Investigating autoimmune polyendocrine syndromes

DIVYA NAMBOODIRI MB BS; **HUI YI NG** MB BS
BERNARD CHAMPION BEc, BScMed, MB BS(Hons 1), FRACP, MMedEd
VERONICA PREDA Bsc(Med), MB BS(Hons), MPH, FRACP, PhD

Case scenarios are used in this section to educate doctors on the best approach to the diagnosis and management of patients with different endocrine problems. The appropriate selection of tests and correct interpretation of test results are discussed.

ENDOCRINOLOGY TODAY 2020; 9(1): 36-40

Dr Namboodiri and Dr Ng are Advanced Trainees in Endocrinology, Dr Champion is an Associate Professor and Dr Preda is a Senior Clinical Lecturer at the Department of Endocrinology, Faculty of Medicine and Health Sciences, Macquarie University Hospital, Sydney, NSW.

SERIES EDITOR: Dr Bernard Champion BEc, BScMed, MB BS(Hons 1), FRACP, MMedEd is an Endocrinologist and Associate Professor in Medicine at Macquarie University, Sydney, NSW.

Autoimmune polyendocrine syndromes (APS) are a group of immune endocrinopathies, characterised by functional impairment of multiple endocrine glands due to loss of immune tolerance.[1] They can also result in various nonendocrine immune disorders such as alopecia, coeliac disease, vitiligo, autoimmune gastritis and pernicious anaemia.[1] They are characterised by circulating antibodies and lymphocytic infiltration of the affected organs, which eventually lead to organ failure.[1] Risk of developing the component autoimmune diseases is influenced by genetic susceptibility and environmental factors. Discrete genes may be involved including the autoimmune regulator gene, *AIRE,* and fork-head box P3 gene, *FOXP3*. There is variation in presentation and symptoms, which can make diagnosis difficult. Diagnosis requires coexistence of at least two autoimmune endocrinopathies.[2]

These syndromes have varied presentations and can manifest sequentially at different stages during a patient's life. An asymptomatic latent period of months to years is characterised by the presence of circulating autoantibodies. One report suggests that more than 20 years could lapse between the diagnosis of one endocrinopathy and diagnosis of another.[3] Hence, long-term follow up of these patients is crucial. Management centres around monitoring and replacement of multiple hormones, along with treatment of other nonendocrine manifestations. Treatment of multiple deficiencies may be complex. The interaction of different hormonal therapies and pharmacological agents also needs to be considered.

Types of APS

APS can be classified based on their modes of inheritance, age at presentation and characteristic patterns of disease combinations. The two major subtypes are APS-1 and APS-2. A third subtype, IPEX (immune dysfunction, polyendocrinopathy, enteropathy, X-linked), has also been described, but is rare.[1]

APS-1

APS-1 is a rare, monogenic form, which usually presents before or during puberty. Although there are no large epidemiological studies on the prevalence of APS-1, and milder forms of APS-1 may go undiagnosed, the estimated prevalence of APS-1 is roughly 1:100,000 in most countries, with a higher prevalence in some places such as Finland (1:25,000) and Sardinia (1:14,000), and among some populations such as Iranian Jews living in Israel (1:9000) and in populations characterised by a high degree of consanguinity.[1,4]

APS-1 is characterised by at least two of the following three major features:[1]

- hypoparathyroidism
- primary adrenal insufficiency (Addison's disease)
- chronic mucocutaneous candidiasis.

Other disease manifestations include: gonadal failure (hypergonadotrophic

Table 1. Classification of autoimmune polyendocrine syndromes (APS)[1,10]

Characteristic	APS-1	APS-2	IPEX
Age of onset	Childhood, usually before puberty	Adolescence to adulthood	Infancy
Males/females	Equally predominant in males and females	Predominantly in females	Males
Prevalence	1:100,000	1:1000	1:1,000,000
Main manifestations	• Addison's disease • Hypoparathyroidism • Chronic mucocutaneous candidiasis	• Addison's disease • Autoimmune thyroid disease • Type 1 diabetes	• Autoimmune enteropathy • Type 1 diabetes • Eczema
Other associated manifestations	Primary ovarian insufficiency, autoimmune thyroid disease, type 1 diabetes, autoimmune gastritis, enteritis with malabsorption, hepatitis, pancreatitis, pneumonitis, nephritis, vitiligo, alopecia, nail dystrophy, enamel hypoplasia, keratitis, retinitis	Autoimmune gastritis, alopecia, vitiligo, coeliac disease, primary ovarian insufficiency	Autoimmune thyroid disease, haemolytic anaemia, thrombocytopenia
Usual genes and mode of inheritance	*AIRE*, autosomal recessive and dominant	Polygenic: *HLA*, genes encoding CTLA-4, PTPN22, CD-25 interleukin-2 receptor	*FOXP3*, X-linked recessive

