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Paper

Clinical phenotypes of autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy seen in the Northern Ireland paediatric population over the last 30 years.

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ABSTRACT

Autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED), also known as autoimmune polyendocrinopathy syndrome type 1, is a rare autosomal recessive disorder with a variable and evolving phenotypic course. It is caused by mutations in the autoimmune regulator (AIRE) gene. APECED syndrome is diagnosed clinically by the presence of 2 from 3 major criteria; chronic mucocutaneous candidasis, primary hypoparathyroidism and primary adrenocortical insufficiency. Many of the patients develop all three before the age of 20 years. There is also a wide spectrum of other associated conditions including endocrine and non endocrine manifestations. This paper reviews the clinical phenotypes seen in the paediatric population of Northern Ireland during the last 30 years detailed from a retrospective review of clinical notes. Eight patients were identified with APECED and all patients were found to be homozygous for the c.964del13 mutation.

A wide clinical variation is apparent within APECED syndrome. Paediatricians should be vigilant of the diagnosis when they encounter any of the features described and consider the future development of associated diseases. In confirmed APECED syndrome, clinical and laboratory investigation is essential to initiate early treatment in the patient and other affected members of the family.

Key words: APECED, c.964del13, candidiasis, hypoparathyroidism, adrenal insufficiency.

INTRODUCTION

Autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED) or autoimmune polyglandular syndrome type 1 is a rare and debilitating disorder of childhood. It is inherited in an autosomal recessive manner with mutations in the autoimmune regulator (AIRE) gene. Clinical diagnosis requires the presence of two from three major criteria; chronic mucocutaneous candidiasis, autoimmune hypoparathyroidism and autoimmune adrenal failure[1-6]. If a sibling has the syndrome only one of the above manifestations is required[1].

Mucocutaneous candidiasis is the most common first presenting feature, typically developing in infancy or early childhood. Hypoparathyroidism usually develops around the age of 7 years with adrenocortical deficiency developing by the age of 13 years [4,7,8]. All three cardinal features usually occur by the age of 20 years with additional manifestations developing until at least the fifth decade[1]. The diagnosis of APECED can be challenging as it can present with one major and several minor manifestations or with several minor manifestations and characteristic ectodermal dystrophy[9].

This paper highlights the age of presentation of each of the major criteria and the range of minor criteria seen in the paediatric population of Northern Ireland in the last 30 years.

PRESENTATION AND CLINICAL COURSE

Patient 1 (male) was found incidentally at the age of 4.8 years to have hypocalcaemia secondary to hypoparathyroidism (serum calcium 1.46mmol/L, parathormone (PTH) <5pg/ml) and was commenced on alfacalcidol and calcium supplements.

He later presented at the age of 5.4 years with a hypoglycaemic seizure following an anaesthetic. Serum cortisol was 1082nmol/L. He was advised to avoid prolonged fasts and to take hydrocortisone if unwell or if requiring a general anaesthetic. He has had several further episodes of hypoglycaemia for which no cause has been identified despite extensive investigation. At 5.8 years he presented with photophobia due to punctate epitheliopathy possibly secondary to vitamin A deficiency. At this time genetic testing revealed the c.964del13 mutation. Aged 6.2 years he was found to have candidiasis of his oral mucosa, finger nails and toenails and at 10.2 years he developed small patches of alopecia. Isolated mineralocorticoid deficiency (serum sodium 127mmol/L, plasma renin activity elevated at 24.2ng/ml/

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hr and aldosterone 183pmol/L) presented at 11.4 years and he commenced fludrocortisone treatment. Cortisol response to Synacthen has to date been normal. Adrenal antibodies changed to positive when rechecked aged 11.2 years, having previously been negative 21 months earlier.

Patient 2 (female, sister of patient 3) presented at 1.7 years with stridor and a seizure secondary to hypocalcaemia (serum calcium 1.1mmol/L, PTH <3pg/ml). Initially she was commenced on alfacalcidol. At endocrine review aged 2.5 years oral candidiasis was found and adrenal antibodies were positive. She was found to be homozygous for the c.964del13 mutation.

