A woman in her 50s with chronic fatigue syndrome, sepsis and hyponatraemia

A woman who had had chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME) for almost ten years was hospitalised because of pneumonia with sepsis. While in hospital she developed hyponatraemia, and another underlying diagnosis was revealed.

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A woman in her 50s was found at home by her husband, who was unable to communicate with her. She had been coughing and feeling lethargic and unwell for the previous few days. The woman used no drugs on a regular basis. When the ambulance crew arrived, she was disorientated, with a Glasgow Coma Scale (GCS) score of 13. Her temperature was 40.5 °C. She was given 500 ml Ringer's acetate intravenously on her way to Acute Admissions.

In Acute Admissions, she could move her extremities, was free of pain and her neck was not stiff. Her GCS score was unchanged. Her skin was dry, warm and without petechiae. Her blood pressure was low (88/61 mm Hg – 105/51 mm Hg – 91/60 mm Hg – despite infusion of 2 000 ml Ringer's acetate. Her pulse was regular, between 113 and 126 beats/minute, her temperature was 39.7 °C, SpO_2 was 97 % with 3 l O_2 and her respiratory rate 20–25 per minute. On auscultation, reduced respiratory sound over the right lung, most pronounced basally.

Blood tests on admission are shown in Table 1. Blood gases were taken arterially in room air. The urine strip test showed traces of albumin and blood, otherwise normal findings. The rapid urine antigen test for pneumococcus was negative. Chest x-ray showed an opacity in hilar position on the right side, consistent with pneumonia infiltrate.

The patient's history together with clinical and biochemical findings were consistent with pneumonia with severe sepsis – she met three of four SIRS criteria (systemic inflammatory response syndrome) and was disorientated in addition. Meningitis/encephalitis was less probable since the clinical findings indicated a pulmonary infection and she did not have a stiff neck and was not photophobic, nor did she have headache, nausea or petechiae.

An exploratory neurological examination was conducted, without pathological findings, but Donders' test was probably not performed.

Treatment commenced with penicillin, 5 mill. IU × 4 and gentamicin 360 mg × 1 intravenously. She was moved to the Intensive Care Department, where because of her persistently low blood pressure despite rehydration treatment, she received vasopressor therapy in the form of noradrenaline. She did not require ventilatory support.

Some nine years earlier, the patient had been put on 100 % invalidity following an upper respiratory tract infection, because of nautical vertigo, fatigue, lethargy and occasional numbness of the arms and legs. She had also developed problems with loose stools and reduced appetite, and had lost 13 kg. She had low blood pressure of around 100/70 mm Hg (compared with 140/90 mm Hg previously), headache and joint pain.

She was assessed by her GP, a neurologist, an ear, nose and throat specialist, an ophthalmologist and a gastroenterologist, without any definite diagnosis being made. Gastroscopy with biopsy showed non-specific changes, colonoscopy with biopsy was normal, CT abdomen revealed hepatic steatosis (at the time the patient drank about 10 units of alcohol per month), while an MRI of the small intestine revealed no definite pathology. MRI of the head was normal, and the conclusion after a neurological assessment was balance disorder, probably as a sequela of an influenza-like illness. Values for TSH and free T_4 were normal. After two years of extensive workup, she finally received the diagnosis myalgic encephalomyelitis (ME). She was put on a disability pension and stated up to the time of the current hospitalisation that she had permanently reduced quality of life.

The day after her admission the patient was awake, in reduced general condition. She had difficulty finding words and was slightly disorientated. She still did not have a stiff neck, rash or headache, so no lumbar puncture was performed. A clinical examination revealed normal conditions apart from abundant crepitations over the whole surface of her right lung. She still had a tendency to hypotension, with systolic pressure of 90–100 mg Hg, but normal diuresis and normalised renal function. Noradrenaline was tapered and discontinued, and she was

moved to a ward, where her antibiotics treatment continued.

