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What you need to know about migraine in Hughes syndrome patients

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Abstract

Background: Headache, often migrainous, is common in patients with antiphospholipid antibodies, whether or not they meet Sydney criteria for a definite diagnosis of Hughes syndrome. Migraine may be a harbinger of stroke in this patient population and even refractory migraine may be highly responsive to antithrombotic therapy in this clinical context.
Purpose: To summarize what is known to date about managing this important manifestation of the immune-mediated hypercoagulable Hughes syndrome.
Results: We provide a suggested management algorithm for refractory headache in this unique patient population.
Conclusion: Most neurologists don't see or recognize many aPL-positive patients in their practice, so hematologists and rheumatologists who see these patients should recognize that refractory headache may be a manifestation of their immune-mediated hypercoagulable disorder and understand that the potential risks of not addressing this issue may be high.

Keywords

Hughes syndrome, antiphospholipid syndrome, antiphospholipid antibodies, migraine, antithrombotic therapy

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Introduction

Rheumatologists and hematologists may not always ask their patients about headaches; however, it is a common issue in patients with antiphospholipid antibodies (aPL), with or without associated lupus, and whether they meet the Sydney criteria for a diagnosis of definite Hughes syndrome. Refractory migraine may improve significantly or even resolve with antithrombotic therapy in these patients,[1] and when not recognized, stroke at a young age may result.[2,3] Many neurologists have few or no diagnosed aPL-positive patients in their practice, so it is imperative for hematologists and rheumatologists who see these patients to recognize and manage headaches that may be a manifestation of their immune-mediated hypercoagulable disorder as the risk to benefit ratio of not initiating antithrombotic trials in this unique patient population may be high.

Refractory migraine can be a harbinger of stroke in young aPL-positive patients

Case report #1. A 36-year-old woman had a history of migraine with aura beginning in adolescence. The headaches were episodic and easy to abort until age 31 when during her second pregnancy they became daily, disabling and refractory to multiple preventive and abortive trials. Two years later, she began to develop occasional TIA-like episodes which were attributed to "complicated migraine," even though she had never experienced the neurological symptoms before. Brain MRI was normal. A few months later, she had a large ischemic stroke. She was then treated with aspirin but had another stroke 3 months later. Lupus anticoagulant (LA) and anticardiolipin antibody (aCL) testing was positive, so warfarin was added to aspirin which resulted in resolution of her headaches, but she remained severely disabled due to stroke sequelae.

Migraine is the most common neurological manifestation in patients with Hughes syndrome, occurring in 20.2% of 1000 patients in the Euro-Phospholipid cohort.[4] Headache was also the most common symptom reported in an online questionnaire of Hughes syndrome patients.[5]

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In 1992, Nencini et al. found that 18% of patients aged 15–44 with TIA or stroke had aCL and/or LA.[6] The aPL-positive patients had significantly more prior cerebral ischemic events ($p = 0.014$), a higher likelihood of recurrent cerebral and systemic thrombotic events during follow-up than the aPL-negative patients and cerebral angiography was negative in all aPL-positive patients.

Due to the frequent responsiveness to antithrombotic therapy, it has been hypothesized that migraine in aPL-positive patients may occur due to aPL-induced microthrombosis/cerebral vascular sludging.[7] This hypothesis has been supported by human autopsy and animal studies in addition to clinical experience. Leach et al. noted widespread cerebral microthrombosis on autopsy of a young antiphospholipid syndrome (APS) patient with recurrent TIA's and complex partial seizures.[8] Similarly, in a well-established APS mouse model, mice develop neuropsychiatric changes and microthrombosis of capillaries visible by electron microscopy, but not routine histology.[9] Cevestro et al. found a 4-fold greater risk for the presence of one or more aPL in 284 patients with migraine compared to 225 controls.[10] Migraine, particularly with aura, has long been associated with an increased risk for stroke[11] and it has been suggested that aPL may be the missing link between migraine and stroke.[12] In 1993, Silvestrini et al, identified 162 patients with a history of ischemic stroke; ten of these patients had aPL and a history of migraine was present in six of the 10 aPL-positive patients compared to only five of the 152 aPL-negative patients ($p < 0.0001$).[3] They noted that migraine may be "prominent" and present for "a long time" before the stroke in the aPL-positive patients. In 2002, Cuadrado et al. published a series of eight young aPL-positive patients with stroke;[2] stroke was preceded by migraine in all patients by a mean of 29 (range 9–72) months. More recently, a meta-analysis of 43 studies found the presence of aPL was associated with a 5.5-fold increased risk for stroke or TIA.[13] Finally, multi-infarct dementia was diagnosed in 2.5% of patients (mean age 34 years) in the Euro-Phospholipid Project.[4]

Given the strong association between aPL-positivity, migraine, and stroke, it is imperative for hematologists and rheumatologists to recognize refractory migraine in aPL-positive patients and understand that it may be a harbinger of stroke in this context without intervention.

