Infantile Refsum disease (IRD) is a rare autosomal recessive disorder of peroxisome biogenesis characterized by generalized peroxisomal metabolic dysfunction, including accumulation of very long-chain fatty acids (VLCFAs) and phytanic acid (PA), as well as decreased plasmalogen contents (PL). An effective therapy for this intractable disease has not been established, and only supportive management with docosahexaenoic acid supplementation and low PA diet has been reported so far. A boy of 3 years and 8 months presented with facial dysmorphism, transaminitis, and psychomotor retardation. Biochemical analysis showed elevated PA and VLCFAs, with reduced PL in the serum. Immunofluorescence study of fibroblasts from the patient indicated a mosaic pattern of catalase-positive and -negative particles, and molecular analysis revealed compound heterozygous mutations of PEX6. The failure of medical management to prevent the progression of clinical symptoms and abnormal biochemistry prompted us to consider liver transplantation (LT). With the chances of receiving a deceased donor liver being poor, we performed a living-donor LT from the patient’s heterozygous mother. At 6-month follow-up, the patient’s serum PA levels had normalized. VLCFAs and PL levels had declined and increased, respectively. To the best of our knowledge, this is the second reported case in which IRD was treated by living-donor LT by using a heterozygous donor. Only long-term follow-up will reveal if there is any clinical improvement in the present case. With the liver being a major site for peroxisomal pathways, its replacement by LT may work as a form of partial enzyme therapy for patients with IRD.
adrenoleukodystrophy, patients with IRD may survive beyond the age of 10 years.1, 2 Historically, the standard treatment of IRD has been supportive treatment by using a low phytanic acid (PA) diet and docosahexaenoic acid (DHA) supplementation.1, 2, 4 Enzyme replacement was first attempted in Belgium in 2003 by using hepatocyte transplantation (HT). The patient was a 4-year-old girl with severe hearing and visual impairment, together with failure to thrive.5 Subsequently, in 2005, the first case of living-donor liver transplantation (LDLT) in a mildly symptomatic 6-month-old infant who was the sibling of a severely neurologically impaired older sister was reported.6 We herein describe a case of IRD in a patient who underwent LDLT by using a liver graft from a heterozygous parent and the short-term clinical outcome.

**CASE PRESENTATION**

The patient was a boy of 3 years and 8 months of age (body weight: 12.2 kg, –1.6 SD) who was born at full term after an uneventful pregnancy of 39 weeks and 1 day. His birth weight was 2490 g. He had been followed since birth because of a large anterior fontanelle (8 × 8 cm), early infantile-onset transaminitis, psychomotor retardation, and facial dysmorphism (Fig 1). After 6 months, he had poor visual contact, apparent hypoacusia, muscle hypotonia, nystagmus, and splenomegaly. At 18 months, elevated levels of PA and very long-chain fatty acids (VLCFAs), reduced tendency of plasmalogen contents (PL), decreased DHA, and the presence of abnormal total bile acid were detected (Table 1), suggesting a diagnosis of IRD. Immunofluorescent studies using anti-human catalase antibody revealed a mosaic immunofluorescence pattern with both positive and negative catalase-containing particles in the fibroblasts (Fig 2 B and C), in contrast to numerous particles in all fibroblasts from the control (A).

**TABLE 1 The Perioperative Biochemical Parameters**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Normal Range</th>
<th>At Diagnosis, 18 mo</th>
<th>Before LT</th>
<th>Postoperative Day</th>
</tr>
</thead>
<tbody>
<tr>
<td>AST</td>
<td>24–43 U/L</td>
<td>75</td>
<td>417</td>
<td>65, 65, 41, 42</td>
</tr>
<tr>
<td>ALT</td>
<td>9–30 U/L</td>
<td>45</td>
<td>188</td>
<td>137, 113, 51</td>
</tr>
<tr>
<td>TBA</td>
<td>0–10 μmol/L</td>
<td>28.9</td>
<td>22.5</td>
<td>1.8, 2.0, 1.2</td>
</tr>
<tr>
<td>VLCFAs</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C24:0/C22:0</td>
<td>1.05 ± 0.006</td>
<td>1.43</td>
<td>1.67</td>
<td>1.03, 1.20, 1.24</td>
</tr>
<tr>
<td>C25:0/C22:0</td>
<td>0.024 ± 0.006</td>
<td>0.126</td>
<td>0.125</td>
<td>0.043, 0.041, 0.054</td>
</tr>
<tr>
<td>C26:0/C22:0</td>
<td>0.012 ± 0.005</td>
<td>0.209</td>
<td>0.232</td>
<td>0.097, 0.120, 0.118</td>
</tr>
<tr>
<td>PA/C16:0</td>
<td>0.0099 ± 0.0008</td>
<td>0.0040</td>
<td>0.0157</td>
<td>0.0005, 0.0005, 0.0005</td>
</tr>
<tr>
<td>PL/C16:0</td>
<td>0.01–0.03</td>
<td>0.009</td>
<td>0.012</td>
<td>0.017, 0.011, 0.010</td>
</tr>
<tr>
<td>DHA/C16:0</td>
<td>0.1–0.3</td>
<td>0.026</td>
<td>0.261</td>
<td>0.243, 0.217, 0.246</td>
</tr>
</tbody>
</table>

