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Case Report

A Long Term Follow Up in a rh-IGF1 Treated Donohue Syndrome Girl

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Abstract

Donohue Syndrome (DS) is a rare genetic entity which requires early diagnosis and genetic counselling. The long-term aim of therapy would be to improve glycaemic control, to promote linear growth and to prolong longevity. To date, recombinant human insulin-like growth factor 1 (rh-IGF1) is the only treatment shown to be able to avoid, at least in some patients, the rapid and fatal outcome of leprechaunism. In our knowledge, this is one of the longest treatment with rh-IGF1 in a patient with DS, and we can suppose that this treatment has contributed to the patient's survival, improving growth and clinical parameters. Despite the persistence of diabetes and the poor effect on HbA1c levels, our patient is still alive and has a reasonably good health status at the age of 5 years. In addition, after 2 years and 4 months of rh-IGF1 treatment, she shows no adverse effects. According to this experience, we suggest that rh-IGF1 should be considered as initial treatment option instead of final option in patients with severe insulin resistance syndromes. Longer term studies are needed to better analyse the risk-benefit ratio of such treatment, the ideal doses, the administration route and the age at which it should be started.

Keywords: Donohue Syndrome; Insulin-resistance; Rh-IGF1; Neonatal hyperglycaemia

Abbreviations

DS: Donohue Syndrome; Rh-IGF1: Recombinant Human Insulin-Like Growth Factor 1; INSR: Insulin Receptor

Introduction

Donohue Syndrome (DS; leprechaunism; OMIM 246200) is a very rare autosomal recessive disease affecting less than one in a million live births, resulting from either homozygous or compound heterozygous mutations in two alleles of the insulin receptor gene (INSR; 19 p13.3-p13.2). It is the most severe form of inherited insulin-resistance disorders and most patients die as a result of respiratory tract infection before 2 years of age [1]. DS is characterized by dysmorphic features, pre- and post-natal growth failure and abnormal glucose metabolism with severe hyperinsulinemia, fasting hypoglycaemia and postprandial hyperglycaemia [2,3]. There is not a clearly effective treatment for DS. Management is not standardized but aims to normalize blood glucose. Treatment options include frequent feeding, insulin and antidiabetic drugs. It was described that the exogenous supplementation of recombinant human insulin-like growth factor 1 (rh-IGF1) can rescue the defective INSR insulin pathway via IGF1 receptor activation, resulting in prolonged patient survival [4-6]. Nevertheless, the efficacy of rh-IGF1 treatment to improve metabolic and clinical parameters in the long-term is still controversial. Optimal timing, dosing and duration of therapy, as well as the relative risks and benefits, have not been properly established [7]. We report the case of a surviving 5-years-old Pakistan girl with genetically proven DS, treated with rh-IGF1 therapy from the age of two.

Case Presentation

The patient was born at 35^{+3} weeks of gestation through caesarean section because of severe intrauterine growth retardation. She was the second child of healthy non-consanguineous parents of Pakistan origin. Her birth weight was 1322 g (-2.76 SDS), her birth length was 39 cm (-2.86 SDS) and her head circumference was 31,2 cm (0.72 SDS). At birth she developed early neonatal jaundice. On physical examination, she was found to have several dysmorphic features, lipoatrophy, muscle wasting, generalized hypertrichosis, hyperpigmentation of the skin, acanthosis nigricans, severe swollen abdomen, relatively large hands, feet and clitoris hypertrophy. She also showed elfin-like face with prominent eyes, thick lips, wide nostrils, large low set ears, and depressed nasal bridge. In addition, she had a systolic murmur. Laboratory investigations showed severe hyperglycaemia (ranging between 170 to 316 mg/dl), fasting hypoglycemia (ranging between 30 to 40 mg/dl), severe hyperinsulinemia (>3000 microU/ml; normal range 1.9-23 microU/ml), high C-peptide levels (30 ng/ml; normal range 0.8-4.0 ng/ml) and glycosuria. No acidosis or ketonuria were found. Echocardiogram showed patent ductus arteriosus and small secondum atrial septal defect with normal left ventricular function. Abdominal ultrasound found ovarian and renal enlargement. Partial parental nutrition was required for the severe failure to thrive and intravenous insulin therapy was started to normalize blood glucose. Nevertheless, the glycaemic control get worse and the patient developed a significant increase of insulin requirement within few weeks. Insulin therapy was discontinued at three months of life due to the poor efficacy on glycaemic control. Since her condition were stable, she was discharged from the hospital with frequent oral feeding. Genetic

