ORGAN SPECIFIC AUTOIMMUNE DISEASES

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Course DL-992
1.0 CE/Contact Hour
Level: Intermediate

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ORGAN SPECIFIC AUTOIMMUNE DISEASES

OBJECTIVES:
Upon completion of this course, the participant will be able to:
1. Compare hypothyroidism and hyperthyroidism and discuss the two related autoimmune diseases.
2. Identify and describe the autoantibodies associated with each autoimmune disease discussed.
3. Describe Autoimmune Polyglandular Syndromes 1 and 2.
4. Identify and discuss the non-HLA genes that contribute to autoimmune diseases.
5. Discuss the development of Pernicious Anemia in Autoimmune Polyglandular Syndromes

Autoimmune Diseases
Autoimmune diseases are generally divided into two categories: organ-specific and systemic. In systemic autoimmune diseases such as systemic lupus erythematosus (SLE), scleroderma, and rheumatoid arthritis (RA), an immune response is directed against one or several self antigens present throughout the body. Organ-specific autoimmune disorders usually target an antigen(s) present on a single organ or tissue and an immune response is limited to that specific organ. Within this group, the endocrine system appears to be a common target for autoimmune disease and will be the primary focus of this article. (Table1)

Development of Organ-Specific Autoimmune Diseases
Prevention of the development of lymphocytes that are capable of mounting an immune response to autoantigens, and thus the development of autoimmunity, is critical to the establishment of immune tolerance to self. During the normal maturation process of T cells in the thymus and B cells in the bone marrow, the induction of central tolerance eliminates those cells that have a strong reactivity against self antigens. If any of these B or T lymphocytes escape central tolerance, peripheral tolerance throughout the body can eliminate the autoreactive cells by apoptosis or by rendering them anergic (unresponsive). Other regulatory mechanisms include a subset of T cells called T regulatory cells (Tregs) that are generated in the thymus and function in the periphery. These cells have the ability to modulate an immune response including downregulation of one that is autoimmune in nature. Various subsets of Tregs exist and can be differentiated by their surface markers and inhibitory cytokines secreted. For example, CD4+CD25+ Tregs are dependent on interleukin-2 (IL-2) for survival and secrete the cytokines, interleukin-10 (IL-10) or transforming growth factor-beta (TGF-β). These cells can suppress the activation and proliferation of autoreactive lymphocytes by cell to cell contact or through the elaboration of IL-10 or TGF-β.

All autoimmune diseases are chronic disorders that develop over a period of years. Autoantibodies appear in most of these disorders long before the appearance of clinical manifestations. The break in self tolerance is extremely complex and is believed to be multifactorial. Genetic susceptibility, environmental triggers and a defective immune regulatory system seem to play the largest role in the loss of self tolerance. Genetic factors determining susceptibility to autoimmune diseases involve multiple genes (polygenic). The
primary genes linked to autoimmunity are those of the major histocompatibility complex (MHC) in humans, referred to as Human Leukocyte Antigens (HLA). The purpose of the MHC is to present antigens in the context of Class I or Class II HLA molecules to T cells for the development of cellular and humoral immunity. Familial clustering of autoimmune diseases is very common. The inheritance of specific MHC alleles provides a foundation whereupon autoimmunity can develop. However, it is becoming evident that a number of non-HMC susceptibility genes play a role in the predisposition to many autoimmune diseases including the *AIRE* *CTLA-4* and *PTNP22* genes that will subsequently be discussed.

<table>
<thead>
<tr>
<th>Disease</th>
<th>Genetics</th>
<th>Autoantibodies</th>
<th>Gland</th>
</tr>
</thead>
<tbody>
<tr>
<td>Graves disease</td>
<td>HLA DR-4 and DR-5 HLA-DQA1*0501</td>
<td>Thyroid stimulating immunoglobulin (TSI), anti-thyroglobulin (ATG), thyroid peroxidase (TPO)</td>
<td>Thyroid</td>
</tr>
<tr>
<td>Hashimoto Thyroiditis</td>
<td>HLA-DR-4 and DR-5</td>
<td>TPO, ATG, TBII</td>
<td>Thyroid</td>
</tr>
<tr>
<td>Type 1 Diabetes</td>
<td>HLA-DQB1<em>0302, DQA1</em>0301-DQB<em>0302 on HLA-DR4 and DQA</em>0501-DQB*0201 on HLA-DR3</td>
<td>Glutamic acid decarboxylase (GAD), insulin, islet cell antibody-512 (ICA-512)</td>
<td>Pancreas</td>
</tr>
<tr>
<td>Celiac Disease</td>
<td>HLA DQ-2 and DQ-8</td>
<td>Transglutimase-2 (TGs)</td>
<td>Small Intestine</td>
</tr>
<tr>
<td>Addison Disease</td>
<td></td>
<td>21-hydroxylase (21-OH), 17-hydroxylase (17-OH), P450 side chain cleavage enzyme</td>
<td>Adrenal cortex</td>
</tr>
</tbody>
</table>

**Thyroid Diseases**

Thyroid abnormalities are relatively common. Aberrant thyroid functioning due to an autoimmune disorder can affect up to 10% of the population (1).