At 3 years she was noted to have 2 small areas of hypopigmentation. At 5.2 years she presented acutely with vomiting and dehydration and gave a clear history of craving salty foods. She was diagnosed with mineralocorticoid deficiency (serum sodium 125mmol/L, serum potassium 5.8mmol/L, although random cortisols (1287nmol/L and 876nmol/L) were normal). Treatment with fludrocortisone and hydrocortisone was started.

At 6.3 years she was diagnosed by the ophthalmologist with a 'dry eye condition'.

Patient 3 (male, brother of patient 2) was screened for APECED at the age of 1.6 years. He was found to carry a homozygous mutation in the AIRE gene. He had attended previously with chronic idiopathic urticaria and recurrent candidiasis. At 1.9 years he was admitted to the paediatric intensive care unit with a lower respiratory tract infection secondary to influenza A. Following several episodes of septicaemia he was diagnosed with IgG-2 subclass deficiency and commenced subcutaneous immunoglobulin infusion 2 weekly. He is now 4.5 years old and has had no further problems attributable to APECED.

Patient 4 (male) presented at 3 years with a hypocalcaemic seizure (serum calcium 1.24mmol/L, PTH <3pg/ml). He had a history of standing on his tip toes appearing to have muscle cramps and intermittent spasms in his arms consistent with tetany. He was commenced on calcium supplements and alfacalcidol. Around 6 years he was found to have increased pigmentation of a scar on his abdomen and right arm. At 6.4 years he was diagnosed with Addison's disease by his general paediatrician (serum sodium 133mmol/L, potassium 3.6mmol/L, aldosterone 209pmol/L, random cortisol 29nmol/L) and commenced replacement treatment with hydrocortisone and fludrocortisone. At 10.3 years adrenal antibodies were positive and he was found to be homozygous for the c.964del13 mutation. At 11.6 years he was noted to have buccal candidiasis and at 13 years vitiligo. He experienced wide fluctuations in serum calcium levels from symptomatic hypocalcaemia to hypercalcaemia requiring frequent inpatient treatment. The possibility of non compliance with treatment was raised so he was changed from alfacalcidol, half-life 30-35 hours, to calcitriol, half-life 5-6 hours, which allowed blood monitoring of the medication and more rapid correction of high or low calcium concentration. Renal ultrasound showed nephrocalcinosis.

Patient 5 (female sibling of patient 8) experienced measles encephalitis at 1.9 years but recovered well. She then presented aged 2.9 years with cough, tetany of hands and feet and stridor. She was found to be hypocalcaemic (serum calcium 1.65mmol/L). She was noted to have candida infection of her thumb nail and mouth requiring frequent antifungal treatment.

Exocrine pancreatic insufficiency was diagnosed and treated from 5.4 years after a 3 month history of bulky pale loose motions and high faecal fat content. Sweat test and jejunal biopsy were normal. Further testing aged 12.5 years confirmed deficiency of trypsin and only very small amounts of amylase and lipase in duodenal juices. When 7.3 years she showed decreased height velocity, weight loss, skin pigmentation, nausea, vomiting and abdominal pain. Maximum cortisol (260nmol/L) response to Synacthen was suboptimal, baseline ACTH >800pg/mL, serum sodium 122mmol/L and potassium 4.1mmol/L. She was commenced on hydrocortisone and fludrocortisone replacement. An oral glucose tolerance test was normal. Vitiligo and keratitis of the cornea were identified at 11.1 years. At 11.7 years she was diagnosed with type 1 diabetes. Poor height velocity noted at 13.4 years prompted a pituitary stimulation test which found high levels of growth hormone. Repeat jejunal biopsy was normal. When she was 15.6 years she was diagnosed with primary ovarian failure (early breast development around 14.3 years had not developed further and a small amount of pubic hair had been noted at 15 years with no progression). Investigations showed high gonadotrophins (FSH 61u/L, LH 28.3u/L) and low 17β-estradiol (<50pmol/L). Ultrasound showed a slight increase in uterine size and ovaries appeared normal. Adrenal and ovarian antibodies were present. She was commenced on ethinylestradiol which was subsequently changed to Cyclo-Progynova.

