Prothrombotic Disorders in Children With Moyamoya Syndrome

Mariana Bonduel, MD; Mirta Hepner, PhD; Gabriela Sciuccati, MD; Aurora Feliú Torres, MD; Silvia Tenembaum, MD

Background and Purpose—Moyamoya syndrome is an uncommon chronic occlusive cerebrovascular disease in children. The origin of moyamoya syndrome remains undetermined. The role of the prothrombotic disorders contributing to its pathogenesis has not been completely elucidated. The purpose of this study was to determine the frequency of prothrombotic disorders in a pediatric population with moyamoya syndrome.

Methods—From May 1992 to April 2000, a prospective study of 10 consecutive children with moyamoya syndrome was carried out at a single center. Evaluation included the following assays: protein C, protein S, antithrombin, plasminogen, activated protein C resistance, factor V Leiden, and prothrombin gene mutations. Lupus anticoagulant, antiphospholipid antibodies, and anti-β2-glycoprotein I antibodies assays were also performed. The clinical characteristics, underlying diseases, family history of thrombosis, radiological findings, treatment, and outcome were also recorded.

Results—In our series, prothrombotic disorders were detected in 4 patients (40%). Inherited protein S deficiency was found in 1 patient; lupus anticoagulant and antiphospholipid antibodies were detected in the remaining 3 patients. One presented persistent lupus anticoagulant for 2.7 years until his death. In the case of the other 2 patients, 1 has maintained lupus anticoagulant for 9 months, whereas the other has kept antiphospholipid/anti-β2-glycoprotein I antibodies for 10 months.

Conclusions—We report the hemostatic data of the largest prospective pediatric study carried out at a single center in the western hemisphere. In 4 patients (40%), a prothrombotic disorder was detected. It is tempting to speculate that these hemostatic abnormalities may contribute to the pathogenesis of moyamoya syndrome in some of our patients. (Stroke. 2001;32:1786-1792.)

Key Words: antiphospholipid antibodies ■ child ■ etiology ■ moyamoya disease

Moyamoya syndrome (MMS) is a rare chronic occlusive cerebrovascular disorder in children characterized by a progressive stenosis or occlusion of the internal carotid artery and proximal cerebral arteries with an extensive network of cerebral collaterals.1,2 Although primary and secondary forms associated with a variety of entities have been recognized, its origin remains undetermined.2–14 The contribution of prothrombotic disorders to the pathogenesis of MMS in children is still to be elucidated because available data are related only to retrospective studies of few patients.15–25 The main aim of this work was to perform a prospective study, including a complete hemostatic evaluation, to determine the frequency of prothrombotic disorders in a pediatric population with MMS.

Subjects and Methods
From May 1992 to April 2000, a prospective study of 80 consecutive children with arterial ischemic stroke (AIS; age range, 1 month to 18 years) referred for study to our department was carried out. Ten fulfilled the angiographic criteria of MMS (6 girls, 4 boys; median age, 6.6 years; range, 1.0 to 14.9 years). The diagnosis of MMS by cerebral angiography showed bilateral stenosis or occlusion of the distal internal carotid and proximal cerebral arteries associated with an abnormal network of collateral vessels at the base of the brain. Patients with primary and secondary forms of MMS were included in this study.

Data concerning clinical presentation, underlying diseases and/or circumstantial risk factors, radiological findings, family history of thrombosis, treatment, and outcome were recorded.

After parental informed consent was obtained, blood samples were collected into 0.11 mol/L sodium citrate at a ratio of 9:1 by clean venipuncture. Blood was centrifuged at 2500 g for 15 minutes. Platelet-poor plasma was immediately processed or stored at −70°C.

Evaluation for prothrombotic disorders included the following assays in all patients: prothrombin time; activated partial thromboplastin time; thrombin time; reptilase time; fibrinogen; and factors V, VIII, and XII activity by standard procedures. Functional activities of protein C, antithrombin, and plasminogen were measured by amidolytic assays (chromogenic substrates, Chromogenix AB) and protein C and protein S by clotting assays with a model ST4 coagulometer (Diagnostica Stago). Immunological measurements of protein C, protein S (total and free), antithrombin, and plasminogen were made by Laurell’s technique26 with polyclonal rabbit antibodies against the respective antigens (protein C, protein S, and antithrombin, Dakopatts; ASSERA plasminogen, Diagnostica Stago). Free protein S was assayed by precipitating bound protein with polyethylene glycol