**Graves Disease**

Graves disease is a well-characterized autoimmune disorder and the most common cause of hyperthyroidism. Due to continual stimulation, the thyroid gland becomes enlarged as a result of widespread hypertrophy and hyperplasia. The gland takes up increased amounts of iodine and secretes greater than normal quantities of triiodothyronine (T3) and thyroxine (T4). A number of autoantibodies play a major role in the development of the disease including: thyroid stimulating immunoglobulin (TSI), anti-thyroglobulin (ATG), and anti-thyroid peroxidase (TPO). TSI, a primary cause of Graves disease, is an autoantibody that binds to the thyroid stimulating hormone (TSH) receptor present on the surface of the thyroid. TSI is capable of activating the thyroid in the same manner as TSH. Because of continual stimulation by TSI binding to the TSH receptor, the thyroid gland becomes enlarged due to widespread hypertrophy and hyperplasia. The end result is an increased uptake of iodine and secretion of greater than normal quantities of triiodothyronine (T3) and thyroxine (T4). Consequently, the metabolic activity of most tissues throughout the body...
will increase due to an increased secretion of T3 and T4. Disease onset is usually between the ages of 20 to 40 years old. Some of the clinical manifestations include weight loss, heat intolerance, warm moist skin, nervousness, increased sweating, and insomnia. A characteristic finding in Graves disease is exophthalmos, a protrusion of the eyeballs. The protrusion appears to be due to a marked infiltration of T lymphocytes. Recently, it has been demonstrated that fibroblasts within the infiltrate express the TSH receptor and become a target of a T cell autoimmune response. If the exophthalmos becomes severe, vision can be damaged, and dryness and infections of the eye occur.

Genetic predisposition, including an increased incidence among family members and a strong concordance rate in identical twins, is evident as is a female predominance in Graves disease. HLA Class II genes DR4 and DR5 have been linked and there is a strong association of HLA-DQA1*0501 in Caucasians with Graves disease. Mutations in the CTLA-4 gene have been reported.

It is important to keep in mind that the diagnostic laboratory approach to autoimmune endocrinopathies is two-fold. One is assessment of the hormone levels of the gland and end organ function. The other is determination of autoantibodies present to the specific gland in question. Only a trained MD endocrinologist can make a diagnosis. Initial laboratory findings include an increased level of free T4 and a decreased TSH concentration. Further determination of the presence of autoantibodies (TSI, TPO, and ATG) would contribute to the laboratory diagnosis of Graves disease. TSI autoantibodies are evident in most cases of Graves disease.

**Hashimoto Thyroiditis**

In primary hypothyroidism, decreased levels of T3 and T4 are formed due to an abnormality of the thyroid gland itself. Most cases of primary hypothyroidism are caused by an autoimmune disease process. Hashimoto thyroiditis is a slowly progressing destruction of the thyroid gland by an infiltrate of autoreactive T cells and anti-thyroid antibodies. Both immune mechanisms destroy the thyroid epithelial cells. Autoantibodies to thyroid peroxidase (TPO) are present in greater than 99% of patients diagnosed with the disease. Within the thyroid gland, TPO is an enzyme that is essential for the addition of iodine onto tyrosine residues on thyroglobulin (precursor of thyroxine) for the production of (T4) and (T3). Autoantibodies to thyroglobulin (ATG) and thyrotropin-binding inhibitory immunoglobulin (TBII) can also be present. TBII binds to the TSH receptor on the surface of the thyroid gland thereby inhibiting TSH from binding.

Disease onset is usually between 46-65 years of age with a female predominance. Clinical manifestations are mostly the opposite of Graves disease and include fatigue, somnolence, weight gain, depression, and decreased cardiac output. In severe cases with almost a total lack of thyroid hormones, myxedema can develop. Myxedema is an edematous appearance of the face and a characteristic bagginess under the eyes. There is an association between HLA-DR4 and DR5 with an increased prevalence of Hashimoto’s. Interestingly, in relatives of patients with Graves or Hashimoto thyroiditis, half of the siblings and parents had thyroid autoantibodies but no evidence of clinical disease.

