# Autoimmune polyglandular syndrome type 1 in Saudi children

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## ABSTRACT

**الأهداف:** وصف المظاهر السريرية، والحيوية، والكيميائية، والمناعية، لمتلازمة المناعة الذاتية متعددة الغدد النوع الأول (APS-1) في سكان السعوديون.

**الطريقة:** استعرضت الملفات الطبية لسبع عائلات سعودية مكونة من 20 من الأبناء المتضررين. وأجريت الدراسة في عيادة الغدد الصماء لدى الأطفال – مستشفى الملك فيصل التخصصي ومركز الأبحاث – الرياض – المملكة العربية السعودية و دامت لمعدل زمني 6 عام ابتداءاً من يناير2000م إلى ديسمبر 2009م. تراوحت أعمار الأطفال المصابين من 17-2 عام. و ضمت الدراسة المصابين الذين لديهم ما لا يقل عن 2 صفة من أصل 3 صفة لهذا المرض.

**النتائج:** أصيب 14 طفل من حديثي الولادة بالتهابات فطرية ظهرت في الشهر الأول من العمر على شكل ترشيحات مخاطية جلدية مزمنة في الأظافر والفم. وكان نقص إفراز الغدة الجار الدرقية من أكثر أمراض الغدد شيوعاً بين هؤلاء الأطفال. كان هناك 8 مرضى لديهم قصور في نشاط الغدة الدرقية المعروفة باسم مرض أديسون. تم تشخيص نقص إفراز الغدة الدرقية في 3 طفل، بينما 9 طفل كان لديهم فقدان كامل للشعر. كما شملت اضطرابات الغدد الصماء والمناعة الذاتية الأخرى على داء السكري من النوع الأول، ونقص هرمون النمو، ومرض حساسية القمح، والتهاب الكبد الذاتي، والتهاب القرنية، وملتحمة العين.

**خاتمة:** بالرغم من أن مرض متلازمة المناعة الذاتية (APS-1) متعددة الغدد النوع الأول مرض غير شائع نسبياً في الأطفال السعوديين، إلا أنه يؤثر على عدة غدد صماء، و يرتبط بعدة أمراض مناعية ذاتية ويعتبر فقدان الشعر الكامل صفة منتشرة في هذا المرض.

**Objectives:** To describe the clinical, biochemical, and immunological manifestations of autoimmune polyglandular syndrome type 1 (APS-1) in a Saudi population.

**Methods:** The medical files of 7 consanguineous Saudi families with 20 affected siblings were retrospectively reviewed. They were followed at the Pediatric Endocrinology Clinic, King Faisal Specialist Hospital and Research Center, Riyadh, Saudi Arabia for a mean duration of 6 years (January 2000 to December 2009). The age of the affected children ranged from 2-17 years. The included patients had at least 2 out of the 3 major clinical diagnostic criteria of APS-1.

**Results:** Fourteen children had neonatal chronic mucocutaneous candidiasis affecting the nails and mouth. The most commonly presenting endocrine disease among APS-1 patients was hypoparathyroidism. Eight patients had autoimmune Addison's disease. Hypothyroidism was diagnosed in 3 patients, and 9 patients had alopecia universalis. Other endocrine and autoimmune disorders were infrequently seen including type 1 diabetes, growth hormone deficiency, celiac disease, autoimmune hepatitis, and keratoconjuctivitis.

**Conclusion:** Autoimmune polyglandular syndrome type 1, although an uncommon disorder in Saudi children affects multiple endocrine glands, and is associated with several autoimmune diseases where alopecia universalis is a common finding.

