Case Report

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Polyneuropathy and Gastritis in Autoimmune Polyendocrine Syndrome Type 1 in a Young Adult: Uncommon Presentation of a Rare Disease

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Abstract

Autoimmune Polyendocrine Syndrome type1 (APS-1), sometimes called, autoimmune polyglandular syndrome type 1, and autoimmune-polyendocrinopathy-candidiasis-ectodermal-dystrophy (APECED), is a rare recessive disorder with diverse features that occurs due to mutations in the autoimmune regulator (AIRE) gene inducing autoimmunity. This report summarizes the diagnosis of APS 1 in a 17-year-old young man presenting with vomiting, diarrhea, and limb weakness. Investigation reveals mixed features of endocrinopathies including hypoparathyroidism, hypothyroidism, adrenal insufficiency, and hypogonadism. Although autoimmune keratitis, hepatitis, pancreatitis, pneumonitis, and nephritis are common systemic affection of this condition, the reported case presents with severe sensory-motor polyneuropathy and pangastritis. He carries a single heterozygous copy of the missense variant (NM_000383.3 c.841G>A chr21:45709913 p.Ala281Thr) in exon 7 of the AIRE.

Keywords: Autoimmune Polyendocrine Syndrome Type 1, APS 1, Autoimmune Polyglandular Syndrome Type 1, APECED, Polyneuropathy, Hereditary neuropathy, Gastritis

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Introduction

Autoimmune Polyendocrine Syndrome denotes a group of hereditary disorders that can be of two major clinical types- juvenile and adult.[1]

The juvenile type is known as Autoimmune Polyendocrine Syndrome type1 (APS 1), Autoimmune Polyglandular Syndrome Type 1, Autoimmune-Polyendocrinopathy-Candidiasis-Ectodermal-Dystrophy (APECED), or Whitaker syndrome.[2,3]

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It occurs due to mutation of the autoimmune regulator (AIRE) gene, is monogenic and rare with autosomal recessive inheritance.[3] On the other hand, APS 2, APS 3, and APS 4 are adult types, common and polygenic.[1] APS 1 has a diverse clinical presentation of a variable range of endocrine dysfunction and non-endocrine features. Hypoparathyroidism, hypofunction of adrenals, hypogonadism, vitiligo, and candidiasis are common.[4]Autoimmunity can involve multiple systems of the body manifesting as autoimmune keratitis, retinitis, gastritis, celiac disease, alopecia, hepatitis, pancreatitis, pneumonitis, and nephritis.[4,5] These non-endocrine manifestations are present in more than two-thirds of the cases. APS 1 is a rare recessive disorder prevalent among certain ethnic groups like the Finns, Iranian Jews, and Sardinians.[5] It is extremely rare among Americans, to occur only once in two to three million live births.[2,6] Reports from Asian countries are even fewer in counts. Not only the cases are rare but also they are variably insidious to manifest.[2,3] A Norwegian survey showed that one-third of the APS 1 cases manifest at least one feature of the disease in childhood and other features come to notice at variable ages of adulthood.[4,5,6] At times the diagnosis is delayed

as late as the death of a sibling.[2] All these facts contribute to the challenges in reaching an authentic and confident diagnosis of this condition.[7] This report is about a young man with extreme generalized weakness, limb weakness, weight loss, and long-standing gastrointestinal symptoms. Investigations endorse him as a case of APS 1 with AIRE gene mutation. He has manifestations of endocrine, gastrointestinal, and peripheral nerve involvement which make up a relatively uncommon combination of phenotypic features of this rare genetic disease.

