

A case of Berardinelli-Seip congenital lipodystrophy and diabetes: presentation, diagnosis and management

A case of congenital lipodystrophy and diabetes is presented, with special focus on the diagnostic and therapeutic challenges faced by the paediatric endocrinology team (physicians, nurses and diabetes educators) during the infant's hospital course.

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Congenital generalised lipodystrophy is a rare autosomal recessive disorder characterised by an absence of subcutaneous fat and muscular hypertrophy. Affected individuals commonly develop insulin resistance and diabetes mellitus between 15–20 years of age. Congenital lipodystrophy is an extremely rare cause of neonatal diabetes. Affected infants are often found to be hyperglycaemic (but rarely ketotic). This case report will review the presentation, diagnosis and the management plan and treatment goals for an infant with congenital lipodystrophy and diabetes.

The case report

A preterm male infant was born at 36 weeks' gestation, weighing 1,586g. The infant's parents were first cousins of Indian origin. His mother, a 31-year-old, denied any history of diabetes. The pregnancy was complicated by intrauterine growth retardation (IUGR) and a low amniotic fluid index. Labour was induced because of severe IUGR.

The infant's Apgar scores were 8 and 9 at one minute and five minutes. He was admitted to the neonatal intensive care unit (NICU) because of a severely wasted appearance. A physical examination at birth, revealed the following:

- A temperature of 37°C
- Heart rate: 110 beats/min
- Respiratory rate: 32 breaths/min
- Blood pressure: 85/47
- The infant was very pale with light skin
- The head was normocephalic without deformities
- Cardiovascular and respiratory examinations were normal
- The abdomen was soft, not distended, with mild hepatomegaly
- A genitourinary examination showed

bilateral descended testicles

- A neurological examination showed excellent tone
- Weight, length and frontal occipital circumference were below the third percentile
- The newborn infant was noted to have severe wasting of adipose tissue with mild acanthosis nigricans in the armpits.

The infant's initial blood glucose level was 10mmol/L, but at 24 hours of life the infant became hyperglycaemic with a blood glucose measurement of 46.6mmol/L. At the age of 25 hours, an insulin drip was started (0.1 units/kg/hr) and the paediatric endocrinology team was consulted.

The medical work-up

Based on the physical examination and documentation of hyperglycaemia, a diagnosis of congenital generalised lipodystrophy with diabetes was presumed.

Laboratory work

The following measurements were noted:

- A very high insulin level (1,380pmol/L)
- A very high triglyceride level (4mmol/L)
- High glycated haemoglobin (HbA1c; 5.7%)
- Cholesterol, thyroid and liver enzyme levels were normal.

Radiological studies

An abdominal ultrasound scan showed no pancreatic abnormalities.

Genetic testing

Testing for mutations associated with congenital generalised lipodystrophy showed a positive mutation in the Berardinelli-Seip congenital lipodystrophy 2 (*BSCL2*) gene, confirming the diagnosis of Berardinelli-

Keywords

lipodystrophy; Berardinelli-Seip congenital lipodystrophy; BSCL; diabetes

Key points

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1. Congenital generalised lipodystrophy is a rare complex syndrome that carries many therapeutic challenges in early infancy.
2. Therapy is even more difficult when diabetes is also present.
3. A number of obstacles were encountered in managing this infant.

Seip syndrome. The parents were offered genetic testing, but they declined.

Management plan and goals

A number of obstacles were encountered in treating this infant with congenital generalised lipodystrophy with diabetes (TABLE 1).

On day seven, the infant started to feed on breast milk with the addition of formula milk (NeoSure 22). He was feeding every three hours and at that time, the insulin therapy was changed from an insulin drip to basal-bolus subcutaneous insulin synchronised with feeds, as follows:

1. Insulin glargine (an insulin analogue with a prolonged duration of action), 0.25 units daily
2. Insulin lispro (a fast-acting, short-lived insulin analogue), 0.25 units every six hours (every other feed) for glucose levels 16–25mmol/L and 0.5 units for glucose levels above 25mmol/L.

1. Difficulty in preparing very low dose insulin

Most manufacturers of commercially available insulin advise against any form of dilution to prevent the possibility of dysfunction.

2. Insulin administration

This was difficult in a very thin newborn infant with lack of subcutaneous fat. Intramuscular insulin injection may cause erratic insulin absorption.

3. Predicting milk intake

Like any normal newborn infant, feeding could be variable. Predicting milk intake was difficult and the infant experienced hypoglycaemic episodes on days that he was not able to finish or tolerate feeds.

4. Consequences of multiple blood 'sticks' and frequent blood draws

Frequent testing for blood glucose levels has potential to cause anaemia. To prevent this, the frequency and amount of blood testing was monitored.

5. Psychological factors

Psychological support was provided for the parents to help them deal with the diagnosis.

6. Consideration of leptin therapy

Leptin therapy on a compassionate-use basis was precluded by the difficulty of establishing follow-up since the parents intended to go back to their country of origin.

