REVIEW ARTICLE

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Autoimmune Polyendocrine Syndromes

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N Engl J Med 2018;378:1132-41.
DOI: 10.1056/NEJMra1713301

Autoimmune polyendocrine syndromes comprise a diverse group of clinical conditions characterized by functional impairment of multiple endocrine glands due to loss of immune tolerance. These syndromes also frequently include conditions such as alopecia, vitiligo, celiac disease, and autoimmune gastritis with vitamin B_{12} deficiency that affect nonendocrine organs. Failure of multiple glands in an individual patient was first described by Schmidt,[1] who in 1926 reported the combination of hypothyroidism and adrenal insufficiency with lymphocytic infiltration of both the thyroid and adrenal glands. We have now come to appreciate that these syndromes can be broadly categorized as rare monogenic forms, such as autoimmune polyendocrine syndrome type 1 (APS-1), and a more common polygenic variety, autoimmune polyendocrine syndrome type 2 (APS-2).

Autoimmune polyendocrine syndromes are insidious and are characterized by circulating autoantibodies and lymphocytic infiltration of the affected tissues or organs, eventually leading to organ failure. The syndromes can occur in patients from early infancy to old age, and new components of a given syndrome can appear throughout life. There is marked variation in the frequencies and patterns of autoimmunity in affected patients and their families, and the risk of the development of various organ-specific autoimmune diseases is most likely due to a combination of genetic susceptibility and environmental factors.

Monogenic autoimmune polyendocrine syndromes have provided an opportunity to learn more about specific factors that are critical for maintaining immune tolerance. In parallel, major advances in characterizing autoimmunity in patients, such as the identification of new autoantibody targets associated with distinct diseases and their manifestations, have occurred. This article reviews some of these important developments and discusses approaches for the appropriate diagnosis and longitudinal follow-up of affected patients.

Autoimmune Polyendocrine Syndrome Type 1

APS-1, also named autoimmune polyendocrinopathy–candidiasis–ectodermal dystrophy (APECED; Online Mendelian Inheritance in Man [OMIM] number, 240300), is a rare autosomal recessive disease caused by mutations in the autoimmune regulator gene (*AIRE*).[2,3] The estimated prevalence is roughly 1:100,000 in most countries, with a higher prevalence in some countries such as Finland (1:25,000) and Sardinia (1:14,000) and among Persian Jews living in Israel (1:9000).[4]

Clinical Features

APS-1 is characterized by the development of at least two of three cardinal components during childhood — chronic mucocutaneous candidiasis, hypoparathyroidism, and primary adrenal insufficiency (Addison's disease).[4] Other typical components include enamel hypoplasia and enteropathy with chronic diarrhea or

constipation. Primary ovarian insufficiency, affecting approximately 60% of women with APS-1 before they reach 30 years of age (Fig. 1), is common. Other classic components are less frequent but may include bilateral keratitis, often accompanied by severe photophobia, and periodic fever with rash, as well as autoimmunity-induced hepatitis, pneumonitis, nephritis, exocrine pancreatitis, and functional asplenia.[5-9] Such findings should prompt clinicians to consider the diagnosis of APS-1, especially in young persons. On rare occasions, retinitis, metaphyseal dysplasia, pure red-cell aplasia,[8] and polyarthritis[10] have been associated with APS-1 (Fig. 1).

Several case series indicate that the phenotype and age at symptom onset vary greatly, even within the same family,[6-8,11] implying that other genes, such as major histocompatibility complex genes,[12] or environmental exposures influence the phenotype and natural course. For example, a recent Norwegian survey reported that all three main components of APS-1 developed in only 40% of affected patients.[6] In some affected persons, a single minor component develops during childhood and the first main manifestation later, during adulthood. This wide variation in presentation and symptomatology makes the diagnosis of APS-1 challenging.

In most patients with APS-1, disease manifestations develop earlier and are usually more severe than in patients with APS-2. Typically in a given patient with APS-1, an average of 4 or 5 manifestations of the syndrome develop, but as few as 1 or as many as 20 may occur. Owing to chronic mucocutaneous candidiasis, patients are also susceptible to squamous-cell carcinoma of the oral mucosa and esophagus over time. As compared with the general population, patients with APS-1 have an increased rate of death due to cancer,[13] adrenal and hypocalcemic crises, and certain conditions induced by aberrant autoimmune responses, particularly hepatitis, nephritis, and pneumonitis.

