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.

Lipodystrophy
Disorders characterised by selective deficiency of adipose tissue – ectopic fat accumulation can cause serious metabolic implications[1]

- **Congenital**
  - **Generalised**
  - **Partial**
- **Acquired**
  - **Generalised**
  - **Partial**

Familial partial lipodystrophy 2 (FPLD2)/Dunnigan variety lipodystrophy

Autosomal dominant mutations in LMNA gene[1]

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 individuals[3]

Metabolic complications[2]

- Insulin resistance
- Hypertriglyceridaemia
- Hypertension
- Hepatic steatosis

Females more severely affected[3]

Management

- First line: low-fat diet[1, 2]
- Leptin replacement therapy[4]

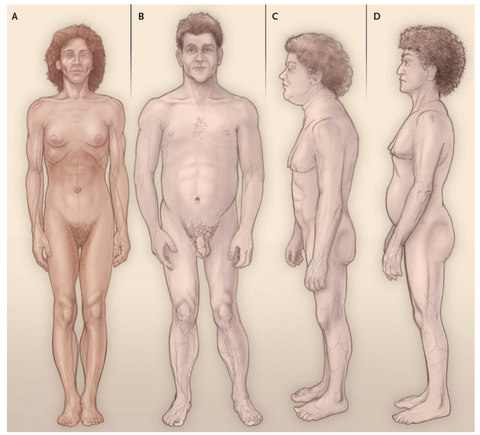

Fig 1: patients with congenital generalised and familial partial lipodystrophies (Garg, A., 2016)
A: congenital generalised lipodystrophy 1
B: congenital generalised lipodystrophy 2
C: familial partial lipodystrophy 2
D: familial partial lipodystrophy 3

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

7 females (12.6 [9.1-21.3] years old)

5 males (16.4 [13.6-18.7] years old)

Insulin resistant diabetes – 3 females

Age of diagnosis: 12, 14, 19-22

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

Mild hepatic steatosis
1 male, 3 females
Aged 10-15 at diagnosis

Mental health issues
1 male, 2 females

None of our cohort developed any co-morbidities younger than 10 years
No significant relationships between age and worsening metabolic parameters for either gender

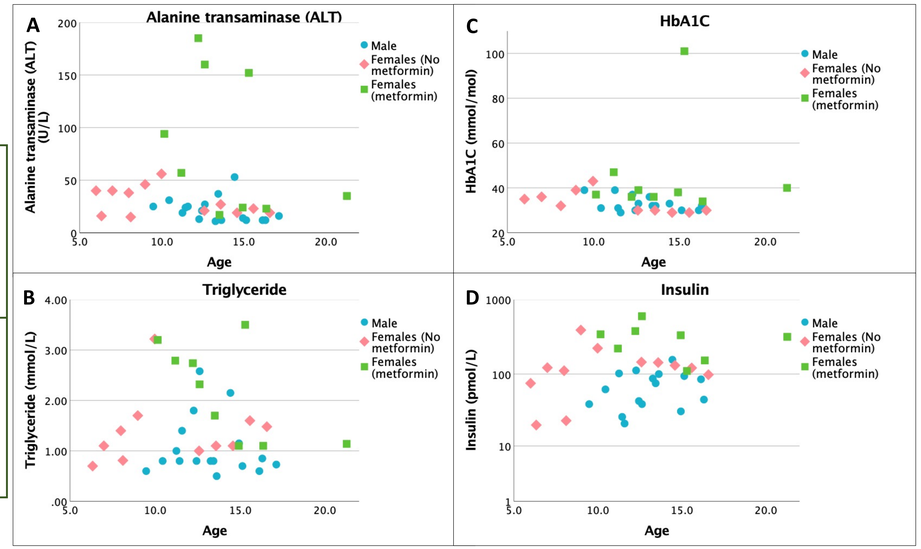

Fig 2: Alanine transaminase (A), triglyceride (B), HbA1C (C), and insulin (D) levels plotted against decimal age for female and male FPLD2 patients and patients on metformin

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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