



ISSN: 0976-3031

Available Online at <http://www.recentscientific.com>

International Journal of Recent Scientific Research
Vol. 6, Issue, 7, pp.5058-5061, July, 2015

*International Journal
of Recent Scientific
Research*

RESEARCH ARTICLE

AUTOIMMUNE POLYENDOCRINE SYNDROME TYPE 1 (APS-1) IN SAUDI ARABIA

Amer O. Al Ali*¹, Osamah A. Al Ayed², Sharifa D. A. Al Issa³, Abdullah N. Al Jurayyan⁴ and PNasir A. M. Al Jurayyan⁵

¹Senior Fellow in Pediatric Endocrinology

²Junior Fellow in Pediatric Endocrinology

³Senior Registrar in Pediatric Endocrinology

⁴Consultant Immunologist

⁵Pediatric and Consultant Pediatric Endocrinologist

ARTICLE INFO

Article History:

Received 2nd, June, 2015

Received in revised form 10th, June, 2015

Accepted 4th, July, 2015

Published online 28th, July, 2015

Key words:

autoimmune, polyendocrine, syndrome, type 1, Saudi Arabia

ABSTRACT

Background: Autoimmune polyendocrine syndrome type 1 (APS-1) is a rare autosomal recessive disorder which is characterized by multiple organ-specific autoimmunity as well as ectodermal manifestations.

Design and Setting: A retrospective, hospital-based study conducted at King Khalid University Hospital (KKUH), Riyadh, Saudi Arabia in the period January 1995 and December 2014.

Material and Methods: Medical records of children with the diagnosis of autoimmune endocrinopathy were retrospectively reviewed. Data included age, sex, family history, clinical characteristics and results of relevant laboratory investigations.

Results: Five patients from three families were diagnosed with APS-1. All patients had hypoparathyroidism at variable onset, ranging from two to ten years while only four patients had autoimmune adrenal-deficiency (AAD). Several autoimmune disorders were associated.

Conclusion: Autoimmune polyendocrine syndrome (APS-1) is not an uncommon in Saudi children. It is associated with several autoimmune disorders.

Copyright © Amer O. Al Ali et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution and reproduction in any medium, provided the original work is properly cited.

INTRODUCTION

The autoimmune polyendocrine syndromes are diverse, and their diversity is characteristic that is both clinically important and instructive when their basic immunologic features are considered (Table 1). The autoimmune polyendocrine syndrome type 1 (APS-1), the so called, autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED), is rare autosomal recessive disorder⁽¹⁻²⁾ caused by mutations in a single gene on chromosome 21q 22.3 named AIRE (auto-immune regulator).⁽³⁻⁶⁾ The gene encodes a protein with the characteristics of a transcription factor and is expressed in various tissues including the thymus and the lymph nodes.⁽³⁾

APS-1 is characterized by multiple organ-specific autoimmunity as well as ectodermal manifestations.^(1-2,7-10) The disease is usually begins in childhood with chronic mucocutaneous candidiasis, and later the patients contract autoimmune destruction of endocrine as well as non-endocrine organs resulting in a variable phenotype. Typically, the patients display a variety of auto-bodies against intracellular

key enzymes 21-hydroxylase (21 α OH), side-chain cleavage enzyme (SCC), and 17- α -hydroxylase (17 α OH), which are all present in the adrenal cortex, and the other two are also present in the gonads.^(1,11) Auto-antibodies against glutamic acid decarboxylase 65 (GAD-65), a major auto antigen in type 1 diabetes mellitus, are also common in APS-1.^(1,12-14)

The cytochromes P450 are reported in association with autoimmune hepatitis. Also, hypoparathyroidism has been suggested to be the result from an autoimmune reaction directed against the extracellular domain of the calcium-sensory receptor (Ca SR) on parathyroid cells.⁽¹⁾ In this report, we describe five Saudi children with APS-1, from a major teaching hospital, central province, Riyadh, Saudi Arabia

MATERIALS AND METHODS

This is a retrospective hospital-based study, conducted at the Pediatric Endocrine Unit, King Khalid University Hospital (KKUH), Riyadh, Saudi Arabia. The KKUH is the main teaching hospital of King Saud University and considered as

*Corresponding author: Amer O. Al Ali
Senior Fellow in Pediatric Endocrinology

one of the major referral hospitals in the central province of Saudi Arabia.

