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CASE REPORT

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Reversible coma with raised intracranial pressure: an unusual clinical manifestation of CADASIL

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Abstract A 50-year-old woman presented with recurrent episodes of headache, nausea and disturbed consciousness that were fully reversible within a few days. Clinical and radiological findings suggested raised intracranial pressure, which on one occasion was confirmed by intracranial pressure monitoring. Magnetic resonance imaging performed in the asymptomatic interval disclosed a diffuse leukoencephalopathy. Brain biopsy surprisingly revealed the typical vascular changes of CADASIL and subtle endothelial alterations. The white matter showed edematous changes and reactive gliosis. Mutational analysis of the *Notch3* gene revealed a previously unreported mutation. We suggest that a transient disturbance of the blood-brain barrier related to the underlying vascular pathology may have caused this unusual presentation of CADASIL.

Keywords CADASIL · Raised intracranial pressure · Electron microscopy · *Notch 3*

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Introduction

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is a microangiopathic condition, causing ischemic stroke and progressive cognitive deficits [15, 18]. Additional manifestations include migraine with aura, psychiatric disturbance, and epileptic seizures [5]. Mutations in *Notch 3* [9, 12] result in abnormal accumulation of the extracellular domain of the Notch 3 receptor in blood vessels, granular deposits within the vascular basal membrane and degeneration of vascular smooth muscle cells [11, 17]. Consistent with these changes recent studies have provided evidence for a disturbed vascular reactivity in CADASIL [4, 14]. In addition to the prominent alterations of vascular smooth muscle cells subtle morphological changes within the vascular endothelium have been described [16]. We report on a patient who presented with recurrent episodes of disturbed consciousness with documented raised intracranial pressure (ICP) on one occasion. Our findings raise the possibility of intermittent blood-brain barrier (BBB) dysfunction probably related to the underlying vasculopathy.

Case report

The 50-year-old normotensive woman had been admitted three times within 10 months, each time presenting with severe, bilateral, non-throbbing headache, nausea, somnolence and signs of raised ICP on CT. Preceding the first episode she had a urinary tract infection, which was treated with co-trimoxazole, whereas the second episode occurred following diarrhea. Preceding the last episode the patient had received a booster injection of a tetanus vaccination. The first injection had been given 2 weeks before without any side effects. On admission the patient was somnolent and there was a slight hemiparesis on the right. Blood pressure was within normal limits. There were no laboratory signs of sepsis, or metabolic disturbances that would have explained the clinical status. In particular, there was no electrolyte imbalance or hypoglycemia. Within the next few hours she developed coma and her right pupil became dilated and non-reactive to light. CT suggested generalized brain edema with raised ICP, which was verified by

