

APECED

INFORMATION FOR PATIENTS

Jaakko Perheentupa, Professor of Pediatrics (emeritus), with sections written by
Sirkku Niissalo and Riina Richardson, Specialists of Oral Medicine (Oral Candidiasis),
and Eeva-Marja Sankila, Ophthalmologist (Eye Problems)
Helsinki University Hospital

October 2006

*People who suffer from rare disease and parents of such children should learn to know the
disease well, because taking responsibility for their own care is imperative.
This text is meant to help that.*

responses and questions: Jaakko.Perheentupa@Saunalahti.Fi

The name APECED (Autoimmune PolyEndocrinopathy-Candidiasis-Ectodermal Dystrophy) points to the three groups of problems that are commonly part of this disease. “Endocrinopathy” is a hormonal disturbance, most commonly a lack of hormone. In “polyendocrinopathy” the lack of several hormones is common. “Autoimmune” indicates how these disturbances arise: the body’s immune system, that is meant to protect against bacteria, fungi, viruses and cancer cells, destroys its own tissues. “Candidiasis” is an infection caused by a yeast fungus – inflammation of the mucous membranes and skin is part of the weakness of the immune system in APECED. “Ectodermal dystrophy” means abnormality of some surface tissues: teeth, skin, nails and, most importantly, the cornea of the eyes.

What causes APECED?

APECED is a recessively inherited disease. It appears only in persons who have inherited a faulty AIRE (autoimmune regulator) gene from both parents. Genes are paired; one of the pair is inherited from the father and the other from the mother. We are all carriers of recessively inherited disease genes: in some of our 19800 gene pairs one of the two genes is faulty. These don’t affect the carrier, because the faulty gene’s normal partner is enough to take care of the normal function. If the father and mother both happen to be carriers of the same disease gene, there is always the risk that those sperm and egg cells that happen to combine in conception both contain the same faulty gene. Then the resulting child has the disease. This inheritance pattern explains why APECED often shows up in siblings, but not in different generations of the family. The faulty AIRE gene has travelled in both parents’ families from an ancestor, perhaps common to both the parents, to on average half the children from generation to generation without giving any sign of itself, until two carriers have children together. If we think of a large number of such families, one quarter of their children inherit the disease gene from both parents and have the disease, half are carriers like their parents, and one quarter don’t inherit either of the faulty AIRE genes. In the case of each child pure chance determines which one of the three AIRE gene inheritances he or she receives. With very good luck none of such carrier couple’s children get the disease, on the other hand with very bad luck all of them can get it. APECED patients’ children don’t get the disease unless two patients have children together, in which case all their children get the disease. When a patient and carrier have children half of them on average get the disease.

The previously unknown AIRE-gene was identified in research of Finnish APECED patient’s families in 1997. AIRE’s task is to eliminate the possibility of the immune system’s attack of own tissues. Intensive research is ongoing to clarify its function more accurately and hopefully to bring in the future better treatment for patients with APECED. Nearly 60 different mutations of the AIRE gene are now known.

How common is APECED?

APECED is rare, but it seems to appear in all populations. It has been found mostly in Finns, Sardinians and Iranian Jews. In these populations its occurrence is one case in 20 000 – 40 000 newborn. On the other hand, in families with APECED on average 25% of children have it. Because of the rarity of APECED it is often unknown to doctors, and supervision of patient care should be given to endocrinologists, doctors who take care of persons with hormonal disturbances.

What kind of disease is APECED?

APECED can cause different disorders, called disease components. At least some of these appear sooner or later in all patients, but the appearance and progress of the disease vary greatly. For many patients the first component appears already by two years and for most by ten years of age, but for some rare individuals not until their thirties. For many, new components appear as they get older. Without appropriate care some components are life threatening, and most require regular monitoring. Therefore regular specialist care for all patients is necessary.

Oral yeast infection is the most common component and usually the first. It is also the only one to have appeared in all the Finnish patients at least periodically. Some kind of hormonal disturbance seems to develop in all patients before long, and some patients have got three or even four of them. Parathyroid failure is the most common of these, and usually the first; about 85% of patients get it. Adrenal cortex failure is nearly as common (about 80%); it appears most often after the parathyroid failure, but there is also a group of patients in which it is the only hormonal disturbance. In two out of three female patients the ovaries atrophy prematurely, in about half of them so early that ovarian hormone replacement is already required to bring about or complete the pubertal development. For the others this failure appears as an early menopause. Testicle damage is much rarer (25%). One in five patients get at some stage insulin-dependent diabetes, most of them only at adult age. Thyroid failure is slightly less common (20%). Pituitary growth hormone deficiency develops in a few percent of patients.

Vitamin B₁₂ absorption failure (pernicious anaemia, 30%) results from autoimmune destruction of the parietal cells of the stomach mucous membrane. Along with hydrochloric acid those cells secrete the intrinsic factor, which is necessary for absorption of vitamin B₁₂ from the intestine. If vitamin B₁₂ deficiency remains untreated, serious anaemia and other problems will gradually appear. Prolonged diarrhoea (22%) and chronic serious constipation (25%) appear alone or, in some patients, alternately. Loss of the spleen (20%) makes the patient more susceptible to dangerous bacterial infections, but that can be corrected with vaccinations. High medication requiring blood pressure (20%) also appears to be a component of APECED. Some patient's blood pressure increases from eating lots of liquorice, which should be avoided. Liver inflammation i.e. hepatitis (18%) is often chronic and can continue for a long time untreated showing few symptoms, but it can also be really serious. Periodic rash with fever can be the first component or develop later (15%), it has always disappeared after some months .

