به نام خدا

Autoimmune Polyendocrine Syndromes

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Review Article

٢٠١٨

- **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, who in ١٩٢٦ 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 ١ (**APS-١**)

- a ***more common*** polygenic variety, autoimmune polyendocrine syndrome type ٢ (***APS-*** ٢).

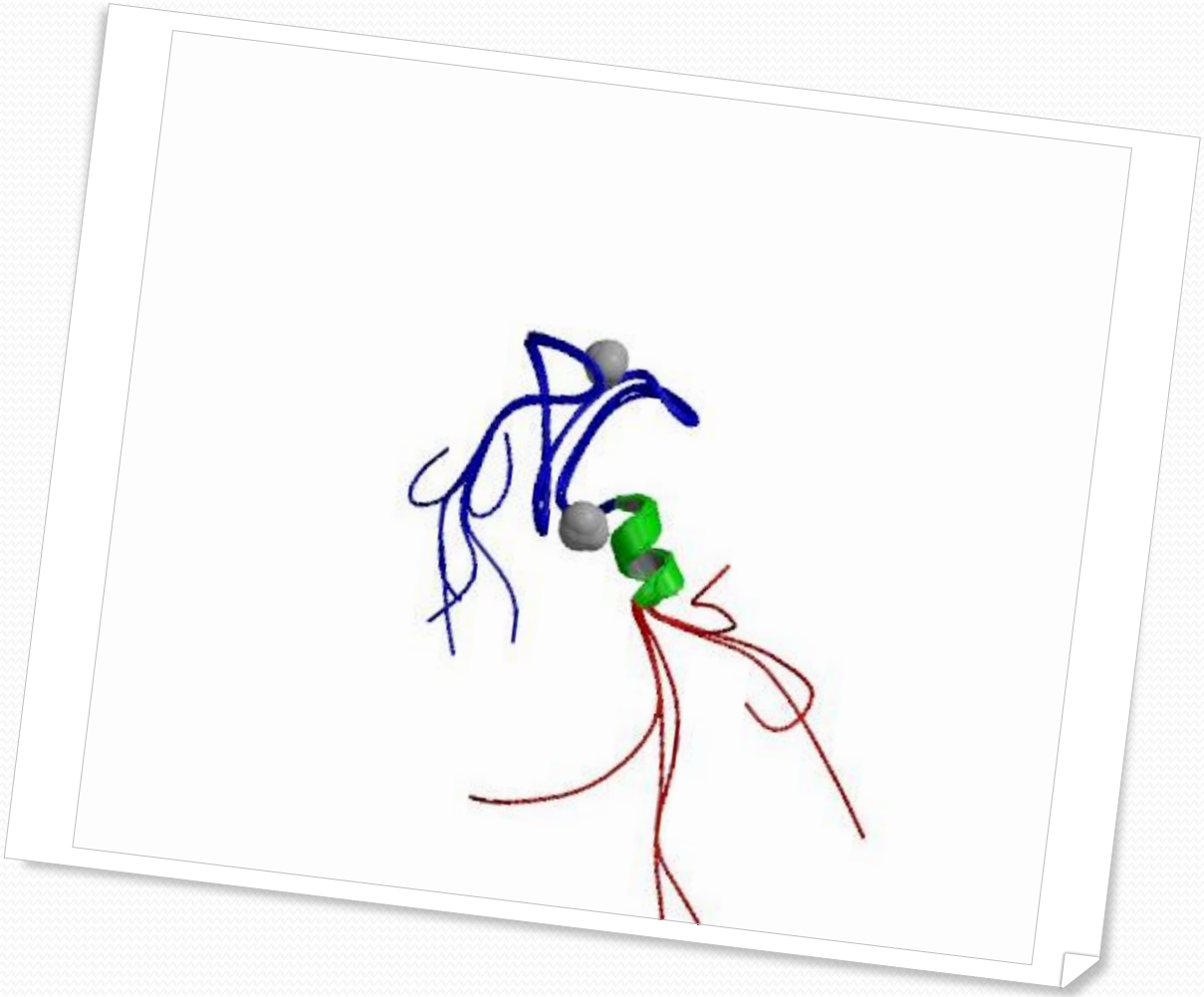
- Autoimmune polyendocrine syndromes are insidious and are characterized by :

➢ circulating autoantibodies

➢ 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.