Four days after her admission, her penicillin dose was reduced to 2 mill. IU × 4 intravenously because of clinical improvement and falling infection markers. Cultures of blood samples taken on admission showed no microbial growth. A deep nasal swab showed abundant growth of Staphylococcus aureus, regarded as normal flora. However, the patient had falling serum sodium to 121 mmol/l (137–145 mmol/l) despite infusion of a total of 2 l NaCl 9 mg/ml. A number of laboratory tests, shown in Table 2, were performed as part of hyponatraemia assessment, but the results were only available after her discharge.

Table 1 Blood tests on admission

Test	Value	Reference range
Venous tests		
Blood sedimentation rate (mm/h)	19	1–17
CRP (mg/l)	101	0–4
Leukocytes (· 10^9/l	7.9	3.5–10
Haemoglobin (g/100 ml)	14.2	11.7–15.3
Thrombocytes, (· 10^9/l	155	145–390
INR	1.4	0.8–1.2
Bilirubin (µmol/l)	7	5–25
Albumin (g/l)	38	36–45
Free calcium (mmol/l)	1.14	1.15–1.35
Sodium (mmol/1)	135	137–145
Potassium (mmol/1)	4.2	3.6–5.0
Carbamide (mmol/l)	5.5	3.1–7.9
Creatinine (µmol/l)	118	45–90
eGFR (ml/min/1.73m^2)	46	> 60
Glucose (mmol/l)	5.7	4–6
Arterial blood gas		
pH	7.39	7.35–7.45
pCO_2 (kPa)	4.9	4.7–6.0
pO_2 (kPa)	9.5	10–14
Bicarbonate (mmol/l)	22	22–26
Base excess (mmol/l)	–3	± 3
Lactate (mmol/l)	0.7	0.4–0.8

She thus developed severe hyponatraemia after admission. Patients with pneumonia may develop hyponatraemia because of the syndrome of inappropriate secretion of antidiuretic hormone (SIADH). In patients with this condition, increased secretion of antidiuretic hormone (ADH) leads to increased resorption of water in the kidneys and hence to hyponatraemia. These patients do not need fluid therapy unless they are hypovolaemic, and treatment of their pneumonia will normally correct the hyponatraemia.

Hypotension leads to hyponatraemia as a result of increased ADH secretion from the pituitary gland. Pronounced hypothyroidism can also cause hyponatraemia due to the SIADH phenomenon. Hypotension and hyponatraemia should arouse suspicion of adrenal insufficiency (1). Similarly, adrenal insufficiency should be a differential diagnosis for patients with inexplicable or refractory hypotension that requires fluid or vasopressor therapy (2).

Six days after admission, the woman was discharged in relatively good general condition. She was treated further with phenoxymethylpenicillin 660 mg × 4 and potassium chloride 750 mg × 3. Blood tests now showed CRP 69 mg/l (0–4 mg/l), leukocytes 4.4 · 10^9/l (3.5–10 · 10^9/l), sodium 131 mmol/l (137–145 mmol/l), potassium 3.2 mmol/l (3.6–5.0 mmol/l), creatinine 47 µmol/l (45–90 µmol/l).

Thyroid tests – TSH 0.78 mIU/l (0.5–3.6 mIU/l) and free T_4: 4.5 pmol/l (6–20 pmol/l) – led to the condition being perceived as hypothyroidism. She was started on levothyroxine 25 µg × 1, a dose that her GP doubled after a week. Follow-up at the hospital «electrolyte clinic» was agreed.

The patient's hypokalaemia on discharge could have various causes. She had been treated with noradrenaline and salbutamol, and both can cause potassium to move into cells. High-dose penicillin in addition to gentamicin can lead to renal potassium loss. Serum magnesium was measured the day after admission, and was 0.63 mmol/l (0.71–0.94 mmol/l). Hypomagnesemia can reduce the tubular reabsorption of potassium and may have contributed to the hypokalaemia.