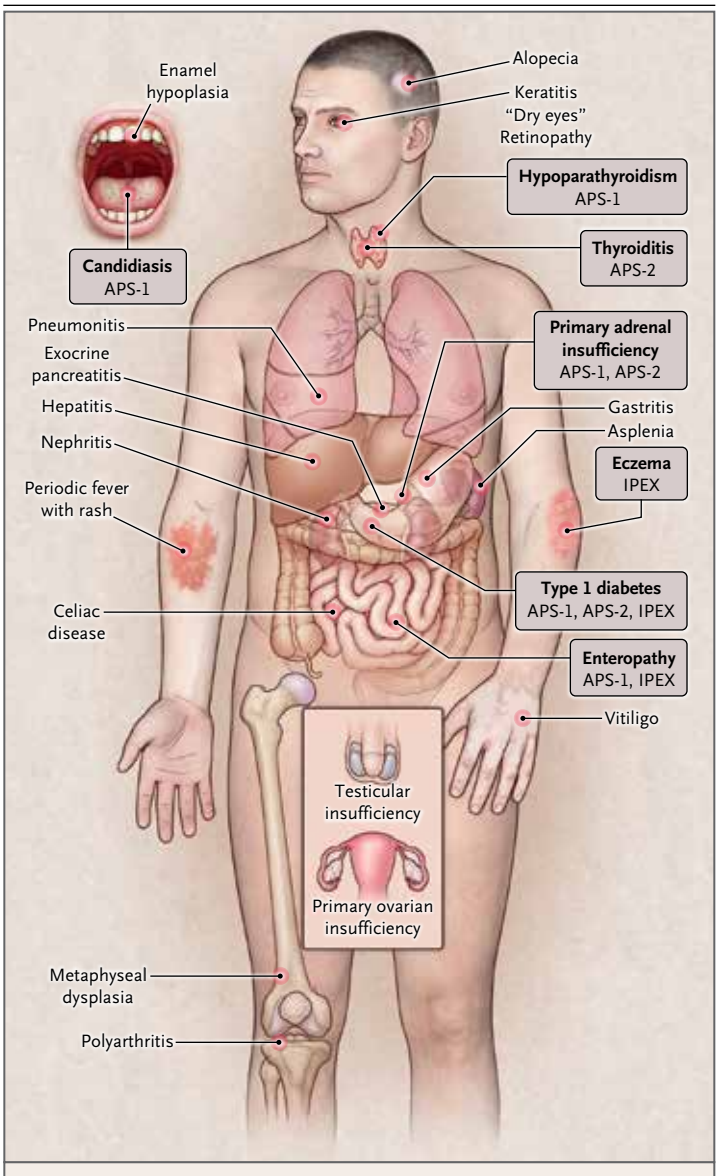

Figure 1. Organ-Specific Manifestations of Autoimmune Polyendocrine Syndromes.

Shown are the main manifestations of autoimmune polyendocrine syndrome type 1 (APS-1), APS-2, and X-linked immunodysregulation, polyendocrinopathy, and enteropathy (IPEX). Primary adrenal insufficiency is a characteristic of both APS-1 and APS-2; type 1 diabetes is a characteristic of APS-1, APS-2, and IPEX; and enteropathy is a characteristic of APS-1 and IPEX.

GENETICS AND DISEASE MECHANISMS

The basis for the spectrum of pleomorphic autoimmune manifestations of APS-1 has become clearer from studies of the defective gene in patients (*AIRE*) and mouse models (*Aire*). Aire, which is expressed in thymic medullary epithelial cells[14] and in a rare population of peripheral dendritic cells,[15] mediates the ectopic expression of thousands of otherwise tissue-restricted proteins, enabling their peptides to be displayed to developing T cells (Fig. 2A). Such unique antigen presentation helps to promote the negative selection of autoreactive thymocytes, as well as self-tolerance (i.e., a process that keeps the immune system from attacking the body's own tissues and organs). Thus, if Aire is nonfunc-

