**Introduction**

Donohue syndrome (DS), also known as Leprechaunism, describes a rare form of congenital insulin resistance associated with refractory hyperglycemia, hyperinsulinism and severe, characteristic musculoskeletal deformities and facial dysmorphia. Prognosis of DS is poor and most individuals die early in infancy.

**Case Report:** We report a long-surviving male patient with Donohue syndrome suffering from diabetic foot lesions at the age of 13. Long survival was most likely in part related to anaplerotic therapy containing aspartate and citrate – two citric acid cycle intermediate metabolites missing in DS. When first seen in our outpatient clinic, the boy had several ulcers on the heel, the forefront and lower leg. Conventional treatment with off-loading, wound debridement and antibiotic therapy was initiated. After 12 weeks, ulcers had resolved almost completely – despite insufficient glycemic control.

**Discussion:** The nutritional concept of anaplerotic therapy has never been reported in DS before and may be crucial in order to aim at prolonged survival as long as better treatment options are not available. Long term diabetic complications such as diabetic foot syndrome have not been observed in DS yet, but must be expected when patients survive infancy.

**Keywords:** Diabetic foot; Nutrition and diet; Neuropathy; Insulin sensitivity

**Abstract**

Background: Donohue syndrome (DS), also known as Leprechaunism, describes a rare form of congenital insulin resistance associated with refractory hyperglycemia, hyperinsulinism and severe, characteristic musculoskeletal deformities and facial dysmorphia. Prognosis of DS is poor and most individuals die early in infancy.

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**Introduction**

Donohue syndrome (DS), first described by the Canadian pathologist William L. Donohue in 1948 [1], is the most severe form of an insulin-receptor defect with minimal or no residual function [2]. DS is very rare with less than 1/1.000.000 births and due to homozygous or compound-heterozygous mutations of the insulin-receptor gene located on the short arm of chromosome 19 (INSR 19p13.2). Several mutations of the gene have been discovered so far, including a nonsense mutation causing a frame shift [3], a single missense mutation or a single codon change that altered isoleucine to methionine in the receptor protein [4]. The mutation either causes malfunction of the receptor’s auto-phosphorylation leading to a complete shutdown of the downstream signal cascade or a conformational change in the alpha/beta-subunit leading to the inability of insulin binding to its receptor [5].

Donohue syndrome, formerly referred to as leprechaunism, is initially characterized by severe intrauterine growth restriction. The term Leprechaunism has largely been abandoned since it is perceived by parents as stigmatizing. It was derived from “Elfin” features that patients with DS typically display: additional to post-natal growth retardation are protuberant and low-set ears, flaring nostrils, and thick lips. Physical features comprise an enlarged clitoris in affected females, and an enlarged penis in affected males. Additionally, lipatrophy and muscular hypotrophy are found as well as typical symptoms of insulin resistance, such as hirsutism and acanthosis nigricans. Excessive hyperglycemia followed by phases of hypoglycemia together with severe hyperinsulinemia is present in all patients with DS. Hyperglycemia does not respond to conventional anti-hyperglycemic treatment, whereas insulin therapy or insulin sensitizers such as rosiglitazone are nevertheless applied in those patients. Additionally, therapy with recombinant human insulin-like growth factor I (IGF-I) is frequently established and provides – due to its homology with insulin and its receptors - some glycemic control and acceleration of growth. However, prognosis of DS remains...
poor and most individuals die early in infancy.

Here we describe the first case of a 13-year old male patient with DS who suffered from diabetic foot lesions, which were subjected to conventional wound- and systemic treatment. Diabetic foot syndrome as the most severe complication of diabetes mellitus and has never been described in patients with DS before.

Case Presentation

The boy was delivered in April 2000 after 38 weeks of gestation by caesarian section as the second twin of consanguineous Turkish parents. Both the boy and his brother showed the clinical phenotype of leprechaunism and DS was diagnosed according to clinical and biochemical features. A molecular characterization of the underlying mutation was not consented by the parents. Prenatal development of the boy was characterized by severe intrauterine growth retardation, which lead to a prolonged postnatal hospitalization of 8 weeks. From early on he suffered from severe hyperglycemias refractory to insulin treatment followed by phases of hypoglycemia. Blood glucose levels were mostly between 2.8 and 27.8 mmol/l. Continuous nutrition every 2 hours was necessary in order to avoid severe hypoglycemia. At the age of 3 years, treatment with the PPAR gamma agonist rosiglitazone was initiated at a dose of 4mg/d. However, glycemic control was not achieved and the boy subsequently suffered from recurrent urinary and respiratory infections, compelling a continuous antibiotic treatment with trimethoprim and later erythromycin.