Case report

A 17-year-old teenager presented to a private clinic in Sylhet, Bangladesh, with extreme generalized weakness, loss of appetite, and loss of weight for 3 years. His parents mentioned that he suffered from failure to thrive as a child. He had a history of lethargy, easy fatigability, cold intolerance, upper abdominal pain, frequent loose stool, and vomiting but had no history of fever, rash, oral thrush, pigmentation, cough, sputum,muscle cramp, palpitation, breathlessness, and exposure to a tuberculosis patient. Both of his parents were diabetic but he had healthy siblings. He had been a madrasa student from where he had to quit on account of health issues. He had a mild form of paresthesia of limbs, difficulty in rising from squat, but with no gross motor paralysis.He had normal linear growth, dentition, and sleep.

On examination, he was ill-looking, and malnourished (Figure 1), weighed 36 kg, of normal mental state, height 154 cm, pulse 132/min, blood pressure 110/63 mmHg, SPO_2 100%, axillary temperature 97.9^o F, height 154 cm, BMI 15.17. His secondary sex characters were normally developed, normally distributed body hair and normal external genitalia. He showed mild quadriparesis with 4/5 muscle power, normal muscle tone, normal gait, and diminished jerks in all four limbs. He had an intact sensory system and cranial nerves. He had no dental abnormality and calcification in the tympanic membrane.

Routine blood tests including complete blood counts, peripheral blood smear, blood glucose, serum creatinine, electrolytes, bilirubin, total protein, albumin, globulin, liver enzymes including alkaline phosphatase and prothrombin time were within normal ranges but serum calcium (7.5 mg/dl) was low and phosphate (5.0 mg/dl) was high. Erythrocyte sedimentation rate (ESR) was 12 mm in the first hour and C-reactive protein (CRP) was 5 mg/dl. His plain radiograph and high-resolution computed tomographic scan of the chest were normal.

Stool routine microscopy showed undigested muscle fiber, vegetable fiber, numerous budding yeast, increased bacterial flora, and positive occult blood test. Stool elastase and chymotrypsin were normal and fat globules were absent. Endoscopy of the upper gastrointestinal tract revealed pangastritis (Figure 2) but a duodenal biopsy was unremarkable. Ultrasonography and computed tomographic scan (plain and contrast) of the abdomen and pelvis showed mild fatty infiltration of the liver with otherwise normal features. Colonoscopy and barium follow-through were normal. Serum ferritin (132ng/ml), folic acid (7.2 ng/ml) and vitamin B12 (454 pg/ml) were normal but vitamin D level was low (9.8 ng/ml). Viral markers for HIV, HCV, and HBV were negative. Antinuclear antibody was negative. Food IgG antibody testing showed high IgG levels for egg white, plums, corn, and fresh peas. Several endocrine abnormalities were noted (Table 1). Serum parathormone (PTH), testosterone and free thyroxin-4 (FT4) levels were low whereas adrenocorticotropic hormone (ACTH), thyroid-stimulating hormone (TSH), and prolactin levels were high and cortisol, follicle-stimulating hormone (FSH), luteinizing hormone (LH), insulin-like growth factor (IGF), sex hormone-binding globulin (SHBG) levels were within normal ranges.

Next-generation whole-exome sequencing studies, done in a national reference laboratory of New Delhi, India, revealed (Table 2) a novel heterozygous missense variant (NM_000383.3 c.841G>A chr21:45709913 p.Ala281Thr) in exon 7 of the autoimmune regulator (AIRE), a Variant of Uncertain Significance (VUS), with autosomal dominant inheritance, associated with APS-1. MRI of the brain showed bilateral frontal, parietal and temporal diffuse T2 hyperintense signal in white matter. Mild

