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Regression from stage 3 to stage 2 type 1 diabetes mellitus after discontinuing growth hormone therapy

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Summary

Multiple research studies address the anti-insulinemic effect of growth hormone (GH). We report a case of a patient with anterior hypopituitarism on GH replacement who later developed type 1 diabetes mellitus (T1DM). Recombinant human growth hormone (rhGH) therapy was discontinued at the time of growth completion. Because of significantly improved glycemic control, this patient was weaned off subcutaneous insulin. He regressed from stage 3 to stage 2 T1DM and remained in this status for at least 2 years and until the writing of this paper. The diagnosis of T1DM was established based on relatively low C-peptide and insulin levels for the degree of hyperglycemia as well as seropositivity of zinc transporter antibody and islet antigen-2 antibody. Additional laboratory data obtained 2 months after discontinuing rhGH revealed improved endogenous insulin secretion. This case report calls attention to the diabetogenic effect of GH therapy in the setting of T1DM. It also demonstrates the possibility of regression from stage 3 T1DM requiring insulin therapy to stage 2 T1DM with asymptomatic dysglycemia after discontinuing rhGH.

Learning points

- Given the diabetogenic effect of growth hormone, blood glucose levels should be monitored in patients with type 1 diabetes mellitus (T1DM) on insulin therapy and recombinant human growth hormone (rhGH) replacement.
- Clinicians should closely monitor for risk of hypoglycemia after discontinuing rhGH among T1DM patients who are on insulin treatment.
- The discontinuation of rhGH in the setting of T1DM may cause regression of symptomatic T1DM to asymptomatic dysglycemia requiring no insulin treatment.

Background

The development of type 1 diabetes mellitus (T1DM) has been classified into three stages. Stage 1 includes the presence of two or more islet autoantibodies with normoglycemia and no symptoms. Stage 2 presents with mild dysglycemia and no symptoms of T1DM. Stage 3 is defined as the onset of symptomatic T1DM according to criteria set by the American Diabetes Association (1).

Young (1941) reported a diabetogenic effect of crude anterior pituitary gland extract injected subcutaneously into dogs (2). The effect of growth hormone (GH) on glucose homeostasis has been well described. GH influences glucose homeostasis by inducing hepatic gluconeogenesis and counteracting insulin action through a variety of biochemical pathways. The principal mechanism through

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which GH counteracts insulin action is by inhibiting the anabolic action of insulin on adipose tissue, leading to increased free fatty acids, which can give rise to insulin resistance (3).

The reported incidence of T2DM was six times higher in children treated with rhGH than in untreated children. In contrast, there was no significant difference reported in the incidence and age at diagnosis of T1DM between rhGH-treated children and untreated individuals (4).

Case presentation

We report an 18-year-old Caucasian male with a history of anterior hypopituitarism secondary to craniopharyngioma that was diagnosed at 3 years of age. He was initially treated with neurosurgical excision of the craniopharyngioma followed by cranial radiation therapy. He was subsequently diagnosed with central hypothyroidism, central adrenal insufficiency, and then GH deficiency. He was started on recombinant human growth hormone (rhGH) at 4 years and 9 months of age. He demonstrated normal pubertal onset and progressed with normal pubertal gonadotropin and testosterone levels. When he reached 14 years, he presented with increased urination and increased thirst. Central diabetes insipidus was highly suspected given his hypopituitarism. However, his laboratory workup revealed new-onset T1DM. His body mass index (BMI) at the time of diagnosis with T1DM was 21.55 kg/m^2 at 77.8 percentile. His hemoglobin A1c (HbA1c) was checked twice several years before the diagnosis of T1DM and reported normal. His family history was remarkable for one cousin diagnosed with T1DM, a paternal grandmother diagnosed with multiple sclerosis, and a maternal great-grandmother diagnosed with systemic lupus erythematosus.

Investigation

Fasting laboratory workup showed serum osmolality of 301 mOsm/kg (normal range (NR): 270–295 mOsm/kg), urine osmolality of 914 mOsm/kg (NR: 50–1400 mOsm/kg), serum blood glucose of 297 mg/dL, elevated A1c at 11.7%, corrected serum sodium for hyperglycemia of 144 mmol/L (NR: 135–148 mmol/L), potassium 4.4 mmol/L (NR: 3.5–5.5 mmol/L), CO_2 24 mmol/L (NR: 22–32 mmol/L), and beta-hydroxybutyrate of 1.23 mmol/L (NR: <0.30 mmol/L). His insulin-like growth factor-1 was within the therapeutic range at 558 ng/mL (NR: 220–574 ng/mL). Subsequent laboratory results revealed a C-peptide of 1.4 ng/mL (NR: 0.8–3.5 ng/mL) and an insulin level of 10 ulU/mL (NR: 3–19 uIU/mL) with serum glucose of 395 mg/dL. He tested positive for zinc transporter antibody with a titer of 137.6 U/mL (NR: 0.0–15.0 U/mL) and for islet antigen 2 (IA-2) antibody at 8.5 U/mL (NR: 0.0–0.8 U/mL). Glutamic acid decarboxylase (GAD) antibody as well as insulin antibody were negative.

