Lupus Anticoagulants in Children

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ABSTRACT

Although a great deal of information is available in the literature on the frequency, clinical/laboratory findings and significance of lupus anticoagulants in adults, little is known about such acquired inhibitors in children. Clinical and laboratory findings are presented on seven non-hemophilic children, four females and three males, ranging in ages from three to 14 years, who developed such inhibitors. In most, the inhibitor is a transient phenomena and is not associated with a bleeding or thrombotic diathesis.

Introduction

The development of acquired inhibitors of coagulation in healthy children is unusual.6 In most incidences, these inhibitors are found in children with a severe congenital coagulation factor deficiency who have received replacement therapy and represent antibody response directed against the absent coagulation factor.9 Reports in the literature of lupus anticoagulants in the pediatric age group are even more limited.2,10 Clinical and laboratory features are reported on seven non-hemophilic children ranging in age from three to 14 years with lupus anticoagulants and document the transient nature of these inhibitors.

Materials and Methods

Blood was collected by standard venipuncture technique in a 9:1 ratio of blood to 3.8 percent trisodium citrate. Platelet poor plasma was obtained by centrifugation at 1600 g for 10 minutes at room temperature. Pooled normal plasma was prepared as previously described.5

Patients included two males and five females ranging in age from three years to 14 years. All were referred to the coagulation laboratory at the Medical University either because of a history of bleeding or because of an abnormality of a coagulation study noted on routine pre-operative examination. No history of drug ingestion is present in our patients, particularly drugs like hydralazine, chlorpromazine, etc., at the time of evaluation.

Coagulation Studies

The prothrombin time (PT) and activated partial thromboplastin time (APTT) were performed using previously described established methods.4 Platelet counts were obtained using the Coulter S Plus instrument. Normal reference
ranges in our laboratory for these studies are 11 to 13.2 secs., 21 to 30 secs., and 140 to 440 × 10⁹ per L, respectively.

The presence of a circulating anticoagulant was detected by performing a PT and/or APTT on a 1:1 mixture of patient plasma plus pooled normal plasma, depending on which initial screening test was abnormal. All mixtures were assayed immediately. Controls consisted of a 1:1 mixture of pooled normal plasma and buffer in place of patient plasma. Demonstration of phospholipid dependence of the inhibitors was assessed by performing a tissue thromboplastin inhibition test (TTIT) according to the method of Schleider, et al. Lupus anticoagulant presence was defined in this test as the ratio of clotting times of the patient mixture to that of the control mixture of 1.3 or greater in the absence of inhibitors to specific coagulation factors. Factor assays V, VII, VIII, and IX were performed using congenitally deficient plasmas according to established methodologies.

Results

The clinical and laboratory data are presented in table I. Only one patient (#5) had an underlying systemic disorder, in this case systemic lupus erythematosus. Three others (#2, 4, and 7) had a history of upper respiratory tract infection prior to being referred to the coagulation laboratory. In only one (#2) was excessive bruising noted as a significant clinical finding. Recurrent epistaxis (#1) was the only complaint in one patient, and two others (#3 and 6) were essentially asymptomatic but had abnormal coagulation studies prior to admission for tonsillectomy. None had a past history of bleeding or a family history of a bleeding diathesis. A prolonged APTT was the only abnormal test in five patients. One patient had a slightly prolonged PT; in the other, both the PT and APTT were mildly prolonged. On mixing studies, five of six plasma samples tested showed no correction of the PT and/or APTT indicating the presence of an inhibitor. With the exception of the patient with systemic lupus erythematosus (factor II-30 U per dl, VII-24 U per dl, IX-40 U per dl, X-36 U per dl, VIII activity-224 U per dl), factor levels were normal in all patients (data not shown). All six patients who had sufficient sample for testing had an abnormal TTIT consistent with the presence of a lupus anticoagulant. Follow up testing was available on five of the seven patients. In four of them, the inhibitor proved to be transitory with disappearance of the abnormal coagula-

