ISSN : (Online): 3008-038X
Abbreviation: J Derm Cse Rep
DOI : 10.61705/jdcr.18.2.2025.52.58

Journal of Dermatological Case Reports

A Pediatric Case presenting with Autoimmune Polyglandular Syndrome Type 1 with Homozygous AIRE C.607C>T (P.Arg203Ter) Mutation: A Novel Gene Mutation

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Abstract:

Autoimmune Polyglandular Syndrome Type 1 (APS-1), or APECED, is a rare autosomal recessive disorder caused by mutations in the AIRE gene, critical for establishing central immune tolerance. We present a case of an 8-year-old female exhibiting classic APS-1 manifestations: chronic mucocutaneous candidiasis, hypoparathyroidism, ectodermal dystrophy, and confirmed AIRE mutation (c.607C>T, p.Arg203Ter). Clinical evaluation revealed hypocalcemia, hyperphosphatemia, low PTH, and vitamin D deficiency. Management included oral calcium and calcitriol with close biochemical monitoring. The case underscores the importance of genetic testing for accurate diagnosis and long-term management. Due to risks of nephrocalcinosis from calcium therapy, renal ultrasound was planned. This report highlights the very rare mutation of AIRE gene which is c.607C>T (p.Arg203Ter) it also highlights the and discusses the potential renal complications in the context of calcium homeostasis. Early identification and targeted management are crucial in preventing disease progression and complications in pediatric APS-1 patients

Keywords:

Autoimmune Polyglandular Syndrome Type 1, pediatric endocrinology, hypoparathyroidism, candidiasis, nephrocalcinosis

Received : 16-04-2025 **Revised : 23-04-2025** **Accepted: 15-05-2025** **Published : 30-05-2025**

Introduction

Abnormal Autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED), another name for Autoimmune Polyglandular Syndrome Type 1 (APS-1), is a systemic autoimmune illness that affects both endocrine and non- endocrine organs [1]. The development of APECED is caused by mutations in the Autoimmune Regulator (AIRE) gene [2]. The AIRE, which has 14 coding exons and is found at chromosome position 21q22.3, generates a transcription regulator with 545 amino acids and a molecular weight of 58 kDa [3].

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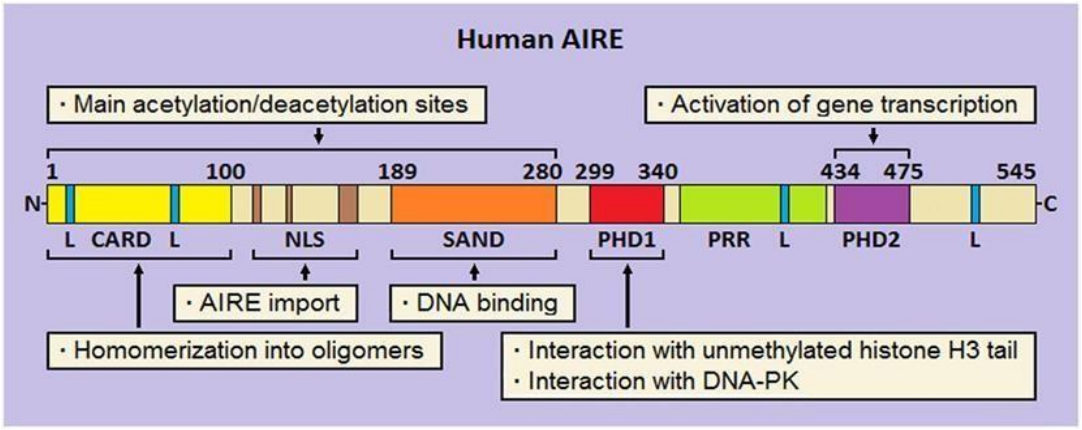

