EP332: A Novel Clinical Phenotype of Acquired Partial Lipodystrophy Associated with Intensive Childhood Cytostatic Treatment

Introduction
- Lipodystrophy is a rare clinical syndrome characterized by subcutaneous fat loss, metabolic syndrome and fat maldistribution.
- Common causes are HIV therapy, specific genetic mutations and autoimmune disease.
- Partial lipodystrophy of the limbs with severe insulin resistance has been reported.

Methods
- Detailed description of two cases with this specific phenotype
- Both patients were referred for treatment refractory type 2 diabetes

Patient 1: Case history
- 43 year old Caucasian female
- Treated with intensive polychemotherapy for leukemic lymphosarcoma at age 6 through 13
- Presented with treatment resistant diabetes, hypertension and dyslipidemia
- Complaints: central fat deposition, high glucose levels
- Current therapy: atorvastatine, tolbutamide, lantus in increasing dose
- Physical: BP 170/100 mmHg, bmi 23 kg/m²; Notable excess fat deposition at face, trunk, upper arms. Lipatrophy of hips and distal extremities

Patient 2: Case history
- 22 year old Caucasian female
- Treated with high dose cyclophosphamide and total body irradiation for aplastic anemia at age 12
- Presented with treatment resistant diabetes, hyperglycemia
- Complaints: recurrent graft-versus-host of the skin. High glucose levels despite metformin. Central fat deposition
- Current therapy: metformin, s.c. insulin in increasing dose
- Physical: BP 160/90 mmHg, bmi 22 kg/m²; Severe fibrous skin scarring due to GvHD, notable lipatrophy of extremities and hips, excess fat deposition at the trunk

Patient 1: Relevant laboratory results

<table>
<thead>
<tr>
<th>Test</th>
<th>Before pioglitazone</th>
<th>After pioglitazone</th>
<th>Reference values</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALAT</td>
<td>42</td>
<td>26</td>
<td>&lt; 34 U/L</td>
</tr>
<tr>
<td>Gamma GT</td>
<td>118</td>
<td>51</td>
<td>&lt; 38 U/L</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>1.8</td>
<td>+</td>
<td>&lt; 2.30 mmol/L</td>
</tr>
<tr>
<td>HbA1c</td>
<td>66</td>
<td>36</td>
<td>&lt; 42 mmol/mol Hb</td>
</tr>
<tr>
<td>Fasting glucose</td>
<td>3.3</td>
<td>5.1</td>
<td>3.1 – 6.0 mmol/L</td>
</tr>
<tr>
<td>C-peptide</td>
<td>4.1</td>
<td>2.1</td>
<td>0.3 – 1.5 mmol/L</td>
</tr>
<tr>
<td>Leptin</td>
<td>35.1</td>
<td>55.5</td>
<td>3.7 – 11.1 µg/L</td>
</tr>
</tbody>
</table>

*While taking high dose statin therapy

Patient 2: Relevant laboratory results

<table>
<thead>
<tr>
<th>Test</th>
<th>Before pioglitazone</th>
<th>After pioglitazone</th>
<th>Reference values</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALAT</td>
<td>74</td>
<td>67</td>
<td>&lt; 34 U/L</td>
</tr>
<tr>
<td>Gamma GT</td>
<td>222</td>
<td>70</td>
<td>&lt; 38 U/L</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>29.9</td>
<td>8.8</td>
<td>&lt; 2.30 mmol/L</td>
</tr>
<tr>
<td>HbA1c</td>
<td>52*</td>
<td>34*</td>
<td>&lt; 42 mmol/mol Hb</td>
</tr>
<tr>
<td>Fasting glucose</td>
<td>10.9</td>
<td>4.6</td>
<td>3.4 – 6.0 mmol/L</td>
</tr>
<tr>
<td>C-peptide</td>
<td>2.0</td>
<td>ND</td>
<td>0.3 – 1.3 mmol/L</td>
</tr>
<tr>
<td>Leptin</td>
<td>15.5</td>
<td>ND</td>
<td>3.3 – 11.1 µg/L</td>
</tr>
</tbody>
</table>

*Falsely low due to high red blood cell turn over. Fructosamine was 407 µmol/L (ref: 0 – 285) before treatment

Patient 1: Clinical course
- After initiation of pioglitazone 30mg once daily, blood pressure, glucose metabolism and liver enzymes normalized. No change in fat maldistribution

Patient 2: Clinical course
- After careful initiation of pioglitazone 30mg once daily, insulin requirement decreased dramatically. Also, blood pressure, liver enzymes and triglycerides improved. No change in fat maldistribution

Conclusions
- Acquired partial lipodystrophy can be associated with intensive cytostatic treatment in childhood.
- This phenotype, characterized by loss of subcutaneous fat at the extremities and buttocks in the presence of elevated leptin levels, did not match previously reported types of lipodystrophy.
- Pioglitazone treatment appears to be particularly effective at treating the specific associated metabolic disorders.

References
1) Garg A.: J Clin Endocrinol Metab 2011
2) Strickland LR et al. Diabetes Care 2013

Acknowledgments
We would like to thank the patients for their permission to present their clinical case histories

Contact
m.f.nijhoff@lumc.nl

Patients: Case history

Patient 1: Clinical course

Patient 2: Clinical course