Hypotension may have stimulated the renin-angiotensin-aldosterone system and contributed to renal potassium loss. A low aldosterone level was admittedly measured on admission, but this can be explained by infusion of NaCl 9 mg/ml during sampling. The addition of salt and fluid inhibits excretion of renin, while a low potassium level inhibits release of aldosterone (1). Generally, thyroid levels may be pathological in acute illness – high or low level of TSH/free T_4. Consequently, these results should be interpreted with caution and the tests possibly repeated when the patient is in a stable phase. A low level of TSH and free T_4 should arouse suspicion of pathology in the hypophysis/hypothalamus.

As soon as the results of the hormone analyses were available, the patient was contacted by telephone. She came for a further consultation and was then lethargic, tired and dizzy. She explained that for the past five months, she had had problems with varying sight in her left eye. She had seen a general ophthalmologist, but so far without any conclusion. She did not report headache, nausea or a craving for salt, but felt very tired and was unable to eat; her fluid intake was adequate.

At the clinical examination she was orientated with respect to time, place and situation, but tired. She had no signs of hyperpigmentation of the skin or the mouth cavity.

Table 2 Laboratory tests taken day 4 as part of hyponatraemia assessment. Patient received NaCl 9 mg/ml infusion while the tests were being conducted

Test	Value	Reference range
Venous tests		
Sodium (mmol/1)	121	137–145
Potassium (mmol/1)	3.3	3.6–5.0
Glucose (mmol/l)	5	4–6
Creatinine (μmol/l)	41	45–90
Effective p-osmolality (mmol/kg)	247	281–295
Cortisol, morning (nmol/l)	81	138–690
Cortisol, evening (nmol/l)	62	< 50 % of measured morning value 7–9 a.m.
ACTH, morning (pmol/l)	2.2	< 10.2
ACTH, evening (pmol/l)	< 1.1	< 50 % of measured morning value 7–9 a.m.
Aldosterone (pmol/l)	53	Seated 61–1 068, lying < 653
Renin activity nmol/l	< 0.2	< 1.5
TSH (mIU/l)	0.78	0.5–3.6
Free T_4 (pmol/l)	4.5	8–21
Urine tests		
Urine sodium (mmol/1)	163	> 30 with hyponatraemia indicates use of diuretics, SIADH, adrenal insufficiency
Urine potassium (mmol/1)	13.1	< 20 with hypokalaemia indicates extrarenal loss
Urine creatinine (mmol/1)	5.13	U-potassium/u-creatinine > 1.5 indicates nephrogenous loss
Urine osmolality (nmol/kg)	561	200–800

Her weight was 56.8 kg, body mass index (BMI) 19.2 kg/m^2. The blood pressure measurements were: sitting 98/50 mm Hg, pulse 80 regular, standing immediately 88/62 mm Hg, pulse 102 regular and standing after three minutes 70/43 mm Hg, pulse 110 regular. She then became dizzy. Donders' test revealed a normal field of vision for the right eye and a reduced field temporally for the left eye.

Blood tests showed sodium 136 mmol/l (137–145 mmol/l), potassium 4.8 mmol/l (3.6–5.0 mmol/l). Further hormone analyses were performed on suspicion of hypopituitarism; see Table 3.

Clinical and laboratory findings were consistent with secondary adrenal insufficiency. Treatment with cortisone acetate tablets began – 50 mg in the morning and 25 mg in the evening for three days, then 25 mg in the morning and 12.5 mg in the evening. An MRI scan of the pituitary gland was ordered. Potassium chloride was discontinued as normokalaemia had been attained.

At follow-up two weeks later, the patient related that she felt considerably better. «I'm like a new person.» The dizziness was gone, she had a good appetite, was sleeping well and for the first time in many years felt that she had energy. She did not experience an orthostatic fall in blood pressure any longer. New blood tests showed sodium 141 mmol/l (137–145 mmol/l), potassium 4.5 mmol/l (3.6–5.0 mmol/l), creatinine 52 μmol/l (45–90 μmol/l), carbamide 5.6 mmol/l (3.1–7.9 mmol/l), glucose 4.9 mmol/l (4–6 mmol/l), TSH 0.21 mIU/l (0.5–3.6 mIU/l) and free T_4 15.3 pmol/l (8–21 pmol/l).