Patients with auto-immune disorders were reviewed, including age, sex, family history, clinical characteristics and the relevant laboratory investigations. Autoimmune polyendocrine syndrome type 1 (APS-1) was diagnosed according to the specific criteria where mucocutaneous candidiasis, hypoparathyroidism, and adrenal insufficiency (Addison's disease), constituted the classical triad in APS-1 (Table 1).

RESULTS

During the period under review (January 1995 and December 2014), more than 70 patients with autoimmune endocrine disorders were evaluated, five patients from three families were diagnosed to have autoimmune polyendocrine syndrome type 1 (APS-1). The demographic data and clinical features of patients were summarized in Table 2. All reported families were consanguineous; however, there were no familial link between these families. All had infantile chronic mucocutaneous candidiasis (CMC) affecting the nails and mouth. Patients with CMC were treated with intermittent courses of fluconazole, and local nystatin, aqueous solution or cream with variable response.⁽⁵⁻¹⁶⁾

Table 1 Features of autoimmune polyendocrine syndromes

Feature	APS-I	APS-II	X-linked polyendocrinopathy immune dysfunction and diabetic
Prevalence	Rare	Common	Very rare
Time of onset	Infancy	Infancy / adulthood	Neonatal period
Gene and inheritance	AIRE (on chromosome 21) recessive	Polygenies	X-linked
Common phenotype	Candidiasis Hypoparathyroidism Addison's disease	Addison's disease Type 1 DM Chronic thyroiditis	Neonatal diabetes, malabsorption
Immune deficiency	Asplenism, susceptibility to candida	None	Overwhelming autoimmunity Loss of regulating T-cell
Associated with diabetes	Yes (18%)	Yes (20%)	Yes (majority)

Type 1 DM – type 1 diabetes mellitus
APS – autoimmune polyendocrine syndrome

All patients had hypoparathyroidism (HP), at variable onset, ranging from two to ten years. The majority being presented with hypocalcemic tetany. Patients were treated with calcium supplementation, and one alpha drops (1-alpha-hydroxycholecalciferol) or calcitriol (1,25 dihydroxycholecalciferol).⁽¹²⁾ Four patients had autoimmune adrenal deficiency (AAD), presented with lethargy, darkening of skin, and were found to have low cortisol and elevated adrenocorticotrophic hormone ACTH levels. In, all patients, positive anti-adrenal antibodies (anti-21-OH) were found. The onset of CMG and HT preceded AAD. Of interest to find three other siblings in family 1, with other isolated autoimmune endocrinopathy, a 5 year-old boy with type 1 Diabetes Mellitus and elevated anti-GAD 65 antibodies, a 3 year-old boy with hypothyroidism, and a 2 year-old-girl with hypoparathyroidism. A patient, from family 1, also developed celiac disease proved by intestinal biopsy, hypothyroidism, and keratoconjunctivitis, autoimmune hepatitis and type 1 diabetes mellitus. A patient, from family 2, developed type 1 diabetes mellitus with elevated (anti-GAD-antibodies and alopecia universalis).

DISCUSSION

Autoimmunepolyendocrine syndrome type 1 (APS-1), also called autoimmune polyendocrinopathy candidiasis ectodermal dystrophy (APECED), is a rare autosomal recessive disorder, due to mutation in AIRE gene "autoimmune regulator", with an incidence of 1:100,000.⁽¹⁻²⁾ It is more common among Finns, Sardinians and Iranians Jews.⁽¹⁸⁻¹⁹⁾ In Saudi Arabia, Bin Abbas *et al*⁽¹⁹⁾ has shown that it is not that uncommon which was supported by our study. In a country where the consanguineous mating is very high, approaching 60% this is not unusual.^(20,21) The diagnosis is made when a child has at least two of the following pathologies; muco-cutaneous candidiasis (CMC), hypoparathyroidism or Addison disease (ADD),⁽¹⁻²⁾ chronic muco-cutaneous candidiasis (CMC) generally presenting early in life, as in our series, and is the most frequent finding in APS. Hypoparathyroidism (HP) is the first endocrine disorders and usually occurs after CMC and before autoimmune adrenal insufficiency (AAD), and can occur as late in adulthood.^(1,2,7,10,15,19) In this series, all patients had CMC and HP. Autoimmune adrenal insufficiency (AAD) is usually the third disease to appear during the course of APSI, with a peak incidence of 15 years.⁽¹⁹⁾ The 21-hydroxylase (21-OH) antibodies were considered the most common antibodies in APS-I.⁽¹¹⁾

