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Type 1 Diabetes: Molecular, Cellular and Clinical Immunology

## Chapter 8

### Autoimmune Polyendocrine Syndromes

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Examples of Polyendocrine Autoimmune Syndromes include:

1. Autoimmune polyglandular syndrome type I(1) (APS-I, APECED: autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy, MIM number 240300[Online **Mendelian Inheritance in Man**])
2. The autoimmune polyendocrine syndrome type II (APS-II, Schmidt's syndrome MIM number 269200) (2-4)
3. IPEX (Immunodysregulation, Polyendocrinopathy and Enteropathy, X-Linked), also termed XLAAD X-Linked Autoimmunity Allergic-Dysregulation Syndrome or XPID X-Linked Polyendocrinopathy, Immune Dysfunction and Diarrhea, MIM number 304790 and 300292)
4. Non-organ-specific autoimmunity (e.g., lupus erythematosus) associated with anti-insulin receptor antibodies(5;6)
5. Thymic tumors with associated endocrinopathy(7-9)
6. Graves' disease associated with insulin autoimmune syndrome(10;11)
7. POEMS syndrome (Polyneuropathy, Organomegaly, Endocrinopathy, M-spike, Skin changes MIM 192240)(12;13)
8. Congenital rubella infection followed by development of thyroiditis and type 1 diabetes +/- other autoimmune disorders.

The diverse names given to the polyendocrine autoimmune syndromes reflect the large number of studies and case reports concerning these patients and heterogeneity in their clinical presentation. The two major autoimmune endocrine syndromes, APS-I and APS-II, both have Addison's disease as a prominent component. The major autoimmune polyendocrine syndromes have a strong genetic component with the type II syndrome occurring in multiple generations and the type I syndrome in siblings.

The major illnesses associated with both APS-I and APS-II are listed in Table 8.1 and differences between the syndromes are outlined in Table 8.2. Knowledge of disease associations and inheritance pattern facilitates early diagnosis of component illnesses. Patients with APS-I and APS-II develop multiple diseases over time and approximately one out of seven relatives of such patients have an undiagnosed autoimmune disorder (most often hypothyroidism for the type II syndrome)(14). The individual polyendocrine autoimmune syndromes, their immunogenetics, pathogenesis and selected aspects of therapy will be reviewed in this chapter.

#### Autoimmune Polyendocrine Syndrome Type 1 (APS-I)

Major components of the APS-I autoimmune polyendocrine syndrome (also termed APECED autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (15-18) include hypoparathyroidism, mucocutaneous candidiasis, Addison's disease, and hepatitis(1) (Table 8.1). Other diseases associated with APS-I include primary hypothyroidism, a malabsorption syndrome(19), vitiligo, pernicious anemia, type 1 diabetes, alopecia(20), primary hypogonadism(21), cutaneous abnormalities(1), and pure red cell aplasia(22;23). Of note, in a study by Friedman and coworkers(24) four of nine patients with APS-I were asplenic.

An unusual manifestation of the disorder is the development of refractory diarrhea/obstipation that may be related to "autoimmune" destruction of enterochromaffin or enterochromaffin like cells, associated with specific autoantibodies(25;26). Intestinal manifestations associated with APS-1 include both obstipation and severe malabsorption. Kampe and coworkers have reported that antibodies to Histidine Decarboxylase are associated with a history of intestinal dysfunction(27) and multiple reports document loss of gastric and intestinal endocrine cells (27). A number of rare manifestations of APS-1 are particularly troublesome. A number of patients have been reported with severe lung disease, often leading to death. The lung disorders have been described as autoimmune bronchiolitis, bronchiolitis obliterans organizing pneumonia, chronic hypersensitivity pneumonitis(15;28;29). Patients are at risk for developing esophageal and oral cancers presumably related to chronic candida infections.

The onset of the disease is usually in infancy. Chronic mucocutaneous candidiasis is often the first disease detected, followed by the later development of adrenal insufficiency. The etiology of the mucocutaneous candidiasis in the absence of systemic candidiasis in the APS-I syndrome has been related to anti-cytokine autoantibodies (anti-IL17A, IL17F and IL22) related to Th17 T cells (30) and depressed production of IL17F and IL22 by peripheral blood mononuclear cells. (31) Decades may elapse between the diagnosis of one disease and another in the same individual and the order of disease appearance is not invariant.

The syndrome is almost always inherited in an autosomal recessive manner linked to mutation of the AIRE gene (32) (AIRE: Autoimmune Regulator gene) on chromosome 21(33); (34). The immunodeficiency underlying disease susceptibility is secondary to autosomal recessive mutations of this transcription factor(35). Studies of autoimmune disorders including Addison's disease, but in patients without the APS-I syndrome, indicate that AIRE mutations are not involved in these more common diseases(138). In contrast, there is evidence that in rare diseases with abnormal T cell development (e.g. T-B-SCID, Omenn syndrome (OM1M 603 554) there is abnormal thymocyte epithelial interaction and deficient thymic AIRE and lack of expression of AIRE dependent "peripheral" molecules such as insulin (36). There is no association of the overall syndrome with specific HLA class II alleles, though there is increasing evidence that specific HLA alleles determine the probability of the specific organs targeted by an individual(37). In particular DQB1\*0602 appears to protect from type 1 diabetes and DR3 increase the risk of type 1 diabetes in patients with the APS-I syndrome, as it does for the common variety of type 1A diabetes.

The knockout of the AIRE gene by two groups in mouse models indicates that mice lacking AIRE develop widespread but clinically mild autoimmunity. In particular autoantibodies reacting with multiple organs and T cell infiltrates of multiple organs are observed (38;39). A potentially very important finding is a decrease in expression within the thymus of what have been termed "peripheral antigens"(39). Hanahan and coworkers coined the term peripheral antigen expressing cells, for cells within the thymus that express "Peripheral" molecules such as insulin(40).

It is now apparent that multiple such molecules are expressed within subsets of cells within the thymus, with relatively few cells expressing any given molecule, but many thymic cells expressing multiple different "peripheral antigens" (41-46). It is likely that the cell types expressing these molecules are both thymic epithelial cells and cells of the macrophage, dendritic lineage. For instance, with loss of AIRE gene function, insulin message(47) disappears from the thymus(39). Altering insulin expression in the thymus (e.g. insulin 2 gene knockout in NOD mouse) can have a dramatic effect on development of autoimmunity (48;48-52) and the protection afforded by the insulin gene 5'VNTR in man is associated with greater thymic insulin message (42;53). Thus an attractive hypothesis is that mutations of the AIRE gene (e.g. APS-I syndrome) cause loss of peripheral antigen expression in the thymus(54) and probably decreased deletion of autoreactive T lymphocytes that target such

peripheral antigens. Of note, peripheral antigens are also expressed within other lymphoid organs(55).

A single family has been described with an autosomal dominant form of the disease (thyroiditis prominent in this family)(56), and of note Anderson and colleagues have produced an animal model of the dominant mutation found in this family(57). The specific knockin mutation (G228W) of AIRE functioned as a dominant negative recruiting wild type AIRE away from active sites of transcription, decreased thymic messenger RNA for multiple AIRE regulated thymic genes, and develop lachrymal, salivary, and thyroid infiltrates and progressive peripheral neuropathy. Of note with the mutation on an NOD background diabetes is not accelerated and the mice do not develop pancreatitis (found in NOD mice with homozygous knockouts of AIRE). AIRE presumably acts by altering transcription of multiple thymic genes and has important interaction with chromatin(57).

