Lipoprotein (a): Its Role in Childhood Thromboembolism

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ABSTRACT. **Purpose.** Elevated lipoprotein (a) [LP (a)] concentrations are independent risk factors of coronary heart disease or stroke in young adults. To clarify its role in childhood thromboembolism, LP (a) was measured in 72 children with thromboembolism.

**Methods.** In addition to LP (a), defects of the protein C anticoagulant system, antithrombin, and antiphospholipid antibodies were investigated in children with arterial (n = 36) or venous (n = 36) thrombosis.

**Results.** Enhanced LP (a) >50 mg/dL was diagnosed in 8 out of 36 children with arterial and 5 out of 36 patients with venous thrombosis. Of the 72 children, 25 showed the factor V Leiden mutation, 10 showed protein C deficiency, 2 showed antithrombin deficiency, and 4 showed primary antiphospholipid syndrome. Three children with increased LP (a) were heterozygous for the factor V Leiden mutation, and 1 girl showed additional protein C deficiency.

**Conclusions.** Data of this study indicate that increased concentrations of LP (a) play an important role in childhood thrombosis. Pediatrics 1997;99(6). URL: http://www.pediatrics.org/cgi/content/full/99/6/e11; childhood thrombosis, lipoprotein (a), factor V Leiden, protein C.

**ABBREVIATIONS.** LP (a), lipoprotein (a); LDL, low-density lipoprotein; apo, apolipoprotein.

Lipoprotein (a) [LP (a)] is a cholesterol-rich plasma lipoprotein with a lipid composition similar to that of low-density lipoproteins (LDL). The protein composition is different from that of LDL, consisting of two major proteins, apolipoprotein B and apo (a)1,2 LP (a) levels vary from person to person but are genetically determined as a dominant trait, minimally affected by race, age, and sex.3,4 Numerous groups agree in their findings that individuals with increased concentrations of LP (a) have a higher risk of premature coronary heart disease,5,6–7 unrelated to the remaining lipoproteins. In addition, the risk of stroke8,9–12 as well as for restenosis after coronary artery bypass surgery13,14 correlates highly with increased LP (a) concentrations. Little is known, however, about the relation between increased LP (a) concentrations and childhood thrombosis at various sites. We used a commercially available enzyme-linked immunosorbent assay to measure LP (a) in a population of children with arterial or venous thrombosis.

**METHODS**

Seventy-two infants and children aged from birth to 18 years consecutively recruited between 1992 and 1996 and primarily treated for arterial (n = 36) or venous (n = 36) thrombosis were enrolled in this study. In the majority of cases arterial thrombosis occurred in the central nervous system. Sixteen of 36 infants developed embolic stroke or multiple thrombosis in the neonatal period (attributable to the uncertainty in differentiating between embolic and local stroke in the majority of cases investigated, all children with initial symptoms of stroke were categorized in the arterial group). In addition, 11 children >1 year of age suffered an ischemic embolic, local, or lacunar stroke. Left intracardial thrombus formation was diagnosed in 4 of 36 patients, the femoral artery was occluded in two children and aortic thrombosis was found in two infants. Venous thromboses were found in the femoral vein (n = 10), renal veins (n = 8), superior caval vein (n = 6), central nervous system (n = 7), and portal vein (n = 5), respectively. In the majority of cases, underlying diseases triggering the thromboembolic event were diagnosed. As in previous reports, asphyxia, systemic infections, dehydration, congenital heart disease, and central lines were commonly associated with the vascular occlusion reported.15,16–19

Fasting venous blood samples for coagulation studies were obtained in the acute phase of the vascular accident and at least 6 months after the thrombotic episode when the children were free of anticoagulant medication. In infants and children with suspected inherited thrombophilia the final diagnosis was made when DNA-based assays confirmed the diagnosis (Arg506 to Gln mutation of the factor V gene) or when repeatedly measured plasma concentrations were outside the age-appropriate reference range and family screening confirmed the suspected inherited coagulation defect.20–22 Although the mean ± 2 standard deviation of the plasma values in the control children was 25 mg/dL, we chose the markedly elevated cut-off level of LP (a) >50 mg/dL (2 × 25 mg/dL) according to Margaglione et al23 in the present study. In addition, bearing in mind the importance of LP (a) as a risk factor of familial thrombophilia, family data are included in this report.

