Case Report

Effects of Inherited Thrombophilic Mutations in an Adolescent with Antiphospholipid Syndrome and Systemic Lupus Erythematosus

ERIC A. HIGGINBOTHAM, SHERRI A. ZIMMERMAN, THAD A. HOWARD, LAURA SCHANBERG, DEBORAH KREDICH, and RUSSELL E. WARE

ABSTRACT. Thrombophilia can result from either inherited or acquired conditions. We describe a teenager who developed extensive thrombosis requiring aggressive and prolonged anticoagulation. Laboratory evaluation revealed an acquired lupus anticoagulant, consistent with the antiphospholipid antibody syndrome (APS). DNA analysis revealed inherited thrombophilic mutations in the factor V and methylene tetrahydrofolate reductase genes. We believe that the combination of inherited and acquired hypercoagulable conditions affected her therapeutic response to anticoagulant therapy. Inherited thrombophilic DNA mutations may contribute to the hypercoagulability observed in patients with acquired thrombophilic conditions such as APS and systemic lupus erythematosus. (J Rheumatol 2001;28:370–2)

Key Indexing Terms:
ANTIPHOSPHOLIPID SYNDROME LOW MOLECULAR WEIGHT HEPARIN
LUPUS ANTICOAGULANT SYSTEMIC LUPUS ERYTHEMATOSUS THROMBOPHILIA

Thrombophilia is an increased tendency to form or maintain clots, usually presenting at a young age. Thrombophilia results from either acquired or inherited conditions. Recognized causes of acquired thrombophilia include oral contraceptives (OC), pregnancy, malignancy, antiphospholipid antibody syndrome (APS), and others[1]. However, clinical thrombosis occurs only in a subset of patients with acquired thrombophilic conditions. For example, many patients with systemic lupus erythematosus (SLE) have antiphospholipid antibodies or a lupus anticoagulant (LAC), but only some will develop thrombosis.

Inherited thrombophilia traditionally includes deficiencies of circulating anticoagulants protein C, protein S, antithrombin III, and plasminogen activator[2]. Recently, the factor V Leiden mutation and specific DNA mutations in the methylene tetrahydrofolate reductase (MTHFR) and prothrombin genes have been associated with venous and arterial thrombosis in adults[2]. There is evidence that these and other inherited mutations affect children as well[3,4], although their importance remains incompletely defined.

The combination of acquired and inherited thrombophilia may represent a potent hypercoagulable state. We describe a teenager who developed extensive venous thrombosis requiring months of high dose heparin therapy. Laboratory evaluation revealed a LAC as well as thrombophilic factor V and MTHFR mutations. The combination of inherited and acquired thrombophilic conditions likely increased her risk for thrombosis and influenced her therapeutic response. We speculate that inherited thrombophilia can affect the clinical expression of patients with acquired thrombophilic conditions such as APS and SLE.

CASE REPORT

A previously healthy 15-year-old Caucasian girl taking low estrogen OC (Orthocept®) for contraception prophylaxis developed painful subcutaneous nodules on both lower extremities. Significant laboratory studies included an elevated erythrocyte sedimentation rate (61 mm/h), positive antinuclear antibody titer (1:2560, speckled), and elevated anti-dsDNA (143 IU/ml). Direct antiglobulin test was weakly positive for IgG and C3. Serum complement studies were normal and antibodies to extractable nuclear antigens (Ro, La, Sm, and RNP) were negative. She was diagnosed with erythema nodosum and probable SLE. She discontinued OC and the nodules resolved with ibuprofen. Six weeks later she developed progressive left leg swelling. Doppler ultrasonography documented common femoral vein thrombus extending into the proximal to mid-left superficial femoral vein. She was hospitalized for evaluation and treatment. Medical and family history were negative for thrombosis. The maternal grandmother has SLE. Medications included only ibuprofen. She denied alopecia, mouth sores, rash, fever, or joint symptoms.