**Table 8.1. Disease Associations**

<i>Autoimmune Polyendocrine Syndrome Type 1</i>		<i>Autoimmune Polyendocrine Syndrome Type II</i>	
	<i>Incidence</i>		<i>Incidence</i>
Mucocutaneous candidiasis(1;58)	C*	Addison's disease(59)	C
Addison's disease(1;58)	C		
Hypoparathyroidism(58)	C		
Chronic active hepatitis(1;58;60)	C		
Graves' disease	I	Graves' disease	I
Autoimmune thyroiditis(58;61)	I	Autoimmune thyroiditis(62)	C
Pernicious anemia	C	Pernicious anemia(63;64)	C
Vitiligo	C	Vitiligo(63;65-67)	C
Type 1 DM (18%) (1;58)	I	Type 1 DM (50%)	C
Alopecia(20;68;69)	I	Alopecia	I
		Myasthenia gravis(70;71)	I
Malabsorption syndrome(19;58)	I	Celiac disease, Dermatitis herpetiformis(72-74)	C
IgA deficiency	I	IgA deficiency(67)	I
		Serositis(75)	R
Asplenism(24)	C		
Ectodermal dysplasia(1)	C		
Keratitis(76)	C		
Hypogonadism(21;58)	C	Hypogonadism(77)	I
		Stiff-man syndrome(78)	R
		Parkinsons disease	I
Dental enamel and nail dystrophy(1)	C		
		Idiopathic heart block(63)	R
Pure red cell aplasia(22)	R		
		Idiopathic thrombocytopenia(79;80)	I
		Hypophysitis(81;82)	I
R			
Autoimmune Bronchiolitis(83)	R		
Hashimoto/Encephalopathy	R		

\*C=common within syndrome; R=rare; I=intermediate

Patients with APS-1 express autoantibodies reacting with a remarkable diversity of autoantigens, both autoantibodies specifically only detected in APS-1 patients and autoantibodies found in common isolated examples of the autoimmune disorder (e.g. 21-hydroxylase autoantibodies for Addison's disease). Kampe and coworkers have recently described the presence of autoantibodies reacting with NALP5 in approximately 50% of patients with APS-1 and hypoparathyroidism, but not found in patients with isolated hypoparathyroidism(84). The NALP5 gene is specifically expressed in the parathyroid and ovary. Patients without hypoparathyroidism, despite having the APS-1 syndrome lacked NALP5 autoantibodies which were measured with a fluid phase radioassay. Prospective studies are needed to define when autoantibodies to NALP5 appear and whether they disappear following the development of hypoparathyroidism in a subset of patients, thus correlating with lack of the autoantibodies in approximately 50% of the APS-1 patients with hypoparathyroidism. Why NALP5 should be highly expressed in the parathyroid glands and why they are such a prominent target of autoantibodies in this particular syndrome are unknown. The molecule NALP5 (NACHT leucine-rich-repeat protein 5) is a member of a family of molecules important for activating the innate immune system as part of the inflammasome pathway and are potent activators of interleukin 1(85-87). They are involved in processes as diverse as autoinflammatory diseases, the inflammation secondary to the sensing of urate crystals in gout(88), and even (NALP3) the adjuvant effects of alum(89). A polymorphism of NALP1 has been associated with vitiligo(90).

Particular patterns of anti-adrenal autoantibodies are associated with this syndrome (91-93). The presence of anti-adrenal autoantibodies (e.g. 21-hydroxylase) is strongly associated with subsequent development of Addison's disease. In addition, anti-GAD autoantibodies of patients with the APS I syndrome differ from anti-GAD autoantibodies of typical patients with type 1 diabetes in terms of being able to react with GAD on Western blots and inhibit enzymatic activity. A minority (18%) of patients with APS I develop type 1 diabetes(58). Many patients express ICA and anti-GAD autoantibodies ["restricted" ICA (41%)] with relatively little progression to diabetes. Patients expressing multiple anti-islet autoantibodies are at higher risk for progression to diabetes. APS-I patients express additional autoantibodies consistent with widespread loss of tolerance to multiple self antigens(94). A study by Soderbergh and coworkers have analyzed the prevalence of a series of autoantibodies in patients with APS-1(95) with for instance IA-2 autoantibodies highly associated with type 1 diabetes, while GAD autoantibodies were more associated with intestinal dysfunction. Hypogonadism was associated with side-chain cleavage enzyme (SCC) while Addison's disease was associated with both SCC autoantibodies and 21-hydroxylase autoantibodies.

**Table 8.2. Comparison of APS-I and APS-II**

<i>APS-I</i>	<i>APS-II</i>
Onset infancy	Older onset
Siblings affected (autosomal recessive, Chromosome 21, AIRE gene)	Multiple generations
Not HLA associated but specific disease	DR3/DR4 associated
Autoantibodies to Type 1 Interferons and Th17 cytokines (IL17A, IL17F, IL22)	No defined immunodeficiency
Asplenism	No autoantibodies to cytokines
Mucocutaneous candidiasis	

## Diagnosis

The diagnosis of APS-I is usually made with finding 2 or 3 of the following: mucocutaneous candidiasis, hypoparathyroidism and/or adrenal insufficiency (or autoantibodies against CYP450c21, 21 hydroxylase). It has recently been reported that 100% of patients with APS-1 express autoantibodies reacting with interferon-omega and the great majority express autoantibodies reacting with interferon alpha(96;97). We have developed an ELISA format assay utilizing time resolved fluorescence of Europium to detect autoantibodies and can confirm the very high prevalence of anti-interferon autoantibodies in patients with APS-1(97). The autoantibodies are apparently first to develop and remain throughout the disease course, a very remarkable finding. Thus an initial diagnostic screen can be performed for autoantibodies reacting with interferons (a subset of patients with myasthenia gravis and thymoma as well as patients treated with interferons also produce anti-interferon antibodies). Final diagnosis is usually dependent upon direct sequencing, with difficulty arising in defining mutations on both genes in the presence of deletions.

Given that the individual components of disease develop over years to decades, one must be vigilant for other associated autoimmune disorders. Perheentupa recommends that individuals under the age of 30 years with any of the following: chronic or recurring mucocutaneous candidiasis, hypoparathyroidism, adrenal insufficiency, chronic gastrointestinal disease characterized by obstipation, diarrhea or steatorrhea, alopecia, vitiligo, noninfectious hepatitis, keratoconjunctivitis or urticaria-like erythema with fever should be closely evaluated for signs of ectodermal dysplasia and consideration for AIRE gene mutational analysis entertained. If more than one of these components is identified, the individuals should be closely followed for the development of additional disease. Siblings of affected individuals need only have one of the above to warrant more aggressive surveillance (98). Of note, multiple mutations of the AIRE gene have been implicated in the pathogenesis of disease. Therefore, the sensitivity of mutational analysis is dependent upon the number of mutations screened for and the underlying prevalence of the mutations in the population (32).