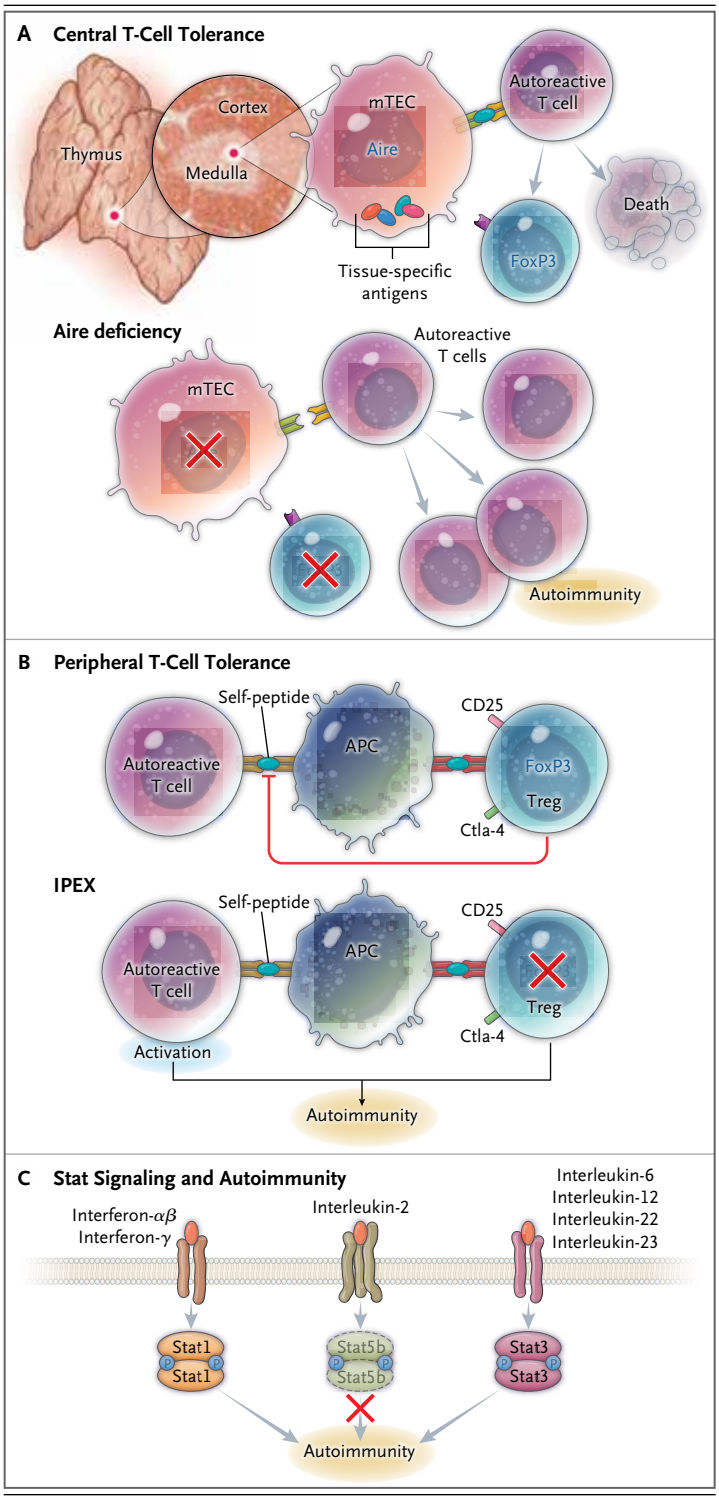

Figure 2. Key Immunoregulatory Pathways Involved in the Pathogenesis of Autoimmune Polyendocrine Syndromes.

Panel A (top) shows that in cases of normal central immune tolerance, the autoimmune regulator (Aire) that is expressed in medullary thymic epithelial cells (mTEC) promotes expression of tissue-specific antigens, which are displayed on the surface. Autoreactive T cells with affinity for self-proteins either die by apoptosis or become forkhead box P3 (FoxP3)–expressing regulatory T cells (Tregs). When Aire is lacking (Panel A, bottom), the tissue-specific antigens are not displayed on the mTEC surface and autoreactive T cells escape to the general circulation and peripheral lymphoid organs, where they can cause autoimmune reactions and APS-1. A lack of Tregs also contributes to autoimmunity. Panel B (top) shows how FoxP3+ Tregs harness autoreactive T cells by interacting with antigen-presenting cells (APCs). *FoxP3* mutations (Panel B, bottom) or mutations in other genes that are key to the function of Tregs (cytotoxic T-lymphocyte antigen 4 [Ctla-4] and CD25) remove the inhibition of autoreactive T cells, which then cause autoimmunity and IPEX and IPEX-like syndromes. Panel C shows signal transducers and activators of transcription (Stats), which are transducers of cell-surface cytokine signaling; Stats interact with interferon and interleukin receptors at the cell surface. After phosphorylation by Janus kinases, Stats dimerize and translocate to the nucleus. Mutations that lead to constitutively active forms of Stat1 or Stat3 promote autoimmunity; loss-of-function mutations in *Stat5b* also lead to autoimmunity. The exact mechanisms need to be further dissected, but loss of Stat5b could be due to the improper expression of FoxP3, a known target of Stat5b.

tional or absent, many autoreactive T cells with specificity for given antigens can escape deletion and may later be able to initiate autoimmune disease (Fig. 2A). Findings indicate that Aire controls immune tolerance by an additional mechanism — the induction of a unique population of FoxP3+ regulatory T cells (Tregs) in the thymus that have the ability to suppress autoreactive cells.[16,17] Thus, not only do more autoreactive cells escape deletion, but the Tregs that are normally in place to limit the activities of autoreactive cells either are not developed or are dysfunctional (Fig. 2A).

