Bleeding in a patient taking Lorenzo's oil: evidence for a vascular defect

BC Chai, WS Etches, MW Stewart, K Siminoski

Summary
We describe a man with adrenoleukodystrophy receiving Lorenzo's oil (glycerol trioleate and glycerol trierucate) who developed purpura, petechiae, and bleeding. Bleeding time was markedly increased (> 20 min), although he had only borderline thrombocytopenia (120 x 10^9/l) and conventional platelet aggregation studies were normal (except for a borderline response to low concentration collagen), as were results using a new technique employing immobilised von Willebrand factor. Together these results suggest that bleeding in this man resulted from a defect in vascular wall function or in the interaction of platelets with the endothelium.

Keywords: adrenoleukodystrophy, platelets, fatty acids, bleeding time

In adrenoleukodystrophy there is tissue accumulation of very-long-chain fatty acids (VLCFA), probably resulting from a deficiency of lignoceroyl-CoA ligase activity. An experimental dietary therapy restricts VLCFA intake and provides supplementation with long-chain fatty acids (LCFA) in the form of Lorenzo's oil (a combination of glycerol trioleate and glycerol trierucate). Recently this regimen has been found to induce thrombocytopenia, although significant clinical bleeding has not been reported as a consequence. We describe a man with ALD who developed bleeding problems on this diet, and in whom tests suggested a defect in vascular wall function or in platelet-endothelial interaction.

Case report
A 37-year-old man with adrenoleukodystrophy was placed on dietary therapy that restricted total fat intake to 15% of calories and added glycerol trioleate as 20% of total calories. A low-dose fish oil supplement was also started to avoid deficiencies (1 g/day; approximately 30% omega-3 fatty acids). Other medications included cortisone, fludrocortisone, ranitidine, and baclofen. Platelet count was 242 x 10^9/l at initiation of dietary therapy and did not change during the following eight months. Treatment was then switched to Lorenzo's oil (80% glycerol trioleate and 20% glycerol trierucate) when platelets were 230 x 10^9/l (table). Four weeks later the platelet count had decreased to 133 x 10^9/l. The patient was started on ketorolac trimethamine (10 mg bid) for neuropathic pain and two days later he developed a spontaneous petechial rash on the right forearm. Platelet count was 108 x 10^9/l. Ketorolac was discontinued, Lorenzo's oil was switched back to glycerol trioleate, and platelet count returned to pretreatment values within two weeks.

Lorenzo's oil was reintroduced when platelet count was 254 x 10^9/l and conventional platelet aggregation studies performed as a baseline were normal. At 5% of calories platelet count decreased to a low of 161 x 10^9/l. Lorenzo's oil was then increased incrementally every four weeks. At 10% of calories platelets declined to 136 x 10^9/l, while platelet function studies remained normal. Platelet function was also marked by the presence of petechiae on the lower legs and buttocks. Platelet aggregation was significantly diminished.

Adrenoleukodystrophy
- inheritance: X-linked co-dominant
- cause of tissue damage: accumulation of VLCFAs
- genetic defect: abnormal peroxisomal ATP-binding transporter
- phenotypes:
  - cerebral form: brain affected, male infants and children
  - adrenomyeloneuropathy: spinal cord and peripheral nerves affected, male adolescents and adults
  - adrenal and testicular failure: occurs in either type
- mothers of affected males: multiple sclerosis-like manifestations, endocrine abnormalities uncommon
- diagnosis: serum LCFAs elevated
- treatment: none proven

Lorenzo's oil
- composition: LCFAs, 80% glycerol trioleate, 20% glycerol trierucate
- theory: competes with VLCFAs which do not accumulate, tissue damage avoided
- evidence of effectiveness: marked decline of serum VLCFAs; positive clinical response in some anecdotal cases
Table  Haematological parameters during administration of Lorenzo's oil

