BACKGROUND

- Lipodystrophies are a heterogeneous group of diseases characterized by abnormal fat distribution.
- Familial partial lipodystrophy 2 (FPLD2) is an autosomal dominant condition due to mutations in the LMNA gene.
- It is characterized by selective loss of subcutaneous adipose tissue from the limbs and trunk, and accumulation of fat in the neck and face.
- Usually associated with a variety of metabolic disorders including insulin resistance, diabetes mellitus, dyslipidemia, hepatic steatosis and high blood pressure.

OBJECTIVES

To study the clinical and molecular features of 2 subjects with FPLD.

SUBJECTS AND METHODS

Utilizing Next Generation Sequencing (NGS) we carried out mutational analysis of LMNA gene in a woman and her daughter with FPLD phenotype.

CLINICAL PRESENTATION

MOTHER AND DAUGHTER

- Diabetes detected less than 30 years of age.
- On insulin from the time of diagnosis
- No history of Diabetic ketoacidosis
- Hypertriglyceridemia

Family history:
Maternal uncle and younger sister with similar fat distribution.

Examination: In both mother and daughter

- Cushingoid facies
- Acanthosis nigricans
- Prominent veins - UL>LL
- Calf muscles and deltoid appear prominent
- Vulval fat appears hypertrophic
- Hepatomegaly

Body composition was assessed by DXA scan

<table>
<thead>
<tr>
<th>REGION</th>
<th>FAT (gm)</th>
<th>% FAT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lt Arm</td>
<td>249.6</td>
<td>13.7</td>
</tr>
<tr>
<td>Rt Arm</td>
<td>295</td>
<td>15</td>
</tr>
<tr>
<td>Trunk</td>
<td>3361.2</td>
<td>14.2</td>
</tr>
<tr>
<td>Lt Leg</td>
<td>837.7</td>
<td>12.0</td>
</tr>
<tr>
<td>Rt Leg</td>
<td>1053</td>
<td>14.3</td>
</tr>
<tr>
<td>Head</td>
<td>833</td>
<td>20.3</td>
</tr>
<tr>
<td>Total</td>
<td>6629.7</td>
<td>14.4</td>
</tr>
</tbody>
</table>

Limbs and trunk had very less fat with increased fat in the head.

RESULTS OF GENETIC TESTS

The NGS of LMNA gene showed that mother and daughter were both heterozygous for a reported c.1444C > T missense mutation which causes the substitution of the Arginine at residue 482 by a Tryptophan. This identified mutation was confirmed by Sanger sequencing.

INVESTIGATIONS

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Mother</th>
<th>Daughter</th>
</tr>
</thead>
<tbody>
<tr>
<td>C-peptide (ng/ml) Fasting 2h Post-meal</td>
<td>3.2 3.6</td>
<td>1.43 3.67</td>
</tr>
<tr>
<td>Fasting insulin (Î¼U/ml)</td>
<td>52.5</td>
<td>6.99</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>23.33</td>
<td>3.11</td>
</tr>
<tr>
<td>Triglycerides (mg/dl)</td>
<td>118 (on treatment)</td>
<td>1070</td>
</tr>
</tbody>
</table>

HOMA-IR- Homeostatic model assessment of Insulin resistance

DISCUSSION

- The subject and her mother were diagnosed to have diabetes mellitus at young age, never had keto-acidosis, had cushingoid appearance of face, features of insulin resistance, fat atrophy in the limbs with prominent muscle contours, and hepatomegaly consistent with familial partial lipodystrophy.
- Both subjects also had elevated C-peptide levels and HOMA-IR suggestive of insulin resistance, and Dual energy X-ray absorptiometry showed increased fat in the face with decreased limb fat confirming fat redistribution. Further, genetic testing helped in confirming the diagnosis.
- With this diagnosis, Metformin was added and better glycaemic control was achieved.

CONCLUSIONS

Our subjects had a clinical form of FPLD2 due to a mutation affecting LMNA gene. A high index of clinical suspicion based on the phenotype, followed by appropriate biochemical and genetic testing led to the diagnosis in this family. A clear understanding of the disease process is very important to choose the right treatment modalities, predict the natural history of the disease and to determine the prognosis.

REFERENCES


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