Reversal of metabolic derangement in patient with congenital generalised lipodystrophy treated with metreleptin

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Introduction

- **Lipodystrophy** (LD) syndromes are a heterogeneous cluster of complex, life-threatening, rare diseases associated with **reduced levels of leptin,** resulting in syndromes that frequently include severe metabolic abnormalities including **diabetes mellitus and dyslipidaemia**.[1]
- LD is categorised according to severity and manner of acquisition, and among the major subtypes is **congenital generalised lipodystrophy** (CGL), which is a rare, severe form of autosomal recessive LD associated with a near total absence of adipose tissue, driven by a mean leptin level as low as 1ng/mL.[1] Laboratory findings are characterised by elevated triglycerides (TGs), severe insulin resistance, and impaired glycaemic control.[2]
- In the absence of effective treatment, CGL can have a **very poor prognosis**, with patients progressing to liver cirrhosis, cardiovascular complications of diabetes, pancreatitis, and/or end-stage renal disease.[1]
- **Metreleptin** is a **leptin-replacement** therapy indicated as an adjunct to diet as a replacement therapy to treat the complications of leptin deficiency in LD patients.[3] We report the use of metreleptin in a paediatric patient with CGL.

Case report

This case was a 16-year-old Emirati female diagnosed with CGL in early childhood based on clinical signs (scant subcutaneous fat, prominent muscles, large jaw, hands and feet, acanthosis and hirsutism). Genetic testing revealed the pathological homozygous mutation, c.158del p.(Gly53Alafs*8) in AGPAT2, which codes for 1-acylglycerol-3-phosphate O-acyltransferase 2 – a key enzyme in the adipogenesis pathway.

Childhood

- Normal growth (height and body mass index in the 50–75th centile).
- Glucose/insulin parameters normal.
- TGs only slightly elevated at 1.65–3.02mmol/L (146.1–267.5mg/dL).
- Liver enzymes normal.

Age 14 years

- Severe acanthosis.
- Diabetes with HbA1c 7.7%, increasing to 9.0% over 9 months.
  - insulin 0.5U/kg/day was started, then dose was increased gradually.
  - insulin resistance within months, and dose reached 3.6U/kg/day.
- Elevated triglycerides 4.09–7.48mmol/L (158.2–289.2mg/dL).
  - persistent, despite fenofibrate 145mg/day.
- Elevated liver enzymes (aspartate aminotransferase [AST] 41–59IU/L and alanine aminotransferase [ALT] 57–81IU/L).
- Fatty liver disease according to ultrasound.

Commenced metreleptin s.c. 5mg/day

- Immediate and significant reduction in glucose levels.
- Rapid decline in HbA1c (**Figure 2**).
- Insulin lispro stopped within 3 days.
- Insulin lantus taped to 5U/day and stopped 3 months later; HbA1c 5.2% 8 months after insulin stopped.
- Fasting plasma glucose normal (3.9–5.6mmol/L).
- Post-prandial glucose normal (<7.5mmol/L)
- Liver enzymes normalized within 3 months, and remained normal 1 year later (AST 12–16IU/L and ALT 5–14IU/L).

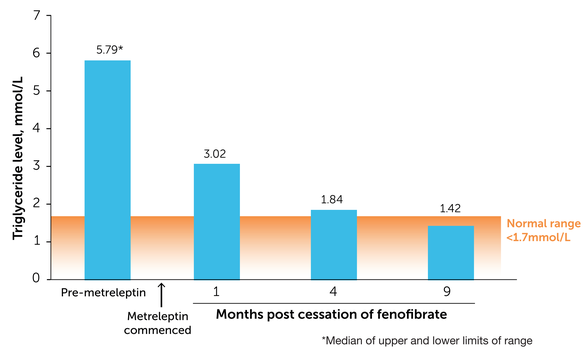
TG and HbA1c evolution after stopping fenofibrate and insulin

- Fenofibrate and insulin stopped 3 months after metreleptin commenced. TG results are shown in **Figure 1**.
- HbA1c levels progressively declined on metreleptin (**Figure 2**).

Conclusions

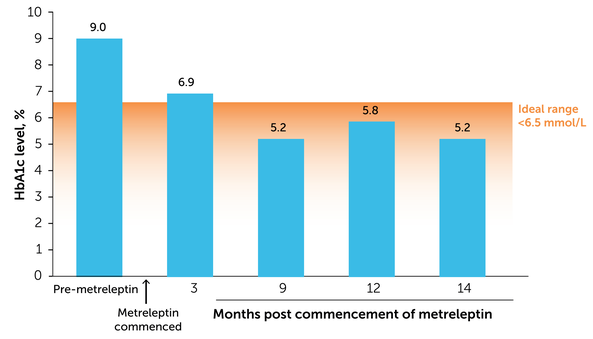
- In this patient with CGL emerging during childhood, metreleptin monotherapy resulted in complete reversal of hyperglycaemia and hypertriglyceridaemia and normalisation of hypertransaminasaemia.
- The normalisation of liver enzymes is promising for possible long-term prevention of liver cirrhosis, which is a serious and potentially fatal complication in patients with CGL.

Figure 1. Evolution of TG levels following commencement of metreleptin and cessation of fenofibrate



*Median of upper and lower limits of range

Figure 2. Evolution of HbA1c levels following commencement of metreleptin



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