ALT, alanine aminotransferase; AST, aspartate aminotransferase; TBA, total bile acid

Initially, the patient was managed with DHA supplementation (450 mg/day) and a low PA diet. However, the symptoms gradually worsened and there was a further increase in the levels of PA and VLCFAs. In view of a previous report of a good response in a mildly symptomatic patient with IRD who underwent liver transplantation (LT) early in life,6 we considered performing LT in our patient. His chances of receiving a graft from a deceased donor were poor because of the low priority.
of his case. We therefore decided to perform LDLT. Approval was obtained from the institutional ethics committee to proceed with LDLT. Additional preoperative workup was performed. Funduscopy revealed retinitis pigmentosa (Fig 3). Brain MRI with fluid-attenuated inversion recovery sequencing revealed a hyperintense signal in the white matter of the right frontal cortex, periventricular region, and pons (Fig 4). On auditory brainstem response, there was a severe increase in threshold response on the right (80 dB) and left (90 dB). Peripheral nerve conduction tests remained within the normal range except for a decrease in the right median nerve conduction velocity (39 m/second, –2.9 SD).

A left lateral segment liver graft weighing 287 g (representing 2.39% of the graft-to-recipient weight ratio) was procured from the patient’s mother. The operation used a standard LDLT technique, which has been described elsewhere. A histology of the explanted liver showed a low lipid content with oil red O staining. Immunosuppressive treatment consisting of tacrolimus and prednisolone was administered. The patient’s postoperative course was uneventful, and he was discharged on postoperative day 33 without any surgical complications.

A rapid lowering of PA and VLCFA plasma concentration levels was observed after LDLT. The patient’s PA levels normalized within 7 days (Table 1). At 5 months after LDLT, the patient’s general condition appeared to have improved and he started to attend a special support school while receiving immunosuppression treatment (tacrolimus and prednisolone). At 6 months after LDLT, serum PA levels remained within normal range, and his low PA diet was gradually lifted (Table 2). Furthermore, PL levels were trending upward (Table 1). A peripheral nerve conduction test (right median nerve) showed improvement (52.5 m/second, –0.48 SD); however, funduscopy, auditory brainstem response, brain MRI, and a somatosensory evoked potential test showed no significant changes.

**DISCUSSION**

The present case highlighted 2 important clinical issues: (1) IRD can be successfully treated by LDLT early in life (with a subsequent normalization of PA); and (2) the levels of VLCFAs, PA, and PL in the serum should be analyzed when screening for peroxisomal diseases such as IRD.

The metabolic profile of IRD demonstrates multiple derangements of the peroxisomal metabolism, characterized by multiple peroxisomal metabolic deficiencies, which result in the accumulation of VLCFAs, PA, pristanic acid, and di- and trihydroxycholestanolic acid, and the deficiency of PL in plasma. It should be noted that PA is mainly derived from dietary sources. ZS including IRD is genetically heterogeneous due to mutations in one of the 12 different genetic PEX genes that code for PEXs that participate in the biogenesis of peroxisomes. When IRD is suspected based on the previously described abnormal biochemical parameters, cultured skin fibroblasts should be examined to confirm the peroxisomal assembly. The diagnosis can be determined by the identification

<table>
<thead>
<tr>
<th>Normal Range</th>
<th>10 mo</th>
<th>Before LT</th>
<th>After 1 mo</th>
<th>After 3 mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>CSF PA/IS</td>
<td>nd</td>
<td>0.008</td>
<td>0.013</td>
<td>0.010</td>
</tr>
<tr>
<td>Serum PA/C16:0</td>
<td>0.0009 ± 0.0008</td>
<td>0.0040</td>
<td>0.0157</td>
<td>0.0005</td>
</tr>
</tbody>
</table>

CSF, cerebrospinal fluid; IS, internal standard; nd, not detected; PA, phytanic acid.
of mutations in a gene sequence analysis of the PEX gene.\textsuperscript{8,9}

There is currently no curative treatment of IRD. Owing to the complex nature of the disorder and the plurality of the enzyme deficiencies, multidisciplinary treatment is required, although it is mainly supportive therapy. The progressive pathologic changes and severe neurologic, together with liver, dysfunction are inevitable.\textsuperscript{1,2,4} However, according to recent reports, the optimal treatment regimen, including dietary restriction, showed the PA to decrease to normal levels, which thus makes it possible to avoid a loss of vision,\textsuperscript{10} and the developmental delay experienced by the patient thereafter gradually improved.\textsuperscript{1,11}

HT\textsuperscript{5,12,13} is an alternative to LT for the treatment of liver-based inborn errors of metabolism. In HT, the aim is to replace a single deficient enzyme or its product. The procedure is less invasive than LT and can be performed repeatedly; however, the number of transplanted cells usually represents only \(\sim 5\%\) of the theoretical liver mass, and cell function often declines after \(\sim 9\) months.\textsuperscript{12,13} Therefore, HT is not yet an accepted conventional treatment. In addition, IRD, being a PBD, is inherently a systemic disease, and some of the relevant clinical effects remain unknown.