## Table 8.3

### 6 month evaluation APS–1 Perheentupa

- Physical exam for mucocutaneous candidiasis, tetany, hyperpigmentation or stigmata of hypothyroidism
- Blood work for electrolytes, calcium, phosphorus, magnesium, alkaline phosphatase, HbA1c, ACTH, TSH, renin, CBC with smear for Howell-Jolly bodies and platelet count
- Serum analysis for autoantibodies: 21-hydroxylase (adrenal insufficiency), GAD65 (diabetes mellitus), 17-hydroxylase, CYP450sc (hypogonadism, adrenal insufficiency), tryptophan hydroxylase (intestine chromaffin cell loss), H/K ATPase and Intrinsic factor (pernicious anemia), thyroid peroxidase (hypothyroidism)
- If hypoparathyroid, check calcium and phosphorus every 6 to 8 weeks
- If Howell-Jolly bodies are identified, ultrasound spleen

## Surveillance

Once the diagnosis of APS-I is established, the individuals should be referred to a center with experience following these patients and enrolled in a systematic screening regimen with the goal of identifying developing autoimmune disease prior to significant clinical sequelae are reached. Ideally, these individuals should be evaluated every six months for maintenance of their current endocrine disorders and surveillance for future disorders. Table 8.3 outlines recommended screening tests. Mucocutaneous candidiasis may manifest itself anywhere in the GI tract. Therefore, the organism may be identified from the oral mucosa or stool smears. Individuals with symptoms of dysphasia or chest pain should be evaluated by endoscopy to identify strictures. Of note, sudden hypercalcemia in hypoparathyroid individuals may mark the beginning of adrenal insufficiency and deserves evaluation (99). The gastrointestinal system may be involved Table 8.4 (25;26;98). Symptoms of diarrhea, malabsorption with failure to thrive in children and/or obstipation may be identified. These symptoms maybe due to the underlying endocrine disease (e.g. diarrhea with the hypocalcemia of hypoparathyroidism) or may be a manifestation of a new disorder. Evaluation of these symptoms may require investigation for other autoimmune GI disorders such as pernicious anemia and celiac disease, evaluation for fat malabsorption that may be observed with exocrine pancreatic insufficiency and consideration of an autoantibody to endocrine cells of the GI tract, and close consultation with a gastroenterologist. Monitoring for asplenism which can develop over time is also important (100).Table 8.5 lists conditions that have been rarely identified in individuals with APS-I (98).

## Table 8.4: Gastrointestinal involvement– APS-I

- Pernicious anemia – most common GI problem
- Diarrhea secondary to hypocalcemia
- Autoimmune attack of endocrine cells in GI tract resulting in malabsorption, diarrhea, or constipation
- Secretory failure of exocrine pancreas resulting in fat malabsorption
- Celiac disease
- Autoimmune hepatitis

## Table 8.5

### Unusual manifestations of disease – APS-I

- Pituitary hormone deficiency (diabetes insipidus, growth hormone, gonadotropic, ACTH deficiency)
- Autoimmune disease (hyperthyroidism, rheumatoid arthritis, Sjogren's syndrome, periodic fever with rash, antisperm autoimmunity, hemolytic anemia)
- Hemetologic manifestations (pure red cell aplasia, autoimmune hemolytic anemia, splenomegaly and pancytopenia, Ig A deficiency)
- Ocular disease (iridocyclitis, optic nerve atrophy, retinal degeneration)
- Other organ system involvement (nephritis, cholelithiasis, Bronchiolitis obliterans organizing pneumonia, Lymphocytic myocarditis)
- Hypokalemia with or without hypertension
- Metaphyseal dysostosis

#### **Treatment**

Patient education is a critical element of a successful treatment plan. These individuals often suffer from multiple endocrinopathies and are at risk for the development of further disease. They must be aware of signs and symptoms of new disease and carry with them information about their disease, should emergency care be needed (98). Treatment will in part depend upon the autoimmune disorder identified (table 8.6). Of note, aggressive therapy of oral candidiasis (101) is indicated in an effort to prevent the late complication of epithelial carcinoma. Any lesions that are suspicious should be biopsied (98). Keratoconjunctivitis must also be aggressively treated to prevent a decrease in visual acuity (76). Asplenic individuals are also at risk for fulminant sepsis (102). They must be aggressively identified as described and immunized for hemophilus influenza, meningococcus and pneumococcus. If the individual mounts an inadequate antibody response, daily antibiotics are indicated, as prophylaxis and emergency care should be sought for fever (table 8.6).

## Table 8.6 :Treatment – APS-I

- Treat individual endocrine disorders as identified
- In general, no live virus vaccines
- Asplenic individuals should be immunized with meningococcal and hemophilus influenza type b vaccines and antibody response followed. If there is no response to the pneumococcal vaccine, prophylactic antibiotics are indicated
- Oral candida should be aggressively treated (amphotericin lozenge, fluconazole or ketoconazole as indicated) with biopsy of suspicious oral lesions
- Keratoconjunctivitis treated with topical steroids and vitamin A
- Immunosuppression may be indicated for hepatitis, refractory diarrhea or other refractory disorders
- Patients must be adequately informed of potential for future disease and instructed to seek care if concerning symptoms arise
- Patients should carry written warning of disease symptoms/complications
- Patient web site: <http://www.empower.org.nz>

### **Autoimmune Polyendocrine Syndrome Type II (APS-II, Schmidt's Syndrome)**

The type II syndrome is the most common autoimmune polyendocrine syndrome(103). In 1926, Schmidt described two subjects with thyroiditis and Addison's disease(2). Other diseases of the APS II include Graves' disease (thyrotoxicosis), primary hypothyroidism(62), insulin-dependent or type 1A diabetes mellitus (IDDM), celiac disease(74;104-106) vitiligo(63;65-67) serositis(75), IgA deficiency(67), primary hypogonadism(77), stiff-man syndrome(78), alopecia, pernicious anemia(63;64), myasthenia gravis(70), and Parkinson's disease. Organ-specific autoantibodies in the absence of overt disease is also frequently present in patients and their relatives(107). Some authors divide the APS-II syndrome based upon the specific disease components reserving APS-II for Addison's disease plus autoimmune thyroid disease or type 1 diabetes (e.g. APS-III for thyroid autoimmunity plus other autoimmune (not Addison's or hypoparathyroidism); APS-IV for two or more other organ specific autoimmune diseases). In that the additional divisions at present provide limited prognostic information (e.g. patient with diabetes and thyroiditis at risk for Addison's) we will use APS-II as inclusive of multiple autoimmune disorders with one or more autoimmune endocrine diseases but distinguished from APS-I with its unique triad of hypoparathyroidism, mucocutaneous candidiasis and Addison's disease and identified mutation of the AIRE gene.

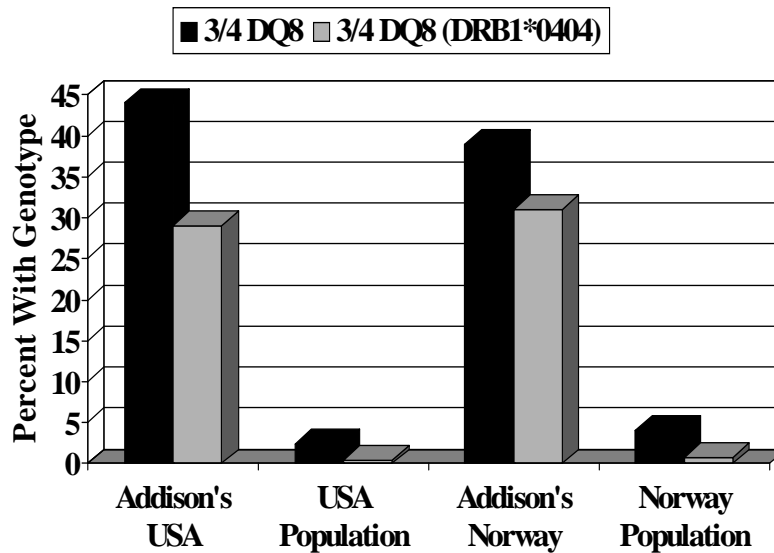
There has been a marked increase in knowledge concerning genetic determinants of disorders such as Type 1A diabetes given whole genome screens analyzing thousands of patients and controls(108). The majority of the genes influencing susceptibility outside of the major histocompatibility complex have extremely small odds ratios (often less than 1.2) and thus their analysis in relatively uncommon disorders such as APS-II is problematic. The major polymorphism (*PTPN22* or Lymphocyte Specific Phosphatase R620W) of one of the strongest type 1A diabetes non-MHC genes(109) is associated with Addison's disease(110-113), but the remainder of the other multiple loci have not been studied for Addison's disease in detail/ have conflicting findings with limited power(114-116). With large genome-wide studies of common disorders such as Graves' disease and Hashimoto's thyroiditis multiple immune related genes (e.g. CTLA4, *PTPN22*, FCRL3) clearly influence disease with relatively small odds ratios(117;118) with evidence of MHC heterogeneity between



