Case Reports

Lysosomal Acid Lipase Deficiency in Japan: A Case Report of Siblings and a Literature Review of Cases in Japan

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We report on two siblings with early onset lysosomal acid lipase deficiency or Wolman disease. Their parents had a consanguineous marriage. The children showed evidence of abdominal distension and failed to thrive, despite having regular nutrition. At 3–4 months of age, their abdominal distension and jaundice progressed rapidly and they died of liver failure. Sebelipase alfa, a recombinant form of human lysosomal acid lipase has recently been used as an enzyme replacement therapy in patients with later-onset cholesteryl ester storage disease. Therefore, we investigated cases of lysosomal acid lipase deficiency in Japan and found that the number of cases was extremely low. Only 14 cases of Wolman disease and seven cases of cholesteryl ester storage disease were reported. As it is now possible to treat lysosomal acid lipase deficiency, it is important to increase awareness of this disease among pediatricians and doctors working in internal medicine. (J Nippon Med Sch 2018; 85: 131–137)

Key words: lysosomal acid lipase deficiency, Wolman disease, Japan

Introduction

Lysosomal acid lipase (LAL) deficiency (LALD) is a multisystemic autosomal recessive storage disease caused by mutations in the LIPA (OMIM #278000) gene. LALD leads to an accumulation of cholesteryl esters and triglycerides in the lysosomes of the liver, spleen, and cardiovascular system and patients develop progressive liver dysfunction as well as cardiovascular disease. LALD presents as two major clinical phenotypes: infantile-onset Wolman disease (WD) and later-onset cholesteryl ester storage disease (CESD). WD is a rare, neonatal-onset, fulminant subtype marked by decreased LAL activity that results in massive lysosomal accumulation of cholesteryl esters and triglycerides, predominantly in the liver, spleen, adrenal glands, bone marrow, lymph nodes, and macrophages. The symptoms in infants with WD include vomiting, diarrhea, and massive hepatosplenomegaly with adrenal calcifications evident by two to four months of age. In contrast, CESD is a later-onset subtype, often unrecognized, although present in infancy, childhood or adulthood, depending on residual in vitro LAL activity. The progressive lysosomal cholesteryl ester and triglyceride accumulation leads to a characteristic liver pathology: elevated serum transaminases and elevated serum LDL-cholesterol and triglycerides, with normal to low HDL-cholesterol concentrations (type IIb hyperlipoproteinemia). Premature death is due to liver failure and/or accelerated atherosclerotic disease secondary to chronic hyperlipidemia.

Recently, Sebelipase alfa (SBC-102; Alexion Pharmaceuticals, New Haven, CT), a recombinant human LAL was used as an investigational enzyme replacement therapy in patients with CESD. This showed that the enzyme replacement therapy was well tolerated resulting in rapidly decreased serum transaminases. These outcomes were sustained after long-term dosing with an improvement in patients’ serum lipid profiles. Here, we report on a case of siblings with WD. Furthermore, we summarize reported cases of LALD in Japan.

Case 1

A two-month-old girl was admitted to our hospital due to abdominal distension (Fig. 1a). Abdominal distention and hepatosplenomegaly with frequent diarrhea and
vomiting had been observed 30 days after birth. Her family history revealed that her parents were consanguineous, being first cousins, and the patient was the youngest of three children. Her oldest sister displayed similar symptoms and had died 80 days after birth. Examination of her blood showed moderate anemia with thrombocytopenia (Hb 9.6 g/dL, Ht 26.6%, RBC 378 × 10³/μL, WBC 5,800 /μL, platelets 65 × 10³/μL). Biochemical analysis showed total protein 6.2 g/dL (albumin 63%), total bilirubin 1.1 mg/dL, ALT 92 U, AST 14 U, LDH 1,003 IU, γ-GTP 22.6 U/L, total lipid 672 mg/dL, total cholesterol 97 mg/dL, free cholesterol 91 mg/dL, phospholipid 210 mg/dL, triglyceride 521 mg/dL, β-lipoprotein 612 mg/dL, free fatty acid 1.03 mEq/L, and HDL-cholesterol 46.0 mg/dL. Bone marrow analysis showed a marked increase in foamy cells (Fig. 1b). Abdominal computed tomography (CT) revealed marked hepatosplenomegaly and enlargement of the adrenal glands with calcification (Fig. 1c). At three months of age, anemia and jaundice had rapidly progressed and she died 114 days after birth. Her LAL enzyme activity was markedly decreased, [¹⁴C]-triolein: 0.7 against 25.0 +/- 15.1, [¹⁴C]-cholesterol olate: 0.003 against 3.0 +/- 2.3 nmol/mg protein/hr, controls. Mutational analysis of her LIPA gene showed a single substitution within exon 3: c.169C>G and p.Tyr22Ter (homozygous). This mutation changed a tyrosine codon (TAC) in codon 22 to a termination codon (TAG) and lead to unstable mRNA and very low levels of enzyme activity. She was diagnosed as having WD.

