European Journal of Neurology 2006, 13: 363–370

# Correlation of cognitive status, MRI- and SPECT-imaging in CADASIL patients

R. Scheid[a,b], C. Preul[b], T. Lincke[c], G. Matthes[a], M. L. Schroeter[a,b], T. Guthke[a], D. Yves von Cramon[a,b] and O. Sabri[c]

[a]*Day Clinic of Cognitive Neurology, University of Leipzig, Germany;* [b]*Max Planck Institute for Human Cognitive and Brain Sciences, Leipzig, Germany; and* [c]*Department of Nuclear Medicine, University of Leipzig, Germany*

**Keywords:**
CADASIL, cognition, magnetic resonance imaging, risk factors, sensorineural hearing loss, SPECT

Received 23 February 2005
Accepted 7 April 2005

Although there is evidence for correlations between disability and magnetic resonance imaging (MRI) total lesion volume in autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), the significance of structural MRI abnormalities for cognitive dysfunction remains controversial. We performed detailed neuropsychological testing, high resolution MRI, and Tc-99m-ethyl cysteinate-dimer SPECT in three CADASIL patients. MR-images were rated independently by two investigators for the presence of white matter lesions, lacunar infarcts, microbleeds, and ventricular enlargement. Cortical atrophy was quantified by the use of automatic morphometric assessment of the cortical thickness. In addition, laboratory and patients' history data were collected in order to assess the individual vascular risk factor profile. The differences in cognitive performance between the three patients are neither explained by structural-, or functional neuroimaging, nor by the patient-specific vascular risk factor profiles. The neuroradiologically least affected patient met criteria for dementia, whereas the most severely affected patient was in the best clinical and cognitive state. Conventional structural and functional neuroimaging is important for the diagnosis of CADASIL, but it is no sufficient surrogate marker for the associated cognitive decline. Detailed neuropsychological assessment seems to be more useful, particularly with respect to the implementation of reliable outcome parameters in possible therapeutic trials.

## Introduction

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is an inherited vasculopathy of small arteries and arterioles of the brain and other organs. The disorder is caused by a mutation in the transmembrane receptor product of the Notch3 gene at chromosome 19 [1,2]. In the third decade, almost all gene carriers show pathologic findings on magnetic resonance imaging (MRI). Different from other types of cerebral small vessel disease (CSVD) [3] white matter lesions (WMLs) often affect the temporopolar white matter and the subcortical temporopolar and superior frontal U-fiber-system [4,5].

The specific relationships between MRI abnormalities and cognitive state are neither clear in CADASIL nor in CSVD in general [6–9]. Several recent studies reported correlations between MRI- and clinical findings in CADASIL, both for conventional [10,11] and advanced imaging techniques [12,13]. However, the results remain controversial [14,15] and correlations seem to be weak at best. It furthermore has been speculated that in the absence of strong genotype–phenotype relationships [16,17] the specific phenotype in CADASIL patients might be influenced by gene–environment interactions, and in particular by conventional cardiovascular risk factors [18,19].

We investigated a kindred of three newly diagnosed CADASIL patients with a variety of neuropsychological, neuroimaging, and laboratory tools, which is not easily feasible in large patient populations. The aim of our study was to further evaluate the potential of both neuroimaging and laboratory data to serve as surrogate markers, focusing on cognitive state.

## Patient descriptions

*Patient 1* is a 41-year-old right-handed male with a history of recurring TIAs (pure sensory, pure motor, sensory-motor) since 1995. There is no history of

Correspondence: Dr Rainer Scheid, Day Clinic of Cognitive Neurology, University of Leipzig, Liebigstr. 22a, 04103 Leipzig, Germany (tel.: +49 341 9724980; fax: +49 341 9724989; e-mail: scheid@cbs.mpg.de).

migraine, but the patient has suffered from bilateral sensorineural hearing loss since childhood. Since the middle of 1999 progressive memory loss and behavioral changes have been reported. Eventually, after a first epileptic seizure in February 2001 the patient was continuously unfit for work. Neurological examinations in April 2001 and November 2003 showed a slight right hemiparesis and a mild dysarthria. Extracranial/transcranial Doppler/Duplex-ultrasound (CCS/TCCS) and echocardiography were normal. Twenty-four-hour blood pressure-monitoring results were unremarkable. Genetic testing (Professor E. Tournier Lasserve, Hopital Lariboisiere, Paris, France) revealed a Notch3 mutation (C622T) in exon 4, leading to the amino acid change R182C.