Initial laboratory findings would include an increased TSH and decreased free T4. Further identification of autoantibodies to TPO, ATG, or TBII would contribute to the lab diagnosis.

**Carbohydrate Metabolism**

**Type 1 Diabetes**

Type I diabetes accounts for 5-10% of all patients with diabetes mellitus. The vast majority of diabetics are classified as Type II. Type II is an insulin resistance disorder and is
becoming a worldwide epidemic that is largely connected to the explosion of obesity in adults and children.

Type I diabetes is characterized by a total deficiency of insulin. Recently, it has been proposed that the disorder be divided into Type IA and Type IB. Type IB represents a non-immune loss of beta cells in the pancreas, whereas Type IA is considered an organ-specific autoimmune disease. The disease most commonly develops in genetically susceptible children, frequently with a fairly abrupt onset following a trigger (viral or environmental). There is an immune-mediated destruction of the pancreatic beta cells in the islets of Langerhans that produce the insulin. Autoantibodies and autoreactive T cells react against beta cell antigens producing a macrophage, cytokine, and CD8+ mediated destruction of the cells. A progressive loss of insulin release develops and eventually manifests itself as hyperglycemia. Classic symptoms of diabetes such as hyperglycemia, polydipsia, and polyuria, and possibly ketoacidosis will occur. Late complications that develop over time are microvascular disease, retinopathy, nephropathy, and neuropathy.

A strong genetic susceptibility plays an important role in the development of this disease. HLA class II genes from the DR and DQ alleles, including DQB1*0302 and a combination of DQA1*0301-DQB*0302 on HLA-DR4 and DQA*0501-DQB*0201 on the HLA-DR3, produces a synergistically increased risk. There is a familial clustering among first-degree relatives and the highest risk is found in monozygotic (identical) twins.

Autoantibodies are present before the clinical onset of hyperglycemia. Some of the beta cell antigens for which antibodies have been described are glutamic acid decarboxylase (GAD), insulin (IAA), and islet cell (ICA-512), a member of the protein tyrosine phosphatase (PTP). By the time hyperglycemia appears, one or more of these autoantibodies are present in greater than 85% of individuals. Detection of these antibodies contributes to the diagnosis of Type I diabetes and allows for identification of at-risk individuals, especially first-degree relatives. The American Diabetic Association recommends that a fasting and/or 2-hour glucose determination should be used for diagnosis. Fasting glucose levels and Hgb A1c are commonly used for glucose monitoring during the disease process and testing for nephropathy-related microalbuminuria is necessary as the disease ensues.

**Celiac Disease**

Celiac disease, also known as gluten-sensitive enteropathy, is a common non-allergic inflammatory disorder of the small intestine. It was an unrecognized autoimmune disease until the transglutaminase-2 autoantibody was demonstrated. The disease develops in genetically susceptible individuals who ingest wheat gluten (composed of gliadin and glutein) and related proteins occurring in barley and rye. A loss of tolerance to gluten leads to the development of an autoreactive T cell-mediated chronic infiltration of the mucosa of the small intestine. The distinct lesions of the mucosa include villous atrophy and crypt hyperplasia. The clinical manifestations of diarrhea, weight loss, and poor nutrient absorption appear. A chronic, blistering skin lesion called dermatitis herpetiformis occurs in some patients with celiac disease. HLA class 2 genes, specifically HLA-DQ2 and DQ8 are strongly linked to susceptibility and present in greater than 97% of individuals with the disease. The concordance rate among identical twins is a striking 75%.

Celiac disease is associated with antibodies to endomysial tissue (loose connective tissue around smooth muscle fibers). Demonstration of these antibodies in patients’ serum was done by indirect immunofluorescence on endomysial tissue from a monkey. In the late 1990s, the transglutaminase-2 enzyme (TG2) was recognized as the specific antigen for the anti-endomysial autoantibody. Transglutaminase-2 is a deaminating enzyme that deaminates (hydrolysis of amide group) on gliadin and forms a TG2-deaminated gliadin complex on the
protein. An autoantibody to this complex is produced that can be easily detected with EIA using recombinant human TG2.

Laboratory testing usually begins with the demonstration of the anti-TG2. This is a highly specific marker for celiac disease and is the prerequisite for performing the small intestine biopsy, which is considered the gold standard for diagnosis.

A strict gluten-free (barley, wheat, and rye) diet is the only treatment for the disease.