Autoimmune Polyendocrine Syndrome Type ١



- APS-١, also named:
  autoimmune polyendocrinopathy–candidiasis–
  ectodermal dystrophy (APECED)
- rare autosomal recessive disease caused by mutations in the autoimmune regulator gene (AIRE)
- The estimated prevalence is roughly ١:١٠٠,٠٠٠ in most countries, with a higher prevalence in some countries such as Finland (١:٢٥,٠٠٠) and Sardinia (١:١٤,٠٠٠) and among Persian Jews living in Israel (١:٩٠٠٠).

Clinical Features APS-١ is:

development of at least two of three cardinal components during childhood :

- chronic mucocutaneous candidiasis,
- hypoparathyroidism,
- primary adrenal insufficiency (Addison's disease)

Other typical components include:

- enamel hypoplasia
- enteropathy with chronic diarrhea or constipation.
- Primary ovarian insufficiency, affecting approximately ٤٠% of women with APS١ before they reach ٣٠ years of age (is common)

- Other classic components are less frequent
- bilateral keratitis, often accompanied by severe photophobia

- periodic fever with rash
- autoimmunity induced: hepatitis , pneumonitis, nephritis exocrine pancreatitis , functional asplenia

- On rare occasions, retinitis, metaphyseal dysplasia, pure red-cell aplasia, and polyarthritis

- a recent Norwegian survey reported that all three main components of APS-١ developed in only ٤٠% of affected patients.

- 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-١ challenging.

- In most patients with APS-١, disease manifestations develop earlier and are usually more severe than in patients with APS-٢.

- Typically in a given patient with APS-١, an average of ٤ or ٥ manifestations of the syndrome develop, but as few as ١ or as many as ٢٠ 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-١ have an increased rate of death due to :

  - cancer

  - adrenal and hypocalcemic crises

  - certain conditions induced by aberrant autoimmune responses, particularly hepatitis, nephritis, and pneumonitis

Genetics and Disease Mechanisms The basis for the spectrum of pleomorphic autoimmune manifestations of APS-١ has become clearer from studies of the defective gene in patients (AIRE) , which is expressed in:

- thymic medullary epithelial cells
- in a rare population of peripheral dendritic cells, mediates the ectopic expression

- Autoantibodies to type ١ interferons, namely interferon-ω and interferon-α, are the most prevalent type of autoantibody in APS-١ and are present in almost all patients

- In our experience, the diagnosis of APS-١ is often delayed and sometimes made only after the death of the patient, on diagnosis of a sibling.
- Availability of AIRE sequencing and specific autoantibody tests have uncovered milder and more atypical cases of APS-١ in persons without two of the three main components

- Since more than ٩٥% of patients with APS-١ have autoantibodies to type ١ interferons, broad testing for such antibodies in suspected cases may be useful.
- A widely available test to detect autoantibodies quickly would be a cost-effective tool for first-line screening before genetic testing

APS-١

Genes and mode of inheritance

- AIRE
  (autoimmune regulator)
- autosomal recessive and dominant

Immune phenotype

- Autoantibodies against

-- interferon-ω and interferon-α (>٩٥%),

-- organ-specific intracellular proteins

APS-١

Typical age at onset

- Childhood, adolescence

Prevalence

- ١:١٠٠,٠٠٠

APS-١

Main manifestations

- Addison's disease
- hypoparathyroidism
- chronic mucocutaneous candidiasis

Other, associated manifestations

- Primary ovarian insufficiency
- autoimmune thyroid disease
- type ١ diabetes
- gastritis
- enteritis with malabsorption
- hepatitis
- pancreatitis
- pneumonitis
- nephritis
- vitiligo
- alopecia
- nail dystrophy
- enamel hypoplasia
- keratitis
- retinitis

