

NOTES FOR DOCTORS TREATING PATIENTS WITH APECED/APS-I

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DIAGNOSING APECED

APECED was traditionally thought to require two of the triplet chronic mucocutaneous candidosis (MC), hypoparathyroidism (HP) and adrenocortical failure (AF). Such combination does indeed give firm diagnosis, but many patients' life is in danger before such criterion is fulfilled. The early clinical picture may not include any of those three or only MC, but may be dominated by one or more of hepatitis, keratopathy, periodic rash with fever, chronic diarrhoea and severe obstipation. These should be recognized as potential early components of APECED. Observing any one of them in an infant or young child calls for scrutiny for the other components of APECED, including the visible oral, ophthalmic, and dermal features (table at the end). Search for *AIRE* mutations should be considered, particularly if more than one component is present. The same holds for apparently isolated HP or AF, especially in children, but even in anyone under 30 years of age.

General on follow-up and management

The goal is to recognize early the development of new disease components, which may appear throughout life (see Table at the end) and provide adequate treatment thus that the patient's well-being is maintained. The patient should be aware of the new serious components which may develop and know what new symptoms call for prompt medical attention. Every patient should, in addition to possible local doctor's follow-up, be seen by appropriate specialists, particularly an endocrinologist at least once yearly, and immediately when new symptoms appear. AF, ovarian atrophy, gastric parietal cell destruction and hepatitis can be predicted on the basis of antibody tests and hormone measurements, but not so diabetes mellitus (DM), hypothyroidism (HT) and HP. A patient who has two or all of HP, AF and DM, is usually complicated to treat and requires follow-up by an endocrinologist, because those diseases and their treatments influence each other. Of these notes, most concern MC, HP and AD, because these have given most problems.

Information to carry. The patient/parents should be provided with written information about the disease and the treatment needs, particularly in situations of emergency.

1. Candidosis

The diagnosis of oral candidosis is visual, confirmed by yeast culture strongly positive for *Candida albicans*. The infection can be symptomless with only intermittent angular cheilosis, the labial corners being ulcerated and inflamed. More severe forms include acute inflammation of most of the oral mucosa, hyperplastic chronic disease with thick white coating of the tongue, and atrophic disease with scant coatings and a scarred thin mucosa with leukoplakia-like areas. Oesophagitis usually gives pain behind sternum and/or swallowing difficulty that, if not controlled by candidocidal therapy described below, call for endoscopy. Abdominal pain, flatulence and diarrhea may point to intestinal candidosis, which is supported by plentiful *C. albicans* growth in faecal culture, and good response to systemic candidocidal medication. The infection may spread to the skin, most commonly of the hands if they are often wet, and skin and nails if the child keeps fingers in mouth. It may even

spread to facial skin. Nails can get thick and dark or wear away. Female patients can get an itchy genital discharge caused by yeast inflammation of the mucous membranes.

Follow-up and management

The goal is to have the infection in strict control for the sake of eating and appearance and, particularly, to repel development over the years of oral and oesophageal carcinoma. Also, development of resistant *Candida albicans* strains should be avoided.

Strict follow-up of the oral situation is necessary, preferably having the patient seen by an oral specialist at least once yearly, and promptly if an ulcer or sore point appears and does not heal in a week. Such lesions must be biopsied without delay. Oral hygiene and dental condition must be taken care of as well as possible. Sharp edges of teeth must be smoothed down to prevent damage to the mucous membrane, and irritating toothpastes and foods should be avoided. Smoking predisposes to both yeast inflammation and cancer, and should hence by all means be avoided.

Drug therapy of oral candidosis is primarily local, taking 100 mg of amphotericin B as suspension or 10 mg as a lozenge, and 1-2 ml nystatine oral suspension, both 4 times daily for a 4-6 week period, continuing for a week after healing of the mouth. Then follows **preventative** dosage, taking both medications similarly for at least 1 week of each 4-week period. If the mouth does not stay well with this program, the medication should be used every second week. If this is not enough, the nystatine suspension can be taken continuously and the amphotericin B for 1-2 weeks out of four. Only if this approach fails, fluconazol or other azol group fungal medications are resorted to, only temporarily and only on the basis of sensitivity determination, to avoid development of a resistant *Candida* population that could colonise the mucous membranes for a long time. These systemic medications may over months replace completely eroded nails by healthy regrowth, but they offer no help for thickened candidotic nails. Those must first be removed by a podiatrist using 40% urea paste.