Refractory migraine is often responsive to antithrombotic therapy in aPL-positive patients

Case report #2. A 43-year-old female had a history of occasional migraine with aura (onset age 11) and recurrent stress fractures (metatarsal and femur) when distance running in adolescence—a clinical clue that may suggest aPL.[14] At age 40, she developed an escalation in migraine frequency and severity to daily requiring four preventive medications which provided only modest control. She also developed daily "blank spells" in her thinking and word finding difficulties. Brain MRI was normal. 2 years later, her 41-year-old brother had a large ischemic stroke and was diagnosed with triple positive IgM Hughes syndrome. This prompted aPL testing in the patient who was persistently positive for low titer IgM aCL and antiphosphatidylserine antibodies. She was given a trial of aspirin (up to 325 mg daily) without benefit, but a subsequent trial of clopidogrel 75 mg daily resulted in complete resolution of her headaches and memory loss. Nine months later, the headaches and cognitive dysfunction recurred followed by occasional 10–20-min episodes of left-hand numbness/discoordination. A trial of the addition of enoxaparin 1 mg/kg twice daily resulted in complete resolution of migraine, memory loss and TIA's. A trial of changing enoxaparin to warfarin (target INR 2.5) resulted in erratic levels and was not as effective as enoxaparin which was resumed. Subsequently, a trial of apixaban resulted in similar efficacy as enoxaparin and she has been stable on the combination of apixaban 5 mg twice daily and clopidogrel 75 mg daily without migraine, memory loss, TIA, or bleeding for the last 7 years.

Cuadrado et al. reported in 2001 that Hughes syndrome patients treated with anticoagulation for a thrombotic event often reported improvement or resolution of intractable headaches, "mental fuzziness" and/or dysarthria.[5] As a result, they proposed a 2-week "heparin therapeutic trial" in aPL-positive patients with refractory migraine. They treated 21 patients with refractory headaches with a 2-week trial of dalteparin 10,000 units daily. All patients also had memory impairment. Headaches were aborted in 19 of 21 and improved in the other two. Memory loss was improved subjectively in all patients.[15] Similar findings were subsequently published in case reports;[16,17] however, the "heparin therapeutic trial," never became common practice.

We subsequently published our experience in 75 aPL-positive patients with refractory migraine given a trial of antithrombotic therapy.[1] Our results were similar to those reported by prior investigators. The response rate to any anti-thrombotic therapy was 90% with 83% of patients experiencing a major response (50%–100% improvement). For many patients, the response was life-altering. No patient experienced stroke and there were no bleeding events during any of the 2–4-week therapeutic trials.

aPL-positive patients with refractory migraine not meeting Sydney criteria respond similarly to antithrombotic trials as to those meeting the criteria, including patients with only non-criteria aPL

The Sydney (revised Sapporo) criteria for a diagnosis of definite APS require a clinical event (thrombosis or specific pregnancy morbidity) and persistent moderate or high titer

aPL, which are significantly greater than the assay cutoff levels. "Criteria" aPL include aCL and anti-β2GP1 (anti-beta-2 microglobulin 1) IgG/IgM antibodies and the lupus anticoagulant. Since the publication of the Sapporo criteria in 1999, several "non-criteria" aPL[18,19] have become commercially available and multiple "non-criteria" clinical manifestations/associations have been described.[19] Analysis of our patients with aPL and migraine showed response to antithrombotic therapy was not statistically different between patients meeting and not meeting Sydney criteria nor in patients with only non-criteria aPL.[1] This is similar to data published in 1640 patients with obstetric aPL/APS in the EuroAPS registry,[20] in which fetal-maternal outcomes were similar in treated patients meeting and not meeting Sydney criteria.

