Autoimmune Endocrine Diseases

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Abstract: Autoimmune endocrine diseases occur most frequently among various autoimmune diseases. Among autoimmune endocrine diseases, Graves’ disease, Hashimoto’s disease, type 1 diabetes mellitus, and Addison’s disease are especially frequent in daily clinical practice. Graves’ disease produces thyrotoxicosis due to the effects of the anti-TSH receptor antibody upon the thyroid gland and diverse symptoms due to its effects on extrathyroid tissues. Hashimoto’s disease is the most frequently encountered autoimmune disorder, and cellular immunity is thought to be involved. Guidelines for the diagnosis of these thyroid diseases have been provided by the Japan Thyroid Association. Autoimmune mechanisms are involved in many cases of type 1 diabetes mellitus. Type 1 diabetes mellitus has a wide spectrum of clinical disease states ranging from the rapid onset form, which develops diabetes mellitus within several days, to SPIDDM, which slowly progresses over years. Addison’s disease is also an autoimmune disorder in many cases and may present polyglandular autoimmune syndrome with complications by other organ-specific autoimmune disorders.

Key words: Graves’ disease; Hashimoto’s disease; Type 1 diabetes mellitus; Addison’s disease

Introduction

It is generally recognized that endocrine organs may contract various organ-specific autoimmune diseases, which, except for Base-dow’s disease (Graves’ disease) in which autoantibodies possess endocrine gland-stimulating activity, present diverse clinical features due to endocrine hypofunction through autoimmune mechanisms. Widely known among these disorders is polyglandular autoimmune syndrome involving autoimmune endocrine diseases of several organs.

This paper presents brief accounts of Graves’ disease, Hashimoto’s disease, type 1 diabetes mellitus, and Addison’s disease, which are frequently seen autoimmune endocrine diseases in daily clinical practice.

Graves’ Disease

1. Pathophysiology

The disease is characterized by the presence of an autoantibody that recognizes the TSH receptor of the thyroid gland. The anti-TSH receptor antibody causes thyrotoxicosis and various extrathyroid symptoms.
thyroid with low internal echo level. Enhanced internal blood flow is noted on Doppler ultrasonography.

4. Essentials of diagnosis
Guidelines for the diagnosis of thyroid diseases (the sixth draft) have been provided by the Japan Thyroid Association.2) The association’s guidelines for the diagnosis of Graves’ disease are cited in Table 1. These guidelines are available at the Japan Thyroid Association’s website (http://thyroid.umin.ac.jp/flame.html).

5. Treatment
(1) Antithyroid drugs: These drugs are

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Table 1 Guidelines for the Diagnosis of Graves’ Disease

<table>
<thead>
<tr>
<th>a) Clinical findings</th>
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</thead>
<tbody>
<tr>
<td>1. Signs of thyrotoxicosis such as tachycardia, weight loss, finger tremor, and sweating</td>
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<tr>
<td>2. Diffuse enlargement of the thyroid gland</td>
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<tr>
<td>3. Exophthalmos and/or specific ophthalmopathy</td>
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</table>

<table>
<thead>
<tr>
<th>b) Laboratory findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Elevation in serum free thyroxine (FT₄) level</td>
</tr>
<tr>
<td>2. Suppression of serum thyroid stimulating hormone (TSH): less than 0.1μU/ml</td>
</tr>
<tr>
<td>3. Positive for anti-TSH receptor antibody (TRAb or TBII) or thyroid stimulating antibody (TSAb)</td>
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<tr>
<td>4. Elevated radioactive iodine (or ¹³¹I) uptake to the thyroid gland</td>
</tr>
</tbody>
</table>

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Notes
1. Decrease of serum cholesterol and increase of serum alkaline phosphatase are often observed.
2. There are rare cases with free triiodothyronine (FT₃) elevation alone and normal FT₄.
3. A patient shall be said to have “euthyroid Graves’ disease” or “euthyroid ophthalmopathy”, if he/she has ophthalmopathy and is positive for TRAb or TSAb, but shows normal FT₄ and TSH.
4. In an elderly patient, clinical symptoms and signs including an enlargement of the thyroid gland, may not be clear.
5. In children, decreased scholastic ability, accelerated growth, restlessness and other symptoms are observed.
often used as drugs of first choice for the treatment of Graves’ disease in Japan. Usually, methimazole (MMI) with a slightly higher potency is instituted at a dosage level of 15–30 mg/day, followed by a gradual dose reduction over several years. In case of any adverse reaction occurring (except for agranulocytosis) or during lactation, the drug is replaced with propylthiouracil (PTU). Antithyroid drugs are drugs of first choice for pregnant women.

2) Radioactive iodine therapy: Patients in whom antithyroid drugs cannot be used and middle-aged and older patients who respond poorly to the therapy regimens are better indicated for the use of radioiodine. At present, the therapy is feasible at outpatient services. Therapeutic effects become evident about 6 months after the start of medication, with subsequent development of late hypothyroidism in many cases.

