

## NOTES FOR DOCTORS TREATING PATIENTS WITH APECED/APS-I

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### 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 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 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.

**Drug therapy.** For daily maintenance we use an individualized dose (usually in the range of 0.2 – 1.2 mg daily) of crystalline dihydrotacysterol (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  $\mu$ 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 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 goal.** The deficiencies should be substituted for individualized to provide full well-being 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.

**Cortisol** deficiency should be given daily with three doses of hydrocortisone (total of 10-15 mg/m<sup>2</sup>) 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/m<sup>2</sup>) is a better alternative. Importantly, introduction of glucocorticoid substitution and changes in its dosage interfere with the treatment of HP and DM.

**Aldosterone** is replaced with one daily dose (average 0.1 mg/m<sup>2</sup>) 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.

**Dehydroepiandrosterone sulphate** substitution (12.5 – 25 mg daily) to treat the androgen deficiency can be tried. Some postpubertal female patients experience improved 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<sup>®</sup> injectable solution) depending on body size and condition and get straight away to hospital treatment. When travelling she/he should carry Solu-Cortef<sup>®</sup>, 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. HT is treated with thyroxin aiming at a TSH-value in the normal range.

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 B<sub>12</sub> malabsorption. Follow-up with P-B<sub>12</sub> vitamin determination is required and, when it approaches subnormal level, replacement therapy, either quarterly injections or daily per oral medication..

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. **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.

9. **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.