Other neurological and non-neurological symptoms often also improve with antithrombotic therapy in these patients

Non-headache symptoms reported to improve or resolve by aPL-positive patients given a trial of antithrombotic therapy by various investigators have included TIA's, memory loss, lethargy, seizures, vertigo, tinnitus, visual change, dysarthria, unsteady gait, fatigue, chest pain, shortness of breath, claudication, abdominal pain, livedo reticularis, recurrent line clotting and requirement for intraluminal alteplase, difficulty with suboptimal blood flow during phlebotomy, hypertension control, dysautonomia, neuropathic pain, arthralgia, bone pain in patients with stress fractures or avascular necrosis (AVN), hip pain (suggesting possible early AVN), thrombosed hemorrhoids, and leg ulcers.[1,5,15,21]

Different patients respond differently to different antiplatelet agents and anticoagulants

Case report #3: A 63-year-old woman with triple positive APS and a history of recurrent venous thrombosis (VTE) was maintained on warfarin (goal INR 2.5). While there was not recurrent thrombosis on warfarin, she experienced near daily disabling migraines for 10 years and tried every available migraine preventive and abortive agent without response. A trial of adding low dose aspirin to warfarin, clopidogrel to warfarin and a trial of increasing her goal INR to 3 did not result in headache improvement. She was educated on the existing data recommending avoidance of the direct acting oral coagulants (DOACs) in triple positive APS, but she desired a trial of apixaban, given a labile INR and frequent epistaxis on warfarin. The change from warfarin to apixaban 5 mg twice daily resulted in an 80% reduction in the frequency and severity of her headaches and the epistaxis resolved. A trial of the addition of clopidogrel to apixaban did not result in incremental benefit, but a trial of the addition of low dose aspirin resulted in even further improvement, making the occasional headaches easier to abort. She has maintained a regimen of apixaban 5 mg twice daily and aspirin 81 mg daily for 6 years with only occasional easily aborted headaches without bleeding or clotting despite triple positivity. This patient's experience illustrates the extent of trial and error that is sometimes required to define an effective regimen, the use of shared decision making and that different patients respond differently to different antithrombotic agents. In contrast to this patient's experience, our data showed that clopidogrel was more effective overall in this context than aspirin, with clopidogrel resulting in an 84% response rate (67% major) compared to a 47% response rate (21% major) for aspirin (up to 325 mg daily). Likewise, while most patients did well with apixaban, there were a few patients for whom enoxaparin or warfarin was more effective. A trial of various agents in sequence or in combination may be necessary to define each patient's optimal "symptom-derived regimen."

Some aPL-positive patients require a higher than standard dose of anticoagulants

Just as some aPL-positive patients require a higher INR for optimal symptom control,[21] some patients may require a higher dose of other forms of anticoagulation, including apixaban.[1,22] In the original dose escalation trials of apixaban, doses as high as 25 mg twice daily were given to healthy people without bleeding.[23] The recommended dose of apixaban in the first week following an acute VTE is 10 mg twice daily and a small subset of our patients requires this dose (alone or in combination with antiplatelet therapy) long term for optimal migraine control. We have experience with one patient with a history of multiple arterial thrombotic events on warfarin, who has done well for years on a dose of apixaban 12.5 mg twice daily and clopidogrel 75 mg daily without recurrent clotting or bleeding.

Fatal bleeding risk is low in patients maintained on an "individualized symptom-derived" antithrombotic regimen

In our study, there were no major bleeding events during any of the 2–4-week therapeutic trials. All patients with a significant response to antithrombotic therapy elected to continue the regimen that resulted in significant clinical improvement. Major non-fatal bleeding episodes occurred in three of 69 (4.4%) patients followed for an average of 29.9 (range 5–100) months and all three occurred due to a bleeding risk factor. Two cases involved posterior epistaxis that resolved with cauterization. Interruption in the antithrombotic regimen was not required and there was no recurrence of bleeding in either case after years of subsequent follow-up. The third event was a small intracerebral hemorrhage in a patient who fell and hit her head. She returned

to her prior baseline and resumed antithrombotic therapy without recurrent bleeding. We hypothesize that symptomatic response to antithrombotic therapy in aPL-positive patients may reflect normalization/near normalization of presumed prothrombotic imbalance which might account for the relatively few bleeding events seen in our patients maintained on an "individualized symptom-derived" antithrombotic regimen. Ruiz et al. who published their experience treating patients with Hughes syndrome with warfarin to a target INR of 3.5, also reported that all major bleeding episodes in their study occurred in the context of a bleeding risk factor[24] and none were fatal. When considering the risk to benefit ratio of a trial of antithrombotic therapy in these patients, it is important to recognize that even on anticoagulation, patients with Hughes syndrome are at a greater risk of clotting than bleeding. Ruiz et al. found a risk of thrombosis of 9.1 per 100 patient years despite high dose warfarin which was greater than the bleeding risk (all non-fatal) of 6 per 100 patient years.[24] In the Euro-Phospholipid trial, the risk of fatal clotting during 10 years of follow-up was 3.5-fold greater than the risk of fatal bleeding despite the majority of patients being treated with single or dual antithrombotic therapy.[25]

