was fully alert. Serum and urinary osmolarity became normal, urinary specific gravity was 1005–1025. She recovered from ovarian hyperstimulation syndrome and laparotomy during the next month.

Brain MRI and CT performed during the next five years were normal, as were repeated neurological and psychiatric examinations. The patient's IQ was 126–130.

Severe serositis with ascites and hydrothorax due to ovarian hyperstimulation syndrome syndrome and haemoperitoneum due to tubal pregnancy, with hypovolaemia, anaemia, and hyposmolar serum concentrations masked an SIADH that was heralded by seizures, followed by a prolonged lethargic state. Collateral evidence of SIADH was obtained by normal creatinine clearance[2] with urine hyperconcentration. The symptoms of CNS water intoxication, as usual,[2,3] appeared during a sudden decrease in Na^+ serum concentration, and were treated slowly to avoid central pontine myelinolisis. During SIADH, CT showed several patchy areas of hypolucency, resembling severe lesions of acute hypoxic-ischaemic encephalopathy with brain oedema.[4,5] Hypoxic-anoxic lesions are, however, usually caused by residual neurological or psychiatric deficit, and CT shows evolution of lesions, with ventricular enlargement and leucomalacy.[4,5] In this patient instead the hypolucencies disappeared, the patient had no neurological or psychiatric alterations, and later CT and MRI did not show residual areas of altered signal corresponding to early hypolucencies. Furthermore, unlike the situation in hypoxic-anoxic lesions,[4,5] the basal ganglia did not seem to be involved, and the ventricular system was not narrowed as in severe brain oedema. We concluded therefore that water intoxication induced CT images of patchy hypolucencies rather than the expected homogeneous hypolucency.

MARCO ONOFRJ
ASTRID THOMAS
DONATO MELCHIONDA
TOMMASO FULGENTE
Department of Neurology, Institute of Neurology and Behavioural Sciences, State University of Chieti, Chieti, Italy
AMEDEO COSTANTINI
MICHELE SCESI
Intensive Care Unit, State University of Chieti, Chieti, Italy

Correspondence to: Professor Marco Onofrj, Clinica Neurologica, Ospedale ex Pediatrico, Via Martiri Lancianesi 6, 66100 Chieti, Italy.

1 Schenker JG, Ezra J. Complications of assisted reproductive techniques. *Fertil Steril* 1994;3: 411–22.
2 Narins RG. Therapy of hyponatremia: Does haste make waste? [editorial] *N Engl J* Med 1986;314:1573–5
3 Bleck TP, Smith MC, Pierre-Louis SJ, Jares JJ, Murray J, Hansen CA. Neurologic complications of critical medical illnesses. *Crit Care Med*, 1993;21:98–103
4 Tippin J, Adams HP, Smoker WRK. Early computed tomographic abnormalities following profound cerebral hypoxia. *Arch Neurol* 1984;41:1098.
5 De Reuck J, Decoo D, Vienne J, Strijckmans K, Lehmahieu I. Significance of white matter lucencies in posthypoxic-ischemic encephalopathy: comparison of clinical status and of computed and positron emission tomographic findings. *Eur Neurol* 1992;32:334–9.

Thyrotoxic Hashimoto's encephalopathy

Thyroid disease is associated with several neurological disorders,[1] of which one of the rarest and least well understood is Hashimoto's encephalopathy. This was originally postulated to be a distinct disease entity by Brain *et al* in 1966[2] and there have subsequently been case reports substantiating the hypothesis that it represents a unique condition.[3–5] The characteristic features are a subacute onset of confusion with altered consciousness, seizures, and stroke-like events that respond to steroids and which occur in the context of high anti-microsomal antibody titres.[3] To date all the patients reported have been either euthyroid or hypothyroid at the time of presentation. We present a patient with Hashimoto's encephalopathy with pronounced thyrotoxicosis, that was successfully managed with steroids, carbimazole, and propanolol.