Ectodermal (external) tissue abnormalities are permanent tooth enamel deficiency (75%), pitting of the nails (50%), hair loss i.e. alopecia (39%), exceptionally thin ear drums and their calcification (33%), white patches on the skin i.e. vitiligo (30%) and inflammation of the cornea i.e. keratitis (22%).

General Treatment

The responsibility for medical care should belong to a hospital doctor well acquainted with APECED, usually a university or other large central hospital's children's or adults' endocrinologist. Patients who live far from hospital should also have their "own" local doctor who knows them well. Division of responsibility between these doctors will depend on the disease components and difficulties, and living conditions. Thorough endocrinological clarification of the situation is needed at least once a year. Follow up at the central hospital's oral and dental diseases unit is also important, because most of the patients need a check up every half year, and all at least once a year.

The disease components and their treatments can influence each other. A patient with hypoparathyroidism together with Addison's disease can have problems because of this, and these certainly come to a person who also has diabetes. One disease component's imbalance can upset the control of the others. Hormone deficiency replacement medication doesn't much affect the treatment of usual contagious and other diseases, but these often require more intensive follow up of the components of APECED and changes in the replacement medication. Patients should get to hospital care much more easily than basically healthy persons. This applies particularly to vomiting or diarrhoeal diseases and especially to child patients. It is important to get normal vaccinations, but vaccinations containing living viruses must be avoided (measles-mumps-rubella vaccination, chickenpox vaccination and yellow fever vaccination). When an influenza epidemic threatens the patient should get an influenza vaccination.

In case of accidents and emergencies the patient should have a "SOS" bracelet or pendant, on which the doctor has written information about the disease, medication dosages and special needs in emergency situations. When travelling abroad a written treatment summary in English should be carried.

Candidiasis i.e. yeast infection (section on the mouth by Drs Sirkku Niissalo and Riina Richardson).

Candidiasis, infection of the mucous membranes and skin caused by a yeast fungus, appears firstly as an inflammation of the mouth, continuous or sporadic. Its severity varies with the individual. In mild form it causes breaking, redness and soreness of the corners of the mouth. The whole mouth can be so sore that when eating something sour it stings. The tongue and mucous membranes of the cheeks can have a white or grey covering of yeast. The inflammation can spread to the oesophagus and make swallowing feel difficult with pain in the middle of the chest, sometimes a piece of food remaining in the oesophagus. It can spread to the intestines and cause abdominal pain, flatulence and diarrhoea. A reddish and watery yeast rash can appear on the skin of the hands, and nails can get thick and dark or wear away, these problems can be avoided if the child is prevented to keep fingers in mouth. Sometimes the infection spreads to the facial skin. Female patients can get an itchy discharge caused by yeast inflammation of the mucous membranes of the genitals.

Yeast infection worsens or appears often during a course of antibiotics, high-dose "cortisone treatment"¹ and overall weakening of condition during sicknesses. Its tight control is very important, because if it continues long it could cause mouth or oesophagus mucous membrane cancer. Such has developed in six of our over 25-year-old patients (10%). Damage to the mucous membranes of the mouth should be avoided. Mucous membrane damage and wounds heal slowly and with difficulty and could promote yeast infection outbreak or worsening, and predispose to cancer. Oral hygiene and dental health must be taken care of as well as possible. Sharp tooth edges and broken or decayed teeth have to be fixed straight away, because they can damage the mucous membrane. The same applies to broken or badly positioned removable false teeth. Also, food that is sharp or likely to scratch should be avoided. Tomato, citrus fruits, kiwi, capsicum and Mexican and other strongly spiced food, and generally sour food irritate the mouth and should be avoided. The ability of sour food (lingonberry and citrus fruit) to calm yeast infection is very small, and hence their use has no basis and is not recommended. Even though the mouth is felt to tolerate sourness, the disease has already led to tooth enamel damage predisposing to further acid attack and sour foods do¹

¹ "Cortisone treatment" means in informal everyday language medication with strong synthetic derivatives of hydrocortisone, which may produce harmful side effects, see page 11.

further weaken the enamel. This predisposes teeth to the formation of cavities, erosion of the neck of the tooth and irritating grating of teeth. The wearing away of teeth, their shortening and reduced bite can cause jaw joint problems. This condition is difficult and expensive to repair. Fixing teeth with plastic filler material should be avoided. The plastic filler sticks only weakly to the damaged enamel, hence the seam leaks readily, which may produce new cavities and risk neighbouring teeth. Preserving one's own teeth is especially important, because the sore mucous membranes poorly withstand pressure from a dental prosthesis. Acrylic parts of the prosthesis are good growing grounds for yeast fungi. The false teeth should always be removed at night, disinfected according to the dentist's directions and stored dry. Dental braces containing acrylic parts should be avoided.

Toothpaste should be chosen correctly. Pastes containing powerful whitening agents put too much stress on sore mucous membranes, and those containing abrasives wear away weak enamel. Mild pastes are thus recommended, they are also suitable for dry mouths, e.g. Biotene[®], Salutem[®]², and for grating teeth green Elmex[®] and Sensodyne[®]. From time to time many patients suffer from mouth afta-ulcers. Changing to a toothpaste void of the foaming agent sodium laurylsulphate (Biotene[®], Salutem[®]), reduces the occurrence of these ulcers. Afta-ulcers can be treated with afta-plasters (Aftab[®]) and glucocorticoid spray (e.g. Beconase aqua[®], Nasacort[®]). If the afta-ulcers are very big or there are many of them at the same time, they can disturb eating and speaking. In this case one can use a local anaesthetic (Xylocain[®] gargle). Good oral hygiene promotes the healing of all mouth ulcers. If cleaning the mouth is difficult because of ulcers, one can supplement brushing by using a disinfecting chlorhexidine based mouthwash (e.g. OralB[®]). Chlorhexidine affects yeast fungi as well as bacteria and hence does not add to the risk of yeast infection. Powerful mouthwashes are often too strong and can irritate the mucous membranes.