Long-term efficacy is high. In our study, most responders to antithrombotic therapy continued to respond for the duration of follow-up (average 29.9 months). Three of 52 patients who initially had a major response to antiplatelet therapy developed recurrent headaches after a responsive period of 5–18 months. Headaches resolved long term in each case by adding anticoagulation.[1] Three of 29 patients maintained on dual therapy lost efficacy after 23–86 months. Our experience suggests that loss of efficacy to dual antithrombotic therapy should prompt evaluation for other exacerbating factors, including APS valvular disease and consideration of perimenopausal headaches. Our limited experience suggests that estrogen, when administered transdermally (which has a much lower thrombotic risk compared to oral estrogen), may be well-tolerated in aPL-positive patients treated with anticoagulation which may protect against the prothrombotic effects of estrogen. However, risks and benefits should be carefully considered as the use of hormone replacement therapy in this context has not been studied. If an explanation for headache escalation is not found and the patient has failed trials of the newer migraine preventives, including botulinum toxin injections, calcitonin gene related peptide antagonists (gepants), and serotonin (5-HT)1F receptor agonists (ditans), consideration should be given to a trial of immune modulatory therapy, for example, anti-CD20 monoclonal antibody therapy.[1]

Suggested approach for aPL-positive patients with refractory headache

1. Given the risk for stroke, when evaluating an aPL-positive patient who has experienced new focal neurological symptoms, it is appropriate to assume these symptoms are more likely to represent TIA than to be secondary to migraine and a trial of antithrombotic therapy, usually starting with antiplatelet therapy, is recommended prior to more migraine preventive trials. The recommended trial duration for each agent is 2–4 weeks, but many responsive patients note dramatic symptomatic improvement within days (Figure 1).

2. For patients with a prior history of VTE not being treated with anticoagulation, we recommend starting with a trial of anticoagulation. In the absence of triple positivity or a history of an arterial thrombotic event, we recommend starting with apixaban 5 mg twice daily. Apixaban has been shown to have a reduced risk of bleeding and clotting compared to rivaroxaban in real world data of 37,236 patients with VTE[26] and there are

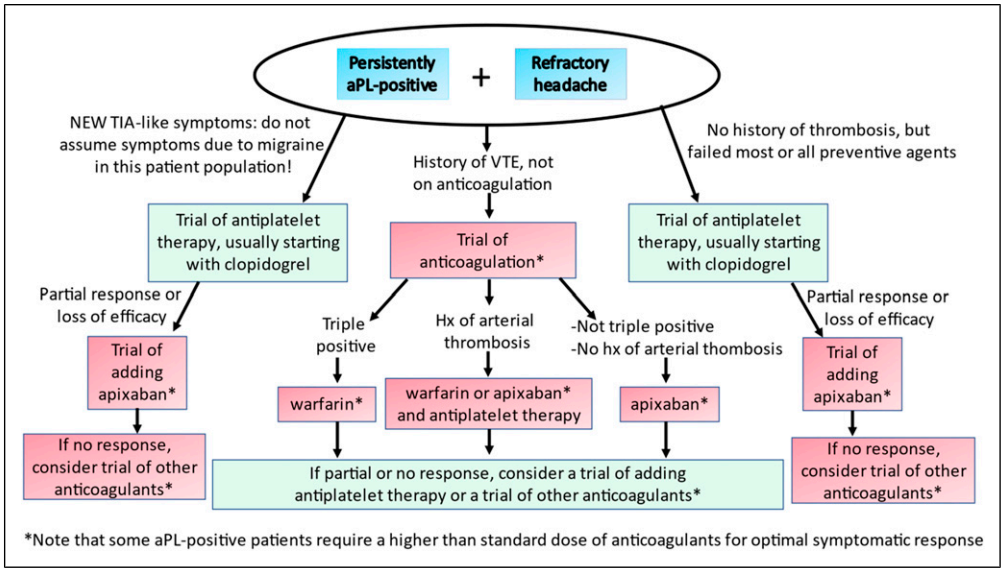

Figure 1. Proposed treatment algorithm.

Table 1. Advantages of DOACs compared to warfarin.