Graves' disease and Hashimoto's thyroiditis(117;119). Loci associated with Addison's disease outside of the MHC include NALP1 (PR215, minor allele coding SNPrs I2150220) (120) CTLA4-Ala17 (OR = 2.4), Programmed Death Ligand PDL1 (OR=1.3) and CYP27B1C (-R60)A (OR=1.5 vitamin D I (121) ce hydroxylase. (120)

Genetic abnormalities underlying disease susceptibility for APS-II are partially defined and consist primarily of alleles of genes within the major histocompatibility complex. Initial studies associated APS-II with the class I HLA allele B8 (14). HLA-B8 is in linkage disequilibrium with HLA-DR3, which is in turn in strong linkage disequilibrium with DQ2 (DQA1\*0501, DQB1\*0201). The primary association of APS-II, similar to many autoimmune disorders appears to be with class II HLA alleles (immune response genes) and in particular with DQ2 and DQ8. Thus APS-II is strongly associated with human leukocyte (HLA) haplotypes with DR3/DQ2 [DQ2:DQA1\*0501, DQB1\*0201) and DR4/DQ8 (DQ8:DQA1\*0301, DQB1\*0302) and with DRB1\*0404(122-124) particularly in the rare multiplex Addison's disease families) (125-128). A recent study from our group indicates that the association with HLA-B8 is not simply due to its linkage disequilibrium with DR3-DQ2. In multiplex Addison's disease families, 95% of DR3 haplotypes have HLA-B8 compared to approximately 50% of control U.S. DR3 haplotypes. The DR3-DQ2-B8 (3.8) of Addison's disease differs from the usual 3.8.1 (A1) extended haplotype in terms of less often being conserved to A1. This suggests that either B8 itself increases risk or other alleles between DQ and HLA B or B8 itself increases risks and loci between HLA-B and HLA-A decrease Addison's risk of the 3.8.1 conserved extended haplotype.

## Addison's: DR3/4 DQ8 DRB1\*0404



U.S. Odds Ratio: 3/4 DQ8= 32; 3/4 DQ8 DRB1\*0404 = 98

U.S. Risk= 1/200 Addison's with 3/4 DQ8 DR0404 (1/500 Norway)

Information from Yu et al JCEM, 84:328-335, Myhre et al JCEM, 87:618-623,2002

Many of the diseases of the type II syndrome are associated with HLA antigens HLA-DR3 or HLA-DR4 (122;126;129) (Table 8.4) Primary adrenal insufficiency in the type II, but not the type 1 syndrome, is strongly associated with both HLA-DR3 and HLA-DR4(122). The association of HLA markers with disease can correlate with inheritance of a common HLA-

haplotype within families, but haplotypes with DR3 are often introduced into the family by more than one relative(122). Other HLA-B8 and DR3 associated illnesses include selective IgA deficiency(130-132) juvenile dermatomyositis, and dermatitis herpetiformis(74), alopecia, scleroderma(133), autoimmune thrombocytopenia purpura(134), hypophysitis(81;82) metaphyseal osteopenia(135), and serositis(75). A recent report implicates HLA-C as having a greater association with Hashimoto's thyroiditis than class II HLA alleles, though multiple MHC alleles contribute(136).

Several diseases that manifest in patients with polyendocrine autoimmune syndromes are not associated with HLA-B8 or HLA-DR3 in population studies. These disorders include vitiligo(137), pernicious anemia(138), and autoimmune goitrous thyroiditis(139-141). Addison's disease patients also frequently have DQ8, DQB1\*0602, and DR5 associated haplotypes(different from patients with type 1 diabetes). In our studies, approximately 30% of patients with Addison's disease are DR3/4, DQ2/DQ8 heterozygous compared to 2.4% of the general U.S. population. This occurs in the U.S. for patients with or without type 1 diabetes. Between 70 to 80% of DR4 alleles in patients with Addison's disease have DRB1 allele 0404. This is similar to a national study of Addison's disease patients in Norway(123). Such genotypic associations are likely to vary by country depending on the frequency of specific HLA DR and DQ haplotypes.

Another allele of an MHC gene that is associated with Addison's disease is the "5.1" allele of the atypical class I HLA molecule MIC-A(142;143). The MIC-A5.1 allele has a very strong association with Addison's disease that is not accounted for by linkage disequilibrium with DR3 or DR4 (142;144), but with extended haplotypes and association of MICA alleles with HLA-B alleles (5.1 with B8 and MICA5 with HLA B15 may not be a causative gene(124). The MHC class II transactivator gene on chromosome 16 influences expression of class II molecules. A single report indicates association of a polymorphism of this gene with a G allele present in 67% of patients with Addison's disease (n=128) versus 49% of controls(124).

## **ENVIRONMENTAL FACTORS**

Initiating factors for the type II syndrome and its component illnesses are not established except for celiac disease (wheat protein gliadin) (145), the insulin autoimmune syndrome (e.g. methimazole), myasthenia gravis (rarely penicillamine(146)), type 1A diabetes (rarely congenital rubella), Graves' disease (rarely anti-CD52 monoclonal treating patients with multiple sclerosis(147)) and hypothyroidism (interferon therapy associated with thyroid autoimmunity and diabetes(148-152)). Patients with celiac disease, which is characterized by atrophy of intestinal villi associated with lymphocytic infiltration, have autoantibodies reacting with transglutaminase (the endomysial antigen)(105) and with less specificity and sensitivity with the wheat protein gliadin. In contrast to the lack of specificity with gliadin antibody assays, assays of antibodies to deamidated gliadin appear highly specific, and respond to removal of gliadin from the diet more rapidly than transglutaminase autoantibodies(153). Removal of gliadin from the diet restores intestinal villi to normal(154);107). There is a well developed hypothesis in terms of the pathogenesis of celiac disease with the deamidation of gliadin by transglutaminase leading to increased binding of the deamidated peptide to HLA DQ2 and DQ8 class II molecules and activation of the disease by presentation of the peptides to T lymphocytes(155).

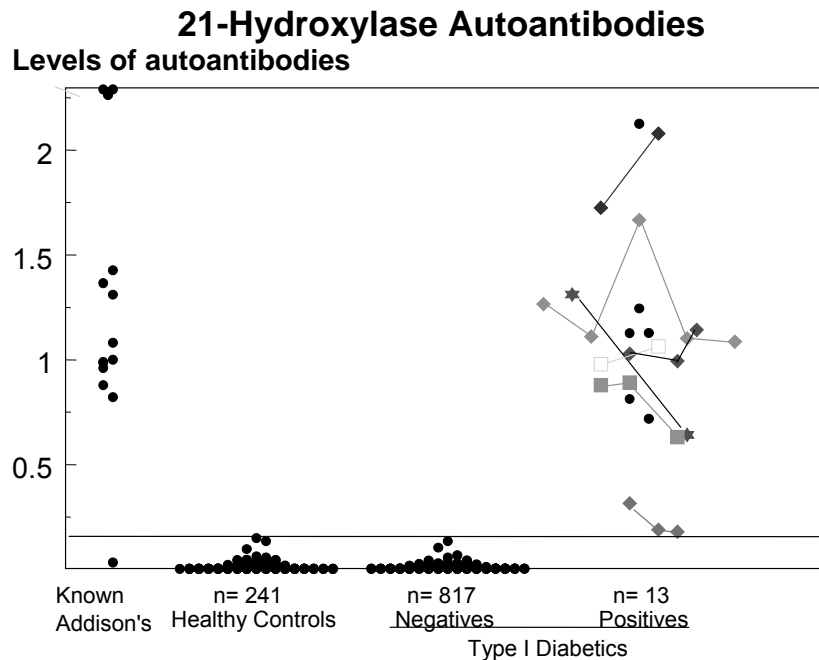
Controversial data suggest that ingestion of the milk protein bovine albumin in the first few months of life may be associated with type 1 diabetes(156) while other investigators implicate casein, and studies from Denver and Germany implicate early (<3 months) ingestion of wheat. A recent study of omega-3 and omega-6 fatty acid ingestion(157) analyzing both dietary history and levels of fatty acids in prospectively obtained red cells associates increased ingestion with decreased risk of developing islet autoimmunity(157). These dietary factors appear to increase/decrease risk of islet autoimmunity less than 2-3