A 49 year old woman presented with a six month history of weight loss and a three month history of proximal arm pain and hand tremor. Two weeks before admission she developed a progressive left sided weakness involving the arm and leg in conjunction with a left hemianaesthesia. On examination at admission she was flushed, feverish, and tachycardic with a hyperdynamic circulation. Her thyroid gland was slightly enlarged but there was no associated bruit. Cranial nerve examination disclosed left visual inattention as the only abnormality. Limb examination showed a moderately severe left hemiparesis with left sensory inattention, generalised hypereflexia, and bilaterally extensor plantar responses. She had wasting of the shoulder girdle muscles and adhesive capsulitis of the shoulder joints bilaterally. In the days immediately after admission she became drowsy, confused, and had florid visual hallucinations, while independently having runs of paroxysmal atrial fibrillation. As a result of the original negative findings (see later) dexamethasone (12 mg/day) and acyclovir were started with the presumptive diagnosis of an encephalitis or vasculitis. On this regime she made a dramatic improvement, which was further enhanced by the treatment of her thyrotoxicosis on receipt of her thyroid function tests. The introduction of carbimazole and propanolol was then followed by a reduction in the dexamethasone and a cessation of the acyclovir. Attempted steroid weaning over subsequent days provoked a recrudescence of her focal symptoms on two occasions, with weakness of her right arm. Eventually the patient was stabilised on prednisolone (40 mg/day) and discharged on a slowly reducing course with no relapses three months after discharge.

Investigations performed during her inpatient stay showed that full blood count, erythrocite sedimentation rate, urea, electrolytes, glucose, liver function tests, and serum immunoglobulins were normal. Protein electrophoresis showed an acute phase response with a C reactive protein of 32 mg/l. Her autoantibody screen and VDRL/TPHA serology were negative, but her thyroid function tests showed her to be thyrotoxic with TSH less than 0·03 U/l, free T4 >80 pmol/l, and free T3 41 pmol/l. Her thyroid microsomal antibodies were positive at a titre of 1:6400. Her CSF analysis was normal with negative oligoclonal bands and repeated blood cultures were negative. Her chest radiograph was normal but her ECG showed a sinus tachycardia with episodes of paroxysmal atrial fibrillation. Her EEG showed occasional brief bursts of frontal slow activity which spread posteriorly and brain CT with contrast and MRI with gadolinium were normal. In addition a transthoracic and transoesophageal ECG along with MRI of her heart were all normal.

These results show that she had a pronounced thyrotoxicosis with antimicrosomal antibodies. There was no evidence for any fixed structural lesion within the CNS accounting for her neurological condition as evidenced by her normal brain CT and MRI.

Autoimmune thyroid disease can be considered as a range of clinical disorders reflecting the variety of autoantibodies present. Hashimoto's disease is characterised by the presence of thyroid antimicrosomal antibodies and has rarely been associated with an encephalopathic process of unknown aetiology. All previously described patients have either been euthyroid or hypothyroid and this is the first description of an encephalopathy in combination with thyrotoxicosis. As the mechanism of encephalopathy is uncertain the term thyroid related encephalopathy is preferable. Although atrial fibrillation was present in our patient, the normal heart and head imaging argues against an embolic cause for her condition. Furthermore, her remarkable steroid responsiveness suggests an autoimmune cause for her fluctuating multifocal encephalopathy.

Various mechanisms have been postulated to account for this unusual condition. One possibility is demyelination, which can virtually be discounted on the basis of our results as both MRI and CSF were normal. More likely explanations are either a multifocal abnormality of cerebral perfusion or a patchy defect of metabolism.

This patient completes the repertoire of thyroid states seen in thyroid related encephalopathies and emphasises the need to assess thyroid function and autoantibody status in patients presenting with encephalopathy and stroke-like events in the absence of structural or infective aetiologies.

ROGER BARKER
JOHN ZAJICEK
IAIN WILKINSON
Department of Neurology, Addenbrooke's Hospital, Cambridge CB2 6SP, UK

Correspondence to: Dr Roger Barker, National Hospital for Neurology and Neurosurgery, Queen Square, London WC1N 3BG, UK.

1 Thrush DC, Boddie HG. Episodic encephalopathy associated with thyroid disorders. *J Neurol Neurosurg Psychiatry* 1974; 37:696–700.
2 Lord Brain, Jellinek EH, Ball K. Hashimoto's disease and encephalopathy. *Lancet* 1966;ii: 512–4.
3 Shaw PJ, Walls TJ, Newman PK, Cleland PG, Cartlidge NEF. Hashimoto's encephalopathy: A steroid-responsive disorder associated with high anti-thyroid antibody titers-report of 5 cases. *Neurology* 1991;41:228–33.
4 Ishii K, Hayashi A, Tamaoka A, Mizusawa H, Shoji S. A case of Hashimoto's encephalopathy with a relapsing course related to the menstrual cycle. *Clinical Neurology* 1993;33: 995–7.
5 Shein M, Apter A, Dickerman Z, Tyano S, Gadoth N. Encephalopathy in compensated Hashimoto thyroiditis: A clinical expression of autoimmune cerebral vasculitis. *Brain Dev* 1986;8:60–4.

