Pathogenesis of antiphospholipid antibody syndrome needs further exploration
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Introduction
Antiphospholipid antibody syndrome (APLAS) is an autoimmune thrombophilic condition with or without connective tissue diseases, most commonly systemic lupus erythematosus (SLE) manifested by vascular thrombosis or fetal wastage, associated with antiphospholipid antibodies (APLA). Variety of clinical features has been associated with antiphospholipid (APL) antibodies. Hughes and his team from Hammersmith Hospital, London, first described the syndrome in 1983 and they noted that the increase in anticardiolipin antibodies (aCL) in a cohort of SLE patients was associated with vascular thrombosis, recurrent abortions, and thrombocytopenia.¹

The clinical manifestations have expanded to include thrombocytopenia, hemolytic anemia, cardiac valve disease, pulmonary hypertension, nephropathy, skin ulcers, livedo reticularis, cognitive dysfunction, and premature atherosclerosis.² The prevalence of the disease among the different patient populations in India has been reported to be between 25.5% and 51.5%.³ Compilation of the Pubmed studies available from India (Table 1) clearly shows that there are gaps in the evidence base for the prevalence of APLAS and its association with other diseases.

### Table 1: Studies from India on the prevalence of APLAS

<table>
<thead>
<tr>
<th>Authors</th>
<th>Clinical Manifestations</th>
<th>Prevalence of APLAS</th>
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<tbody>
<tr>
<td>Makhija et al. (2008)⁴</td>
<td>Young stroke</td>
<td>25% of 36 pediatric subjects</td>
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<td>Chandrashekara et al. (2003)³</td>
<td>All thrombotic conditions like deep vein thrombosis, ischemic heart disease, stroke, and other vascular episodes</td>
<td>22.5% out of 302 patients (screened only for aCL IgG)</td>
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<tr>
<td>Vora et al. (2008)⁵</td>
<td>Recurrent pregnancy wastage</td>
<td>44.9% out of 381 subjects</td>
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<tr>
<td>Mishra et al. (2007)⁶</td>
<td>Young myocardial infarction (MI)</td>
<td>35% out of 40 subjects</td>
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<tr>
<td>Vora et al. (2008)⁷</td>
<td>Recurrent pregnancy wastage</td>
<td>42.6% in 431 patients</td>
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<tr>
<td>Vora et al. (2007)⁸</td>
<td>Thrombosis in postpartum period</td>
<td>37.55% of 32 women</td>
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<tr>
<td>Ghosh et al. (2006)⁹</td>
<td>Recurrent pregnancy loss</td>
<td>27.7% of 155 women</td>
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<tr>
<td>Velayuthaprabhu et al. (2005)¹⁰</td>
<td>Recurrent pregnancy loss</td>
<td>51.6% of 155 women</td>
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<tr>
<td>Singh et al. (2001)¹¹</td>
<td>Young MI and stroke</td>
<td>18.18% patients (4/22) in the stroke subgroup and, 4.16% (1/24) patients in MI subgroup had raised aCL titters</td>
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<tr>
<td>Kaneria et al. (1999)¹²</td>
<td>Recurrent pregnancy wastage</td>
<td>32% of 50 patients</td>
</tr>
<tr>
<td>Chakrabarti et al. (1999)¹³</td>
<td>Recurrent pregnancy wastage</td>
<td>42% of the patients</td>
</tr>
</tbody>
</table>
The major clinical manifestations of APLAS are vascular thrombosis and fetal wastage. The pregnancy failure could be partially explained by the associated vascular events.\(^{14}\) The antiphospholipids are a heterogenous group of antibodies targeted against a wide variety of phospholipids, namely cardiolipin, phosphatidyl serine, annexin VA (natural anticoagulant), prothrombin III, and complexed prothrombin. Many years after the discovery of aCL antibodies, it was found that these antibodies mainly target beta 2-glycoprotein 1 (\(\beta 2\)GPI), which acts as a cofactor in binding to phospholipids. Therefore, the pathogenic aCL antibodies are indeed antibodies to beta2-glycoprotein 1. In addition, studies based on animal models have revealed the role of complement proteins in disease development, as the pathognomonic manifestations were not observed in complement knockout mice. However, the evidence is insufficient on how these antibodies lead to thrombosis. Antibodies reacting to clotting factors phospholipid explain the in vivo prolongation of phospholipid dependant clotting process.

The vascular thrombosis occurs only in episodes and not as a continuous ongoing process, even in the presence of APL autoantibodies. In asymptomatic patients, thrombosis may not always develop in the presence of APL. In a follow-up study conducted for 5 years among asymptomatic, APLA-positive patients, the development of clot reported only in 8.1\% of the subjects.\(^{15}\) This is explained by two-hit theory as the precipitating mechanism for vascular thrombosis.\(^{16}\) It has been demonstrated in experimental models as well as in clinical observations that infections, surgical intervention or other procoagulant factor may precipitate thrombosis.\(^{16,17,18}\) Studies have demonstrated that initiation of these triggering events may affect endothelial cells, platelets, procoagulant factors, or on inhibition of anticoagulant factors or complement activation.\(^{19}\)

The platelets play a crucial role in the development of thrombus both in natural circumstances and during pathological conditions. The presence of excess of activated platelet in circulation has been described in patients with APLA using different representative markers. In the recently published article in the current issue of this journal, the in vivo and in vitro studies carried out by Singh et al. demonstrated the presence of activated platelets have several altered functions. The presence of activated platelets was demonstrated in this study without any anti-platelet drug. The study had compared APLAS patients with healthy controls with no APLA antibody and have demonstrated the pivotal role played by the platelets in the development of thrombosis.\(^{20}\) The present study provides evidence to demonstrate the presence of circulating activated platelets in APLAS patients.

However, it is crucial to explore whether the activation of platelet is a primary or a secondary event. In animal experiments using anti-beta-2- microglobulin, they have demonstrated the activation of platelet to occur in the presence of a primary triggering event, independent of anti-beta-2-microglobulin.\(^{16}\) In another study conducted in animal models, Jankowski et al. demonstrated that the platelets should be activated prior to the development of thrombi. They used a photochemically induced model of arterial thrombosis in hamsters to evaluate the procoagulant effect of a murine monoclonal IgG with lupus anticoagulant activity reacting with hamster \(\beta 2\)GPI.\(^{21}\) Irrespective of the first triggering event, the platelets are essential to complete the thrombosis. The studies comparing the presence of activation of platelet in quiescent stage and active thrombotic stage should clarify the sequence of events. The additional probability is that different varieties of APLA, depending on its epitope specificity, may trigger alternative mechanism. Clinical experience and published data have suggested incomplete protection on recurrent thrombosis or pregnancy loss only with anti-platelet strategy.\(^{22}\) Low molecular weight heparin (LMWH) or oral anticoagulants are required to improve the outcome. Detailed study on pathogenic mechanism, if possible using individualized anti-thrombotic strategies, is warranted.

Competing interests
The authors declare that they have no competing interests.

Citation

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References
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