Various disease-causing mutations are distributed throughout *AIRE* (Fig. S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org); to date, more than 100 different mutations have been reported. The most common is the so-called Finnish major mutation (p.R257X), located in the SAND domain (named for the following protein families: Sp100, AIRE-1, NucP41/75, DEAF-1). The Finnish major mutation is especially prevalent in people in Finland, Russia, and Eastern Europe.[8,18] Another common mutation is the so-called 13 base-pair deletion (p.C322del13) in the histone protein reading region called plant homeodomain 1

(PHD1), prevalent in persons from Norway, the British Isles, France, and North America.[6,7,19] In addition, patients with unique dominant negative mutations in *AIRE* and autosomal dominant inheritance have recently been identified. These dominant negative mutations are associated with milder disease, which is often accompanied by pernicious anemia, vitiligo, autoimmune thyroid disease, and type 1 diabetes[20-22] and can be confused with the much more common condition APS-2, which has a complex inheritance. The dominant gene variants are located in both the PHD1 and the SAND domains (Fig. S1 in the Supplementary Appendix). Since AIRE is active as a multimer, it seems that changes in critical amino acids in mutant AIRE inhibit wild-type AIRE, thus creating the dominant negative effect. According to the Exome Aggregation Consortium (ExAC) database, these variants are present in populations at frequencies of at least 0.1% (http://exac.broadinstitute.org).[21] It is likely that in many families with "nonclassic" dominant APS-1, the condition remains undiagnosed.

AUTOANTIBODIES

As an early marker of T-cell–mediated loss of immune tolerance in patients with APS-1, disease-associated organ-specific autoantibodies may appear, often targeting intracellular proteins that have key functions in affected organs (Table 1, and Table S1 in the Supplementary Appendix). Many of the autoantibodies are fairly specific to APS-1, such as NALP5 (NACHT, leucine-rich repeat, pyrin domain–containing protein 5, an autoantibody expressed in the parathyroid and to some extent in the ovaries, which is also known as NLRP5 [NOD-like receptor family, pyrin domain–containing protein 5]),[23] BPI fold-containing family B member 1 (BPIFB1),[24] the potassium-channel regulator KCNRG (expressed in the lung),[25] and transglutaminase 4 (expressed solely in the prostate gland).[26] Other autoantibodies observed in APS-1 also appear in more common autoimmune diseases, such as those targeting glutamic acid decarboxylase 65 in type 1 diabetes,[27] 21-hydroxylase in Addison's disease,[28] and side-chain cleavage enzyme in autoimmune primary ovarian insufficiency,[29] pointing to possible commonalities in the pathogenesis of these various entities.

In contrast to the autoantibodies mentioned above, systemic autoantibodies to certain cytokines are highly prevalent in many, if not most, patients with APS-1. Autoantibodies to type 1 interferons, namely interferon-ω and interferon-α, are the most prevalent type of autoantibody in APS-1 and are present in almost all patients[30,31] (except those with dominant negative mutations[21]). In addition to being seen in APS-1, interferon antibodies are also consistently seen in myasthenia gravis and thymomas,[32,33] as well as in patients with so-called "mild" recombination activating gene (*RAG*) mutations.[34] In patients with APS-1, autoantibodies to the interleukin-17 family of cytokines, especially interleukin-22,[35,36] reach a prevalence exceeding 90% in some series.[35]

In our experience, the diagnosis of APS-1 is often delayed and sometimes made only after the death of the patient, on diagnosis of a sibling.[37] Availability of *AIRE* sequencing and specific autoantibody tests have uncovered milder and more atypical cases of APS-1 in persons without two of the three main components.[38] In such patients, minor components can be very helpful diagnostic hints. Some minor components of APS-1 develop early in life (keratitis, periodic fever with rash, and autoimmune hepatitis),[7] whereas others occur later (primary ovarian insufficiency in patients younger than 30 years of age and enamel hypoplasia).[6] Since more than 95% of patients with APS-1 have autoantibodies to type 1 interferons,[6,8] broad testing for such antibodies in suspected cases may be useful. In Figure 3, we summarize current knowledge in a diagnostic workup scheme. A widely available test to detect autoantibodies quickly would be a cost-effective tool for first-line screening before genetic testing.