Table 2 The demographic data and clinical features of patients with APS1

Patient No.	Family No.	Sex	Age at onset	Clinical feature	Remarks
					Other associated autoimmune disease
1		M	10 y	CMC (Infancy), HP (10 y), AAD (10 y)	Atrophic gastritis, pernicious anemia
2	1	F	8 y	CMC (Infancy), HP (8 y), AAD (9 y)	Celiac disease, hypothyroidism, pernicious anemia, Died at 15 y acute fulminant hepatitis, over-wheeling sepsis
3		M	6 y	CMC (Infancy), HP (6 y), AAD (9 y)	Keratoconjunctivitis, acute autoimmune, hepatitis, type 1 diabetes mellitus
4	2	F	4 y	CMC (Infancy), HP (4 y), AAD (6 y)	Atropic gastroenteritis type 1 diabetes mellitus
5	3.	F	3 y	CMC (Infancy), HP (3 y), AAD (6 y)	Iridiocyclitis

M – male, F- female, Y-year, chronic mucocutaneous-candidiasis (CMC), hypoparathyroidism (HP), autoimmune adrenal deficiency (AAD)

APS-1 is associated with other autoimmune disorders (type 1 diabetes mellitus, vitiligo, alopecia, hepatitis, pernicious anemia and primary hypothyroidism and has been also been linked to asplenia.^(9,22,23)

Of interest in our series, type 1 diabetes mellitus has been described in two patients, both of them had islet cell antibodies (GAD 65), i.e. 40%, which indicates that type 1 diabetes is common compared to other report.⁽¹³⁻¹⁴⁾

The first description of autoimmune thyroiditis in patients with APS-1 was in 1964. *Betterle et al* reported Hashimoto's thyroiditis in 10% of their patients, developing at a mean age of 20 years, all were positive for thyroid microsomal auto-antibodies. Thyroid auto-antibodies 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.⁽²⁴⁾

Malabsorption due to atrophic gastritis and celiac disease are commonly associated with APS-1. The prevalence of celiac disease was 12.5%. This can lead to pernicious anemia.^(25,26) Autoimmune hepatitis has described in 8-26% of APS-1 patients. The age of clinical presentation ranged from 5 to 21 years, and the clinical course could vary from asymptomatic to fulminant hepatic failure. Autoimmune hepatitis was found in one patient who presented at 11 years of age.⁽¹⁹⁾

An association with alopecia was reported for the first time in 1946. 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. Alopecia universalis (AV) is uncommon in APS-1 patients. In our series, one patient had AV which was a striking feature.⁽¹⁹⁾

Finally, autoimmune polyendocrine syndrome type 1 (APS-1), is not that uncommon in Saudi children. It was associated with various other autoimmune organ-specific disorders, such as hypothyroidism, type 1 diabetes, pernicious anemia, malabsorption, celiac disease, autoimmune hepatitis and alopecia, some can be life-threatening conditions.

Acknowledgement

The authors would like to thank Ms. Loida M. Sese for typing the manuscript and extend their thanks and appreciations to Miss Hadeel N. Al Jurayyan for her help in preparing this manuscript.

References

1. Ahonen P, Myllarniemi S, Kahanpaa A, Perheentupa J. Ketoconazole is effective against the chronic mucocutaneous candidiasis of autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED). *Acta Med Scan* 1986;220(4):333-9.
2. Ahonen P, Myllarniemi S, Sipila 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.

