

Strokes, Cutis Marmorata Telangiectatica Congenita, and Factor V Leiden

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Cutis marmorata telangiectatica congenita is an uncommon, congenital cutaneous condition typified by persistent cutis marmorata and other associated abnormalities. Progressive neurologic complications are generally not a feature of the disorder. A case is reported of cutis marmorata telangiectatica congenita associated with diffuse cerebrovascular infarcts at 7 months of age. Moyamoya-like vascular abnormalities were demonstrated in addition to the factor V Leiden mutation, a congenital hypercoagulable disorder. This novel case illustrates the importance of evaluating children with strokes for congenital thrombophilic disorders. © 1998 by Elsevier Science Inc. All rights reserved.

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Introduction

Cutis marmorata telangiectatica congenita (CMTC) is an uncommon, congenital cutaneous condition typified by the presence of persistent cutis marmorata, phlebectasia, telangiectasis, and superficial ulceration [1,2]. CMTC is associated with other abnormalities in up to two thirds of CMTC patients, including hemihypertrophy (or hemiatrophy), syndactyly, cleft palate, dystrophic teeth, glaucoma, mental retardation, Sturge-Weber syndrome, macrocephaly, varicosities, capillary and cavernous hemangiomas, delayed psychomotor development, and congenital hypothyroidism [1,2]. Progressive neurologic complications have generally not been a feature of this disorder but were described in three individuals who developed frequent recurrent transient stroke-like hemipareses with migraine-like features in childhood [3]. The present report describes a child with CMTC associated with hypertrophy of the lower limb and congenital ophthalmologic abnormalities, who developed multiple diffuse cerebrovascular infarcts at 7 months of age. In addition to moyamoya-like vascular abnormalities, this child was found to have an underlying congenital hypercoagulable disorder caused by a mutation of coagulation factor V (Leiden mutation).

Case Report

The patient was a 10-month-old white girl at the time of referral for evaluation on the childhood stroke study, a study designed to evaluate underlying coagulation abnormalities in children with stroke. The study was approved by the Institutional Review Board on Investigations Involving Human Beings of the Children's Hospital Medical Center, and appropriate informed consent was obtained. At birth the child had generalized prominent mottling of the skin in a reticular pattern (cutis marmorata), a high-pitched cry, and a poor suck response (Fig 1). An ophthalmology evaluation diagnosed persistent hyperplastic primary vitreous (PHPV), and a vitrectomy and lensectomy of the right eye were performed at 14 weeks of age. At 5 months of age, she was diagnosed with left hip dysplasia and hypertrophy of the right lower extremity with a leg length discrepancy of 2 cm. At 7 months of age, she was hospitalized for the abrupt onset of right-sided seizures, fever, and loss of spontaneous movement on the right side. Persistent cutaneous mottling was again noted. A urinary tract infection resulting from Escherichia coli was diagnosed. An electroencephalogram demonstrated left hemispheric suppression of background activity. Computed tomography of the head revealed localized cerebral edema in the left frontal and left parietal convexity. A magnetic resonance imaging scan of the brain demonstrated multiple areas of gyral edema in the left frontal region, frontoparietal regions, and medial frontal lobes bilaterally near the vertex. These findings were consistent with areas of ischemia/infarction. A skin biopsy to exclude vasculitis was normal. Testing to exclude a collagen vascular disorder vielded negative results for antinuclear antibody and antineutrophil cytoplasm autoantibodies. Immunoglobulin (Ig) levels were normal for age for IgG, IgA, and IgM. Thyroid-stimulating hormone and T4 levels were normal. A serum amino acid analysis was normal, including normal homocysteine levels. A cerebral arteriogram performed at 8 months of age demonstrated a moyamoya pattern of vaso-occlusive

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Figure 1. Patient, age 10 months, with persistent cutis marmorata.

disease and areas of decreased vascularization in a watershed distribution (Fig 2).

Coagulation studies were normal for age, including protein C, protein S, antithrombin III, tissue plasminogen activator antigen, plasminogen, and plasminogen-activator inhibitor levels. Anticardiolipin antibody levels (IgG, IgM, and IgA) were normal. The anticoagulant response to activated protein C (APC) was performed as previously described, using a predilution of one volume sample plasma with four volumes factor \overline{V} deficient plasma (V-DEF Plasma, Chromogenix AB, Mölndal, Sweden), and the results were expressed as a ratio of patient sample to normal pooled plasma [4]. The ratio on the patient was 0.71; mother, 1.06; father, 0.72 (normal > 0.80). For the determination of the factor V Leiden mutation, genomic deoxyribonucleic acid was prepared on the propositus, parents, and family members, and a 224 base-pair fragment of the factor V gene was amplified and then digested with Mnl-1 restriction enzyme, with separation of the fragments on a 2% agarose gel, as previously described [4]. The patient and father demonstrated bands consistent with heterozygous factor V Leiden. Studies of the mother were normal.

Since the identification of the underlying thrombophilia, the patient has been receiving aspirin, 10 mg daily, with no further cerebrovascular thromboses. The seizure disorder is treated with phenobarbital.

Discussion

Children with CMTC have a unique congenital vasculopathy of unknown origin, often associated with other abnormalities [1,2]. Childhood strokes have been a feature of CMTC in only three reported children with symptoms of cerebral ischemia beginning at 3 to 4 years of age and associated with recurrent migraine-like episodes [3]. Arteriography was normal in one child and demonstrated bilateral dissections of the internal carotids with reduced flow in the other. One child had anticardiolipin antibodies.