A mouth specialist should be contacted if ulcers appear in the mouth, especially if they are in an unusual place and have an unusual appearance, or if they don't heal in a week with usual treatment. The condition of a dental prosthesis should be checked by the dentist regularly. There are no wasted visits because of this problem!

Smoking is a factor strongly predisposing to yeast infection, and it should be avoided in all forms. Because APECED involves the risk of oral cancer why increase the risk by continuing to smoke, or even by starting it!

Saliva secretion decreases with age, and many medicines reduce it or change the saliva's composition causing the mouth to feel dry. Reduced saliva secretion favours yeast fungi and increases dental decay. The dentist can advise on problems associated with a dry mouth. Treatment preparations for a dry mouth are available without prescription in pharmacies and well-stocked cosmetic shops. As a home remedy one can use sugar-free camomile tea to gargle and the mucous membranes can be lightly lubricated with normal cooking oil. A person with a dry mouth should avoid strong, alcohol-containing mouthwashes. Water should be drunk abundantly.

When mouth inflammation appears, localised medical treatment should begin immediately². Two medications should be used simultaneously four times daily, after meals and in the evening, when the mouth has been first rinsed with water. First take into the mouth 1-2 ml of nystatine suspension (Mycostatin[®]), keep it in the mouth for a few minutes and at

² Longterm preventative medication by azol-group medicines is no longer used, because it appeared that it often caused loss of efficacy of the medication: so called, medication resistant yeast population development.

the same time spread it to every part of the mouth with the tongue. Then put into the mouth³ an amphotericin-B (Fungizone[®]) tablet, leaving it to slowly dissolve in the mouth without biting. Both medications get to be swallowed in the end. Little children can be given only nystatine suspension e.g. by pipette, if sucking the tablets doesn't work. These medications should be continued without a break for 4-6 weeks, and at least a week more after the inflammation has totally healed (this is the **treatment dosage**).

After this change to a **preventative dosage**, seeing first if the mouth stays healthy for 3 weeks without medication. If it does, then either one of the above mentioned medications are taken at the same dosage for a week, then alternating a 3 week break and one week's medication. If the mouth doesn't stay healthy during the 3 week break, alternate the medication and interval weekly. If this still doesn't keep the mouth healthy use the nystatine suspension continuously, and the Fungizone tablets 1-2 weeks out of four. Preventative dosage of the nystatine suspension can be changed to a three times daily dose of 3 ml.

If the mouth inflammation reappears during the preventative dosage, one has to return to the 4-6 weeks treatment dosage to be followed by an increased preventative dosage, having a week's break first then alternating a 2 week medication period and a 2 weeks break. If the mouth doesn't stay healthy by this method, contact the doctor responsible for mouth treatment (usually at the central hospital mouth diseases outpatients clinic) to test the fungus population's sensitivity to medication, and treating accordingly. Every patient should have her or his mouth checked at the central hospital mouth diseases outpatients' clinic at least once a year.

On infected corners of the mouth apply a medicinal cream regularly several times a day, continuing for 4-5 days even after the corners of the mouth have healed. Suitable creams are the non-prescription natamycin (Pimafucin[®]) and the prescription medication amorolphine hydrochloride (Loceryl[®]). Decspanthenol ointment (Bepanthen[®]) is a suitable for regular application to prevent inflammation of dry mouth corners. Abundant yeast growth inside the mouth maintains inflammation of the corners of the mouth, and the mouth corner treatment alone is not usually enough or its effectiveness remains short-lived. Repeated mouth corner inflammation calls for combining its local treatment with the above oral treatment dosage. Mycostatin suspension can be licked at the same time onto the lips. Disinfecting chlorohexidine gel (Corsodyl[®]) is good to use for the lips and tongue, if the mouth's mucous membranes can stand it without irritation. Chlorohexidine could discolour the teeth's surface, but the colour comes off easily with dentist's cleaning.

Inflammation of the oesophagus (oesophagitis) usually heals with the above treatment in 1-2 weeks. If the symptoms still continue, get in touch with you own doctor in order to get it checked. Prolonged diarrhoea and other digestive complaints should be dealt with in the same way. With genital inflammation in female patients it is best to get the doctor's help.

Hands should be constantly kept dry, because dampness encourages the spread of yeast infection to the skin of the hands. The above mentioned creams work against this skin infection. It is important that the skin is treated often with the cream to get healed, because medication resistant fungus populations readily develop on the skin. Medication for yeast infection of nails doesn't really help; the medication can not get into the nails because they lack own fluid circulation. Yeast infection of the nails can be treated with 40% urea paste and

³ The product name can vary in different countries.

at the same time starting long term medication, for which itraconazol (Sporanox[®]) appears to be best.