Another important feature in his first years was massive dental caries, apart from other problems such as persistent severe growth retardation and clinical signs of insulin resistance (hirsutism, acanthosis nigricans). Meanwhile, the patients’ brother had died at the age of 18 months due to cerebral hemorrhage after volatile anesthesia. At the age of 4, the boy suffered from sepsis caused by Pseudomonas aeruginosa after surgical treatment of an inguinal hernia. During sepsis a severe ketoacidosis occurred. The absence of citric acid cycle intermediate metabolites aspartate and succinate was held responsible and subsequently, an anaplerotic therapy containing aspartate and citrate together with a ketogenic diet was initiated. Additionally, the boy received intravenous lipid nutrition and – later on – 3-OH-butyrat orally. Upon these measures the patient’s clinical condition significantly improved despite persisting hyperglycemia. subsequently, all antidiabetic treatment was stopped. At the age of 13, the boy developed clinical signs of a diabetic foot syndrome and was referred to our Diabetes outpatient clinic. On admission, the growth-restricted boy (height 97 cm, weight 13 kg) showed the typical clinical appearance of DS. His physical condition was stable, blood pressure was within normal range and he was afebrile. Peripheral pulses were palpable, whereas neuropathy assessment was not possible due to the boy’s mental retardation. He presented with three ulcers: one lesion of about 3x1.5cm on the forefoot, stage IB according to Wagner-Armstrong, one ulcer on the lower leg of about 4x4.5cm, also stage IB and a deeper lesion of 3x3cm, Wagner-Armstrong
stage IIB, on his right heel (Figure 1 a-c). Bacterial smears were taken and showed a mixed flora of Klebsiella species, Enterococcus faecalis and Staphylococcus aureus. We initiated antibiotic treatment with amoxicillin/clavulanic acid and started standard wound care consisting of cleansing and debriding the ulcers. The boy received a heel-wedge off-loading shoe-cast and parents were advised to apply it during daytime. Additionally, a dermatologist excluded lvedo vasculopathy on the lower leg by skin biopsy and histology.

After 4 weeks of treatment, the wound situation had substantially improved (Figure 2 a-c) – despite the persistent hyperglycemia. After a treatment period of 12 weeks, ulcers of the lower leg and the heel were fully epithelialized and the ulcer of the forefoot was in complete clinical remission (Figure 3 a-c). After that we lost the patient to follow-up. He was only seen by his local pediatrician. One year later, the boy succumbed to pneumonia.

Discussion

Here we report the first case of a patient with Donohue syndrome suffering from diabetic foot syndrome at the age of 13. Most interestingly he showed a good response to conventional treatment by immobilization, off-loading and anti-infective treatment despite poor glycemic control due to the untreatable diabetes.

The boy’s unexpected long survival until the age of 13 is in contrast to most DS patients who die within the first years of infancy. We understand this as likely success of an experimental nutritional concept, that was established when the patient was 4 years old. Prior to initiation of the nutritional concept, treatment with recombinant human insulin-like growth factor 1 (IGF-1) as used in other DS patients [6-8], had been considered but was not applied in the boy. The nutritional concept was mainly based on the consideration of a lacking cellular glucose uptake caused by the underlying insulin receptor defect leading to glucagon-dependent lipolysis and free fatty acid metabolism – a situation comparable to ketoadicosis in type 1 diabetes. Since glucose is not available for the citric acid cycle, its replenishment with necessary intermediates, the so called anaplerosis as a strategy for future therapies. Neuropharmacology. 2013; 331-337.

We therefore conclude that an experimental nutritional concept is crucial in patients with DS in order to aim at prolonged survival as long as better treatment options are not available. Both anaplerotic therapy and ketogenic diet have proven to be safe in children with epileptic seizures [9,10] and can therefore be tried as therapeutic options in DS.

Clinical decisions are challenging in DS not only because of the untreatable molecular defect but also for ethical reasons when parents are faced with the medical consequences of consanguinity. This report shall widen the narrow window of therapeutic opportunities in DS.

References