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hyperintensity was also seen in the middle cerebellar peduncles of both sides extending along the dentate nucleus suggesting a metachromatic or leukodystrophic picture. Nerve Conduction Studies (NCS) revealed severe sensory-motor polyneuropathy with no response in lower limbs and uniformly demyelinating neuropathy in upper limbs (Figure 3). Sural nerve biopsy and histopathology showed epineurial neovascularization with thickening of the vessel wall. No inflammation, onion bulbs, or acute axonal breakdown were seen. K-pal staining revealed severe uniform loss of myelinated fibers. Several thinly myelinated fibers, suggesting demyelination, were also seen and some showed dysmorphic myelin sheath. Axonal regeneration was not prominent. All these histological features were compatible with hereditary neuropathy. Lumbar puncture and the cerebrospinal fluid study showed cell 01/cu-mm, protein 33mg/dl, glucose 55mg/dl, and chlorides 104 mmol/L, and absent oligoclonal bands.
Multidisciplinary consultation and discussion based on the clinical and laboratory features led to the diagnosis of APS 1 with a rare variant of AIRE mutation resulting in an uncommon combination of phenotypic manifestations comprising of hypoparathyroidism, hypothyroidism, hypogonadism, gastritis, and hereditary polyneuropathy.

Figure 1: General ill health and emaciation in the patient

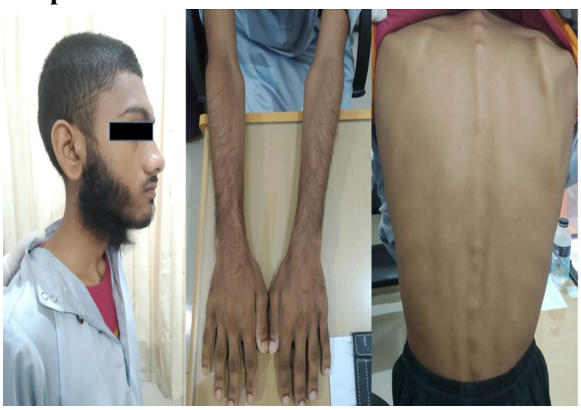

Figure 2: Endoscopy of upper gastrointestinal tract showing pangastritis

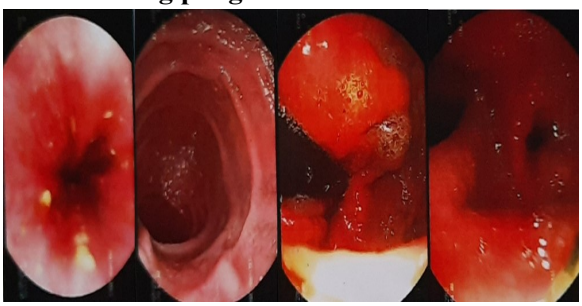

Figure 3: Nerve conduction study tracing upper limb (left) and lower limb (right)

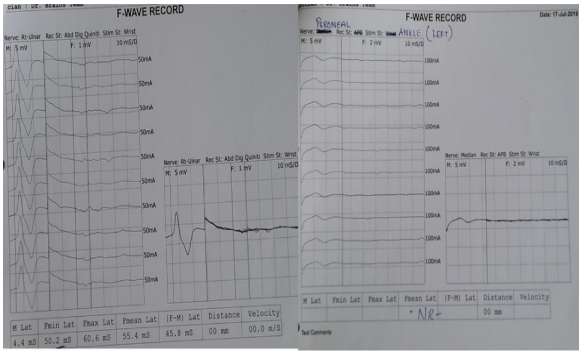

Table 1: Hormone levels

S/N	Test	Patient value	Normal range	Remarks
1	Serum PTH	6.7 pg/ml	9.2-44.6 pg/ ml	Low
2	Serum ACTH	83.7 pg/ml	7.2-63.3 pg/ml	High
3	Morning Cortisol	16.74 ug/dl	10-20 ug/dl	Normal
4	Serum Testosterone	97.98 ng/dl	249-836 ng/dl	Low
5	Serum SHBG	15.2 nmol/L	10-57 nmol/L	Normal
6	Serum FSH	1.56 mIU/ml	1.7-12 mIU/ml	Low
7	Serum LH	1.65 mIU/ml	1.42-15.4 mIU/ml	Normal
8	Serum TSH	6.4 uIU/ml	0.5-5.0 uIU/ml	Increased
9	Serum FT4	1.21 ug/dl	5.0-11.0 ug/dL	Low
10	Serum IGF	310 ng/ml	173-414 ng/ml	Normal
11	S. Prolactin	44.4 ng/ml	3-25 ng/ml	Increased