Parathyroid failure i.e. hypoparathyroidism

The parathyroids, four smaller-than-pea size glands behind the thyroid gland in front of the neck, precisely control with their hormone the levels of calcium and phosphate in the blood. In a healthy person the plasma/serum calcium concentration (P/S-Ca) is 2.15-2.51 mmol/l (Ca ion 1.16-1.30 mmol/l); it determines muscles' and nerves' sensitivity to irritation, and takes part in many important activities in cells. When the Ca-concentration falls slightly (e.g. in fasting) healthy parathyroids increase their secretion, releasing calcium and phosphate from their large stores in the skeleton (bone strength depends on calcium phosphate). At the same time calcium excretion in the urine decreases and phosphate excretion increases, so the end result is that in blood Ca-concentration increases and phosphate concentration stays the same or decreases. If the Ca-concentration increases after a calcium-rich meal or, e.g. after taking a calcium tablet, hormone secretion decreases and calcium transfers to the bones.

When hormone secretion is deficient (hypoparathyroidism) the blood's Ca-concentration decreases to less than normal (hypocalcemia) and more slowly the phosphate level increases to greater than normal (hyperphosphatemia). Both changes increase nervous and muscular irritability, and if the hormonal deficiency is severe it could lead to an attack of cramps or even unconsciousness. The parathyroid hormone also regulates magnesium, and hypoparathyroidism may lead to magnesium (Mg) deficiency. Most of the body magnesium is in the cells and the body's magnesium deficiency doesn't always show as a smaller than normal (0.71 – 0.94 mmol/l) Mg level in blood plasma.

Symptoms and diagnosis. Hypocalcemia causes numbness and tingling in the limbs, pinching in the abdomen and runny faeces, and in serious cases stiffness and cramping in the hands, at worst even an unconscious cramp attack. In mild hypocalcemia one can just feel unwell and tired. Many patients experience weakening of mental and physical functions. Movements can become clumsy so that a child could be told off at school and even fall. Hypocalcemia can be confirmed in most people by the "Chvostek test": when the curved middle finger's tip is used as a hammer to knock at slightly different points on the underside of the bone ridge felt in front of the ear, a distinct twitch in the upper lip indicates hypocalcemia, and a twitch in the whole half of the face its severe level. Most patients use this test to confirm their feeling of hypocalcemia.

The diagnosis is confirmed by the finding of hypocalcemia with hyperphosphatemia in a patient who has other symptoms indicating APECED, usually at least oral yeast infection. Only when there aren't these indications, determination of the concentration parathyroid hormone in blood is helpful.

Magnesium deficiency can cause painful muscle cramps, in which the muscle becomes hard. In a serious case joints may lock in strange positions. The diagnosis of magnesium deficiency is clear when the APECED patient's muscle cramps are not connected with hypocalcemia and only stop with magnesium medication. Yet serum Mg level may remain in (the lower half of) the normal range.

Treatment. Parathyroid hormone is not available for therapy. Hence vitamin D derivatives have to be used in its replacement. They increase the blood Ca concentration like the hormone, but are less effective than the hormone in reducing plasma phosphate concentration. Importantly, they do not reduce the excretion of Ca into the urine. Hence patients whose blood Ca-concentration is at normal level with the help of medication, excrete more Ca into the urine than normal persons. This entails the risk of kidney damage through

Ca precipitation. In addition, a regular daily supplement of Ca, Mg and calciferol (vitamin D) is recommended.

However, to minimize the disturbance of well-being the plasma Ca concentration should be maintained in the lower half of the normal range or only slightly below it, between 2.10 and 2.30 mmol/l (Ca ion 1.10-1.18 mmol/l). This can be done without risking the kidneys, provided that

- 1) the total daily liquid (water) consumption is regularly at least 2.5-3 litres in adult patients and proportionately less in children, to keep urine dilute,
- 2) the Ca and Mg supplement is given as Ca- and Mg-citrate; this increases urinary citrate and alkalinity which helps keeping Ca in solution, and
- 3) eating should be regular, particularly with regard to the daily amount of milk products (not more than 0.5 litres) and other Ca-rich food.

If these conditions can't be fulfilled, then the 24-hour urinary amount of Ca should not exceed 0.1 mmol/kg body weight and a subnormal plasma Ca level may have to be accepted to fulfil that rule.

Plasma/serum Mg concentration should stay in the upper half (0.82 – 0.94 mmol/l) of the normal level, and phosphate should be at the normal level (before puberty 1.2-1.8 mmol/l, during puberty 0.95-1.75 and after it 0.9-1.5 mmol/l).

Vitamin D derivatives differ in the speed and duration of their effect. The commonly used ones are dihydrotachysterol (DHT, Dygratyl[®]), calcitriol (Rocaltrol[®]) and alphacalcidol (Etalpa[®]). They are quite different: DHT acts slower and longer, after 7 days of taking a dose half of it remains (half-time). Alphacalcidol and calcitriol act faster and shorter with half-time of 1 and 2 days, correspondingly. DHT is given once daily, and the two others twice daily. The right dosage varies with the individual and has to be found for each patient. For some patients the requirement remains steady, while for others the dose needs to be readjusted at times according to laboratory monitoring.

⁴

The daily Ca supplement varies between 500 and 1500 mg depending on the size of the patient. It must be divided in 3-4 doses. It helps to reduce the relative variation of the daily total C intake, and its increase or discontinuation allows rapid reaction to hypo- and hypercalcemia, respectively. The Mg supplement, 50 to 200 mg, daily secures the maintenance of normal body Mg content. The calciferol supplement, 10 µg is a provision for possible needs not covered by the derivatives.

