

## A Rare Case of Donohue Syndrome in a Neonate: A Case Report

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### ABSTRACT

**BACKGROUND AND OBJECTIVE:** Donohue syndrome (DS) is an extremely rare and usually fatal inherited disease resulted from mutations in the INSR (Insulin Receptor) gene and delineated by severe insulin resistance with fasting hypoglycemia, postprandial hyperglycemia, and facial dysmorphism. Optimal treatment of these cases is unclear and most DS cases die during the first two years of life. Herein, we introduce a case of leprechaunism due to the rarity of this syndrome (one case in every four million birth) revealed by clinical and laboratory findings.

**CASE REPORT:** We present a 4-day old boy with an abnormal facial appearance, low birth weight who was admitted to the Neonatal Intensive Care Unit (NICU) due to poor feeding and jaundice. The patient had coarse facies, hypertrichosis, abdominal distention, genitomegaly, and acanthosis nigricans. Laboratory examinations revealed fasting hypoglycemia, postprandial hyperglycemia, and hyperinsulinemia. The diagnosis of Donohue Syndrome was characterized by the combination of dysmorphic features and biochemical results. Supportive care such as normalizing blood glucose and continuous feeding was initiated. He was discharged with good condition several days later but was admitted again at 6 months of age due to sepsis and then died.

**CONCLUSION:** According to the present case report, close monitoring of blood glucose as well as caring to prevent infection and sepsis is recommended.

**KEY WORDS:** *Leprechaunism, Donohue Syndrome, Insulin Resistance, Craniofacial Abnormalities.*

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## Introduction

**L**eprechaunism or Donohue's Syndrome (DS) is an extremely rare disease with a prevalence of one in four million live births. Donohue Syndrome was first reported by Donohue & Uchida in one case of siblings born to first-degree relatives in 1948 and 1954. Neonates were presented with typical facial manifestations resembling the creatures of Irish myths (1). Donohue's Syndrome is an autosomal recessive genetic disorder caused by a gene mutation in insulin receptors resulting in severe insulin resistance and it usually affects children born to first cousins. The number of reported cases is less than one hundred in the world (1).

Rabson-Mendenhall syndrome, type A and B insulin resistance, lipodystrophies, and HAIR-AN syndrome constitute other types of insulin resistance syndrome. Significant hypertrichosis, coarse facies, intrauterine growth restriction, fasting hypoglycemia, postprandial hyperglycemia due to insulin resistance are specific features of this syndrome. The majority of these cases die in the first year of life (2, 3). Timely diagnosis of Leprechaunism is necessary. Knowledge of common clinical features, even with minimal laboratory findings, can help the physician identify the condition and begin initial supportive measures. Herein, given the rarity of this syndrome and limited studies, we introduce a case of leprechaunism which was identified by distinct and dysmorphic craniofacial characteristics, and metabolic symptoms in a male neonate.

## Case Report

The study protocol was verified by the Ethics Committee of National Research Institute of Tuberculosis and Lung Diseases (NRITLD), Shahid Beheshti University of Medical Sciences (IR.SBMU.NRITLD.REC.1400.006).

Informed consent was provided for the purpose of publication of images and other clinical information in this case report. Also, in this paper, no identifiable personal details are included. A 4-day old male neonate was referred to the Neonatal Intensive Care Unit (NICU) of the Shahid Sayyad Shirazi hospital in

Gorgan, Iran due to poor feeding and jaundice. The patient had a history of low birth weight (2060 gr, <5% percentile). Head circumference was 32.5cm (<5% percentile) and height was 43cm (<5% percentile). Apgar score at 1 minute after birth was 8 and at 5 minutes after birth was 9.

Due to the breech presentation of the fetus, delivery was performed by cesarean section at gestational age (GA) of 38 weeks to a 27-year-old healthy mother. Abdominal ultrasonography at GA of 36 weeks revealed intrauterine growth retardation (IUGR). History indicated non-consanguinity of the parents. The patient had an 8-year-old healthy brother. The mother had no obvious drug history during pregnancy. The patient had various typical dysmorphic craniofacial features (Figure 1A,C) and abdominal distention (Figure 1B) in presentation.

Biochemical analysis showed fasting hypoglycemia (53 mg/dl), postprandial hyperglycemia (206 mg/dl), severe hyperinsulinemia (>500 mic unit/ml), direct hyperbilirubinemia (total bilirubin= 8.4 mg/dl, direct bilirubin= 5.5 mg/dl) and mild elevated liver aminotransaminase (AST=88, ALT=110). Urine Mucopolysaccharides were negative.

An abdominal ultrasound scan revealed normal findings (without enlargement of liver, spleen, renal) except diffuse dilatation of intestinal loops. Echocardiography demonstrated mild myocardial hypertrophy. The diagnosis of Donohue Syndrome was characterized by the combination of dysmorphic features and biochemical results.

To prevent excessive insulin production, continuous nasogastric feeding was initiated which would be stimulated by oral intake, and antibiotics were initiated. Blood glucose was measured and postprandial hyperglycemia was treated via insulin administration. The patient received FFP and vitamin K because of coagulopathy. After two weeks, improvement of the patient's condition was achieved and he was discharged from the hospital. Follow up visit in the pediatric clinic was recommended. Five months later, the patient was brought to our hospital in a critical condition; diagnosed with sepsis, antibiotic treatment was administered, but death occurred after 4 days at 6 months of age.