Blood samples were drawn from a peripheral vein into pre-marked 3-mL plastic tubes (citrate 3.8%/blood 1:10; Saarstedt, Nümbrecht, Germany), immediately placed on iced water and centrifuged at 4°C at 3000 g for 20 minutes. Platelet-poor plasma was snap-frozen and stored in plastic tubes at −70°C. LP (a) concentrations were measured with the enzyme-linked immunosorbent assay technique (COALIZA LP (a); Chromogenix, Mölndal, Sweden). The detection limit was .5 mg/dL and LP (a) was quantified between 1 and 100 mg/dL. In addition, the factor V Leiden mutation (DNA prepared from ethylenediamine-tetraacetic acid blood), factor V, protein C, protein S, antithrombin, and antiphospholipid antibodies (immunglobulin M/immunglobulin G) were measured as described earlier.24

Calculations of median and ranges and nonparametric statistics (Wilcoxon-Mann-Whitney U test) were performed with the Apple computer Stat view program.
RESULTS

Table 1 shows the overall distribution of genetic risk factors for familial thrombophilia in children with arterial and venous thrombosis. Eight of 36 (22%) patients with arterial vascular insults and 5 of 36 (14%) with venous thrombosis showed Lp (a) concentrations $>50$ mg/dL. In addition, 244 age- and sex-matched healthy controls showed significantly lower ($P < .001$) median (range) Lp (a) plasma values of 7 mg/dL (0 to 39) compared with 15 mg/dL (0 to 165) in children with venous thrombosis, and 15 mg/dL (0 to 145) in patients with arterial vascular insults, respectively. However, median (range) Lp (a) concentrations in infants and children with venous vascular occlusion were no different from Lp (a) values in the arterial group. With special regard to the markedly elevated cut-off level of $>50$ mg/dL chosen in this study, single patient values are given in Table 2.12 However, if we had chosen mean $\pm$ 2 SD Lp (a) values of the control children, the vascular accident would also have been classified as Lp (a)-related in 5 of the remaining 28 patients (arterial) and 2 of 31 in the venous group.

In addition, 25 of the 72 children showed the factor V Leiden mutation, 10 protein C type I deficiency, and two antithrombin type I deficiency. Four of the 72 children showed primary antiphospholipid syndrome. Three children with increased Lp (a) were heterozygous for the factor V Leiden mutation, and one girl showed an additional protein C deficiency (Table 2). Eleven of 13 patients with thrombosis and Lp (a) $>50$ mg/dL had a positive family history of early myocardial infarction ($n = 6$), stroke ($n = 4$), or venous thrombosis ($n = 1$) (Table 2).

DISCUSSION

Data of this study indicate that 58% of children with arterial thrombosis and 80% of children with venous thrombosis had genetic risk factors of familial thrombophilia. Besides inherited defects in the protein C anticoagulant pathway, recently reported in a smaller group of children,23 increased concentrations of Lp (a) play an important role in the etiology of childhood thromboembolism.