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Autoimmune polyglandular syndrome type 1 (APS-1) is an autoimmune disease characterized by destruction of endocrine tissues, chronic mucocutaneous candidiasis (CMC), and additional

ectodermal disorders. The clinical diagnosis of APS-1 is based on the presence of at least 2 out of the 3 following diagnostic criteria: CMC, chronic hypoparathyroidism (HP), and autoimmune adrenal insufficiency (AAD). However, patients often develop other diseases as well, such as: hypogonadism, alopecia, chronic hepatitis, chronic atrophic gastritis, pernicious anemia, vitiligo, malabsorption, hypothyroidism, keratoconjunctivitis, hypophysitis, and type 1 diabetes.[1-4] Autoimmune polyglandular syndrome type 1, also known as autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED), is distinguished from autoimmune polyglandular syndrome 2 (APS-2). The autoimmune regulator (AIRE) gene responsible for APECED is expressed in cells involved in induction and maintenance of immune tolerance. Genetic alterations of the single gene are associated with APECED. As a specific therapy is not currently available, treatment consists of hormone replacement and caring for clinical symptoms.[5] Autoimmune polyglandular syndrome type 1 was previously described in several ethnic groups including Finns, Sardinians, and Iranian Jews.[1] The aim of this study is to describe the clinical, biochemical, and immunological manifestations of APS-1 in a Saudi population.

**Methods.** Seven consanguineous Saudi Arabian families with 20 affected siblings (11 female, 9 male) were followed at the Pediatric Endocrinology Clinic, King Faisal Specialist Hospital and Research Center, Riyadh, Saudi Arabia for a mean duration of 6 years (2-10 years) (January 2000 to December 2009). The age of the affected children ranged from 2-17 years (mean 11 years). One to 7 siblings were affected in each family. The included patients had at least 2 out of the 3 major clinical diagnostic criteria mentioned above. Patients with one disease component of APS-1 were excluded. Five families originated from the central province of Saudi Arabia, and the other 2 families were from the southern and southwestern provinces. All patients had 3-4 monthly clinic visits at the Pediatric Endocrinology Clinic where clinical and laboratory evaluations were performed. Laboratory assessment included complete blood counts, bone profile including calcium, magnesium, phosphorus, and alkaline phosphatase, electrolytes profile including sodium, potassium, and chloride, hepatic profile including alanine aminotransferase, aspartate aminotransferase, bilirubin level, and hemoglobin A1C. Hormonal assessment included parathyroid hormone level (PTH), 25 hydroxyvitamin D, free thyroxine level (FT4), thyroid stimulating hormone (TSH), cortisol level, adrenocorticotropic hormone (ACTH), vitamin B12 level (B12), follicular stimulating hormone (FSH), leuteinizing hormone (LH), testosterone level, estradiol level, and growth hormone (GH) stimulation test for short patients. Diagnosis of HP was based on low serum calcium, high inorganic phosphate, and low levels of PTH measured by the electro chemiluminometric method. Diagnosis of AAD was established by low cortisol reserve in response to synthetic ACTH provocative test and/or simultaneous low random cortisol level and elevated ACTH level. Immunological investigations as a screening for other associated immunological disorders were performed such as celiac disease antibodies including anti gliadin IgA, anti gliadin IgG (by fluoro enzyme immunoassay), anti reticulin IgA, anti endomysium IgA (by immunofluorescent antibody), and anti tissue transglutaminase IgA (by enzyme-linked immunosorbent assay), anti adrenal antibodies such anti 21 hydroxylase antibodies (21-OH abs), and anti 17 hydroxylase antibodies (17-OH abs) (by indirect immunofluorescent antibody test), anti gastric parietal cell antibodies (by enzyme-linked immunosorbent assay), anti thyroid peroxidase antibodies (TPO abs) (by electrochemiluminescent assay), anti glutamic acid decarboxylase 65 antibodies (GAD65 abs) (by radioimmunoassay) and liver kidney microsome antibodies (LKM abs) (by enzyme-linked immunosorbent assay). Genetic studies of affected children were previously reported and showed mutations in AIRE genes.[5] This study was approved by the institutional research ethics committee.