An MRI scan of the pituitary gland (Fig. 1a) revealed a large (31 mm × 29 mm × 26 mm) cystic intracellular tumour, with a large supracellular component that raised the optic nerve decussation. The finding was assumed to represent either a craniopharyngioma or a cystic pituitary macroadenoma.

An endocrinologist was consulted. Because the patient did not have elevated prolactin and had insulin-like growth factor 1 (IGF-1) in the lower normal range, she was referred for neurosurgery.

In a neuro-ophthalmological assessment prior to the operation, best corrected visual acuity was 1.6 for the right eye and 0.25 for the left eye. The patient read Ishihara's colour plates a little hesitantly with the right eye and did not manage any plates with the left eye. Field of vision tested with threshold perimetry (Fig. 2A) showed a bitemporal reduction in sensitivity, but more so for the left eye. The left pupil had a slightly impaired direct light reflex. A fundoscopic examination revealed the left optic nerve to be a little pale compared with the right, compatible with slight optic atrophy. Neurological status was otherwise normal.

The patient underwent surgery with transsphenoidal resection of the tumour in the hypophyseal recess, with uncomplicated post-operative course.

An MRI scan of the pituitary gland immediately postoperatively (Fig. 1B) showed no sign of residual tumour, and the optic paths

Table 3 Laboratory tests taken as part of assessment of hypopituitarism

Test	Value	Reference range
Cortisol, morning (nmol/l)	55	138–690
ACTH, morning (nmol/l)	1.7	< 10.2
Aldosterone (pmol/l)	1 330	Sitting 61–1 068, lying < 653
Renin activity nmol/l	2.8	< 1.5
FSH (IU/l)	1.9	Postmenopausal > 20
LH (IU/l)	< 0.6	> 15
Prolactin (mIU/l	869	50–700
IGF-1 (nmol/l)	19.4	11–40

