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Case Report

Successful rhIGF1 treatment for over 5 years in a patient with severe insulin resistance due to homozygous insulin receptor mutation

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Abstract

Background Congenital insulin resistance syndromes are caused by biallelic mutations within the insulin receptor gene (*INSR*). Recombinant human insulin-like growth factor (rhIGF1) has been used with mixed success; however, rigorous assessment of its efficacy is lacking. Here, we describe a child with a homozygous mutation in *INSR* successfully treated with rhIGF1 for more than 5 years.

Case report The patient presented with osmotic diabetes symptoms and was noted to have dysplastic dentition, hypertrichosis, coarse and dysmorphic facial features. Acanthosis nigricans, skin tags and rugated hyperkeratosis were also evident on the posterior neck, axilla and groin. A homozygous *INSR* essential splice site mutation (c.1268 + 2T > C, p.G374 fs*12) was identified, for which both parents were found to be heterozygous. The patient was treated with twice daily injections of rhIGF1 and metformin for more than 5 years with improvement in her acanthosis nigricans, hyperkeratosis and hypertrichosis. A dramatic fall in fasting insulin, HOMA–IR and HbA_{1c} has been maintained over the entire course of treatment without adverse effects. Her linear growth velocity has remained on target for her predicted adult height.

Discussion Our case demonstrates the effectiveness of rhIGF1 as an early treatment in a patient with a biallelic mutation within *INSR* without evidence of fluid retention, retinopathy, muscle pain, heart failure, cerebral infarcts or benign intracranial hypertension. Her case suggests rhIGF1 can and should be considered as an initial treatment option instead of as a final option in those with *INSR* mutations.

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Introduction

Congenital insulin resistance syndromes are caused by biallelic mutations within the insulin receptor gene (*INSR*). These include Donohue syndrome and Rabson–Mendenhall syndrome. Type A insulin resistance, which typically presents later in life, is commonly caused by *INSR* mutations, although these are usually heterozygous. Pathogenic mutations may reduce cell-surface expression of the receptor, impair insulin binding and/or receptor autophosphorylation, or perturb recycling kinetics. Receptor dysfunction leads to extreme insulin resistance and usually diabetes mellitus allied to linear growth retardation and soft tissue overgrowth [1].

Although the clinical severity of the trophic features is on a spectrum determined by the degree of dysfunction caused by the underlying mutations, all syndromic forms share clinical features of profound insulin resistance and ultimately hyperglycaemia poorly responsive to exogenous insulin. Those with Donohue syndrome rarely survive beyond infancy, whereas those with Rabson–Mendenhall syndrome typically survive into childhood or early adulthood [1,2]. Those with marked type A insulin resistance typically do not present to clinical attention until adolescence.

Recombinant human insulin-like growth factor (rhIGF1) has been used with mixed success in children with recessive infantile insulin-resistance syndromes [3–5]. Here, we describe a child with a homozygous mutation in *INSR* successfully treated with rhIGF1 for more than 5 years.

Case report

At 26 months of age, a Caucasian child was referred to the paediatric endocrine clinic at the University of Chicago because of glycosuria. Despite the glycosuria and associated

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What's new?

- Our case highlights the utility of noninsulin-based therapy over many years in an individual with a homozygous mutation in *INSR*.
- rhIGF1 therapy has successfully resulted in euglycaemia without significant sequelae.

nocturia, as well as random glucose levels > 11.1 mmol/l, the diagnosis of diabetes mellitus was questioned because she exhibited fasting hypoglycaemia. She was born via spontaneous vaginal delivery at 37 weeks of gestation, weighing 1984 g. She was up-to-date with her vaccinations and was meeting all her developmental milestones. Her mother had diet-controlled gestational diabetes but there was no other family history of diabetes. Her parents are first cousins of eastern European descent.