Treatment

He was started on subcutaneous (s.c.) insulin with a total daily dose of 0.8 units/kg/day for glycemic control. Levothyroxine, rhGH, and hydrocortisone replacement therapies were all continued.

Outcome and follow-up

Shortly after the onset of T1DM, the patient demonstrated a 6- to 9-month honeymoon period when he only required 2–4 units of long-acting insulin per day and a weak carbohydrate ratio and rarely required any correction doses of short-acting insulin for hyperglycemia. When the honeymoon period was over, his insulin requirement increased back to approximately 0.8 units/kg/day.

While the patient was on insulin treatment between 14 and 16 years of age, his BMI was fluctuating between 22.51 kg/m^2 at 83.9 percentile and 25.28 kg/m^2 at 89.25 percentile. After 2 years of treatment with s.c. insulin, linear growth was completed at 16 years of age, and rhGH was held. One month later, the patient underwent a repeat of the GH stimulation test. GH peak of 0.4 ng/mL confirmed the persistence of significant GH deficiency and indicated the need for adult GH replacement.

Interestingly, the patient's blood glucose decreased considerably after holding rhGH, and insulin requirements decreased dramatically until he was completely weaned off s.c. insulin about 1 month after holding rhGH. Through shared decision-making with the family, it was agreed upon to temporarily hold off on initiating adult GH replacement. Three months after discontinuing rhGH therapy, about 2 months after completely stopping the s.c. insulin, we obtained an oral glucose tolerance test and repeated HbA1c, C-peptide, and insulin levels, as well as antibody screening for T1DM for reevaluation.

Laboratory reevaluation revealed ongoing positive IA-2 antibody and transporter antibody with higher IA-2 antibody titer (>120 U/mL (NR: 0.0–7.4 U/mL)) and lower zinc transporter antibody titer (53.8 U/mL (NR: 0.0–15.0 U/mL)). GAD antibody as well as insulin antibody remained negative. His fasting blood glucose was 93 mg/dL with fasting C-peptide of 1.0 ng/mL ng/mL (NR: 0.8–3.5 ng/mL) and fasting insulin level of 6 µIU/mL (NR: 3–19 µIU/mL).

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His 2-h blood glucose was 184 mg/dL with 2-h postprandial C-peptide of 3.8 ng/mL (NR: 0.8–3.5 ng/mL) and 2-h insulin level of 20 µIU/mL (3–19 µIU/mL) (Table 1). Furthermore, his serial HbA1c measurements in the follow-up visits have remained stable between 5.4% and 6.8% over 24 months and until the writing of this paper, while the patient has been completely off s.c. insulin and without dietary carbohydrate restrictions (Fig. 1). During this period of time, he did not report any polyuria, polydipsia, or fatigue. His BMI gradually dropped from 24.54 kg/m² at 83.96 percentile to 21.88 kg/m² at 46 percentile.

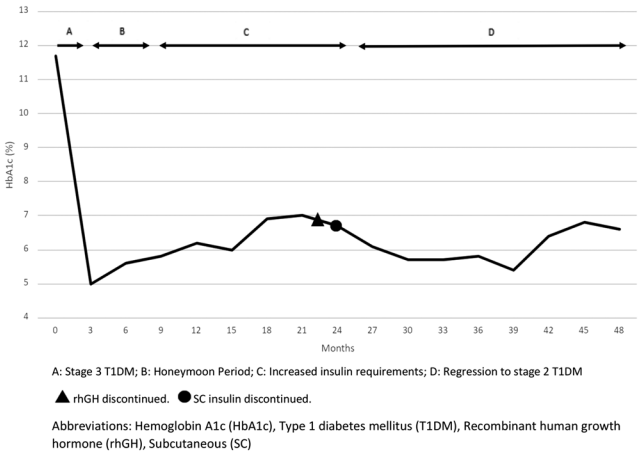

Figure 1
HbA1c trend after the onset of T1DM as well as before and after holding rhGH. (A) Stage 3 T1DM; (B) honeymoon period; (C) increased insulin requirements; (D) regression to stage 2 T1DM. HbA1c, hemoglobin A1c; rhGH, recombinant human growth hormone; s.c., subcutaneous; T1DM, type 1 diabetes mellitus.