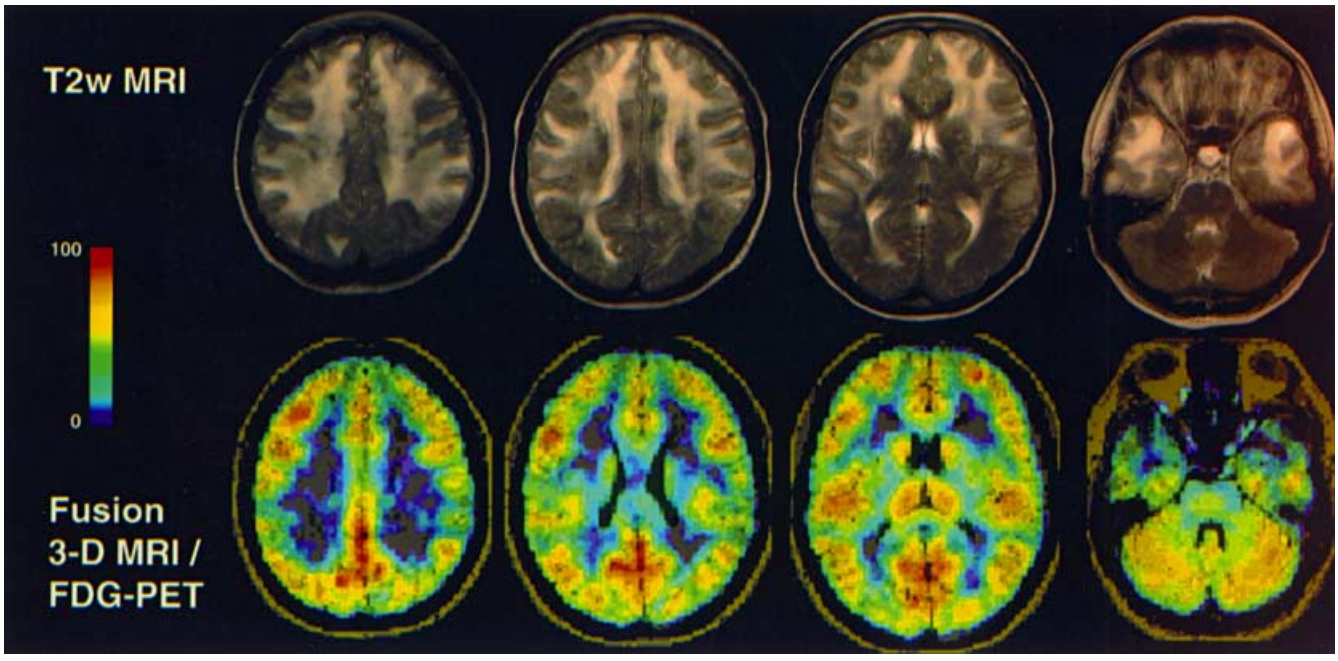

Fig. 1 T2-weighted MRI scans (*T2w MRI*) showing diffuse hyperintensities in the white matter of both hemispheres, and fusion MRI/FDG-PET revealing generalized hypometabolism in corresponding areas

ICP monitoring (p_{max}=80 cm H_2O). CSF was normal except for a slightly elevated cell count (9 cells/µl; 86% lymphocytes). EEG showed generalized slowing but no epileptic activity. Following osmotherapy with glycerol, hyperventilation and i.v. steroids, her clinical status rapidly improved and symptoms were completely reversible within 14 days. History revealed that she had repeatedly experienced strong bilateral headache without altered consciousness accompanying urinary tract infections in the past. There was no history of migraine, ischemic episodes, cognitive decline or other neurological manifestations.

Between episodes, neurological examination was normal. MRI consistently showed extensive bilateral white matter hyperintensities (T2-weighted images) without obvious lacunar infarcts or brain stem lesions (Fig. 1). Fusion MRI/FDG-PET revealed generalized hypometabolic areas in the white matter of both hemispheres (Fig. 1). Laboratory investigations including metabolic causes of leukoencephalopathy were unrevealing. CADASIL had been discussed as a possible diagnosis, but was rejected (1) because of the unusual clinical presentation and (2) because of the apparent mismatch between extensive white matter changes and the absence of lacunar infarcts. Because of the recurrent occurrence and dynamic nature of symptoms, it was finally decided to perform a brain biopsy to exclude diseases that might require targeted therapeutical intervention. After having discussed the risks and diagnostic possibilities of the procedure with the responsible physicians, the patient gave her informed consent for a stereotactic brain biopsy.

The preoperative CT scans showed diffuse hypodensity of the supratentorial white matter (Fig. 2A). Stereotactic brain biopsy was performed through a right frontal burr hole (Fig. 2B) in a localization in which pathologically altered tissue (see Fig. 1) could be obtained at a minimal risk for perioperative complications. The postoperative course was without complications. Since then, the patient has worked full-time in her profession.

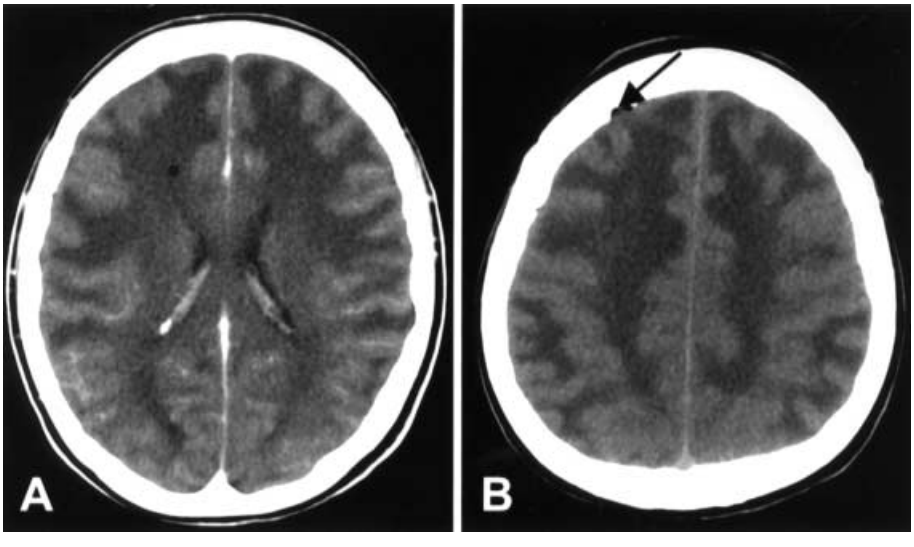

Fig. 2 **A** Preoperative CT scans showing diffuse bilateral hypodensity of white matter (*black circle* target point). **B** Postoperative CT with small air inclusion indicating the localization of burr hole for stereotactic biopsy (*arrow*)

