardiographic and cerebral CT or MRI evaluation are recommended in all patients with APS. Furthermore, ruling out APS should be recommended in the clinical approach to dementia, especially in young patients.

KEY WORDS: Antiphospholipid syndrome, Dementia, Vascular dementia, Multi-infarct dementia, Sneddon’s syndrome, Binswanger’s disease.

Dementia is being increasingly diagnosed in clinical practice and has a high disability impact in a patient’s daily life. Alzheimer’s disease is the main cause of dementia, followed by vascular multi-infarct dementia, Parkinson’s disease, frontal lobe dementia and, less commonly, other metabolic and reversible causes of dementia [1].

The antiphospholipid syndrome (APS) is an autoimmune pro-thrombotic condition characterized by venous and/or arterial thrombosis and pregnancy morbidity in the presence of antiphospholipid antibodies (aPL), i.e. lupus anticoagulant (LA) and antithrombunderivates (aCL) [2]. Involvement of cerebral large vessels is frequent in APS and patients usually present clinically with transient ischaemic attacks (TIA) and strokes. However, a wide spectrum of other neurological features has been described, including chorea, epilepsy, multiple sclerosis-like lesions, psychiatric features, migraine and also dementia, among others [2, 3].

A relationship between dementia and APS has been proposed by several authors [2–7]. Although most studies have focused on patients with dementia and cerebral vascular lesions, less severe cognitive impairment has also been associated with the presence of aPL in the absence of imaging lesions in the brain [7]. Furthermore, the ischaemic stroke in Sneddon’s syndrome may overlap with APS and some of these patients suffer from severe vascular dementia. The objective of this study was to analyse the clinical and radiological features of patients with dementia associated with APS, highlighting the importance of early diagnosis of this condition.

Patients and methods

Patients were identified by a computer-assisted (MEDLINE, National Library of Medicine, Bethesda, MD) search of the
<table>
<thead>
<tr>
<th>Author</th>
<th>Gender/age</th>
<th>Diagnosis</th>
<th>Associated Sneddon(^a)</th>
<th>Other manifestation</th>
<th>Dementia diagnosis</th>
<th>aPL</th>
<th>CNS imaging</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>2. Asherson et al. [12]</td>
<td>F:33</td>
<td>SLE</td>
<td>+</td>
<td>L.R., migraine, DVT, AHA, TIA, chorea, VL</td>
<td>7yr later</td>
<td>LA, aCL-</td>
<td>CT: multiple cortical infarcts and thalamic lacunar infarct</td>
<td>AC, S, D</td>
</tr>
<tr>
<td>3. Asherson et al. [12]</td>
<td>F:32</td>
<td>SLE</td>
<td>+</td>
<td>Migraine, LR, CPA DVT, thrombocytopenia</td>
<td>7yr later</td>
<td>LA, aCL-</td>
<td>CT: multiple cortical infarcts</td>
<td>AC, D, ASA</td>
</tr>
<tr>
<td>4. Asherson et al. [12]</td>
<td>F:43</td>
<td>SLE</td>
<td>–</td>
<td>Migraine, SA (2), sup. thrombophlebitis</td>
<td>1.5yr later</td>
<td>aCL IgG</td>
<td>CT: multiple bilateral small lacunar and subcortical infarcts in the frontal and occipital white matter</td>
<td>AC</td>
</tr>
<tr>
<td>5. Coull et al. [13](b)</td>
<td>M:59</td>
<td>PAPS</td>
<td>–</td>
<td>CVA, AHA, MI</td>
<td>Simultaneously</td>
<td>aCL+</td>
<td>CT: bilateral cortical cerebral infarcts</td>
<td>S</td>
</tr>
<tr>
<td>14. Westerman et al. [16](b)</td>
<td>M:54</td>
<td>Lupus-like</td>
<td>–</td>
<td>Thrombocytopenia</td>
<td>Simultaneously</td>
<td>aCL IgG</td>
<td>CT: multiple cortical and subcortical hyperintense areas</td>
<td>NR</td>
</tr>
<tr>
<td>15. Charles et al. [17]</td>
<td>F:16</td>
<td>PAPS</td>
<td>+</td>
<td>Thrombocytopenia, LR, VL</td>
<td>Simultaneously</td>
<td>aCL+</td>
<td>CT: bilateral thalamic lesions of high signal intensity (infarctions)</td>
<td>NR</td>
</tr>
<tr>
<td>18. Robin et al. [19]</td>
<td>F:43</td>
<td>SLE</td>
<td>–</td>
<td>Skin ulcers</td>
<td>2yr later</td>
<td>LA+</td>
<td>CT: atrophy and subcortical low-attenuation areas MRI: hyperintensities in periventricular white matter</td>
<td>S</td>
</tr>
<tr>
<td>21. Tomimoto et al. [22]</td>
<td>F:60</td>
<td>PAPS</td>
<td>–</td>
<td>Simultaneously</td>
<td>LA+</td>
<td>MRI: diffuse patchy hyperintensities in basal ganglia and cerebral white matter</td>
<td>SPECT: bilaterally decreased perfusion</td>
<td></td>
</tr>
<tr>
<td>25. Rodríguez Campello et al. [26]</td>
<td>F:50</td>
<td>PAPS</td>
<td>+</td>
<td>Thrombocytopenia, LR</td>
<td>Simultaneously</td>
<td>LA, aCL+</td>
<td>CT: cortical and subcortical infarcts and atrophy. MRI: cortical infarcts and white matter hyperintensities</td>
<td>ASA</td>
</tr>
<tr>
<td>26. PC 1</td>
<td>F:79</td>
<td>PAPS</td>
<td>–</td>
<td>Thrombocytopenia, CVA, DVT, PE, SA (2), migraine, seizures</td>
<td>1yr later</td>
<td>LA</td>
<td>MRI: cortical, subcortical and basal ganglia infarcts, atrophy</td>
<td>AC</td>
</tr>
<tr>
<td>27. PC 2</td>
<td>F:49</td>
<td>Lupus-like</td>
<td>–</td>
<td>Thrombocytopenia, CVA, VL, seizures</td>
<td>Simultaneously</td>
<td>LA, aCL+</td>
<td>MRI: cortical and subcortical infarcts and periventricular white matter hyperintensities</td>
<td>S, AC</td>
</tr>
<tr>
<td>28. PC 3</td>
<td>F:69</td>
<td>SLE</td>
<td>–</td>
<td>MI, DVT, CVA</td>
<td>2yr later</td>
<td>LA, aCL</td>
<td>MRI: cortical infarct in right parietal lobe</td>
<td>AC</td>
</tr>
<tr>
<td>29. PC 4</td>
<td>F:72</td>
<td>SLE</td>
<td>+</td>
<td>LR, thrombocytopenia, CVA, DVT, TIA</td>
<td>4yr later</td>
<td>LA, aCL</td>
<td>MRI: cortical infarct in occipital lobe and atrophy</td>
<td>AC</td>
</tr>
<tr>
<td>30. PC 5</td>
<td>F:52</td>
<td>SLE</td>
<td>–</td>
<td>Thrombocytopenia, VL</td>
<td>4yr later</td>
<td>LA, aCL+</td>
<td>CT: cortical infarcts</td>
<td>S</td>
</tr>
</tbody>
</table>