2. Hypoparathyroidism

The diagnosis. The combination of hypocalcemia, hyperphosphatemia and normal plasma level of creatinine indicates deficient parathyroid hormone action. If the patient has chronic oral candidosis or other features of APECED, the diagnosis of APECED HP is certain. Otherwise, HP is differentiated from pseudo-HP by absence of supranormal plasma parathyroid hormone levels. If the clinical diagnosis of APECED is in doubt, search for *AIRE* mutation should be considered.

Follow-up and management

The goal is to maintain calcemia in the lower half of its normal range and magnesemia in the upper half of its normal range, and to avoid excessive calciuria, particularly, high urinary concentration of Ca. Hence, the patients should consume at least 1.5 – 3.5 litres of water (depending on size) daily in different forms, excluding acidic and sugary drinks, which would risk their enamel-deficient teeth. Phosphatemia should preferably be in the normal range but, even if milk products and other phosphate rich foods are replaced with Ca tablets and other protein, exceptions have to be accepted in some children. Hypocalcemia, even mild one, may

cause tiredness and impair mental capacity. Calciuria is higher than in non-hypoparathyroid persons with identical calcemia. Hence, calcemia of high normal range, not to speak of hypercalcemia, may risk the kidneys, particularly, if the patient is not consuming water as recommended. Magnesium deficiency tends to develop in patients with HP and cause problems (tetany, impaired control of calcemia and kalemia), particularly in patients with both HP and AF.

Follow-up. APECED patients without HP should have plasma Ca (P-Ca) and phosphate (P-Pi) determined at least annually, even in absence of symptoms suggesting HP. Parathyroid hormone (PTH) determination has no role in the follow-up. Of HP patients particularly those with AF and /or DM (HP-AF-DM patients) should have P-Ca checked at least at 1.5-2 month intervals, and 3 to 7 days (depending on the drug used) after change of medication (including cortisol replacement). P-Mg, P-Pi, and 24-h urinary-Ca (dU-Ca) should be checked at 4-6 month intervals. HP-AF patients tend to have unsteady calcemia. Mature patients may learn to recognize the symptoms of hypercalcemia and hypocalcemia. They should have the right to go to laboratory for P-Ca check, receive the result for adjusting the medication or contacting the doctor, at own discretion. However, hypercalcemia risking the kidneys may develop without giving clear symptoms, even after years of normocalcemia. The desired level is for P-Ca 2.10-2.30 mmol/l (P-Ca-ion 1.05-1.15 mmol/l) and for P-Mg 0.85-1.00 mmol/l. dU-Ca over 0.1 mmol/kg may be a sign of danger. Expressly the 24-h urine should be determined. An annual ultrasound check of the kidneys for calcification is recommended.

Drug therapy. For daily maintenance we use an individualized dose (usually in the range of 0.2 – 1.2 mg daily) of crystalline dihydrotycysterol (DHT), because of having plenty of favourable experience with it and appreciating the duration (average half-time 7 days) and rapidity of its effect, which are neither too low nor too high. We believe that in patients with labile calcemia, DHT gives better stability than the shorter acting alternatives. Many others use successfully alphacalcidol ($T_{1/2}$ 2 days) or calcitriol ($T_{1/2}$ 1 day); we use them only with DHT when an additional rapid effect is needed and the patient has diarrhea or otherwise temporarily impaired absorption of Ca. A daily Ca supplement is also recommended because these patients excrete more Ca in urine than non-hypoparathyroid persons at similar calcemia, and because interrupting it allows rapid lowering of too high calcemia. We give 2-3 (or more when needed) daily doses of 100-500 mg (as elementary Ca, dose depending on the size of patient), preferably as citrate to enhance its absorption and to increase urinary citrate thus helping the Ca stay in solution. It should be given outside meals in order not to inhibit Mg absorption. Larger doses should not be given at once to avoid transient hypercalcemia (non-hypoparathyroid subject reacts to rise in calcemia by shutting down PTH secretion, not so the HP patient). A diet with plenty of green vegetables, wholemeal, nut, fruits, fish and fresh meat may provide adequate Mg intake. Otherwise Mg should be provided in tablet form (50-200 mg daily, preferably as citrate) with meals, separately from Ca tablets. We believe that these patients should also receive 5-10 μ g cholecalciferol as supplement daily, because the derivatives may not cover all functions of D-vitamin.