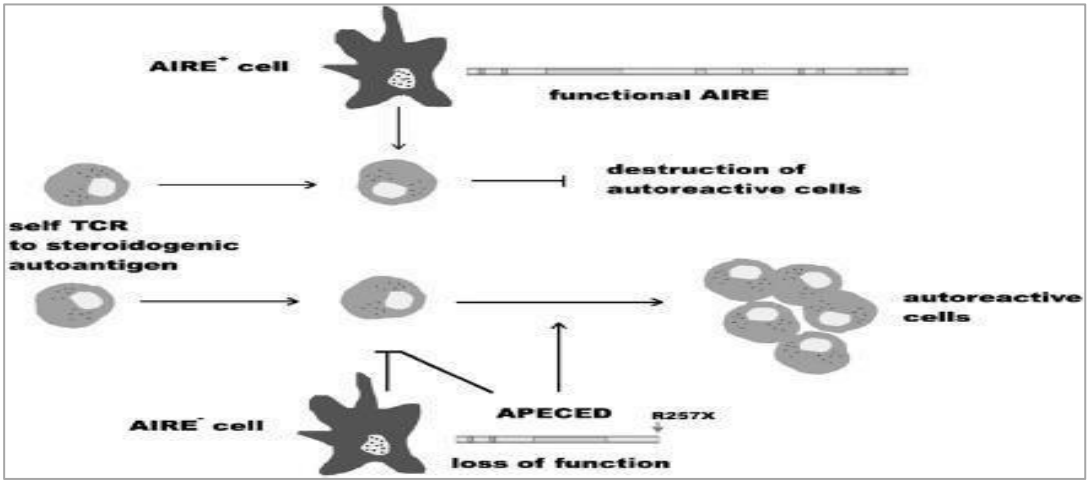

AIRE plays a role in regulating the expression of tissue-specific antigens (TSAs), which are crucial for the process of negative selection by ensuring the presentation of the full range of self-antigens at the site of negative selection, leading to the removal of any self-reactive T cells, therefore, mutations in AIRE impair self-tolerance and increase autoreactive immune cells that target multiple tissues [4].

Mutations in the AIRE gene, which is found in chromosome 21's short arm, cause autoimmune polyglandular syndrome type 1. APS-1 is inherited in an autosomal recessive manner . The autoimmune regulator protein is encoded by the AIRE gene. The AIRE gene has more than 60 known mutations, which may account for the disease's variation in presentation and progression. One of the two most prevalent mutations is present in more than 95% of APS-1 patients:

Arginine substitution at position 257

- Nomenclature: Often denoted as p.R257X or c.769C>T (p.Arg257Ter)
- Type: Nonsense mutation – it converts an arginine codon (CGA) to a stop codon (TGA), leading to premature termination of the AIRE protein.

Base pair deletion in exon 8

- Nomenclature: Often denoted as c.964del13;
- Type: Frame shift mutation – causes a shift in the reading frame and leads to a non-functional AIRE protein [5,7]

Homozygous Nonsense Substitution in AIRE Gene: c.607C>T (p.Arg203Ter) 607C>T: This notation means that at nucleotide position 607, the normal cytosine (C) is replaced by a thymine (T) p.Arg203Ter: At the protein level, this substitution changes the amino acid arginine (Arg) at position 203 to a termination codon (Ter or stop codon which is very rare Presentation. The rare autoimmune condition known as autoimmune

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polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED) or autoimmune polyglandular syndrome type 1 (APS-1) is caused by autosomal recessive mutations of the human autoimmune regulatory (AIRE) gene.

APECED are characterized by a triad of chronic mucocutaneous candidiasis (CMC), adrenal insufficiency (AI), and hypoparathyroidism (HP) [5] Chronic mucocutaneous candidiasis, autoimmune adrenocortical insufficiency (Addison's disease), and hypoparathyroidism are at least two of the main characteristics that define the syndrome. Gonadal failure, type 1A diabetes mellitus, hypothyroidism, vitiligo, alopecia, pernicious anemia, chronic diarrhea, autoimmune hepatitis, and keratoconjunctivitis are additional APS-1 autoimmune disorders.