3. Betterle C, Greggio NA, Volpato M. Clinical review 93. Autoimmune polyglandular syndrome type 1. *J Clin Endocrinol Metab* 1998;83:1049-1055.
4. Bin Abbas BS, Faiyaz-Ul-Haque M, Al Fares AH, Al Gazlan SS, Bhuiyan JA, Al Muhsen SZ. Autoimmune polyglandular syndrome type 1 in Saudi Arabia. *Saudi Med J* 2010;31(7):788-92.
5. Eisenbarth GS, Gottlieb PA. Autoimmune polyendocrine syndromes. *N Eng J Med* 2004;350:2068-79.
6. El Mouzan MI, Al Salloum AA, Al Herbish AS, Qurachi MM, Al Omar AA. Regional variations in the prevalence of consanguinity in Saudi Arabia. *Saudi Med J* 2007;28:1881-4.
7. Friedman TC, Thomac PM, Fleisher TA, *et al*. Frequent occurrence of asplenia and cholelithiasis in patients with autoimmune polyglandular disease type 1. *Am J Med* 1991;91:625-630.
8. Gylling M, Tuomi T, Bjorses P, Kontiainen S, Partanen J, Christie MR, Knip M, Perheentupa J, Miettinen A. β -cell autoantibodies, human leukocyte antigen II alleles, and type 1 diabetes in autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy. *J Clin Endocrinol Metab* 2000;85:4434-4440.
9. Hogenauer C, Meyer RL, Netto GJ, *et al*. Malabsorption due to cholecystokinin deficiency in a patient with autoimmune polyglandular syndrome type 1. *N Engl J Med* 2001;344:270-4.
10. Kumar PG, Laloraya M, She JX. Population genetics and functions of the autoimmune regulator (AIRE). *Endocrinol Metab Clin North Am* 2002;31:321-338.
11. Kumar V, Rajudhyaksha M, Wortsam J. Celiac disease associated autoimmune endocrinopathies. *Clin Diagn Lab Immunol* 2001;8:4678-685.
12. Mathis D, Benoist C. A decade of AIRE. *Nat Rev Immunol* 2007;7:645-650.
13. Meloni A, Furcas M, *et al*. Autoantibodies against type 1 interferons as an additional diagnostic criterion for autoimmune polyendocrine syndrome type 1. *J Clin Endocrinol Metab* 2008;93:4389-97.
14. Owen CJ, Cheetham TD. Diagnosis and management of polyendocrinopathy syndromes. *Endocrinol Metab Clin North Am* 2009;38:419-436.
15. Perniola R, Falorni A, Clemente MG, Forini F, Accogli E, Lobreglio G. Organ-specific and non-organ-specific autoantibodies in children and young adults with autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED). *Eur J Endocrinol* 2000;143:497-503.
16. Pollak U, Bar-sever Z, Hoffer V, *et al*. Asplenia and functional hyposplenism in autoimmune polyglandular syndrome type 1. *Eur J Pediatr* 2009;168:233-235.
17. Saedi-Wong S, Al Frayh AR, Wong HY. Socio-economic-epidemiology of consanguineous matings in Saudi Arabian population. *J Asian Afr Stu* 1989;24:47-52.
18. Sarinda M, Dennis C. Clinical phenotypes of autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy seen in the Northern Ireland paediatric population over the last 30 years. *Ulster Med J* 2012;81(3):118-122.

19. Soderbergh A, Myhre A, Kwall O, *et al.* Prevalence and clinical associations of 10 defined autoantibodies in autoimmune polyendocrine syndrome type 1. *J Clin Endocrinol Metab* 2004;89(2):557-562.
20. Su M, Anderson MS. AIRE : an update. *Curr Opin Immunol* 2004;16:746-752.
21. The 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;12:399-403.
22. Thomas HE, Kay TW. Beta cell destruction in the development of autoimmune diabetes in the non-obese diabetic (NOD) mouse. *Diabetes Metab Res Rev* 2000;16:251-61.
23. Winqvist O, Karlsson FA, Kampe O. 21-hydroxylase, a major autoantigen in idiopathic Addison's disease. *Lancet* 1992;339:1559-1562.
24. Winter KK, Sinaii N, Reynolds J, Peterson D, Dowdy K, Cutler (Jr.) GB. Long-term treatment of 12 children with chronic hypoparathyroidism : a randomized trial comparing synthetic human parathyroid hormone 1-34 versus calcitriol and calcium. *J Clin Endocrinol Metab* 2010;95(6):2680-2688.
25. Winter WE, Harris N, Schatz D. Type 1 diabetes islet autoantibody markers. *Diabetes Technol Ther* 2002; 4:817-39.
26. Zlotogora J, Shapiro MS. Polyglandular auto-immune syndrome type 1 among Iranian Jews. *J Med Genet* 1992; 29:824-826.

How to cite this article:

Amer O. Al Ali., Autoimmune Polyendocrine Syndrome type 1 (aps-1) in Saudi Arabia. *International Journal of Recent Scientific Research* Vol. 6, Issue, 7, pp.5058-5061, July, 2015