<table>
<thead>
<tr>
<th>Dose of Lorenzo's oil (% calories)</th>
<th>0</th>
<th>20</th>
<th>20+</th>
<th>0</th>
<th>5</th>
<th>10</th>
<th>15</th>
<th>20</th>
<th>0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platelet count (x 10^9/l)</td>
<td>230</td>
<td>133</td>
<td>108</td>
<td>254</td>
<td>161</td>
<td>136</td>
<td>134</td>
<td>120</td>
<td>208</td>
</tr>
<tr>
<td>Bleeding time (min)</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>Platelet aggregation</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>collagen (1 µg/ml)</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>D</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>collagen (5 µg/ml)</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>D</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
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<tr>
<td>epinephrine (1, 5, 50 µM)</td>
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<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
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<tr>
<td>ADP (1, 2, 4, 10 µM)</td>
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<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
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<tr>
<td>ristocetin (0.5, 1.2, 1.5 mg/ml)</td>
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<td>N</td>
<td>N</td>
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<td>N</td>
<td>N</td>
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<tr>
<td>arachidonic acid (0.5 mg/ml)</td>
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<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
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<tr>
<td>VWF beads</td>
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<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
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</tr>
</tbody>
</table>

+ = values when ketorolac was added to therapy; ND = not determined; N = normal; D = very slightly decreased; ADP = adenosine diphosphate; VWF = von Willebrand's factor.

evaluated at this time by a recently described technique utilising von Willebrand factor immobilised onto polystyrene beads. In this method, platelet activation is assessed by measuring adenosine triphosphate release from platelet-dense granules induced by the beads. The patient's results were within the established normal range (n = 60). A bleeding time test was performed at this point as the upper range of normal at 8.0 min. There were no bleeding episodes until Lorenzo's oil was increased to 20% of daily intake. Mild nose bleeds occurred without any local pathology. Haemorrhoids, which had previously bled only rarely, began to ooze at the mouth with each bowel movement, with a large volume of blood. Bruising and petechiae occurred on various areas of the skin with either no or minimal trauma. Platelet count was minimally reduced (normal range 200,000–400,000/µl). Platelet aggregation studies were performed at this time, and von Willebrand factor bead-induced aggregation and conventional platelet aggregation studies remained normal except for a borderline response to low concentration collagen (1 µg/ml). The bleeding time, however, was elevated at greater than 20 minutes. Lorenzo's oil was discontinued, and in three weeks bleeding time decreased to 12 min and platelets increased to 208 x 10^9/l. He had no further bleeding. Prothrombin time and partial thromboplastin time were normal. At no time did he take aspirin-containing medications.

Discussion

The first bleeding episode in our patient was probably the result of platelet dysfunction arising from the addition of ketorolac to therapy, since the petechiae occurred two days after the drug was begun, and stopped when it was discontinued. When Lorenzo's oil was subsequently reintroduced, significant clinical bleeding began again at a dose of 20% of calories. Platelet counts had declined but were minimally below the lower range of normal, a level at which some bleeding does not usually occur. Moreover, von Willebrand factor bead-induced platelet activation fell within normal limits. Previous studies have suggested that the von Willebrand factor bead methodology is more sensitive for subtle abnormalities of platelet activation than are conventional aggregation studies using soluble agonists. Bleeding time, however, had increased from 8.0 min on 10% Lorenzo's oil to more than 20 min at a 20% dose. This constellation of changes, which has not been reported previously for LCFA-supplemented diets (either for Lorenzo's oil or for fish oils) suggests a defect in endothelial function or platelet-endothelial interaction.

Fish oils have been shown to alter production of a variety of endothelial and platelet factors that are involved in coagulation. These changes result in a mild prolongation of bleeding time that is rarely greater than 3 to 4 min, and which does not produce clinical bleeding. Neither Lorenzo's oil nor erucic acid have been investigated for their effects on endothelial and platelet parameters, but similar mechanisms are likely.

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