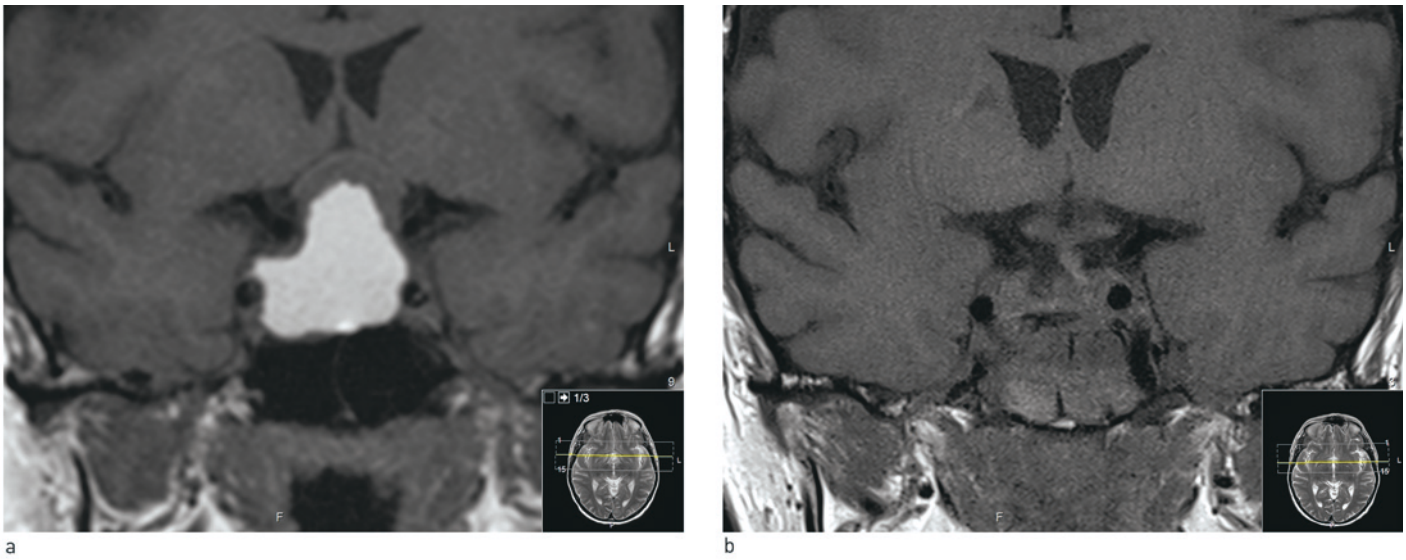

Figure 1 *Coronary T1-weighted MRI images without contrast. a) Large opacity in sella turcica that extends up in the suprasella direction. The optic nerves and optic nerve decussations have been pushed upwards and are seen as a thin, half-moon shaped strip above the tumour. The tumour has a solid component with a low signal just under the optic paths. The large cystic component is seen with a high signal and parallels the internal carotid artery bilaterally. b) Post-operative status. Tumour was removed transphenoidally. There are copious blood products in the sphenoidal sinus. The optic nerves and optic nerve decussations are now lying free and their thickness has normalised. Under them the pituitary stalk is seen in the mid-line with a slight deviation to the left (right in the picture)*

were free. The histology results revealed that the tumour was a non-hormone-producing pituitary adenoma with a low level of the proliferation marker ki67.

A synacthen test was performed at follow-up three months postoperatively, and was normal. The treatment with cortisone acetate could be discontinued. She continued with levothyroxine 50 µg × 1. The function of the growth hormone axis was not tested, but the possibility of growth hormone deficiency cannot be excluded, even though IGF-1 lay in the normal range.

The patient experienced rapid postoperative normalisation of her vision. At a check-up with the ophthalmologist five months after the operation, best corrected visual acuity was 1.25 for both eyes. She now read Ishihara's colour plates for both eyes, but still more easily with the right than with the left. Threshold perimetry (Fig. 2B) revealed considerable improvement in the earlier bitemporal reduction in sensitivity.

Discussion

Chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME) is a disease without a definite, unambiguous aetiology. An estimated 10 000–20 000 people in Norway are affected, to various degrees (4). One trigger for conditions are infectious diseases (4), and our patient was told this was the cause in her case.

In addition to inexplicable exhaustion, which substantially reduces their functional level compared with previously, patients with this condition have several different physical and cognitive symptoms as a rule. These include orthostatic hypotension, vertigo, general weakness, musculoskeletal pain and nausea (4). Similar symptoms also often occur in patients with adrenal insufficiency (5).

Chronic fatigue syndrome/myalgic encephalomyelitis is an exclusion diagnosis, without biological markers, and it should only be made after a thorough review of the patient's history of illness, a clinical examination and supplementary tests. Other physical and mental illness that can explain the symptoms must be excluded, and defined diagnostic criteria must be used (4).

Among the differential diagnoses that must be excluded is adrenal insufficiency. This can be done by measuring s-cortisol in the morning – cortisol is among the recommended blood tests in the Norwegian Directorate of Health's guide (4). If there is still suspicion of adrenal insufficiency, testing with synthetic adrenocorticotropic hormone (ACTH) can be performed. With secondary (pituitary) adrenal insufficiency, the test can be used if the insufficiency has lasted for more than about six weeks. A rise in cortisol to less than 500 nmol/l after 30 minutes has traditionally been perceived as pathological. With the new, specific immunoassays for cortisol, the normal limit will be lower (l). The test is traditionally carried out with supraphysiological doses of synthetic ACTH (250 µg), which with partial adrenal insufficiency may yield false-positive results (6).