At 16 years old she experienced light headedness, blurred vision and hypertension which was felt to be attributable to acute nephritis and nephrocalcinosis . A renal biopsy revealed patchy scarring. She was commenced on enalapril and bendrofluazide. Around this time she also had further seizures not attributable to biochemical disturbances. Electroencephalogram was abnormal and she was commenced on carbamazepine.

Patient 6 (male) was diagnosed with asthma when 4.8 years old. He then presented aged 5.5 years with a hypocalcaemic seizure (serum calcium 1.44mmol/l, PTH 6pg/mL). He also gave a history of having a 'funny' feeling in his arms and legs intermittently for a few weeks prior to admission. He was commenced on alfacalcidol and calcium supplements. Genetic testing showed he was homozygous for the c.964del13 mutation. A decreased height velocity was noted aged 7.6 years (height had fallen from the 50th to the 25th centile over 2.5 years). Glucagon and insulin stimulation tests revealed a low growth hormone response (maximum growth hormone 4.3ng/ml) and low IGF-1 5.1mmol/L. Growth hormone treatment commenced at 8 years. MRI showed no evidence of any abnormality in the pituitary gland or adjacent structures. He was diagnosed with isolated mineralocorticoid deficiency at 8 years (serum sodium 132mmol/L, renin 22.63ng/ml/h, aldosterone 152pmol/L, positive adrenal antibodies) and commenced on fludrocortisone replacement. Synacthen testing revealed a normal cortisol response (maximum cortisol response 517 nmol/L, baseline ACTH 53ng/L).

Patient 7 (male) was admitted to hospital aged 0.9 years with a lower respiratory tract infection complicated by a small pleural effusion and erythema multiforme requiring 12 days intravenous antibiotics. At review aged 1.1 years he was reported to have poor energy, decreased appetite and abdominal distension. Examination identified 3-4cm of hepatomegaly and 2-3cm splenomegaly. Investigations revealed thrombocytopenia and elevated liver enzymes (ALT >150OU/L, AST 1508U/L). Bone marrow examination was normal. Autoantibody screen revealed a smooth muscle antibody titre 1:80, antimitochondrial antibodies positive, titre 1:40 and liver/kidney microsomal antibody titre 1:320. Liver biopsy was performed and the diagnosis of autoimmune hepatitis type 2 made. He was commenced initially on prednisolone aged 2 years and subsequently on azathioprine 5 months later. He was found to have decreased bone density and prednisolone was stopped but after 5 months restarted due to an acute rise in liver enzymes.

He was admitted to the paediatric intensive care unit aged 4.5 years with severe dehydration and salt loss (serum sodium 105mmol/l, aldosterone <70pmol/L, renin 14.64ng/ml/hr, adrenal antibodies positive). Fludrocortisone was commenced. At 5.3 years he was noted to have marked oral candidiasis.

Two years later he experienced mid back pain and thoracolumbar spine xray showed generalized slight reduction in bone density, partial collapse of the body of T9 and minimal reduction in height anteriorly of the body of T8. Further investigations revealed serum calcium 2.53mmol/L, PTH <5pg/ml and he was found to be homozygous for the c.964del13 mutation. At 8.8 years he was diagnosed with severe autoimmune keratitis with significant involvement of both cornea requiring a corneal graft.

MRI scan performed at 9.2 years showed further vertebral changes on a background of osteoporosis most likely as a result of his ongoing need for high dose glucocorticoids. He was commenced on bisphosphonates.

Patient 8 (female sibling of patient 5) had experienced transient hypocalcaemia as a neonate which resolved until 2.4 years when she presented with tetany (serum calcium 1.5mmol/L, phosphate 3.22mmol/L). She commenced alfacalcidol. Prophylactic ketoconazole was required from 3.5 years as candida of her nails and mucous membranes became a recurring problem.

At 6.8 years she developed glycosuria. An oral glucose tolerance test was normal but following intermittently raised random plasma glucose levels she commenced insulin aged 7.3 years. At this time vitiligo and grey streaking of her hair and eyelashes were observed.