Table 2: Gene sequencing report (Next generation sequencing)

Gene	Chromosomal coordinates	Exon location	Variant	Zygosity	Condition group	Significance	Inheritance
AIRE	chr21:45709913 NM_000383.3	7	c.841G>A p.Ala281Thr	Heterozygous	APECED	VUS	Autosomal dominant
Secondary findings and interpretation							
Gene	**Chromosomal coordinates**	**Exon location**	**Variant**	**Zygosity**	**Condition group**	**Significance**	**Inheritance**
None							

Discussion

Autoimmune Polyendocrine Syndrome Type 1 (APS-1) is a rare hereditary disorder causing autoimmune dysfunction of many organs of the body including endocrine glands, liver,gastrointestinal tract, pancreas, kidneys, lungs, and tissues of ectodermal origin.[7] It results from mutations in the AIRE gene which causes unwanted immune responses against body tissues due to defect in cell mediated immunity.[5] The extensive nature of involvement makes this clinical condition too diverse and obscure to be recognized with ease.Clinical features are dependent on the organs involved, and the degree of clinical severity, course of manifestations also vary from case to case.[6] This article reports a case of APS 1 manifested in early teens initially with gastrointestinal symptoms later on with peripheral neuropathy on top of variable degree of subclinical hypoparathyroidism, hypothyroidism, adrenal insufficiency, and hypogonadism. The peripheral nerves affected by autoimmunity is less frequently encountered in APS 1 case reports.[2]

Most of the classical APS 1 cases present in early childhood with mucocutaneous candidiasis, sometimes appearing in newborns.[1] Some of the older researchers considered this feature as one of the diagnostic triad comprising of candidiasis, autoimmune hypoparathyroidism, and Addison's disease.[8,9] The AIRE gene mutation generates immunity against proteins of the IL-17 pathway that are important for defense against Candida.[10,11] There was no history of oro-genital candidiasis in the reported case but he passed significant quantity of budding yeast in stool. His mother had chronic oral thrush refractory to treatment, but she was not screened for AIRE mutation. Gastrointestinal features in the form of chronic abdominal pain, chronic loose motion and vomiting were the presenting features in this patient. Extensive gut evaluation for organic lesion and malabsorption only revealed pangastritis on endoscopy. About one tenth to one third of patients with Celiac disease have polyglandular abnormality but is more related to APS 2.[12] Fat malabsorption is found in 20% of APS 1 cases but stool fat globules were absent in the index case.[10]Vitamin D deficiency was found with normal levels of iron, folic acid and vitamin B_{12}. Hypovitaminosis D could be attributed to inadequate diet and sun exposure.

Of the endocrine abnormalities occurringin APS 1, the most common one ishypoparathyroidism, and in some, this is the only endocrinopathy present.[4] Though the reported patient did not have overt tetany, but had lethargy and easy fatigability. The low serum calcium could be attributed to low vitamin D or hypoparathyroidism, but marginally raised serum phosphate with low parathormone and normal alkaline phosphatase imposes the likelihood of this endocrine abnormality. He had cold intolerance, and generalized weakness with raised TSH and low FT_4 indicating primary hypothyroidism, though autoimmune thyroid disease and type 1 diabetes mellitus are more common in APS 2.[4,13]

Addison's disease is the second common endocrine abnormality in APS 1 and can also be

present in APS 2.[7,14] Elevated serum ACTH and low cortisol levels are expected in Addison's disease, but the case report shows elevated ACTH with normal levels of the latter, suggesting early adrenal insufficiency.[15]The patient had low serum testosterone, normal sex hormone binding globulin and raised prolactin in the absence of any striking clinical feature, and with normal pubertal progression. APS 1 is an uncommon cause of hypogonadism in young adults but this is a common endocrine abnormality among the AIRE mutants.The mild form of hyperprolactinemia found in the patient may be due to hypothyroidism.[16,17]