Case 2

The youngest sister of the patient described in Case 1 was admitted to our hospital when she was one month old with marked abdominal distention. Extensive hepatosplenomegaly was observed with calcification of the adrenal glands. Hematological and chemical examination showed she had mild anemia and lymphocytes with foamy cells as well as liver dysfunction. After four months of age, her abdominal distension and jaundice had progressed despite conservative therapies, such as a low fat and low cholesterol diet. She died when she was six months old. The autopsy showed a general malaise, with a body weight of 4 kg and marked jaundice. Massive storage of lipids was evident in her liver (500 g; Fig. 2a), spleen (300 g), lymph nodes, bone marrow, lung (Fig. 2b), alimentary tract (Fig. 2c) and adrenal glands (13.2 g, 14.5 g), which also showed marked calcification and ne-
Two Siblings with LALD

Fig. 2 Pathological findings of case 2

a: Liver; In the liver, hepatomegaly (500 g), foamy and vacuolated hepatocytes showing lipid storage, and marked perisinusoidal and periportal fibrosis were observed with marked disarrangement of hepatic cords and slight proliferation of bile ducts and marked bile stasis of the intrahepatic bile ducts (Hematoxylin and eosin staining).
b: Lung; Marked infiltration of lipid-laden macrophages in alveolar spaces and the interstitium (Hematoxylin and eosin staining).
c: Alimentary tract; Marked infiltration of foamy cells was noted in the mucosa. (Hematoxylin and eosin staining).
d: Adrenal glands; In the adrenal glands, marked hypertrophy (left 13.2 g, right 14.5 g), swelling, and vacuolization of cortical cells were observed with massive calcification and/or marked reticulofibrosis in the zona fasciculata and the zona reticularis. (Hematoxylin and eosin staining).

Fig. 3 Pedigree chart of cases 1 and 2

BBD

E

F

REPORTED CASES OF LALD IN JAPAN (TABLE 1)
Surprisingly, reported cases of patients with WD or CESD are extremely rare in Japan. Only 14 cases of patients with WD and seven cases of CESD have been officially reported, including publications in the Japanese language. In addition, most of the reported cases of WD were diagnosed by clinical and/or pathological findings only. Several cases analyzed genetic alternations of the LIPA gene in these patients, with the characteristic mutated position. The clinical findings from each of the cases of WD were similar, such as adrenal calcifications or enlargement, abdominal distension, diarrhea, failure to thrive, hepatomegaly, icterus, and splenomegaly. In contrast, the CESD cases reported in Japan were confirmed by genetic analysis and the clinical findings varied with each case as well as previous reports.