**Results.** The demographic data and clinical manifestations of the 7 Saudi families are summarized in **Table 1**. All reported families were consanguineous; however, there was no familial link between these families. Family pedigrees are shown in **Figure 1**. Fourteen children had neonatal CMC affecting the nails and mouth. They presented as persistent mouth thrush and/or nail pitting (**Figure 2**), 2 children had infantile-onset CMC, and 2 had childhood-onset CMC presenting at the age of 2-3 years. One patient with a neonatal onset of CMC had esophageal candida infection and presented with dysphagia. Patients with CMC were treated with intermittent courses of fluconazole with a variable response. All reported patients in this series had HP. Three children had neonatal HP, 7 had infantile HP, and 10 had childhood onset of HP. The onset of childhood HP ranged from one to 10 years. Ten of these children presented with hypocalcemic convulsions, 5 presented with hypocalcemic tetany. Hypocalcemia was detected in the remaining patients during routine screening. Patients with HP were treated with calcium supplementation, and the active form of vitamin D such as One Alpha drops (1-alpha-hydroxycholecalciferol) or calcitriol (1,25-dihydrocholecalciferol). Calcium

**Table 1 -** Clinical manifestations of autoimmune polyglandular syndrome type 1 Saudi patients.

| Family No. | Patient No. | Gender | Current age (yrs) | Duration of follow-up (yrs) | Onset of | | | | | | | Others |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | CMC | HP | AAD | HT | AU | T1DM | NC | |
| 1 | 1 | F | 14 | 8 | 1st week | 10 years | 10 years | | 10 years | | | |
| 1 | 2 | F | 17 | 8 | 1st week | 1st month | 6 years | | | | 8 years | PGF (15 yrs), AH (10 yrs) |
| 1 | 3 | F | 12 | 8 | 1st week | 1st month | | | 4 years | 4 years | 11 years | B12D (4 years) |
| 1 | 4 | M | 15 | 8 | 1st week | 1st month | | 10 years | 8 years | | 12 years | IR (4 years) |
| 2 | 5 | F | 16 | 7 | 1st month | 3 years | | | | | | CD (12 years) |
| 2 | 6 | F | 15 | 7 | | 4 years | 10 years | | | | | AH (8 years) |
| 2 | 7 | M | 11 | 7 | 1st week | 2 years | | | 8 years | 3 years | | |
| 2 | 8 | M | 2 | 2 | 1st week | 1st year | | 2 years | | | | |
| 2 | 9 | F | 12 | 7 | 1st week | 1st year | 8 years | 11 years | 6 years | | 10 years | |
| 2 | 10 | M | 7 | 7 | | 2 years | 7 years | | | | | |
| 2 | 11 | M | 12 | 7 | 1st week | 10 months | | | 4 years | 7 years | 10 years | OC (1 year) |
| 3 | 12 | M | 8 | 4 | 1st month | 2 years | | | | | | |
| 3 | 13 | F | 6 | 4 | 1st year | 1st year | | | | | | |
| 4 | 14 | M | 9 | 5 | 1st week | 1st year | 8 years | | | | | KP (6 years) |
| 5 | 15 | F | 10 | 5 | 1st week | 4 years | 6 years | | 9 years | | 4 years | AH (8 years) |
| 5 | 16 | F | 11 | 5 | 1st week | 5 years | | | 8 years | | | |
| 6 | 17 | F | 11 | 7 | 3 years | 5 years | | | | | | |
| 6 | 18 | M | 13 | 7 | 1st year | 4 years | | | | | | |
| 7 | 19 | M | 8 | 3 | 2 years | 1st year | 5 years | | 5 years | | | |
| 7 | 20 | F | 10 | 4 | 1st week | 1st year | | | | | | |

CMC - chronic mucocutaneous candidiasis, HP - hypoparathyroidism, AAD - autoimmune Addison's disease, HT - hypothyroidism, AU - alopecia universalis, T1DM - type 1 diabetes, NC - nephrocalcinosis, PGF - primary gonadal failure, B12D - vitamin B12 deficiency, IR - iridiocyclitis, CD - celiac disease, OC - onychosis, KP - keratopathy, AH - autoimmune hepatitis