**Addison Disease**

Addison disease, a rare disorder, is a primary adrenal gland insufficiency that is the result of a progressive autoimmune destruction of the cortex layer of the adrenal gland including the steroidogenic cells that generate three classes of hormones. The steroid hormones produced by the cortex are glucocorticoids (primarily cortisol), mineralocorticoids (aldosterone) and sex hormones (androgens and estrogens). The steroid cell autoantibodies found to react with all three layers of the adrenal cortex are directed against P450 steroidogenic enzymes including 21-hydroxylase (21-OH) and 17-hydroxylase (17-OH) and a P450 side chain cleavage enzyme (P450sc).

More than 60% of all primary adrenal gland insufficiencies are due to Addison disease. Addison disease appears between the ages of 30-60 years. Patients experience severe fatigue, weight loss, muscle weakness, a salt craving, and a darkening (bronzng) of the skin on the face, neck, and back of the hands.

Initial laboratory results showing an increased level of ACTH and decreased cortisol would point to a primary adrenal insufficiency. Autoantibody testing would contribute to the diagnosis.

Addison disease is more commonly associated with other autoimmune disorders. In 1980, Neufeld, et al. (3) divided the clusters of autoimmune polyglandular insufficiencies into two separate disorders called Autoimmune Polyglandular Syndrome 1 and 2 (APS-1, APS-2). Type 1A diabetes, Graves disease, Hashimoto thyroiditis, celiac disease, pernicious anemia, and/or hypoparathyroidism are typically manifested in each syndrome (Table 2). The age of onset and modes of inheritance help to differentiate the two syndromes.

<table>
<thead>
<tr>
<th></th>
<th>APS-1</th>
<th>APS-2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age of onset</td>
<td>childhood</td>
<td>adult</td>
</tr>
<tr>
<td>Genetics</td>
<td>AIRE gene</td>
<td>CTLA-4, PTPN-22, HLA-DR 3 and DR4</td>
</tr>
<tr>
<td>Type 1A diabetes</td>
<td>+/-</td>
<td>++</td>
</tr>
<tr>
<td>Addison disease</td>
<td>+</td>
<td>+/-</td>
</tr>
<tr>
<td>Graves disease</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Hashimoto thyroiditis</td>
<td>+/-</td>
<td>++</td>
</tr>
<tr>
<td>Celiac disease</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Pernicious anemia</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Hypoparathyroidism</td>
<td>++</td>
<td>+/-</td>
</tr>
<tr>
<td>Other disorders commonly present</td>
<td>Mucocutaneous candidiasis</td>
<td>Autoimmune atrophic gastritis, vitiligo, alopecia, hypogonadism</td>
</tr>
</tbody>
</table>

Eisenbarth and Gottlieb (4) stated that there is probably no one shared antigen that leads to the involvement of multiple glands, but rather several self-antigens that become
likely targets when tolerance is broken. As stated earlier, the break in tolerance is usually multifactorial and may also involve environmental triggers such as infections and inflammation occurring in genetically-predisposed people.

**APS-1** (Autoimmune polyendocrine syndrome type 1)

APS-1 is a rare disorder that arises in early childhood or adolescence. The syndrome is caused by mutations in the candidate susceptibility gene, *AIRE* (autoimmune regulator). *AIRE* codes for a transcription factor present in the thymus that is essential for the deletion of T cells that react with autoantigens. If the AIRE protein is defective, central tolerance will not be established to a number of autoantigens and autoreactive T cells will escape from the thymus. A mucocutaneous candidiasis is typically present in APS-1 along with hypoparathyroidism and Addison disease. The presence of two of the three components is necessary to make a proper diagnosis. The recurring candidiasis, found in 50 to 100% of the patients, affects the skin, nails, and oral mucosa. It is usually the first disorder to appear, primarily in infants and children before the age of 5 years. There is no evidence that the candidiasis is due to a T cell deficiency and seems to be an integral part of APS-1. Hypoparathyroidism, usually the first endocrine disorder to arise, develops before the child is 10 years old. Severe hypocalcemia can result. The autoantigen has not been fully characterized but recently NACHT-leucine-rich-repeat protein (NALP5) has been identified as the probable autoantigen in the cytoplasm of parathyroid chief cells (5). Addison disease becomes evident between the ages of 10-30 years. Other endocrinopathies, as listed in Table 2, can also be present. There is a lymphocyte infiltrate and a T-cell mediated destruction of all the target glands involved.

Initial laboratory tests would include specific hormone levels, end-organ function, and determination of autoantibodies to the endocrine glands involved.

**APS-2** (Autoimmune polyendocrine syndrome type 2)

Although more common than APS-1, APS-2 is also a rare disorder. It arises in early adulthood, with an increased prevalence in women. Addison disease, along with the development of a thyroid disorder or Type I diabetes are the most frequent combinations. However, diagnosis can be difficult because polyglandular involvement may not become evident for years.