Methodology

This case report follows a retrospective observational methodology focused on a pediatric female patient presenting with classical features of Autoimmune Polyglandular Syndrome Type 1 (APS-1), including hypoparathyroidism, chronic mucocutaneous candidiasis, and ectodermal abnormalities. Clinical data were gathered through review of hospital records, laboratory results, and physical examination findings. Laboratory investigations confirmed hypocalcemia, hyperphosphatemia, low PTH, and vitamin D deficiency. Genetic analysis revealed a rare homozygous nonsense mutation in the AIRE gene: c.607C>T (p.Arg203Ter). Management included oral calcium and calcitriol supplementation, with close biochemical and clinical monitoring. Renal ultrasound was planned to assess for nephrocalcinosis due to risk from calcium therapy. Ethical approval was obtained, and informed consent was secured from the patient's guardians.

Case Report

Baby Faiqa Jan female 8 yr old child presented with a constellation of symptoms including tingling pain in both upper and lower limbs, intermittent carpopedal spasms, recurrent oral candidiasis, nail dystrophy, hypocalcaemia, and confirmed hypoparathyroidism. Laboratory investigations further support the clinical picture, revealing elevated serum phosphorus along with reduced levels of calcium, parathyroid hormone (PTH), and vitamin D. Given the combination of ectodermal abnormalities, endocrine dysfunction, and chronic mucocutaneous candidiasis, she is suspected to have Autoimmune Polyendocrine Syndrome Type 1 (APS-1), also known as Autoimmune Polyendocrinopathy-Candidiasis-Ectodermal Dystrophy (APECED), and after under going genetic evaluation for pathogenic mutations in the AIRE gene she is detected with homozygous nonsense mutation in the AIRE gene: c.607C>T (p.Arg203Ter).

Investigations:

- Complete Blood Count (CBC):
- Hemoglobin: 11.5 g/dL
- Total Leukocyte Count: 12,000/mm³
- Platelet Count: 300,000/mm³
- Neutrophils: 60%
- Lymphocytes: 35%
- Monocytes: 3% , Eosinophils: 1%
- Basophils: 1%
- Serum Electrolytes:
- Sodium (Na+): 138 mmol/L
- Potassium (K+): 4.7 mmol/L
- Blood Glucose: Random Blood Glucose: 95 mg/dL
- Serum Total Calcium:6.1 mg/dL
- Serum Phosphate: 7.5 mg/dL
- Parathyroid Hormone (PTH):2.36pg/mL
- 25(OH) Vitamin D: 21.4 ng/mL

Hospital Course:

The child was started on **oral calcium supplementation** using **calcium gluconate** at a dose of 50 mg daily for 6 days, The supplements were given with meals to enhance absorption. Due to the low parathyroid hormone (PTH) level, **active vitamin D (calcitriol)** was initiated at 0.25 mcg/day orally for 6 days to facilitate intestinal calcium absorption. vitaminD3 60K Units for 3 days.

The child was monitored closely with repeat serum calcium, phosphate, PTH, and creatinine levels every few days. Clinical signs such as tingling, muscle cramps, seizures, or lethargy were also observed.

Dietary counseling was provided, encouraging a **balanced diet rich in calcium** and advising the avoidance of phosphorus-rich soft drinks and processed foods. The child was referred to

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pediatric endocrinology for further evaluation. For long-term management, **renal ultrasound** was planned to assess for **nephrocalcinosis after intake of calicum**, and medication doses were titrated based on laboratory trends and clinical response.

Discharge Plan and FollowUp:

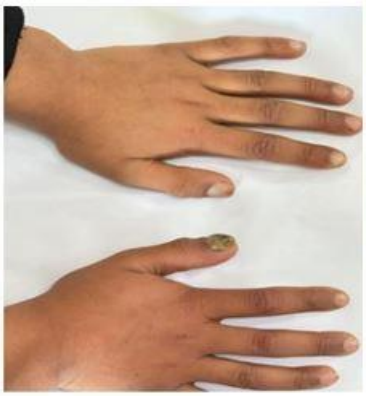
Faiqa Jan was discharged in stable condition. She was advised regular endocrinology follow-up every Friday, with plans for continued evaluation of adrenal function and possible genetic confirmation of AIRE mutation. Patient and family were counseled on compliance with medications and the importance of follow-up monitoring.