If hyperphosphatemia is not corrected, the possibilities of reducing food phosphate content should be considered with a dietician. It requires at least giving up ordinary milk, because there are lots of phosphate in milk besides Ca. There are no other methods, and normophosphatemia is not always achieved.

Follow up. Our rule is that serum/plasma Ca concentration is checked at intervals no longer 6 to 8 weeks, and serum/plasma phosphate and creatinine levels and 24-hour urine Ca at each second time. Some patients need more intense, at times almost continuous, checking because of imbalance in Ca levels, and all patients need checking in disturbance and risk situations

⁴ My experience is with DHT and my rules for its use are the following. When the dose has to be increased, take on the first day in addition to the new dose an extra one of 7 fold the dose increment. E.g. when increasing the dose from 4 to 4½ tablets, the first day dose is $7 \times \frac{1}{2} = 3\frac{1}{2}$ tablets on top of the 4½ tablets. On the day of decreasing the dosage leave untaken 7 fold the decrement in dose. E.g. when the dose is reduced from 4½ to 4 tablets, take on the first day only ½ a tablet (subtract from the dose of 4 tablets $7 \times \frac{1}{2} = 3\frac{1}{2}$). In severe hypocalcemia situations I temporarily add the faster and shorter acting alphacalcidol, by injection if needed.

(see the following paragraph). Hypercalcemia and hypocalcemia may develop even after long steady periods of normocalcemia. Particularly the symptoms of hypercalcemia are important to identify by the patient, because they should be dealt with quickly. The ideal arrangement is that the patient gets the results S/P-Ca determination directly from the laboratory. That helps her/him to relate the feelings with the actual Ca level, particularly to recognize hyper- and hypocalcemia. The patient should have the right to go to the laboratory whenever she/he feels that necessary. The arrangement should be this: when the patient feels that her/his blood Ca level is too high or low, she/he goes to the laboratory, gets the result, and then contacts the doctor if necessary. A serum sample can be sent in a small plastic tube (obtainable from the laboratory) in a normal envelope, preferably to a laboratory that does many of these analyses. It is best to take a blood sample before eating in the morning, but one must often compromise.

Important to remember. A person whose parathyroid function is normal, doesn't have problems with big changes in the amount of Ca consumed, like when fasting, eating exceptionally Ca-rich food or even a handful of Ca tablets. This is because parathyroid hormone secretion increases or decreases, according to blood Ca level, in a few minutes to keep the concentration normal. This flexibility is completely lacking from patients with hypoparathyroidism. They are in danger of both hypocalcemia from a decrease in Ca intake (e.g. in fasting, during illness) and hypercalcemia from consuming an exceptionally large amount of Ca. Hence the amount of Ca eaten in calcium-rich foods and possible Ca tablets, should stay as even as possible from one day to the next. Also, the Ca tablets should be divided into 3-4 daily doses. Fever is associated with a tendency to have hypocalcemia-hyperphosphatemia, because appetite may have lost and fever increases the blood phosphate level. Then hypocalcemic symptoms may appear. On the other hand, sudden decrease in exercise, e.g. bed rest after an accident, means a danger of hypercalcemia. If on top of hypoparathyroidism the patient has Addison's disease, it is good to remember that hydrocortisone and its relatives decrease the absorption of Ca from the intestines. After increasing the cortisol dosage one should be ready with an extra Ca dose for hypocalcemia, and after cortisol reduction to for hypercalcemia. After such changes S/P Ca should be monitored to estimate possible required changes in medication.

Hypercalcemia. In the case of hypercalcemia we interrupt Ca substitution for a week, at the same time reducing dihydrotacysterol. In the case of severe hypercalcemia (S/P-Ca over 2.8 mmol/l, calcium ion over 1.4 mmol/l) taking DHT is interrupted until laboratory results indicate S/P-Ca reduction to near the desired level. A one third smaller than previous dosage should be taken after this, because hypercalcemia easily reappears in this situation. Also, food with lots of Ca should be left away for a week: milk, cheese, tinned fish (in which the fish have bones) and green vegetables. In bad cases (S/P Ca over 3.0 mmol/l, calcium ion over 1.5 mmol/l) it is an emergency situation, which requires immediate hospital care.

Adrenal cortex deficiency i.e. Addison's disease

The adrenal glands are two (in an adult, 4-5 g in weight) glands on top of the kidneys in the back wall of the abdominal cavity. Their cortex forms, in reality, three glands which each secrete a different hormone: the "stress hormone" cortisol, the salt hormone aldosterone and male sex hormone related dehydroepiandrosterone (DHEA). Cortisol and aldosterone are critical for life, and DHEA is the only one of its kind in women and obviously important. **Cortisol** secretion has a daily rhythm – more in the early morning and less in the late evening. It participates diversely in regulating metabolism, and is especially important for gathering strength in physical and mental stress situations. At these times its secretion

increases. With lack of cortisol a person wastes away, and the ability to do things lessens or totally collapses, leading to life-threatening danger, especially in stress situations. Excess also has negative effects, among others: slowing growth of children, weakening bones and muscles, and making the face and body fatter.⁴

The aim of treatment is to give the organs just that amount of cortisol that a healthy adrenal gland would secrete, to maintain as well as possible a normal situation. If the dosage is correct it should not cause any damage or dangers, on the contrary it is vital. **Cortisol replacement treatment should never be stopped, but on the contrary in sudden sicknesses and stress situations the dose should be increased.** It has happened that a person with Addison's disease has had an accident or developed a febrile disease in circumstances in which the physician available not happened to know this disease. Every doctor knows that "cortisone therapy" may have harmful effects, and it so happened that the physician discontinued this replacement therapy instead of increasing it, with fateful result.