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8000 (3.75%) for 30 minutes at 4°C, followed by electroimmunoassay according to the method by Comp et al. Free protein S was expressed in units per milliliter and calculated by extrapolation from a standard curve constructed with serial dilutions of normal pool plasma calibrated against a reference preparation code 93/590 from the National Institute for Biological Standards and Control (Hertfordshire, United Kingdom) in which the free protein S level of the pool was 0.98 U/mL. Presence of activated protein C resistance was tested by use of a commercial kit with factor V–deficient plasma as a prediluent for plasma samples (Chromogenix AB). DNA analyses were performed as previously described. Children having a thrombotic event in all cases. In our study, subsequent controls for antibodies were assayed by ELISA technique with a commercial kit (QUANTA Lite β2-GPI IgG, Inova Diagnostics). The results were expressed in IgG anti–β2-GPI units. Values >20 IgG anti–β2-GPI units were considered abnormal.

According to reported criteria for the antiphospholipid syndrome (APS), only those patients with APS and positive LA test results and/or positive IgG and/or IgM ACA at moderate to high levels (>20 GPL/MPL units in 2 determinations performed >8 weeks apart) were considered positive for APS.

In children with suspected inherited prothrombotic disorders, the final diagnosis was made when repeatedly measured plasma concentrations of the coagulation proteins investigated (3 to 6 months after the thrombotic episode) were outside the age-appropriate reference range and the findings in family studies of abnormal laboratory results confirmed the suspected inherited coagulation defect. LA, ACA, and anti–β2-GPI antibodies were tested within 1 week of the thrombotic event in all cases. In our study, subsequent controls for LA, ACA, and anti–β2-GPI antibodies were done every 2 months in children with APS to control the time course of these abnormal results. Their parents were also studied to discard familial APS.

To establish the normal laboratory reference values, 100 healthy adults (50 men, 50 women; mean age, 37.2 years; range, 25 to 49 years) receiving no medications were studied. With informed parental consent, 60 healthy children (33 boys, 27 girls; mean age, 8.6 years; range, 1 to 16 years) admitted to the hospital for elective minor surgery or as potential bone marrow donors were eligible for normal reference ranges. The children were gathered in groups of 20 each (45 years).

Results
The median age at diagnosis was 6.6 years. A female predominance was found. No patient was of Asian descent. All patients had multiple AIS; 1 patient with an anterior communicating artery aneurysm also had an intracranial hemorrhage. Table 1 shows the baseline demographics, underlying diseases, risk factors, clinical features at presentation, radiological findings, family history of thrombosis, treatment, and outcome of the patients studied.

Inherited and acquired prothrombotic disorders were detected in 4 (40%) of the 10 children studied. In our series, inherited protein S deficiency was found in 1 patient; LA and ACA were detected in the remaining 3 patients. One of them presented with persistent LA for 2.7 years until his death. In the case of the other 2 patients, until now, I has maintained LA for 9 months, and the other has kept ACA/anti–β2-GPI antibodies for 10 months. LA and ACA tested repeatedly every 2 months showed the persistence of a similar pattern of laboratory features (screening and confirmatory tests) in the 2 patients with LA and stable ACA/anti–β2-GPI antibodies values in the remaining patient. The laboratory findings of these patients are summarized in Table 2.

The child with common variable immunodeficiency died of cerebral hemorrhage after developing a severe coagulopathy for liver insufficiency.

Two patients underwent surgical revascularization (en- cephaloduroarteriosynangiosis); I died 3 days after the surgery given that revascularization failed to halt the progression of cerebral ischemia, whereas the other is still alive and has had progressive improvement after the procedure. The remaining 7 patients are alive with follow-up periods ranging from 5 to 107 months (median, 26 months). These children have received aspirin and have developed different kinds of disabilities (data shown in Table 1).

Discussion
MMS has been described in all ethnic groups but remains rare outside Japan.2–4,33 In the western hemisphere, it is most often related to another underlying condition.5–8 In our series, 40% of the patients had an associated disease; I presented with common variable immunodeficiency, an entity that has not yet been reported in patients with MMS. Most of our patients were <10 years of age, and AIS or transient ischemic attack was the predominant initial complications, as in other pediatric series.2–5 Aneurysm, detected in only 1 of our patients, has rarely been described in children.2–3

The origin of MMS remains undetermined. It is not clear whether it is a congenital arterial dysplasia or a syndrome caused by nonspecific vascular reaction.10–14 Genetic factors have been suggested to contribute to the origin in some familial or sporadic cases of MMS in the Japanese population.6,34,35 However, natural inhibitors of the coagulation are encoded by genes located in chromosomes that have not yet been involved in MMS. Strong HLA class II antigen correlations have been found for several autoantibodies, including LA and ACA, in patients with some autoimmune diseases.36 Therefore, further studies are necessary to clarify multiple genetic factors that are definitely linked with MMS in different ethnic groups.

