Antiphospholipid Syndrome in the Elderly: Caution

Jean-Charles Piette, MD; Patrice Cacoub, MD

Ten years after its identification, thousands of articles and 2 books have made the APS popular. Subsequently, the diagnosis of a possible APS is now frequently considered in daily practice, not only by subspecialists but also by general practitioners, in patients with thrombosis, sometimes whatever their age at the time of the first vascular event. We wish to emphasize here the potential hazards associated with a diagnosis of APS in elderly patients.

Historically, APS was first identified as a subset of patients with SLE because of the strong association observed in this disorder between the occurrence of thrombosis, either arterial or venous, and/or miscarriages and the presence of aPL (ie, Lupus anticoagulant) and/or aCL. Later, APS was also recognized in patients who had no features of SLE, leading to the concept of a “primary APS.” A set of criteria has been proposed to discriminate primary from SLE-related APS. Although aPL may be encountered in multiple circumstances, primary and SLE-related appear to be the 2 major variants of APS.

APS usually affects young patients. This is obviously true for SLE-related APS, given that spontaneously occurring SLE is restricted primarily to women with functional ovaries. This also applies to primary APS, as illustrated by data summarized in the Table. In reported series, the first vascular event usually occurs in young adults and rarely in people >60 years old. This age distribution not only reflects a possible bias, ie, the younger the age at first thrombosis, the higher the likelihood of having extensive coagulation tests performed to determine its cause, but also the uncertain significance of positive tests for aPL in the elderly. On the one hand, although data in the literature remain scarce and conflicting, it has been suggested that the prevalence of aCL increases with age in normal subjects. On the other hand, aPL are commonly found in a wide range of situations that frequently occur in the elderly, such as long-term administration of diverse drugs, rheumatoid factor, monoclonal gamopathy of uncertain origin, advanced renal or hepatic dysfunction, polymyalgia rheumatica/temporal arteritis, myeloproliferative disorders, lymphomas, and solid cancers. For example, in a prospective epidemiological study performed in a department of internal medicine on 1014 patients, 70 (mean age, 69 years) had aPL; among these, cancer was found in 14 and was the most frequent associated disease. In the Italian registry on aPL, of 360 patients or subjects, 4 developed non-Hodgkin’s lymphoma during follow-up. Malignancies are a major concern indeed, given that venous thrombosis, especially when recurrent, may be their presenting manifestation. Similarly, a paraneoplastic “marantic” endocarditis may masquerade as an aPL-related valvulopathy complicated by multiple emboli. Furthermore, it has been shown not only that aCL are more prevalent in patients with various forms of malignancies compared with healthy control subjects but also that among the former, aCL, especially in high titers, are associated with a higher incidence of thromboembolic events. The risk exists that positive determinations of aPL may lead physicians to consider a diagnosis of primary APS and prevent them from looking for a possible occult malignancy. In this setting, it should be recalled that APS cannot be considered an explanation for long-lasting fever, sweating, weight loss (except in the rare case of APS-related chronic adrenal failure), or spleen enlargement not due to portal hypertension.

The last point to be discussed is management. Prospective trials are not yet available, but all retrospective studies strongly suggest that recurrent thrombotic events can be efficiently prevented by long-term anticoagulation, especially when aimed at an international normalized ratio of ≥3. Serious bleeding may sometimes occur, but it is assumed that the risk/benefit ratio favors the use of this regimen. However, it should be kept in mind that these data have been

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**Age (Years) at First Thrombosis (Unless Specified) in Patients With Primary APS**

<table>
<thead>
<tr>
<th>Author (Reference)</th>
<th>Year</th>
<th>n</th>
<th>Mean±SD</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asherson (1)*</td>
<td>1989</td>
<td>70</td>
<td>38.5</td>
<td>21–59</td>
</tr>
<tr>
<td>Font (5)</td>
<td>1991</td>
<td>11</td>
<td>32.7±11</td>
<td>22–55</td>
</tr>
<tr>
<td>Rosove (3)†</td>
<td>1992</td>
<td>70</td>
<td>45.5±17</td>
<td></td>
</tr>
<tr>
<td>Vianna (6)*</td>
<td>1994</td>
<td>58</td>
<td>32±10</td>
<td></td>
</tr>
<tr>
<td>Khamashita (4)‡</td>
<td>1995</td>
<td>62</td>
<td>35</td>
<td>18–66</td>
</tr>
<tr>
<td>Cabral (7)</td>
<td>1995</td>
<td>10</td>
<td>32.9±10</td>
<td>20–49</td>
</tr>
<tr>
<td>Knic-Barrie (8)*§</td>
<td>1997</td>
<td>35</td>
<td>41.2±15</td>
<td></td>
</tr>
<tr>
<td>Piette (9)</td>
<td>1998</td>
<td>61</td>
<td>33.8±12</td>
<td>10–65</td>
</tr>
<tr>
<td>Asherson (10)¶</td>
<td>1998</td>
<td>28</td>
<td>41.4±14</td>
<td>17–74</td>
</tr>
</tbody>
</table>

*Also included women with recurrent miscarriages only: 4% in Reference 1, low but not specified in References 6 and 8.
†APS was of the primary form in only 73% of patients. Age was not explicitly referred to as age at first vascular event.
‡Age was median, not mean.
§Age at APS diagnosis.
¶Age at occurrence of “catastrophic” APS. Before catastrophic APS, the oldest patient had a 17-year history of recurrent venous thrombosis/pulmonary embolism.
obtained from series of young patients with primary or SLE-related APS. Age has been demonstrated to be a risk factor for severe bleeding episodes in patients placed on long-term anticoagulation, and we have similar experience in APS. Therefore, the relevance of this regimen remains to be demonstrated in elderly patients with APS. Whether or not “true” primary APS occurs de novo after the age of 60 years, an answer is expected for the aging cohort of patients with clear-cut APS who remain recurrence-free under oral anticoagulation but persistently have demonstrable aPL.

In conclusion, additional data on aPL in the elderly are needed. Within this population, several cross-sectional studies have suggested that the presence of aCL might be an independent risk factor for a precise thrombotic event, such as ischemic stroke. In an individual patient, however, the diagnosis of APS requires more than a single low-positive determination. To date, primary APS should be regarded as a disease that affects mainly young or middle-aged adults. In elderly patients presenting with thrombosis and repeatedly positive tests for aPL, a possible underlying disorder needs to be considered, especially hematological or solid malignancy. Ongoing studies will demonstrate whether other biological markers, such as antibodies directed at β2-glycoprotein I or prothrombin, might help to distinguish, among aPL, those who belong to the autoimmune/thrombogenic subset from those who are just an epiphenomenon. In daily practice, because of its potential hazards, long-term anticoagulation should be discussed on an individual basis in elderly patients with APS.

References
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