JACC: CASE REPORTS VOL. 20, 2023

EDITORIAL COMMENT

Testing for Hypercoagulability in Patients With Unexplained Arterial Thromboembolism*

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Most acute ischemic arterial events are a result of atherosclerotic plaque disruption with superimposed thrombus formation or embolism from the heart, and guidelines provide evidence-based recommendations for their diagnosis and management. Less commonly, acute ischemic arterial events occur in patients who do not have atherosclerosis or an identified embolic source and seem to be otherwise unexplained. Without knowledge of the underlying cause, clinicians find it challenging to manage these patients.

In this issue of *JACC: Case Reports*, Kalogeras et al[1] describe a previously healthy 24-year-old man who presented with acute anterior ST-segment elevation myocardial infarction. After administration of dual antiplatelet therapy (aspirin plus ticagrelor), he underwent emergency coronary angiography, which demonstrated a large burden of thrombus occluding the left anterior descending coronary artery with no evidence of underlying atherosclerosis or dissection. He was given intravenous tirofiban and underwent thrombus aspiration with partial restoration of coronary flow. Further investigations revealed no evidence of atrial fibrillation or a patent foramen ovale, but cardiac ultrasound examination showed an apical inferolateral wall thrombus; therefore, he was started on treatment with a vitamin K antagonist (acenocoumarol) with low-molecular-weight heparin (LMWH) bridging. Repeat angiogram before discharge showed complete restoration of coronary flow with no residual thrombus. Despite treatment with therapeutic anticoagulation and antiplatelet therapy, he was readmitted several weeks later with a large cardioembolic stroke, and he later died in hospital.

The occurrence of unexplained acute arterial thromboembolism in a young patient without an identifiable underlying cause was strongly suggestive of a hypercoagulable state, and this seemed to be confirmed by the finding of qualitative (type II) protein S deficiency, characterized by normal protein S antigen levels with reduced function. Based on this experience, Kalogeras et al[1] suggest the need to test for hypercoagulability in patients with arterial thromboembolism, and particularly in younger patients with otherwise unexplained events.

There are no high-quality data to inform the role for hypercoagulability testing in patients with unexplained arterial thromboembolism. Our approach is to focus the workup on potential causes of hypercoagulability that if diagnosed are expected to alter patient management. In **Table 1**, we list systemic illnesses (eg, cancer, autoimmune or autoinflammatory disorders) and acquired conditions (eg, antiphospholipid antibody syndrome, heparin-induced thrombocytopenia, paroxysmal nocturnal hemoglobinuria, JAK2 mutation with or without myeloproliferative neoplasm manifestations) associated with hypercoagulability that, if diagnosed, would alter clinical management.

Is there a role for testing for inherited thrombophilia in patients with unexplained arterial thromboembolism? The most common causes of inherited thrombophilia include the factor V Leiden (F5

*Editorials published in *JACC: Case Reports* reflect the views of the authors and do not necessarily represent the views of *JACC: Case Reports* or the American College of Cardiology.

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

ISSN 2666-0849 https://doi.org/10.1016/j.jaccas.2023.101944

TABLE 1 Evaluation of Hypercoagulability in Patients With Unexplained Arterial Thromboembolism

Categories	Conditions	Comments
Systemic conditions	Cancer Autoimmune or auto-inflammatory disorders Infections (eg, COVID) Substance use (eg, anabolic steroids) Medications (eg, hormone replacement therapy)	Restrict testing to conditions associated with a hypercoagulable state that could alter clinical management
Acquired hypercoagulable disorders	Antiphospholipid testing: aCL IgG, IgM; ab2GPI IgG, IgM; lupus anticoagulant Myeloproliferative neoplasms: Complete blood count, JAK 2 mutational analysis HIT or autoimmune HIT: HIT EIA and functional assay. Thrombotic microangiopathy: hemolytic screen, examination of blood smear for schistocytes Paroxysmal nocturnal hemoglobinuria: flow cytometry for PNH screen	Perform testing in patients with relevant clinical findings or in those who are young or experience refractory or recurrent thrombosis despite therapy. Diagnosis of these conditions is expected to alter clinical management
Inherited thrombophilia	Genetic testing: Factor V Leiden (F5 G1691A), prothrombin gene mutation (F2 G20210A) Coagulation testing: protein C, protein S, antithrombin	Consider selective testing in young patients or strong family history of venous or arterial thrombosis in whom the presence of a high-risk thrombophilia (eg, compound heterozygosity; PC, PS, or AT deficiency) may prompt consideration for long-term anticoagulation