The cytotoxic T lymphocyte gene (CTLA-4) and the protein tyrosine non-receptor type 22 (PTPN22) are strongly linked to an increased susceptibility to the disease. The CTLA-4 gene codes for a protein receptor on CTL that can inhibit T cell responses. A mutation of the gene produces a defective receptor that is unable to shut off T cells including autoreactive T cells. The PTPN22 gene codes for a protein tyrosine phosphatase involved in the down regulation of T cells through T-cell receptor signaling. HLA class II genes DR3 and DR4 are also linked to the disease.

As with APS-1, determination of hormone levels, end organ function, and autoantibodies to the specific endocrine gland involved would be included in the first laboratory tests performed.

**Pernicious Anemia**

In APS-1 and APS-2 a chronic atrophic gastritis characterized by an autoimmune destruction of parietal cells in the gastric mucosa can appear. A T cell infiltration and autoantibodies to the gastric proton pump enzyme, H+/K+ ATPase, lead to decreased secretion of H+ ions, gastric mucosal atrophy, and eventual loss of parietal cells. Parietal cells also secrete intrinsic factor, which is needed for the absorption of Vitamin B12. If parietal cell loss is severe enough, little or no intrinsic factor (IF) is secreted, and B12 absorption will not occur. Subsequently, pernicious anemia can develop with the presence
of autoantibodies to IF. Type 1 intrinsic factor antibodies inhibit the formation of an IF-Vitamin B12 complex and Type 2 autoantibodies prohibit the binding of the B12-IF complex to receptors on the ileum where absorption of Vitamin B12 occurs. A deficiency of Vitamin B12 will lead to the development of a megaloblastic anemia.

**Conclusion**

Our knowledge of the complex family of autoimmune endocrinopathies has grown in the last few decades. Polygenic predisposition is apparent in most of these autoimmune diseases. HLA genotyping can detect the different MHC alleles that appear repeatedly in these disorders. The recent association of non-HLA susceptibility genes (such as AIRE, PTPN22, and CTLA-4) with many of these autoimmune endocrinopathies has contributed to understanding the major role that regulatory mechanisms play in preventing these disorders. Insight into the ability of CD4+CD25+ Treg cells to suppress autoreactive cells is essential. However, the clinical laboratory detection of organ-specific autoantibodies in high risk (genetically predisposed) individuals remains central to the diagnosis of current and/or future autoimmune disease and can be utilized for screening first degree relatives. Autoimmune Polyglandular Syndromes demonstrate the tendency for these endocrinopathies to occur in clusters especially in families.

**References**

Review Questions
Course #DL-992

Choose the one best answer.

1. In Graves disease, the primary autoantibody found is:
   a. TSI
   b. glutamic acid decarboxylase
   c. anti-thyroglobulin
   d. transglutimase-2

2. The obesity epidemic has led to:
   a. increased incidence of Type IA diabetes
   b. increased incidence of Hashimoto thyroiditis
   c. growing number of Type II diabetes cases
   d. emergence of Addison disease.

3. The AIRE gene codes for a protein that:
   a. stimulates the TSH receptor on the thyroid gland.
   b. is essential for the elimination of autoreactive T cells in the thymus.
   c. is present in all autoantibodies in Autoimmune Polyglandular Syndrome I.
   d. is present on the gastric proton pump.

4. After an initial laboratory evaluation of Graves disease, you would expect:
   a. an increased number of Treg cells.
   b. an increased TSH and decreased free T4.
   c. a decreased TSH and increased free T4.
   d. the appearance of GAD autoantibodies.

5. In Type 1A diabetes, autoantibodies commonly found react with:
   a. GAD
   b. TG-2
   c. TSI
   d. parietal cells

6. The age of onset for APS I is:
   a. primarily in children.
   b. usually in young adults.
   c. only in the elderly.
   d. only in middle-aged adults.

7. Exophthalmos may appear in:
   a. Addison disease
   b. Hashimoto thyroiditis
   c. Graves disease
   d. pernicious anemia
8. The first disorder to manifest itself in APS 1 is usually:
   a. Addison disease
   b. mucocutaneous candidiasis
   c. hypoparathyroidism
   d. pernicious anemia

9. The enzyme, H+K+ ATPase, is essential to:
   a. functioning of CTLA-4 protein.
   b. establishment of central tolerance.
   c. operation of the gastric proton pump.
   d. formation of TG2 autoantibodies.

10. The autoantibodies formed in Addison disease are to the:
    a. adrenal medulla steroid layer.
    b. ACTH binding site on the adrenal gland.
    c. cortisol binding site.
    d. adrenal cortex.