Abbreviations: *AIRE* = autoimmune regulator gene; *FOXP3* = fork-head box P3; IPEX = immune dysfunction, polyendocrinopathy, enteropathy, X-linked; *HLA* = human leukocyte antigen.

hypogonadism including premature ovarian failure), type 1 diabetes, autoimmune gastritis, pernicious anaemia, autoimmune hepatitis, alopecia, vitiligo, keratoconjunctivitis and asplenia (Table 1).

Normally, developing T-cells with a potential reactivity for self-antigens are eliminated during early differentiation of the thymus by a process called immune tolerance. In APS-1, there is an underlying mutation of the *AIRE* gene, resulting in loss of immune tolerance with subsequent release of autoreactive T cells into the periphery, which then results in multiple autoimmune disorders.[5] The loss of immune tolerance is thought to be in both central and peripheral pathways.[6,7] More than 100 different mutations of the *AIRE* gene have been identified to date. APS-1 has an autosomal recessive inheritance, onset is usually before the age of 15 years and it is equally predominant in males and females.[1]

Recently, patients with a unique dominant negative mutation in the *AIRE* gene and autosomal dominant inheritance have been identified.[1] These individuals have a milder form of the syndrome and can often present with pernicious anaemia, vitiligo, type 1 diabetes and autoimmune thyroid disease, which can be difficult to diagnose as they can be confused with the more common APS-2.[1]

APS-2

APS-2 is a more common, adult-onset, polygenic form of APS, with a higher prevalence (1:1000) than APS-1. It is characterised by at least two of the following endocrinopathies (Table 1):[1]

- type 1 diabetes
- autoimmune thyroid disease
- Addison's disease.

Adrenal insufficiency is the initial manifestation in 50% of patients. The incidence is higher among females. Family members across multiple generations are often affected.[3] The pathogenesis is less clear and involves both human leucocyte antigen (*HLA*) and non-*HLA* genes. Alleles of *HLA* determine the targeting of specific tissues by autoreactive T cells, which leads to organ-specific autoimmunity as a result of loss of tolerance. Non-*HLA* genes also contribute to autoimmunity and, depending on the polymorphism, potentially predispose to a loss of tolerance of the organ involved.[5] There are various classifications of APS-2 in the literature based on combinations of component diseases.[8,9] These different classifications can be confusing so, recently, all of these have been collectively termed as APS 2.[8]

IPEX

IPEX is a rare and fulminant form of APS, characterised by early-onset type 1 diabetes, autoimmune enteropathy with intractable diarrhoea, malabsorption and dermatitis (Table 1). It is caused by mutations in the *FOXP3* gene, which results in the absence or dysfunction of regulatory T cells. Many features of IPEX overlap with APS-1, but the presentation of IPEX is usually in infancy, only in males and is often fatal if not promptly treated.[1]

Diagnosis and management

Diagnostic work-up of patients with APS includes assessment of endocrine function and consideration of serological screening for relevant organ-specific antibodies (Tables 2 and 3). There is a clear association between the presence of organ-specific autoantibodies and progression to disease.[9] Presymptomatic recognition of autoimmune disease minimises associated morbidity and mortality.[9] In the presence of one endocrine manifestation, it is important to screen long term for the development of others, particularly Addison's disease and type 1 diabetes. The clinical significance of classifying APS lies in screening patients and first-degree relatives for associated autoimmune diseases, as one in seven first-degree relatives have an unrecognised endocrine disorder.[5] Patients should be counselled about the symptoms of other autoimmune disorders for which they are at high risk. Management includes:

Table 2. Evaluation and management of APS-1

	Screening antibodies	Functional screening	Therapy
Type 1 diabetes	IAA, GAD, IA-2 antibodies ZnT8 if above are negative	Glucose	Insulin
Autoimmune thyroid disease	Anti-TPO, anti-Tg, TR antibody	TSH, FT4	Thyroxine; antithyroid medications in Graves' disease
Primary adrenal insufficiency	21-OH*, 17-OH*, SCC	Cortisol, ACTH	Hydrocortisone
Primary ovarian insufficiency	17-OH antibody	FSH, LH, oestradiol/testosterone	Oestradiol/testosterone
Hypoparathyroidism	CaSR antibody	PTH, calcium phosphate	Vitamin D
Autoimmune gastritis	H+/K+-ATPase gastric parietal cell	Endoscopy, RBC	Iron, vitamin B12
Pernicious anaemia	Intrinsic factor	Vitamin B12	Vitamin B12 replacement

Abbreviations: 17-OH = 17-hydroxylase; 21-OH = 21-hydroxylase; ACTH = adrenocorticotropic hormone; APS = autoimmune polyendocrine syndromes; CaSR = calcium sensing receptor; FT4 = free thyroxine; GAD = glutamic acid decarboxylase; FSH = follicle stimulating hormone; H+/K+-ATPase = hydrogen potassium ATPase; IA-2 = islet antigen-2; IAA = insulin autoantibody; LH = luteinising hormone; PTH = parathyroid hormone; RBC = red blood cell; SCC = side-chain cleavage; Tg = thyroglobulin; TPO = thyroid peroxidase; TR = thyroid receptor; TSH = thyroid stimulating hormone; ZnT8 = zinc transporter 8.
*Sensitivity for organ-specific antibodies apart from islet autoantibodies is low (e.g. 21-OH, 17-OH, ovarian).

- hormone replacement therapy as required
- monitoring for the development of other endocrine and nonendocrine manifestations and their treatment (Tables 2 and 3).

Patients with APS-1 are best managed by a multidisciplinary team led by an endocrinologist or paediatric endocrinologist. It is recommended that patients have two follow-up visits a year and asymptomatic carriers be followed up at least annually.[1] Children should be followed up regularly by their paediatric endocrinologist until later adulthood.

Case 1. APS-1

Tina is a 25-year-old woman who is concerned about her severe fatigue, which has significant impact on activities of daily living. She was diagnosed with type 1 diabetes at the age of 2 years. Over the following years, she developed multiple other autoimmune disorders: Hashimoto's thyroiditis at age 10 years (positive anti-TPO 559 IU/L); chronic idiopathic urticaria and angioedema; and a recent diagnosis of pernicious anaemia. Her brother also has type 1 diabetes. Tina's current medications include thyroxine 100 mcg daily, immunosuppressive therapy with mycophenolate 500 mg twice a day, a leukotriene receptor antagonist, montelukast, for chronic idiopathic urticaria and the oral contraceptive pill (OCP) for regulation of menstrual cycles.

What initial investigations should be ordered?

Tests that Tina should have to screen for the presence of other autoimmune diseases are

Table 3. Evaluation and management of APS-2

	Screening antibodies	Functional screening	Therapy
Primary adrenal insufficiency	21-OH, 17-OH, SCC	Cortisol, ACTH	Hydrocortisone
Autoimmune thyroid disease	Anti-TPO, anti-Tg, TR antibody	TSH, FT4, FT3	Thyroxine; antithyroid medications in Graves' disease
Type 1 diabetes	IAA, GAD antibodies, IA-2 ZnT8 if above are negative	Glucose	Insulin
Coeliac disease	tTG, IgA, DGP	Endoscopy, biopsy	Gluten–free diet
Primary ovarian insufficiency	17-OH antibody	FSH, LH, oestradiol/testosterone	Oestradiol/testosterone

Abbreviations: 17-OH = 17-hydroxylase; 21-OH = 21-hydroxylase; ACTH = adrenocorticotropic hormone; DGP = deamidated gliadin peptide; FT3 = free triiodothyonine; FT4 = free thyroxine; GAD = glutamic acid decarboxylase; FSH = follicle stimulating hormone; IA-2 = islet antigen-2; IAA = insulin autoantibody; IgA = immunoglobulin A; LH = luteinising hormone; SCC = side-chain cleavage; Tg = thyroglobulin; TPO = thyroid peroxidase; TR = thyroid receptor; TSH = thyroid stimulating hormone; tTG = tissue transglutaminase; ZnT8 = zinc transporter 8.

outlined in Box 1. As Tina is taking the OCP, morning cortisol is likely to be falsely elevated due to an increase in cortisol-binding globulin. Therefore, repeat morning cortisol should be performed after the OCP has been discontinued for six weeks. Table 4 shows her blood test results.