fold. A number of drugs are associated with induction of autoimmunity including interferon- $\alpha$  (thyroiditis)(158). Remarkably (159;160) 1/3 of multiple sclerosis patients treated with an anti-CD52 monoclonal antibody developed Graves' disease(147). Apparently non-multiple sclerosis patients treated with the same monoclonal do not develop Graves' disease.

## AUTOANTIBODIES

Families with the type II polyendocrine syndrome should be evaluated over time to detect the presence of organ-specific antibodies indicating the possibility of a future endocrine malfunction (Table 8.7). All such relatives should be advised of the early symptoms and signs of the principal component diseases. Even though signs and symptoms of disease may be absent, patients with multiple disorders should be screened every few years with measurement of anti-islet antibodies, 21-hydroxylase autoantibodies and transglutaminase autoantibodies, a sensitive thyrotropin assay, and measurement of serum B12 levels(161).

ACTH and cosyntropin(adrenocorticotropin)-stimulated cortisol determination (the cosyntropin test if ACTH increasing or if symptoms/signs present) is indicated if 21-hydroxylase autoantibodies are detected(122;162). Assays of anti-islet cell antibodies(163), (164) anti-thyroid and anti-adrenal antibodies(21-hydroxylase)(59;165-168) and anti-ovarian antibodies(77;169) help identify subjects at increased disease risk. Screening of patients with Type I diabetes for 21-hydroxylase autoantibodies indicates that 1.5% are positive. Approximately 20 percent of APS-II patients expressing 21-hydroxylase autoantibodies progressed to overt Addison's disease with long-term follow-up(up to approximately 20 years)(170)



Yu et al, JCEM, 1999

More than 20 years may elapse between the onset on one endocrinopathy and the diagnosis of the next. As many as 40-50% of subjects with Addison's disease will develop an associated endocrinopathy. A distinction must be made for subjects with isolated thyroid disease (relatively frequent in the general population) who have no family history of polyglandular syndrome type II. Such individuals have a relatively low probability of

developing additional autoimmune disorders in comparison with individuals with rare autoimmune disorders such as Addison's disease or myasthenia gravis.

Rarely, hypoparathyroidism, a specific endocrine disturbance present in the type 1 syndrome, is identified in a patient with type II syndrome. Hypoparathyroidism in such type II polyendocrine autoimmune patients may result from a "suppressive" autoantibody(171;172) rather than parathyroid destruction as in the type 1 syndrome and activating antibodies to the calcium receptor (173). In a patient with the type II syndrome, celiac disease is a more frequent cause of hypocalcemia than hypoparathyroidism.

Several autoantibodies are both disease specific (e.g., anti-acetylcholine receptor antibodies in myasthenia gravis(174) and anti-TSH receptor antibodies in Graves' disease(175)) and causal. "Causal" autoantibodies are associated with transplacental disease transmission. Other autoantibodies (e.g., antithyroid autoantibodies including anti-thyroid peroxidase, formerly termed anti-microsomal, and anti-thyroglobulin) are as frequent among patients and relatives as to be of little predictive value. For example, a relative with anti-thyroid peroxidase autoantibodies has a low risk of hypothyroidism unless evidence of abnormal thyroid function is also present (e.g., elevated TSH). In a similar manner, many individuals may have antibodies to parietal cells, H<sup>+</sup>/K<sup>+</sup> adenosine triphosphatase of the stomach(176;177) and intrinsic factor, but the autoantibodies do not correlate well with abnormal gastric acid secretion or development of pernicious anemia(138).

In the APS-II syndrome, many ICA-positive individuals do not progress to diabetes, and diabetes risk is much lower than for ICA-positive first-degree relatives of patients with type 1 diabetes(163;164). These non-progressing ICA-positive polyendocrine patients usually express what has been termed "selective" or restricted ICA(163). Such ICA reacts only with islet B cells (insulin producing), not A cells (glucagon producing) within rat islets and fail to react with mouse islets. They represent unusual high titer autoantibodies reacting with glutamic acid decarboxylase (GAD), which is not expressed at detectable levels in mouse islets. This unusual form of ICA confers a lower risk of type 1 diabetes as compared with nonrestricted ICA (reacts with multiple islet molecules) for both polyendocrine patients and relatives of patients with type 1 diabetes. If multiple anti-islet autoantibodies (of GAD, insulin and IA-2) are present, there is a high risk of diabetes.

Table 8.7. Type 1A Diabetes and Polyendocrine Autoimmunity

- 
- As many as 18% of APS-I patients become diabetic as do approximately 15% of patients with Addison's disease (non-APS-I)
  - "Restricted" or GAD-ICA is common among APS II patients with lower risk of progression to diabetes unless IA-2 autoantibodies are present
  - APS-I and II: DQA1\*0102/DQB1\*0602 Protection from Diabetes
  - APS-II: Later mean age of diabetes onset than typical type 1A patients
  - APS-I: Anti-GAD autoantibodies react with GAD on Western blots and inhibit enzymatic activity (178)
- 

Other autoantibodies associated with the type II syndrome include anti-melanocytic, anti-adrenal (35) and anti-gonadal autoantibodies(166). Anti-adrenal cortical antibodies have been used to predict adrenal insufficiency in the type 1 syndrome (in particular 21-hydroxylase). It is noteworthy that many of the polyendocrine autoantibodies react with intracellular enzymes, including thyroid peroxidase (Hashimoto's thyroiditis), glutamic acid decarboxylase (type 1 diabetes and stiff-man syndrome), 21 hydroxylase (Addison's disease), and cytochrome P450 cholesterol side chain cleavage enzyme(91) (Addison's disease). In addition, antibodies to hormones can be present, including anti-insulin, anti-

thyroxine, and anti-intrinsic factor antibodies (pernicious anemia). It is now relatively easy to develop highly specific and sensitive assays for autoantibodies reacting with non-modified proteins with in vitro transcription and translation of cDNAs of the relevant protein. The specificity of ELISA format assays can be enhanced with competition with fluid phase molecules and detection with fluorescence assays(179). Dr. Hutton and colleagues utilized identification of tissue specificity followed by development of fluid phase radioassay to define the fourth major islet autoantigen, namely the beta cell Zinc transporter(ZnT8)(180).

Antibodies to specific receptors are characteristic of given disorders (anti-acetylcholine receptor antibodies of myasthenia gravis, anti-TSH receptor antibodies of Graves' disease or hypothyroidism(181), and oocyte sperm receptor autoantibodies associated with oophoritis). The large variety of target molecules, (e.g., type 1 diabetes), presence of high affinity IgG autoantibodies, and the sequential appearance over months or years of specific antibodies or disorders suggest that the production of most autoantibodies is secondary to tissue destruction and are antigen "driven"(182).

