Postheparin Plasma Lipoprotein Lipase Activity in Heterozygotes of Familial Lipoprotein Lipase Deficiency

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Type I familial hyperlipoproteinemia is a rare disease associated with marked hyperchylomicronemia and normal very low density lipoproteins (VLDL) in plasma. Among several subtypes the most common cause of this disease is thought to be lipoprotein lipase (LPL) deficiency.

The purpose of this communication is to report a case of primary LPL deficiency in a female infant, whose chylemia was detected at the age of 5 days, and to investigate the serum lipoprotein pattern and LPL activity in the family members.

CASE REPORT

The patient, who was born without particular accident during perinatal period, visited an obstetrician for the routine screening of congenital metabolic disorders and for evaluation of jaundice at the age of 5 days. Her parents are healthy and they are first cousins (her grandmothers are sisters). Her 3-year-old
brother is in good health. None has suffered from ischemic heart diseases, liver
diseases or hyperlipidemias in her family.

When the serum bilirubin was examined, the obstetrician noticed that her
serum was quite turbid. And two weeks later he reexamined her serum, which
was still turbid. Then the patient was referred to our hospital for the further
examination at the age of 23 days.

On admission she looked quite healthy and neither jaundice nor cyanosis was
observed. But her skin looked very white and there were several fine yellowish
papules on her cheeks and anterior chest. The liver and spleen were palpable 1
cm beneath the costal margin. Ophthalmoscopy revealed so-called lipemia
retinalis in both fundi.

All chemical analyses but serum lipid levels were made after the serum
turbidity had been resolved by restricting dietary fat. Laboratory findings were
normal with blood urea nitrogen, bilirubin, SGOT, SGPT, alkaline phosphatase
and uric acid. The white blood cell count was 17,200, with 19% neutrophils, 57% lymphocytes, 20% monocytes, 3% eosinophils, and 1% basophils. The red cell
count was 3,570,000, the hemoglobin 10.9 g/100 ml, the hematocrit 31.8%, and the
platelet 794,000. Serum amylase was 22 IU/liter. The lipid levels were 2,256
mg/100 ml in triglycerides (TG), 840 mg/100 ml in total cholesterol, and 660 mg/
100 ml in phospholipids.

To determine the subtype of the hyperlipoproteinemia in the patient, agarose
gel electrophoresis of serum and ultracentrifugation analysis (Havel et al. 1955)
were performed. The former disclosed an extreme accumulation of the lipo-
protein on zero point, which was chylomicron fraction, normal bands of VLDL
and low density lipoproteins (LDL), and thin band of high density lipoproteins
(HDL) 2 & 3. The latter analysis revealed that TG and cholesterol in the
chylomicron fraction were distinctly high and HDL fraction was low (Table 1).
These results indicated that the patient suffered from type I hyperlipo-
proteinemia.

Two distinguish the subtype of type I hyperlipoproteinemia in this patient,
LPL activity in the postheparin plasma (PHP) was assayed with hepatic tri-

| Table 1. Lipoprotein analysis in the patient and her family (mg/100 ml) |
|-----------------------|----------------|----------|--------|--------|--------|
|                       | Serum | Chylo | VLDL | LDL   | HDL 2 & 3 |
| Patient               |       |       |      |       |        |
| TG                    | 4,794 | 4,657 | 88   | 41    | 8      |
| TC                    | 560   | 507   | 17   | 31    | 5      |
| Father                |       |       |      |       |        |
| TG                    | 53    | -     | 18   | 23    | 12     |
| TC                    | 106   | -     | 5    | 63    | 38     |
| Mother                |       |       |      |       |        |
| TG                    | 106   | -     | 60   | 26    | 20     |
| TC                    | 175   | -     | 16   | 113   | 42     |
| Brother               |       |       |      |       |        |
| TG                    | 67    | -     | 28   | 23    | 16     |
| TC                    | 135   | -     | 8    | 101   | 27     |
LPL in Heterozygotes of LPL Deficiency

Table 2. Two postheparin plasma lipase activities and apoproteins in the patient and her family

<table>
<thead>
<tr>
<th></th>
<th>Patient</th>
<th>Mother</th>
<th>Father</th>
<th>Brother</th>
<th>Control (± s.d.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LPL (μmoles/ml/hr)</td>
<td>1.1</td>
<td>3.6</td>
<td>6.7</td>
<td>3.7</td>
<td>6.2 ± 2.1</td>
</tr>
<tr>
<td>H-TGL (μmoles/ml/hr)</td>
<td>18.0</td>
<td>6.6</td>
<td>8.0</td>
<td>16.8</td>
<td>8.8 ± 2.9</td>
</tr>
<tr>
<td>Apoproteins (mg/100 ml)</td>
<td>Pre</td>
<td>29 70 100 105 83</td>
<td>Post</td>
<td>M 111 +15</td>
<td>F 115 +15</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4 27 34 30 24</td>
<td></td>
<td>M 31 ±5</td>
<td>F 34 ±7</td>
</tr>
<tr>
<td></td>
<td></td>
<td>63 129 95 52 85</td>
<td></td>
<td>M 99 ±23</td>
<td>F 100 ±19</td>
</tr>
<tr>
<td>C-II</td>
<td>19.9</td>
<td>7.1</td>
<td>5.1</td>
<td>1.8</td>
<td>3.8 ±1.35</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>F 3.82 ±1.38</td>
</tr>
<tr>
<td></td>
<td>14.0</td>
<td>6.0</td>
<td>3.8</td>
<td>2.3</td>
<td>3.2 ±1.89</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>F 4.09 ±1.37</td>
</tr>
</tbody>
</table>