Aldosterone controls the excretion of salt into the urine, so that the amount of salt in the body remains correct. The blood volume depends on the amount of salt. When a healthy person eats a lot of salt, aldosterone secretion stops and the extra salt is removed in the urine. If salt is lacking from the diet, aldosterone secretion increases so that salt excretion into the urine stops almost completely. In aldosterone deficiency the body loses too much salt to the urine and there is a danger of failure of blood circulation i.e. shock. A mild lack appears before long as weight loss, reduction of sodium (Na) concentration in the blood and a slower increase in potassium (K) concentration. If a person secretes too much or receives too much aldosterone (or its substitute fludrocortisone), blood volume increases too much, causing the blood pressure to increase. At the same time the blood's potassium concentration decreases. Aldosterone makes the kidney hold on to sodium, partly by excreting potassium in its place.

DHEA is not a hormone per se, but is converted into the sex hormones testosterone and estrogen. Women with adrenal insufficiency have low levels of androgens which is important to maintain pubic and under-arm hair. Men obtain sufficient levels of androgens from the testis.

Symptoms and diagnosis. Adrenal cortex failure causes a feeling of physical and mental weakness, lack of strength, tiredness, darkening of the skin and mucous membranes, weight loss, nausea, depression and lowered blood pressure. Both mental and physical capabilities are weakened. Aldosterone deficiency causes reduction of weight, lowered blood pressure which is bad especially when standing up and is connected with fainting, and often a craving for salt. If the patient has previously had hypoparathyroidism, symptoms of hypercalcemia could appear because lack of cortisol increases the absorption of calcium from food. Failure of cortisol and aldosterone secretion doesn't always happen at the same time – there could be years between them. Both deficiencies can develop slowly over years or quickly, over the course of only a few weeks. The deficiencies can be revealed by blood hormone measurements. Typically cortisol concentrations are low and the concentration of the pituitary hormone (ACTH, **adrenocorticotrophic hormone**) that stimulates cortisol secretion, increases. Cortisol measurements are sometimes difficult to interpret. In these cases, the ACTH-stimulation test can be used to reveal adrenal failure. Reduction of aldosterone secretion is revealed first by the increased levels of the hormone rennin, later followed by decrease in the serum sodium concentration and increase in the potassium concentration in serum.

Basic treatment of adrenal failure. Cortisol deficiency is usually remedied by hydrocortisone⁵ or the longer and stronger acting prednisolone. In maintenance therapy hydrocortisone tablets are taken twice (in the morning when waking up and between 5-6 pm) or trice daily (7-8 am, 1-2 pm and 7-8 pm). The latter is preferred during growth in children. For the individual the best day and evening times can be found by trying different times and recording what feels best. In order to imitate normal daily changes the morning dose is usually the biggest. The dose depends on the patient's size (on average 10-12 mg per square metre of body surface: for an adult 15-25 mg per day)⁶ – as a rule, the smallest dose with which the person can feel well is given⁶. An unnecessarily large dose when used continuously weakens bones, and slows growth in children. The dosage should be increased on the patient's or parents' initiative in very stressful situations, such as during fever (over 39.0 °C) and especially strenuous physical activity lasting hours (e.g. hiking). It is doubled for as long as the stress continues and, in prolonged stress, divided in four doses to be given at six hour intervals. In extreme situations it is tripled. It is also increased during anaesthesia and operations. The increase shouldn't be given too readily to a child, because if extra is given often, it slows growth.

Aldosterone deficiency is replaced by fludrocortone (Florinef®) tablets – one dose in the morning. Finding the right individual dose is important. When the dose is right the patient feels good, there is no craving for salt, blood pressure is normal when measured lying down and neither does the “upper pressure” (systolic) fall by more than 10-14 mm of when measured first sitting, and then standing up (a greater drop indicates that the dose is too small). Moreover, the plasma renin activity is normal (a greater than normal activity indicates under treatment, and a smaller than normal activity, over treatment). Because salt excretion control is lacking, the amount of salt consumed should stay at the same level each day. Exceptional sweating, diarrhoea and vomiting, and fasting lead to a lack of salt, if not compensated by increased intake (1.0-1.5 g a day per 10 kilograms of body weight). If the patient has continuous diarrhoea and/or vomiting, he or she should be hospitalised without delay. In these situations and during fasting before an operation, the patient should receive an intravenous saline solution. **Too much salt** for too long leads to an increase in blood pressure. Blood pressure measurement at least a few times a year is part of monitoring of this disease. If blood pressure has risen, you can participate in the monitoring by getting (e.g. from a pharmacy) a good quality blood pressure meter. The need for aldosterone replacement treatment could decrease with age or even stop for unknown reasons. If a person suffering from Addison's disease has been shown to have increased blood pressure, it is first to be suspected that the Florinef dose it too big, even though it was earlier suitable. Also, use of liquorice can be a reason for the increase, and should be avoided. Plasma renin determination is important for evaluating the situation.

In the case of serious illness, e.g. vomiting and diarrhoea 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 size and condition and get straight away to hospital treatment. At home and when travelling one should carry Solu-Cortef® injectable solution for stress situations, and when travelling in foreign countries have a more detailed English language description of the disease and its treatment. The patient and/or family member/travelling companion should be prepared to give the injection.

⁵ In medication , cortisol is traditionally, for historical reasons, called hydrocortisone.