Material and methods

Serial biopsies were taken over a distance of 30 mm between frontal cortical brain tissue adjacent to the burr hole (Fig. 2B) and the target point in an area of the white matter showing clear signal hyperintensities on T2-weighted preoperative MRIs. Two specimens were used for intraoperative smear preparations, seven specimens were fixed in 4% buffered formaldehyde and processed for light microscopy, and four were fixed in 2.5% buffered glutaraldehyde and embedded in Epon-Araldite for electron microscopy. Smear preparations were stained with methylene blue. The following stainings of 5-µm-thick sections were performed for light microscopy: hematoxylin and eosin, Klüver-Barrera, and periodic acid-Schiff reaction. Immunohistochemistry included stainings for glial fibrillary acidic protein (GFAP), CD45 and CD68. Semithin sections were stained with toluidine blue. Thin sections were stained with uranyl acetate and lead citrate.

Results

The intraoperative smear preparations showed moderately vacuolated brain tissue with pale appearance of the neuropil, and reactive astrocytes. Investigation of paraffin-embedded material confirmed reactive gliosis (Fig. 3A), and pallor of the white matter in myelin stainings. Semithin sections showed less closely packed myelin sheets than in normal brain tissue and widened perivascular spaces (Fig. 3B). Furthermore, semithin sections surprisingly revealed moderate thickening of vessel walls and small, dark-blue-stained granular material in close contact to the tunica media (Fig. 3B). Active demyelination by macrophages and leukocyte infiltration was excluded by immunohistochemical stainings for CD68 and CD45.

Electron microscopy showed increased extracellular volume with some widely separated, frequently hypomyelinated axons, reactive astrocytes, and rarely axonal degeneration in the white matter (Fig. 3C). In the walls of small arteries within the white and the gray matter, abundant electron-dense, granular deposits in variably sized microvessels, located close to the vascular smooth muscle cells, were seen (Fig. 4A, B), as previously described in CADASIL patients (granular osmiophilic material, GOM). The vessel walls were slightly thickened, and the number