3) Subtotal thyroidectomy: This is preferred for refractory juvenile cases of Graves’ disease with notable enlargement of the thyroid.

Hashimoto’s Disease

1. Pathophysiology
This disease occurs in nearly one out of every ten middle-aged women and is an organ-specific autoimmune disorder with the highest prevalence. The etiology remains unclear, although cellular immunity and antibody-dependent cytotoxicity are generally thought to be involved.

2. Clinical features and physical findings
Firm diffuse enlargement of the thyroid is the only finding if thyroid hypofunction is not present. The disease progresses into hypothyroidism to produce generalized edema, weight gain, subjective symptoms such as fatigueability, sensitivity to the cold and diarrhea, and physical findings such as hoarseness, dry skin, falling of the lateral one-third of both eyebrows, bradycardia, and a prolonged relaxation phase of the Achilles tendon reflex.

<table>
<thead>
<tr>
<th>Table 2 Guidelines for the Diagnosis of Chronic Thyroiditis (Hashimoto’s Disease)</th>
</tr>
</thead>
<tbody>
<tr>
<td>a) Clinical findings</td>
</tr>
<tr>
<td>1. Diffuse swelling of the thyroid gland without any other cause (such as Graves’ disease)</td>
</tr>
<tr>
<td>b) Laboratory findings</td>
</tr>
<tr>
<td>1. Positive for anti-thyroid microsomal antibody or anti-thyroid peroxidase (TPO) antibody</td>
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<tr>
<td>2. Positive for anti-thyroglobulin antibody</td>
</tr>
<tr>
<td>3. Lymphocytic infiltration in the thyroid gland confirmed with cytological examination</td>
</tr>
<tr>
<td>Notes</td>
</tr>
<tr>
<td>1. A patient shall be suspected to have chronic thyroiditis, if he/she has primary hypothyroidism without any other cause to induce hypothyroidism.</td>
</tr>
<tr>
<td>2. A patient shall be suspected to have chronic thyroiditis, if he/she has anti-thyroid microsomal antibody and/or anti-thyroglobulin antibody without thyroid dysfunction nor goiter formation.</td>
</tr>
<tr>
<td>3. If a patient with thyroid neoplasm has anti-thyroid antibody by chance, he or she should be considered to have chronic thyroiditis.</td>
</tr>
<tr>
<td>4. A patient is possible to have chronic thyroiditis if hypechoic and/or inhomogeneous pattern was observed in thyroid ultrasonography.</td>
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</table>

3. Laboratory findings
   (1) Routine examination: Increased ESR, elevation in serum γ-globulin (increased ZTT and TTT values), elevations in CPK and LDH, and high serum cholesterol level are noted.
   (2) Endocrine tests: Free T₃ and free T₄ in serum are lowered and TSH is elevated. Latent hypothyroidism with a normal thyroid hormone level and with elevation in TSH alone is also frequently observed.
   (3) Immunological tests: Patients are positive for anti-thyroid peroxidase (TPO) antibody and for anti-thyroglobulin (Tg) antibody.

4. Essentials of diagnosis
The diagnosis guidelines (the sixth draft) provided by the Japan Thyroid Association are shown in Table 2. Occasionally, patients may present transient symptoms of thyrotoxicosis, which is called painless thyroiditis.

5. Treatment
Replacement therapy with T₄ preparations is
performed in patients with hypothyroidism. It is a common practice to use a low dose level for initiating T4 drug therapy, with subsequent gradual dosage increase until serum TSH level becomes normalized. The therapy should be started at a dose level of 12.5 μg/day especially in elderly patients and severe cases because of the potential risk of angina pectoris or cardiac failure.

**Type 1 Diabetes Mellitus**

1. **Pathophysiology**

The diagnostic criteria and classification of diabetes mellitus into two types depicting disease states—in insulin-dependent diabetes mellitus (IDDM) and non-insulin-dependent diabetes mellitus (NIDDM)—were revised in 1999 to those classifying the disease into four types based on etiology, i.e., types 1 and 2, other particular mechanisms or disorders (inclusive of genetic abnormalities), and gestational diabetes.

Type 1 diabetes denotes diabetes mellitus, which develops due to destruction of pancreatic β cells. The disease under this category is further classified into type 1A, which arises through autoimmune mechanisms, and type 1B, which is of non-autoimmune nature.

Type 1A disease of autoimmune etiology includes the slow-progressing insulin-dependent diabetes mellitus (SPIDDM) besides the rapid-onset type, which is typical of conventional IDDM. SPIDDM is a disease form that presents clinical features close to type 2 diabetes mellitus but progresses over several years with depression of pancreatic β cell function and ultimately into an insulin-dependent status. In both these forms of type 1A, the anti-islet autoantibody (to be described below) is detected. The anti-islet autoantibody is not demonstrated in cases of type 1B disease.

Recently, attention has been focused on the presence of fulminant type 1 diabetes mellitus in which ketoacidosis develops in a period of several days (mean: 4 days), occasionally taking a fatal clinical course.

