

Early-onset Chronic Keratitis as the First Presenting Component of Autoimmune Polyendocrine Syndrome Type 1: A Case Report and Review of the Literature

Enver Şimşek¹, Tülay Şimşek², Oğuz Çilingir³

¹Eskişehir Osmangazi University Faculty of Medicine, Department of Pediatrics, Clinic of Pediatric Endocrinology, Eskişehir, Türkiye

²Eskişehir Osmangazi University Faculty of Medicine, Department of Ophthalmology, Eskişehir, Türkiye

³Eskişehir Osmangazi University Faculty of Medicine, Department of Medical Genetics, Eskişehir, Türkiye

What is already known on this topic?

Autoimmune polyendocrine syndrome type 1 (APS-1) is a rare autosomal recessive disease. APS-1 is characterized by the clinical triad of chronic mucocutaneous candidiasis (CMC), hypoparathyroidism, and primary adrenocortical insufficiency. It has been reported that the complete triad is present in only 50 % of patients by the age of 20 years. When a rare or atypical component is the presenting feature of APS-1 and the diagnosis is made based on the classic triad, the diagnosis is usually delayed.

What this study adds?

This case presented with CMC and recurrent idiopathic keratitis. Pediatric ophthalmologists should consider APS-1 in the differential diagnosis of early-onset recurrent keratitis in children if it is associated with one or more of the major triad of APS-1.

Abstract

Autoimmune polyendocrine syndrome type 1 (APS-1), also referred to as autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy, is a rare monogenic autosomal recessive autoimmune disease. It is caused by mutations in the autoimmune regulator (*AIRE*) gene. APS-1 is diagnosed clinically by the presence of two of the three major components: chronic mucocutaneous candidiasis, hypoparathyroidism (HPT), and primary adrenocortical insufficiency. A 3.3-year-old girl presented with a carpopedal spasm to the pediatric emergency clinic. She had a history of recurrent keratitis, and chronic candidiasis, manifesting as urinary tract infections and oral thrush. HPT was diagnosed based on low serum concentrations of calcium and parathyroid hormone and elevated serum concentrations of phosphate, and treatment with calcium and calcitriol supplementation was started. Genetic testing identified a homozygous nonsense mutation, c.769C > T (p.R257X), in exon 6 of *AIRE* which has been reported previously. At the age of 5.6 years, she presented with adrenal crisis, and treatment with hydrocortisone and fludrocortisone was started. This case demonstrates that unexplained chronic keratitis in children may be the first and most severe component of this syndrome. The classic triad of APS-1 may also appear in the first decade of life.

Keywords: *AIRE* mutation, APS1, keratopathy, children, hypoparathyroidism

Cite this article as: Şimşek E, Şimşek T, Çilingir O. Early-onset chronic keratitis as the first presenting component of autoimmune polyendocrine syndrome type 1: a case report and review of the literature. J Clin Res Pediatr Endocrinol. 2025;17(3):359-364



Address for Correspondence: Enver Şimşek Prof. MD, Eskişehir Osmangazi University Faculty of Medicine, Department of Pediatrics, Clinic of Pediatric Endocrinology, Eskişehir, Türkiye
E-mail: enversimsek06@hotmail.com **ORCID:** orcid.org/0000-0003-0120-9976

Conflict of interest: None declared

Received: 25.09.2023

Accepted: 30.11.2023

Epub: 12.12.2023

Publication date: 22.08.2025



©Copyright 2025 by Turkish Society for Pediatric Endocrinology and Diabetes / The Journal of Clinical Research in Pediatric Endocrinology published by Galenos Publishing House. Licensed under a Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 (CC BY-NC-ND) International License.

Introduction

Autoimmune polyendocrine syndrome type 1 (APS-1) is a rare autosomal recessive disease caused by mutations in the human autoimmune regulator (*AIRE*) gene located on chromosome 21q22.3 (1,2). *AIRE* encodes a protein, AIRE, which acts as a regulator of the process of gene transcription and is essential for self-tolerance. AIRE deficiency leads to the escape and extra-thymic dissemination of autoreactive T-cell clones leading to the onset of autoimmune reactions against several tissue-specific self-antigens (1,2). Autoantibodies against type 1 interferons (IFN) (IFN- α and IFN- ω) are specific findings for APS-1 (3).