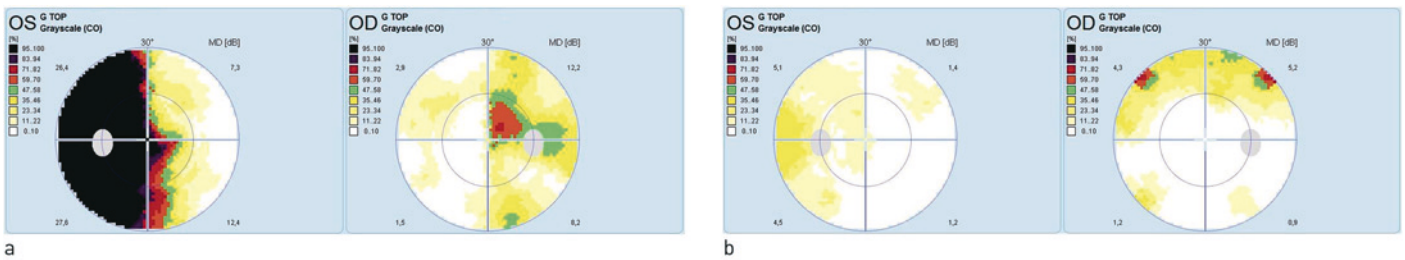

Figure 2 *Threshold perimetry for right and left eye taken before and after the operation. The colour scale indicates percentage deviation from the normal. Mean deviation (MD) indicates reduction in sensitivity (measured in dB) in four visual field quadrants. a) Before the operation there was a bitemporal reduction in sensitivity, more so for the left eye. B) After the operation there was a considerable improvement in performance*

