Case Report
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AN INFANT WITH LEPRECHAUNISM, AMBIGUOUS GENITALIA AND POOR GLYCEMIC CONTROL: A MANAGEMENT CHALLENGE

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Abstract

Introduction. Leprechaunism is a rare autosomal recessive condition characterized by dysmorhic features, growth failure and disordered glucose homeostasis.

Case report. A term infant was born to a first cousin, who previously lost a baby with Leprechaunism. Pregnancy and delivery were uneventful. Birth weight, length and head circumference were all below the third centile. Clinical examination at birth reveals large low set ears, depressed nasal bridge, gingival hyperplasia, prominent nipples, umbilical hernia, lipodystrophy, hypertrichosis, and wrinkled loose skin. Examination of the genitalia showed a prominent phallus, posterior fusion of the labioscrotal folds and no palpable gonads. A clinical diagnosis of Leprechaunism was made based on the family history and the clinical phenotype. In addition to the presence of ambiguous genitalia, management of this infant was complicated by poor glycemic control with frequent hyper and hypoglycemic episodes.

Insulin was inappropriately high (1626.1 mU/mL, normal 3-17 Mu/mL) when glucose was relatively low (3.2 mmol/L) indicating insulin resistance. ACTH stimulation test confirmed an intact adrenal function with normal 17 hydroxyprogesterone and cortisol. Testosterone and adrenal androgens were normal. Chromosomal study showed 46 XX and MRI abdomen revealed normal pancreas and internal female organs. Accordingly, this infant was assigned as a female.

Severe hyper and hypoglycemic episodes responded to introduction of frequent nasogastric formula milk feeding together with insulin glargine. Glycemic control improved with glycated hemoglobin of 8%.

Conclusion. This case report illustrates a management challenge of a newborn infant with Leprechaunism, ambiguous genitalia and poor glycemic control and discuss treatment options.

Key words: ambiguous genitalia, Donohue syndrome, glycemic control, Leprechaunism.

INTRODUCTION

Leprechaunism, also called Donohue syndrome, is an autosomal recessive disorder characterized by intra and extra-uterine growth retardation (1-5). Mutations in the insulin receptors gene have been linked to the pathogenesis of Donohue syndrome (6-11). This gene is located at 19p13.2.

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In the last decade many mutations of this gene have been identified (3, 4, 7-11). The characteristic features of Leprechaunism include elfin-like face, small head, large low set ears, flat nasal bridge, thick lips, hirsutism, absence of subcutaneous fat, and growth retardation (1-7). This rare disease can also present with endocrine manifestations including hyperplasia of islets of pancreas, cystic ovary, and precocious puberty (5, 7, 12-14). It shares some clinical features with Rabson-Mendenhall syndrome, which is also caused by insulin receptor gene mutations. However, while patients with Donohue syndrome usually die within the first year of life, patients with Rabson-Mendenhall syndrome can reach adult age (2-4). In addition to these two syndromes, insulin receptor gene mutations can be also found in pubertal girls with hyperinsulinism, hyperandrogenism, and acanthosis nigricans (type A Syndrome of Insulin Resistance) (3).

Herein, we report on a newborn baby with Leprechaunism, ambiguous genitalia and poor glycemic control and discuss the management challenges and treatment options.

CASE REPORT

A term infant was born to parents who are first cousins. These parents have 5 living children and a baby died at the age of 2 months with clinical diagnosis of Leprechaunism (Fig. 1). The proband was delivered by spontaneous vaginal delivery at 40 weeks gestation following an uneventful pregnancy with birth weight of 2 kg, length of 43 cm, and head circumference of 32 cm, all well below the third centile. Clinical examination revealed large low set ears, depressed nasal bridge, gingival hyperplasia, prominent nipples, umbilical hernia, lipodystrophy, hypertrichosis and wrinkled loose skin. Examination of the genitalia showed a prominent phallus, posterior fusion of the labioscrotal folds and no palpable gonads (grade 2 Prader score).

