An Audit of Thrombophilia Testing in Patients with Ischemic Stroke or Transient Ischemic Attack: The Futility of Testing

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Objectives: Many patients admitted with an ischemic stroke or transient ischemic attack (TIA) undergo thrombophilia testing. There is limited evidence to support this practice. We examined the effect of thrombophilia testing on management of patients admitted with an ischemic stroke or TIA. *Materials and Methods:* In this retrospective observational single-center study, we identified patients who were admitted with stroke or TIA and underwent thrombophilia testing over a 45-month period. We reviewed their electronic medical records to assess whether testing affected clinical management, defined as anticoagulation treatment by the time of discharge due to a positive test result. Secondary endpoints included potential misdiagnosis due to false positive results and cost of testing. *Results:* Testing was performed in 143 patients with a stroke or TIA. Forty-four patients (31%) had at least 1 positive test result. The most common positive tests were an elevated factor VIII activity (18% of patients tested) and decreased protein S activity (11% of patients tested). Both of these tests are subject to acute phase effects. Testing altered clinical management in only 1 patient (1% of total patients tested). Thirty-three patients (75%) have the potential for carrying a misdiagnosis due to a positive test that was never repeated for confirmation or repeated too soon after the initial positive test. The annual cost of testing was approximately $62,000. *Conclusions:* Thrombophilia testing in the acute inpatient setting rarely impacted the clinical management of patients admitted with a stroke or TIA. By avoiding thrombophilia testing, both the potential for misdiagnosis and health care costs can be reduced. Therefore, we have discontinued thrombophilia testing in in-patients with a diagnosis of stroke.

Key Words: Stroke—thrombophilia testing—hypercoagulable workup—hereditary thrombophilia—antiphospholipid antibodies—Ischemic stroke—antithrombin deficiency—protein C deficiency

Introduction

The annual incidence of a new or recurrent stroke in the United States is approximately 795,000 people.[1] For patients with an initial stroke or transient ischemic attack (TIA), it is imperative to prevent a future stroke with the use of antiplatelet agents and by treating risk factors such as hypertension, hyperlipidemia, and atrial fibrillation.[2]

Many adult patients, usually with cryptogenic stroke and TIAs, also undergo inherited and acquired thrombophilia testing to identify a potential cause and possibly determine short- and long-term anticoagulation for secondary stroke prophylaxis. However, there is a paucity of evidence to support this practice. Because there are no well-defined guidelines for testing, adult patients with

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stroke or TIA are often tested for thrombophilia as part of the acute diagnostic evaluation.[3] We have previously shown that during the acute setting, thrombophilia testing in patients with venous thromboembolism is potentially harmful.[4] Similarly, during the acute setting of an ischemic stroke or TIA, concurrent anticoagulation or acute phase effects can lead to inaccurate test results.[4]

Herein, we audited thrombophilia testing for patients admitted with a stroke or TIA at our institution. We investigated if inpatient thrombophilia testing during the acute setting affected clinical management. In addition, we sought to determine whether thrombophilia testing during the acute setting was potentially harmful to patients.

Materials and Methods

Study Population

We performed a retrospective audit of all consecutive adult patients admitted with an ischemic arterial stroke or TIA that underwent thrombophilia testing over a 45-month period (January 1, 2011 to September 30, 2014) at 2 university hospitals affiliated with the University of Texas Southwestern Medical Center. All inpatients having at least 1 thrombophilia test performed were identified through the laboratory information system. Patient charts were then reviewed to identify the patients who had thrombophilia testing performed as part of the diagnostic workup for stroke or TIA. The University of Texas Southwestern Medical Center Institutional Review Board approved the study and waived the requirement of informed consent.

Inclusion and Exclusion Criteria

All subjects admitted with an ischemic arterial stroke or TIA and undergoing thrombophilia testing were included. Subjects were excluded if they underwent thrombophilia testing for other reasons aside from evaluation of arterial ischemic stroke or TIA. The diagnosis of stroke or TIA was determined by neurologist documentation within the electronic medical record.

Study Objectives

The primary study objective was to determine if thrombophilia testing during the inpatient setting affected clinical management of patients admitted with an ischemic stroke or TIA. We define a change in clinical management as whether the patient was treated with anticoagulation by the time of discharge based on positive thrombophilia test results. A secondary aim was assessing possible harm caused by thrombophilia testing. We defined this as misdiagnosis of a thrombophilia defect due to a false positive test result (as a consequence of consumption of natural anticoagulants during the acute phase or due to the use of concurrent anticoagulation at the time of testing) leading to unnecessary anticoagulation, potential for a false positive diagnosis (if a positive test was never repeated after the acute setting to confirm the defect), and total cost of unnecessary testing. A conservative estimate of $100 per thrombophilia marker was used.[3]

Data Extraction

Clinical information obtained from the electronic medical record included age, sex, stroke versus TIA based on neurologist documentation, anticoagulation at the time of testing, tests ordered, test results, whether abnormal test results were repeated to confirm a diagnosis, and whether the patient was discharged with anticoagulation. Tests included lupus anticoagulant (LA), anticardiolipin, anti-β2 glycoprotein I (aβ2GPI), antiphosphatidylserine (aPS), antiprothrombin (aPT) antibodies, activated protein C resistance (APCR), factor V Leiden (FVL), prothrombin gene mutation (PGM), protein C (PC) activity, protein S (PS) activity, antithrombin (AT) activity, and factor VIII (FVIII) activity.

Laboratory Tests

FVL and PGM were performed by molecular methods. PC, PS, and AT were considered deficient only when the activity was <60%. Confirmation of a deficiency of the natural anticoagulants required reproducibility of the deficiency in a second sample while off anticoagulation for at least 2 weeks and at least 4 weeks after the acute thrombotic event. FVIII activity was considered significantly elevated if levels were ≥200% after repeat testing more than 6 months later. LA was positive if either the dilute Russell's viper venom time ratio or silica clotting time ratio was diagnostic. aβ2GPI and antiphosphatidylserine were positive if > 99th percentile, and a positive anticardiolipin was ≥40 MPL or GPL. If an antiphospholipid antibody test was positive ≥12 weeks later, only then was the patient considered to have antiphospholipid syndrome.

Statistical Analysis

Categorical data were expressed as counts and percentages while continuous variables were expressed as medians (range; interquartile range [IQR]) and means when appropriate. Data were recorded and analyzed using Microsoft Excel 2010 (Microsoft Corporation, Seattle, WA).

Results

Demographics

A total of 1274 inpatients had ≥1 thrombophilia test performed, of which 143 patients had a diagnosis of an ischemic arterial stroke or TIA. The median age at presentation was 51 years (19-90, [IQR: 40-61.5 years]), and 83 patients were females (58%). Sixty-nine (48%), 58 (41%),