Discussion

Autoimmune polyglandular syndrome type 1 is due to decreased central tolerance, resulting in autoimmunity. Since the discovery of the AIRE gene, there have been considerable advances in understanding this disorder. AIRE is expressed in the thymic medullary cells and encodes for a DNA-binding protein, an autoimmune regulator. The hypothesis is that this protein helps regulate the thymic expression of various tissue-specific antigens, leading to the elimination of autoreactive T cells. In its absence, autoreactive cells escape the negative selection and get released into circulation.[5]

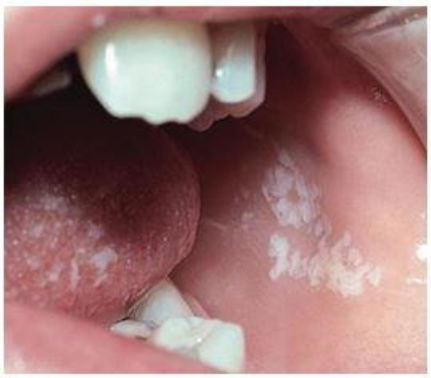
APECED are characterized by a triad of chronic mucocutaneous candidiasis (CMC), adrenal insufficiency (AI), and hypoparathyroidism (HP) [5][6]. In our case report patient has tingling pain in both upper and lower limbs, intermittent carpopedal spasms recurrent oral candidiasis, nail dystrophy, hypocalcaemia, and confirmed hypoparathyroidism.

Nail dystrophy



patient diagnosed with (APS-1)

Mucocutaneous candidiasis



Chronic superficial *Candida albicans*infection is often the first sign of APS-1, It ranges in severity from mild angular stomatitis to extensive oral involvement with white plaques or erythema. Severe or chronic mucositis may lead to esophageal involvement or intestinal symptoms like diarrhea. Good oral hygiene, avoidance of irritants, and regular dental care are crucial for prevention. Initial treatment includes topical polyenes (nystatin and amphotericin B) for 4–6 weeks. Azoles are used sparingly due to resistance risk. Pulse prophylaxis may be necessary for recurrent cases. Corner of mouth infections are treated with topical antifungals. Refractory or systemic cases may need systemic antifungals or specialist referral.[7] . To treat oral candiasis **Nystatin** oral suspension: 100,000 units/mL, typically 4–6 mL swished and swallowed 4 times a day for 7–14 days.

Hypoparathyroidism is a common early endocrine feature of APS-I, affecting up to 85% of patients by age 30, and is more prevalent in females. Symptoms may be subtle initially, including muscle cramps and paraesthesia, but severe hypocalcaemia can cause seizures, especially during illness or fasting. Diagnosis is based on hypocalcaemia, hyperphosphataemia, low or normal PTH, normal creatinine, and often low magnesium. APS-I should be suspected in all non-iatrogenic hypoparathyroidism cases. Anti-NALP5 antibodies may help predict disease onset.[8]

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Twice-daily synthetic PTH offers stable calcium levels but is not yet standard; vitamin D derivatives remain the main therapy. Preferred drugs include dihydrotachysterol (longer-acting), alphacalcidol, and calcitriol (shorter-acting), chosen based on patient needs and drug availability. Dihydrotachysterol is more stable, while short-acting forms are used in acute settings like diarrhoea. Long- acting calciferol should be avoided due to risk of prolonged hypercalcaemia.
Daily calcium supplements (100–500 mg per dose, 2–3 times/day) are essential, ideally as Ca-citrate and taken between meals. .[9]

In our case report calcium gluconate and calicitrol and Vitamin D3 supplementation is given in this case.
Adrenal insufficiency in APS-I typically develops between ages 5–15, with 78% affected by age 30. Symptoms include fatigue, salt craving, hypotension, weight loss, and skin/mucosal hyperpigmentation. Biochemically, low cortisol and aldosterone, high ACTH and renin activity are characteristic. Autoantibodies against 21-hydroxylase, side-chain cleavage enzyme, and AADC often precede symptoms. Early detection via ACTH stimulation tests and renin monitoring is crucial to prevent adrenal crisis.