ab2GP1 = anti-beta2 glycoprotein 1; aPL = antiphospholipid; AT = antithrombin; EIA = enzyme immunoassay; HIT = heparin-induced thrombocytopenia; Ig = immunoglobulin; JAK2 = Janus kinase 2; PNH = paroxysmal nocturnal hemoglobinuria. PC = protein C; PS = protein S.

G1691A) and prothrombin gene (F2 G20210A) variants, and deficiencies of protein C, protein S, and antithrombin, collectively found in 5% to 10% of the general population. Inherited thrombophilias have consistently been associated with a ≥2- to 8-fold risk of first-ever venous thromboembolism (VTE), but their association with recurrent VTE or arterial thromboembolism is much weaker.[2,3] After initial enthusiasm for routine thrombophilia testing in patients with unexplained VTE, guidelines now indicate that this factor has limited relevance in patients with VTE because, in most cases, the finding of an inherited thrombophilic disorder does not change management or improve the clinical outcome.[4] In patients with arterial thromboembolism, there is even less evidence to guide testing for inherited thrombophilia, and opinions are conflicting. However, several recent expert groups as well as the British Society for Haematology guidelines recommend against routine inherited thrombophilia testing in patients with unexplained arterial thromboembolism.[3,5,6] Our approach is to restrict testing to younger patients (age <50 years) and to those with a strong family history of venous or arterial thrombosis in whom the presence of a high-risk thrombophilia may influence decisions regarding the choice, initiation, or duration of anticoagulation (**Table 1**).

Returning to the case, we agree that it is reasonable to test for inherited thrombophilia in this 24-year-old man with unexplained arterial thromboembolism. However, we would also like to highlight several important issues about testing. First, acute thrombosis can decreased blood levels of protein C, protein S, and antithrombin, which complicates interpretation of the results, and anticoagulation use can interfere with the assays. Second, recognizing the potential influences of preanalytical and analytical variables on observed blood levels, International Society of Thrombosis and Haemostasis guidelines recommend repeat measurement ≥4 weeks after the first test to confirm the diagnosis of protein S deficiency.[7] It is unclear whether Kalogeras et al[1] were able to confirm deficiency on repeat testing. Third, because protein C and S are vitamin K-dependent proteins with a short half-life, vitamin K antagonist therapy should be initiated cautiously in affected individuals to avoid further lowering of blood levels, which could lead to a transient exacerbation of hypercoagulability and severe thrombotic complications, including skin necrosis. Avoidance of a high initial dose of a vitamin K antagonist and the use of short-term bridging anticoagulation using heparin or LMWH may help to mitigate these risks.[8]

In summary, there is no high-quality evidence to inform the role of routine evaluation of hypercoagulability in patients with unexplained arterial thromboembolism, and it is unlikely that randomized trials will ever be performed to address this issue. We suggest that evaluation for systemic disorders associated with hypercoagulability and testing for

acquired and inherited thrombophilias is reasonable in patients who have relevant clinical findings, and in selected patients in whom the results may influence decisions about the choice, initiation, or duration of treatment. In this patient, a diagnosis of protein S deficiency informed the need for careful initiation of vitamin K antagonist with LMWH bridging and would have strengthened the case for indefinite anticoagulation.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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KEY WORDS acute coronary syndrome, protein S, stroke, testing, thrombophilia, unexplained arterial embolism