A clinical diagnosis of

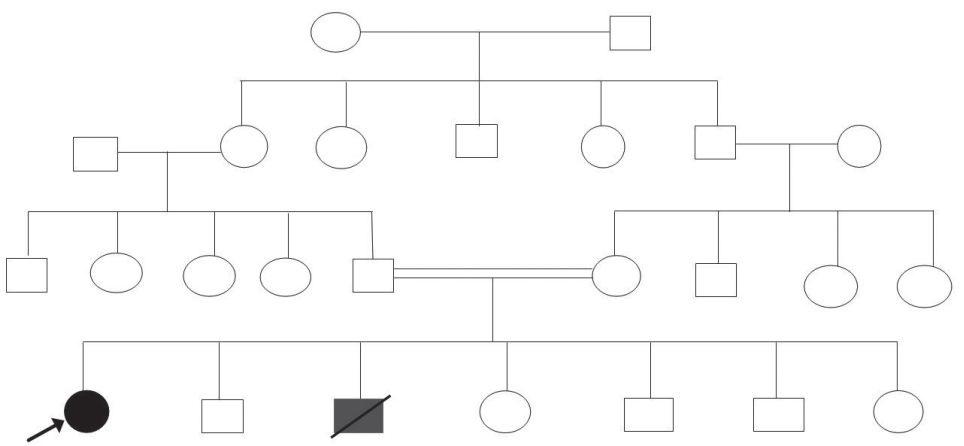

Figure 1. Family pedigree.

Leprechaunism was made based on the family history and the clinical phenotype. In addition to the presence of ambiguous genitalia, management of this infant was complicated by poor glycemic control.

The baby was started on formula milk; 120 ml/kg/day. Glycemic control was poor with frequent hypo and hyperglycemia. Insulin was inappropriately high (1626.1 mU/ml, normal 3-17 Mu/ml) when glucose was relatively low (3.2 mmol/L), both before and after feeding, indicating insulin resistance. Serum growth hormone was high (46 µg /L, 32 µg /L (normal 5-27 µg /L) while insulin-like growth factor 1 was low (30µg/L, normal level 82-166µg/L) and insulin like growth factor binding protein 3 was 0.15 mg/L (normal 0.81-1.9). Karyotyping showed 46 XX. Molecular study of insulin receptors gene failed to identify any mutation. Serum 17 hydroxyprogesterone was initially high (450 ng/dl, normal < 300 ng/ml). Accordingly a standard short ACTH stimulation test (Table 1) was performed that revealed normal adrenal function.

Serum androgens (testosterone, androstandione, dihydroepiandrosterone, dihydroepiandrosterone sulphate) and urinary steroid profile were normal. DNA sequencing of the CYP21A2 gene for congenital adrenal hyperplasia was normal.

MRI of the abdomen revealed a normal size pancreas, normal uterus and bilateral ovarian cysts. Echocardiography showed patent ductus arteriosus and small secondum atrial septal defect with normal left ventricular function. With this radiological, endocrine and chromosomal profile, the family was informed that the ambiguous genitalia are not secondary to hormonal abnormality and accordingly this infant was assigned as a female after detailed discussion with the parents.

As serum glucose remains unstable with frequent severe hyper and hypoglycemia, nasogastric feeding was commenced and milk increased to 150-180 mL/kg/day. Insulin glargine 0.5 unit/kg twice a day was started that achieved reasonable glycemic control with blood glucose maintained between 4 and 8 mmol/L and HbA1c (glycated hemoglobin) of 8%.

DISCUSSION

Leprechaunism is a rare autosomal recessively inherited disorder with an estimated incidence of at least 1 in 4 million live births (1-7, 15). Although mutated insulin receptors gene is implicated in the pathogenesis of Leprechaunism, variable hormonal abnormalities were reported in this condition (16-19). Consanguinity, which

Table 1. ACTH stimulation test

Time in minutes	**Cortisol µg/dL** (normal 4-34 µg/dL)	**17HP** (normal <300 ng/dL)
0	10.6	50
30	53	150
60	59	180

ACTH: Adrenocorticotrophic hormone
17HP: 17 Hydroxyprogesterone

is widely spread in the Middle East, increases the risk of autosomal recessive disorders as shown in this patient, whose parents are first cousins (20).