Adrenal insufficiency treatment is individualized, aiming for physiological glucocorticoid replacement using hydrocortisone (10–15 mg/m²/day, in 2–3 doses) or alternatives like cortisone acetate. Dosage adjustments are essential during illness, stress, or malabsorption (e.g. diarrhoea), and glucocorticoid therapy may affect calcium and glucose balance. Patients should double or triple doses during fever or major stress, and carry emergency hydrocortisone injections (100 mg) and medical ID. Mineralocorticoid deficiency is treated with fludrocortisone (0.05–0.2 mg daily), adjusting for climate or clinical signs. Optimal dosing targets normal posture-related BP changes and high-normal renin activity.[10][11]

Renal complications are caused by T-cell infiltration in renal tubules and the development of anti-proximal tubular and Anticollecting duct-specific autoantibodies in some APECED patients. Renal disorders range from mild renal impairment in patients with nephrocalcinosis to a rapidly progressive renal failure requiring kidney transplantation followed by tubule interstitial nephritis (TIN). Although more than 80% of patients with APECED have hypoparathyroidism,nephrocalcinosis is observed in some patients, suggesting that iatrogenic impaired calcium homeostasis may deteriorate patients' condition . As this case is having increase calcium there is high chances of having nephrocalcinosis. Regardless of previous investigations, estimations regarding the prevalence of renal complications in these patients are controversial, and the mechanism underly ing the renal pathologies is not fully understood. [12,13]

Our study finding of hypocalcemia is present which is in contrast with the review article conducted by Shafiei et al the most common cause of renal involve ment in APECED patients is nephrocalcinosis. The prev alence of nephrocalcinosis in that review was 52%.[14]

Several clinical conditions may induce nephrocalcinosis during the course of the disease, such as vitamin D replacement, congenital hypothyroidism, inherited tubulopathies, and RTA; hypoparathyroidism-induced hypercalciuria seems to be the most common cause as the fractional excretion of calcium increases and the tubular absorption of calcium decreases due to the lack of PTH. Nephrocalcinosis occurs through hypercalciuria with hypercalcemia or hypercalciuria with no hyper calcemia[15]

A study by Laakso and colleagues showed that APECED patients suffered from lower serum calcium, higher serum phosphate, and higher urine calcium secretion [16]. Therefore, hypercalciuria-induced without hypercalcemianephrocalcinosis in APECED patients is probably the most among these patients. Based on clini cal and laboratory findings in APECED patients; to elucidate the underlying mechanism of nephrocalcinosis in APCED patients, we suggested two theories.

First, mutations in calcium-sensing receptors (CASR) can sup press PTH levels and exert a hypercalciurichypocalcemiacondition. Circulating autoantibodies against CASR in APECED patients, particularly activating antibodies, consolidate this theory [17,18].

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Second, vitamin D therapy may cause iatrogenic hypercalciuria at the initiation of treatment, therefore ongoing assessment of nephro calcinosis is warranted [19]. It is suggested that calcium should be maintained just below or within the lower nor mal range to prevent nephrocalcinosis, nephrolithiasis, and renal failure [20].

Conclusion

This case highlights the classical triad of Autoimmune Polyglandular Syndrome Type 1 (APS-1) in a pediatric patient, emphasizing the importance of early recognition of its hallmark features—chronic mucocutaneous candidiasis, hypoparathyroidism, and ectodermal dystrophy. Genetic analysis revealed a novel homozygous nonsense mutation in the AIRE gene (c.607C>T; p.Arg203Ter), which leads to premature protein truncation and is likely pathogenic. This previously unreported variant expands the known mutational spectrum of APS-1. The case also illustrates the complexity of managing hypoparathyroidism, particularly the risk of nephrocalcinosis from chronic calcium and vitamin D therapy. Molecular confirmation provided diagnostic clarity and enabled genetic counseling for the consanguineous family. This report reinforces the critical role of integrating clinical, biochemical, and genetic data in diagnosing rare autoimmune disorders. Our findings contribute valuable insight into the genotype-phenotype correlation in APS-1.

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