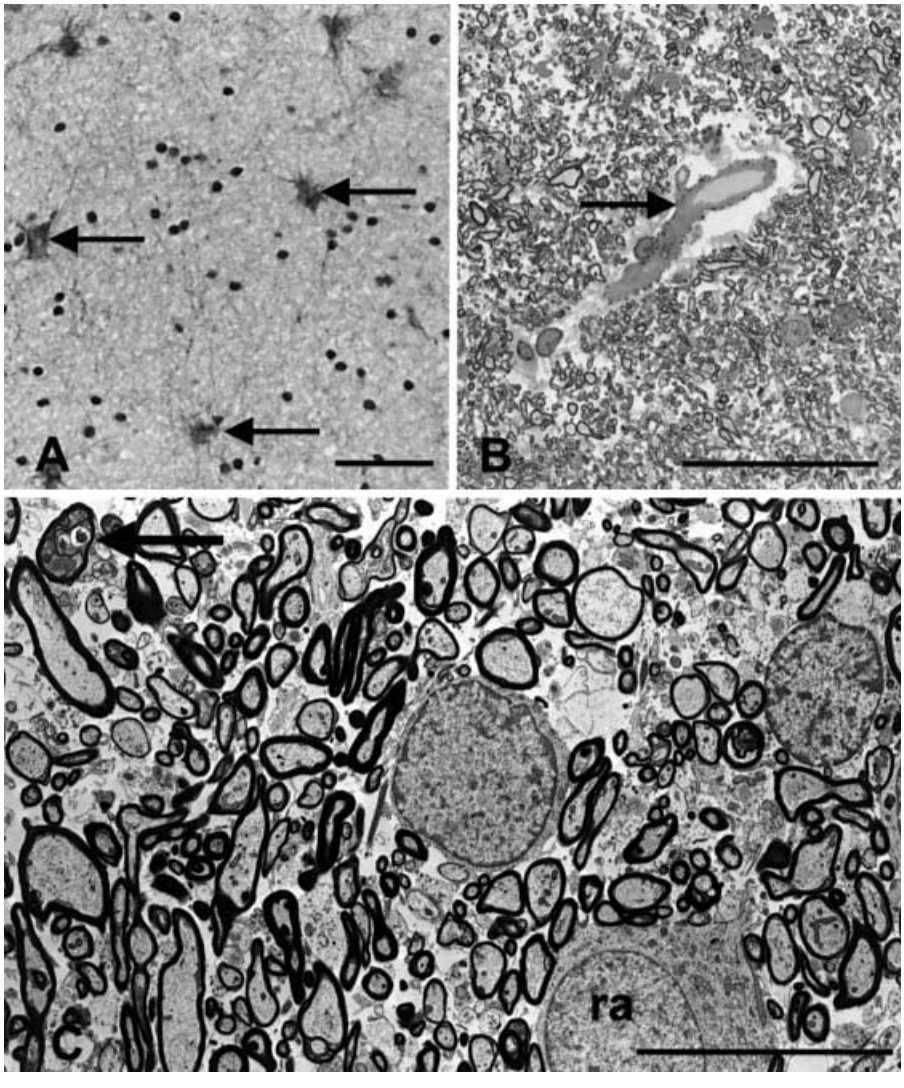

Fig. 3 **A** White matter showing reactive astrocytes (*arrows*) with enlarged cytoplasm and numerous fibrillary processes; immunostaining for glial fibrillary acidic protein. **B** Semithin sections revealing edematous changes, increase of cellularity, and granular material (*arrow*) within the vessel walls. **C** Electron microscopy showing diffuse hypomyelination, increased extracellular volume, reactive astrocytes (*ra*), and occasionally degenerating axons (*arrow*). *Bars* **A**, **B** 60 µm; **C** 15 µm

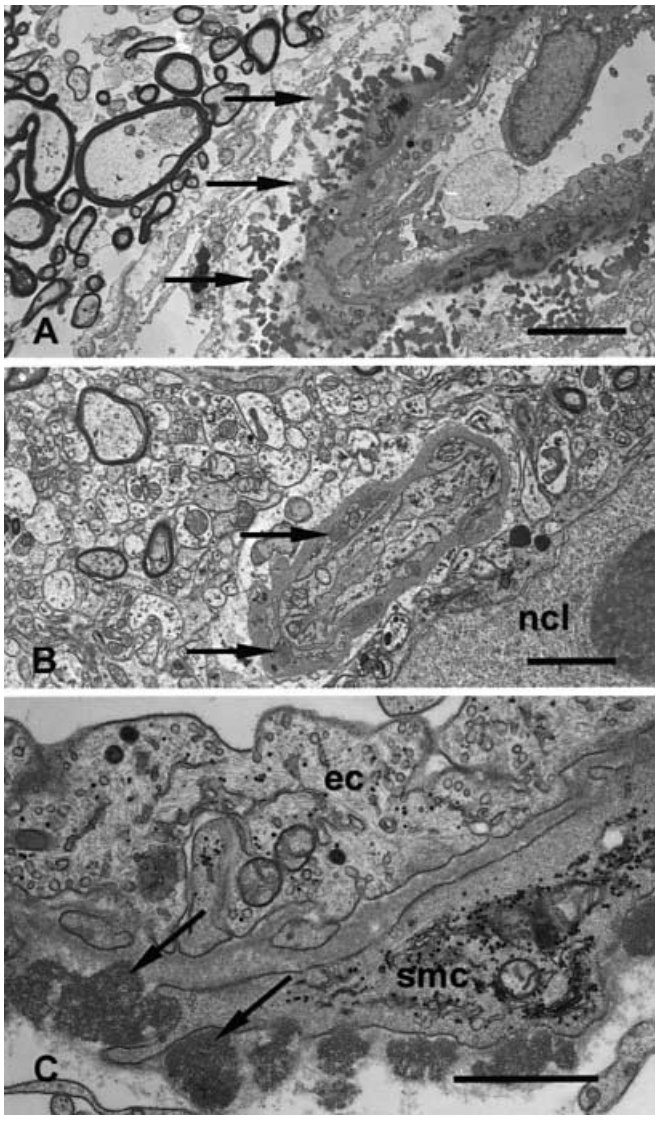

Fig. 4 **A** GOM (*arrows*) in a small artery of the white matter. Note rarefaction of vascular smooth muscle cells. **B** Small blood vessel with GOM (*arrows*) close to a vital neuron in the gray matter (*ncl* nucleus). **C** Endothelial cells (*ec*) showing increase of cytoplasmic filamentous structures. GOM (*arrows*) was found in close relation to vascular smooth muscle cells (*smc*) (*GOM* Granular osmiophilic material). *Bars* **A** 5 μm; **B** 2 μm; **C** 1 μm