2. **Clinical features and physical findings**

There are no symptoms/findings specific to type 1 diabetes mellitus. Most patients are non-obese, with more severe symptoms of weight loss, polyuria and thirst due to marked hyperglycemia, and are prone to diabetic coma. In fulminant type 1 diabetes mellitus, about 70% of patients develop common cold-like symptoms such as upper abdominal pain, fever, and headache before the onset of diabetes mellitus.

3. **Laboratory findings**

(1) **Routine examination**: A diagnosis of diabetes mellitus can be established according to the diagnostic criteria for diabetes mellitus. HbA1c is usually elevated but this parameter remains at normal to a slight elevation in cases of the fulminant form of type 1B disease. Exocrine pancreatic enzymes such as elastase I and amylase are elevated in the fulminant form. Acidosis is often present among cases of type 1 disease other than SPIDDM.

(2) **Endocrine tests**: The fasting serum C peptide level (<0.5 ng/ml) and urinary C peptide output (<10 μg/day) are lowered due to depressed insulin secretory function. These are not the case with SPIDDM.

(3) **Immunological tests**: Patients with type 1A disease are positive for anti-glutamic acid decarboxylase (GAD) antibody being anti-islet autoantibody, islet cell antibody (ICA), anti-insulin autoantibody (IAA), and IA-2 antibody. Patients with the fulminant form of type 1 diabetes are negative for these autoantibodies. Of human leukocyte antigens, patients often possess HLA-DR4 or -DR9 and are negative for HLA-DR2.

4. **Essentials of diagnosis**

Anti-GAD antibody can be measured routinely and must be determined positively when type 1 diabetes mellitus is suspected. In the fulminant form, common cold-like symptoms frequently precede the onset of the disease,
so urine tests for glucose (and ketones) are essential in patients with colds complaining of lassitude.

5. Treatment

Usually, an intensive insulin therapy regimen consisting of a dose of a regular (or rapid-acting) insulin is undertaken before every meal and a dose of an intermediate-acting (or long-acting) insulin at bedtime. If the blood glucose level is still poorly controlled with this regimen, then continuous subcutaneous insulin infusion (CSII) is performed. It has been shown that low-dose insulin provides a protective effect for pancreatic β cells, and replacement with insulin therapy is required in patients with SPIDDM receiving sulfonylureas.

Addison’s Disease

1. Pathophysiology

Addison’s disease is caused by destruction of the adrenal cortices resulting in chronic adrenocortical insufficiency. Leading causes are autoimmune destruction, termed idiopathic, and tuberculosis. In the idiopathic entity, the disease may present polyglandular autoimmune syndrome involving complications by other organ-specific autoimmune disorders (i.e., type 1 diabetes mellitus, Hashimoto’s disease, idiopathic hypoparathyroidism, gonadal hypofunction, mucocutaneous candidiasis, and pernicious anemia). These are classified into type I caused by juvenile-onset autoimmune regulator (AIRE) gene abnormality, type II, being an adult-onset disease without associated non-endocrine disorder, and type III, which does not involve Addison’s disease.4)

2. Clinical features and physical findings

Hyperpigmentation due to increased secretion of ACTH is a characteristic clinical feature. Aldosterone-cortisol-adrenal androgen deficit symptoms are also noted.

3. Laboratory findings

(1) Routine examination: Hypoglycemia, hyponatremia, hyperkalemia, and peripheral blood eosinophilia are present.

(2) Endocrine tests: Diagnostic findings include elevated plasma ACTH, low plasma and urine cortisol levels, low plasma aldosterone level, low plasma DHEA-S value, decrease in urinary 17-OHCS/17-KS, and no or low plasma cortisol in the rapid ACTH test.

(3) Immunological tests: Autoantibodies recognizing steroid-synthesizing enzymes are detected but these laboratory tests have not been generally adopted to date.

4. Essentials of diagnosis

When there are diverse nonspecific symptoms, the disease must be deduced from skin pigmentation and routine laboratory test data. Caution must be exercised because if the disease is left undiagnosed and without adequate steroid substitution therapy, some types of stress may precipitate adrenal crisis (acute adrenal insufficiency) with a fatal outcome.

5. Treatment

Replacement therapy with hydrocortisone at 20mg/day is a common practice. A divided dose in the morning may be greater than the one given in the early evening to be in harmony with circadian rhythm in cortisol secretion. The dose of hydrocortisone should be raised 2- to 3-fold the usual dose (40–60mg/day) in case of common cold with pyrexia or other infections, trauma, or surgery.

Conclusions

Endocrine diseases in which autoimmune mechanisms are considered to be involved, besides the four above-mentioned diseases, include lymphocytic adenohypophysitis, lymphocytic infundibuloneurohypophysitis, and idiopathic hypoparathyroidism. Autoimmune endocrine disorders are most frequent among various autoimmune diseases, so it is of importance to always keep this fact in mind in daily
clinical practice to achieve diagnosis and treatment in such cases.

REFERENCES