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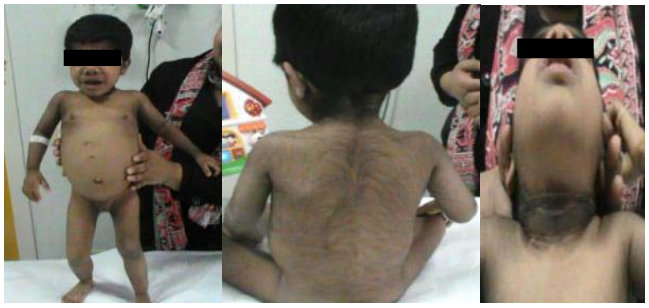

Figure 1: Physical characteristics before therapy.

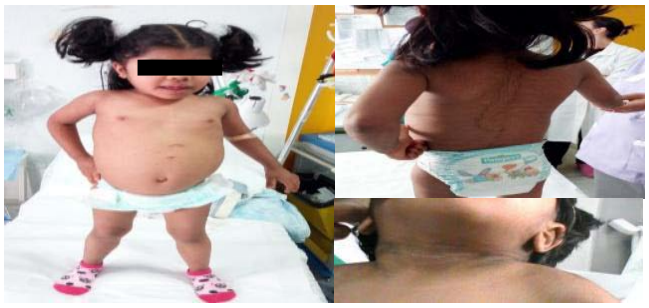

Figure 2: Physical characteristics after 28 months of rh-IGF1 therapy.

analysis has been performed by the Molecular Genetics Laboratory of the Addenbrooke's Hospital, Cambridge, and confirmed the clinical suspect of DS. A homozygous mutation in exon 4 of the insulin receptor gene (c.1049C>T), resulting in an abnormal INSR protein [p. (Ser 350 Leu)], was detected by fluorescent sequencing analysis and Multiplex Ligation-dependent Probe Amplification (MLPA). Genetic analysis of the parents was not performed. During the first year of life the patient showed poor growth, persistently high glycaemic variability with fasting hypoglycaemia (between 40 to 50 mg/dl) and postprandial hyperglycaemia (between 200 to 400 mg/dl), and severe hyperinsulinism. By 7 months of age, HbA1c increased to 70 mmol/l (corresponding to 8.5%). By 18 months of age, HbA1c was 76 mmol/l (corresponding to 9%), urine examination showed mild microalbuminuria (3.38 mg/dl, normal value <2 mg/dl) and abdominal ultrasound revealed nephrolithiasis and slight liver enlargement. Her growth was poor and her weight and height were respectively -4.3 and -5.2 standard deviation for age and gender. Mental development and learning were acceptable, but motor development was delayed due to marked muscle hypotonia. At 2 years 8 months of age HbA1c was 114 mmol/l (corresponding to 12.5%). At that time our Hospital Ethical Committee approved rh-IGF1 as off-label therapy for DS and the patient underwent to twice-daily subcutaneous injections of rh-IGF1 with a daily dose of 0.16 mg/kg. The physical characteristics before therapy are shown in (Figure 1). Since then, serum IGF1 levels have been monitored to evaluate efficacy and toxicity. After 2 years 4 months of rh-IGF1 treatment, at the age of 6, the patient shows improved general condition, muscular tropisms and growth parameters. Hypertrichosis, acanthosis nigricans and clitoromegaly became less evident although hyperglycaemia and hyperinsulinemia persisted (Figure 2). Despite persistently high values of HbA1c she has no sign of retinopathy or neuropathy, while microalbuminuria remained stable over time. Moreover, she never experienced

Table 1: Laboratory findings after 28 months of rh-IGF1 therapy.

Labs data		Normal range
HbA1c (mmol/l / %)	132 / 14.3	<38 / <6.6
Insulin (mIU/ml)	338	1.9-23
C-peptide (ng/ml)	6.7	0.8-4.2
Fasting glucose (mg/dl)	192	60-110
HOMA-IR	160	0.23-2.5
IGF-1 (ng/ml)	93	33-172

significant ketosis or other complications often described in patients with DS. No adverse effects of the rh-IGF1 treatment have been noted, especially hypoglycaemia, with some concerns about tooth enlargement and adenoid hypertrophy. Serial abdominal ultrasounds and echocardiography didn't show any significant change from the initial evaluation. Main clinical and laboratory findings after 28 months of rh-IGF1 therapy are shown in (Table 1).