**Figure 1. Clinical manifestations of Leprechaunism in the present case.** A: Coarse and triangular facies, hypertrichosis, skin creases. B: Abdominal distention, macrophallus, and large feet, large low set ears. C: Gingival and lip hyperplasia, infraorbital creases, nipple hypertrophy, prominent eyes.

## Discussion

In the present study, we described a rare case of leprechaunism owing to the rarity of this syndrome in a 4-day-old neonate revealed by dysmorphic characteristics of face and laboratory findings consistent with Donohue Syndrome as well as mild myocardial hypertrophy. Donohue syndrome (DS) is a scarce condition with insulin resistance disorder and autosomal recessive inheritance (4). Mutations related to this condition are detected in the coding sequence of the INSR gene (insulin receptor) in the short arm of chromosome 19 (19p13.2), which produces inactive receptor molecules (5). More than 150 mutations have been identified in the insulin receptor gene (6).

This condition mainly occurs due to the lack of complete functional insulin receptor and the receptor produced by the mutant allele that is only about 15% as effective as the normal receptor. The beta cells in the pancreas, which produce and store insulin and release it as needed, are often very large or numerous. Insulin through the insulin receptor has both metabolic and mitogenic effects on its target cells (5, 6). Intracellular glucose uptake is impaired in patients with Donohue syndrome, and atrophy develops due to the disruption of insulin-dependent adipose-muscle tissue without replacement (6).

The typical presentations of Donohue Syndrome (DS) include various unique physical features such as abnormalities in the craniofacial region with elfin

appearance (high arched narrow palate, hypertelorism, proptosis, infra-orbital folds, thick lower lip vermillion, gingival hypertrophy, thickening of nasal alae, large low set ears), skin abnormalities (large hands, long foot), abdominal distention (enlargement of kidneys, liver, and spleen), genitomegaly; and metabolic findings such hyperinsulinemia and extremely high plasma C-peptide levels with fluctuating blood glucose levels (fasting hypoglycemia, postprandial hyperglycemia), hypertrichosis, acanthosis nigricans, virilization, failure to thrive (FTT), lipodystrophy, and eventually ketoacidosis (7, 8).

Studies have shown that hypertrophic cardiomyopathy occurs in infants with congenital hyperinsulinism, including infants of diabetic mothers, and in other conditions with insulin resistance. (9). It is worth noting that most of the symptoms related to DS might be different from patient to patient in the intensity of the manifestations (10, 11). The recognition of DS is based on the combination of distinguishing features, clinical investigation, laboratory analysis, especially marked hyperinsulinemia (7).

The treatment of DS should be guided based on the distinctive symptoms that are present in each patient, and necessitate the joint efforts of multidisciplinary experts, including pediatricians, endocrinologists, dermatologists, and other health professionals (7). Optimal and standard management is not determined but the goal of treatment is to control and maintain

blood glucose in normal ranges. Administration of metformin in combination with pioglitazone or rosiglitazone is the first line of treatment via suppression of hepatic glucose output (1). Persistent feeding might be effective (12). The timely and ongoing administration of recombinant human IGF-1 alone or along with IGFBP 3 has demonstrated beneficial metabolic effects by stimulating peripheral glucose consumption and suppression of gluconeogenesis in the liver to reduce hyperinsulinemia and related characteristics (13). The optimal timing, dose, and duration of the IGF-1 in the treatment of DS patients have not been correctly determined. The recommended doses are from 80 to 1,120 µg/kg/day (13).

In 2008, Fukunaga et al. reported a case of leprechaunism who lived more than 2 years due to long-term treatment with rh IGF-1 therapy (14). Relative risks and benefits have not been specified as well (15). The use of continuous subcutaneous insulin pump therapy seems to be promising (5). Alternative treatment is administration of recombinant methionyl human leptin (r-met-hu-leptin). In a study by Cochran et al., 40–60% decrease in fasting blood glucose and a significant improvement in glycosylated Hb levels have been reported with administration of r met hu leptin in combination with metformin (200 mg) and pioglitazone in two siblings affected by RMS after ten months treatment. Novel treatment with mecasermin in combination with IGF 1 resulted in good outcomes based on a recent case report by Plamper et al. Lymphoid hypertrophy is the only adverse side effect that has been reported (13).

Most affected infants with Donohue syndrome die during the first year of life (2, 4, 7, 12). The main causes

of mortality include recurrent respiratory infections, cardiomyopathy, and complications of hypoglycemia. It is noteworthy that families at risk for having children with Donohue syndrome can have healthy offspring by preimplantation genetic analysis (10). Genetic counseling and genetic analysis can prevent patients, physicians, and families from repeating their experience of this difficult event (9).

In the present study, we introduced a rare case of a 4-day-old neonate with DS identified by specific physical characteristics. The dysmorphic features that were seen in our patient were similar to other patients reviewed in the literature. Our case had also biochemical criteria of DS such as postprandial hyperglycemia, fasting hypoglycemia and hyperinsulinemia. Cholestatic jaundice (direct hyperbilirubinemia) with elevated liver enzymes were also observed. Similar to other studies, our DS case became unwell progressively due to sepsis, resulting in death.

According to the present case report, close monitoring of blood glucose as well as close attention to prevent infection and sepsis is recommended. Management of these cases requires multidisciplinary consultations such as neonatologists, pediatric gastroenterologists, endocrinologists, and cardiologists.

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