Coexistence of growth hormone deficiency and autoimmune polyglandular syndrome type 3

Robert Krysiak, Bogusław Okopień

Department of Internal Medicine and Clinical Pharmacology, Medical University of Silesia, Katowice, Poland

Correspondence to: Robert Krysiak, MD., PhD.
Department of Internal Medicine and Clinical Pharmacology,
Medical University of Silesia, Medyków 18, 40-752 Katowice, Poland.
TEL/FAX: +4832 2523902; E-MAIL: r.krysiak@interia.pl

Submitted: 2011-11-05 Accepted: 2012-12-22 Published online: 2012-05-27

Key words: **growth hormone; hypopituitarism; Graves disease; type 1 diabetes mellitus**

Neuroendocrinol Lett 2012; **33**(3):301–303 **PMID:** 22635089 NEL330312C12

Abstract

Both adult-onset growth hormone deficiency and autoimmune polyglandular syndrome are more frequent clinical entities than previously thought. In light of research carried out in recent years, it seems that growth hormone deficiency may be associated with proinflammatory state. This study describes a unique case of adult-onset growth hormone deficiency secondary to a traumatic brain injury in a young man, which was followed by the development of autoimmune polyglandular syndrome type 3. We discuss diagnostic and treatment dilemmas associated with discovering and management of both disorders in this patient. We conclude that in predisposed individuals growth hormone deficiency may lead to the development of autoimmune disorders of endocrine glands and/or exacerbate their clinical course.

INTRODUCTION

Autoimmune polyglandular syndromes (APS) are clinical entities characterised by the association of two or more organ-specific autoimmune endocrine disorders and nonendocrine autoimmunopathies (Michels & Gottlieb 2010; Betterle & Zanchetta 2003). In light of research carried out in recent years, the real frequency of their occurrence is much higher than previously thought (Michels & Gottlieb 2010). Based on the clinical manifestation, they may be classified as one of four different types (Betterle & Zanchetta 2003). Growth hormone deficiency (GHD) in adults has only recently been recognised as a clinically important syndrome which is associated with increased morbidity and probably also with increased mortality (van Aken & Lamberts 2005; Toogood and Stewart 2008). Its presence leads to many unfavourable changes in body composition (increased fat mass and decreased lean mass), lipid metabolism, cardiovascular disorders, and may worsen quality of life. In many patients the disease may be either asymptomatic or present with relatively moderate subjective symptoms (van Aken & Lamberts 2005; Toogood and Stewart 2008).

CASE REPORT

To the best of our knowledge, so far, only few studies have reported cases of the coexistence of GHD with APS type 1 (Bensing *et al.* 2007; Franzese *et al.* 1999, 2 (Papathanasiou *et al.* 2007) and 3 (Quintos *et al.* 2010). We report here a case of a man who developed APS type 3, defined as the combination of autoimmune thyroid disease with the exception of Addison's disease (Betterle & Zanchetta 2003), several months after the development of adult-onset GHD. At the age of 28, our male patient was involved in a car accident, the consequences of which were multiple traumas, including traumatic brain injury. Shortly

CASE REPORT

afterwards he noticed a decrease in muscle strength and mass, changes in body composition (visceral fat deposits), fatigue, lack of energy, emotional liability and impaired quality of life, suggesting hypopituitarism. Laboratory findings showed undetectable plasma levels of GH. The GH responses in the insulin tolerance test (2.2 μg/L) and after combined administration of glucagon and propanolol (2.9 μg/L) were blunted, which were accompanied by low plasma levels of insulin growth factor 1 (68 ng/mL) and insulin growth factor binding protein 3 (2.54 μg/mL) (reference range for insulin growth factor 1 and insulin growth factor binding protein 3 in men between the ages of 21 and 30: 114–350 ng/mL and 3.4–7.2 μg/mL, respectively). Levels of FSH (6.2 U/L), LH (5.7 U/L), prolactin (12.3 μg/L) and TSH (1.56 mU/L) were within the reference range. The TSH response to TRH administration was normal (an increase by 15.2 mU/L). A magnetic resonance imaging showed no abnormalities. Transglutaminase antibodies were then negative. Because GHD in adults in our country are not covered by public medical insurance, the patient was not prescribed with recombinant human GH replacement therapy and received only symptomatic treatment. Eight months later, he was admitted to our clinic because of weight loss (11 kg in 4 month) despite increased appetite, hyperactivity, heat intolerance, irritability and tachycardia. Laboratory examination revealed evidence of overt hyperthyroidism (TSH – 0.001 mU/L, reference values: 0.4–4.5 mU/L; free thyroxine – 2.20 ng/mL, reference values: 0.90–1.7 ng/dL; free triiodothyronine – 8.85 pg/mL, reference values: 2.70–5.30 pg/mL), which was secondary to Graves' disease (thyrotropin receptor antibodies – 21.2 U/L, reference values <1.0 U/L; diffused thyroid hypoechogenecity on sonography) and therefore, the patient started methimazole treatment (40 mg daily). Two months later he was again admitted to hospital. Although most of his symptoms resolved, he continued to lose weight, as well as developed polydipsia (oral fluid intake: 10 L) and poliuria (24-h urinary output: 8 L). Laboratory investigation revealed that he had severe hyperglycemia (fasting plasma glucose – 402 mg/dL; glycated hemoglobin: 14.1%). He was found to have positive circulating autoantibodies to islet autoantigens, glutamic acid decarboxylase and tyrosine phosphatase (ICA512/IA-2), as well as low fasting C-peptide levels (0.2 ng/mL, reference range: 0.6–2.9 ng/mL), which increased only slightly after intravenous administration of 1 mg glucagon. Thus, a diagnosis of type 1 diabetes was made and the patient started intensive insulin therapy. Because the index patient met the criteria of APS, he was assessed for the presence of other autoimmunities. His family history was for autoimmune disorders was unremarkable. Normal morning plasma ACTH levels (42 pg/mL), morning plasma cortisol (7.1 μg/dL) and a normal peak cortisol level in a 250 μg cosyntropin stimulation test (20.2 μg/dL), plasma renin activity (2.2 ng/mL/hr) and plasma aldosterone levels (59 pg/mL) within the reference range, as well as the lack of 21-hydroxylase and 17α-hydroxylase antibodies ruled out the presence of adrenal insufficiency. However, anti-transglutaminase antibodies were positive. HLA typing showed that the presence of the DRB1*04:DQA1*03:03-DQB1*04:01 haplotype. Presently, four years later, his thyroid function and diabetes are effectively controlled. After radioiodine therapy for Graves' disease he requires treatment with L-thyroxine and because of diabetes he receives intensive insulin therapy.