Cerebral salt wasting syndrome

Excessive natriuresis, resulting in hyponatraemia and polyuria, is an often recognised complication after subarachnoid haemorrhage. Initially this was attributed to inappropriate antidiuretic hormone (ADH) secretion resulting in water retention, bu

recently it has become clear that hyponatraemia in the cerebral salt wasting syndrome is accompanied by hypovolaemia.[1,2]

We report a patient with cerebral salt wasting after aneurysmal subarachnoid haemorrhage who showed remarkable changes in urine production during surgery. A 46 year old woman was admitted with severe headache and vomiting. Physical examination was unremarkable. Brain CT showed a subarachnoid haemorrhage with blood in the suprasellar cisterns and the left Sylvian fissure. Two days later she developed mild hyponatraemia and polyuria; salt and fluid loss were fully compensated by 0·9% NaCl infusion. On day 9 she was found unconscious with respiratory failure and bradycardia and CT disclosed a recurrent subarachnoid haemorrhage in the left Sylvian fissure. The patient regained consciousness and she gradually recovered from a mild aphasia and right facial weakness. However, from day 12 onwards she again developed a progressive polyuria of up to 21 200 ml per day (on day 22) and a 24 hour renal sodium loss of 2630 mmol. The plasma sodium range was between 128 and 142 mmol/l, and the colloid osmotic pressure was between 18·7 and 24·0 mm Hg. Serum ADH concentrations were normal. Treatment with fludrocortisone had no effect on renal sodium loss. Despite the extreme polyuria plasma atrial natriuretic protein concentrations were within the normal range (up to 11·1 pmol/l, normal 3–23 pmol/l); atrial natriuretic protein in CSF was not assessed. Daily transcranial Doppler sonography was indicative of cerebral vasospasm and therefore angiography was postponed until day 22. An aneurysm of the left middle cerebral artery was disclosed, which was successfully clipped on day 24. Whereas the diuresis 24 hours before and after the neurosurgical procedure was 600–700 ml/hour, the mean intraoperative (from incision to the last suture) production of urine was 150 ml/hour. The largest reduction in diuresis was seen while the dura was open. Soon after suturing the dura, urine production rose to preoperative values. Two days after surgery diuresis decreased remarkably and was back to normal on the fourth day after operation. Repeated measurements of plasma sodium were also normal. The patient had fully recovered two months after the operation.

Our patient had a very pronounced urinary sodium loss of up to 60 g per day. Opening of the dura resulted in a decrease in diuresis of 75%. Both a reactive increase of CSF production and a decrease in the intracranial pressure may have been important. Because an increase of atrial natriuretic protein in CSF (and maybe other humoral factors) results in a decrease in CSF production and an increase in natriuresis,[3] an increase in CSF production after loss of CSF through the open dura may have induced a decrease of atrial natriuretic protein, resulting in a decrease in natriuresis.

In patients with subarachnoid haemorrhage Dóczi and Bodosi found a linear correlation between the intracranial pressure and atrial natriuretic protein concentrations in CSF.[4] So lowering the intracranial pressure might result in reduced concentrations of atrial natriuretic protein in CSF and lead to an increase in CSF production and a decrease in natriuresis.[3]

If either assumption is correct, continuous CSF drainage—for example, by an external lumbar drain—may be an effective treatment for the cerebral salt wasting syndrome, especially in more severe cases.

WM MULLENERS
Department of Neurology
WIM VERHAGEN
RHMA BARTELS
Department of Neurosurgery,
Canisius Wilhelmina Hospital,
Nijmegen, The Netherlands

Correspondence to: Dr WIM Verhagen, Canisius Wilhelmina Ziekenhuis, Department of Neurology, PO Box 9015, 6500 GS Nijmegen, The Netherlands.

1 Nelson PB, Seif SM, Maroon JC, Robinson AG. Hyponatremia in intracranial disease: perhaps not the syndrome of inappropriate secretion of antidiuretic hormone (SIADH). *J Neurosurg* 1981;55:938–41.
2 Wijdicks EFM, Vermeulen M, Ten Haaf JA, Hijdra A, Bakker WH, Van Gijn J. Volume depletion and natriuresis in patients with a ruptured intracranial aneurysm. *Ann Neurol* 1985;18:211–6.
3 Juul R, Edvinsson L, Ekman R, Frederiksen TA, Unsgard G, Gisvold SE. Atrial natriuretic peptide-LI following subarachnoid haemorrhage in man. *Acta Neurochir (Wien)* 1990;106:18–23.
4 Dóczi T, Bodosi M. The central neuroendocrine regulation of brain water and electrolytes, and resorption of cerebrospinal fluid (CSF). In: Gjerris F, Borgesen SE, Sorensen PS, eds. *Outflow of cerebrospinal fluid. Alfred Benzon Symposium 27.* Copenhagen: Munksgaard, 1989:282–90.