What is the likely diagnosis?

Tina has multiple autoimmune diseases with endocrine and nonendocrine manifestations of type 1 diabetes, Hashimoto's thyroid disease and pernicious anaemia. She has negative dominant APS-1 with a milder disease, and a family history of autoimmunity (her brother).

The patient is considering pregnancy in the future. What is your approach?

The reproductive hormone profile and anti-Mullerian hormone (AMH) level should be reassessed after Tina has discontinued the OCP for six weeks. It is important to assess fertility as there is a risk of premature ovarian failure with APS, although at present her 17-hydroxylase (17-OH) antibodies are negative. Mycophenolate is teratogenic and she would need to be changed to a nonteratogenic immunosuppressant, bearing in mind the risk of relapse of chronic idiopathic urticaria and angioedema.

How should this patient be managed in the long term?

Tina should have regular serological and functional screening tests for sequential development of other autoimmune diseases later in life. She should have regular thyroid function tests, measurement of glycated haemoglobin (HbA_{1c}) and serum vitamin B12 levels, and full blood count.

Learning points

Diagnosis and classification of APS can be challenging due to the significant overlap of component diseases, which can manifest at various stages of life. Early screening and detection of these diseases is important to achieve optimal outcomes. There is increased risk of first-degree family members being affected, so screening of first-degree relatives is important.

Case 2. APS-2

Ben is a 31-year-old man with well-controlled type 1 diabetes (glutamic acid decarboxylase [GAD] 831IU/mL, negative islet antigen 2 [IA-2] and islet cell antibody counts) and autoimmune thyroiditis. He presents for evaluation of infertility. Ben had normal pubertal development of secondary sexual characteristics and denied a history of testicular trauma or surgery. On examination, his body mass index is 38.1kg/m^2, he has an underdeveloped penis (less than 4cm) and bilateral small testes (8mL in volume).

What initial investigations should be ordered?

Initial tests should include an assessment of Ben's gonadal axis, with early morning serum levels of testosterone, luteinising hormone (LH), follicle stimulating hormone (FSH) and sex hormone binding globulin (SHBG), given his obesity (Table 5). Presence of steroid-producing cell autoantibodies, sperm autoantibodies or antibodies against germ cell or Leydig cells would indicate an autoimmune aetiology for hypogonadism.

Subsequent investigations should include a complete pituitary panel (including prolactin) and a pituitary MRI, to rule out a secondary cause of hypogonadism, both of which had unremarkable results in Ben's case. Other investigations that should be considered are semen analysis, which shows azoospermia in Ben's case, and a karyotype for exclusion of chromosomal abnormalities which, in this case, was normal. A microdeletion study may be considered to look for genetic causes of impaired spermatogenesis.

1. Tests to screen Tina for presence of other autoimmune diseases

Serological

- 21-OH and side-chain cleavage antibodies (for Addison's disease)
- 17-OH antibodies (for Addison's disease, primary ovarian insufficiency)
- Total IgA, tTG-IgA antibodies, DGP antibody (for coeliac disease)

Functional

- Early morning cortisol, ACTH
- Serum calcium levels
- Serum vitamin B12, FBC, iron studies
- FSH, LH, oestradiol and progesterone to rule out gonadal failure

Abbreviations: 17-OH = 17-hydroxylase; 21-OH = 21-hydroxylase; ACTH = adrenocorticotropic hormone; DGP = deamidated gliadin peptide; FBC = full blood count; FSH = follicle stimulating hormone; LH = luteinising hormone; tTG-IgA = tissue transglutaminase-immunoglobulin A.

What is the most likely diagnosis?

Ben most likely has APS-2 given the adult onset of his immune endocrinopathies and the

Table 4. Tina's blood test results

Test	Result
Cortisol (at 0930 h)	519 nmol/L (reference range, 138 to 650 nmol/L)
ACTH	2.7 pmol/L (<12.1 pmol/L)
Calcium	2.3 mmol/L (reference range, 2.11 to 2.55 mmol/L); hence screening for CaSr antibodies (for hypoparathyroidism) was not performed
Iron studies	Normal
Coeliac serology	Negative
Thyroid function tests	TSH 2.8 mIU/L, FT4 13 pmol/L
AMH	Low at 12.9 pmol/L (reference range, 14 to 30 pmol/L), suggesting reduced ovarian reserve; OCP can lower the AMH level
17-OH antibody	Negative

Abbreviations: 17-OH = 17-hydroxylase; ACTH = adrenocorticotropic hormone; AMH = anti-Mullerian hormone; CaSr = calcium sensing receptor; FT4 = free thyroxine; OCP = oral contraceptive pill; TSH = thyroid stimulating hormone.