(1) In the randomized, double-blind ARISTOTLE trial of 18,201 patients with atrial fibrillation, apixaban 5 mg twice daily compared to warfarin to a target INR of 2–3 was associated with a reduced risk for stroke (hemorrhagic or ischemic), systemic embolism, major bleeding, or death from any cause ($p < 0.001$) despite the DOAC reversal agents not being available at the time of this study.[27] This data has been supported by more recent studies, including a recent study of 56,336 patients with atrial fibrillation using a DOAC compared to warfarin which found lower risks for ischemic stroke, systemic embolism and major bleeding in patients using a DOAC compared to those treated with warfarin.[28]
(2) DOACs inhibit complement activation which plays an important role in the pathogenesis of APS; warfarin does not[29]
(3) There are minimal drug interactions and no food interactions with DOACs, unlike warfarin.
(4) DOACs do not require routine laboratory monitoring.
(5) There is predictable pharmacokinetics with DOACs, and a steady state drug level is achieved, unlike warfarin where the level of anticoagulation can fluctuate significantly (particularly in APS patients), possibly increasing the risk of both bleeding and clotting.
(6) The much shorter half-life (8–12 hours) of DOACs makes treatment initiation and interruption much more convenient than warfarin which has a very long and unpredictable half-life.
(7) There are now effective reversal agents available for the DOACs.

several important advantages of the DOACs compared to warfarin (Table 1). If the patient experiences clear improvement in headache with the anticoagulation trial, but it is incomplete, consideration can be given to a trial of adding antiplatelet therapy and/or a trial of comparing the efficacy of apixaban to other anticoagulants (e.g., warfarin, enoxaparin, fondaparinux) and/or a trial of comparing clopidogrel to aspirin as illustrated by Case Report #3 above. Other antiplatelet agents might also be considered, for example, ticagrelor or dipyridamole. If the patient is triple positive, we recommend starting with a trial of warfarin with trials of other anticoagulants and/or antiplatelet agents being considered (practicing shared decision making) if the response to warfarin is incomplete and/or not well tolerated. If the patient has a history of a prior arterial event, a trial of warfarin alone or apixaban and an antiplatelet agent should be considered.

3. For all other patients, we recommend starting with a trial of antiplatelet therapy, usually starting with clopidogrel 75 mg daily as it was shown to be more effective in this context than aspirin.[1] If there is a definite but incomplete response to clopidogrel, a trial of aspirin starting at low dose and increasing if needed to 325 mg daily should be considered. If there is no response to either antiplatelet agent, they should be discontinued unless there is a high thrombotic risk phenotype, and the decision is made to continue antiplatelet therapy preventively. A trial of anticoagulation may then be considered. If there is a partial response to antiplatelet therapy, consideration should be given to a trial of adding an anticoagulant, usually starting with apixaban with consideration of a trial of others if there is intolerance or an inadequate response. Combination therapy should be continued only if there is definite significant improvement with the addition of the anticoagulant.

4. It is imperative that antithrombotic trials be carried out during a time when the patient is at a reasonable baseline and that no other medication or dietary trials are being carried out so that an association between improvement (or not) and the medication being trialed can be recognized.

5. If there is recurrence of headache after initial response to antiplatelet therapy, we recommend a trial of adding an anticoagulant, usually starting with apixaban 5 mg twice daily. As noted, some aPL-positive patients on warfarin require an INR target greater than the usual 2–3 for optimal symptom control and a small subset of patients treated with apixaban require a dose higher than 5 mg twice daily for optimal symptom control. Higher doses should be maintained only if they provide definite significant symptomatic improvement compared to standard dosing.

6. If there is headache recurrence after initial response to dual antithrombotic therapy and there is failure of the newer migraine preventive agents, including gepants and ditans, other potential causes for headache escalation should be considered. In the rare patient without another explanation for headache escalation, consideration should be given to a trial of anti-CD20 monoclonal antibody therapy.[1]

Conclusion

Refractory headache may be a harbinger of stroke in aPL-positive patients, including those not meeting Sydney criteria for a diagnosis of definite Hughes syndrome. Migraine refractory to usual migraine preventive and abortive agents is often responsive to antithrombotic therapy in these patients with a low risk of fatal bleeding. Since many neurologists may not have or recognize aPL-positive patients in their practice, it often falls to hematologists and rheumatologists to ask aPL-positive patients about refractory headache and to consider antithrombotic interventions which may effectively address this relatively common manifestation of this immune-mediated hypercoagulable disorder.

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