Discussion and Conclusion

Severe insulin resistance, resulting from genetic defects of the insulin receptor or post-insulin receptor signalling, represents a clinical spectrum ranging from Donohue and Rabson–Mendenhall syndromes, caused by bi-allelic INSR mutations, through to the milder phenotype of type A insulin resistance [8]. The Leprechaunism was first described in 1948 by Donohue and Uchida [3]. From 1988 to date, over 130 allelic variants of the INSR gene have been identified, with the majority of them being missense and nonsense mutations [7,9]. In the most severe, autosomal recessive conditions, hyperinsulinemia and abnormal glycaemic metabolism are associated with growth retardation and significant reduction in life expectancy due to complications such as infections, heart failure, cerebral infarcts and ovarian tumours. Other reported associations are hypertrophic cardiomyopathy, cholestasis, renal tubular dysfunction, cystic ovary, precocious puberty and pancreatic islets hyperplasia [7,10]. It is still unclear why affected infants are resistant to ketoacidosis, at least in the first year of life, even with no functional insulin receptor. Indeed, the major clinical problem is hypoglycaemia, followed by post-prandial hyperglycaemia. Suggestions include the action of extremely elevated insulin levels on persisting hepatic IGF-I receptors in the immature liver and the deficiency of GH secretion or action [11]. In our patient, genetic analysis revealed a mutation (c.1049C>T in exon 4 of the INSR gene) that was previously reported by Krook in a patient with Rabson–Mendenhall syndrome and in heterozygote relatives of a patients with leprechaunism [12]. We couldn't perform the genetic analysis of the INSR gene in our patient's parents. Even if definitive genotype-phenotype correlation for INSR defects is difficult to establish because of the rarity of these syndromes and the lack of functional studies, some correlation between genotype and phenotype has been described. Some authors found that mutations that markedly affect insulin binding often result in the most severe phenotypes [13]. The first step towards the development of a mutation database for the INSR gene has been done by Ardon et al [14], collecting all the reported mutations. One patient with a homozygous deletion of the entire INSR gene survived 3.5 years before dying from post-operative complications [15], contrasting with another infant with almost no insulin receptor activity, who failed to thrive and died at 16 weeks of age [16]. Maassen et al [17], found that the degree of insulin binding

among five patients with defects in the INSR did not correspond to the severity of the clinical phenotype, suggesting that the activity of transcriptional factors may also have an important effect. In severe insulin resistance, diabetes can be considered a major therapeutic challenge because conventional therapies, including insulin and insulin sensitizers, fail to improve metabolic control. Rh-IGF1 provides an alternative therapy as IGF1 receptor shares structural and functional homology with the insulin receptor. Therefore, rh-IGF1 can mimic some insulin effects bypassing defective insulin receptors. Both insulin and IGF1 can stimulate the glucose uptake, the glycogen synthesis and the inhibition of protein catabolism [8,18-21]. Furthermore, IGF1 probably inhibits insulin secretion from the β-cells through an IGF1 receptor-mediated pathway [4]. Even if rh-IGF1 treatment has been found to improve clinical and metabolic outcomes in some patients with loss of INSR function [4,19], its efficacy remain controversial. Reports of rh-IGF1 therapy have mostly been of short duration, even if there have been reports of sustained clinical improvement [22,24]. The most impressive responses have been described with very high doses [4,27], while conflicting results have been found with lower doses of rh-IGF1 [23,26]. Unfortunately, some complications related to muscle pain, fluid retention, benign intracranial hypertension and worsening retinopathy were observed when very high doses of rh-IGF1 have been used. In addition, it has been suggested that poor clinical responses may be also due to alterations of IGF binding proteins and increased IGF1 clearance [25]. It is also plausible that dose response is influenced by both the severity of the insulin resistance and the specific underlying genetic defect. Although some reports [22,24,28] found a significant reduction in HbA1c after rh-IGF1 treatment, in our patient HbA1c did not improve and frequent hyperglycaemia persisted. We could speculate that a better result could have been obtained by starting rh-IGF1 treatment earlier, maybe as a first line therapy. In contrast, fundoscopy has been performed every 6 months of treatment and it remained normal. The mild nephromegaly found on the abdominal ultrasound examination didn't get worse over time, and was associated with absent/mild microalbuminuria. The slightly elevated bile acids levels returned to normal, while the routine chemistry and haematological assessments have been normal throughout the treatment. As described in previous reports [19], our patient showed a significant improvement in acanthosis nigricans.

In conclusion, according to this experience, we suggest that rh-IGF1 should be considered as initial treatment option instead of final option in patients with severe insulin resistance syndromes. Longer term studies are needed to better analyse the risk-benefit ratio of such treatment, the ideal doses, the administration route and the age at which it should be started.

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