Aged 8 years she was investigated for a history of steatorrhoea which confirmed exocrine pancreatic insufficiency. Creon was commenced. At 9 years slightly raised liver enzymes were detected which persisted. There was no autoantibody consistent with autoimmune hepatitis. Prophylactic ketoconazole was stopped. Aged 10 years she developed a macrocytic anaemia, positive intrinsic factor antibody, low serum B12 and megaloblastic bone marrow. She responded well to Neo-Cytamen injections 3 monthly. Autoantibodies to ovarian tissue were detected from an early age. She was commenced on low dose ethinylestradiol aged 9.9 years with the hope that oestrogen may have a beneficial effect on the ovaries. This treatment continued for 5.3 years by which stage pubertal signs were progressing and menarche reached at 14.6 years with subsequent regular menstruation. Aged 13.8 years she required a mastoidectomy for cholesteatoma. Recurrent ear infections continued to be a problem. Positive adrenal antibodies were recorded from early childhood. At age 14 years routinely performed investigations showed plasma ACTH 274ng/L and cortisol 165nmol/L but cortisol response to Synacthen stimulation remained normal, as did electrolytes. Due to symptoms of persistent lethargy hydrocortisone replacement was commenced. Initially fludrocortisone was given but withdrawn when she developed fluid retention and hypokalaemia. The slightly abnormal liver function tests returned to normal on physiological hydrocortisone replacement.

Aged 15.9 years she was admitted with frank haematuria and hypertension. Investigations revealed mild nephrocalcinosis and high urinary calcium to creatinine ratio. Renal biopsy demonstrated chronic tubulointerstitial disease. Cystoscopy was normal. Although an autoimmune disorder could not be excluded, the more likely cause was felt to be hypercalcuria secondary to alfacalcidol treatment. Blood pressure gradually settled and antihypertensive treatment (enalapril) discontinued.

DISCUSSION

Major Criteria (Figure 1)

Mucocutaneous candidiasis was present in seven of eight patients. The youngest age of presentation was 1.7 years in a patient tested for the APECED mutation as his other sibling was affected. Age range for the diagnosis of candidiasis varied from 1.7 to 11.6 year (mean 4.8 years old) in contrast to previous reports of it typically being seen within the first year of life.

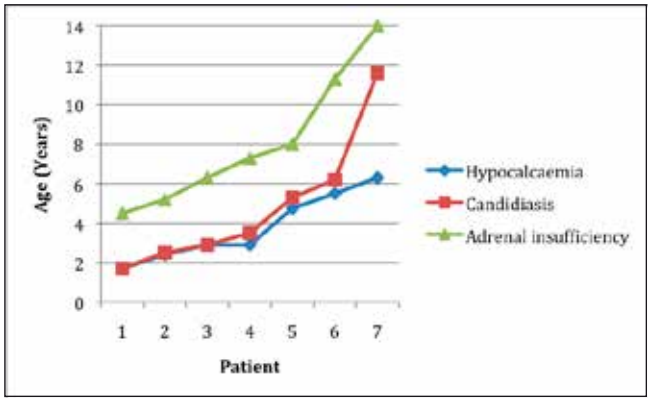

Fig 1. Number of patients affected and age of first presentation of each major criterion

Hypoparathyroidism was detected in 7 patients. In 5 patients this was the initial major feature diagnosed and in one it was diagnosed at the same time as candidiasis. Age range for diagnosis was 1.7- 6.3 years (mean 3.8 years). Hypoparathyroidism is reported in the literature to have a peak incidence between 2 and 11 years old and this was

TABLE 1.

Age (years) at presentation of major and minor criteria for each patient

Patient (number)	Hypocalcaemia	Candidiasis	Mineralocorticoid deficiency	Glucocorticoid deficiency	Pancreatic insufficiency	Visual problems	Vitiligo	Type 1 diabetes	GH Deficiency	Primary ovarian failure	Nephritis/renal disease	Hepatitis	Dental	Pernicious anaemia	Alopecia	Urticaria
1	4.8	6.2	11.3			5.8							8.2		10.2	
2	1.7	2.5	5.2			6.3	3.1									
3		1.7														1
4	2.9	11.6	6.4	6.4			13				14.2					
5	2.9	2.9	7.3	7.3	5.4	11.1	11.1	11.8		15.6	16.2		6			
6	5.5		8						8							
7	6.3	5.3	4.5	4.5		8.8						1.1				
8	2.4	3.5		14	8		7.3	7.3			15.9		5.7	10		

largely seen in this review with only one presenting before 2 years old.