The diagnosis of Leprechaunism is usually based on clinical features, biochemical findings and mutation result. Our patient shows most of the typical features of Leprechaunism reported by other authors including intrauterine growth retardation, microcephaly, gingival hyperplasia, lipodystrophy, hypertrichosis, and wrinkled loose skin. He also satisfied the biochemical criteria including hyperinsulinemia, hyperglycemia and hypoglycemia. However, the mutation analysis fails to identify a gene defect. This could be due to absence of any gene mutation. In this case, the clinical phenotype of Leprehaunism may be caused by post receptor disorder such a defect in insulin like growth factor 1 signaling as proposed by some publications (21). The other possibility is that patient has the gene mutation, but our method was unable to identify it. The method used for this patient was ordinary polymerase chain reaction (PCR). Contamination of PCR product can lead to a false negative result, however, we were assured by the laboratory personnel that was not the case as the study was repeated for quality assurance. Compared to the method used, real time PCR has a better positive predictive value that could have confirmed the diagnosis at gene level. Other possibility of false negative gene study includes missing part of the gene where the mutation resides such as the promoter region. Lastly, use of next generation sequencing strategy such as whole exome sequencing has a better chance to identify an existing mutation compared to ordinary methods.

Management of this infant was a challenge for both the family and the medical team. Ambiguous genitalia and poor glycemic control complicated the management of this severe genetic disease.

Many patients with Leprechaunism were reported to have an enlarged clitoris, however, apparent ambiguous genitalia with atypical sex is rare in these patients (1, 3). Extensive endocrine work up of our patient revealed an intact androgen and steroid biosynthetic pathway. Although difficult to prove in our patient, it seems that ambiguous genitalia is probably caused by intrauterine elevation of androgens.

In Leprechaunism, glucose homeostasis is impaired predominantly secondary to insulin resistance that results from defects in the insulin receptors (3-5, 7-10). Other insulin antagonistic hormones may play a role in the disordered glucose homeostasis in Leprechaunism (3, 5, 13, 16-19). Our patient shows episodes of severe hypo and hyperglycemia that resulted in a poor glycemic control. She had profound hyperinsulinemia even when the blood glucose was low. This indicates defective insulin secretion as well as function. Hypoglycemia associated with leprechaunism may be explained by an accelerated fasting state secondary to insulin resistance, small glycogen stores and a possible defective gluconeogenesis (13). Contrary to this, Roth *et al.* reported that reactive hyperinsulinemia persisting into the postabsorptive phase appears

to antagonize the usual glycogenolytic response to glucagon during fasting, resulting in hypoglycemia despite the presence of large hepatic glycogen stores (17).

Management of hyperglycemia is sometimes a challenge in patients with Leprechaunism. Many approaches have been adopted including oral hypoglycemic agents and different types of insulin with variable results (3-5, 12, 22). Contrary to our patient, Atabek and Pirgon observed some effect of treatment with metformin, but not with insulin glargine in an infant with Leprechaunism and persistent hyperglycemia (23). Geffner *et al.* studied the *in vitro* sensitivity to insulin and other growth factors in peripheral blood of a patient with Leprechaunism and indicated an intact *in vitro* action with high insulin dose despite genetic insulin resistance. This may partially explain our patient response to exogenous insulin, although the insulin dose was not high (14).

Growth hormone (GH) is an insulin antagonistic hormone that tends to raise blood glucose through many mechanisms (16, 18). GH acts through IGF1 and IGFBP3. Our patient had high growth hormone level and low IGF1 and IGFBP3, which may indicate growth hormone resistance. However, we were unable to conduct formal growth hormone stimulation test that may give concrete evidence on growth hormone status. Similarly, Psiachou *et al.* reported a female infant with Leprechaunism who had high fasting GH values and low IGF-I levels implying growth hormone resistance (19). It is postulated that GH resistance was a secondary effect caused by down regulation of GH receptor activity in the presence of high concentrations of insulin proximal to the cell membrane, with consequent limitation of IGF-I formation and cellular growth (19). This was replicated by other researchers who reported on GH resistance in patients with Leprechaunism responded to IGF1 treatment by maintaining normal growth rate (12, 24).

In conclusion, this case report illustrates a management challenge and highlights treatment options of a newborn infant with Leprechaunism, ambiguous genitalia and poor glycemic control.

Conflict of interest

The author declares that he has no conflict of interest.

Consent

Written informed consent was obtained from the patient for publication of this Case report. A copy of the written consent is available for review by the Editor of this journal.

Abbreviations

ACTH: Adrenocorticotrophic hormone; GH: Growth hormone; IGF1: Insulin like growth factor 1; IGFBP3: Insulin like growth factor 1 binding protein 3. PCR: Polymerase chain reaction.

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