X-LINKED IMMUNODYSREGULATION, POLYENDOCRINOPATHY, AND ENTEROPATHY

X-linked immunodysregulation, polyendocrinopathy, and enteropathy (IPEX) (OMIM number, 304790) is an extremely rare inherited syndrome characterized by early-onset type 1 diabetes,[39,40] autoimmune enteropathy with intractable diarrhea and malabsorption, and dermatitis that may be eczematiform, ichthyosiform, or psoriasiform. Eosinophilia and elevated IgE levels are frequently present in patients with IPEX. Kidney disease, most often membranous glomerulonephritis or interstitial nephritis, develops in some patients. Later manifestations of the syndrome may include autoimmune thyroid disease, alopecia, various

Table 1. Classification and Characteristics of Autoimmune Polyendocrine Syndromes.*

Characteristic	APS-1	APS-2	IPEX
Main manifestations	Addison's disease, hypoparathyroidism, chronic mucocutaneous candidiasis	Addison's disease, autoimmune thyroid disease, type 1 diabetes	Autoimmune enteropathy, neonatal type 1 diabetes, eczema
Other, associated manifestations	Primary ovarian insufficiency, autoimmune thyroid disease, type 1 diabetes, gastritis, enteritis with malabsorption, hepatitis, pancreatitis, pneumonitis, nephritis, vitiligo, alopecia, nail dystrophy, enamel hypoplasia, keratitis, retinitis	Autoimmune gastritis, alopecia, vitiligo, celiac disease, primary ovarian insufficiency	Autoimmune thyroid disease, hemolytic anemia, thrombocytopenia
Typical age at onset	Childhood, adolescence	Adolescence to adulthood	Infancy
Prevalence	1:100,000	1:1000	1:1,000,000
Treatment	Hormone replacement, antifungal therapy, immunosuppressive therapy for hepatitis, malabsorption, nephritis, pneumonitis, keratitis	Hormone replacement	Hormone replacement, bone marrow transplantation
Complications, including death	Adrenal and hypocalcemic crises, cancer in mouth and esophagus	Adrenal crisis, complications of diabetes	Infections
Genes and mode of inheritance	*AIRE*, autosomal recessive and dominant	Polygenic: MHC and others	*FOXP3*, X-linked
Immune phenotype	Autoantibodies against interferon-ω and interferon-α (>95%), organ-specific intracellular proteins	Autoantibodies against 21-hydroxylase, GAD65, IA-2, thyrotropin receptor, TPO	Autoantibodies against GAD65, lymphocytosis, eosinophilia, overproduction of cytokines, hyper IgE

* AIRE denotes autoimmune regulator; APS-1 autoimmune polyendocrine syndrome (APS) type 1; APS-2 APS type 2; FOXP3 forkhead box P3; GAD65 glutamic acid decarboxylase 65; IA-2 islet antigen 2; IPEX X-linked immunodysregulation, polyendocrinopathy, and enteropathy; MHC major histocompatibility complex; and TPO thyroid peroxidase.

autoimmune cytopenias, hepatitis, and exocrine pancreatitis.[41] Many features overlap with APS-1, but they usually develop much earlier in life than in APS-1. IPEX is frequently fatal in the first few years of life unless patients are promptly treated with immunosuppressive agents or, if possible, with allogeneic bone marrow transplantation, which can cure the disease.[41]

A mouse model of a spontaneously occurring X-linked disease similar to IPEX is called Scurfy. With the use of genetic mapping studies, the defective gene was mapped to mutations in the *Foxp3* gene in Scurfy mice and *FOXP3* in patients with IPEX.[42-44] To date, about 70 different mutations have been reported in patients. FOXP3 is currently recognized as a master transcription factor that is highly expressed in CD4+ Tregs[45] along with other Treg elements, including cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4) and CD25, the high-affinity interleukin-2 receptor (Fig. 2B). The importance of CD25 in Treg function has been underscored by the case of a woman presenting with IPEX-like features who had mutations in the *CD25* gene, which is not on the X chromosome,[46] and emphasizes the importance of interleukin-2 in promoting Treg survival and function.

In patients with IPEX, as in those with APS-1, circulating autoantibodies develop that can be helpful in making the diagnosis. The majority of patients with IPEX have autoantibodies against harmonin and villin,[47] proteins that are part of the molecular machinery involved in the organization and stabilization of the microvilli of the intestinal brush border. These proteins are also expressed in the renal proximal tubule, which may be associated with the high prevalence of enteropathy and nephritis in these patients. Some patients with IPEX have autoantibodies at a very early age, even a few weeks after birth, that are present in type 1 diabetes, including glutamic acid decarboxylase 65 and islet-cell autoantibodies.

Despite the rarity of IPEX, studies of affected patients have revealed a key pathway for self-tolerance (Fig. 2B) that has aided in the understanding of Tregs and has led to research aimed at the development of methods to enhance Treg function in transplantation and as a treatment for autoimmune disorders.[48,49]