Table 5. Ben's test results

Test	Result
Early morning testosterone	Low at 6.7 nmol/L (>10 nmol/L)
Gonadotrophins	Inappropriately normal FSH 10.9 IU/L; LH 3.1IU/L (< 9 IU/L)
SHBG	29 nmol/L (reference range, 15 to 30 nmol/L)

Abbreviations: FSH = follicle stimulating hormone; LH = luteinising hormone; SHGB = sex hormone binding globulin.

constellation of type 1 diabetes and autoimmune thyroiditis. The possibility of autoimmune primary hypogonadism should be considered given the risk of primary hypogonadism with APS-2. Obesity could also be contributing to the picture of hypogonadism through decreasing SHBG, thereby lowering the overall testosterone level, a possible reason being increased temperature of testes resulting in reduced or absent sperm production.

How should this patient be managed?

Ben requires ongoing screening for early detection of other component diseases of APS-2 such as coeliac disease, Addison's disease and pernicious anaemia. Given the finding of azoospermia on semen analysis, a testicular biopsy should be organised to determine the chances of assisted fertility. Ben's testicular biopsy demonstrated the presence of only Sertoli cells with an absence of germ cells, consistent with idiopathic Sertoli cell-only syndrome. Ben and his partner proceeded to have in vitro fertilisation with a sperm donor. In the long term, Ben's gonadotrophin levels should be monitored as he may require hormonal replacement in the future.

Learning points

APS-2 can present with primary hypogonadism and it is important to consider this aetiology in a patient with multiple immune endocrinopathies as well as other contributing factors such as obesity, which can make the diagnosis challenging.

Conclusion

With recent diagnostic and genetic advances, we have a better understanding of the immunopathological course that leads to multiorgan autoimmunity. The classification of APS has important implications for patients and their relatives as it alerts the clinician to the possibility of coexisting autoimmune disease and probable future development of autoimmune disease. Management is often dynamic and involves optimising therapy in the patient's evolving clinical course, and long-term follow-up is crucial (Box 2). **ET**

Case 3 is included in the online version of this article (www.endocrinologytoday.com.au).

2. Practice points on autoimmune polyendocrine syndromes (APS)

- APS involve functional abnormalities in several endocrine and nonendocrine glands.
- Deficits may manifest over time. Screening for other manifestations is important.
- There is variation in presentation and symptoms, which can make diagnosis difficult.
- Counselling patients regarding potential for multiple manifestations is important. Other family members may have unrecognised autoimmune conditions.
- Discrete genes may be involved including the autoimmune regulator gene, *AIRE,* and fork-head box P3 gene, *FOXP3*.
- Treatment of multiple deficiencies may be complex.

References

1. Husebye ES, Anderson MS, Kampe O. Autoimmune polyendocrine syndromes. N Engl J Med 2018; 378: 1132-1141.
2. Kahaly GJ, Frommer L. Polyglandular autoimmune syndromes. J Endocrinol Invest 2018; 41: 91-98.
3. Cutolo M. Autoimmune polyendocrine syndromes. Autoimmun Rev 2014; 13: 85-89.
4. Frommer L, Kahaly GJ. Autoimmune polyendocrinopathy. J Clin Endocrinol Metab 2019; 104: 4769-4782.
5. Michels AW, Gottlieb PA. Autoimmune polyglandular syndromes. Nat Rev Endocrinol 2010; 6: 270-277.
6. Zhao B, Chang L, Fu H, Sun G, Yang W. The role of autoimmune regulator (AIRE) in peripheral tolerance. J Immunol Res 2018; 2018: 3930750. doi: 10.1155/2018/3930750. eCollection 2018.
7. Husebye ES, Anderson MS. Autoimmune polyendocrine syndromes: clues to type 1 diabetes pathogenesis. Immunity 2010; 32: 479-487.
8. Eisenbarth GS, Gottlieb PA. Autoimmune polyendocrine syndromes. N Engl J Med 2004; 350: 2068-2079.
9. Owen CJ, Cheetham TD. Diagnosis and management of polyendocrinopathy syndromes. Endocrinol Metab Clin North Am 2009; 38: 419-436.
10. Hattersley AT, Greeley SAW, Polak M, et al. ISPAD clinical practice consensus guidelines 2018: the diagnosis and management of monogenic diabetes in children and adolescents. Pediatr Diabetes 2018; 19 Suppl 27: S47-S63.