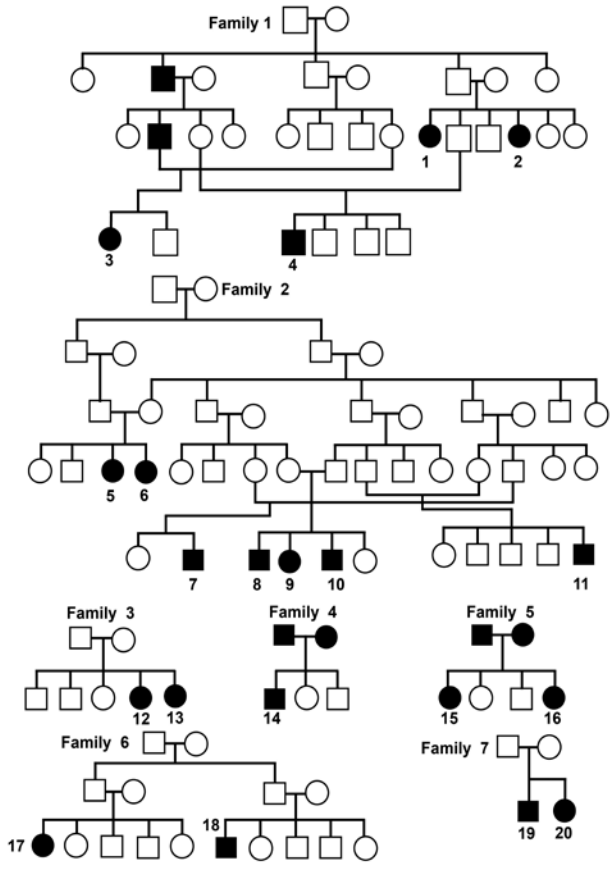


**Figure 1 -** Family pedigrees of 7 Saudi families. Black circles indicate affected females and black squares indicate affected males with autoimmune polyglandular syndrome type 1. Unnumbered squares indicate patients followed in other institutions.