DISCUSSION
Here, we report two babies with WD (Fig. 3). Recently, the drug for enzyme replacement therapy against LALD has been approved and is available in Japan. Thus, WD...
Table 1 WD and CESD cases reported in Japan

<table>
<thead>
<tr>
<th>Patient</th>
<th>Diagnosis</th>
<th>Gender</th>
<th>Age at onset</th>
<th>Age at death/last report</th>
<th>Clinical manifestation</th>
<th>Family history</th>
<th>Consanguity</th>
<th>LAL enzyme activity</th>
<th>LIPA gene analysis</th>
<th>References</th>
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<tbody>
<tr>
<td>1</td>
<td>WD</td>
<td>F</td>
<td>2 months</td>
<td>5 months/dead</td>
<td>AC, AD, D, FIT, HM, I, SM, V</td>
<td>Two of elder sisters of 4 children died at age of 4 months.</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>2</td>
<td>WD</td>
<td>F</td>
<td>5 months</td>
<td>9 months</td>
<td>AC, AD, FIT, D, HM, SM, V</td>
<td>none</td>
<td></td>
<td></td>
<td></td>
<td>3</td>
</tr>
<tr>
<td>3</td>
<td>WD</td>
<td>M</td>
<td>1 month</td>
<td>2 and 1/2 months</td>
<td>AC, AD, D, FIT, HM, SM</td>
<td>none</td>
<td>distantly related</td>
<td></td>
<td></td>
<td>4</td>
</tr>
<tr>
<td>4</td>
<td>WD</td>
<td>F</td>
<td>30 days</td>
<td>114 days/dead</td>
<td>AC, AD, D, FIT, HM, I, SM</td>
<td>Eldest sister of 3 children died at age of 80 days</td>
<td>first cousin</td>
<td>decreased</td>
<td>c.169C&gt;G/p. Y22X in exon 3</td>
<td>5, 6, 7</td>
</tr>
<tr>
<td>5</td>
<td>WD</td>
<td>F</td>
<td>1 month</td>
<td>6 months/dead</td>
<td>AC, AD, D, FIT, I, SM, V</td>
<td>Elder sisters of 4 children died at age of 80 days</td>
<td>first cousin</td>
<td></td>
<td></td>
<td>8</td>
</tr>
<tr>
<td>6</td>
<td>WD</td>
<td>M</td>
<td>35 days</td>
<td>6 month/dead</td>
<td>AC, AD, D, FIT, I, SM</td>
<td>an elder brother died at age of 3 months</td>
<td>consanguity</td>
<td>decreased</td>
<td></td>
<td>9, 10</td>
</tr>
<tr>
<td>7</td>
<td>CESD</td>
<td>F</td>
<td>5 months</td>
<td>final diagnosis was Wilson disease (personal communication)</td>
<td>AD, D, FIT, HM</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>11</td>
</tr>
<tr>
<td>8</td>
<td>WD</td>
<td>F</td>
<td>1 month</td>
<td>76 days/dead</td>
<td>AC, AD, D, FIT, HM, I, SM</td>
<td>consanguity</td>
<td></td>
<td></td>
<td></td>
<td>12, 13, 14</td>
</tr>
<tr>
<td>9</td>
<td>WD</td>
<td>M</td>
<td>1 month</td>
<td>156 days/dead</td>
<td>AC, AD, D, FIT, HM, I, SM</td>
<td>consanguity</td>
<td></td>
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<td></td>
<td>13</td>
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<tr>
<td>10</td>
<td>WD</td>
<td>M</td>
<td>1 month</td>
<td>93 days/dead</td>
<td>AC, AD, D, FIT, HM, I, SM</td>
<td>consanguity</td>
<td></td>
<td></td>
<td></td>
<td>13</td>
</tr>
<tr>
<td>11</td>
<td>WD</td>
<td>F</td>
<td>1 month</td>
<td>86 days/dead</td>
<td>AC, AD, D, FIT, HM, I, SM</td>
<td>younger sister of case 8</td>
<td></td>
<td></td>
<td></td>
<td>14</td>
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<tr>
<td>12</td>
<td>WD</td>
<td>F</td>
<td>1 month</td>
<td>104 days/dead</td>
<td>AC, AD, D, FIT, HM, I, SM</td>
<td>sister of case 9</td>
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<td></td>
<td></td>
<td>14</td>
</tr>
<tr>
<td>13</td>
<td>WD</td>
<td>F</td>
<td>1 day</td>
<td>67 days/dead</td>
<td>AC, AD, D, HM, SM</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>14</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Patient</th>
<th>diagnosis gender</th>
<th>Age at onset</th>
<th>Age at death/last report</th>
<th>Clinical manifestation</th>
<th>Family history</th>
<th>consanguinity</th>
<th>LAL enzyme activity</th>
<th>LIPA gene analysis</th>
<th>references</th>
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<tbody>
<tr>
<td>14</td>
<td>CESD/ mild WD</td>
<td>F</td>
<td>1 month</td>
<td>3 years</td>
<td>AC, AD, HM</td>
<td></td>
<td>decreased</td>
<td></td>
<td>15, 16</td>
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<tr>
<td>15</td>
<td>CESD</td>
<td>M</td>
<td>22 years</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>17, 18</td>
</tr>
<tr>
<td>16</td>
<td>CESD</td>
<td>M</td>
<td>2 years</td>
<td></td>
<td>HM, I</td>
<td></td>
<td></td>
<td></td>
<td>19</td>
</tr>
<tr>
<td>17</td>
<td>WD</td>
<td>F</td>
<td>7 days</td>
<td>5 months/dead</td>
<td>AC, AD, D, FIT, HM, I, SM, V</td>
<td>elder brother died at age of 2 months</td>
<td>none</td>
<td>done</td>
<td>20, 21</td>
</tr>
<tr>
<td>18</td>
<td>CESD</td>
<td>M</td>
<td>junior high school student</td>
<td>alive at 65 years old</td>
<td>HM</td>
<td></td>
<td>decreased</td>
<td></td>
<td>22, 23, 24</td>
</tr>
<tr>
<td>19</td>
<td>CESD</td>
<td>F</td>
<td>13 year</td>
<td>alive</td>
<td>anorexia, liver dysfunction, hypercholesteremia, HM</td>
<td></td>
<td></td>
<td></td>
<td>25, 26, 27</td>
</tr>
<tr>
<td>20</td>
<td>WD</td>
<td></td>
<td>16 weeks fetus tissue (abortion case)</td>
<td>two elder siblings diagnosed Wolman disease (case 17)</td>
<td>both parents have hetero c.890insG in exon 8</td>
<td></td>
<td>homo c.890insG in exon 8</td>
<td></td>
<td>28</td>
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<tr>
<td>21</td>
<td>CESD</td>
<td>M</td>
<td>11 years</td>
<td>alive</td>
<td>HM, SM, liver dysfunction, hypercholesteremia</td>
<td></td>
<td>decreased</td>
<td></td>
<td>29, 30</td>
</tr>
</tbody>
</table>