On admission her thigh was erythematous, warm, and diffusely tender

From the Medicine-Pediatric Residency Training Program, the Division of Hematology/Oncology, and the Division of Rheumatology, Department of Pediatrics, Duke University Medical Center, Durham, North Carolina, USA.

E.A. Higginbotham, MD, Medicine-Pediatric Residency Training Program; S.A. Zimmerman, MD; T.A. Howard, MS; R.E. Ware, MD, PhD, Division of Hematology/Oncology; L. Schanberg, MD; D. Kredich, MD, Division of Rheumatology, Department of Pediatrics.

Address reprint requests to Dr. R.E. Ware, PO Box 2916, DUMC, Durham, NC 27710; E-mail: ware0005@mc.duke.edu

Submitted April 6, 2000 revision accepted August 14, 2000.

with venous distension. Hemogram, chemistries including BUN and creatinine, and urinalysis were normal. Anti-dsDNA was elevated (92 IU/ml). Prothrombin time was normal but activated partial thromboplastin time (aPTT) was elevated (55.5 s, normal 22–34 s). Prolonged 1:1 aPTT incubated mixing study and positive Russell viper venom screen (2.45 U, normal < 1.2 U) were diagnostic for LAC. She had low positive IgG (20 units) and IgM (11 units) anticardiolipin antibodies (normal < 10). Total plasma homocysteine was 8 µM (normal 13 µM). Antithrombin III (119%), protein C (103%), and plasminogen (179%) were normal, while a low functional protein S level (41%, normal ≥ 50%) was believed to be secondary to the thrombus formation. Her diagnosis was antiphospholipid syndrome and probable SLE.

She was initially anticoagulated with low molecular weight heparin (LMWH), 1.5 mg/kg SQ q 12 h, but leg pain and swelling worsened on day 4 despite a LWMH level of 0.5 U/ml. Ultrasonography and magnetic resonance imaging (MRI) documented increased thrombus from the popliteal to external iliac vein. Therapy was changed to unfractionated porcine heparin, but she required high doses (1850 U/h, 26 U/kg/h) to achieve a plasma heparin level of 0.4–0.5 U/ml. She also received methylprednisolone, 1 g intravenously each week, and acetylsalicylic acid 325 mg PO q day. Her symptoms slowly improved and she went home taking continuous intravenous heparin.

After 3 weeks, ultrasonography showed no clot progression. Coumadin was added but quickly stopped after she developed new left leg swelling. She continued taking intravenous heparin for 4 more weeks, then switched to LMWH 2.0 mg/kg SQ q 12 h, maintaining a peak level of 0.8–1.0 U/ml anti-Xa activity. Seven weeks later, she had an abrupt increase in left leg tenderness and swelling; continuous heparin was restarted as well as oral corticosteroids (60 mg prednisone q day), pentoxyfylline (400 mg TID), and hydroxychloroquine (200 mg BID) to treat underlying SLE. After 2 more months, she resumed LMWH 2.0 mg/kg SQ q 12 h. Six months after diagnosis, she began coumadin 10 mg PO q day with an international normalized ratio of 3.0. Twelve months after diagnosis, ultrasonography and MRI showed no clot.

DNA analysis for thrombophilic mutations[5] revealed heterozygosity for factor V G1691A (factor V Leiden) mutation, inherited from her father (Figure 1A), and homozygosity for the C677T MTHFR mutation (Figure 1B).

