Antiphospholipid Antibody-Related Problems, the Orphan Child of Medicine

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Keywords
Thromboembolic disease, Antiphospholipid antibodies, COVID-19, Anticoagulation

Failure to routinely recognize and/or treat immunologic sources of thromboembolic disease has undermined our ability to improve the quality of life of the patients we serve and even compromised their survival. It’s time to bring it into the mainstream. Explanation for persistence of related oversights and potential resolution is presented.

Thromboembolic disease is so common that it is typically treated without workup for underlying processes (other than hyperlipidemia, diabetes, and sometimes for elevated homocysteine levels). Thromboembolic disease complicates surgical procedures, in which it often seems resistant to conventional prophylactic and therapeutic interventions. There is a litany of metabolic derangements that can stimulate thromboembolic activity. These includes, but are not limited to abnormal or deficient Protein C, Protein S, prothrombin, homocysteine, Factor V Leiden, antithrombin III, disseminated intravascular coagulation. These seem relatively rare and their presence could not be invoked to explain the high population prevalence of thromboembolic disease. There is another cause, which actually is commonly present, immunologic, related to antiphospholipid antibodies [1,2].

One of the challenges created by identification of a disorder new to medical diagnosis is that its initial recognition is generally based on extreme manifestations. Catastrophic antiphospholipid syndrome was one such entity. It was/is the tip of the iceberg related to antiphospholipid-related disease. As the most flagrant manifestations of disease are most “newsworthy,” lesser manifestations receive less attention and the spectrum of disease effects may not receive deserved attention. It is perhaps not surprising that antiphospholipid antibodies have been associated with increased thromboembolic events immunologic disorders such as systemic lupus erythematosus [1,3], dermatomyositis [4], scleroderma [5], rheumatoid and psoriatic arthritis [5] and vasculitis [5]. However, they are also commonly present in individuals with thromboembolic disease, including strokes and myocardial infarctions [1,2]. Perhaps not as widely known is their association with certain infections (syphilis, malaria, Lyme disease and viral infections, including hepatitis C and human immunodeficiency virus (HIV) [6-10]. Such antibody induction has been documented as a post-surgical phenomenon [11].

While presence of antiphospholipid antibodies has been recognized in the above-mentioned disorders, there are other circumstances in which their presence would explain therapeutic failures (Table 1). COVID-19 could be added to this list, given associated thromboembolic disease and anticoagulation failures. Verification of their presence would offer an opportunity for more effectively intervention.

Could antiphospholipid antibodies (which are not rare [1]) be responsible for the above-delineated failures, as prophylaxis with the very convenient low molecular weight heparins and factor Xa antagonists have not proven effective [19] in the presence of antiphospholipid antibodies? Thrombotic event prevention in their presence requires utilization of either unfractionated...
Table 1: Publications decrying the resistance of thromboembolic disease to medical intervention.

<table>
<thead>
<tr>
<th>Study</th>
<th>Conclusion</th>
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<tr>
<td>Inadequacy of osocimab and apixaban for prevention of post-surgical thromboembolic complications [12].</td>
<td>Perhaps it is time to initiate a new paradigm, time, to adopt and take responsibility for orphan diseases? It’s time to bring antiphospholipid antibodies into the mainstream. They are an often overlooked source of some of the most common clinical events. Our clinical algorithm could be enhanced by assuming that everyone with thromboembolic disease has antiphospholipid antibodies and assuring that our evaluation algorithm is revised to require proactive disproval of their presence. It is obvious that not all individuals with thromboembolic disease have antiphospholipid antibodies, but the prevalence is not insignificant (15-33%). However, their role will be missed if the possibility is not routinely considered and tested.</td>
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<td>Inadequacy of standard aspirin doses, low molecular heparin and factor Xa inhibitor in preventing or resolving post-surgical thrombotic events [13,14].</td>
<td>As the goal is prevention as well as treatment of thromboembolic events, historical recurrence is an indication for long-term treatment. Treatment for the first episode (attributable to antiphospholipid antibodies) should probably continue for the duration of antibody persistence, an approach which requires further study.</td>
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<td>Inadequacy of low molecular heparin and factor Xa inhibitor in preventing hemophilia-induced tissue damage [15].</td>
<td>Conflict of Interest</td>
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<tr>
<td>Inadequacy of low molecular heparin and factor Xa inhibitor in preventing space-flight related thrombotic events [16].</td>
<td>There are no financial associations or other possible conflicts.</td>
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<td>Inadequacy of traditional low dose aspirin in preventing thromboembolic disease [17].</td>
<td>References</td>
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Antiphospholipid antibody related problems are quite insidious, far outside standard diagnostic algorithms and therefore routinely evade consideration. Algorithms are the basis and the bane of medical practice. Habits are cultivated/developed for assessing information and for its application. Most physicians have a personal litany of standardized questions related to specific patient concerns, symptoms or signs. Our review of systems is also standardized, whether for generic assessment or limited to specific diagnostic considerations. The physical examination we perform follows a personal template, whether incorporating a full examination or targeting select systems. Sometimes referred to as a search image, our technique for examination of laboratory and radiologic studies similarly follows a template, whether conscious or unconscious. It must be noted that this is medical practice by habit, even rote. That is good medicine and assures that distractions don’t compromise our evaluations.

One aspect of medical care relates to recommending/stimulating patient’s development of new habits or modifying those which are ingrained. We have learned how difficult it is to modify or induce new behaviours, whether related to diet, tobacco or other drug usage. We are no different than the patients we serve in facing the challenge of altering algorithms/search images to accommodate new diagnostic or therapeutic issues and implications.