Polyneuropathies as a whole have a low (1%) prevalence rates among general population[18], and the subcategories of it are even lower in prevalence. The authors did not find any central nervous system deficitin spite of the MRI featuresin the patient.Clinicaland neuro-physical features resembled Chronic Inflammatory Demyelinating Polyneuropathy (CIDP).But, sural nerve histopathology revealedabsence of inflammation and presence of epineurial neovascularization, severe uniform loss of myelinated fibers suggesting hereditary polyneuropathy.[20] This re-demonstrates the fact that clinical diagnosis can be changed by histopathological findings in around 40% of patients with neuropathy.[21]Gastritis in APS 1 is associated with sub-acute combined degeneration caused by vitamin B_{12} deficiency, which was not found in this report.[22]Moreover, the absence of oligoclonal bands in cerebrospinal fluid excluded multiple sclerosis and other immune mediated disorders of the central nervous system.[4,20]

The AIRE gene mutations related to classical APS 1 have autosomal recessive mode of transmission.[7,8] However, cases have been identified with mono-allelic mutations of this gene with dominant inheritance, with milder clinical features, and reduced penetrance.[22] Oftedal et al found out heterozygous dominant-negative mutations in the AIRE gene.[23] Genetic studies in the index case revealed single copy (heterogenous) mutations of the AIRE gene in exon location 7 (NM_000383.3 c.841G>A chr21:45709913 p.Ala281Thr), with dominant inheritance. Moreover, researchers find that monogenetic mutations causing autoimmunity are less identified than they exist in reality, and also that the penetrance of the disease is variable (30-40%), rarely reaching hundred percent even among monozygotic twins.[1,25,26] Though only one of the copies of the AIRE gene was found to be mutated in the reported case, other epigenetic issues might have hampered expression of the other gene. Authors consider that both of the parents should undergo exome sequencing to prove whether the genetic defect was transmitted from one of them or it was a result of spontaneous mutation.

Different endocrine gland specific antibodies could serve as evidences for autoimmune process, but were not asked for in this patient, on the ground that the presence of AIRE mutation practically imposes a valid causal relationship with the endocrine dysfunctions and also due to financial reasons.Type1 interferon alpha and omega autoantibodies are important tool for diagnosis of APS 1 in the absence of overt phenotypic features.[4] Interestingly enough, it has been hypothesized from recent study results that these antibodies are associated with severe forms of COVID-19 pneumonitis.[27,28] The reported case has been closely observed during the ongoing COVID-19 pandemic with no clinical or radiological features of this viral infection. Revised criteria for diagnosis of APS 1include testing interferon autoantibodies nowadays, however, genetic analysis is considered to suffice as an alternate tool if antibody detection is not possible.[17]

Conclusion

Autoimmune Polyendocrine Syndrome type 1 is a rare hereditary disease of autoimmunity that has potentials to produce clinical features of multiple endocrine and non-endocrine organs. Prior knowledge about the condition can save from making a wrong diagnosis or a missed diagnosis in clinical practice.