Discussion

To the best of our knowledge, this is the first reported case of a patient with anterior hypopituitarism who developed T1DM and who 2 years later no longer needed exogenous insulin after discontinuing rhGH.

Due to the counteracting effects of rhGH on insulin action (3), daily insulin requirement is reported to be higher in patients with T1DM who are treated with rhGH than diabetic patients who are not treated with rhGH (5). The patient we describe is likely to have a genetic predisposition to develop T1DM. It is possible that the rhGH replacement accelerated the progression to overt T1DM in our patient and likely countered the effects of his endogenous and exogenous insulin activity. Holding rhGH has drastically improved the glycemic control of this patient. He needed no more s.c. insulin, and his HbA1c remained between 5.4% and 6.8% without diabetes symptoms for at least 2 years and until the writing of this paper. Putting our patient back in the status of GH deficiency eliminated the diabetogenic effect from rhGH and likely improved the sensitivity of residual endogenous insulin. This change suggests that our patient is potentially still within the normal limits of T1DM progression and has reverted to stage 2 T1DM (1).

Comparing the laboratory data between the onset of symptomatic T1DM and 2 months after holding rhGH showed an unexpected pattern. The patient's C-peptide and insulin levels were considerably higher in relation to the serum glucose after the withdrawal of rhGH (Table 1). This suggested improvement in markers of beta-cell function in this patient. An *in vitro* study has described a direct long-term effect of GH on proliferation and insulin biosynthesis of pancreatic beta-cells in monolayer culture (6). However, there is no evidence that exogenous GH increases beta-cell number and function in humans. In the patient, we describe that the zinc transporter antibody titer dropped by about 60% after holding rhGH, whereas the IA-2 antibody titer increased significantly. We are not sure if these inverse antibody trends after discontinuing rhGH contributed to the regression from stage 3 to stage 2 T1DM.

Table 1 Comparison between laboratory values before and after holding rhGH.

	Normal range	On rhGH	2 months off rhGH
IGF-1 (ng/mL)	220–574*	558	
IGF-1 *z*-score	−2.0 to +2.0	+2.0	
HbA1c (%)		11.7	5.7
IA-2 Ab (U/mL)	0–0.8, 0–7.4	8.5	>120.0
Insulin Ab (U/mL)	0–0.4	<0.4	<0.4
Zinc transporter Ab (U/mL)	0–15.0	137.6	53.8
GAD Ab (IU/mL)	0–5.0	<5.0	<5.0
Serum glucose (mg/dL)	70–100	397	
Glucose tolerance test			
0 min/fasting			93
60 min			207
120 min			184
C-peptide (ng/mL)	0.8–3.5	1.4	
0 min/fasting			1.0
120 min			3.8
Insulin (µIU/mL)	3–19	10	
0 min/fasting			6
120 min			20

*For his age and Tanner stage.
Ab, antibody; GAD Ab, glutamic acid decarboxylase antibody; HbA1c, hemoglobin A1c; IA-2 Ab, islet antigen 2 antibody; IGF-1, insulin-like growth factor-1; rhGH, recombinant human growth hormone; Zn Ab, zinc transporter antibody.

The development of T1DM in patients who are receiving rhGH is inconsistent with the findings of Villares *et al.* (2013). They stated that GH may prevent autoimmune diabetes in mice models via several immunoregulatory effects (7). Our patient is not the first case reported to develop T1DM while being treated with rhGH. Sadeghi-Nejad (2007) reported a 12-year-old boy who had GH deficiency and developed T1DM 11 months after initiation of rhGH (8). Additionally, Wang *et al.* (2015) reported an 8-year-old boy who developed T1DM 1 month after he was started on rhGH for slow growth (9). GH has been described to stimulate the proliferation of T and B cells and immunoglobulin production. GH also promotes the maturation of myeloid progenitor cells and can modulate cytokine response *in vitro* and in animal models (10). Nevertheless, to date, there is still no concrete evidence to support that rhGH has an immunomodulatory effect that plays a role in the development of autoimmune DM in humans.

To conclude, glycemic control in patients with T1DM and GH deficiency can improve beyond expected when rhGH is discontinued. Additional research is warranted to explore the immunomodulatory effect of rhGH on autoimmune status and whether rhGH improves beta-cell function in the long-term.

Declaration of interest
The authors declare that there is no conflict of interest or financial disclosures that could be perceived as prejudicing the impartiality of the case reported.

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Patient consent
Written informed consent for publication of their clinical details was obtained from the patient and parent of the patient.

Author contribution statement
MA Fischer and GA Elmahmudi drafted and revised the manuscript. BK Goldsweig and SHElrokhsi reviewed and edited the manuscript. SH Elrokhsi is the primary endocrinologist for the patient reported.

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