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Continuous subcutaneous IGF-1 therapy via insulin pump in a patient with Donohue syndrome

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Abstract

Donohue syndrome (DS) is a severe form of congenital insulin resistance due to mutation(s) in the insulin receptor (*INSR*) gene. Given the similarities between insulin and insulin-like growth factor 1 (IGF-1) receptors, recombinant human IGF-1 (rhIGF-1) has been used to treat severe insulin resistance due to *INSR* mutation(s). Traditional subcutaneous therapy may be limited by the shortened IGF-1 half-life in these patients. We report the case of a female with molecularly

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confirmed DS treated with continuous rhIGF-1 therapy via an insulin pump. With treatment, the patient's hemoglobin A1c decreased from 9.8% to 8.8%, and her weight increased by 0.8 kg. Development of an ovarian tumor complicated her course, but it was unclear whether this was related to rhIGF-1 therapy. Limited treatment options exist for patients with DS. The use of continuous rhIGF-1 via an insulin pump may be a viable option, although further experience is needed to establish safety and efficacy.

Keywords

Donohue syndrome; insulin-like growth factor; insulin infusion systems; insulin resistance

Introduction

Donohue syndrome (DS) is the most extreme of the severe insulin resistance (IR) syndromes, caused by homozygous or compound heterozygous mutations of the insulin receptor (*INSR*) gene. DS is characterized by intrauterine growth retardation (IUGR), failure to thrive, fasting hypoglycemia, postprandial hyperglycemia, dysmorphic features, and initial resistance to ketosis (1). Complications include recurrent infections, acanthosis nigricans, rectal prolapse, polycystic ovaries, nephrocalcinosis, and eventual susceptibility to diabetic ketoacidosis. Life expectancy ranges from a few months to a few years (1).

Treatment options for DS are limited. The first line therapy for hyperglycemia and ketosis is high-dose insulin (2). Metformin was attempted with limited success, with one report of improvement in a DS patient (3). Leptin reportedly improved insulin resistance in a milder form of insulin receptoropathy (4). Recombinant human IGF-1 (rhIGF-1) improved glycemic control in patients with severe IR due to *INSR* mutations (5); however, only two studies used rhIGF-1 in the treatment of three DS patients (6, 7). The effect of rhIGF-1 treatment in severe IR may be limited by the decreased circulating IGF-1 half-life associated with insulin receptoropathies (8), thus raising the possibility that administration route could affect efficacy. In this article, we report the case of a female with DS due to complete loss-of-function *INSR* gene mutations treated with continuous rhIGF-1 via a modern insulin pump, in an effort to overcome the reported decreased rhIGF-1 half-life in patients with *INSR* mutations.

Patient presentation

Our patient was the 1595 g (<1st percentile) female product of 36 weeks of gestation, complicated by IUGR and diet-controlled gestational diabetes. She was transferred to our hospital with hyperglycemia and extreme hyperinsulinemia [insulin=4925 uU/mL (34,204 pmol/L)]. She presented with dysmorphic facies, paucity of subcutaneous fat, polycystic ovaries, breast buds, hypertrichosis, and clitoromegaly. She exhibited postprandial hyperglycemia and hypoglycemia after 4–6 h of fasting. Paradoxically elevated adiponectin, elevated sex-hormone binding globulin, and elevated IGF BP-1 were suggestive of an *INSR* mutation syndrome (9) (Table 1). Genetic analysis demonstrated compound heterozygosity for two very early frameshift mutations in the *INSR* gene – c.260_261insG (p.Tyr87X) from her mother, and c.15_24dup10 (p.Ala9fs) from her father – predicted to render her

functionally entirely null for the *INSR*. For the first year of life, her only treatment was frequent feedings, and she showed consistent growth and no hyperglycemia [hemoglobin A1c (HbA1c) 5.1%–5.4%].

By 13 months of age, HbA1c increased to 7.1%. At 16 months, she developed a viral illness and diabetic ketosis, requiring an insulin infusion of 1.5 units/kg/h to suppress ketosis. Metformin was started at 30 mg/kg/day divided twice daily; however hyperglycemia persisted and she required recurrent high-dose subcutaneous insulin for illness-associated ketosis. By 19 months, HbA1c increased to 9.5%. At this point, rhIGF-1 was started at 80 µg/kg/day divided twice daily via subcutaneous injections, and steadily increased to 640 µg/kg/day over the next year. DS complications included severe acanthosis nigricans with skin breakdown and suprainfection. Polycystic ovaries, present since infancy, enlarged with age; cyst marsupialization was conducted at 21 months, during surgical reduction of a large rectal prolapse with ileostomy creation. With increasing abdominal distension and frequent respiratory infections, her respiratory status slowly deteriorated, ultimately requiring oxygen supplementation.