Inherited and acquired prothrombotic disorders have been identified as a cause of AIS in young people.37–39 Several genetic defects contribute to increase the risk of thrombosis.40 Among them, inherited protein S deficiency has been related to arterial thrombotic complications.41–46 However, this abnormality as a prothrombotic disorder is still a controversial issue.40,47 It has been reported that the levels of protein S are influenced by sex, age, pregnancy, and hormonal state.47 In our study, we applied separate local laboratory reference ranges for women and men in the assessment of protein S.
levels in the families studied. Concerning acquired disorders, APS is a heterogeneous group of autoantibodies that includes LA and ACA, which are strongly associated with arterial and venous thrombosis.48 In patients with APS, the vast majority of antibodies detected in conventional anticardiolipin assays bind to epitopes on β2-GPI.49–51 The endothelial cell interaction with these antibodies has been proposed as a probable mechanism to predispose to thrombosis.48,52 Endothelial cell alterations in the vasculopathy of MMS may be a source of autoantigens that drive that autoimmune response. An underlying autoimmune condition, as described in Down’s syndrome, inducing the appearance of these antibodies and a progressive vascular damage, could not be discarded.21

Variable frequency of prothrombotic disorders has been reported in non-MMS children with AIS17,37,38,53; in our previous study, we found these abnormalities in 7 of the 30 children (23%) evaluated.39

Few reports have described the probable relationship between hemostatic abnormalities and MMS.15–25 In our series, a prothrombotic disorder was detected in 4 of our patients (40%). Inherited protein S deficiency was detected in 1 patient, and persistent positive LA or ACA was found for months or even years in the remaining 3 patients.

Optimal treatment of childhood AIS and prothrombotic disorders is still controversial.54 Surgery using different revascularization methods has improved the outcome of

<table>
<thead>
<tr>
<th>Patient/Sex/Age, y</th>
<th>Associated Conditions</th>
<th>Neurological Signs and Symptoms at Presentation</th>
<th>Radiological Findings*</th>
<th>Family History of Thrombosis</th>
<th>Treatment</th>
<th>Outcome</th>
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</thead>
<tbody>
<tr>
<td>1/F/7.8</td>
<td>Down syndrome, esophageal atresia, tracheoesophageal fistula</td>
<td>Hemiparesis</td>
<td>Bilateral internal carotid artery occlusions</td>
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<td>Aspirin</td>
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<td>Aspirin, surgery</td>
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</table>

*Angiographic pictures consisting of abnormal netlike vessels at the base of the brain were found in all patients.
In children with MMS and hypercoagulable state, whether or not surgery has been performed, prophylaxis and treatment with antithrombotic agents have been recommended. Only controlled clinical trial of these pediatric patients could establish whether these therapies can reduce the frequency of thrombotic events and ameliorate the cognitive dysfunction.

We report the hemostatic data of the largest prospective study of pediatric patients with MMS carried out at a single center in the western hemisphere. A large, prospective, multicenter study is required to define the pathogenic significance of these prothrombotic abnormalities and determine the most appropriate therapy in these children.

### References


### Table 2. Laboratory Findings

<table>
<thead>
<tr>
<th>Inherited Protein S Deficiency</th>
<th>Immunological</th>
<th>Proteins Protein S Assays, U/mL</th>
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<td>Patient</td>
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<td>1</td>
<td>0.48 (0.52–1.14)</td>
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<tr>
<td>Mother</td>
<td>0.39 (0.54–1.23)</td>
<td>0.60 (0.63–1.27)</td>
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<tr>
<td>Father</td>
<td>0.94 (0.64–1.36)</td>
<td>1.04 (0.66–1.30)</td>
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</table>

<table>
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<tr>
<th>APS</th>
<th>LA Assays</th>
<th>APTT of 1:1 Plasma Mix</th>
<th>dRVVT, s</th>
<th>Confirmation Assay</th>
<th>IgG ACA, GPL</th>
<th>IgM ACA, MPL</th>
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<td>42 (42)</td>
<td>25</td>
<td>+</td>
<td>38</td>
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Reference values 35–50 Within 7 s of normal pool <25 <6 <6 <20

APTT indicates activated partial thromboplastin time; dRVVT, diluted Russell viper venom time. Local laboratory reference ranges of free, total, and clotting assays of protein S according to age and sex are shown in parentheses.


Vascular Occlusion in Moyamoya: A Multitude of Mechanisms?