\(^a\) Associated Sneddon's syndrome (the co-existence of hypertension, livedo reticularis and stroke).

\(^b\) Microthrombus in cerebral biopsy.

Abbreviations: AC, anticoagulation; AHA, autoimmune haemolytic anaemia; ASA, aspirin; aCL, antiphospholipid antibodies; aPL, antiphospholipid antibodies; APS, antiphospholipid syndrome; CNS, central nervous system; CT, computed tomography; CVA, cerebrovascular accident; D, dipyridamole; F, female; LA, livedo reticularis; LR, livedo reticularis; M, male; MI, myocardial infarction; MRI, magnetic resonance imaging; NR, none reported; PAPS, primary antiphospholipid syndrome; PC, present case; PE, pulmonary embolism; S, steroids; SA, spontaneous abortions; SLE, systemic lupus erythematosus; SPECT, single-photon emission computed tomography; TIA, transient ischaemic attack; VL, valvular lesion.
Dementia and antiphospholipid syndrome

97

literature to locate all cases of APS published in English, Spanish
and French from 1983 (when APS was first defined) to December
2003 (keywords used were: anticardiolipin antibodies, lupus
inhibitor, cardiolipin, coagulation inhibitor, lupus anticoagulant,
antiphospholipid syndrome, antiphospholipid antibodies, multi-
infarct dementia, vascular dementia, Sneddon’s syndrome, Alzhiemer’s disease and Binswanger’s disease).

Cases having Sneddon’s syndrome with dementia but without
aPL were not included. Only cases with well-documented clinical
summaries and relevant information were included in this review.
Data from these cases were summarized using a standardized data
form, including gender, age, diagnosis of the underlying condition,
the major thrombotic clinical manifestations, immunological
features, time of the evolution since the diagnosis of APS until
the development of dementia, imaging features and treatment. Five
new cases with dementia and APS from our clinics were added to
the review. Those patients diagnosed as having dementia who were
included in large APS series, but in whom no well-documented
clinical data were recorded, were not considered for analysis in the
present study.