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References

1. Yukina MY, Larina AA, Vasilyev EV, Troshina EA, Dimitrova DA. Search for Genetic Predictors of Adult Autoimmune Polyendocrine Syndrome in Monozygotic Twins. Clin Med Insights Endocrinol Diabetes. 2021 Apr 19;14:11795514211009796. doi: 10.1177/11795514211009796.
2. Savvateeva EN, Yukina MY, Nuralieva NF, Filippova MA, Gryadunov DA, Troshina EA. Multiplex Autoantibody Detection in Patients with Autoimmune Polyglandular Syndromes. Int J Mol Sci. 2021 May 23;22(11):5502. doi: 10.3390/ijms22115502.
3. Betterle C, Garelli S, Coco G, Burra P. A rare combination of type 3 autoimmune polyendocrine syndrome (APS-3) or multiple autoimmune syndrome (MAS-3). Auto Immun Highlights. 2014 Feb 11;5(1):27-31. doi: 10.1007/s13317-013-0055-6.
4. Husebye ES, Anderson MS, Kämpe O. Autoimmune Polyendocrine Syndromes. N Engl J Med. 2018 Mar 22;378(12):1132-1141. doi: 10.1056/NEJMra1713301.
5. Perniola R, Fierabracci A, Falorni A. Autoimmune Addison's Disease as Part of the Autoimmune Polyglandular Syndrome Type 1: Historical Overview and Current Evidence. Front Immunol. 2021 Feb 26;12:606860. doi: 10.3389/fimmu.2021.606860.
6. Ennab RM, Saadeh NA. A Case of Critical Lower-Limb Ischemia in a 29-Year-Old Man with Autoimmune Polyglandular Syndrome Type 1 (APS-1). Am J Case Rep. 2020 Oct 17;21:e924705. doi: 10.12659/AJCR.924705.
7. Betterle C, Lazzarotto F, Presotto F. Autoimmune polyglandular syndrome Type 2: the tip of an iceberg? Clin Exp Immunol. 2004 Aug;137(2):225-33. doi: 10.1111/j.1365-2249.2004.02561.x.
8. Huppler AR, Bishu S, Gaffen SL. Mucocutaneous candidiasis: the IL-17 pathway and implications for targeted immunotherapy. Arthritis Res Ther. 2012 Jul 23;14(4):217. doi: 10.1186/ar3893.
9. Humbert L, Cornu M, Proust-Lemoine E, Bayry J, Wemeau JL, Vantyghem MC, Sendid B. Chronic Mucocutaneous
10. Candidiasis in Autoimmune Polyendocrine Syndrome Type 1. Front Immunol. 2018 Nov 19;9:2570. doi: 10.3389/fimmu.2018.02570.
11. Perniola R. Twenty Years of AIRE. Front Immunol. 2018 Feb 12;9:98. doi: 10.3389/fimmu.2018.00098.
12. Puel A, Cypowyj S, Maródi L, Abel L, Picard C, Casanova JL. Inborn errors of human IL-17 immunity underlie chronic mucocutaneous candidiasis. CurrOpin Allergy ClinImmunol. 2012 Dec;12(6):616-22. doi: 10.1097/ACI.0b013e328358cc0b.
13. Kahaly GJ, Frommer L, Schuppan D. Celiac Disease and Glandular Autoimmunity. Nutrients. 2018 Jun 25;10(7):814. doi: 10.3390/nu10070814.
14. Kyritsi EM, Kanaka-Gantenbein C. Autoimmune Thyroid Disease in Specific Genetic Syndromes in Childhood and Adolescence. Front Endocrinol (Lausanne). 2020 Aug 19;11:543. doi: 10.3389/fendo.2020.00543.
15. Sajjadi-Jazi SM, Soltani A, Enayati S, KakavandHamidi A, Amoli MM. Autoimmune Polyglandular Syndrome Type 1: a case report. BMC Med Genet. 2019 Aug 16;20(1):143. doi: 10.1186/s12881-019-0870-3.
16. Napier C, Allinson K, Gan EH, Mitchell AL, Gilligan LC, Taylor AE, et al. Natural History of Adrenal Steroidogenesis in Autoimmune Addison's Disease Following Diagnosis and Treatment. J ClinEndocrinolMetab. 2020 Jul 1;105(7):2322–30. doi: 10.1210/clinem/dgaa187
17. Viswanathan V, Eugster EA. Etiology and treatment of hypogonadism in adolescents. PediatrClin North Am. 2011 Oct;58(5):1181-200, doi: 10.1016/j.pcl.2011.07.009.
18. Garelli S, Dalla Costa M, Sabbadin C, Barollo S, Rubin B, Scarpa R, et al. Autoimmune polyendocrine syndrome type 1: an Italian survey on 158 patients. J Endocrinol Invest. 2021 Nov;44(11):2493-2510. doi: 10.1007/s40618-021-01585-6.
19. Hanewinckel R, van Oijen M, Ikram MA, van Doorn PA. The epidemiology and risk factors of chronic polyneuropathy. *Eur J*