COMPETING INTERESTS: None.

Investigating autoimmune polyendocrine syndromes

DIVYA NAMBOODIRI MB BS; **HUI YI NG** MB BS; **BERNARD CHAMPION** BEc, MB BS, MSc(Med)(Hons 1), FRACP, MMedEd
VERONICA PREDA Bsc(Med), MB BS(Hons), MPH, FRACP, PhD

Case 3. APS-2

Deborah is a 67-year-old postmenopausal woman, who is referred to our endocrinology service with a past diagnosis of Addison's disease and hypothyroidism, and recent diagnosis of diabetes and iron deficiency. She reports symptoms of lethargy and is noted to be iron deficient. Her diabetes has been managed with oral hypoglycaemic agents alone to date.

What initial investigations should be ordered?

Given her history of Addison's disease and autoimmune thyroid disease, other autoimmune conditions such as late-onset autoimmune diabetes, hypoparathyroidism, pernicious anaemia and coeliac disease should be considered. The following serological screening and functional tests should be considered.

- Screening tests:
  - intrinsic factor and gastric parietal cell antibody (for pernicious anaemia)
  - total immunoglobulin A (IgA), tTG (tissue transglutaminase)-IgA, deamidated gliadin peptide (DGP) antibody (for coeliac disease)
  - calcium sensing receptor (CaSR) antibody (for hypoparathyroidism)
  - glutamic acid decarboxylase (GAD), islet antigen-2 (IA-2), zinc transporter 8 antibody (ZnT8Ab), islet cell antibody
- Functional tests:
  - thyroid stimulating hormone (TSH), free thyroxine (FT4), free triiodothyronine (FT3)
  - glycated haemoglobin (HbA_{1c}), glucose
  - iron studies, serum vitamin B12 and folate
  - corrected calcium

Table 6 shows Deborah's blood test results. The results indicate Deborah has late-onset autoimmune type 1 diabetes. Iron deficiency is confirmed. Positive intrinsic and gastric parietal cell antibodies suggest pernicious anaemia, although her serum vitamin B12 level is normal.

Table 6. Deborah's blood test results

Test	Results
HbA_{1c}	7.3%
Iron studies	Ferritin 15 mcg/L (reference range, 30 to 200 mcg/L); transferrin 3.5 gm/L (reference range, 2 to 3.2 gm/L)
Intrinsic factor and gastric parietal cell antibody	Positive
TSH	Normal
FBC	Normal
Corrected calcium	2.2
Coeliac serology	Negative
Vitamin B12 and folate	Normal
GAD antibody	> 2000 U/ml (<10 U/mL)
IA-2 antibodies	< 10 (< 10 U/mL)

Abbreviations: FBC = full blood count; GAD = glutamic acid decarboxylase; HbA_{1c} = glycated haemoglobin; IA-2 = islet antigen-2; TSH = thyroid stimulating hormone.

What is the most likely diagnosis?

Deborah has multiple autoimmune endocrinopathies with Addison's disease, Hashimoto's disease, pernicious anaemia and diabetes (autoimmunity testing required). She would be classified as having APS-2.

What is your management plan?

How should Deborah's diabetes be treated? She was referred to a gastroenterologist for investigation of iron deficiency including a gastroscopy and colonoscopy. Her serum vitamin B12 level should be monitored due to positive antibodies for pernicious anaemia, as vitamin B12 replacement therapy may be required. Osteoporosis assessment should also occur in this patient considering her postmenopausal state and history.

Learning points

Early and timely detection of the multiple endocrinopathies in APS can improve patient outcomes and minimise complications. Correct classification is needed, as type 1 diabetes is managed differently to type 2. Regular screening is important and referral to an accredited diabetes centre with input from a multidisciplinary team comprising a diabetes educator, dietitian and endocrinologist, and multiple dose insulin injection therapy need to be considered. **ET**