⁶ A 10 mg tablet can be divided into 4 parts and the dosage determined to 2.5 mg accuracy.

DHEA replacement. DHEA tablets are sometimes used for DHEA replacement for adult female patients with Addison's disease, even though they are not part of normally available medication in all countries. Some adult female patients experience improved mental and physical vitality and sexuality. We recommend that DHEA treatment is given as part of a treatment protocol so that the effects can be evaluated

Follow up. Checks by the responsible doctor are needed, according to the situation, at least twice a year, and the doctor should be contacted if problems occur.

Ovarian atrophy

From puberty ovaries produce estradiol and progesterone, which change a girl physically to be a woman. These hormones are secreted cyclically, which causes the monthly cyclic changes in the uterus. The ovaries also produce egg cells, of which one is released (ovulation) and travels to the uterus in the middle of the period.

If the ovaries are already damaged before the pubertal development or in the middle of it, the development must be started or taken to completion by hormone replacement therapy. Damage to the ovaries after puberty appears as menopause symptoms, as feelings of hot waves, reduction and ending of periods and reduction of breast size. Over time bones also weaken.

Basic treatment of ovarian atrophy. Estradiol is often replaced through the skin by hormone plasters or gel. Patients who get ovarian deficiency before or during puberty begin the treatment with small doses, which are gradually increased over a few years, combining then progesterone replacement in tablet form for about 10 days every month. When that finishes the menstrual flow starts. Replacement therapy develops and maintains the normal condition of breasts and genitals. There is a big interindividual variation in breast size, just as in healthy women. Correctly treated ovarian deficiency doesn't affect sexual life. DHEA replacement can promote it. Because egg cells are not formed, pregnancy can only succeed with donor egg cells.

Other components

Testicular deficiency appears rarely and usually only years after normal pubertal development. Symptoms could be reduction of vigour, weakening of muscle strength and beard growth, shrinking of the testicles and penis and weakening of sexual ability. The testicular hormone, testosterone, is replaced either by injections into the muscles at weekly intervals or with a gel through the skin. These repair the above mentioned changes, except the shrinking of the testes. Lack of sperm can be replaced by sperm donation.

Diabetes. Diabetes of APECED patients results from destruction of the insulin-producing cells in the pancreas, which leads to a lack of insulin. It causes metabolic disturbances of the body's most important fuel, glucose, which appear as an increase in blood sugar. Consequences are the "leakage" of sugar into the urine, excessive urination and continual thirst. These symptoms are connected with weight loss, tiredness and gradual weakening of general condition. This picture of the disease is not distinguishable from "normal" child-type diabetes. When these symptoms appear one should go to the doctor without delay, so that the disease can be easily confirmed from an increase in the blood sugar level and sugary urine. The resulting danger of dehydration can be avoided by starting insulin treatment quickly.

Insulin replacement is preferably given as several regular injections under the skin daily. Eating should be regular and as well the diet should be right. Also, exercise should be plentiful and regular.

Liver inflammation (hepatitis). The amount of ALAT enzyme from the liver in blood should be followed regularly, because its increases point to liver cell damage. Liver inflammation of APECED patients doesn't usually cause any symptoms, but because of its danger it may require long-term immunosuppressive medication. A side effect of this is to increase the predisposition to infection. Rare cases of serious hepatitis are connected to tiredness, poor condition and yellowing of the whites of the eyes, and sometimes yellowing of the skin and itching. It requires immediate hospital treatment.

Vitamin B₁₂ absorption failure (pernicious anaemia). The Intrinsic Factor (IF) secreted by the parietal cells the stomach's mucous membrane is needed for the absorption of vitamin B₁₂ from food. Autoimmune destruction can also target those cells. The monitoring of this condition involves the search for these parietal cell antibodies in the blood, and, when needed, monitoring of vitamin B₁₂ concentration in the blood. Its reduction can be confirmed before anaemia or other consequences appear. Vitamin B₁₂ absorption disturbance treatment is easy: it is given as an injection into the muscles often at the start, and in maintenance treatment at 2-3 month intervals.

Diarrhoea. The APECED patient's susceptibility to loose or watery faeces is often connected to the hypocalcemia of hypoparathyroidism. Diarrhoea can interfere with the absorption of vitamin D medication and calcium, and thus make itself worse. In these situations the patient may need to be given a vitamin D derivative (Etalpha[®]) temporarily by injections into the muscles. The occurrence of diarrhoea requires more intense monitoring of calcium concentration in the blood. Other, rarer reasons are possible; diarrhoea that is not related to hypocalcemia demands special investigation and special treatment.

Constipation. When constipation occurs, the first thing is to confirm that it is not a case of hypercalcemia. Otherwise treatment of constipation involves food containing lots of roughage; vegetables and wholegrain bread. Sometimes more effective treatment is needed under doctor's supervision.

Eye problems (by Eeva-Marja Sankila, M.D., Ph.D.). Reddening of the whites of the eyes and discharges from the eyes could be due to allergic inflammation, microbial inflammation (infection), dryness of eyes or APECED corneal inflammation.