## **PATHOGENESIS**

A central question is what links all the different disorders of the APS-II syndrome? Why do some individuals have a single autoimmune disorder while others have multiple diseases? One hypothesis is that different tissues share the same autoantigen and thus when autoimmunity is directed at one organ it will also affect other organs. This is highly unlikely given the number of different molecules targeted specifically for many autoimmune disorders and the wide discordance in time relative to the appearance of for instance specific autoantibodies and disease. Another hypothesis is that different organs may share immunologically related molecules (mimics) and such mimics may be as simple as short peptides recognized by T lymphocytes. That is also a possibility (see below), but would not explain the wide time differences of disease appearance and spectrum of different illnesses. We believe the most likely link between the diverse diseases is genetic propensity to fail to maintain tolerance to multiple self-molecules, and in particular specific self-peptides. Environmental factors and additional genetic determinants (e.g. specific HLA alleles) then determine the timing of loss of tolerance and the probability that a specific organ will be targeted. For instance, the highest risk (for Type 1 diabetes) HLA genotype DR3-DQ2; DR4-DQ8 is associated with a young age of diabetes onset. Failure to maintain tolerance can be a result of deficient T regulation or enhanced T cell activation. An additional hypothesis is that HLA alleles associated with autoimmunity might be inherently contributing to generalized autoreactivity. We find that hypothesis unattractive in that specific HLA haplotypes can be protective for one autoimmune disorder and promote another. For example DR2/DQB1\*0602 haplotypes are high risk for multiple sclerosis but provide dominant protection for type 1A diabetes.

Both autoreactive T cells and autoantibodies are pathogenic, depending on the specific disease. In Graves' disease, anti-thyrotropin (TSH) autoantibodies lead to thyroid hyperfunction(183) and anti-insulin receptor autoantibodies can result in either hypoglycemia or insulin resistance with hyperglycemia(11;184). Type 1A diabetes is a T cell mediated disorder and an interesting case report describes a child developing diabetes with a mutation eliminating B-lymphocytes and thus autoantibodies (59). Nevertheless, anti-B cell antibodies (anti-DC20) slows progression of C-peptide loss in new onset diabetic patients. (185)

T cell autoimmunity has been much more difficult to study and correlate with disease compared to autoantibodies. Recent advances in T cell immunobiology, studies of animal models, and transfer of autoreactive T lymphocytes or affected human organs into immunodeficient mice should lead to progress in understanding T cell autoimmunity (See chapter on T lymphocytes). For instance, as expected the 21 hydroxylase molecule is a T cell target in Addison's disease.

For decades, experimental animal models of organ-specific autoimmunity have been studied. These were dependent upon the injection of putative autoantigens into animals in the presence of adjuvants that enhance inflammation(80). Thus, thyroiditis can readily be induced in selective strains of mice following injection of thyroglobulin or thyroid peroxidase in Freund's adjuvant. Anti-insulin autoantibodies can be induced in normal Balb/c mice following the administration of insulin peptide B:9-23, and these autoantibodies react with intact insulin and are not absorbed by the immunizing peptide(186). In Balb/c mice expressing an activating molecule in islets (B7.1) immunization with the B:9-23 peptide leads to diabetes. T cell clones reacting with these molecules, or other selected peptides, are generated, and such clones when transferred into naive animals induce disease. Of note, several forms of immunization with such autoreactive clones can be used to make animals refractory to disease induction(187). These studies provide clear evidence that autoreactive T cells are present in normal animals and they can be rapidly activated, given "appropriate" stimulation.

In addition, studies by Tung and associates and Wucherpfennig and colleagues suggests one mechanism whereby properties of T cell recognition may lead to multiple autoimmune disorders(80;188). In studying experimental autoimmune oophoritis, Tang and colleagues identified a peptide of the oocyte sperm receptor (ZP3) that upon injection in adjuvant induced disease. They then identified which of nine amino acids of this peptide were essential to activate autoimmune T cell clones or induce disease. T cells recognize only short peptides presented in the groove of class I or class II major histocompatibility complex (MHC) molecules on antigen-presenting cells. As few as three properly spaced amino acids (of nine) interacting with a T cell receptor can be sufficient to trigger T cell responses. Noting that a peptide of the acetylcholine receptor had the appropriate T cell binding motif associated with experimental oophoritis, they demonstrated that this peptide stimulated an oophoritis-derived T cell clone in vitro and when administered in vivo induced oophoritis. The requirement for sharing of as few as three of nine amino acids of a linear sequence for activation of autoreactive T cells provides a mechanism whereby inflammation directed at one organ may spread to additional tissues by T cell cross reactions to distinct peptides of different tissues. Such a model may also help explain disease associations. For example, Graves' thyroid disease is frequently complicated by autoimmunity directed at extraocular muscles leading to Graves' ophthalmopathy(189). If such a mechanism for the "spreading" of autoimmunity is operative, it implies that mechanisms to suppress autoreactivity are particularly important. The possibilities that "molecular mimicry" may induce autoimmunity are greatly increased if short minimally homologous sequences are sufficient to stimulate cross-reactive T cell clones.

Very important animal models of polyendocrine autoimmunity indicate that loss of regulatory T lymphocytes can result in widespread autoimmunity. These models utilize either neonatal thymectomy or a combination of radiation and immunosuppressive drugs and transfer of T cell subsets to immunodeficient mice to induce autoimmunity (190-196). The general concept is that within the thymus, early in development, a subset of essential regulatory T lymphocytes develops and seeds the periphery. Interference with this normal mechanism results in loss of tolerance to multiple molecules, and thus multiple organs are the target of autoimmunity. This is a rapidly developing field. The IPEX syndrome (see below) with its fatal neonatal autoimmunity and loss of a key regulatory molecule (Foxp3) illustrates how this concept can apply to human autoimmune disorders.

**Table 8.8. Polyendocrine Type II Syndrome Diseases**

Disease	HLA	Association	Initiator	Predominant Mediator	Autoantigen
Graves' disease		DR3	Iodine (rare)	Antibody	TSH

			anti-CD52 (rare)	receptor(105)
Myasthenia gravis	DR3,DR7(197;198)	Thymoma(9;199) (rare) Penicillamine(198) (rare)	Antibody	Acetylcholine receptor
Insulin Receptor Hypoglycemia or diabetes (rare)	?	?	Antibody (200;201)	Insulin receptor
Hypoparathyroidism "geriatric" (rare)	?	?	Antibody(171)	Cell surface inhibitor
Insulin autoimmune	DR4,DRB1*0406(11)	Methimazole(202)	Antibody	Insulin
Celiac disease	DR3/DR2/DQ8	Gluten (common)	T cell	Transglutaminase
Type 1A Diabetes	DR3/4, DQ2/8	Rubella(203) (rare)	T cell	Insulin, GAD, ICA512 (IA-2),GM2-1
Addison's disease	DR3,DR4(122)	?	T cell	21-Hydroxylase P450-5cc(122)
Thyroiditis	DQB1*0201, DQA1*0301(205-207)	Iodine(204) Interferon $\alpha$	T cell	Thyroglobulin, Peroxidase(208)
Pernicious anemia	?	?	T cell	Intrinsic factor H <sup>+</sup> /K <sup>+</sup> ATPase
Vitiligo		Melanoma Antigen Immunization(210)	?	Melanocyte(209)
Chromosome Dysgenesis	DQA1*0301(211;212) DQA1*0301		?	Thyroid, Islet, Celiac(213;214)

(Trisomy21 Turners)

Kriegel and co-workers reported that patients with APS-II have a defect in terms of lymphocyte response to CD4+CD25+ T cell suppression (215). Interruption of normal T cell development can result in multiple autoimmune disorders. The BB rat develops type 1 diabetes and thyroiditis in association with a severe T cell immunodeficiency(216). Neonatal thymectomy induces autoimmunity apparently by removing regulatory T cells(217;218). A series of different regulatory T cells (e.g. CD4+CD25+, NK T cells) are now the subject of intense investigation (219). Of note the Foxp3 molecule is essential for regulatory T lymphocytes and when it is mutated (IPEX syndrome-see below) neonatal autoimmune diabetes results(220;221).