Complications, including death

Adrenal and hypocalcemic crises

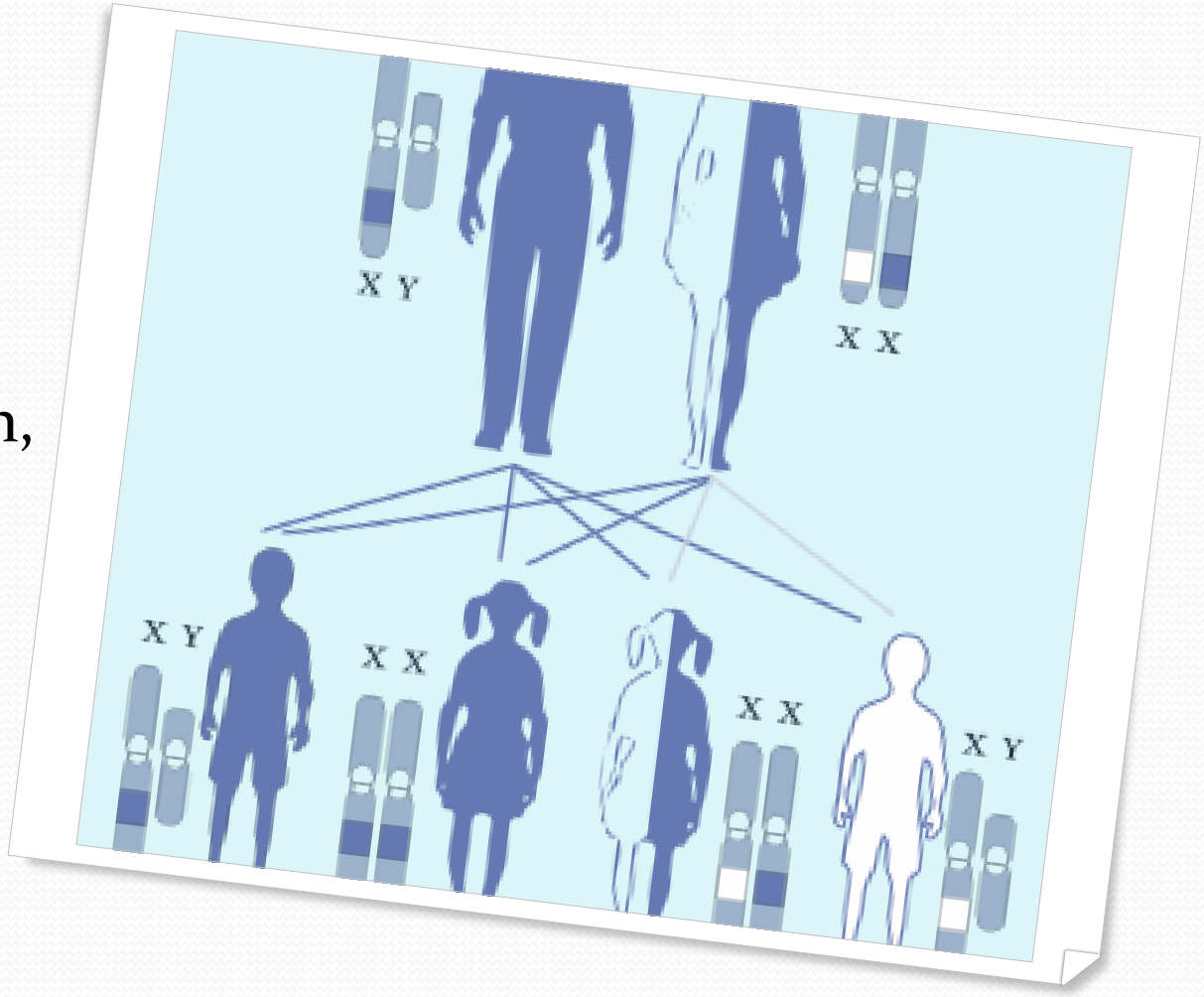
cancer in mouth and esophagus

TREATMENT

- Hormone replacement
- antifungal therapy
- immunosuppressive therapy for:
    - hepatitis
    - malabsorption
    - nephritis
    - pneumonitis
    - keratitis