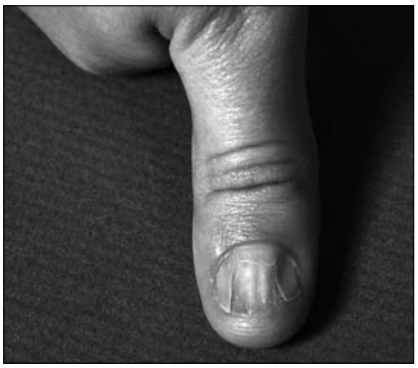

**Figure 2 -** Nail pitting in affected patients with autoimmune polyglandular syndrome type 1.

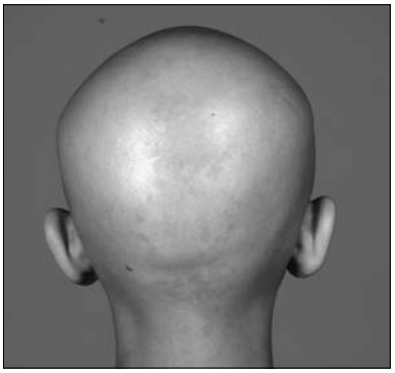

**Figure 3 -** Total loss of scalp hair in a patient with alopecia universalis.

supplementation and vitamin D therapy rendered them eucalcemic and improved their symptoms. Eight patients had AAD; 3 presented with Addisonian crisis, vomiting, dehydration, lethargy, and darkening of skin, and were found to have low cortisol and elevated ACTH levels. The onset of AAD ranged from 5 to 10 years. The other 5 patients were diagnosed during routine screening for AAD. Four patients with AAD and 2 patients who were unaffected with AAD were detected to have positive anti adrenal antibodies; 21-OH abs and 17-OH abs. In all cases, the onset of HP and CMC preceded AAD. Hypothyroidism was diagnosed in 3 patients at the ages of 2, 10, and 11 years. Diagnosis was based on low FT4 level and elevated TSH. Hypothyroid patients were treated with thyroxine replacement therapy. The anti TPO antibody was elevated in hypothyroid patients and 4 euthyroid children with APS-1. Nine patients had alopecia universalis (AU) with the total absence of body hair including scalp (**Figure 3**). The onset of alopecia ranged from 4 to 10 years with a progression from alopecia areata to AU in 2 to 3 years. Azathioprine (Imuran) was tried in 2 patients with no response. A 17-year-old female that presented with primary amenorrhea was diagnosed with hypergonadotropic hypogonadism. She had elevated FSH, LH levels, and low estradiol. Combined estrogen/progesterone hormonal replacement therapy was initiated. Vitamin B12 deficiency, keratoconjuctivitis, onychosis, and iridiocyclitis, was diagnosed in 4 different patients. Type 1 diabetes mellitus was diagnosed in 3 children. One patient was treated with insulin pump therapy. Anti GAD65 abs were elevated in diabetic children and another 2 non-diabetic patients. Celiac disease was diagnosed in one patient based on elevated celiac antibody profile. The diagnosis was confirmed by intestinal biopsy, which showed villous atrophy. Celiac disease antibodies were negative in all other patients. Nephrocalcinosis was detected in 6 children by ultrasonography and treated with hydrochlorthiazide. Autoimmune hepatitis was suspected in 3 patients with elevated liver enzymes. Ultrasonography showed mild hepatomegaly in one patient. The LKM antibody was elevated in one patient with autoimmune hepatitis and another patient with normal liver enzymes. One patient was short and diagnosed with GH deficiency based on low physiological nocturnal GH sampling and pharmacological stimulated tests. Treatment with GH replacement therapy improved his growth velocity. Four children had short stature and normal growth velocity; however, they had normal GH response to provocative tests.

**Discussion.** Autoimmune polyglandular syndrome type 1 is a rare disease with an incidence of 1:100,000. It is more common among Finns (1:25,000), Sardinians (1:14,000), and Iranian Jews (1:6,500 to 1:9,000).[1] In this report, we described the clinical features of 20 children with this syndrome.

In most cases, candidiasis is the first clinical manifestation to appear, usually before the age of 5 years, followed by HP, usually before the age of 10 years, and later by Addison's disease, usually before 15 years of age.[6,7] Chronic mucocutaneous candidiasis generally presents earliest in life and is the most frequent of the 3 main diseases of APS-1. It can appear as early as at the first month after birth up to 21 years of age, with a peak of occurrence in early childhood.[7] It affects the nails, the dermis, and the oral, vaginal, and esophageal mucous membranes. In most cases, the infection is limited to not more than 5% of the skin surface.[7] In rare cases, this disorder can cause important complications; for example, Ahonen et al[7] described 4 cases of esophagitis, with esophageal stricture in one patient, and 11 other cases with periodical retrosternal pain that resolved with oral antifungal therapy. In our series, all patients had CMC, and one patient was affected with esophageal candidiasis. Affected children responded to antifungal therapy.

Hypoparathyroidism is the first endocrine disease to occur during the time course of APS-1. It usually occurs after CMC and before AAD, and can present between 3 months to 44 years of age.[1] In our series, all patients had HP. It is usually difficult to differentiate between neonatal onset of autoimmune HP in APS-1 patients and other common causes of congenital HP in Saudi children such as Sanjad-Sakati syndrome. Autoantibodies to the extracellular domain of the calcium-sensing receptors have been demonstrated in the sera of patients with acquired HP.[8-10]