Pre, before fat restriction; Post, after fat restriction.

glyceride lipase (H-TGL) activity (Table 2). PHP was collected 5 min after the injection of 10 U/kg heparin in children and 20 min in adults. Two triglyceride lipases were separately measured by immunochemical method described by Murase et al. (1980) using specific antibodies to H-TGL. In the patient LPL activity was extremely diminished, whereas H-TGL activity was relatively higher than the normal level.

Furthermore, apoproteins in chylomicrons and VLDL were analyzed both with single radial immunodiffusion using commercial kits (Daiichi Kagaku Yakuhin Co. Ltd.) and with disc gel isoelectric focusing (Kashyap et al. 1981). Apoprotein C-II was evidently present and other apoproteins were all normal both in quantities and in qualities (Table 2, Fig. 1). These results indicated that the patient was deficient in LPL activity.

After admission the patient was administered fat-restricted formula containing 5% vegetable fat and 40% MCT in calory ratio (Fig. 2). But even in 12 days of the regimen the serum TG remained above 3,000 mg/100 ml and the formula was changed to that containing only 0.9% vegetable fat in calory ratio. Consequently serum lipid level rapidly fell down to almost normal range, followed by disappearance of eruptive xanthoma and lipemia retinalis. Thirty-days later the patient was discharged with serum TG level of about 400 mg/100 ml, and was doing well after discharge without any symptoms.

Serum lipoprotein pattern, apoproteins, and two triglyceride lipases were analyzed also in her parents and brother. Lipoprotein pattern (Table 1) and apoproteins (Table 2, Fig. 1) were all normal. On the other hand, LPL activity of the mother and brother was moderately decreased and H-TGL activity of the brother was mildly elevated. Two triglyceride lipase activities were entirely
DISCUSSION

Type I familial hyperlipoproteinemia is characterized by eruptive xanthoma, hepatosplenomegaly, attacks of abdominal pain, and lipemia retinalis. Up to now several different causes have been reported, and the most common causes are LPL deficiency and apoC-II deficiency. The former was first described by Havel.

normal in the father.
and Gordon in 1960, and the latter by Breckenridge in 1970. They are inherited in autosomal recessive fashion. A combination of apoC-II deficiency and very low postheparin LPL activity was reported by Stalenhoef et al. in 1981, and inhibitors of normal adipose tissue LPL were found by Brunzell et al. in 1983. In the latter the mode of inheritance is thought to be autosomal dominant.

In our case postheparin LPL activity was distinctly decreased and H-TGL activity was elevated. There was no abnormality in apoproteins including apoA-I, A-II, C-II, C-III, and E. No primary disorder which may cause hyperlipoproteinemia was detected. The parents of our patient had normal serum lipoprotein pattern. These results indicated that our patient was deficient in LPL activity.

Of the cases of LPL deficiency so far reported, one-third was diagnosed during the first year of life, and the remaining cases were detected before the age of 10 years. Sadan et al. (1977) reported a case which was detected at the age of 8 days. Our case was detected at the age of 5 days, which may be the earliest.

Heterozygotes of LPL deficiency are usually normal in lipoprotein pattern and it is not certain whether lipolytic activity is impaired or not. To investigate the possibility to detect heterozygotes in the family we examined serum lipoprotein pattern and two postheparin lipase activities of the parents and brother. As a result all of them had normal lipoprotein pattern, and the mother and brother were moderately decreased in LPL activity. In 1967 Harlan et al. first reported that the adipose tissue LPL was about 50% of normal in the parents and healthy sibs. And in 1972 Fredrickson and Levy reported that postheparin plasma lipolytic activities in the healthy sibs were intermediate between normal subjects and the patients in eight families. Recently Go et al. (1983) has determined separately LPL and H-TGL activities in obligate heterozygotes of the patient and reported that postheparin lipolytic activity, and the activities of LPL and H-TGL in the mother were moderately decreased. In our case LPL activity of both mother and brother was also decreased, suggesting that the detection of heterozygotes in the family may be rather possible by determining the LPL activity in postheparin plasma. As for H-TGL activity, that of the parents were normal and that of the brother was elevated in our case. But in the case of Go et al. that of mother was rather decreased. So there may be no consistent tendency of H-TGL activity among heterozygotes of LPL deficiency. Much more investigation will be needed to understand the meaning of change in H-TGL activity.

Acknowledgments

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References

1) Breckenridge, W.C., Little, J.A. & Steiner, G. (1970) Hypertriglyceridemia associat-