On examination, she was noted to have dysplastic dentition, coarse facial features, hypertrichosis, prominent lips and deep-set eyes. Acanthosis nigricans, skin tags and rugated hyperkeratosis were evident on the posterior neck, axilla and groin. The areas of her neck with acanthosis were also affected with recurrent fungal dermatitis. Her hands and feet were remarkable for short, widened digits with small nails. She was at the 3rd percentile for height and 10th percentile for weight. Her cardiorespiratory, abdominal and neurological examinations were otherwise unremarkable. Bone age was within one standard deviation of chronological age on repeated assessment when assessed at 3.5 and 6.8 years of age, while abdominal ultrasound demonstrated mild bilateral renal and ovarian hypertrophy. A history of daytime sleepiness, unrefreshing sleep and snoring prompted polysomnography that demonstrated severe obstructive sleep apnoea that was worse in the supine position. These symptoms improved following adenotonsillectomy performed prior to commencing rhIGF1.

Initial laboratory testing revealed a random plasma glucose of 13.4 mmol/l with a fasting glucose of 5.2 mmol/l and extremely elevated insulin levels (Table 1 and Fig. 1). Based on the history of consanguinity, clinical features consistent with Rabson–Mendenhall syndrome and biochemical evidence of severe insulin resistance, genetic testing was performed. A homozygous *INSR* essential splice site mutation (c.1268 + 2T > C) was identified and is predicted to disrupt the native 3′ donor splice site of exon 5 (p.G374 fs*12) [6]. Both parents were found to be heterozygous for the mutation.

At 26 months of age, she commenced and has since been maintained on a dose of ~ 25 mg/kg/day of metformin, along with modest carbohydrate restriction. She demonstrated improvement in HbA_{1c} from 72 to 58 mmol/mol (8.7% to 7.5%). Given the poor prognosis associated with homozygous deleterious *INSR* mutations, her family consented to a protracted trial of rhIGF1. At 42 months of age, she was started on twice-daily injections of rhIGF1 with a daily dose of 1.01 units/kg, rising to her current dose of 1.73 units/kg/day (Table 1).

Table 1 Results before and after rhIGF1 therapy

	Before commencing rhIGF1	After commencing rhIGF1
Age, months	42	110
rhIGF1 dose, units/kg/da)	-	1.73
HbA_{1c}, mmol/mol (%)	58 (7.5)	46 (6.4)
Insulin, pmol/l	4920	1062
C-peptide, nmol/l	1.8	0.8
Fasting glucose, mmol/l	5.2	4.8
HOMA-IR	188.3	37.6
IGF1, nmol/l	4.8	25.3
IGFBP3, µg/ml	1.3	1.4
IGFBP1, ng/ml	17	43
Adiponectin, µg/ml	16	14
Leptin, ng/ml	0.2	0.4
Urine albumin/creatinine, mg/g	209	65.1

HOMA IR, homeostasis model assessment of insulin resistance.

Following more than 5 years of rhIGF1 treatment, her acanthosis nigricans, hyperkeratosis and hypertrichosis have gradually become less prominent. She has grown along the 10th–15th percentile for height and the 10th–20th percentile for weight; with a stably normal bone age that predicts a normal final adult height (154 cm; 10th percentile for an adult female) consistent with her mid-parental height (155 cm). Serial abdominal ultrasounds have failed to demonstrate any significant change in the mild organomegaly originally noted, but she more recently exhibited minimally increased renal cortical echogenicity consistent with the nephrocalcinosis observed in other patients with *INSR* mutations [7]. Her urinary albumin/creatinine ratio improved upon commencing an angiotensin-converting enzyme inhibitor and has remained stable, while her 24–h protein was normal at 92 mg/24 h with urinary calcium excretion (calcium/creatinine) slightly elevated at 0.35.

