Describing the natural history of clinical, biochemical and radiological outcomes of children with familial partial lipodystrophy type 2 (FPLD2) attending the National Severe Insulin Resistance Service: a retrospective cohort study


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Objectives

To describe clinical, biochemical, and radiological outcomes in children with FPLD2, and explore their relationships with age and gender.

Familial partial lipodystrophy 2 (FPLD2)/Dunnigan variety lipodystrophy

Autosomal dominant mutations in LMNA gene

Phenotype (Fig 1 – c)1,2

- Lack of subcutaneous fat deposition in limbs and trunk
- Excess fat accumulation on neck and face
- Manifests around or shortly before puberty – young children with FPLD2 are challenging to distinguish from unaffected individuals3

Generalised Partial

Acquired

Male

Female

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<tr>
<th>Trait</th>
<th>Male</th>
<th>Female</th>
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<tbody>
<tr>
<td>Weight (kg)</td>
<td>5.6</td>
<td>6.3</td>
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<tr>
<td>Height (cm)</td>
<td>108.3</td>
<td>110.2</td>
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Metabolic complications1

- Insulin resistance
- Hypertriglyceridaemia
- Hypertension
- Hepatic steatosis

Females more severely affected4

Management

- First line: low-fat diet1,2
- Leptin replacement therapy4

Methodology

FPLD2 patients attending the paediatrics division of the National Severe Insulin Resistance Service (SIRS) at Addenbrooke’s Hospital (n=12)

Multivariate model

Dependent variables

HbA1C, fasting triglycerides, fasting insulin, ALT

Fixed factors

Subject ID, gender

Covariate

Decimal age

Results

12 patients aged 16.3 [9.1-21.3] (median [range]) years at most recent consultation

All have LMNA R482W 1444 C>t p(Arg482Trp) mutation

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<thead>
<tr>
<th>Trait</th>
<th>Male</th>
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<tr>
<td>Age of diagnosis</td>
<td>12</td>
<td>14</td>
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<td>Age at diagnosis</td>
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Insulin resistant diabetes – 3 females

One of them is also diagnosed with Emery-Dreifuss muscular dystrophy (from another LMNA mutation), and hypertrophic cardiomyopathy

None of our cohort developed any co-morbidities younger than 10 years

No significant relationships between age and worsening metabolic parameters for either gender

Discussion and conclusion

Possible reasons for lack of relationship

1. Patients may be too young to have developed co-morbidities
2. Patients have grown up on a low-fat diet as one of their parents also has FPLD2, which would have delayed/prevented the metabolic complications
3. The rarity of the disease and small sample size means that the study is underpowered

Although the study suggests that screening for metabolic complications at a young age might not be needed, the severity of the metabolic complications with resultant impact on quality of life and life expectancy in individuals with FPLD2 means that there is a moral argument for genetic screening of the children of FPLD2 patients to permit early intervention and identification of complications. We propose that formal screening of co-morbidities before age 10 is unlikely to be of benefit, but clinical input from a multi-disciplinary team should be offered from diagnosis. We intend to repeat this study in the future to see if more develop co-morbidities and at what age, which would help elucidate more of the natural history and variation in phenotypic severity of patients with FPLD2.

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References


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