Chapter 37
Type 1 Diabetes and Comorbidity of Addison's Disease

Helena E. Larsson, Sten-A Ivarsson, and Åke Lernmark

Objectives

The criteria to diagnose diabetes have remained the same with few modifications since the first recommendations were made in 1979 [1]. Once the diagnosis of hyperglycemia (impaired fasting glucose [IFG], impaired glucose tolerance [IGT], or diabetes) is made, the classification of the disease may be complicated. Type 1 diabetes is strongly associated with markers of autoimmune phenomena and a loss of endogenous insulin production, resulting in insulin dependency for life. In addition, type 1 diabetes is strongly associated with other organ-specific autoimmune disorders [2]. Major advances in molecular diagnosis make it also possible to classify diabetes into maturity-onset diabetes of the young (MODY), which is a dominantly inherited form of nonketotic diabetes. MODY usually develops in childhood, adolescence, or young adulthood. Also this disease is characterized by genetic and clinical heterogeneity. Neonatal diabetes may be due to heterozygous gain-of-function mutations in the *KCJN11*gene encoding the Kir6.2 subunit of the potassium adenosine triphosphate (K_{ATP}) channel and may be found in patients diagnosed with permanent diabetes at < 6 months of age [3]. These monogenic types of diabetes are not associated with autoimmune markers of type 1 diabetes.

More importantly, type 1 diabetes is also associated with other organ-specific autoimmune disorders (Table 37.1). First, about 10% of newly diagnosed type 1 diabetes patients develop celiac disease within 5 years of the clinical diagnosis of diabetes [2, 4]. Second, in newly diagnosed type 1 diabetes patients, thyroglobulin autoantibodies may be found among 33% compared to 14% of controls. Similarly, thyroid peroxidase autoantibodies may be found among 38% compared to 6% of controls (Ivarsson, unpublished observations). These thyroid autoantibodies are strong markers for Hashimoto's disease, a disorder that may develop among 20% to 30% of all type 1 diabetes patients. Other diseases of autoimmune character include

H.E. Larsson
Reader in Pediatrics, Department of Clinical Sciences, Lund University/CRC, University Hospital MAS,
SE-20502 Malmö, Sweden

T.F. Davies (ed.), *A Case-Based Guide to Clinical Endocrinology*,

Table 37.1 Organ-specific autoimmunity in type 1 diabetes

Organ-specific autoimmunity	Autoantibody marker
Celiac disease	Tissue transglutaminase
Hashimoto's disease	Thyroperoxidase Thyroglobulin
Atrophic gastritis	H^+,K^+-ATPase
Addison's disease	21-hydroxylase
Adrenal autoimmunity	Side chain cleavage enzyme 17α-hydroxylase
Vitiligo	Tyrosinase

vitiligo, atrophic gastritis, and Addison's disease. The present case report reveals the critical importance of considering Addison's disease as a comorbidity of type 1 diabetes.

Case Presentation

This patient was an 18-year-old man who developed type 1 diabetes at the age of 14. At the time a rather widespread vitiligo had also been noticed. There was no family history of diabetes. The patient had been treated with insulin and he was in satisfactory control.

Four months before admission, he had been anorectic, had developed weakness, and steadily lost weight. He had frequent hypoglycemic attacks despite a reduction in the insulin dosage. One month before admission, he was treated at another hospital due to a serious hypoglycemic attack with convulsions followed by mental confusion lasting for several days.

How the Diagnosis Was Made

On admission to the hospital, his general condition was satisfactory. He had no increased pigmentation of the skin, but widespread vitiligo. Blood pressure was 110/80, serum sodium (s-Na) 140 mmol/L, serum potassium (s-K) 5.6 mmol/L, and serum creatinine 88 μmol/L. Thyroid hormone levels were normal.

The plasma cortisol curve showed low levels of 70 nmol/L at 7 a.m. (normal 200–800), 60 nmol/L at 1 p.m. (normal 100–800), 50 nmol/L at 7 p.m. (normal 50–600), and 40 nmol/L at 1 a.m. (normal 20–400). p-ACTH was 126 pmol/L (normal 30 ± 2.6), p-aldosterone 0.02 nmol/L (normal 0.14–0.85), and p-renin 9.75 μmol/L (normal 2.1–4.0). Basal urinary cortisol excretion was undetectable (< 10 nmol/24 hours). Adrenal autoantibodies were not available.