TABLE 1 Obstacles encountered while treating the infant with congenital generalised lipodystrophy and diabetes.

To achieve the low concentrations, the hospital pharmacist diluted the insulin: each 1mL of insulin was diluted with 3mL of normal saline before each dose, with an estimated viability of one hour. The infant's blood sugar was tested prior to each feed. The short-acting insulin dose was not given when the blood sugar level was below 5.6mmol/L.

The baby had sporadic low blood glucose episodes that were treated with glucose infusions. There were no seizures related to hypoglycaemia. Continuous glucose monitoring was considered for measuring fluctuations in sugar, but lack of ample subcutaneous fat prevented stability of the sensor's needle. The aim of the therapy was to treat the hyperglycaemia while preventing episodes of hypoglycaemia. Blood glucose was kept in the range of 8.3–11mmol/L. The infant required higher doses of insulin each week.

At six weeks of age, the patient had gained weight (2.5kg) and was requiring a larger daily dose of long-acting insulin (2 units/kg/day; total dose of 5 units/day). The patient was discharged home and the family returned to their country of origin. They were instructed to consult with a paediatric endocrinologist upon arrival.

Discussion

Congenital lipodystrophies are rare genetic disorders that affect adipose tissues.¹ A selective loss of body fat predisposes to insulin resistance, fluctuation of glucose levels and diabetes mellitus in affected individuals.² There are different types of congenital lipodystrophies that can be diagnosed as syndromes. Berardinelli-Seip syndrome (BSS) is a rare autosomal recessive condition often considered as a generalised form of the congenital lipodystrophy.³ BSS can be recognised at birth by absence of adipose tissue that leads to a generalised muscular appearance.⁴ Hyperpigmentation, acanthosis nigricans, prominent subcutaneous veins, hepatomegaly and a prominent abdomen can be seen in affected newborns.^{3,4} Hypertriglyceridaemia, hyperinsulinaemia and diabetes are due to fat deficiency⁵ and may require high doses of insulin therapy.³

There are two gene mutations reported in patients diagnosed with Berardinelli-Seip congenital lipodystrophy. *AGPAT2* mutations are responsible for the type 1 disorder while mutations in *BSCL2* cause Berardinelli-Seip congenital lipodystrophy

type 2, as seen in the case described in this report. Patients with *BSCL2* mutations have been linked to an earlier onset of diabetes.⁶ Diabetes mellitus usually starts in the teens, but has previously been described in infancy.⁷

Leptin – a hormone made by fat cells that regulates the amount of fat stored in the body – is deficient in lipodystrophies, due to the loss of fat tissue. Therapy with leptin can improve plasma triglyceride, glucose and glycated haemoglobin (HbA1c) levels and can even decrease liver size; this therapy is expected to be of great benefit once it becomes commercially available.⁸

Summary

Congenital generalised lipodystrophy is a rare and complex syndrome that carries many therapeutic challenges in early infancy. Management is further complicated when a diagnosis of diabetes is established. Leptin treatment has proven successful in controlling both hypertriglyceridaemia and diabetes mellitus; it is a promising therapy for the future.

Patient consent

The author received verbal consent to publish this report from the patient's parents.

References

1. Prieur X., Le May C., Magre J., Cariou B. Congenital lipodystrophies and dyslipidemias. *Curr Atheroscler Rep* 2014;16:437.
2. Garg A. Lipodystrophies: genetic and acquired body fat disorders. *J Clin Endocrinol Metab* 2011;96:3313–25.
3. Cardona-Hernandez R., Suarez-Ortega L., Torres M. Difficult to manage diabetes mellitus associated with generalized congenital lipodystrophy: report of two cases. *An Pediatr (Barc)* 2011;74:126–30 [Article in Spanish].
4. Khandpur S., Kumar A., Khadgawat R. Congenital generalized lipodystrophy of Berardinelli-Seip type: a rare case. *Indian J Dermatol Venereol Leprol* 2011;77:402.
5. Kobashi Y., Schoenbaum A., Hasegawa R.P., Rosenthal D.I. Berardinelli-Seip lipodystrophy. *Skeletal Radiol* 2007;36:999–1003.
6. Agarwal A.K., Simha V., Oral E.A. et al. Phenotypic and genetic heterogeneity in congenital generalized lipodystrophy. *J Clin Endocrinol Metab* 2003;88:4840–47.
7. Van Maldergem L. Berardinelli-Seip Congenital Lipodystrophy. *GeneReviews* 2003 [Online]. Available from: www.ncbi.nlm.nih.gov/books/NBK1212 [Accessed 14 December 2014].
8. Jazet I.M., Jonker J.T., Wijngaarden M.A. et al. Therapy resistant diabetes mellitus and lipodystrophy: leptin therapy leads to improvement. *Ned Tijdschr Geneesk* 2013; 157: A5482 [Article in Dutch].