Epidemiol. 2016;31(1):5-20. doi:10.1007/s10654-015-0094-6
20. Roggenbuck JJ, Boucraut J, Delmont E, Conrad K, Roggenbuck D. Diagnostic insights into chronic-inflammatory demyelinating polyneuropathies. Ann Transl Med. 2018 Sep;6(17):337. doi: 10.21037/atm.2018.07.34.
21. Vallat JM, Ouvrier RA, Pollard JD, Magdelaine C, Zhu D, Nicholson GA, et al. Histopathological findings in hereditary motor and sensory neuropathy of axonal type with onset in early childhood associated with mitofusin 2 mutations. J NeuropatholExp Neurol. 2008 Nov;67(11):1097-102. doi: 10.1097/NEN.0b013e31818b6cbc.
22. Prada V, Massucco S, Venturi C, et al. Diagnostic Value of Sural Nerve Biopsy: Retrospective Analysis of Clinical Cases From 1981 to 2017. *Front Neurol*. 2019;10:1218. Published 2019 Nov 22. doi:10.3389/fneur.2019.01218
23. Ota K, Yamaguchi R, Tsukahara A, et al. Subacute Combined Degeneration of the Spinal Cord Caused by Autoimmune Gastritis. *Intern Med*. 2020;59(17):2113-2116. doi:10.2169/internalmedicine.4684-20
24. Oftedal BE, Hellesen A, Erichsen MM, Bratland E, Vardi A, Perheentupa J, et al. Dominant Mutations in the Autoimmune Regulator AIRE Are Associated with Common Organ-Specific Autoimmune Diseases. Immunity. 2015 Jun 16;42(6):1185-96. doi: 10.1016/j.immuni.2015.04.021. PMID: 26084028.
25. Zheng WB, Li LJ, Zhao DC, Wang O, Jiang Y, Xia WB, Li M. A novel variant in AIRE causing a rare, non-classical autoimmune polyendocrine syndrome type 1. Mol Med Rep. 2020 Aug;22(2):1285-1294. doi: 10.3892/mmr.2020.11227. Epub 2020 Jun 12. PMID: 32627016; PMCID: PMC7339480.
26. Anderson MS, Casanova JL. More than Meets the Eye: Monogenic Autoimmunity Strikes Again. Immunity. 2015 Jun 16;42(6):986-8. doi: 10.1016/j.immuni.2015.06.004. PMID: 26084018.
27. Cinque L, Angeletti C, Orrico A, Castellana S, Ferrito L, Ciuoli C, et al. Novel Pathogenic Variants of the AIRE Gene in Two Autoimmune Polyendocrine Syndrome Type I Cases with Atypical Presentation: Role of the NGS in Diagnostic Pathway and Review of the Literature. Biomedicines. 2020 Dec 19;8(12):631. doi: 10.3390/biomedicines8120631.
28. Bastard P, Orlova E, Sozaeva L, et al. Preexisting autoantibodies to type I IFNs underlie critical COVID-19 pneumonia in patients with APS-1. *J Exp Med*. 2021;218(7):e20210554. doi:10.1084/jem.20210554
29. Meisel C, Akbil B, Meyer T, et al. Mild COVID-19 despite autoantibodies against type I IFNs in autoimmune polyendocrine syndrome type 1. *J Clin Invest*. 2021;131(14):e150867. doi:10.1172/JCI150867