Dryness of eyes symptoms can be very annoying: the eyes sting, there is a feeling of sand in them, and they readily water due to different irritants, like mechanical ventilation or cold air. There may be discharge especially in the morning. Serious dryness of eyes can weaken the vision and also predispose eyes to infection. Dryness of eyes is a common complaint in the population, and especially in APECED patients, who can have several generally predisposing factors. Aging, thyroid gland illnesses and other hormonal changes predispose to dryness of eyes. In addition, patients' eyelid edges are often thickened and inflamed by weakening of the tear gland's normal secretions and the quality and distribution of the tear film over the surface of the eye. Also, the eye's normally protecting eyelashes may be missing. For treatment of dry eyes it is usually sufficient to regularly use artificial tears and to take care of eyelid hygiene. Pharmacies provide several different over-the-counter preparations, from which you can find for yourself suitable artificial tears. More watery drops don't dim vision, but they have a shorter effect than gel preparations, which could cause longer lasting

dimming of vision. The use of gel preparations is certainly beneficial when going to bed to reduce discharge from the eyes in the morning. In long term use, if there is a tendency to allergy, it is safer to use a preservative-free, individual pipette packaged product. Eyelid hygiene includes thorough daily cleaning of the eyelid edge e.g. with diluted children's shampoo and a soft single-use washing pad.

Corneal inflammation is a serious APECED component, which appears as reddening of the whites of the eyes and discharge from the eyes with stinging, a feeling of sand in the eyes and sensitivity to light. When an eye problem appears the first time, one should immediately contact an eye specialist to find out the nature of the complaint. Corneal inflammation requires effective care with eye drops under the regular supervision of an eye doctor. Otherwise there is a danger of the cornea becoming cloudy, a permanent weakening of the eyesight and even blindness. Corneal inflammation seems to appear before 20 years old.

Slowing of growth; growth hormone deficiency; thyroid hormone deficiency. Unusual slowing of growth in height, and especially of growth in general, requires clarification. Thyroid hormone deficiency, hypothyroidism, is a possible cause and it is easy to identify with a blood test. Hypothyroidism has occurred during growing age in only one of our 93 patients. For this person it was the first component of the disease. With other of our patients hypothyroidism only developed in adulthood with few symptoms and was identified in routine check ups. The reason for the slowing of growth must be investigated in every case. Growth hormone deficiency has been identified as the cause in a few patients.

High blood pressure is quite common in APECED patients. It doesn't usually cause any symptoms, except when serious frequent headache. Blood pressure measurement must be a part of a regular routine check up. Hypertension has to be investigated and the pressure must be brought back to normal levels. With some patients the reason is a craving to eat lots of liquorice; which must be abandoned, but this is no easy in case of school age children and youth.

Lack of spleen or its atrophy is recognised by microscopic examination of red blood cells: Howell-Jolly particles, associated with spleen disturbance, can be identified in them. With ultrasound investigation the spleen size can be measured. Spleen deficiency requires vaccination against three bacterial species.

Hair loss (alopecia) results from autoimmune destruction of the hair follicles. It may occur rapidly with the hair falling in clumps. In some patients bald patches regrow after some time, but in others all hair disappear. Sometimes destruction of eyebrows and eyelashes occurs first. There is no effective medication for this problem; the only help for it is a wig. A few of them are needed and they have to be properly looked after. Often the cost of the wigs is compensated within the framework of medical rehabilitation. Many male patients have chosen to show their bald head without experiencing it as a problem.

White patches on the skin (vitiligo). Autoimmune destruction of the cells giving a tan to the skin appears as white patches, which slowly get bigger. They stand out when healthy skin is tanned and rarely disappear by themselves. Many different attempts at treatment have been tried, unfortunately with poor results.

What determines the progress of the disease and can it be predicted?

We don't know why some patients get many disease components and others only a few. Autoantibodies are telltale signs of an ongoing autoimmune process, and can be detected many years before the patient gets the disease. If autoantibodies appear the doctor should be particularly on guard so that decreased organ function can be detected, e.g. 21-hydroxylase and adrenal failure) These phenomena are under intensive investigation and we hope that the methods used for patient monitoring and care can be further improved.

GO IMMEDIATELY TO YOUR OWN DOCTOR:

When one or some of the following appear, especially as a new occurrence:

- Mouth soreness, ulceration (particularly an ulcer that doesn't heal in week), white or grey covering of the inside, pain in the heart region, difficulty in swallowing, stomach complaints: probable yeast infection.
- Numbness and tingling in the limbs, cramping, loose and pinching bowels: hypocalcemia, sometimes magnesium deficiency.
- In a patient with hypoparathyroidism headache, constipation, thirst, night urination, lack of appetite, nausea, sleepiness, loss of weight: hypercalcemia?
- Tiredness, feeling of weakness, thinning, craving for salt: Addison's disease or the need for adjustment of its treatment?
- Thirst, increased urination, night urination, thinning: diabetes?
- Poor condition, yellowing of the whites of the eyes: liver inflammation?
- Stinging in the eyes, feeling of sand in the eyes, sensitivity to light: eye inflammation?

EMERGENCY SITUATIONS

In the case of serious illness, e.g. vomiting and diarrhoea or following a serious accident, patients with Addison's disease must immediately get an injection into the muscle of 25-100 mg hydrocortisone (Solu-Cortef® injectable solution) depending on size and condition and get straight away to hospital treatment. At home and when travelling one should have Solu-Cortef® injectable solution for stress situations, and when travelling in foreign countries have a more detailed English language description of the disease and its treatment. The patient and/or family member/travelling companion should be prepared to give the injection.

SOURCES FOR FURTHER INFORMATION

For patients with Addison's disease there are several patient support group web pages on offer, that can be found on the international patient support groups' webpage www.nvacp.nl, maintained by the Dutch patient support group. A hypoparathyroid patient's association has been founded, which is developing a website: <http://www.hypoparathyroidism.org>