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.

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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.³ 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 arteries³ 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/mm² (normal range for the sural nerve for this age 6000–8000/mm²). 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 pinocytotic 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

Figure 1 T2 weighted MRI showing extensive hyperintense lesions in the brainstem, basal ganglia, and periventricular white matter of the index patient.

material in the media of leptomeningeal and small cerebral penetrating arteries is considered to be a characteristic ultrastructural feature of CADASIL.^{2,3} The pathophysiological relevance of these lesions is unknown and their specificity has still to be established. Deposition of an identical material has also been reported in small vessels of a sural nerve obtained from a patient with suspected CADASIL.⁴ Here we present a patient with very similar ultrastructural findings in a sural nerve biopsy and who was diagnosed as CADASIL based on clinical data, neuroimaging features, and genetic linkage analysis. Ultrastructural changes in the nerve biopsy of this patient, apart from electron dense deposits along abluminal surfaces of endothelial cells and pericytes, were characterised by redundant basal membrane type material, possibly pointing to some metabolic disturbance in extracellular matrix production by endothelial cells, pericytes, and possibly myocytes in larger vessels. The typical fine structural lesions encountered in epineurial or transperineurial capillaries,⁴ meta-arterioles, or small arterioles of sural nerve hardly have any light microscopical equivalent. In addition, large epineurial vessels seemed to be normal. Thus diagnostic confirmation of CADASIL by sural nerve biopsy clearly requires electron microscopy. The same applies to other tissues, as recently shown by Ruchoux *et al.*⁵ Performing skin and muscle biopsies in several members of a family with known CADASIL, these authors found non-specific light microscopical changes in biopsied tissues. Electron microscopy showed thickened vascular basal lamina of capillaries and arterioles with diameters from 10 to 50 μm and patches of granular and electron dense material close to the cell membrane of vascular smooth muscle cells. These and our own findings indicate that the vasculopathy of CADASIL is more widespread than initially reported, despite the fact that, until now, only cerebral vessel pathology has been shown to be of relevance by causing strokes and dementia. Present morphological evidence points to a diffuse microangiopathy throughout the body. More studies are needed to compare the respective values, especially the sensitivity, of skin, muscle,

Figure 2 (A) Low power electron micrograph of a small epineurial arteriole of the sural nerve. Several electron dense, round, or disc shaped precipitates (arrows) can be seen in the basal lamina surrounding pericytes (P). E = Endothelial cells; scale bar = 1 μm . (B) Higher magnification of the area marked in fig 2A showing one electron dense granular deposit (gd) embedded in basal lamina material. pv = Pinocytic vesicles; cf = collagen fibrils; scale bar = 0.2 μm . (C) Another example of dense granular deposit (gd) found in a small epineurial vessel, embedded in the basal lamina (bl) of a pericyte (P); scale bar = 0.2 μm .

and sural nerve biopsies, in establishing the diagnosis of CADASIL.

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