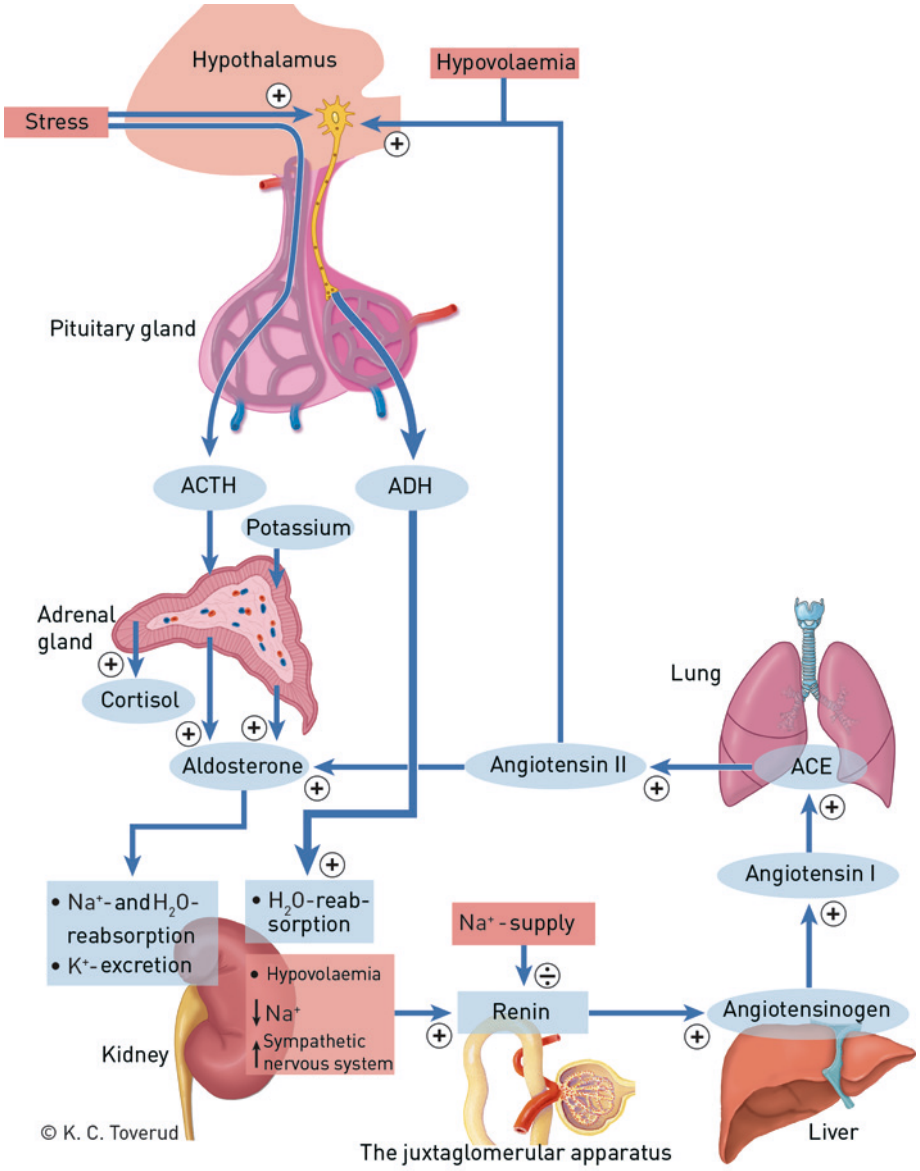

Figure 3 *The most important mechanisms for regulating the water and salt balance. Volume is given priority over osmolality and explains the tendency to a low sodium level with hypovolaemia*

Studies indicate dysfunction in the hypothalamus-pituitary-adrenal axis, resulting among other things in a reduction in the cortisol level in patients with CFS/ME. Cognitive treatment may increase the level of cortisol and is regarded as first-line therapy for patients with the condition. However, treatment with corticosteroids is not recommended for these patients (7–9).

In a Norwegian retrospective study in which 365 patients with suspected CFS/ME were assessed by neurologists, 48 (13.2 %) received the diagnosis and one was found to have adrenal insufficiency (10).

Pituitary adenomas are benign neoplasms with an incidence of about 4.0 per 100 000 per year (11). Adenomas under 10 mm are called microadenomas, those over 10 mm are called macroadenomas. Of all detected macroadenomas, 80 % are non-hormone-producing. Hypopituitarism in patients with macroadenomas may be caused by pinching of the pituitary stalk, compression of hormone-producing tissue in the hypophysis or affection of the hypothalamus (12, 13).

Non-hormone-producing pituitary adenomas are most commonly found by chance, so-called incidentalomas, through MRI/CT scans of the head, but may also have their onset with loss of vision or hypopituitarism. Headache occurs in 40–60 % of the patients and may be due to stretching of the meninges and occasionally to increased intracranial pressure (12, 13). Our patient had a constant headache, loss of vision and severe hypopituitarism with low levels of ACTH, TSH and gonadotropins.

Pituitary adenomas often grow slowly. The MRI scan of the head was described as normal when she received the diagnosis CFS/ME, and it is therefore probable that the pituitary adenoma developed along the way. The original MRI scans are unfortunately not available for further scrutiny.

With primary adrenal insufficiency, hyponatraemia is the most common laboratory finding (in 70–80 %), followed by hyperkalaemia (in 30–40 %). With secondary adrenal insufficiency (hypopituitarism), the renin-angiotensin-aldosterone axis is intact and hypotension and electrolyte imbalance less usual. Hyponatraemia may occur in these patients, particularly in stress situations where the cortisol response is poor, while ADH secretion is intact. This may yield a picture of a SIADH condition (5). Our patient developed severe hyponatraemia during her stay in hospital, and as s-sodium was not measured before admission, it is not certain how long she had had hyponatraemia. Figure 3 illustrates the mechanisms for regulating water and salt balance.

Secondary adrenal insufficiency can be excluded if s-cortisol in a morning sample is at the upper reference limit. In cases of doubt, the test can be supplemented with a synacthen test or insulin tolerance test, which also tests function in the growth hormone axis. In cases of partial insufficiency, the synacthen test may yield a false positive response, but is preferred by many because it has few contraindications and is simple to perform. Low levels of T_4 and low or normal levels of TSH must always arouse suspicion of central hypothyroidism (13). This may have been overlooked in our patient prior to the hospitalisation in question. S-cortisol was not measured as part of the workup for CFS/ME.