At 30 months, our patient presented with respiratory distress and ketosis. High-dose insulin infusion suppressed ketogenesis, but attempts to normalize glucose (with insulin doses briefly up to 14 units/kg/h) were unsuccessful. Then, rhIGF-1 was increased to 560 µg/kg/day and given every 6 h; yet hyperglycemia persisted. Continuous subcutaneous rhIGF-1 infusion at 800 µg/kg/day divided evenly over 24 h was started via an Animas 1200 insulin pump (Animas Corporation, West Chester, PA, USA) and Accucheck Tender infusion set (Roche Diagnostics, Indianapolis, IN, USA) inserted at 30°. To comply with the rh-IGF-1 package insert recommendations for stability and storage (10), the rhIGF-1 reservoir was maintained between 2° and 8°C using a FRIO® insulin pump (FRIO UK Ltd., Haverfordwest, UK) wallet coolant sleeve. (However, given that rh-IGF-1 has not been administered via pump previously, it was unclear whether this was truly necessary.) Infusion set and site were changed daily. There was initial improvement in glycemic control. Over 5 months, rhIGF-1 dose was increased for hyperglycemia to a maximum of 1200 µg/kg/day.

Serum IGF-1 levels were monitored to evaluate efficacy and monitor for toxicity (Supplemental Table 1). IGF-1 level during continuous rhIGF-1 therapy via pump at 1120 µg/kg/day was similar to the level 60 min after a 280 µg/kg subcutaneous rhIGF-1 injection (230 and 212 ng/mL, respectively). IGF-1 was similar with the pump reservoir at room temperature or after 24 h at 7°C (202 and 197 ng/mL, respectively). During rhIGF-1 treatment, HbA1c was used to assess glycemic control. HbA1c increased from 5.1% to 9.5% prior to starting rhIGF-1, decreased to 7.7% on twice daily subcutaneous rhIGF-1, and then rebounded to a peak of 9.8%. Three months after initiation of continuous rhIGF-1, HbA1c was 8.8% (Figure 1). Weight gain increased from 175 g/month on SC IGF-1, to 202 g/month on continuous IGF-1 via pump.

At 35 months, our patient presented acutely with respiratory distress and an enlarged abdomen. Ultrasound indicated a large, cystic structure in the abdomen, and possible ovarian torsion. Bilateral oophorectomy revealed a 1.2 kg right ovarian mass of 16.5×12×9 cm, consistent with juvenile granulosa cell tumor and desmoplastic non invasive implants of

borderline serous tumor. An adult-type granulosa cell tumor was also seen in the left ovary. Postoperatively, she required prolonged intubation for acute respiratory distress syndrome. Her parents decided to withdraw care and she expired at 36 months of age.

Discussion

We describe the use of continuous subcutaneous rhIGF-1 administered via an insulin pump for the treatment of severe IR in a DS patient with genetic mutations predicted to ablate *INSR* function entirely. Glycemic control measured by HbA1c improved with treatment.

The rationale for using rhIGF-1 to treat severe IR syndromes is based on the observation of its direct effects on carbohydrate metabolism. In humans, infusion of rhIGF-1 suppresses hepatic glucose production, stimulates peripheral glucose uptake in muscle and, despite a significant reduction in circulating insulin levels, causes hypoglycemia (11). In patients with type 1 or type 2 diabetes, rhIGF-1 decreased blood glucose similar to exogenous insulin; however, the side-effect profile (edema of the face and hands, jaw tenderness, arthralgias, myalgias and tachycardia) limited its use in situations where insulin administration was effective (12, 13).

The improved glucose homeostasis and reduced insulin resistance caused by IGF-1 is thought to occur through reductions in GH secretion and/or direct effects on peripheral tissues through the IGF-1 receptor (IGF-1R). *INSR* and IGF-1R are 60% homologous, form hybrid receptors, and share very similar intracellular signaling pathways (14–16). IGF-1R are not reportedly expressed, or are expressed at extremely low levels, in canonical insulin responsive tissues—adipocytes and mature hepatocytes. However, both *INSR* and IGF-1R are expressed at comparable levels in the muscle. It was also speculated that, in the context of *INSR* deficiency, fetal patterns of IGF-1R may persist in the liver (17). IGF-1 may additionally exert beneficial effects through an ability to promote or sustain β -cell hyperplasia and high levels of insulin secretion (18). In *INSR* knock-out mice, rhIGF-1 lowered plasma glucose levels by increasing peripheral glucose uptake and decreasing hepatic glucose production; in this case, IGF-1R expression in the liver did not account for its hypoglycemic effect (19), further suggesting the main mechanism of action is likely peripheral, at the level of the muscle.

