recently it has become clear that hypertonia-
triaemia in the cerebral salt wasting syn-
drome is accompanied by hyponatraemia.12

We report a patient with cerebral salt wasting after aneurysmal subarachnoid haemorrhage who showed remarkable changes in plasma protein concentrations. A 46 year old woman was admitted with severe headache and vomiting. Physical examination was unremarkable. Brain CT showed an aneurysm and 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 infusions. On day 9 she was found unconscious with respiratory failure and Bradycardia and CT disclosed a recur-
rent subarachnoid haemorrhage in the left Sylvian fissure. The patient regained con-
siousness 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 20 l/day (day 12) 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 pres- sure was below 18.7 and 24.0 mm Hg. Some changes are normally seen after normal
Treatment with fluoroidecortone had no effect on renal sodium loss. Despite the extreme polyuria plasma atrial natriuretic protein concentrations were within the nor-
mal range (up to 6.8 pmol/ml, normal range 0.2 to 6.8 pmol/ml); atrial natriuretic protein in CSF was not assessed. Daily transcranial Doppler sonography was indicat-
ive of cerebral vasospasm and therefore angiography was performed. A non-femoral 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 closed and suturing the dura, whereas the urina production rose to preoperative values. Two days after surgery diuresis decreased remarkably and was back to normal on the fourth day after operation. Repeated mea-
surements of renal sodium were also nor-
mal. The patient had fully recovered two months after the operation.

Our patient had a very pronounced urina
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 import-
ant. Because an increase of atrial natriuretic protein in CSF (and maybe other humoral factors) results in a decrease in CSF produc-
tion and an increase in natriuresis,1 an increase in CSF production after loss of CSF would be expected. When the dura may have induced a decrease of atrial natriuretic pro-
tein, resulting in a decrease in natriuresis. In patients with subarachnoid haemor-
hage, Dancy and Bodosi found a linear cor-
relation between the amount of intracranial pressure and atrial natriuretic protein concentrations in CSF.1 So lowering the intracranial pres-
ture might result in reduced concentrations of atrial natriuretic protein in CSF and lead to an increase in CSF production and a decrease in natriuresis.1

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, espe-
cially in more severe cases.1

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4 Doczi T, Edvinsson L, M. The central neuro-

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

“Cerebral autosomal dominant arteriopathy with subcortical infarcts and leucoencephalopathy” (CADASIL1) is a newly defined syndrome characterised in the absence of hypertension, by recurrent subcortical ischaemic strokes and by peculiar non-amyloid, non-arteriosclerotic angiopa-
yth of cerebral vessels. On MRI circumscribed subcortical ischaemic lesions and diffuse periventricular hyperintensities 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 D19S522.2

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., 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 myocyt-
cies in the media surrounded by collagen, elastin, and a compact electron dense material.1

The arteriopathy of CADASIL is appar-
ently not restricted to brain vessels as identi-
cal vascular changes have been found in small myocardial arteries1 and sural nerve.1 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 months. 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 explained 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, Thrust dysartria, and hypoaesthesia. Neuropsychological testing showed reduced cognitive performance and flexibility, a deficit in learning and memory, and abnormal visual constructional abilities which were compatible with subcortical dementia. Brain MRI showed extensive hypertensive confluent lesions of the pari-
al and temporal white matter on both sides, mainly in the periventricular and adja-
cent perisylvian regions (fig 1)

Family history showed that the mother of the patient died at the age of 52 with a his-
tory of stroke and dementia. Two siblings
had MRI changes similar to index patient, and one had recurrent episodes of aphasia, headache, and hemianopsia. Six members of this family, three affected and three healthy, have been genotyped with markers around 19q12 to confirm the CADASIL interval. No recombinant was found with any of those markers. Maximum lod scores were obtained with markers D19S226, D19S235, 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. About 120 small and 11 larger and 11 smaller vessels were counted in the endoneurial and epineurial spaces. The largest epineurial arteries (size up to 100 mm) appeared normal. Small and medium sized vessels were unchanged in paraffin sections. The ar- teriolar wall was not thickened on semi-thin sec-
tions and no increase in number of nuclei was evident. The perinerve was not thicken-
ed and there was no increase in endoneural connective tissue. The density of myelinated fibres was 6600/mm1 (normal range for the sural nerve for this age 6000–8000/mm). Myelin degradation prod-
ucts 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). Many of these granules were compatible with capillaries or meta-
arterioles (size 14–15 mm) consisting of endothelial cells sur-
rrounded by pericytes but without the pres-
ence of smooth muscle cells. In some ves-
sels, the basal lamina surrounding the endothelial cells was clearly redundant and tortuous (not shown). Many pinocytic ves-
icles 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

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material in the media of leptomeningeal and small cerebral penetrating arteries is considered to be a characteristic ultrastructural feature of CADASIL. The pathophysiological relevance of these lesions is unknown and their specificity is 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. 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 perineurial capillaries, \( \text{meta-arterioles, or small arterioles of sural nerve} \) 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. 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 \( \mu \text{m} \) 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, and sural nerve biopsies, in establishing the diagnosis of CADASIL.

We thank Dr E Tournier-Lasserve and Dr K Vahedi for performing linkage analysis.

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

**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 cell; scale bar = 1 \( \mu \text{m} \). (B) Higher magnification of the area marked in fig 2A showing one electron dense granular deposit (gd) embedded in basal lamina material. po = Pinocytic vesicles; cf = collagen fibrils; scale bar = 0.2 \( \mu \text{m} \). (C) Another example of dense granular deposit (gd) found in a small epineurial vessel, embedded in the basal lamina (bd) of a pericyte (P); scale bar = 0.2 \( \mu \text{m} \).
A patient with cerebral autosomal dominant arteriopathy with subcortical infarcts and leucoencephalopathy (CADASIL) confirmed by sural nerve biopsy.

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