Autoimmune disorders appear to share a number of "non-specific" abnormalities of T cell function or enumeration including increased numbers of cells expressing class II molecules ("Ia" positive T cells)(222), IL2 receptors, depressed autologous mixed lymphocyte responses(223), and lack of NK T cells(224). Studies of NK T cells in man are controversial with tetramer analysis not confirming decreased numbers in patients with type 1A diabetes, but rather stable wide variation in the percentage of such cells between even normal individuals(225). The above abnormalities appear not to be disease specific and may relate to fundamental abnormalities predisposing to autoimmunity or reflect disease activity.

## IDENTIFICATION OF CASES

Individuals with a single autoimmune disease are at increased risk for the development of a second disease over the general population. Table 8.9 shows the prevalence of autoimmune endocrine disease in the general population and the co-incidence of a second autoimmune disease given that a first exists. In addition, individuals with APS-II syndrome will often develop autoimmunity sequentially over the time course of many years. An individual often will not have polyglandular failure at the onset of clinical symptoms of the initial autoimmune disease. Therefore, a high clinical suspicion for the development of sequential autoimmune diseases must be maintained (226). Specific screening strategies depend on the presenting autoimmune disease. Significant controversy exists regarding the screening tests that should be employed and the frequency of testing performed. For example, in type 1 diabetes, it is generally accepted that routine screening for thyroid disease with biochemical assays should be performed, the frequency of this screening is a source of controversy (227); (228). Even more controversial is the screening for celiac disease in this population. While the elevated risk of celiac disease in the diabetic population has been well established (105;229)-(230), many of these individuals are asymptomatic at the time of identification and the long term sequelae of untreated asymptomatic celiac disease in regards to growth, pubertal development, bone mineralization and gastrointestinal malignancy is unclear.

Tests may include functional biochemical assays and/or serologic studies to identify organ specific autoantibodies. Once a second autoimmune disease is identified more extensive screening is indicated to identify further disease at an early stage. Screening with autoantibodies associated with diabetes (IA-2, insulin and GAD), thyroid disease (TG and/or TPO), Addison's disease (21-hydroxylase), celiac disease (transglutaminase) and autoimmune hepatitis (cytochrome P450 enzymes) in addition to biochemical screening with TSH, free T4, FSH, LH, CBC, and electrolytes may uncover occult autoimmune disease. Once an individual



\*1.2% of individuals identified from patients in Addison's support group (does this underrepresent concomitant illnesses)

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**TABLE 8.9: Prevalence of concomitant autoimmune disease**

Disease or Antibody		GROUP									
		General Population	Type 1A DM	Celiac Disease	Addison's	Hypothyroid	Graves'	Pernicious	Ovarian Failure	Vitiligo	Alopecia
Type 1A DM		.2-.3%	XXXXXXXXXX		1.2%*, 12-14%	4%	1.7%		3%	0.2-0.3	0.20%
	a				u,v,w	aa	ff		y	ll	mm
Anti-Islet Ab		1-3%	88%		6 (ICA)						
	b,c		d		v						
Celiac		1%	9%	XXXXXXXXXXXXXX	1.20%/112, 6/68, 4%	1/22					
	d				v	w, bb, cc	bb				
Transglutaminase Ab		.5-1.0%	12%		5%	6/68 (EVA)	1/22 (EVA)				
	d		d		d	bb	bb				
Addison's (not APS-I)		0.005%	0.44%		XXXXXXXXXXXXXX				3%	0.38%	
	a		d						y	ll	
21-hydroxylase Ab			2.20%		83 - 90%						
	j				u, v						
Hypothyroid		5-9% 0.79% overt	28% overt 1%, 12.9%		14-21%	XXXXXXXXXXXXXX	XXXXXXXXXXXXXX	6/22	28%	17%	15%
	a,e,f,g		k	q,r	u, v, x			ii	y	ll	mm
Peroxidase Ab		11-12%	17-27%	child 18% (autosomal)	23%	47-88%	53%	11/22			
	h,g		d, l, m	q	v, x	r, dd	r	ii			
Thyroglobulin Ab		10%-t 12%	8-16%	child 23%	23.40%			3/22			
	h,g		d, l, m	q	v			ii			
Graves'		0.4-2%		child overt 1%	6, 10-20%	XXXXXXXXXXXXXX	XXXXXXXXXXXXXX	0/22		2%	
	a,e,f,g			q	u,v,w			ii		ll	
TSHRAb			22%				57/61	0/22			
	n						gg	ii			
Pernicious Anemia		.15-.2%	6%	19/159		1/56		XXXXXXXXXXXXXX			1.9%
	a, l		o	s		ee					ll
Anti-Parietal Ab			30%		19.80%						
	o				v						
Ovarian Failure					2-7%				XXXXXXXXXXXXXX		
					v, y, z						
17-hydroxylase Ab					7%						
					z						
Vitiligo		0.40%	9%		7% - 10%			1.6-11%		XXXXXXXXXX	
	a		p		v, w			jj, kk			
Alopecia		1.70%		2%			2.6%				XXXXXXXXXX
				t			hh				
		<b>General Populator</b>	<b>Type 1A DM</b>	<b>Celiac disease</b>	<b>Addison's</b>	<b>Hypothyroid</b>	<b>Graves'</b>	<b>Pernicious</b>	<b>Ovarian Failure</b>	<b>Vitiligo</b>	<b>Alopecia</b>

\*1.2% of individuals identified from patients in Addison's support group (does this underrepresent concomitant illnesses)

is identified as having APS-II syndrome, regular screening for further development of autoimmune disease is indicated (226).

## Therapy

The therapy of the APS-II syndrome depends upon the specific disease manifestation with a few caveats(231). Patients with suspected Addison's disease and hypothyroidism should be evaluated and treated for adrenal insufficiency prior to replacement of thyroid hormone to avoid Addisonian crisis. There is one fascinating case report of a patient with 21-hydroxylase autoantibodies treated for Graves' eye disease with a 6 month course of glucocorticoids. In this patient 21-hydroxylase autoantibodies became negative and adrenal function was restored to normal. This remission was reported to have lasted for 100 months at last follow up(232).

There are a large number of new potent immunosuppressive and immunomodulatory therapies being used in non-endocrine autoimmune diseases and in various stages of clinical development. Rituximab (anti-CD20 antibody) is one of the more interesting having dramatic effects in multiple sclerosis and a relatively large clinical experience for the treatment of B-cell lymphomas. In the NOD mouse model of type 1 diabetes anti-CD20 prevents development of diabetes(233) and a clinical trial in new onset patients (Trialnet) indicates a single course slows but does not permanently arrest loss of C-peptide. Treatment with rituximab induces long-term B cell depletion, but the antibody does not bind to plasma cells, and often has relatively minor effects on autoantibody levels. It may act by influencing presentation of autoantigens by B-lymphocytes or altering B cell regulation. Studies in Graves' disease suggest a potential role, but also potential complications (234-236). Trials of modified anti-CD3 monoclonal antibodies in new onset type 1 diabetes are very advanced with the potential that such antibodies induce regulatory T lymphocytes as well as acutely and transiently depleting T lymphocytes (237-242). A long-term goal is the development of antigen specific therapy for each of the major autoimmune disorders. In experimental animals regulatory T lymphocytes targeting for instance islet specific molecules can effectively block development of disease in spontaneous animal models(243;244).