Several studies documented rhIGF-1 use in patients with severe IR syndromes (5–7, 20), and anecdotal evidence suggests further unpublished use. Decreases in insulin, but not glucose, were seen in two DS children treated with continuous IV rhIGF-1 for 66 and 62 h, respectively. The effect was transitory, as parameters returned to pretreatment values within 24 h of stopping the infusion (7). Nakae et al. demonstrated improved growth and HbA1c stabilization in a long-term DS survivor using subcutaneous injections and continuous rhIGF-1; however, the details of the treatment protocol were not provided (6).

In patients with *INSR* mutations, the clinical effectiveness of rhIGF-1 is related to its pharmacokinetics. Circulating IGF-1 is principally bound to IGFBP-3; free IGF-1 is rapidly degraded. In severe IR syndromes, IGFBP-3 levels are decreased and IGF-1 half-life was reported to be 1–3 h (8), vs. 17–20 h in normal individuals (21). An attempt to overcome

this problem using a rhIGF-1/rhIGFBP-3 complex demonstrated decreased HbA1c and metabolic parameters, suggesting improved first phase insulin secretory response (20).

Given that the rhIGF-1/rhIGFBP-3 complex is no longer commercially available in the US, we used continuous subcutaneous delivery of rhIGF-1 via an insulin pump as an alternative approach for increasing rhIGF-1 bioavailability. Our experience indicated that rhIGF-1 treatment via insulin pump was well tolerated and may have improved glycemic control. Weight gain also appeared favorable at the time. In retrospect, it is unclear how much of this increase may have been due to tumor growth. Efforts to evaluate rhIGF-1 effectiveness were balanced with the desire to limit unnecessary testing. Insulin and C-peptide were followed to examine possible effects on insulin resistance and β -cell function, but were difficult to interpret due to frequent infections.

Despite the potentially beneficial effects, there are theoretical concerns that rhIGF-1 may worsen IR complications, including acanthosis nigricans and cystic ovaries. Our patient developed rapid ovarian enlargement and juvenile granulosa cell tumor. High IGF-1 levels were associated with an increased risk of several types of malignancy, suggesting a role in early transformation or progression of disease (22). IGF-1R phosphorylation upon ligand binding led to activation of Akt pathway and downstream antiapoptotic effects (23). IGF-1 also led to cellular proliferation (24). Although juvenile granulosa cell tumor was reported in another infant with DS, that patient was never treated with rhIGF-1 (25). It was unclear whether the ovarian tumor was related to rhIGF-1 treatment, or reflected the natural progression of DS. Notably, our patient's acanthosis nigricans subjectively improved with rhIGF-1 treatment.

In conclusion, we report the use of an insulin pump for continuous rhIGF-1 infusion in a patient with DS. Therapy seemed to improve glycemic control, although our patient succumbed to disease complications before the full response could be assessed. It is unclear what, if any, role rhIGF-1 therapy played in the development of juvenile granulosa cell tumor. Providers caring for children with severe congenital IR syndromes face a daunting task with limited treatment options. As a solution, treatment with continuous rhIGF-1 via an insulin pump shows promise as a therapy for patients with severe IR syndromes. However, further experience is needed to thoroughly evaluate its safety and effectiveness.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Hemoglobin A1c (HbA1c) and rhIGF-1 administration. HbA1c initially decreased in response to SC rhIGF-1 injections before rebounding. HbA1c decreased after initiation of pump therapy.

Table 1Metabolic markers consistent with *INSR* mutation.

	Patient results	Normal range	Predictive of <i>InsR</i> mutation
Insulin, uU/mL	2855 (19,828) ^a	2–20 (14–139)	
Adiponectin, µg/mL	51 ^b		>7 ^c
IGFBP-1, ng/mL	195 ^b (195)		>30 ^c (>30)
SHBG, nmol/L	839 ^b (839)		>70 ^c (>70)
Leptin, ng/mL	2.1 (2.1)	1.7–10.6 (1.7–10.6)	
IGF-1, ng/mL	84 (84)	7–124 (7–124)	
IGFBP-3, mg/L	0.2 (0.2)	0.9–2.3 (0.9–2.3)	

^a SI units are listed in parenthesis (Insulin, pmol/L; IGFBP-1, µg/L; SHBG, nmol/L; Leptin µg/L; IGF-1, µg/L; IGFBP-3, mg/L).

^b Adiponectin was performed by ARUP laboratories (Salt Lake City, UT, USA) using quantitative ELISA; IGF-BP1 was performed by Esoterix, Inc., (Austin, TX, USA) using RIA; SHBG was performed by Esoterix Inc. using electrochemiluminescent immunoassay.

^c Adiponectin, IGF BP-1, and SHBG were performed in Dr. Semple 's laboratory using two-step time-resolved fluorometric assays, immunoradiometric assay, and chemiluminescent enzyme immunometric assay, respectively.