Patients were defined as having dementia according to the
Diagnostic and Statistical Manual of Mental Disorders (DSM-IV)
[8]. They were classified as having systemic lupus erythematosus
(SLE) if they met four or more criteria of the American College of
Rheumatology [9, 10], as ‘lupus-like’ syndrome if they met only
two or three criteria and as primary APS if they met criteria of the
International Consensus Statement on Preliminary Classification
Criteria for definite APS, and did not meet any of the above
described criteria for SLE or ‘lupus-like’ syndrome [11].

Ethical approval and informed patient consent were not
required because the study was an analysis of patients that were
located by means of a computer-assisted (MEDLINE, National
Library of Medicine, Bethesda, MD) search of the literature.

Results

A total of 25 patients with dementia associated with APS were
found in the literature search [12–26]. We did not include those
cases where clinical, immunological and imaging characteristics
were not described in detail. Five additional patients from our
clinics were also reviewed.

General characteristics

General clinical features of these 30 patients are shown in Table 1.
There were 21 (70%) females and 9 (30%) males. The mean age
of patients was 49 ± 15 yr (range 16–79 yr). Fourteen (47%) of
the patients suffered from primary APS, 9 (30%) had SLE and 7 (23%)
patients had ‘lupus-like’ syndrome. Ten (33%) patients had
Sneddon’s syndrome and 2 (7%) had cerebral lesions described as
Binswanger’s disease.

Clinical presentation

Dementia was the presenting manifestation of the APS in 11 (37%)
patients. A clinically evident past history of CVA was detected in
11 (37%) patients. Other neurological features included migraine
in 7 (23%) patients, seizures in 4 (13%), TIA in 2 (7%), chorea in
2 (7%), and retinal thrombosis in 2 (7%) patients. Thrombotic
glaucoma and optic neuritis were present in 1 (3%) case each. Skin
involvement in the form of livedo reticularis (as a manifestation of
Sneddon’s syndrome) was reported in 10 (33%) patients, and skin
ulcers in 3 (10%). Other APS-related manifestations were as
follows: 8 (27%) patients had heart valve lesions, 7 (23%) deep-
vein thrombosis (DVT), 2 (7%) pulmonary embolism, 3 (10%)
myocardial infarction and 2 (7%) superficial thrombophlebitis.

Previous spontaneous abortions (n = 9) were reported in 5 of the 21
(24%) female patients.

Laboratory profile

Twelve (40%) patients had thrombocytopenia and 2 (7%) had auto-
immune haemolytic anaemia. LA was present in 21/29 (72%)
patients, whilst aCL was present in 24/29 (83%) patients.

Neuroimaging features

Most patients exhibited several types of lesions on cerebral
computed tomography (CT) scan or magnetic resonance imaging
(MRI). Cortical infarcts were detected in 19 (63%) patients,
subcortical infarcts in 9 (30%), basal ganglia infarcts in 7 (23%)
and cerebral atrophy in 11 (37%). Silent brain infarcts (cerebral
ischaemic lesions without any focal neurological features) were
found in 14 (47%) patients.

Treatment and evolution towards dementia

Anticoagulation was used in 14/25 (56%) patients, steroids in
12/25 (48%), aspirin in 6/25 (24%) and dipyridamole in 5/25
(20%). Treatment was not reported for five cases.

In the 19 (63%) patients who presented APS manifestations
previous to the diagnosis of dementia, anticoagulation had been
used in 7 (37%) patients, steroids in 6 (32%), aspirin in 5 (26%)
and dipyridamole in 4 (21%). The mean time of evolution from the
initial APS manifestations to the diagnosis of dementia in these 19
patients was 3.5 yr (range, 1–10 yr).

Discussion

The relationship between dementia and APS has been proposed in
several studies. Mosek et al. [6] studied 87 patients diagnosed as
having dementia and compared them with 69 elderly healthy
controls. They found higher levels of aPL in patients with dementia
than in controls. Juby et al. [27] analysed the prevalence of aCL in
218 elderly patients. They disclosed that 34 patients suffered from
dementia and a significant association between aCL and both
vascular dementia and Alzheimer’s disease was noted. Recently,
Chapman et al. [4] studied 23 patients with primary APS and found
that 13 (56%) fulfilled criteria for dementia using the Hachinski
Ischaemic Score (HIS). Patients with dementia were older, had more
CT scan abnormalities and more electroencephalography changes
than those without dementia. However, the ‘Euro-Phospholipid’
consortium, in their cohort of 1000 APS patients, described the
presence of vascular dementia in only 25 (2.5%) cases [2]. It is
possible that the higher prevalence of dementia in the Chapman
et al. series [4] could be merely due to the small and probably
highly selected group of patients studied, but it could also be due
to the exclusion of SLE patients as it is known that in APS
associated with SLE the incidence of neurological manifestations
is higher than in primary APS [28].