The patient was diagnosed with adrenocortical insufficiency and successively treated with corticoid (about 15 mg hydrocortisone per m^2 body surface) substitution therapy. This was followed by an increase in insulin requirement from 28 U/day to 58 U/day.

Discussion

Type 1 diabetes has a number of comorbidities (Table 37.1). The most common is Hashimoto thyroiditis, which affects almost 20% to 30% of type 1 diabetes patients. At the diagnosis of type 1 diabetes, almost 40% of the patients have thyroperoxidase (TPO) and 33% thyroglobulin autoantibodies (Ivarsson, unpublished observations). Celiac disease is the second most common comorbidity [2, 4]. Although celiac disease is uncommon at the time of diagnosis of type 1 diabetes in children, recent studies demonstrate that about 10% develop celiac disease within 5 years of the diabetes diagnosis. Less common comorbid diseases include atrophic gastritis and Addison's disease.

Addison's disease is a relatively rare but curative cause of recurrent hypoglycemia in patients with type 1 diabetes. A low threshold for investigating patients with type 1 diabetes and recurrent hypoglycemia to detect Addison's disease has therefore been suggested [5]. Addison's disease is strongly associated with HLA DR3–DQ2, the second most common HLA haplotypes in type 1 diabetes. Autoantibodies against 21 hydroxylase (21OH), side-chain cleavage (SCC), and 17α-hydroxylase (17OH) are common in Addison's disease and autoimmune polyendocrine syndrome type II [2, 4]. It has been suggested that measurement of 21OH autoantibodies should be the first step in the immune assessment of patients with Addison's disease and individuals at risk for adrenal autoimmunity such as patients with type 1 diabetes. Due to their low prevalence in Addison's disease, measurement of SCC and 17OH autoantibodies should be indicated only for 21OHAb-negative patients and for those with premature ovarian failure [5].

Lesson Learned

The insulin requirement increases during puberty. When a patient presents with decreasing insulin requirement at this stage, it is important to rule out adrenocortical insufficiency.

References

1. Genuth S, Alberti KG, Bennett P, et al. Follow-up report on the diagnosis of diabetes mellitus. Diabetes Care 2003;26:3160–3167.
2. Rewers M, Norris J, Dabelea D. Epidemiology of type 1 diabetes mellitus. Adv Exp Med Biol 2004;552:219–246.
3. Hattersley AT, Ashcroft FM. Activating mutations in Kir6.2 and neonatal diabetes: new clinical syndromes, new scientific insights, and new therapy. Diabetes 2005;54:2503–2513.
4. Pihoker C, Gilliam LK, Hampe CS, Lernmark A. Autoantibodies in diabetes. Diabetes 2005; 54:S52–61.
5. Likhari T, Magzoub S, Griffiths MJ, Buch HN, Gama R. Screening for Addison's disease in patients with type 1 diabetes mellitus and recurrent hypoglycaemia. Postgrad Med J 2007;83:420–421.

Multiple-Choice Questions

1. The most important genetic factor for type 1 diabetes is:

   A. HLA
   B. *KCJN11* gene
   C. Insulin gene
   D. Glucokinase gene

2. Vitiligo is a comorbidity of:

   A. MODY
   B. Type 1 diabetes
   C. Type 2 diabetes
   D. Impaired fasting glucose (IFG)

3. The following disorders occur with an increased frequency among patients with type 1 diabetes (several options may be correct):

   A. Hashimoto's thyroiditis
   B. Wilms' tumor
   C. Addison's disease
   D. Wegener's granulomatosis

4. Pair the following immune markers with their respective disease.

Autoantibody:	Disease:
A. IA-2	E. Atrophic gastritis
B. H^+K-ATPase	F. Vitiligo
C. Tyrosinase	G. Type 1 Diabetes
D. 21-hydroxylase	H. Addison's disease