When calcemia is slightly over the optimum, we stop Ca medication and reduce the DHT dose, e.g. by 10%, leaving first a gap 7-fold the decrement. If, after a week, P-Ca is in the lower area of the optimum range, we restart the Ca medication. In a more serious situation, P-Ca >2.7 mmol/l (S-Ca-ion >1.39) the whole hP-medication must be interrupted. If after a week P-Ca is in low optimal range or below it, we restart DHT, e.g. a 20% reduced dosage

and consider restarting Ca medication after another check a week later. The patient may react with a new, powerful P-Ca rise to even the reduced dose DHT.

When P-Ca is below the desired level we increase the dose (e.g. by 10%) giving on the first day an additional dose 7-fold the increment.

Supranormal P-Pi should become normal with this substitution therapy. This is not true for all children, and then milk products and other high-phosphate foods should be left out of the diet, ensuring adequate protein and Ca intake by other means.

HP-AF patients sometimes develop hypercalcemia as a result of Na-deficiency dehydration, and the hypercalcemia is only and quickly fixed by rehydration with Na-solution given i.v. Increase in hydrocortisone (or other glucocorticoid) dosage tends to cause hypocalcemia and vice versa. In HP-AF patient's stress situations, e.g. in connection with surgery, when increasing glucocorticoid replacement dosage, one should be anticipate hypocalcemia. Such glucocorticoid increase lasting over 24 hours requires increased Ca intake or adding a short-acting calcipherol derivative (alphacalcidol or calcitriol) for that period (example at the end of the text).

3. Adrenocortical failure

The diagnosis. AF is to be anticipated from appearance of adrenocortical or 21-hydroxylase antibodies in blood, and these should be searched for at least yearly in a patient without AF. With the antibodies present the failure may develop in weeks or years. Failures of cortisol and aldosterone secretion may develop simultaneously or even years apart. Presence of the antibodies calls for follow-up with plasma renin activity (PRA), and P-ACTH and/or P-cortisol response in short ACTH test. With the development of deficient cortisol secretory capacity, the basal plasma cortisol level first rises to become subnormal only when the patient starts to be in danger without replacement. The diagnosis is confirmed when the stimulated level in short i.v. ACTH test is subnormal. Deficiency of aldosterone secretory capacity is likely if PRA is supranormal. It is confirmed if that is associated with subnormal P-Na basally or after limiting Na intake to below 10 mmol/day for a few days.

Follow-up and management

The goal. The deficiencies should be substituted for individualized to provide full wellbeing and safety in the patient's life situation including incidents of sickness and stress. The patient and her/his close family must know how to act in different situations. Excess dosage must be avoided to prevent harmful effects such as arterial hypertension, slowing of longitudinal growth and inappropriate increase in weight.

Replacement medication. Cortisol deficiency should be substituted for daily with three doses of hydrocortisone (total of 10-15 mg/m²) imitating the physiologic rhythm with largest dose in the morning. For someone who is used to this dosage it is not generally worthwhile to change this schedule in adolescence. However, if the patient has problem in remembering the afternoon dose, two doses of prednisolone (total of 2 - 3 mg/m²) is a better alternative. Importantly, introduction of glucocorticoid substitution and changes in its dosage interfere with the balances of HP and DM.

Aldosterone is replaced with one daily dose (average 0.1 mg/m²) of fludrocortisone acetate individualized to provide for normal PRA and blood pressure without salt craving. With sufficient dosage, the systolic blood pressure does not fall more than 10-14 mm Hg when the patient stands up from sitting. The need for replacement is often reduced and may even end

with advancing age. Yet, salt loss may reappear in situations of stress to salt balance, such as vomiting and diarrhea or fasting in preparation for surgery.

Dehydroandrosterone sulphate substitution (12.5 – 25 mg daily) is clearly welcomed by most postpubertal female patients as improving mental and physical vitality and sexuality.

In the case of serious illness, e.g. vomiting and diarrhea or following a serious accident, the patient must immediately get an injection into the muscle of 25-100 mg hydrocortisone (Solu-Cortef[®] injectable solution) depending on body size and condition and get straight away to hospital treatment. When travelling she/he should carry Solu-Cortef[®], and when in foreign country have a more detailed English language instruction for treatment. The patient and/or family member/travelling companion should be prepared to give the injection.