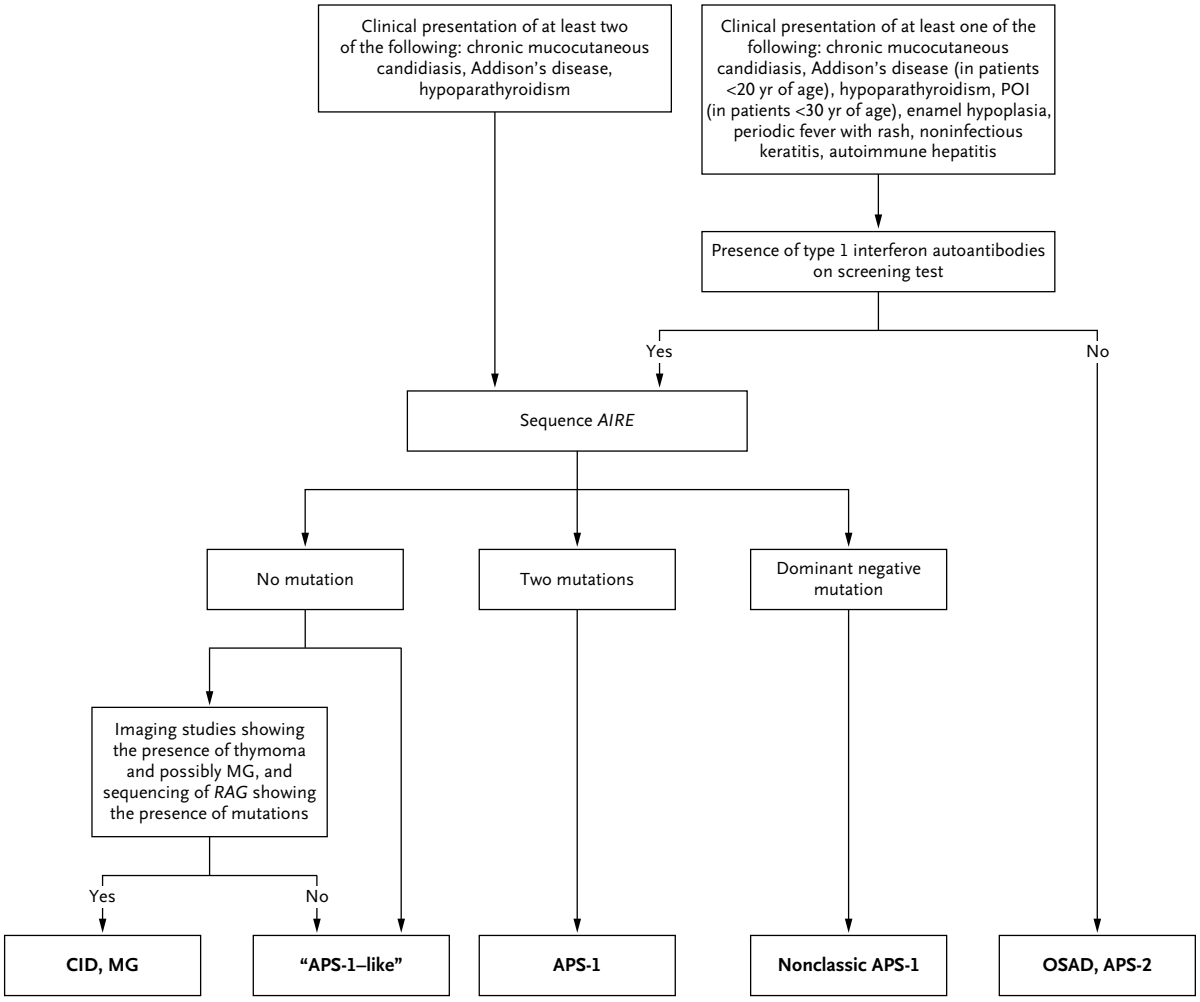

Figure 3. Diagnostic Evaluation for Autoimmune Polyendocrine Syndromes.

Patients with a clinical phenotype suggestive of APS-1 (upper right box) should be screened for interferon autoantibodies before autoimmune regulator gene (*AIRE*) sequencing is performed. Since interferon autoantibody screening currently is available only in research laboratories, consider going directly to sequencing of *AIRE*. Patients with a clinical diagnosis of APS-1 should have *AIRE* sequenced for mutations. Combined immunodeficiency (CID) is due to hypomorphic recombination activating gene (*RAG*) mutations (such as those that occur in the Omenn syndrome) and combined cellular and humoral immune defects with granulomas. MG denotes myasthenia gravis, OSAD organ-specific autoimmunity, and POI primary ovarian insufficiency.