*: Both parents had low value of LAL enzyme activity

Abbreviations: AC, adrenal calcifications or enlargement; AD, abdominal distension; CESD, cholesterol ester storage disease; D, diarrhea; F, female; FTT, failure to thrive; HM, hepatomegaly; I, icterus; M, male; SM, splenomegaly; WD, Wolman disease; V, vomiting
and CESD are now treatable. Patients with CESD are good candidates for the enzyme replacement therapy, although diagnosis of CESD is difficult. Clinically, the age of onset of CESD is variable and it is often unrecognized, particularly in adults, until unexplained hepatomegaly, with or without splenomegaly, elevated transaminase activities, and/or type IIb hyperlipoproteinemia lead to further investigations and subsequent diagnosis\(^1\).

Enzyme replacement therapy for WD is more challenging, although may be effective. Because WD is inherited with strong penetrance, the genetic analysis for the known mutation has become easier. Diagnosing WD may be easier if an older sibling is also affected. However, a reported case suggested it might be necessary to administer intra-uterine enzyme replacement therapy during early trimester pregnancy, if fetal tissue at 22 weeks shows pathological changes which are genetically confirmed as WD (Case 20).

A literature review of LALD cases showed that they were extremely rare in Japan\(^2,3\). The reason for their rarity is unknown, although it could be due to racial diversity. A lack of awareness about LALD may also be a reason. Because LALD is now treatable, we are actively vigilant for patients with LALD.

In conclusion, it is necessary to increase awareness about LALD to pediatricians and doctors of internal medicine in order to detect and treat patients with LALD.

Conflict of Interest: The authors declare no conflict of interest.

References
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