4. Other endocrinopathies

Ovarian failure. Ovarian atrophy may develop at any age from prepuberty to maturity. Circulating steroid cell or 17-hydroxylase antibodies and, later, supranormal serum levels of FSH and LH indicate ovarian failure. Normal hormone substitutive therapy should then be started at pubertal age with gradually increasing continuous estrogen dose to maintain normal pace of feminine development, adding periodic progestagen at appropriate stage. Embryo donation may be successful in bringing about pregnancy.

Diabetes mellitus. Islet cell and GAD antibodies are common in these patients, often in higher titres than seen in patients with isolated type I DM, but appear not always predict DM. Presence of those antibodies calls for follow-up with glycohemoglobin determinations. If DM develops it is in most cases at rather mature age. Its control, when associated with AF and HP, may be quite demanding.

Hypothyroidism (HT). Thyroid gland antibodies are also more common than hypothyroidism. HT appears as a rule relatively late, though it has even occurred as the first endocrine component, at the age of four years.

Growth hormone deficiency affects a few percent of patients.

5. **Hepatitis** is a serious danger for which the patients should be monitored by P-ALAT (ALT) determinations. If it is repeatedly three-fold the upper reference limit or higher without other reasons (azol-drug treatment of candidosis; alcohol abuse and P-GT more elevated than ALAT), the liver should be biopsied. The treatment of a patient with hepatitis requires years-long azathioprin medication (for children 2 mg/kg).

6. **“Pernicious anemia”** Intrinsic factor blocking and parietal cell antibodies herald the development of parietal cell atrophy and vitamin B₁₂ malabsorption. Follow-up with P-B₁₂ vitamin determination is required and, when it approaches subnormal level, replacement therapy.

7. **Renal disease and hypertension.** Blood pressure and P-creatinine level should be checked regularly because hypertension and kidney damage are common. Some hypertensive patients have other features of hypermineralocorticoidism, i.e. subnormal P-K and suppressed PRA, even despite having cortisol deficiency, previous salt loss and no mineralocorticoid replacement. The likely reason for this situation is use of liquorice, which the patient may not

admit. In hypertension of mineralocorticoid replacement patients, reduction of fludrocortisone dose should be the first consideration.

Tubulointerstitial nephritis is an important possibility, it has developed in some 10 per cent of our patients. One of them needed kidney transplantation already at the age of 12 years.

8. **Intestinal dysfunction.** Constipation is a common problem. It often occurs early, even in the first year of life. The cause may be autoimmune destruction of the chromaffine cells of jejunal mucosa. Hypercalcemia is often in the background of temporary constipation. Besides correcting calcemia, no specific treatment methods are known.

Analogously, tendency to loose, even watery stools is often connected with hypocalcemia. Diarrhea can impair the absorption of the vitamin D medication and Ca, and thus worsen itself. In these situations a provisional addition of parenteral calcitriol or alphacalcidol may be needed. The occurrence of diarrhoea requires increased frequency of P-Ca follow-up. Autoimmune destruction of the jejunal chromaffine cells may also result in severe watery diarrhea. It can be confirmed with mucosal biopsy immunostained for serotonin. Such diarrhea is resistant to all other treatments but long-term immunosuppression with cyclosporin A. Other possible causes of chronic diarrhoea are autoimmune failure of exocrine pancreas, intestinal yeast infection and, rarely, deficient reabsorption of bile acids.

9. **Eye problems.** Dryness of eyes is common in APECED patients; it requires regular use of eye moistening drops. A relatively common serious affection is autoimmune keratopathy, which besides the symptom of discharge includes stinging of eyes, feelings of sand in them and sensitivity to light. It demands intensive treatment with glucocorticoid eye drops under regular supervision of an eye specialist. Otherwise there is a danger of clouding of the cornea and weakening of the eyesight, even blindness.

10. **Asplenia.** The spleen is absent in 20% of Finnish patients and the prevalence may increase with age. Patients, in whom lack of spleen hasn't been diagnosed, should have yearly blood smear check for the presence of Howell-Jolly bodies, indicating splenic malfunction. The size of the spleen can be checked with ultrasound. Malfunction of the spleen requires immunization against pneumococci, *H. influenzae* and meningococci.