IPEX

X-linked immunodysregulation, polyendocrinopathy, and enteropathy



IPEX

Main manifestations

- Autoimmune enteropathy
  neonatal type 1 diabetes
  eczema

Other, associated manifestations

Autoimmune thyroid disease
hemolytic anemia
thrombocytopenia

IPEX

Typical age at onset

- infancy

Prevalence

- ١:١,٠٠٠,٠٠٠

IPEX

Genes and mode of inheritance

- FOXP۳, X-linked

Immune phenotype

- Autoantibodies against GAD۶۵
- lymphocytosis
- eosinophili
- overproduction of cytokines ,hyper IgE

IPEX

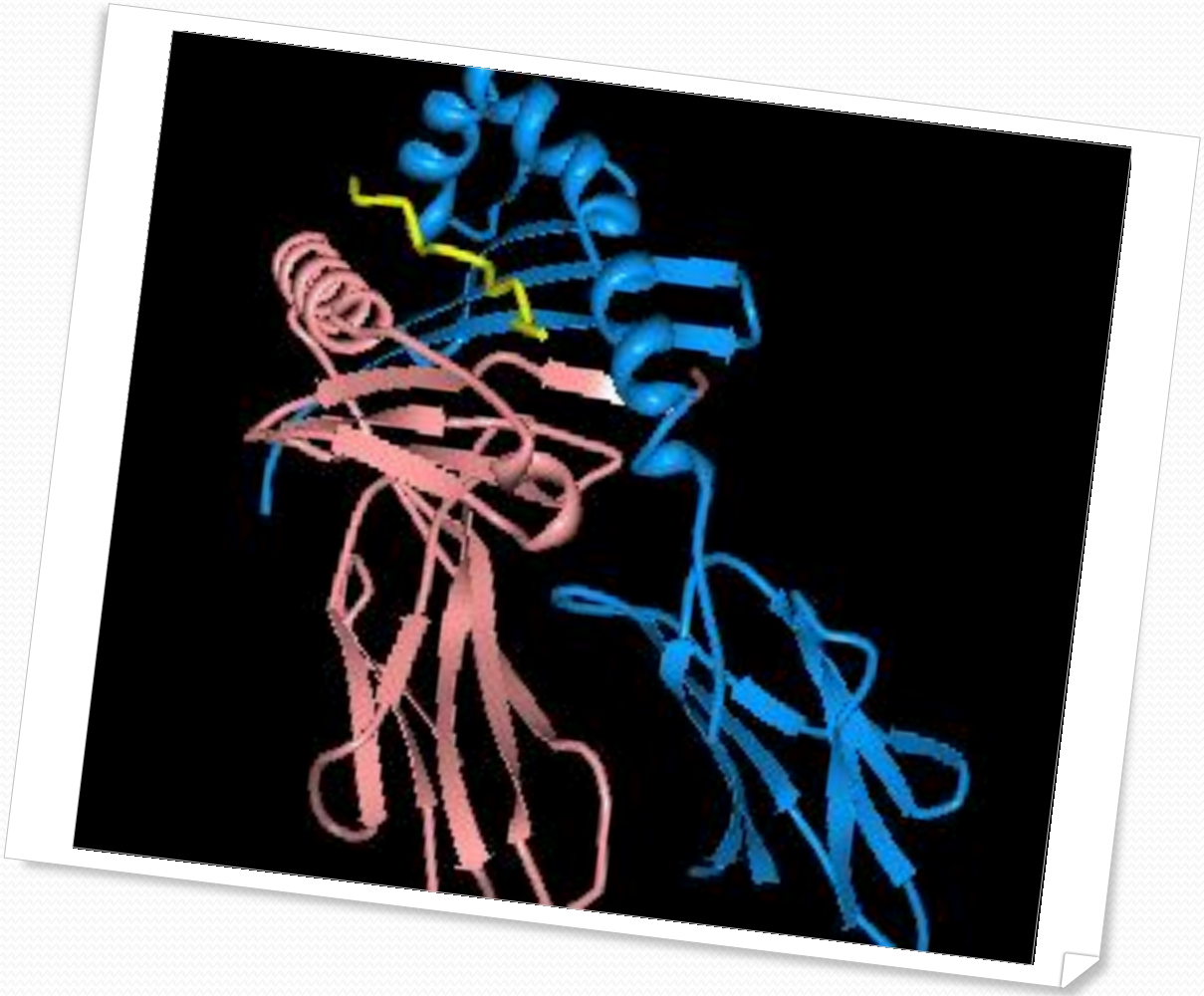
Complications, including death

- Infections

Treatment

- Hormone replacement
- bone marrow transplantation

Autoimmune Poly endocrine Syndrome Type ۲



APS-٢

Main manifestations

- Addison's disease,
- autoimmune thyroid disease
- type ١ diabetes

Other, associated manifestations

- Autoimmune gastritis
- alopecia
- vitiligo
- celiac disease
- primary ovarian insufficiecy

APS-٢

Typical age at onset

- Adolescence to adulthood

Prevalence

- ١:١٠٠٠

APS-٢

Genes and mode of inheritance

Polygenic: MHC and others

Immune phenotype

Autoantibodies against:

- ٢١- hydroxylase
- GAD٦٥
- IA-٢
- thyrotropin receptor
- TPO

APS-٢

Treatment

- Hormone replacement

Complications, including death

- Adrenal crisis
- complications of diabetes

APS-٢

- APS-٢ is far more common than the syndromes already discussed.
- The onset of APS-٢ typically occurs in young adulthood, later than the onset of APS-١
- Women predominate among patients with APS-٢

- ١٠% of patients with APS-٢ and Addison's disease had a relative with adrenal insufficiency.

- approximately ١٠% of patients with APS-٢ and type ١ diabetes had a sibling with the same disease and larger percentage had a sibling with autoimmune thyroid disease.

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Currently, there are no unique tests to detect APS-٢ 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
- glutamic acid decarboxylase ٦٥ in type ١ diabete
- ٢١-hydroxylase in autoimmune Addison's disease

