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ORIGINAL ARTICLE

Calciphylaxis: A Disease of Pannicular Thrombosis

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Abstract

Objective: To identify coagulation risk factors in patients with calciphylaxis and the relationship between anticoagulation use and overall survival.

Patients and Methods: Study subjects were 101 patients with calciphylaxis seen at Mayo Clinic from 1999 to September 2014. Data including thrombophilia profiles were extracted from the medical records of each patient. Survival status was determined using patient registration data and the Social Security Death Index. Survival was estimated using the Kaplan-Meier method, and associations were evaluated using Cox proportional hazards models.

Results: Sixty-four of the 101 patients underwent thrombophilia testing. Of these, a complete test panel was performed in 55 and a partial panel in 9. Severe thrombophilias observed in 60% (33 of 55) of the patients included antiphospholipid antibody syndrome protein C, protein S, or antithrombin deficiencies or combined thrombophilias. Of the 55 patients, severe thrombophilia (85%, 23 of 27) was noted in patients who were not on warfarin at the time of testing (27). Nonsevere thrombophilias included heterozygous factor V Leiden (n=2) and plasminogen deficiency (n=1). For the comparison of survival, patients were divided into 3 treatment categories: Warfarin (n=63), other anticoagulants (n=20), and no anticoagulants (n=18). There was no statistically significant survival difference between treatment groups.

Conclusion: Laboratory testing reveals a strikingly high prevalence of severe thrombophilias in patients with calciphylaxis, underscoring the importance of congenital and acquired thrombotic propensity potentially contributing to the pathogenesis of this disease. These findings may have therapeutic implications; however, to date, survival differences did not vary by therapeutic choice.

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Calciphylaxis is a rare disease characterized by the sudden onset of painful fat necrosis due to vascular medial calcification and thrombosis of small arterioles supplying the adipose tissue. The etiology of this disease remains largely unknown, although various pathogenic mechanisms have been proposed.[1,2] Known risk factors for calciphylaxis include end-stage renal disease, chronic hemodialysis, female sex, obesity, and hyperparathyroidism.[3] Other risk factors that have been suggested include warfarin and prednisone use. Many patients with calciphylaxis are chronically anticoagulated with warfarin as a potential calciphylaxis treatment, and often for coexisting cardiovascular disorders including atrial fibrillation, venous thromboembolism, or heart valve prosthesis.[4] Indeed, warfarin has been implicated as a contributory factor in the pathogenesis of calciphylaxis.[5-8] Warfarin may impact calcium deposition in vessel walls.[9] During our previous study of 15 patients on the efficacy of tissue-plasminogen activator as an adjunctive measure in the treatment of calciphylaxis, we noted that most patients had laboratory parameters that suggested a hypercoagulable state.[5] The association between either congenital or acquired thrombophilia and calciphylaxis has not been

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adequately explored. The objective of the present study was to assess the prevalence of thrombophilic disorders in a cohort of consecutive patients with this diagnosis. We further sought to determine whether warfarin anticoagulation negatively impacts survival in these patients.

PATIENTS AND METHODS

Consecutive patients with the diagnosis of calciphylaxis seen at Mayo Clinic in Rochester, Minnesota, between January 1, 1999, and September 30, 2014, were included in the analysis. Identified cases were scrutinized by 2 independent reviewers including assessment of the clinical history, photos, and skin biopsy findings. Cases were then categorized as "definite," "probable," "possible," or "not consistent with" the calciphylaxis diagnosis. Only "definite" or "probable" cases were included in the final analysis.

Data were collected from a centralized system that contains complete records of all patients treated and followed at Mayo Clinic in Rochester, Minnesota. The Mayo Clinic medical record for each patient contains the details for every inpatient hospitalization, every outpatient visit regardless of the provider, every radiology examination and all laboratory and pathology results (including autopsy reports), death certificates, and relevant correspondence. The medical record was scrutinized for current or previous antithrombotic therapy including all anticoagulant and antiplatelet therapy use. The patients were classified as having exposure to warfarin, aspirin, or other antithrombotic agents if the drug was used for more than 1 month during the 6 months before or after the date when first seen at Mayo Clinic.

The medical records were reviewed to identify patients with thrombophilia testing, when it was performed in relation to the initiation of anticoagulation, and whether the thrombophilia test panel was complete or partial. For those undergoing the complete thrombophilia profile, all assays were performed in the Mayo Clinic Special Coagulation and DNA Diagnostic Laboratories and ordered as a test panel rather than as individual assays. The thrombophilia test panel included assessment for deficiencies of protein C,[10] protein S,[11,12] or antithrombin,[13] dysfibrinogenemia, intravascular coagulation and fibrinolysis, activated protein C resistance[14] (including genotyping for the factor V Leiden [F5 rs6025] mutation,[15] if abnormal), and genotyping for the prothrombin G20210A (F2 rs179963) mutation.[16] Assays for a lupus anticoagulant[17] and IgG and IgM isotype anticardiolipin antibodies were also performed on all patients as was a measure of basal plasma homocysteine.[18] Anticardiolipin antibody and homocysteine assays were performed by the Mayo Clinic Clinical Immunology and Biochemistry Laboratories. Parenteral anticoagulant effect was assessed by reviewing the record and assessing the thrombin time. The thrombin time is exquisitely sensitive to either heparin or direct thrombin inhibitor therapy. For patients with a history of warfarin exposure, concordant assessment of factor VII for those patients with protein C abnormalities and factor II for those with protein S abnormalities was used to discern warfarin effect from a congenital protein deficiency.

"Severe thrombophilias" included antiphospholipid antibody syndrome (lupus anticoagulant, antiphospholipid antibodies), protein C, protein S, or antithrombin deficiencies, homozygous mutations of factor V Leiden or prothrombin *G20210A* gene, or compound heterozygous mutations of these genes. "Nonsevere thrombophilias" were defined as heterozygous mutations of factor V Leiden or prothrombin *G20210A* gene or plasminogen deficiency. Combination of any of the above thrombophilias was also placed into the "severe" category. Elevated fibrin D-dimer and elevated fibrinogen were not included as a thrombophilia for this purpose.

Duration of follow-up was calculated from the date of the calciphylaxis diagnosis to the date of death or last follow-up visit. Survival status, date of death, or date of last follow-up was determined for all patients using their Mayo Clinic registration data or the Social Security Death Index when Mayo data were insufficient. Written questionnaires were sent to all surviving patients or those for whom survival status was unknown. If no reply, 2 follow-up telephone calls were made to ascertain their survival status.

This study was conducted with the approval of the Mayo Clinic Institutional Review Board in accordance with federal

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