Seven of the group studied had positive adrenal antibodies and developed glucocorticoid and/or mineralocorticoid insufficiency at the time of review between 4.5 to 14 years (mean 7.5 years). In 3 patients mineralocorticoid deficiency preceded glucocorticoid deficiency[9]. Patients can be very sensitive to small doses of fludrocortisone causing hypokalaemia[6]. Autoimmune adrenal failure is usually the last of the major features to present and has a peak incidence around 13 years[1-7], later than found in our patients.

Minor Manifestations (Table and Figure 2): -

Visual problems were seen in half of the patients (keratitis in 2, one 'dry eye condition' and one possible vitamin A deficiency). Renal disease with nephrocalcinosis was detected in 3 patients most likely secondary to treatment with alfacalcidol. Two showed additional features of nephritis and renal tubular disease. Four patients had vitiligo and one had alopecia. Three patients had dentinogenesis imperfecta and one had the rarely associated chronic idiopathic urticaria.

Within the group 2 patients developed exocrine pancreatic insufficiency, 2 with type 1 diabetes; primary ovarian failure, growth hormone deficiency, autoimmune hepatitis and pernicious anaemia were each seen in a single patient.

The number of manifestations affecting each patient varied from 2 to 10 (3 patients demonstrated 5, one patient 6 and 2 patients with 10 components). The age at presentation and spectrum of disease is illustrated in the table and figure 2.

Of note patient 3 was diagnosed with IgG2- deficiency; to the authors' knowledge this has not been described before in APECED, however Bereket et al[10] confirmed IgA deficiency in 1995.

Brown and Holland[11] describe 'one of the puzzling components of APECED is severe chronic mucocutaneous candidiasis (CMC).' They confirmed the authors' findings that APECED patients are not susceptible to other overt infections.

Brown and Holland report the work of Puel et al[12] and Kisand et al[13] who have described the functions of autoantibodies to IL-17 and IL-22 in CMC in APECED. This may herald new treatment strategies for the future in APECED.

APECED runs a variable and unpredictable course. The importance of early recognition of the differing components is vital. In patients presenting with any of the major criteria the diagnosis of APECED should be considered and other features actively sought. Perheentupa[6] found the classic criteria to be fulfilled by 5 years of age in only 22% of cases, by 10 years in 67%, by 20 years in 89% and by 30 years in 93.5%. Clinicians need to be aware of the diversity and presentation of the various manifestations of APECED. A fall in height velocity in one patient identified isolated growth hormone deficiency, a relatively rare feature of the syndrome. In addition, failure of pubertal progression may indicate primary gonadal failure as seen in one patient.