APS-1 is characterized by the clinical triad of chronic mucocutaneous candidiasis (CMC), hypoparathyroidism (HPT), and primary adrenocortical insufficiency (PAI). Other endocrine and non-endocrine components, such as type 1 diabetes mellitus, Hashimoto thyroiditis, various ectodermal abnormalities (keratopathy, alopecia, vitiligo, chronic dermatitis, and dental enamel hypoplasia), pernicious anemia, chronic diarrhea, autoimmune hepatitis, cutaneous vasculitis, and primary gonadal failure may occur with different prevalences (4). Clinically, APS-1 is diagnosed by the presence of two major components of the triad or only one if a sibling has already been diagnosed with APS-1 (4). CMC is the most common first clinical manifestation in APS-1 (5). The age at diagnosis of CMC is usually <5 years old (1.0-6.5 years) (6). HPT and adrenal insufficiency arise sequentially following CMC. However, when a rare or atypical component is the presenting feature of the syndrome, the diagnosis of APS-1 is often delayed.

The prevalence of APS-1 varies considerably from population to population. The highest prevalence is found among Persian Jews (1:9000) (7), Sardinians (1:14 000) (8), Finns (1:25 000) (9), and Norwegians (1:90 000) (10).

Here, we present a case of APS-1 in a Turkish girl who presented with CMC and recurrent keratitis in the first year of life, while the other major components presented within the first decade of life.

Case Report

A 3.3-years-old girl of consanguineous Turkish parents (first-degree cousins) was referred by a local outpatient clinic with carpopedal spasms and tetany. She had a history of chronic keratitis, recurrent oral thrush, onychomycoses, and recurrent vulvovaginal candidiasis since 14-months of age. Hospital records from ophthalmology revealed that there was a circular corneal epithelial erosion in the inferior temporal cornea in the left eye (Figure 1A). She was commenced on

moxifloxacin and lubricating eye drops, and ciprofloxacin ointment. The ulcerated area became epithelialized in 15 days, and a very slight corneal haze remained (Figure 1B). The patient was admitted four or more times in a year with the same complaints. At each admission, a similar lesion was observed in the same focus on the cornea. Two years after the first admission, she presented with severe blepharospasm and photophobia. Ophthalmological examination revealed spontaneous corneal perforation at the old ulcerated region. The Seidel test was positive and the iris prolapsed into the perforated corneal region. A corneal haze due to recurrent keratitis was detected in the upper periphery of the cornea in the left eye (Figure 1C). Iris adhesion was improved by a contact lens placement, and the pupil returned to its normal shape. Chronic keratitis was treated by combinations of local antibiotics and corticosteroids.

Her family history revealed that she had healthy parents and a little brother (Figure 2), and no family history of chronic illness, including autoimmune diseases. On physical examination, she was 99 cm tall (75th percentile) with a weight of 15 kg (50-75th percentile), and a body mass index of 14.5 kg/m² (25th percentile). Chvostek and Trousseau's signs were positive. Initial biochemical tests revealed that serum concentration of total calcium was 6.7 mg/dL [reference range (RR) 8.6-10.2]; phosphate, 7.0 mg/dL (RR 3.3-5.6); alkaline phosphatase, 45 U/L (RR 82-325); intact parathyroid hormone, 5.0 pg/mL (RR 10-65); and 25-hydroxyvitamin D, 69 ng/mL (RR 32-85). Based on the clinical and laboratory findings, she was diagnosed with HPT and commenced on oral elementary calcium (50 mg/kg three times daily) and calcitriol (oral, 0.25 mg twice daily). Her plasma calcium level increased to 8.1 mg/dL on the third day of treatment. Based on the presence of the diagnostic dyad of CMC and HPT and the coexistence of chronic keratitis, our presumptive diagnosis was APS-1.