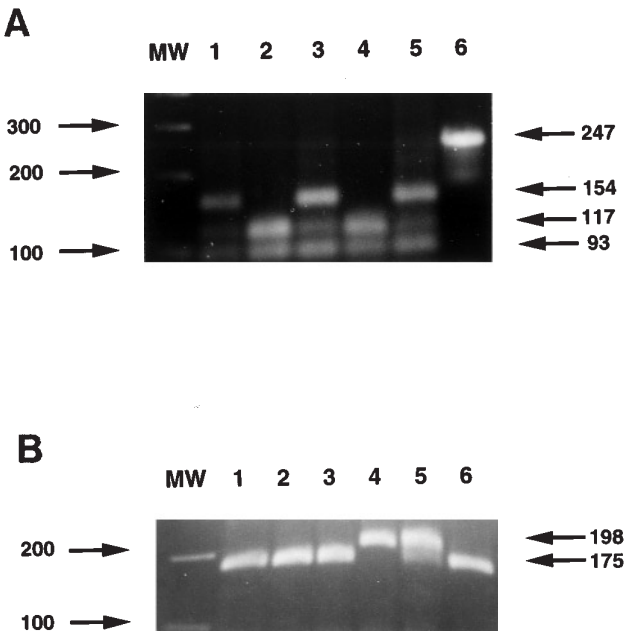

Figure 1. DNA analysis from the patient and her parents for inherited thrombophilic mutations. Methods of genomic DNA purification, restriction enzyme digestion, and interpretation were as described[5]. A. Analysis for the G1691A factor V (Leiden) mutation. Lane 0: molecular weight (MW) markers, Lane 1: patient, Lane 2: mother, Lane 3: father, Lane 4: normal control, Lane 5: control with heterozygous factor V mutation, and Lane 6: uncut DNA. Both patient and her father are heterozygous for the thrombophilic factor V mutation. B. Analysis for the C677T MTHFR mutation. Lane 0: molecular weight (MW) markers; Lane 1: patient, Lane 2: mother, Lane 3: father, Lane 4: normal control, Lane 5: control with a heterozygous MTHFR mutation, and Lane 6: control with a homozygous mutation. The patient and her mother and father are homozygous for the thrombophilic MTHFR mutation.

DISCUSSION

LAC are acquired autoantibodies that prolong the aPTT by binding phospholipid components of the clotting cascade. LAC are associated with hypercoagulability *in vivo*, especially for patients with SLE[6]. By metaanalysis, adults with SLE and LAC have a 42% risk of thrombosis, compared to 12% without LAC[7]. A case-control study of children with SLE showed a high risk of thrombosis (odds ratio = 28.7) for patients with LAC[8]. Since only a subset of SLE patients with LAC will develop thrombosis, additional inherited or acquired modifiers may affect clinical disease expression.

Inherited thrombophilic mutations have the potential to influence the thrombotic risk for patients with LAC. Children and adults who are heterozygous for the G1691A factor V (Leiden) mutation, which causes activated protein C resistance, have a significantly increased risk of venous thrombosis[9-11]. Factor V Leiden is also an independent risk factor for thrombosis in patients with SLE[12], and its combination with OC use is strongly thrombophilic[13]. When inherited in the homozygous state, the C677T MTHFR mutation is associated with hypercoagulability through hyperhomocysteinemia[14].

It is likely that the factor V and MTHFR thrombophilic DNA mutations in our patient provided an inherited tendency toward thrombosis, while her underlying SLE, LAC, and OC use created an additional acquired thrombotic risk. The presence of both acquired and inherited thrombophilia in our patient probably represented a potent hypercoagulable state, although the triggering events and relative importance of each thrombophilic factor are unknown. Moreover, the presence of both acquired and inherited thrombophilia may have influenced her clinical response to anticoagulation therapy. High dose continuous standard heparin, ASA, and pulse steroids were necessary to prevent initial clot extension, and several times she failed LMWH and coumadin therapy. She successfully discontinued heparin only after receiving aggressive immunosuppressive therapy for her underlying autoimmune disease. Clots developing in persons with both acquired and inherited thrombophilia may be especially difficult to treat, although this hypothesis has not been formally studied.

Patients with acquired hypercoagulable conditions such as LAC and SLE may benefit from DNA analysis to identify

inherited thrombophilic mutations. The presence of inherited thrombophilia may identify the subset of patients with LAC and SLE at highest risk for thrombosis, and allow anticipatory guidance or even prophylactic anticoagulation. For patients who develop thrombosis, inherited thrombophilia also may influence the therapeutic response to anticoagulation.

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