OTHER INHERITED FORMS OF AUTOIMMUNE POLYENDOCRINE SYNDROMES

With the use of high-throughput DNA sequencing, other unique monogenic syndromes with endocrine components have been characterized. Common to most is that Treg function is aberrant, giving rise to IPEX-like phenotypes. Some examples are loss-of-function mutations in *STAT5B*, *ITCH*, and *BACH2* and gain-of-function mutations in *STAT1* and *STAT3* (see Table S2 in the Supplementary Appendix for details). An autosomal dominant syndrome characterized by hemolytic anemia, pneumonitis, lymphadenopathy, and hypogammaglobulinemia has been mapped to rare variants in the *CTLA-4* gene[50,51] that appear to destabilize Treg function and activity. However, the clinical presentation in affected patients is much milder than in patients with IPEX. A kindred with a similar clinical presentation was described in which the affected patients had mutations in the lipopolysaccharide-responsive

beige-like anchor (*LRBA*) gene.[52] The mutant LRBA protein alters proper cellular trafficking of CTLA-4. Treatment with a fusion protein composed of the Fc fragment of human IgG1 linked to CTLA-4 (abatacept), which binds to the ligands of CTLA-4, appears to be effective in controlling symptoms in affected patients. Several pedigrees have been identified with activating mutations in the gene *STAT3*, which encodes an important signaling molecule that helps to polarize type 17 helper T (Th17) cell responses (Fig. 2C).[53,54] Autoimmunity that includes type 1 diabetes, autoimmune thyroid disease, hemolytic anemia, and autoimmune thrombocytopenia frequently develops in affected patients.

AUTOIMMUNE POLYENDOCRINE SYNDROME TYPE 2

APS-2 is far more common than the syndromes already discussed. Patients with APS-2 have courses characterized by at least two of the following three endocrinopathies: type 1 diabetes, autoimmune thyroid disease, and Addison's disease.[55] Some authors propose splitting this syndrome into further subtypes, but there is little evidence for distinct causes in such subcategories, so the broader term APS-2 for all these patients seems appropriate. Women predominate among patients with APS-2. In many affected patients, other autoimmune conditions develop, including celiac disease, alopecia, vitiligo, primary ovarian insufficiency, and pernicious anemia (Table 1). Additional manifestations are more frequent among patients with APS-2 who have Addison's disease.[31,56]

The picture emerging from genetic studies of APS-2 is that the same genes and single-nucleotide polymorphisms are associated with several organ-specific autoimmune diseases. Thus, there are more similarities than specific differences when it comes to genetic associations.[55] In general, associations are mostly to genes coding for key regulatory proteins in the adaptive and innate immune system, particularly in the major histocompatibility complex. For example, patients with APS-2 who are at risk for celiac disease generally have variants in DR3-DQ2 and DR4-DQ8,[57] and these same haplotypes confer a risk of type 1 diabetes,[58] autoimmune thyroid disease,[59] and Addison's disease.[56] This explains why all four diseases may develop in the same patient. Other genes associated with a well-established risk of APS-2 include those that encode CTLA-4,[60] protein tyrosine phosphatase, nonreceptor type 22 (PTPN22),[61] the transcriptional regulator protein BACH2,[62,63] and the CD25–interleukin-2 receptor.[64] We find it interesting to note that missense and nonsense mutations in the coding region of several of the genes noted here cause monogenic syndromes (Table S2 in the Supplementary Appendix), pointing to their key role in immunoregulation.

Despite the major advancement in the identification of disease genes, the heritability of APS-2 is complex. Erichsen et al. found that approximately 10% of patients with APS-2 and Addison's disease had a relative with adrenal insufficiency.[56] Another study showed that approximately 10% of patients with APS-2 and type 1 diabetes had a sibling with the same disease, and an even larger percentage had a sibling with autoimmune thyroid disease.[65]

The onset of APS-2 typically occurs in young adulthood, later than the onset of APS-1. Currently, there are no unique tests to detect APS-2 in patients, but testing for autoantibodies may be helpful in assessing disease risk, since the relevant autoantibodies are frequently detectable years before disease onset. Examples are antibodies to thyroid peroxidase in autoimmune thyroid disease,[66] to glutamic acid decarboxylase 65 in type 1 diabetes,[27] and to 21-hydroxylase in autoimmune Addison's disease[28] (Table S1 in the Supplementary Appendix).

IMMUNE CHECKPOINT BLOCKADE AS A NEW TRIGGER FOR AUTOIMMUNE POLYENDOCRINE SYNDROMES

There has recently been rapid development in the use of therapeutic antibodies to activate the immune system to treat cancers. For example, therapeutic antibodies are being used to target the key regulators of peripheral immune tolerance — CTLA-4 and programmed cell death 1 (PD-1). The wider use of monoclonal antibodies in cancer treatment has revealed that autoimmunity-induced side effects develop in some patients.[67] For example, colitis is common, and autoimmune thyroiditis has frequently been seen in patients treated with both CTLA-4 and PD-1 immune checkpoint blockade, with an incidence of more than 10%.[68] Another remarkable side effect is autoimmune hypophysitis, otherwise a very rare disease, in patients treated with anti–

CTLA-4 antibodies, especially ipilimumab.[69] In addition, there are reports that type 1 diabetes is developing in patients after treatment with PD-1 blockade,[70] as is Addison's disease.[71] These developments underscore the importance of key immune regulators in the active suppression of autoimmune reactions.