A patient with cerebral autosomal dominant arteriopathy with subcortical infarcts and leucoencephalopathy (CADASIL) confirmed by sural nerve biopsy

"Cerebral autosomal dominant arteriopathy with subcortical infarcts and leucoencephalopathy" (CADASIL)[1] is a newly defined syndrome characterised, in the absence of hypertension, by recurrent subcortical ischaemic strokes and by peculiar non-amyloid, non-arteriosclerotic angiopathy of cerebral vessels. On MRI circumscribed subcortical ischaemic lesions and diffuse areas of leucoaraiosis are seen both in symptomatic and asymptomatic family members.[2] Recently, genetic linkage analysis in two unrelated French families has assigned the disease locus to chromosome 19q12 with the most likely location of the disease gene between D19S221 and D19S222.[1]

A few postmortem studies have been reported, showing predominant involvement of the cerebral white matter with diffuse myelin loss, multiple small deep infarcts, and occasional haemorrhages.[2] As first reported by Baudrimont *et al*,[3] the small subcortical and leptomeningeal arteries and arterioles display fibrous thickening and an eosinophilic, periodic acid-Schiff (PAS) positive, granular material in the muscle layer. Electron microscopy shows swollen myocytes in the media surrounded by collagen, elastin, and a compact electron dense material.[3]

The arteriopathy of CADASIL is apparently not restricted to brain vessels as identical vascular lesions have been found in small myocardial arteries[3] and sural nerve.[4]

We present a 55 year old woman with a history of recurrent pulmonary embolism from the age of 35. At the age of 40 she experienced a feeling of heaviness in her left arm for about two days. Fifteen years later the patient described episodes of a burning sensation on her tongue and tingling as well as weakness of the left side of her face and her left arm. Six months later she complained of numbness and weakness of her left arm and leg, from which she recovered slowly. No risk factors such as arterial hypertension, diabetes, or migraine were reported. Neurological examination showed a slight left sided ataxia, hemiparesis, and hypaesthesia. Neuropsychological testing showed reduced cognitive performance and flexibility, a deficit in learning and memory, and abnormal visual constructional abilities which were compatible with a subcortical dementia. Brain MRI showed extensive hyperintensive confluent lesions of the parietal and temporal white matter on both sides, mainly in the periventricular and adjacent subcortical regions (fig 1).

Family history showed that the mother of the patient died at the age of 52 with a history of stroke and dementia. Two siblings had MRI changes similar to the index patient, and one had had recurrent episodes of aphasia, headache, and hemianopsia. Six members of this family, three affected and three healthy, have been genotyped with eight chromosome 19 markers spanning the CADASIL interval. No recombinant was found with any of those markers. Maximum lod scores were obtained with markers D19S226, D19S253, and D19S199, strongly suggesting that this family is linked to the CADASIL locus.

A 2 cm long segment of the sural nerve was processed for light and electron microscopy. Six fascicles were present. Around 120 small and large vessels were counted in the endoneurial and epineurial spaces. The largest epineurial arteries (size up to 100 μm) appeared normal. Small epineurial and endoneurial vessels were unchanged in paraffin sections. The arteriolar wall was not thickened on semi-thin sections and no increase in number of nuclei was evident. The perineurium was not thickened and there was no increase of endoneurial connective tissue. The density of myelinated fibres was 6600/mm^2 (normal range for the sural nerve for this age 6000–8000/mm^2). Myelin degradation products were not encountered.

Electron microscopy showed changes in a few epineurial vessels, consisting of electron dense, extracellular granular deposits along the outer aspects of the vessel walls (fig 2A). Most of these granules were on the abluminal surface of pericytes and less often on endothelial cells. Most granules measured 0·2 to 0·5 μm in diameter. However, some measured up to 1·2 × 0·8 μm. Dense deposits were frequently located in thickened basal laminae and were often pushing back the cell membrane of an adjacent pericyte (fig 2 B and C). Most dense deposits were round or oval but some were flat or disc shaped and oriented parallel to the cell surfaces (fig 2A). The number of dense deposits ranged from none to five or six around a single vessel. Some were found in very small arterioles but most were in large capillaries or meta-arterioles (size 14–15 μm) consisting of endothelial cells surrounded by pericytes but without the presence of smooth muscle cells. In some vessels, the basal lamina surrounding the endothelial cells was clearly redundant and tortuous (not shown). Many pinocytic vesicles were found along and underneath the surface of cell membranes. Their density was not altered at the site of close apposition to the cell membrane with the electron dense granular deposits.

The presence of granular electron dense