During the Coronavirus disease-2019 pandemic, she was lost to follow-up for 2.5 years. The patient was admitted to our pediatric emergency clinic again at the age of 6.5 years with a high temperature, nausea, vomiting, and drowsiness. On physical examination, her skin was pale, mucous membranes dry, eyes sunken, skin turgor poor, and axillary temperature 38.7 °C. Vital signs and laboratory findings are shown in Table 1. Laboratory test results revealed hyponatremia (125 mEq/L), hypochloremia (84 mEq/L), hyperkalemia (7.2 mEq/L), metabolic acidosis (pH, 6.9 and HCO₃, 12 mEq/L), and hypoglycemia (38 mg/dL), low serum cortisol value (1.2 mg/dL) and elevated serum adrenocorticotrophic hormone value (653 pg/mL). Based on the clinical and laboratory findings, she was diagnosed with adrenal crisis. Unfortunately, renin activity

was not measured during the adrenal crisis. Tests on organ-specific autoantigens associated with APS-1 were performed. Serum 21-hydroxylase antibody level was 3.9 U/mL (reference < 1.0). Antithyroid (antithyroid peroxidase and antithyroglobulin), anti-islet cell, anti-insulin, anti-glutamic acid decarboxylase 65, antimitochondrial and anti-tissue transglutaminase antibodies were all negative. She was hospitalized for twelve days for an adrenal crisis. Intravenous fluid and hydrocortisone replacement

therapies were started. Three days later, she was followed up with maintenance doses of oral hydrocortisone (15 mg/m² three times daily), with dose adjustments according to concurrent illnesses and stresses, and mineralocorticoid (100 mg once daily). The patient gained weight and remained asymptomatic under replacement therapy with oral elemental calcium, calcitriol, hydrocortisone, and fludrocortisone. Since APS-1 patients may develop asplenia insidiously, the patient was vaccinated against encapsulated bacteria (*pneumococcus*, *meningococcus*, *Haemophilus influenza* type b), and annual influenza vaccination was recommended. One year later, there was widespread vitiligo on her face (Figure 3A) and patch-like hair loss on her occipital scalp (Figure 3B). Six months later, at the age of seven years, the patchy hair loss had been replaced by depigmented hair (Figure 3C).

The concomitant diagnosis of HPT and PAI with a history of oral and urinary candidiasis fulfilled the clinical diagnostic criteria for APS-1. Mutation analysis by next-generation sequencing of the *AIRE* gene identified a documented homozygous missense mutation: c.769C > T (p.R257X)