Lp (a) was first described in human plasma by Berg as a genetic variant of $\beta$-lipoprotein.24 Lp (a) levels are reported to be regulated by a gene located on the long arm of chromosome 6 close to the gene for plasminogen. Complementary DNA sequencing of human apo (a) showed it to be closely homologous with plasminogen.25 This fact is assumed to provide a direct link between thrombogenesis and atherosclerosis.26,27 In addition, it has been speculated that high plasma Lp (a) levels might also be a marker of the early presence of atherosclerotic lesions at extracoronary sites.28

Besides increased Lp (a) levels in children with thrombosis, 11 of 13 patients with thrombosis and Lp (a) $>50$ mg/dL in this study had a positive family history of early myocardial infarction, stroke, or venous thrombosis. These findings confirm literature data claiming that increased levels of Lp (a) in infancy and childhood were significantly associated with thromboembolism in the patients’ parents or

<p>| TABLE 1. Incidence of Genetic Risk Factors for Thrombophilia in Children With Arterial or Venous Thromboembolism |
|----------------------------------------------------------|----------------------------------------------------------|
| Genetic risk factors                                      |                                                      |
| Arterial Thrombosis (n = 36)                              | Venous Thrombosis (n = 36)                              |
| Lp (a)                                                     |                                                      |
| Arterial Thrombosis (n = 36)                              |                                                      |
| Factor V Leiden                                           |                                                      |
| Protein C deficiency type I                               |                                                      |
| Antithrombin deficiency type I                            |                                                      |
| TABLE 2. Lp (a) Concentration, Thrombus Location, and Affected Family Members in Children With Familially Increased Lp(a) and Thromboembolism |</p>
<table>
<thead>
<tr>
<th>Patient Location</th>
<th>Lp (a) mg/dL</th>
<th>Additional Genetic Risk</th>
<th>Affected Family Member</th>
<th>Lp (a): mg/dL Family Member</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female, neonate</td>
<td>Arterial</td>
<td>70</td>
<td>Factor V Leiden</td>
<td>Grandparent</td>
</tr>
<tr>
<td>Male, neonate</td>
<td>Arterial</td>
<td>145</td>
<td>Factor V Leiden</td>
<td>Grandparent</td>
</tr>
<tr>
<td>Male, 5 mo</td>
<td>Arterial</td>
<td>70</td>
<td>Factor V Leiden</td>
<td>Grandparent</td>
</tr>
<tr>
<td>Male, 3 y</td>
<td>Arterial</td>
<td>110</td>
<td>Factor V Leiden</td>
<td>Grandparent</td>
</tr>
<tr>
<td>Male, 5 y</td>
<td>Arterial</td>
<td>90</td>
<td>Factor V Leiden</td>
<td>Grandparent</td>
</tr>
<tr>
<td>Male, 6 y</td>
<td>Arterial</td>
<td>80</td>
<td>Factor V Leiden</td>
<td>Grandparent</td>
</tr>
<tr>
<td>Female, 8 y</td>
<td>Arterial</td>
<td>90</td>
<td>Factor V Leiden</td>
<td>Grandparent</td>
</tr>
<tr>
<td>Female, 13 y</td>
<td>Arterial</td>
<td>85</td>
<td>Protein C deficiency</td>
<td>Grandparent</td>
</tr>
<tr>
<td>Male, neonate</td>
<td>Venous</td>
<td>90</td>
<td>Factor V Leiden</td>
<td>Grandparent</td>
</tr>
<tr>
<td>Male, 3 y</td>
<td>Venous</td>
<td>65</td>
<td>Factor V Leiden</td>
<td>Grandparent</td>
</tr>
<tr>
<td>Male, 4 y</td>
<td>Venous</td>
<td>92</td>
<td>Factor V Leiden</td>
<td>Grandparent</td>
</tr>
<tr>
<td>Male, 10 y</td>
<td>Venous</td>
<td>165</td>
<td>Factor V Leiden</td>
<td>Grandparent</td>
</tr>
<tr>
<td>Male, 13 y</td>
<td>Venous</td>
<td>98</td>
<td>Factor V Leiden</td>
<td>Grandparent</td>
</tr>
</tbody>
</table>

* NA = Not available.
grandparents.29–31 However, further studies are needed to evaluate whether general neonatal Lp (a) screening could detect families at risk of vascular accidents or could prevent the early onset of thromboembolism in the families affected.32

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