TREATMENT AND FOLLOW-UP OF AUTOIMMUNE POLYENDOCRINE SYNDROMES

In general, management of autoimmune polyendocrine syndromes includes hormone-replacement therapy as needed and treatment of complications. Patients with APS-1 are best followed by a multidisciplinary team led by an endocrinologist (who specializes in either children or adults) at a tertiary-care center. Patients should have a minimum of two follow-up visits per year because of the complexity of the entity, and asymptomatic carriers of mutations should be followed at least annually. It is mandatory to check all siblings of patients with APS-1, even if the siblings are adults and seemingly well. Screening for 21-hydroxylase and NALP5 autoantibodies is useful in assessing the risk of the development of adrenal insufficiency and hypoparathyroidism, respectively.

Chronic mucocutaneous candidiasis with oral manifestations is generally managed with oral mycostatin and oral amphotericin B to avoid the problem of drug resistance that is often encountered in association with the continuous use of azole preparations.[4] Azole drugs inhibit steroidogenesis; such inhibition is associated with the risk of inducing adrenal insufficiency, especially in patients who have unrecognized Addison's disease. Hypoparathyroidism is managed with oral vitamin D derivatives in combination with calcium and magnesium supplementation, but it is sometimes difficult to control because of concomitant malabsorption.[72] Some azole compounds may also inhibit the activation of alfacalcidol, an analogue of vitamin D that is used for supplementation. Parathyroid hormone can be administered by either multiple injections or pump, but administration is not recommended for the following reasons: the potential risk of the development of osteosarcoma, a lack of studies verifying efficacy, and high cost.[73] However, it can be useful in patients with hypocalcemia who do not have a response to supplementation owing to malabsorption.

Other symptoms, such as keratitis, pneumonitis, hepatitis, or enteritis, may require immunosuppressive treatment (Table S3 in the Supplementary Appendix). Topical glucocorticoids and cyclosporine may be helpful in the treatment of keratitis, but irreversible corneal scarring develops in many patients who receive such therapy.[74] A new cyclosporine prodrug, which may be used topically, improves bioavailability. Rituximab has been reported to have beneficial effects on pneumonitis and malabsorption,[75] and cyclosporine has improved pancreatic insufficiency.[76] Autoimmune hepatitis in patients with APS-1 can be aggressive and lead to hepatic failure and death if not promptly treated with high-dose glucocorticoids and azathioprine.[11] More studies of immunosuppressive treatment are needed. Since asplenia can develop insidiously in patients with APS-1, we recommend vaccination against pneumococcus (with both 13-valent and 23-valent pneumococcal polysaccharide vaccines), meningococcus, *Haemophilus influenzae* type b, and influenza (Table S4 in the Supplementary Appendix).

Treatment of APS-2 should focus on replacement of missing hormones in accordance with current guidelines for treating the main components of APS-2. Physicians should be particularly aware that a patient with APS-2 is at increased risk for the development of another organ-specific autoimmune disease (Table S4 in the Supplementary Appendix). Massive accumulation of autoimmune diseases in a family, especially with early debut, could indicate a monogenic disease, possibly a "nonclassic" APS-1, especially if vitiligo and pernicious anemia are prevalent.[21]

NEW DIRECTIONS

In the past decade, we have seen the unraveling of new monogenic forms of the autoimmune polyendocrine syndrome and better diagnostic tools, both genetic tests and autoantibody analyses. Research in the next decades should focus on prevention and targeted treatment of autoimmune diseases. More knowledge on genetic mechanisms and environmental triggers may permit subclassifying autoimmune polyendocrine syndromes into distinct entities that have relevance for treatment and prognosis. Combining early and refined diagnostics with personalized genomics could enable physicians to apply early immunomodulatory therapy that would stop the autoimmune process before irreversible organ

damage occurs. Work is currently under way to generate thymic epithelial tissue from stem cells.[77] This approach could eventually be used to correct the expression of AIRE in patients with APS-1 and help reverse the immunopathological course that leads to multiorgan autoimmunity.

Dr. Husebye reports receiving grant support from the Novo Nordisk Foundation, provision of drugs from GlaxoSmithKline, and lecture fees and consulting fees from Shire; Dr. Anderson, owning stock in Medtronic; and Dr. Kämpe, receiving grant support from the Torsten and Ragnar Söderberg Foundations and Novo Nordisk Foundation, serving as a board member for and being a shareholder in Olink Bioscience, being an unpaid consultant for Shire, and holding a pending patent (PCT/SE2015/051189) on FHL1 autoantibody testing in polymyositis. No other potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

We thank Drs. Cindy Wong, Mickie Cheng, and Marianne Øksnes for critically reading an earlier version of the manuscript.

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