The presence of aPL in patients with cognitive problems seems
to be more than an epiphenomenon, as it has been demonstrated in
experimental studies. Shrot et al. [29] performed an elegant study
with BALB/c mice using a staircase test and a T maze alternation
test as cognitive assessment tools. Mice immunized with anti-
γ-glucoprotein I antibodies developed a higher degree of behavioural
and cognitive abnormalities than those that had not been
immunized.

One-third of the patients from our series had Sneddon’s
syndrome. Frances et al. [30] described a specific subset of patients
with this syndrome having aPL who presented more thrombocy-
topenia, mitral regurgitation and irregular livedo reticularis than
patients without aPL. There is controversy concerning whether patients with Sneddon’s syndrome without aPL could be a special group of transient ‘seronegative’ APS patients.

In the present study, almost one-third of patients had valve disease. It is well known that a high proportion of cerebral infarcts have a cardiac embolic origin and that patients with aPL have higher prevalence of valvular abnormalities [31]. Thickening of the valve leaflets is the most common lesion detected by echocardiography in both SLE and primary APS patients. The mitral valve is involved most commonly, followed by the aortic valve [32].

Epilepsy is a common neurological manifestation in APS [2]. Recent studies by Shoenfeld et al. [33] have confirmed a link between this manifestation and cerebrovascular involvement, heart valve lesions and livedo reticularis. In the present series, 13% of the patients with dementia presented seizures, thus reinforcing the role of focal brain ischaemic lesions in the pathogenesis of APS-related epilepsy.

Patients with dementia exhibit a wide variety of cerebral lesions on CT or MRI studies. Cortical and subcortical infarcts are the more frequent findings. Other ischaemic lesions such as lacunar and periventricular infarcts are not uncommon. Cerebral atrophy and white matter lesions (leukoaraisotasis), similar to the lesions found inBinswanger’s disease, are often seen, specially in elderly APS patients [15]. In SLE, these findings have been shown to be in close association with the presence of APS, but other factors, e.g. hypertension, could also contribute to their presence [34]. The continuous improvement and development of new CNS imaging techniques [i.e. positron emission tomography (PET) or single-photon emission computed tomography (SPECT)] will allow to us differentiate the distinct perfusion patterns on these cerebral disorders. Kao et al. [35] studied 22 patients with primary APS with only mild neuropsychiatric manifestations (headache, depression, personality disorders, memory loss and cognitive function deficits) and normal brain MRI. They found that 16 (73%) of the patients had abnormal SPECT findings, mainly diffuse hyperperfusion lesions in cerebral cortex.

It is not only those patients with evident cerebral lesions and cognitive impairment who deserve special attention, but also those patients with an asymptomatic course or subtle decline in cerebral functions having cerebral ischaemic lesions on MRI (silent brain infarcts). Vermeer et al. [36] followed 1077 elderly patients without dementia over 5 yr, with periodical MRI evaluation. Two hundred and seventeen (21%) patients had silent brain infarcts at baseline, with a global cognitive function significantly worse than in those patients without brain infarcts. During the follow-up, 30 (3%) of these patients developed dementia. Erkan et al. [5], in a 10-yr follow-up study of 66 patients with primary APS, found that 3 patients (<30yr old) developed dementia, independently of the presence of CVA. In the present series, previous history of CVA and/or TIA was present in only 11 and 2 patients, respectively; however, silent brain infarcts were present in 14 (47%) patients.

Several strategies have been suggested for the treatment of dementia. The management of atherogenic risk factors (i.e. diabetes, hypertension, hyperlipidaemia) is crucial. However, there is still no evidence that aspirin alone is effective in treating patients with a diagnosis of dementia. In dementia associated with APS, anticoagulant treatment is required, with special care in possible everyday situations with the risk of bleeding. Furthermore, the compliance of demented patients is usually poor, which requires special thought and attention. On the other hand, prevention of dementia should be of paramount importance in those patients with a diagnosis of APS. Unfortunately, it is difficult from the present study to recommend any therapeutic strategy because patients were previously treated with a variety of medications. However, it is worth noting that the majority of patients were not on anticoagulants when the first manifestations of dementia appeared. Therefore, this reinforces the need for active antithrombotic prophylaxis once the diagnosis of APS is made.

In conclusion, dementia can be present in patients with APS in multiple scenarios, such as primary APS, Sneddon’s syndrome or with white matter lesions similar to Binswanger’s disease. Due to the high disability impact and prognostic consequences, we consider that an echocardiographic and cerebral CT or MRI evaluation should be recommended in all patients with APS. Also, it is important to rule out an APS in young subjects with no explicable cause of dementia, and therefore aPL should be tested in these patients in order to prevent disease progression and enable adequate treatment to begin.

### References