## IPEX (Immune Dysfunction Polyendocrinopathy X-linked)

The IPEX syndrome presents in neonates with fatal autoimmunity and this very rare disorder has multiple different names reflecting endocrinopathy, allergic manifestations, intestinal destruction and immune dysregulation (e.g. XLAAD: X-Linked Autoimmunity Allergic-Dysregulation Syndrome or XPID, MIM number 304790 and 300292). Most children with the disorder die in infancy and many die in the first days of life. They manifest neonatal type 1 diabetes, but the cause of death probably relates to massive intestinal involvement and malabsorption. Eighty percent of patients with the IPEX syndrome develop type 1 diabetes. This suggests that in the absence of regulatory T lymphocytes most humans will target and destroy beta cells.(245)

The disease results from mutations that inactivate the Foxp3 transcription factor and the same gene is also mutated in a mouse model (the Scurfy mouse)(4). The pathway this gene controls in T lymphocytes is now identified as central to basic immunology. In particular the gene controls the regulatory function of CD4+CD25+ regulatory T lymphocytes. (191;246) From this discovery it is now apparent why bone marrow transplantation of normal lymphocytes is able to cure the mouse disease, namely the replacement of regulatory lymphocytes is able to control autoimmune reactivity of effector lymphocytes of the Scurfy mouse recipient, despite their lacking the Foxp3 gene.

In that the mouse model is cured with bone marrow transplantation, such therapy has recently been tested in children with the disorder. A child became chimeric after bone

marrow transplantation and a remarkable two-year remission was induced(142), followed by an unusual hematological disease that resulted in death. Partial lymphoid chimerism following bone marrow transplantation can induce remission (247). There are now multiple reports of bone marrow transplantation (247-249) and a report of therapy with Sirolimus(250).

### **Anti-Insulin Receptor Antibodies**

The presence of anti-insulin receptor autoantibodies is characterized by marked insulin resistance, but paradoxically, patients can also have severe hypoglycemia(6). Approximately one third of the subjects have other autoimmune disorders. Characteristically, associated autoimmune diseases are non-organ specific(251-253).

### **Thymic Tumors**

Thymomas and thymic hyperplasia are associated with a series of autoimmune diseases(7-9;254-256). The most common autoimmune diseases are myasthenia gravis and red cell aplasia(257;258). Graves' disease, type 1 diabetes, and Addison's disease may also be associated with thymic tumors. Patients with myasthenia gravis and alopecia totalis are reported to have thymoma (259). Unique anti-acetylcholine receptor autoantibodies may be present with thymoma(256) and disease may be initiated by transcription of molecules within the tumor related to acetylcholine receptors(260). There is a 1997 report of treatment of a patient with thymoma and pure red cell aplasia with octreotide and prednisone(254). Many thymomas lack AIRE expression within the thymoma a potential factor in the development of autoimmunity(261;262). Of note, the one other disease with "frequent" development of anti-cytokine (e.g. anti-interferon and IL17 (autoantibodies besides AIRE mutations are thymoma associated).

### **POEMS Syndrome**

POEMS (Polyneuropathy, Organomegaly, Endocrinopathy, M-protein, Skin changes) patients usually present with a sensory motor polyneuropathy, diabetes mellitus (50%), primary gonadal failure (70%), and a plasma cell dyscrasia with sclerotic bony lesions(263) (13;264). Temporary remission may result following radiotherapy directed at the plasmacytoma and peripheral blood stem cell transplantation has been utilized (265). The syndrome is assumed to be secondary to circulating immunoglobulins but patients have excess vascular endothelial growth factor(266;267) as well as elevated IL1- $\beta$ , IL-6, and TNF- $\alpha$ (264). There is a case report of a presumptive patient with POEMS without polyneuropathy(268). A small series of patients have been treated with thalidomide with decrease in VEGF(269).

### **Insulin Autoimmune Syndrome (Hirata Syndrome)**

The insulin autoimmune syndrome, associated with Graves' disease and methimazole therapy (or other sulfhydryl containing medications) is of particular interest due to a remarkably strong association with a specific HLA haplotype (11). Such patients with elevated titers of anti-insulin autoantibodies frequently present with hypoglycemia. The disease in Japan is essentially confined to DR4-positive individuals with DRB1\*0406(202). Even a Portuguese patient with the syndrome had DRB1\*0406(270). In Hirata syndrome the anti-insulin autoantibodies are polyclonal. Some patients have monoclonal anti-insulin autoantibodies that also induce hypoglycemia and for these patients there is not an HLA association(270).

### **Other Disorders**

Other diseases with polyendocrine manifestations are Kearns-Sayre syndrome(271) diabetes and thyroiditis associated with trisomy 21(272), DIDMOAD syndrome (diabetes insipidus, diabetes mellitus, optic atrophy, and nerve deafness)(273) - (274;275) and congenital rubella(203;276;277) associated with thyroiditis and/or diabetes.

The Kearns-Sayre syndrome is characterized by onset before age 20, external ophthalmoplegia, pigmentary retinal degeneration, and one or more of ataxia, heart block, or high cerebrospinal fluid protein. A number of these patients have Hashimoto's thyroiditis with the suggestion that hypothyroidism is associated with encephalopathy (278), hypoparathyroidism(279) and diabetes mellitus and adrenal insufficiency(280). The disorder is associated with multiple large-scale(281) deletions as well as mutations of mitochondrial DNA (282).

Wolfram syndrome (DIDMOAD syndrome) is characterized by optic atrophy and childhood onset diabetes but the diabetes is not of autoimmune etiology. The gene mutated (wolframin on chromosome 4p16) encodes a glycosylated transmembrane protein of unknown function(273;283) that is localized to the endoplasmic reticulum (ER) and may function to limit ER-stress induced cell death (284).

Diabetes develops in a significant number of adolescents and young adults with a history of congenital rubella infection. These patients frequently have thyroiditis, and despite the development of childhood diabetes infrequently express anti-islet autoantibodies (285).

Karounos and coworkers have described a rubella protein with homology to an islet protein, suggesting that molecular mimicry may initiate disease(286). An alternative hypothesis has been proposed by Rabinowe and coworkers(277). They described long-term T cell subset abnormalities in patients following congenital rubella infection.

## **Conclusions**

Polyendocrine autoimmune syndromes have played an important role in understanding autoimmune disorders and in particular type 1A diabetes. The initial evidence that type 1A diabetes was an autoimmune disorder came from its association with spontaneous Addison's disease, and lack of association with tuberculous Addison's disease(3). The first demonstration of cytoplasmic islet cell autoantibodies occurred in patients with polyendocrine autoimmunity(287).

The existence of families of related autoimmune disorders not only is clinically important but also suggests that these diseases are pathogenically related. This relationship probably is a result of two distinct phenomena. The first is inherited abnormalities of immune function, predisposing to the loss of tolerance to a series of self-antigens. The IPEX syndrome with lack of CD4-CD25 regulatory T cells is very instructive with 80% of such children developing type 1 diabetes. Given such a predisposition, "normal" alleles of HLA genes within the major histocompatibility complex may then lead to targeting of specific organs. The second phenomenon that may link these disorders, especially for tightly linked diseases such as Graves' ophthalmopathy and Graves' thyroid disease, is creation of pathogenic T of B (288) cells reacting with components of more than one tissue. In that T cell clones can respond to peptides that share no identical amino acids (289), depending upon their three dimensional structure, the potential for such T-cell cross-reactivity must be enormous (288).

Finally, the relationships between these diverse disorders suggest that as disease pathogenesis is elucidated and antigen-specific therapies are developed, the improved understanding of pathogenesis and improvements in therapy will be applicable to many autoimmune diseases.

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