Specially adapted MRI scanning is used for diagnostic imaging of pituitary adenomas. Contrast is administered, and high definition series used over the hypophysis in coronal and sagittal plane, which shows the relationship of the tumour to the chiasma and other important surrounding structures. If MRI examination is contraindicated, a CT scan is an alternative. The visual function must be assessed by an ophthalmologist if it is suspected that the pituitary adenoma is affecting the optic nerve decussation or other parts of the optic paths.

Surgery is the first line of treatment for patients with non-hormone-producing macroadenomas. Surgery is indicated in cases of reduced visual function and pituitary apoplexy with impaired vision or ophthalmoparesis (indication for emergency aid). The pro-

lactin level must be measured before the procedure because prolactinomas must almost always be treated medicinally. If there is no clear indication for immediate surgical intervention, one should also wait for the growth hormone and IGF-1 analyses, because data indicate a better outcome for an operation after preliminary treatment with somatostatin analogue (14).

Since the chances of curing hypopituitarism are only marginally greater than the risk of exacerbating the condition with surgery, hypopituitarism alone is no strong indication for surgery (15). Transsphenoidal surgery with microscope and/or endoscope is the preferred surgical method. If the patient cannot undergo surgery, radiotherapy may be an option. The main objective of the treatment is to preserve the visual function. Surgery results in improved visual function in approximately 80 % of patients, often within a few days of the procedure (12, 13). Our patient experienced a subjective normalisation of her vision and end to headache the same day as she underwent surgery.

Glucocorticoid deficiency can be life-threatening, and on clinical suspicion substitution therapy must be started. If possible, hormone analysis should be performed – primary cortisol, TSH, free T_4 and prolactin, possibly also adrenocorticotropic hormone (ACTH), luteinising hormone (LH), follicle-stimulating hormone (FSH), sexual hormone-binding globulin (SHBG), growth hormone, IGF-1, oestradiol (women), testosterone (men) – before starting the therapy. Hypothyroidism is treated with levothyroxine. Thyroxine increases the metabolism and can lead to adrenal crisis, so thyroxine substitution treatment should only be given after glucocorticoid substitution treatment (13). Our patient received a low dose of levothyroxine for two weeks before she started on cortisone acetate. This could have triggered an adrenal crisis. With most patients, appropriate hormone substitution treatment can almost normalise quality of life, morbidity and mortality associated with hypopituitarism (16).

The daily cortisone requirement increases in the event of infections, fever or stress. The daily dose should therefore be doubled or tripled. In case of signs of adrenal insufficiency, fluid and hydrocortisone should be administered intravenously. After the acute phase, the dose is rapidly reduced to the normal maintenance dose. All patients should be equipped with a Norwegian steroid card, which contains information of importance to medical personnel who meet the patient.

Conclusion

We have several aims in presenting this case history. Chronic fatigue syndrome/myalgic encephalomyelitis is an exclusion diagnosis, and adrenal insufficiency must always be excluded before a patient is given the diagnosis. The possibility of adrenal insufficiency should be considered in the case of patients with lethargy/tiredness, vertigo/orthostatism, musculoskeletal pain or hyponatraemia. Similarly, adrenal insufficiency should be a differential diagnosis for patients with inexplicable or refractory hypotension requiring fluid or vasopressor. Hypopituitarism develops over several years as a rule, and when undiagnosed will be an intercurrent disease which sepsis, for example, could exacerbate into adrenal insufficiency and increased mortality. Hyponatraemia of unknown cause, particularly chronic or symptomatic, should also be assessed with adrenal insufficiency in mind.

Our patient had the diagnosis CFS/ME for almost ten years. She was put on a disability pension and had a substantially reduced quality of life. We do not know at what stage she developed hypopituitarism, but a simple test of s-cortisol in the morning and/or s-sodium might have spared her considerable suffering.

The patient has consented to the publication of the article.

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