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Osteoporosis and Antiphospholipid Antibody-related Problems, the Orphan Children of Medicine

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INTRODUCTION

Failure to routinely recognize and/or treat two phenomena, osteoporosis and 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 them into the mainstream. Explanation for persistence of related oversights and potential resolution are present.

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 behaviors, 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.

OSTEOPOROSIS

Exemplary of the challenge is osteoporosis, often overlooked or untreated even when identified. Diagnoses are typically made when their possibility is considered. Fractures are often treated, without recognizing or acting on their implications. Newer training has emphasized recognition of abuse-related trauma, but perhaps insufficiently, the mechanics of injury. Fractures occurring with minimal trauma or even in the absence of identifying trauma are often mechanically treated, often without consideration of why they occurred. Such are highly suspicious for osteoporosis. Setting or casting the fracture addresses only half the problem. A new algorithm needs to be ingrained to assess the likely presence of an osteoporotic explanation and initiate treatment to prevent future events. Similarly, fractures require assessment of their denouement, not just their direct mechanics, but to also review fall history or other contributing factors.

The algorithm challenge also applies to examination of radiographic studies. Chest radiographic evaluation has perhaps gotten so rote that pathology in the vertebral column (also visible on a chest x-ray, especially the lateral view) is often overlooked [1]. Compression fractures are readily recognizable on lateral chest x-ray and usually identify the presence of osteoporosis. The algorithm must change, with conscious effort to assure that the vertebrae are normal in appearance. That brings up the subject of bone density studies. The range of normal values is predicated on intact vertebrae. Bone density in the presence of vertebral compression fractures is the

composite of the original bone and that added through compression. Bone density measurements would be artificially elevated, such that any "normal" value would be misleading and might actually suggest deficiency – osteoporosis.
Perhaps it is time to initiate a new paradigm? Assume everyone has osteoporosis and assure that your evaluation algorithm is revised to require proactive negation of the presence of osteoporosis.

Antiphospholipid Antibodies

The second orphan disease is even more insidious, far outside standard diagnostic algorithms and therefore routinely evades consideration. 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 [2, 3]. 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 [2, 4], dermatomyositis [5], scleroderma [6], rheumatoid and psoriatic arthritis [6] and vasculitis [6]. They are commonly present in individuals with thromboembolic disease, including strokes and myocardial infarctions [2, 3]. 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) [7-11]. Such antibody induction has been documented as a post-surgical phenomenon [12].

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 [2]) 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 [20] in the presence of antiphospholipid antibodies? Thrombotic event prevention in their presence requires utilization of either unfractionated heparin [21], high doses warfarin (producing prothrombin time INR of 3.0-3.5 [22] (with lesser doses generally ineffective) or antiplatelet-based strategies which reduce their function as inducers of thrombosis. The efficacy of the latter intervention suggests, at least in the post-transcatheter aortic-valve replacement study [14], that antiphospholipid antibodies were present.
When disorders are associated with significant thromboembolic phenomena, it seems reasonable to prospectively identify their antiphospholipid antibody status. Given the implications for choice of medication and dosage, identifying their presence would be expected to have a major impact on medical intervention decisions. So, what should be measured? Perhaps the most reasonable approach is to assess for presence of IgG, IgM and IgA antibodies to anticardiolipin and to beta-2-glycoprotein I (BGPI I) and antibodies to anti-phosphatidylserine/prothrombin [3].

CONCLUSION

Perhaps it is time to initiate new paradigms, time to become a foster parent, to adopt and take responsibility for orphan diseases? It's time to bring osteoporosis and antiphospholipid antibodies into the mainstream. Osteoporosis has significant clinical implications The suggestion is that we modify our approach by assuming that everyone has osteoporosis and assure that our evaluation algorithm is revised to require proactive negation of the presence of osteoporosis. Similarly, antiphospholipid antibodies are phenomena with significant clinical implications. 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.

Table 1: Publications Decrying the Resistance of Thromboembolic Disease to Medical Intervention

• Inadequacy of osocimab and apixaban for prevention of post-surgical thromboembolic complications [13].
• Inadequacy of standard aspirin doses, low molecular heparin and factor Xa inhibitor in preventing or resolving post-surgical thrombotic events [14, 15].
• Inadequacy of low molecular heparin and factor Xa inhibitor in preventing hemophilia-induced tissue damage [16].
• Inadequacy of low molecular heparin and factor Xa inhibitor in preventing space-flight related thrombotic events [17].
• Inadequacy of traditional low dose aspirin in preventing thromboembolic disease [18].
• Inadequacy of standard anticoagulation doses to prevent thromboembolic disease in high risk patients [19].

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ETHICAL STATEMENT

Author has provided an entirely original work containing an accurate account of the work performed as well as an objective discussion of its significance and appropriately cited the work of others.

CONFLICT OF INTEREST

The author declares none

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AUTHORS' CONTRIBUTION

BMR is responsible for conceptualization; data curation; formal analysis; investigation; methodology; project administration; resources; validation; visualization; writing of original draft, its review and subsequent editing.

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