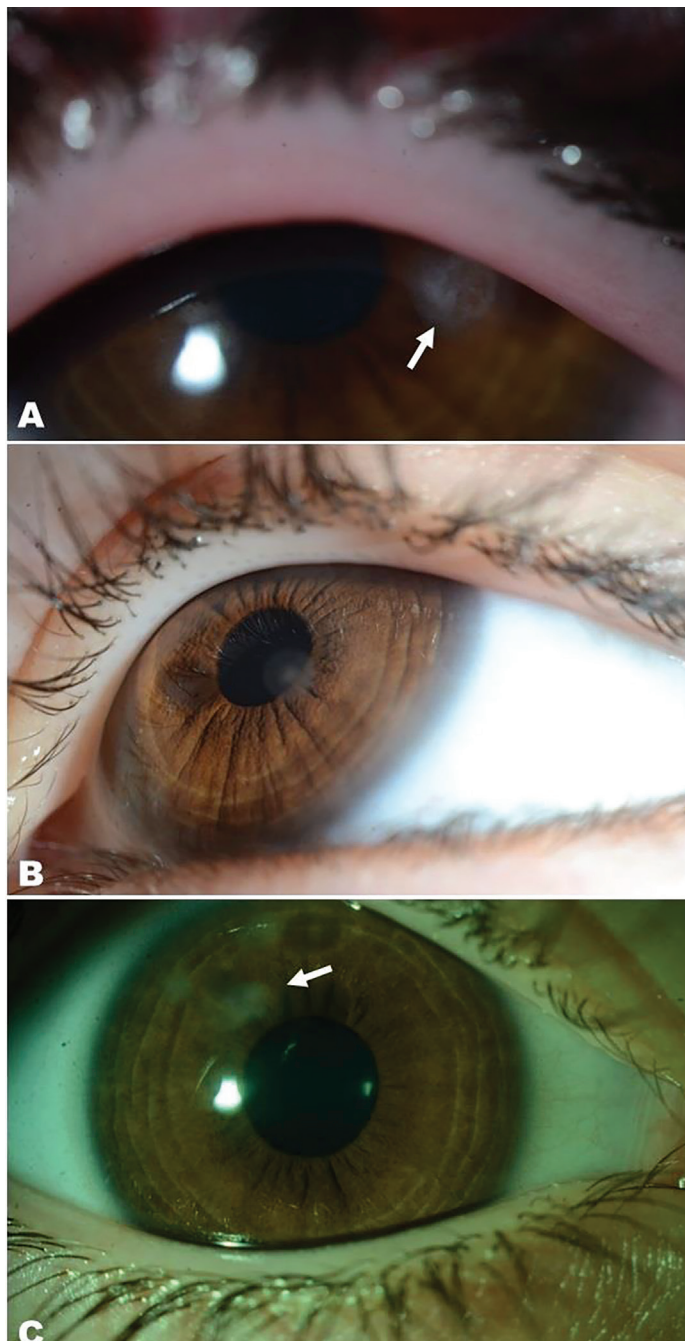


Figure 1. (A) Corneal ulcer and infiltrate (arrow) in the left eye; B) Healing of the keratitis after treatment; C) Haze in the peripheral cornea of the left eye (arrow) due to previous keratitis attacks

Table 1. Vital signs and laboratory findings at admission

Clinical and laboratory findings (reference range)	
Vital signs	
Systolic BP, mmHg	85
Diastolic BP, mmHg	55
Heart rate, beats/min	112
Respiratory, rate/min	35
Laboratory findings	
Sodium, mEq/L (135-145)	125
Potassium, mEq/L (3.5-4.5)	7.2
Chloride, mEq/L (96-106)	84
HCO ₃ ⁻ , mEq/L (22-26)	12
pH, (7.35-7.45)	6.9
Calcium, mEq/L (8.6-10.2)	7.1
Phosphorus, mEq/L (3.5-5.6)	6.9
Glucose, mg/dL (65-99)	38
Blood urea, mg/dL (5-18)	> 100
Creatinine, mg/dL (0.5-1.2)	1.1
Hemoglobin, g/dL (13-16)	10.2
WBC, K/mL (4.8-13.1)	18.4
Neutrophil, % (33-77)	84
Lymphocyte, % (11-59)	10
Platelets, K/mL (189-394)	218
CRP, mg/L (0.0-5.0)	266
Procalcitonin, ng/mL (0.0-0.046)	2.25
Fibrinogen, mg/dL (170-420)	532
Cortisol, mg/dL (during hypoglycaemia; ≥20.0)	1.2
ACTH, pg/mL (8.5-65.5)	653
PTH, pg/mL (15-65)	4.7
25-OH vitamin D, ng/mL (32-85)	19.8
FT4, ng/dL (0.96-1.77)	1.39
TSH, mIU/mL (0.7-5.97)	1.86
Urinary sodium, mEq/L (*)	111

*During hyponatremia high or low urine sodium concentrations (typically with 20 mEq/L as cutoff) can be used for differential diagnosis.

BP: blood pressure, WBC: white blood cell count, CRP: C-reactive protein, ACTH: adrenocorticotropic hormone, PTH: parathyroid hormone, FT4: free thyroxine, TSH: thyroid-stimulating hormone, TPO-Ab: thyroid peroxidase antibody

in exon 6. In addition, her parents and brother were identified as heterozygous carriers of the same mutations (Figure 2), which is consistent with the autosomal recessive pattern.