The bilateral moyamoya-like vascular changes in our patient have not previously been reported in children with CMTC, but they are likely related to the underlying vasculopathy. Moyamoya as a primary disease is a rare, chronic occlusive cerebrovascular disorder characterized by progressive stenosis of the arteries of the



Figure 2. Cerebral arteriogram. Lateral (A) and frontal (B) views of a left internal carotid injection demonstrate significant narrowing of the carotid terminus and proximal middle and anterior cerebral arteries (arrows). Hypertrophied lenticulostriate arteries consistent with a moyamoya pattern of vaso-occlusive disease are present (small arrows). These findings were bilateral. Abrupt cutoff of angular artery branches on the lateral view is consistent with me peripheral small vessel occlusion (arrowheads). (C) Frontal view of the same injection in a later phase demonstrates an area of decreased vascularization consistent with watershed infarction. Collateral circulation via irregular pial vessels is present (curved arrows).

circle of Willis [5,6]. Initially, stenosis involves the intracranial carotid arteries bilaterally, and it subsequently may progress to involve both the middle cerebral artery and the posterior cerebral arteries. In conjunction with progressive stenosis and eventual occlusion of major arteries at the base of the skull an abnormal capillary network develops at the base of the brain. These vascular changes can result in ischemic strokes or cerebral hemorrhages. The cause of moyamoya is unknown. A similar vasculopathy involving the formation of abnormal, small moyamoya vessels distal to the narrowing of the carotid arteries may also be a secondary process. Moyamoya-like vascular abnormalities have been reported associated with neurocutaneous diseases such as tuberous sclerosis, neurofibromatosis, and encephalotrigeminal angiomatosis, as well as other disorders, including periarteritis nodosa, Down syndrome, sickle cell disease, Fanconi anemia, cyanotic congenital heart disease, encroachment of tumor emanating from the pituitary region, type I glycogenosis, and radiation therapy [6]. None of these conditions was present in our patient.

The cerebrovascular infarcts in our patient occurred in a diffuse pattern and appeared disproportionate to the degree of underlying vasculopathy. We postulate that the early onset and unusual severity of the strokes were due to the underlying prothrombotic disorder, factor V Leiden, which is associated with resistance to the anticoagulant effects of protein C. The underlying hypercoagulable state was further aggravated by an acute urinary tract infection. The coagulopathy, associated with altered blood flow within abnormal blood vessels, resulted in cerebrovascular thrombosis.

As recently reviewed, inherited and acquired disorders of blood coagulation and fibrinolysis result in prothrombotic conditions that predispose to stroke [6,7]. These abnormalities include prekallikrein deficiency, factor XII deficiency, defective release of plasminogen activator, antithrombin III deficiency, proteins C and S deficiency, and heparin cofactor II deficiency. Antiphospholipid antibody syndrome, which includes the lupus anticoagulant and anticardiolipin antibodies, also predisposes to thrombosis and stroke in childhood [8]. Interestingly, one of the cases of CMTC and recurrent strokes reported by Baxter et al. demonstrated abnormal levels of anticardiolipin IgG antibodies [3]. More recently, resistance to APC has been associated with strokes in children [9]. The importance of identifying an underlying thrombophilic disorder in children with strokes lies in the potential for the prevention of recurrent cerebrovascular thromboses with antiplatelet/anticoagulant therapy. The value of such therapy in children, however, is currently unproven.

As recently reviewed, APC resistance has been found to be the most frequently inherited cause of thrombosis, with an incidence of APC resistance ranging from 17.5-64% in cohorts of patients reported from various studies [10]. The molecular alteration underlying the phenomenon of APC resistance is an amino acid substitution at the cleavage site of factor V (Arg^{506} to Gln, factor V Leiden), which is due to a single point mutation (G to A) at position 1691 of the factor V gene [10]. This mutation results in resistance of activated factor V to cleavage by APC. In a study of 169 healthy children at our institution the prevalence of heterozygosity for the mutant factor V Leiden mutation using polymerase chain reaction was 7 of 169 (4.1%) [4]. In other studies the prevalence of carriers of the APC resistance/factor V Leiden trait has been determined to be 2-7% in the general adult population [10].

The retinal abnormality PHPV in our patient is unique and has not been reported before in association with CMTC. PHPV is a rare benign developmental disorder of the eye in which the embryonic hyaloid artery fails to regress normally, resulting in abnormal lenticular development and secondary changes of the retina and globe [11]. PHPV has been described in association with fetal alcohol syndrome, fetal hydantoin syndrome, midline congenital cranial defects, and trisomy syndromes 13, 15, 18, and 21 [11]. Cataract formation, retinal detachment, retinal hemorrhage, and retinal dysplasia are often associated findings [11].

In summary, this novel case demonstrates the association of CMTC with diffuse cerebrovascular infarcts and the factor V Leiden mutation. It is postulated that cerebrovascular thrombosis occurred as a result of the congenital hypercoagulable state in association with altered blood flow within areas of the moyamoya-like vascular malformation. The identification of congenital thrombophilia in children with strokes is important because of the potential for therapeutic antiplatelet/ anticoagulation therapy in the prevention of recurrent cerebrovascular thrombosis.

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