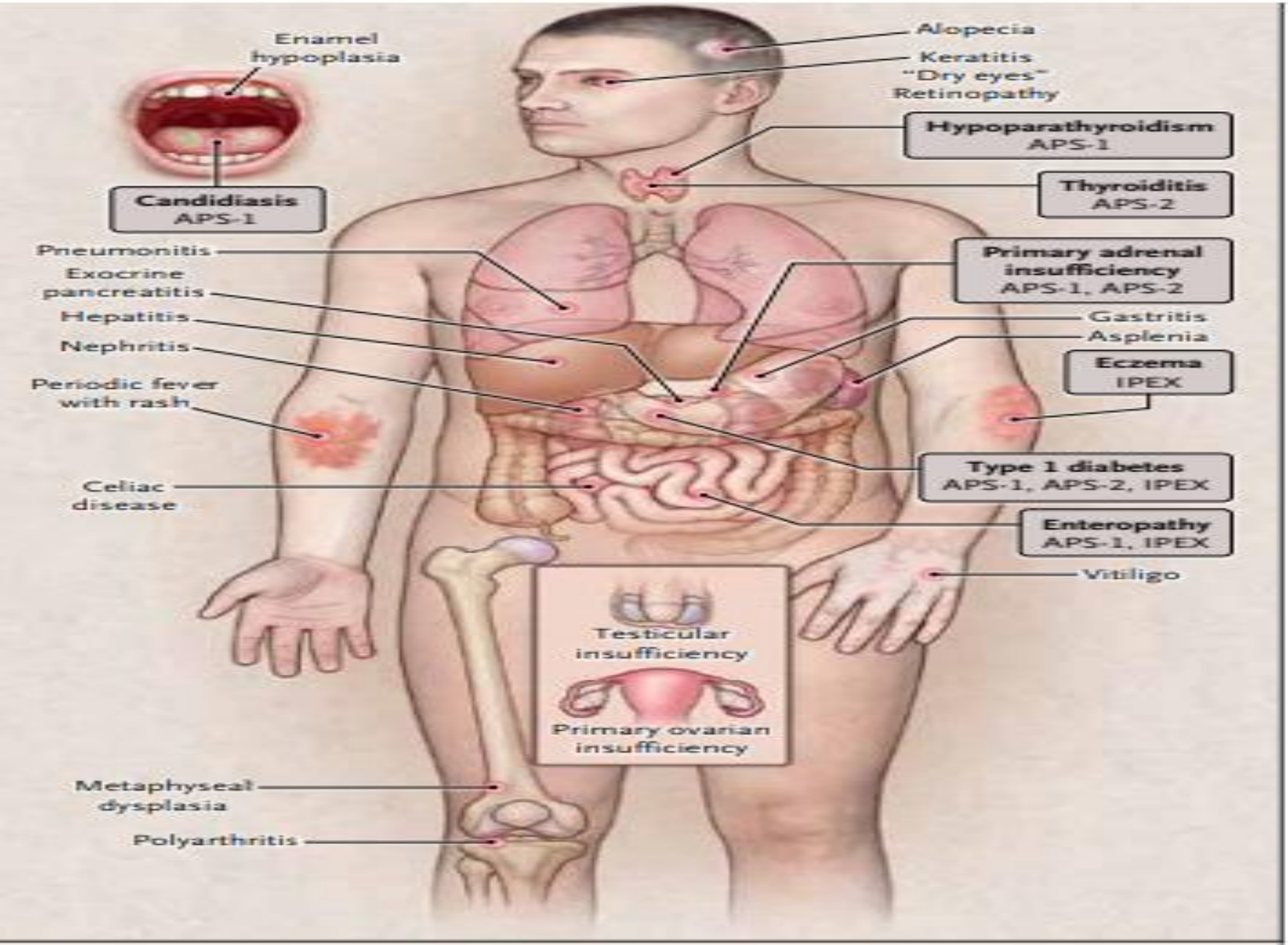

Figure 1. **Organ-Specific Manifestations of Autoimmune Polyendocrine Syndromes.**

Immune CheckKpoint 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

- therapeutic antibodies are being used to target the key regulators of peripheral immune tolerance — CTLA-۴ and programmed cell death (PD-۱).
- The wider use of monoclonal antibodies in cancer treatment has revealed that autoimmunity-induced side effects develop in some patients.
- colitis is common, and autoimmune thyroiditis has frequently been seen in patients treated with both CTLA-۴ and PD-۱ immune checkpoint blockade, with an incidence of more than ۱۰%.

- Another remarkable side effect is autoimmune hypophysitis, otherwise a very rare disease, in patients t CTLA-۴ antibodies, especially ipilimumab. In addition, there are reports that type ۱ diabetes is developing in patients after treatment with PD-۱ blockade, as is Addison's disease.
- 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
  - treatment of complications.
- Patients with APS-١ are best followed by a multidisciplinary team led by an endocrinologist (who specializes in either children or adults) at a tertiarycare 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-١, even if the siblings are adults and seemingly well.
- Screening for ٢١-hydroxylase and NALP٥ 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. 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. 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.

- 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

- Topical glucocorticoids and cyclosporine may be helpful in the treatment of keratitis, but irreversible corneal scarring develops in many patients who receive such therapy

- Rituximab has been reported to have beneficial effects on pneumonitis and malabsorption

- cyclosporine has improved pancreatic insufficiency.

- Autoimmune hepatitis in patients with APS-١ can be aggressive and lead to hepatic failure and death if not promptly treated with high-dose glucocorticoids and azathioprine.

- Since asplenia can develop insidiously in patients with APS-١, we recommend vaccination against pneumococcus (with both ١٣-valent and ٢٣-valent pneumococcal polysaccharide vaccines), meningococcus, Haemophilus influenzae type b, and influenza

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 demage occure*

- Work is currently under way to generate thymic epithelial tissue from **stem cells.**

- This approach could eventually be used to correct the **expression of AIRE** in patients with APS-١ and help reverse the immunopathological course that leads to multiorgan autoimmunity.


با تشکر از توجه شما