Discussion

APS-1 is a rare autosomal recessive autoimmune disease that is caused by variants in the *AIRE* gene. The classic clinical triad of APS-1 is CMC, HPT, and PAI. It has been reported that the complete triad was present in only half of patients with APS-1 by the age of 20 years (2,11). CMC, except in Persian Jews, is the most common and the first presenting component, typically developing in infancy or early childhood (11). However, in a study of 23 Persian Jews (12), only four patients presented with CMC. The median age of onset for CMC was 3 years (range 0.08-33 years). In the present case, CMC appeared at 14 months old as recurrent

moniliasis and urinary tract candidial infections. HPT usually appears next after CMC, with the peak incidence between the age of 2-11 years (6,11), and it is the most common endocrine component in APS-1 patients. PAI appears most commonly following CMC and HPT in the second or third decades (11,13). PAI is generally the second most common endocrinopathy in patients with APS-1 with the peak incidence around 12 years of age. The diagnosis of PAI is usually made when the patient presents with the symptoms and signs of adrenal crisis. Thus, if the diagnosis of APS-1 is made based on the complete classical triad, the diagnosis is usually delayed. Even if a component of the classical triad is accompanied by one of the other minor components, such as alopecia, vitiligo, nail dystrophy, dental enamel dysplasia, or keratopathy, investigating APS-1 may be a reasonable approach. Once the diagnosis is confirmed, life-long follow-up through a multidisciplinary team should be planned without delay. Close monitoring of calcium, calcitriol, and glucocorticoid, and mineralocorticoid maintenance doses are important to avoid life-threatening events, including hypocalcemia and/or adrenal crisis. In the present case, following CMC and keratitis, HPT was diagnosed at the age of 3.2 years. The coexistence of CMC and HPT suggested the diagnosis of APS-1.

The reported ocular manifestations of APS-1 include chronic persistent keratoconjunctivitis, dry eye, iridocyclitis, cataract, retinal detachment, and optic atrophy (14). Keratitis is the first manifestation in only 3-14 % of APS-1 cases and the frequency varies between 25% and 50% (11,14). Chronic keratitis was reported as the first presenting sign before any evidence of systemic disease in three of 69 Finnish patients with APS-1, and 25 % of cases with keratitis were bilateral (15). APS-1-associated keratopathy has been suggested to be an essential feature of APS-1 rather than

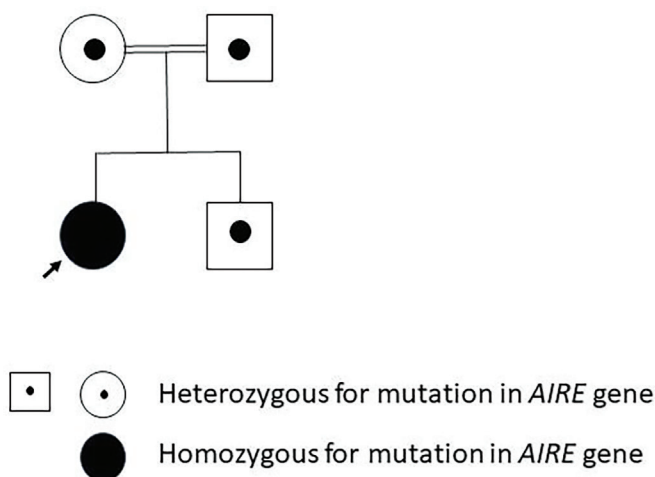


Figure 2. Family pedigree



Figure 3. (A) Widespread vitiligo on her face; B) Patch-like hair loss on occipital area; and C) Hair regrew in the hair loss area but was depigmented

a secondary manifestation. Chronic keratitis is usually accompanied by severe photophobia, blepharospasm, conjunctival redness, and decreased visual acuity. Keratitis in APS-1 patients is characterized by recurrent attacks and may lead to irreversible scarring, deep vascularization, and blindness (15). In the present case, keratitis was the second manifestation of the syndrome, following CMC. Alopecia, vitiligo, and nail dystrophy were also later accompanying manifestations. Topical steroids and antibiotics were used for the treatment of keratitis. The presentation of this case suggests that pediatric ophthalmologists should consider APS-1 in the differential diagnosis of early-onset and recurrent keratitis in children.