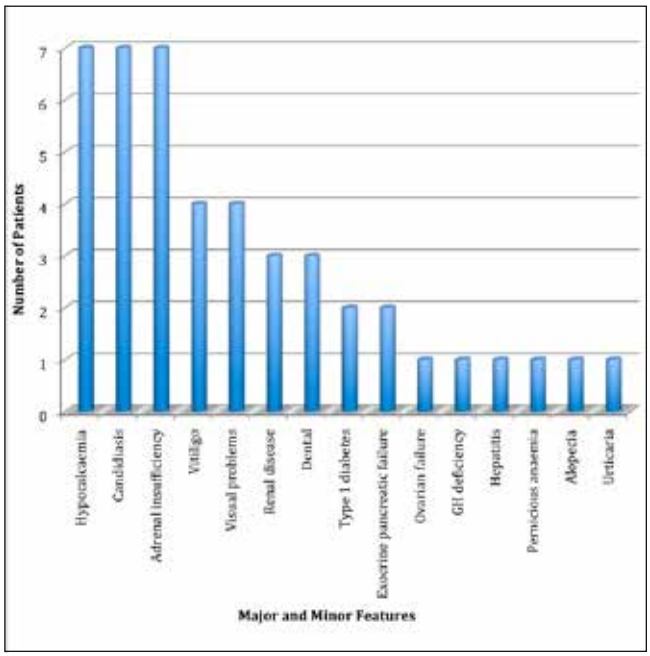

Fig 2. Number of patients affected by each manifestation of APECED

Early and correct diagnosis ultimately allows for intervention and management to prevent potentially life threatening events. Investigations are tailored to treatment and the development of new signs and symptoms with annual laboratory testing for evolving endocrine deficiencies. Families should be made aware of the potential later manifestations of the syndrome.

Any siblings of known affected individuals require clinical assessment. If the genetic mutation is not known or not

requested, family members should be followed up clinically. APECED is a rare disease but important to recognize and treat early to avoid significant morbidity and mortality. As well as the physical impact of the diagnosis, the psychological and emotional burden placed on families and patients should not be underestimated. Long-term follow-up is essential which includes an effective transition from paediatric to adult care.

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REFERENCES

1. Neufeld M, Maclaren NK, Blizzard RM. Two types of autoimmune Addison's disease associated with different polyglandular autoimmune (PGA) syndromes. *Medicine (Baltimore)*.1981; **60(5):** 355-62
2. Ahonen P, Myllarnierni S, Silpila I, Perheentupa J. Clinical variation of autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED) in a series of 68 patients. *N Engl J Med*. 1990; **322(26)**:1829-36
3. Zlotogora J, Shapiro MS. Polyglandular autoimmune syndrome type 1 among Iranian Jews. *J Med Genet*. 1992; **29(11):**824-6
4. Betterle C, Greggio NA, Volpato M. Clinical review 93: autoimmune polyglandular syndrome type 1. *J Clin Endocrinol Metab*. 1998; **83(4):** 1049-55
5. Myhre AG, Halonen M, Eskelin P, Ekwall O, Hedstrand H, Rorsman F, et al. Autoimmune polyendocrine syndrome type 1 (APS 1) in Norway. *Clin Endocrinol (Oxf)*. 2001; **54(2):** 211-7
6. Perheentupa J. APS-1/APECED: the clinical disease and therapy. *Endocrinol Metab Clin North Am*. 2002; **31(2):** 295-320
7. Betterle C, Dal Pra C, Mantero F, Zanchetta R. Autoimmune adrenal insufficiency and autoimmune polyendocrine syndromes: autoantibodies, autoantigens, and their applicability in diagnosis and disease prediction. *Endocr Rev*. 2002; **23(3):**327-64
8. Pearce SH, Cheetham TD. Autoimmune polyendocrinopathy syndrome type 1: treat with kid gloves. *Clin Endocrinol (Oxf)*. 2001; **54(4):** 433-5
9. Owen CJ, Cheetham TD. Diagnosis and management of polyendocrinopathy syndromes. *Endocrinol Metab Clin North Am*. 2009; **38(2)**: 419-36
10. Bereket A, Lowenheim M, Blethen SL, Kane P, Wilson TA. Intestinal lymphangiectasia in a patient with autoimmune polyglandular disease type I and steatorrhea. *J Clin Endocrinol Metab*. 1995; **80(3)**: 933-5
11. Browne SK, Holland SM.Anti-cytokine autoantibodies explain some chronic mucocutaneous candidiasis. *Immunol Cell Biol*. 2010; **88(8)**: 614–5
12. Puel A, Doffinger R, Natividad A, Chrabieh M, Barcenas-Morales G, Picard C et al. Autoantibodies against IL-17A, IL-17F, and IL-22 in patients with chronic mucocutaneous candidiasis and autoimmune polyendocrine syndrome type I. *J Exp Med*. 2010; **207(2)**: 291–297.
13. Kisand K, Boe Wolff AS, Podkrajsek KT, Tserel L, Link M, Kisand KV et al. Chronic mucocutaneous candidiasis in APECED or thymoma patients correlates with autoimmunity to Th17-associated cytokines. *J Exp Med*. 2010; **207(2)**: 299–308.