Our study is the first which shows that adult-onset GHD may predispose to the development of APS. Because individuals with GHD have increased plasma levels of interleukin 6 (Leonsson *et al.* 2003), whereas treatment with recombinant human GH results in a decrease in circulating levels of interleukin-6 and C-reactive protein (Sesmilo *et al.* 2000), the development of APS in this subject might have been secondary to the proinflammatory state associated with the impaired production of GH.

GHD is a disease with a prevalence in the general population of around 4 in 10 000 (Toogood & Stewart 2008). Taking into account that APS, in its overt and subclinical form, seems to occur much more frequently than previously estimated but, because of physicians' inadequate knowledge about its existence, is rarely diagnosed, a simple coincidence of both clinical entities in the same patient, cannot be totally ruled out. Some findings seem to contradict this explanation, making it very unlikely. Both Graves disease and type 1 diabetes developed only several months after establishing the diagnosis of GHD, and appeared almost in the same time. What's more, although anti-transgluminase antibodies were absent just after the traumatic event, 10 months later they were found in the plasma of our patient. Finally, taking into account sex (autoimmune disorders occur mainly in women) and no previous autoimmune disorders in his family, our patient seemed to be at a low risk for APS.

Because the index patient is only one of very few subjects with concomitant presence of GHD and APS, and one of two diagnosed with APS type 3, it should be assumed that the impaired release of GH induces the development of APS only in selected groups of patients with a susceptible genetic profile. This was the case in the index patient having DRB1*04:DQA1*03:03-DQB1*04:01 haplotype, which is associated with the increased risk of the development of APS type 3.

GHD was the only pituitary abnormality found in the index subject. Therefore, although prolactin exhibits a complex proinflammatory action (Orbach & Shoenfeld 2007), while glucocorticoids produce multidirectional anti-inflammatory effects (Gessi *et al.* 2010), the development of APS cannot be attributed to an impaired secretion of any other pituitary hormone, particularly to hyperprolactinemia and secondary adrenal insufficiency.

CONCLUSION

To sum up, GHD may lead to the development of autoimmune disorders of endocrine glands and/or exacerbate their clinical course. This situation probably takes place in patients demonstrating a susceptible genetic background for autoimmune diseases.

Conflict of interest statement

The authors declare that there is no conflict of interest.

REFERENCES

1 Bensing S, Fetissov SO, Mulder J, Perheentupa J, Gustafsson J, Husebye ES, et al (2007). Pituitary autoantibodies in autoimmune polyendocrine syndrome type 1. Proc Natl Acad Sci. USA **104:** 949–954.

2 Betterle C, Zanchetta R (2003). Update on autoimmune polyendocrine syndromes (APS). Acta Biomed. **74:** 9–33.

3 Franzese A, Valerio G, Di Maio S, Iannucci MP, Bloise A, Tenore A (1999). Growth hormone insufficiency in a girl with the autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy. J Endocrinol Invest. **22:** 66–69.

4 Gessi S, Merighi S, Borea PA (2010). Glucocorticoid's pharmacology: past, present and future. Curr Pharm Des. **16:** 3540–3553.

5 Leonsson M, Hulthe J, Johannsson G, Wiklund O, Wikstrand J, Bengtsson BA, et al (2003). Increased Interleukin-6 levels in pituitary-deficient patients are independently related to their carotid intima-media thickness. Clin Endocrinol. (Oxf) **59:** 242–250.

6 Michels AW, Gottlieb PA (2010). Autoimmune polyglandular syndromes. Nat Rev Endocrinol. **6:** 270–277.

7 Orbach H, Shoenfeld Y (2007). Hyperprolactinemia and autoimmune diseases. Autoimmun Rev. **6:** 537–542.

8 Papathanasiou A, Kousta E, Skarpa V, Papachileos P, Petrou V, Hadjiathanasiou C (2007). Growth hormone deficiency in a patient with autoimmune polyendocrinopathy type 2. Hormones (Athens). **6:** 247–250.

9 Quintos JB, Grover M, Boney CM, Salas M (2010). Autoimmune polyglandular syndrome Type 3 and growth hormone deficiency. Pediatr Diabetes. **11:** 438–442.

10 Sesmilo G, Biller BM, Llevadot J, Hayden D, Hanson G, Rifai N, et al (2000). Effects of growth hormone administration on inflammatory and other cardiovascular risk markers in men with growth hormone deficiency. A randomized, controlled clinical trial. Ann Intern Med. **133:** 111–122.

11 Toogood AA, Stewart PM (2008). Hypopituitarism: clinical features, diagnosis, and management. Endocrinol Metab Clin North Am. **37:** 235–261.

12 van Aken MO, Lamberts SW (2005). Diagnosis and treatment of hypopituitarism: an update. Pituitary. **8:** 183–191.