Introduction of rhIGF1 therapy resulted in improved glycaemic control and reduced insulin resistance, in addition to the regression of some of the clinical evidence of insulin resistance (Fig. 1 and Table 1). The dramatic falls in fasting insulin, HOMA–IR and HbA_{1c} have been maintained over the entire course of treatment without adverse affects on lipid profile or renal function. Her mild fasting hypoglycaemia has remained stable, while her postprandial glucose excursions assessed by home glucose monitoring remain stably improved. Prior to commencing rhIGF1, she experienced notable clinical difficulty with recurrent viral infections that resulted in dehydration, ketosis and hospitalization, whereas

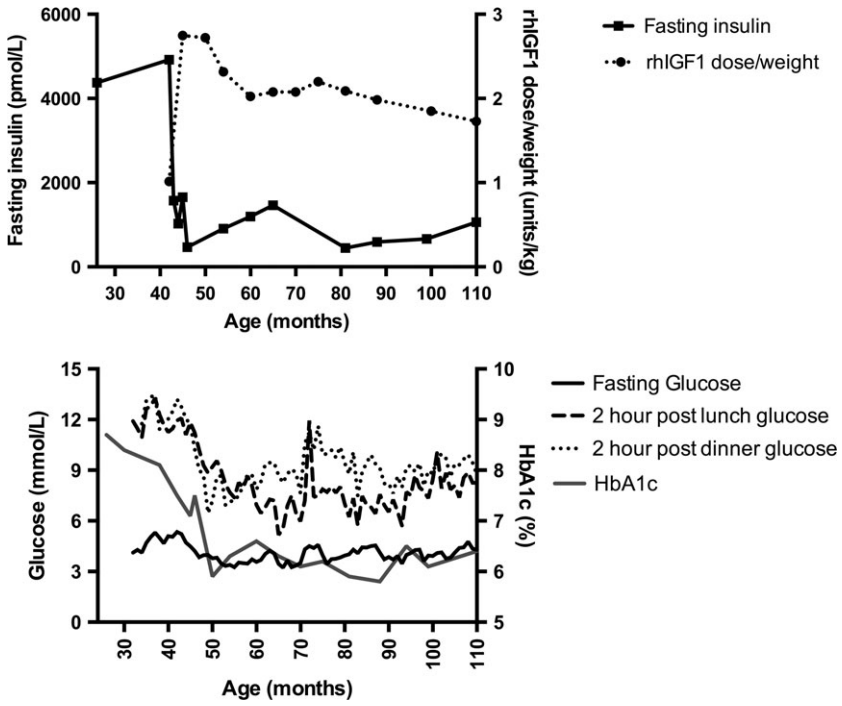

FIGURE 1 Glycaemic control before and after initiation of rhIGF1.

since commencing rhIGF1 she has not required hospitalization or developed significant ketosis while ill.

At 5.75 years of age the proband had a BMI of 15.8 kg/m^2 (67th percentile), and showed no evidence of complications associated with either long-term rhIGF1 treatment, or those observed in other patients with *INSR* mutations, including fluid retention, retinopathy, muscle pain, heart failure, cerebral infarcts and benign intracranial hypertension [8]. A mixed meal was performed on the proband after withholding the morning dose of rhIGF–1. Her father and mother, then 31 and 23 years of age and with BMIs of 35.0 kg/m^2 and 25.5 kg/m^2 respectively, were also tested. Both the proband and her father display significant degrees of insulin resistance in response a mixed meal (Fig. 2).

Discussion

The insulin receptor is a ubiquitous heterotetrameric transmembrane protein. The extracellular α–subunits permit insulin binding, which results in trans autophosphorylation of the intracellular β–subunits [2]. The phenotypic spectrum caused by loss-of-function mutations is explained by different degrees of receptor dysfunction, affecting, for example, *INSR* expression and processing or insulin-binding capacity