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age/sex</th>
<th>Diagnosis</th>
<th>PT† (sec)</th>
<th>APTT‡ (sec)</th>
<th>Mixing Study§</th>
<th>TTITW (x10⁷/L)</th>
<th>PT Count</th>
<th>Follow Up</th>
</tr>
</thead>
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<tr>
<td>1</td>
<td>3 F</td>
<td>Epistaxis</td>
<td>12.6</td>
<td>67.7</td>
<td>NC</td>
<td>1.3</td>
<td>378</td>
<td>Normal studies 4 months later</td>
</tr>
<tr>
<td>2</td>
<td>4 F</td>
<td>URI</td>
<td>11.8</td>
<td>45.6</td>
<td>NC</td>
<td>1.3</td>
<td>395</td>
<td>Normal studies 3 months later</td>
</tr>
<tr>
<td>3</td>
<td>4 M</td>
<td>Tonsillitis</td>
<td>12.0</td>
<td>37.9</td>
<td>NC</td>
<td>ND</td>
<td>275</td>
<td>Normal studies 9 months later</td>
</tr>
<tr>
<td>4</td>
<td>7 M</td>
<td>URI</td>
<td>13.0</td>
<td>45.7</td>
<td>NC</td>
<td>2.8</td>
<td>---</td>
<td>None available</td>
</tr>
<tr>
<td>5</td>
<td>10 F</td>
<td>SLE</td>
<td>16.1</td>
<td>34.6</td>
<td>NC</td>
<td>1.5</td>
<td>226</td>
<td>Abnormal studies 1 year later</td>
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<tr>
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<td>12 F</td>
<td>Tonsillitis</td>
<td>13.2</td>
<td>31.8</td>
<td>C</td>
<td>1.4</td>
<td>---</td>
<td>Normal studies 5 months later</td>
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<tr>
<td>7</td>
<td>14 F</td>
<td>URI</td>
<td>13.3</td>
<td>25.8</td>
<td>--</td>
<td>1.4</td>
<td>150</td>
<td>None available</td>
</tr>
</tbody>
</table>

*URI - Upper respiratory tract infection; SLE - Systemic lupus erythematosus.
†Prothrombin time
‡Activated partial thromboplastin
§NC - No correction; C - Correction
||TTIT - Tissue thromboplastin inhibition test. See text for details.
tion parameter(s) taking three to nine months. The patient with systemic erythematous continued to demonstrate an inhibitor when assessed as late as one year later. None of these patients had any events of either arterial or venous thrombotic disease.

Discussion

Lupus anticoagulants are acquired inhibitors of coagulation which have been described in a wide variety of clinical settings, most particularly in patients with underlying autoimmune disorders, in patients receiving certain medications (antibiotics in children, hydralazine, hydrochloride, procainamide hydrochloride, clorpromazine, and quinine), and individuals who are otherwise healthy. A great deal has been written lately because of the paradoxical association of these inhibitors in adult patients with a thrombotic tendency rather than a bleeding diathesis. The limited number of reports in the literature would not only suggest that these inhibitors are rare in children, but make it difficult to know the clinical presentation and natural history of these anticoagulants in this age group. Brodeur et al documented five children with inhibitors, two of whom they felt had lupus anticoagulants based on a positive tissue thromboplastin inhibition test. It should be noted, however, that one of their patients had anti-factor VIII and IX antibodies in addition to the supposed lupus anticoagulant. Even though the TTIT was positive in the latter patient, Triplett et al have since shown that this test is not diagnostic for lupus anticoagulants in the presence of specific coagulation inhibitors. The other patient with a positive TTIT was a nine month old female who had antecedent cytomegalic virus hepatitis. Unfortunately, no follow up was given on this patient.

No definitive precipitating cause for the development of lupus anticoagulant was found in our cases except in the child who had systemic lupus erythematosus and the other child with Epstein Barr virus hepatitis. Interestingly, three of the patients in our study had a history of symptoms consistent with an upper respiratory tract infection two to three weeks prior to being seen and two others had evident tonsillitis at the time of examination. No viral or bacterial studies were performed on any of the five patients. Clinical bleeding was not a significant problem with any of the patients, although patient #1 did have several episodes of epistaxis. Incidental bruising was noted in patient #2 several days following the onset of her upper respiratory infection, but this resolved by the time she was seen in the coagulation laboratory. Follow up laboratory evaluation was available on five of the children. Patient #5 with systemic lupus erythematosus continued to have abnormal coagulation studies as late as one year follow up. In four of the other patients (#1, 2, 3, and 6) the PT and/or APTT had returned to normal by three to nine months.

These results would suggest that the lupus anticoagulant in children may be more common than previously suspected. These inhibitors appear to be transient and quite possibly related to antecedent viral infections. Although this series is limited, it would appear that unlike in the adult, associated clinical arterial or venous thrombotic disease is not part of this disorder.

References