In the preceding article, Bonduel et al present the findings from the largest and only prospective study to date assessing the association of prothrombotic abnormalities and moyamoya syndrome in childhood. The study confirms an association that has previously only been suggested by isolated case reports or small case series. The study by Bonduel et al confirms the validity and strength of this group of investigators in the study of prothrombotic disorders in childhood stroke, including an age-matched control group.

Moyamoya syndrome is characterized by the angiographic findings of bilateral stenotic and occlusive changes in the terminal portion of the internal carotid artery and a coexisting abnormal vascular network (moyamoya vessels) at the base of the brain. The angiographic findings are associated clinically with recurrent transient ischemic attacks (TIAs) and cerebral infarcts, and beginning in the second decade of life, with subarachnoid hemorrhage due to rupture of the fragile collateral network of vessels.1,2 The disorder can be idiopathic or associated with genetic disorders, including Down syndrome, William syndrome, and neurofibromatosis, or can result from acquired vasculopathies, including posttrauination vasculopathy. The age of onset of moyamoya disease has two peaks, with the larger one at 5 years and a smaller one at 30 to 49 years.3 Disease represented by the early peak is termed the juvenile type, while disease at the latter peak is termed the adult type.

The underlying pathogenesis of moyamoya disease is unknown. Attempts to halt the progression, which manifests as overt recurrent strokes or as gradual cognitive decline in affected children, include medical and surgical approaches. Surgical revascularization techniques, including encephaloduroarteriosynangiosis, can ameliorate the progression of the disease and prevent the gradual cognitive decline. The efficacy and safety of antithrombotic treatment for children with moyamoya disease is controversial, and there is scant evidence on which to rationally base therapy. Although aspirin is frequently used for secondary stroke prevention in children with moyamoya, there is a reluctance to go to more powerful agents, including oral anticoagulants, when aspirin fails to prevent recurrent cerebral ischemic events, for two reasons. First, there is concern about the risk of subarachnoid hemorrhage. Second, many of the TIAs appear to be provoked by hyperventilation, which suggests that the underlying pathogenesis is primarily flow related with associated vasospasm as opposed to a thromboembolic phenomenon.4 Evidence for a vasoreactive pathogenesis is also suggested by the amelioration of TIAs in many children with Dia-

mox, which presumably works by increasing pH and vasodilatation.

The finding of prothrombotic abnormalities in 4 in 10 non-Japanese children with moyamoya syndrome in this study has important implications. The presence of prothrombotic abnormalities increases the tendency to use antithrombotic treatment, including anticoagulants, which in moyamoya must be balanced against the significant risks of hemorrhage. In addition, children with ischemic stroke having multiple risk factors have a worse outcome than those with single risk factors.5

The existence of acquired antiphospholipid antibodies, including anticardiolipin antibody and lupus anticoagulant in children, is frequently described in children with ischemic stroke of any etiology.6 The presence of antiphospholipid antibodies, which comprised the prothrombotic abnormalities found in 3 of the 4 children with moyamoya in the current study, is intriguing. The origin of these antibodies is enigmatic. Damage to the vascular endothelial or subendothelial structures as occurs in any vasculopathy, including moyamoya, could trigger the formation of secondary antiphospholipid antibodies responding to the exposed phospholipid components of the endothelial cell membrane. Alternatively, the presence of thrombosis, in the case of moyamoya syndrome arising due to the vascular disorder or flow alterations from stenosis, could result in the formation of antiphospholipid antibodies as a result of the activation of the coagulation cascade. Alternatively, the antiphospholipid antibodies could arise independently as part of an as yet unidentified systemic disease underlying the moyamoya syndrome. In any case, once present the antibodies may play a role in promoting further thrombosis and recurrent ischemic events. The latter would promote the use of antithrombotic agents in children with moyamoya and prothrombotic disorders. Recent evidence, however, derived from more than 200 children with stroke tested for anticardiolipin antibody from our center and the Great Ormond Street Children’s Hospital cohort in the United Kingdom, indicates that anticardiolipin antibody does not predict an increased risk of recurrent stroke in children, in contrast to the situation in adults.7 Whether the same is true for lupus anticoagulant in children with stroke is unknown.

The current study contributes information to our understanding the pathogenesis and associations of moyamoya disease in childhood. Future studies will be needed to confirm, in larger prospective series of children with moyamoya, the presence of prothrombotic disorders, their implication for the risk of recurrent TIA or stroke, and whether antithrombotic therapy should be increased in children with
prothrombotic disorders and moyamoya disease. The recent formation of a childhood stroke study group in conjunction with the National Institute for Neurological Disorders and Stroke will enable large multicenter studies to elucidate the mechanisms and optimal treatment strategies for this and other types of childhood stroke.

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Toronto, Ontario, Canada

References
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