Anti-IFN- α and anti-IFN- ω autoantibodies have high specificity for APS-1 (3,10). Testing for anti-IFN antibodies when there is clinical suspicion may be helpful for rapid and more convincing diagnosis of APS-1. In the present case, we could not assay anti-IFN antibodies, because this test was not available in our hospital at the time. The diagnosis was confirmed by sequencing of the *AIRE* gene mutation to differentiate APS-1 from APS-1-like conditions, including APS-2 and X-linked immunoregulation, polyendocrinopathy, and enteropathy syndromes. APS-1 is a monogenic, autosomal recessive disease caused by a mutation in the *AIRE* gene. In the present case there was a homozygous nonsense c.769C > T (p.R257X) mutation in the *AIRE* gene. To date, more than 140 different mutations in the *AIRE* gene have been reported worldwide (16). The c769C > T (p.Arg257stop) nonsense mutation is the most common variant with documented in at least 125 cases previously (1,2,17,18,19). It is a frequent mutation in Finnish (1,2,18), Norwegian (5), Italian (19), Turkish (20), and Serbian patients (17). R257X in exon 6 changes an arginine codon to a stop codon at amino acid position 257, which encodes a truncated, non-functional protein of 256 amino acids. The second most frequent mutation is c.967_979del13 (p.C322del13) which is prevalent in Norwegian, British, French, North American, and Indian patients (5,21,22). The other frequent mutation c.415C > T (p.139X) is prevalent in Sardinian patients (4). In contrast, p.V80G and p.X46L + 59aa mutations were reported only from Indian patients (22). Other variants have been reported as isolated cases. Heterozygous dominant-negative *AIRE* mutations in the plant homeodomain 1 domain have also been described in Persian Jews (23). These dominant-negative mutations are associated with milder diseases.

APS-1 is characterized by high phenotypic heterogeneity, with wide variability in the number of clinical manifestations and there is often a delay in the diagnosis. PAI usually presents as a life-threatening adrenal crisis. Therefore, early diagnosis of APS-1 is important, even

in the absence of the main triad. APS-1 should be considered in children who have one of the major components of the classical triad with coexistence of one of the minor manifestations. The presented case had HPT by the time she attended pediatric endocrinology, and she had a history of CMC and chronic keratitis. This case highlights that early diagnosis of APS-1, close monitoring of affected children by pediatric endocrinologists, and periodic evaluation of biochemical and hormonal parameters are essential to prevent severe and life-threatening events. Patients and their parents should be educated in regard of symptoms and sick day management for adrenal insufficiency and HPT.

Conclusion

The diagnosis of APS-1 is usually delayed due to wide variations in clinical presentations. The presented case highlighted that early diagnosis of APS-1 is important to avoid severe and life-threatening events associated with this syndrome and also shows that recurrent keratitis in children may be an early and severe manifestation of APS-1. The diagnosis of APS-1 should be considered in all patients presenting with one of the major clinical manifestations coexistent with other minor manifestations of the disease. The diagnosis can be confirmed by sequencing the *AIRE* gene where available.

Ethics

Informed Consent: Written informed consent for publication of clinical details and images were obtained from parents.

Acknowledgments

We would like to thank the guardians of the patient for their cooperation.

Footnotes

Authorship Contributions

Surgical and Medical Practices: Enver Şimşek, Tülay Şimşek, Oğuz Çilingir, Concept: Enver Şimşek, Tülay Şimşek, Design: Enver Şimşek, Tülay Şimşek, Data Collection or Processing: Enver Şimşek, Tülay Şimşek, Oğuz Çilingir, Analysis or Interpretation: Enver Şimşek, Tülay Şimşek, Oğuz Çilingir, Literature Search: Enver Şimşek, Writing: Enver Şimşek, Tülay Şimşek.