LT has been successfully used in enzyme supplementation and the replacement of inborn errors of metabolism.\textsuperscript{14,15} LT is a potential alternative in the management of IRD as it provides a lifelong supply of peroxisomal enzyme within the allograft. LDLT from the mother of a patient with IRD was reported to be successful in improving the patient’s abnormal biochemistry, as well as achieving neurologic stabilization and improvement over a follow-up period of 4 years.\textsuperscript{5} Furthermore, at 10 years after LT, the index patient is attending a special support school and is able to see, hear and speak. In comparison, her elder sister, who underwent HT at 4 years of age\textsuperscript{5}, currently continues to demonstrate severe visual, hearing and neurologic impairment (Dr Etienne Marc Sokal, personal communication, 2014). LT was chosen as the treatment in our present case after considering these personal communication scenarios, and the fact that patients with IRD typically live beyond the age of 10 years but eventually die of severe encephalopathy with only supportive medical management.\textsuperscript{1,2}

The routine application of LT in the treatment of IRD is controversial because it provides only partial enzyme replacement, as the peroxisomes are expressed in all tissues.\textsuperscript{1,2} Nevertheless, the clinical effects of LT include a reduction in serum VLCFA and PA levels.\textsuperscript{6} In the present case, we continued to provide DHA supplementation and a low PA diet until LT was performed. The patient’s PA level normalized by day 7 after LT and a reduction in VLCFA levels was also noted. After LT, we discontinued DHA supplementation because it is controversial whether oral administration of DHA has any clinical benefit.\textsuperscript{1,2,4} The patient’s low PA diet was gradually lifted with reference to the metabolic profiles in the patient’s serum (Table 1).

One of the delicate issues in LT for IRD is timing. Postponing a transplant could lead to additional neurologic insult and a higher likelihood of inferior neurodevelopmental outcomes. LT may be considered in young patients, such as the present case, whose symptoms have not progressed beyond the mild type. Although LDLT did not cure the patient’s disorder, we hypothesize that the normalization of the PA levels may prevent the progression of hearing loss, polyneuropathy, and retinitis pigmentosa. These improvements may lead to a higher quality of life due to the mitigation of the low PA diet. The posttransplant follow-up routine involves trimestral multidisciplinary medical assessments, including brain MRI and metabolic profiling.

With continued success, we believe that LT may evolve as a feasible option for the treatment of IRD. A prospective evaluation with long-term outcomes may address the ethical concerns and the validity of LDLT as a treatment of IRD. Nevertheless, close long-term clinical and metabolic follow-up should be maintained after LT.

**ACKNOWLEDGMENTS**

The authors thank Professor Lionel Van Maldergem (Centre de Génétique Humaine, Université de Franche-Comté, Besancon, France), Professor Etienne Marc Sokal (Pediatric Hepatology and Gastroenterology and Cell Transplant Center, Université Catholique de Louvain, Cliniques Universitaires Saint-Luc, Brussels, Belgium), and Professor Jean-Bernard Otte (Université Catholique de Louvain, Belgium Cliniques Universitaires Saint-Luc, Brussels, Belgium) for their personal communication about the prognosis of sibling cases and advice on performing the LDLT operation. The authors also thank Professor Vidyadhar Mali of the Department of Pediatric Surgery, National University Hospital, Singapore, for his assistance in proofreading and editing this manuscript.

**ABBREVIATIONS**

DHA: docosahexaenoic acid
HT: hepatocyte transplantation
IRD: infantile Refsum disease
LDLT: living-donor liver transplantation
LT: liver transplantation
PA: phytanic acid
PBD: peroxisome biogenesis disorder
PEX: peroxin
PL: plasmalogen contents
VLCFA: very long-chain fatty acid
ZS: Zellweger syndrome
REFERENCES


Living-Donor Liver Transplantation From a Heterozygous Parent for Infantile Refsum Disease
Masatoshi Matsunami, Nobuyuki Shimozawa, Akinari Fukuda, Tadayuki Kumagai, Masaya Kubota, Pin Fee Chong and Mureo Kasahara
Pediatrics 2016;137;
DOI: 10.1542/peds.2015-3102 originally published online May 24, 2016;
Living-Donor Liver Transplantation From a Heterozygous Parent for Infantile Refsum Disease

Masatoshi Matsunami, Nobuyuki Shimozawa, Akinari Fukuda, Tadayuki Kumagai, Masaya Kubota, Pin Fee Chong and Mureo Kasahara

*Pediatrics* 2016;137;
DOI: 10.1542/peds.2015-3102 originally published online May 24, 2016;

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://pediatrics.aappublications.org/content/137/6/e20153102