Autoimmune adrenal insufficiency is usually the third disease to appear during the time course of APS-1. It usually occurs between 6 months and 41 years of age, with a peak incidence at the age of 13 years.[5,6] Autoimmune adrenal insufficiency occurs in 60-100% of cases of APS-1.[6,7,11] In our series, AAD developed in 8 of 20 (40%) of the patients at a mean age of 7.5 years. Anti adrenal antibodies were found in 50% of AAD affected patients and 2 patients who were unaffected with AAD. Anti adrenal antibodies were requested during the first few months of AAD diagnosis. The 21-OH abs were considered the most common antibody present in APS patients. Anti adrenal antibodies can also be detected in patients with APS-1 in the absence of clinical AAD. Betterle et al[1] studied 20 patients with CMC and HP initially without AAD, and 11 (55%) were found to be anti adrenal antibody positive. Nine of these patients were followed up and assessed by ACTH test; 8 developed clinical and one subclinical AAD after a mean follow-up period of 30 months. These data indicate that subjects with CMC and HP should

be tested for anti adrenal antibodies and, if positive, carefully followed up because of the high risk of fast progression to clinical AAD.

Autoimmune polyglandular syndrome type 1 is associated with hypergonadotropic hypogonadism in 17-50% of the cases.[1,6] Gonadal failure can occur before the age of 40 years (secondary amenorrhea) or even before the normal age of puberty (primary amenorrhea).[4] In our series, one patient reached the pubertal age and developed primary amenorrhea.

Type 1 diabetes has been described in 1.2-12% of patients with APS-1;[1,6,7] most of them had islet cell antibodies (IC abs) and/or GAD65 abs.[4] The IC abs were also found in 18-28% of APS-1 patients without type 1 diabetes.[4] In our series, 3 patients had type 1 diabetes. The GAD65 abs were elevated in diabetic children and another 2 non-diabetic patients. The occurrence of type 1 diabetes in 15% of our patients indicates that type 1 diabetes is common in Saudi APS-1 patients compared with other published reports.[1]

The first description of autoimmune thyroiditis in APS-1 was in 1964.[12] Betterle et al[1] reported Hashimoto's thyroiditis in 10% of their cases, which developed at a mean age of 20 years; all were positive for thyroid microsomal autoantibodies. Thyroid autoantibodies, in the absence of clinical thyroid disorders, were found in 27% of the remaining patients, all of whom maintained normal thyroid function during follow-up.[1] In our series, 3 patients had hypothyroidism with positive TPO abs, and TPO abs were positive in another 4 euthyroid patients.

Isolated or multiple pituitary defects secondary to lymphocytic hypophysitis have been described in APS-1. In the large series of Ahonen et al,[7] one case of secondary hypogonadism has been described. In the series of Betterle,[1] 2 cases with an isolated defect of GH production and another with idiopathic diabetes insipidus have been reported. The GH deficiency was also reported in 2 Saudi children with APS-1.[13] In our series, one child was diagnosed with GH deficiency and had normal morphological architecture of the pituitary gland by MRI.

Autoimmune hepatitis has been described in 8-26% of APS-1 cases.[6,7] The age of clinical presentation ranged from 5 to 21 years, and the clinical course could vary from asymptomatic to fulminant hepatic failure.[1,7] Autoimmune hepatitis was suspected in 3 of our patients with elevated liver enzymes. The LKM antibody was elevated in one patient with autoimmune hepatitis and another patient with normal liver enzymes.

An association of alopecia with APS-1 was reported for the first time in 1946.[14] The frequency of this disorder varies from 29-32%. It may involve scalp, eyelashes, eyebrows, axilla, and pubis, and it may appear at any age from 3 to 30 years.[6,7] Alopecia universalis is uncommon in APS-1 cases. In our series, 9 patients (45%) had AU with a mean age of onset of 6.8 years. Alopecia universalis was a striking feature in our patients, which contributed to their emotional instability.

In conclusion, APS-1, although it is an uncommon disorder in Saudi children, affects multiple endocrine glands, and is associated with several autoimmune diseases where alopecia universalis is a common finding in this limited number of patients.

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