Financial Disclosure: The authors declared that this study received no financial support.

References

- Nagamine K, Peterson P, Scott HS, Kudoh J, Minoshima S, Heino M, Krohn KJ, Lalioti MD, Mullis PE, Antonarakis SE, Kawasaki K, Asakawa S, Ito F, Shimizu N. Positional cloning of the APECED gene. *Nat Genet.* 1997;17:393-398.
- Finnish-German APECED Consortium. An autoimmune disease, APECED, caused by mutations in a novel gene featuring two PHD-type zinc-finger domains. *Nat Genet.* 1997;17:399-403.
- Meloni A, Furcas M, Cetani F, Marcocci C, Falorni A, Perniola R, Pura M, Bøe Wolff AS, Husebye ES, Lilic D, Ryan KR, Gennery AR, Cant AJ, Abinun M, Spickett GP, Arkwright PD, Denning D, Costigan C, Dominguez M, McConnell V, Willcox N, Meager A. Autoantibodies against type I interferons as an additional diagnostic criterion for autoimmune polyendocrine syndrome type I. *J Clin Endocrinol Metab.* 2008;93:4389-4397. Epub 2008 Aug 26.
- Meloni A, Willcox N, Meager A, Atzeni M, Wolff AS, Husebye ES, Furcas M, Rosatelli MC, Cao A, Congia M. Autoimmune polyendocrine syndrome type 1: an extensive longitudinal study in Sardinian patients. *J Clin Endocrinol Metab.* 2012;97:1114-1124. Epub 2012 Feb 16.
- Bruserud Ø, Oftedal BE, Landegren N, Erichsen MM, Bratland E, Lima K, Jørgensen AP, Myhre AG, Svartberg J, Fougner KJ, Bakke Å, Nedrebø BG, Mella B, Breivik L, Viken MK, Knappskog PM, Marthinussen MC, Løvås K, Kämpe O, Wolff AB, Husebye ES. A longitudinal follow-up of autoimmune polyendocrine syndrome type 1. *J Clin Endocrinol Metab.* 2016;101:2975-2983. Epub 2016 Jun 2.
- Husebye ES, Perheentupa J, Rautemaa R, Kämpe O. Clinical manifestations and management of patients with autoimmune polyendocrine syndrome type I. *J Intern Med.* 2009;265:514-529.
- Zlotogora J, Shapiro MS. Polyglandular autoimmune syndrome type I among Iranian Jews. *J Med Genet.* 1992;29:824-826.
- Rosatelli MC, Meloni A, Meloni A, Devoto M, Cao A, Scott HS, Peterson P, Heino M, Krohn KJ, Nagamine K, Kudoh J, Shimizu N, Antonarakis SE. A common mutation in Sardinian autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy patients. *Hum Genet.* 1998;103:428-434.
- Ahonen P, Myllärniemi S, Sipilä I, Perheentupa J. Clinical variation of autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED) in a series of 68 patients. *N Engl J Med.* 1990;322:1829-1836.
- Wolff AS, Erichsen MM, Meager A, Magitta NF, Myhre AG, Bollerslev J, Fougner KJ, Lima K, Knappskog PM, Husebye ES. Autoimmune polyendocrine syndrome type 1 in Norway: phenotypic variation, autoantibodies, and novel mutations in the autoimmune regulator gene. *J Clin Endocrinol Metab.* 2007;92:595-603. Epub 2006 Nov 21.
- Perheentupa J. Autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy. *J Clin Endocrinol Metab.* 2006;91:2843-2850. Epub 2006 May 9.
- Weiler FG, Dias-da-Silva MR, Lazaretti-Castro M. Autoimmune polyendocrine syndrome type 1: case report and review of literature. *Arq Bras Endocrinol Metabol.* 2012;56:54-66.