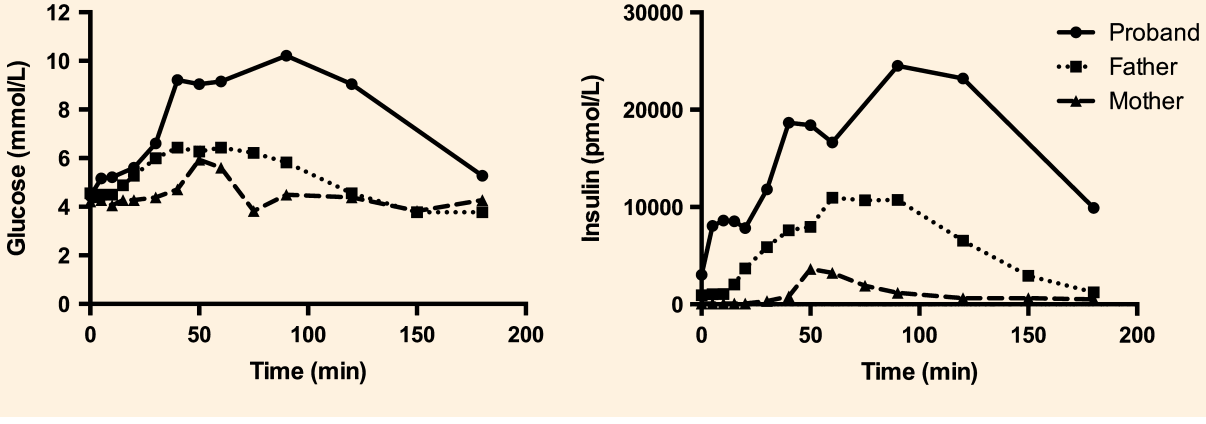

FIGURE 2 Mixed meal tolerance testing in the proband and her parents.

[1]. Donohue syndrome and Rabson–Mendenhall syndrome are historical terms that predate the advent of genetic testing and represent opposite ends of clinical spectrum of disease caused by biallelic deleterious *INSR* mutations. In the more severe, autosomal recessive receptoropathies, hyperinsulinaemia and dysglycaemia are accompanied by linear growth retardation, overgrowth of many soft tissues, and significant reduction in life expectancy due to complications including infections, intractable ketosis, heart failure, cerebral infarcts and ovarian tumours [9–12].

Pharmacotherapeutic options include insulin-sensitizing and replacement therapies [13]. rhIGF1 is commonly used in the most extreme cases. Endocrine IGF1 is produced in the liver following stimulation by growth hormone and has a molecular structure similar to that of insulin [14]. IGF1 shares common post-receptor signalling pathways with insulin, and can also activate insulin receptors at high doses, but its cognate receptor is expressed at low levels, if at all, in mature fat cells and hepatocytes, both of which are insulin responsive [15]. High doses of insulin and IGF1 can activate each other's receptors, and it is thought likely that at least some of the trophic features of hyperinsulinaemic states such as ovarian enlargement and acanthosis nigricans, which are seen even in those with no functional insulin receptor, may be mediated by pathological hyperactivation of the IGF1 receptor.

Reports of treating insulin-resistant syndromes with rhIGF1 have mostly been of short duration [16]. However, there have been reports of sustained clinical improvement with administration of rhIGF1 alone or in conjunction with its rapidly cleared binding protein IGFBP3 [5]. It is likely that differences in response relate to differences in dose, as well as in the age and/or clinical severity of the patient. Although rhIGF1 has also been shown to reduce insulin resistance in other conditions such as Type 2 diabetes [8,17], there are potential risks to be considered when using rhIGF1, based on its trophic effects, including concerns regarding tooth size and craniofacial growth [18]. High levels of IGF1 have been associated with increased risk of malignancies [19]; however, data on the long-term use of rhIGF1 and any possible association with increased risk for malignancy or other serious complications are lacking. There is limited safety data on other insulin-sensitizing agents in childhood, but it has been suggested that earlier initiation of rhIGF1 treatment may prevent or delay eventual loss of β–cell function and the need for exogenous insulin [20].

Our case demonstrates the effectiveness of rhIGF1 as an early treatment in a patient with Rabson–Mendenhall syndrome without any significant side effects. Although long-term data are lacking, both glycaemic and clinical improvements are still evident after 5 years of use. These results suggest that rhIGF1 can and should be considered as an initial treatment option instead of as a final option in those with *INSR* mutations.

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Competing interests

Ipsen Biopharmaceuticals (previously Tercica) provided the Increlex (rhIGF) for compassionate use. Dr Greeley participated in a one-time advisory meeting on the treatment of patients with rhIGF1 sponsored by Ipsen. He and the other authors have no other potential conflicts of interest to disclose.

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