An example of instruction for the substitution medication of adult HP-AF patient subjected to major surgery

Hydrocortisone i.m. to be given 20 mg the night before the operation, 50 mg 4 hr before the operation., and i.v. 50 mg at the induction of general anaesthesia. Then during the day of operation 20 mg be given i.v./i.m. at 6 hour intervals. Depending on the condition, 10(-20) mg be given p.o./i.v. at 6 hour intervals on the day following the day of operation, and 10->5 mg at 6 hour intervals p.o. on the second day, then, if the recovery goes proceeds normally, returning to the patient's normal maintenance dosage. Diflucan solution to be given 50 mg i.v. at the start of the operation. DHT and Fludrocortisone to be interrupted only for the fasting period, returning both at the normal dosage when they can be given orally. NaCl solution to be given 50 mmol/day as physiological solution during fasting, and then stepwise less when returning to eating. Calcijex[®] (calcitriol) or Etalpa[®] (alphacalcidol) solution to be given on the day of surgery i.v. 1.0 ml (1 microg Calcijex or 2 microg Etalpa) and, when using Calcijex, the same dose on the first postoperative day. P-Ca and P-Mg monitoring are

important at least once daily, the optimum levels are for P-Ca 2.10-2.30 mmol/l, ionised Ca 1.05-1.15 mmol/l, P-Mg 0.85-1,0 mmol/l. If P-Ca doesn't stay at this level, the amount of Calcijex or Etalpa solution can be doubled, and its use continued until the patient eats normally and P-Ca stays at the desired level. With hypocalcemia Ca glucobionate is added to the i.v. infusion, and given if needed as a bolus injection.

TABLE . Prevalences¹ (%) of the diagnostic dyad (at least two of MC, HP and AF) and the most common disease components by age (on birthdays) with age ranges at their appearance in the series of 91 Finnish patients

Age, yr	Age range (median) at appearance, yr	1	2	5	10	15	20	30	40	50	
Diagnostic dyad		0	0	21	70	85	94	97	99	99	2.2 – 35 (7.0)
Classic triad											
Candidosis		17	30	48	83	93	96	98	100	100	0.2 – 31 (5.4)
Hypoparathyroidism		0	6	34	65	77	83	85	87	88	1.6 – 43 (6.0)
Adrenal failure		0	0	8	40	63	72	78	81	84	3.5 – 41 (10.0)
All three		0	0	3	25	50	56	64	71	76	3.5 – 43 (11.3)
Other endocrine disorders											
Ovarian failure		35	53	60	69	–	36				
Testicular failure		8	12	28	–	37					
Diabetes mellitus		0	0	2	3	7	10	13	23	33	4.1– 58 (23.5)
Hypothyroidism		0	0	1	1	1	4	14	21	31	4.7 – 45 (26.5)
Skin disorders											
Alopecia		0	0	5	16	29	33	39	39	39	2.5 – 30 (10.3)
Vitiligo		1	1	2	9	17	20	27	31		0.7 – 45 (12.7)
Rash with fever		3	7	10	12	13	14	14	15		0.7 – 31 (2.8)
Gastrointestinal disorders											
Pernicious anemia		0	0	0	3	10	16	20	28	31	6.1 – 48 (17.2)
Severe obstipation		1	1	8	10	14	18	21	26		1.0 – 31 (13.0)
Chronic diarrhea ²		0	0	8	13	16	17	22	22	22	2.5 – 27 (6.6)
Hepatitis		1	2	5	12	16	18	18	18	18	0.7 – 16 (8.0)
Eye disorders											
Keratoconjunctivitis		0	5	11	18	20	21	22	22	22	1.3 – 16 (5.4)

In a subgroup of 68 patients prevalence was 77% for enamel hypoplasia of permanent teeth, 52% for pitted fingernail dystrophy, and 33% for Ca salt deposits of the tympanic membranes. ¹Estimated from the observed incidence rates over the age intervals, assuming

that all patients live until the age of 50 yr. ²Does not include the diarrhea associated with hypocalcemia.

References

1. Perheentupa J. Autoimmune polyendocrinopathy-candidosis-ectodermal dystrophy. *J Clin Endocrinol Metab* 2006;91(8):2843-50
2. Perheentupa J. APS-I/APECED: the clinical disease and therapy. *Endocrinol Metab Clin N Amer* 2002;31:295-320