- Orlova EM, Sozaeva LS, Kareva MA, Oftedal BE, Wolff ASB, Breivik L, Zakharova EY, Ivanova ON, Kämpe O, Dedov II, Knappskog PM, Peterkova VA, Husebye ES. Expanding the phenotypic and genotypic landscape of autoimmune polyendocrine syndrome type 1. *J Clin Endocrinol Metab.* 2017;102:3546-3556.
- GASS JD. The syndrome of keratoconjunctivitis, superficial moniliasis, idiopathic hypoparathyroidism and Addison's disease. *Am J Ophthalmol.* 1962;54:660-674.
- Tarkkanen A, Merenmies L. Corneal pathology and outcome of keratoplasty in autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED). *Acta Ophthalmol Scand.* 2001;79:204-207.
- Bruserud Ø, Oftedal BE, Wolff AB, Husebye ES. AIRE-mutations and autoimmune disease. *Curr Opin Immunol.* 2016;43:8-15. Epub 2016 Aug 6.
- Fierabracci A, Lanzillotta M, Vorgučin I, Palma A, Katanić D, Betterle C. Report of two siblings with APECED in Serbia: is there a founder effect of c.769C > T AIRE genotype? *Ital J Pediatr.* 2021;47:126.
- Björse P, Halonen M, Palvimo JJ, Kolmer M, Aaltonen J, Ellonen P, Perheentupa J, Ulmanen I, Peltonen L. Mutations in the AIRE gene: effects on subcellular location and transactivation function of the autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy protein. *Am J Hum Genet.* 2000;66:378-392.
- Cihakova D, Trebusak K, Heino M, Fadeyev V, Tiulpakov A, Battelino T, Tar A, Halász Z, Blümel P, Tawfik S, Krohn K, Lebl J, Peterson P. Novel AIRE mutations and P450 cytochrome autoantibodies in Central and Eastern European patients with APECED. *Hum Mutat.* 2001;18:225-232.
- Fierabracci A, Pellegrino M, Frasca F, Kilic SS, Betterle C. APECED in Turkey: a case report and insights on genetic and phenotypic variability. *Clin Immunol.* 2018;194:60-66. Epub 2018 Jul 3.
- Ferre EM, Rose SR, Rosenzweig SD, Burbelo PD, Romito KR, Niemela JE, Rosen LB, Break TJ, Gu W, Hunsberger S, Browne SK, Hsu AP, Rampertap S, Swamydas M, Collar AL, Kong HH, Lee CR, Chascsa D, Simcox T, Pham A, Bondici A, Natarajan M, Monsale J, Kleiner DE, Quezado M, Alevizos I, Moutsopoulos NM, Yockey L, Frein C, Soldatos A, Calvo KR, Adjemian J, Similuk MN, Lang DM, Stone KD, Uzel G, Kopp JB, Bishop RJ, Holland SM, Olivier KN, Fleisher TA, Heller T, Winer KK, Lionakis MS. Redefined clinical features and diagnostic criteria in autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy. *JCI Insight.* 2016;1:e88782.
- Zaidi G, Bhatia V, Sahoo SK, Sarangi AN, Bharti N, Zhang L, Yu L, Eriksson D, Bensing S, Kämpe O, Bharani N, Yachha SK, Bhansali A, Sachan A, Jain V, Shah N, Aggarwal R, Aggarwal A, Srinivasan M, Agarwal S, Bhatia E. Autoimmune polyendocrine syndrome type 1 in an Indian cohort: a longitudinal study. *Endocr Connect.* 2017;6:289-296. Epub 2017 Apr 26.
- Oftedal BE, Hellesøen A, Erichsen MM, Bratland E, Vardi A, Perheentupa J, Kemp EH, Fiskerstrand T, Viken MK, Weetman AP, Fleishman SJ, Banka S, Newman WG, Sewell WA, Sozaeva LS, Zayats T, Haugarvoll K, Orlova EM, Haavik J, Johansson S, Knappskog PM, Løvås K, Wolff AS, Abramson J, Husebye ES. Dominant mutations in the autoimmune regulator AIRE are associated with common organ-specific autoimmune diseases. *Immunity.* 2015;42:1185-1196.