of smooth muscle cells was decreased as compared with normal intracerebral small arteries. The endothelial cells were characterized by a flattened shape, electron-dense cytoplasm, and increased amounts of intracellular microfilaments (Fig. 4C). The ultrastructural appearance of cell-cell contacts was not obviously altered compared to normal intracerebral vessels. After the diagnosis of CADASIL had been made by electron microscopy, a mutational analysis of the *Notch3* gene was performed, which revealed a previously unreported mutation (C134W) within exon 4.

Discussion

Three aspects of this case are unusual when compared with previously reported CADASIL cases: (1) the clinical phenotype with recurrent episodes of impaired consciousness progressing to coma on one occasion and complete reversibility of symptoms, (2) raised ICP in the acute episode as documented by the clinical findings and direct intracranial measurement, and (3) the opportunity to directly correlate brain biopsy tissue obtained in the asymptomatic interval with neuroimaging findings.

Impaired consciousness and coma have previously been described as a rare complication of CADASIL in gene carriers with a history of migraine [2]. In the present case there was no history of migraine and the character of the headache present during each episode was different from migraine headache. Also, EEG and MRI provided no evidence for (non-convulsive) seizures or ischemia – both possible causes for impaired consciousness in CADASIL. Four aspects support the hypothesis that the clinical symptoms in this patient were due to raised ICP: (1) the symptoms, in particular unilateral pupillary dilation were those of raised ICP; (2) neuroimaging was consistent with generalized edema; (3) ICP was measured and documented to be high on one occasion, and (4) symptoms quickly resolved following specific therapy.

The findings in this patient suggest a temporary dysfunction of the BBB, which is strongly dependent on an intact vascular endothelium but also on other factors including the integrity of astrocytes that surround blood vessels [8]. Endothelial cells from CADASIL patients may show subtle ultrastructural alterations [15, 16]. Such changes were also observed in endothelial cells of the present case; however, there were no additional morphological abnormalities different from reported cases with more typical clinical presentation. The biopsy was performed during the asymptomatic interval, and therefore the results might not reflect the situation during the symptomatic episodes. However, it seems possible that the subtle endothelial alterations in conjunction with glial changes in CADASIL render the endothelium susceptible to external stimuli influencing BBB permeability in this patient.

In the present case there was no evidence for a metabolic disturbance, sepsis or other conditions that would have explained raised ICP. However, there was a striking coincidence between minor infections or a booster vaccination and the onset of symptoms. It remains hypothetical whether these immunological reactions had any causal connection with the symptomatic episodes. However, we consider it as a noteworthy detail in the patients history, indicating that the individual clinical manifestation could be determined by the combination of extrinsic factors and CADASIL-specific morphological changes.

Histological and ultrastructural examination of white matter that had appeared hyperintense on T2-weighted images showed moderate changes consistent with edema, reactive gliosis, diffuse hypomyelination, and rarely axonal degeneration. These changes reflect the situation at the

time of biopsy after three symptomatic episodes, probably associated with raised ICP, and thus it is difficult to differentiate between secondary reactive changes due to these acute events and the morphological correlates of CADASIL-associated leukoencephalopathy. However, the presented results are consistent with recent neuroimaging data that have provided indirect evidence for gliosis, edema, and diffuse hypomyelination as the morphological substrate underlying T2-white matter hyperintensities in CADASIL using modified MRI protocols [1, 3, 7].

The *Notch3* mutation found in this patient has not been reported before. However, we are cautious about attributing the particular phenotype in this patient to this specific mutation, given that the mutation is fully within the expected spectrum of mutations, i.e., a missense mutation leading to an odd number of cysteine residues within the respective EGF-repeat domain [6, 10].

In the present case CADASIL had initially been discussed as a possible diagnosis, but was considered unlikely because of the unusual clinical phenotype and the contrast between extensive white matter changes in the MRI scans and the lack of evidence for lacunar infarcts. Since the disease can be diagnosed by less invasive means [13, 19], clinicians should be aware of the broad phenotypic spectrum of CADASIL, which may include unusual clinical presentations.

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