*Patient II*, the mother of patient I, is a 65-year-old right-handed woman who also has a history of bilateral sensorineural hearing loss. In June 1993 she suffered the first stroke with a right-sided hemiparesis, which resolved completely. In October 1997 the patient developed a subacute right-sided hemiparesis. Anticoagulation with phenprocoumon was started. Neurological examinations in January and November 2003 showed only a mild right hemiparesis. The patient was independent in all activities of daily living. CCS/TCCS, echocardiography, and 24-h blood pressure monitoring results were unremarkable. Genetic testing revealed the same Notch3 mutation as in patient I.

*Patient III* is a 53-year-old right-handed man, and is a great-cousin of patient I. The patient has a history of progressive bilateral senorineural hearing loss of childhood onset, too. In addition, the patient was under medical supervision for mild arterial hypertension and hypercholesterolemia, which was treated with simvastatin. In August 2004 there was a first transient monoparesis of the left lower limb. Antiplatelet agents (dipyridamole, aspirin) and enalapril were prescribed. Neurological examination in November 2004 was normal. The patient was independent in all activities of daily living, and he was able to do his job as electrical engineer. CCS/TCCS and echocardiography findings were normal. Twenty-four-hour blood pressure monitoring showed marginally elevated diastolic blood pressures. Genetic testing revealed the same Notch3 mutation as in the two other patients.

## Methods

### MRI

Magnetic resonance imaging was performed on a 3Tesla whole body system (Medspec 3T/100; Bruker, Ettlingen, Germany, or Magnetom TRIO; Siemens, Erlangen, Germany). The imaging protocol consisted of four scans of the same geometry (20 slices, axial and coronal planes, slice thickness 2 mm, slice gap 2.5 mm): (i) 2D T1-weighted reduced power multislice modified driven equilibrium Fourier transform (MDEFT)-images [20]. (ii) 2D T2-weighted fast spin-echo (FSE) scans. (iii) 3D T1-weighted MDEFT-images. (iv) 2D T2*-weighted gradient echo images.

Because of the lack of commonly agreed concepts regarding the use of MRI rating scales of WMLs and CSVD [21] a recently proposed rating scale, which is an extension of the scale of van Swieten [22] was used for grading of the MRI lesions [23]. Extent and site of diffuse WMLs were assessed separately, the semiquantitative rating scale ranging from absent = 0, to severe = 3. In addition, all sharply demarcated lesions isointense to CSF on the T1- and T2-weighted images suggesting lacunar infarcts (LIs) were registered on each slice according to their anatomical location. The total number and site of LIs was calculated separately for the three patients. The same procedure was performed for circumscribed hypointense lesions on the T2*-images, representing cerebral microbleeds (MBs) [24,25]. All MR-images were evaluated independently by two neuroradiologically experienced readers (RS, CP), and the coefficient of agreement ($\kappa$) was calculated [26]. The width of the third ventricle was used to estimate major inner brain atrophy. An automated segmentation algorithm for the assessment of the cortical thickness was applied to quantify overall cortical atrophy [27].

### SPECT

Patients were injected i.v. with 600 MBq Tc-99m-ethyl cysteinate-dimer (ECD) under standard resting conditions. SPECT acquisition with a brain dedicated gamma camera (Ceraspect, DSI, Waltham, MA, USA) was started 30 min post-injection. Photons were registered in a $128 \times 128 \times 64$ matrix during 30 min. Datasets were reconstructed by filtered backprojection. SPECT study analysis was performed with the software BRASS (Nuclear Diagnostics, Stockholm, Sweden). Ratios of mean count rates in pre-defined three-dimensional volumes of interest (VOIs) to mean cerebellar counts were calculated for 16 brain regions covering major cortical and subcortical gray matter structures. Because visual analysis did not reveal significant asymmetries or bilateral reductions of cerebellar tracer uptake, the application of the cerebellum as reference region was considered reasonable. Furthermore individual patient SPECT studies were automatically compared to a mean count template of non-pathological Tc-99m-ECD SPECT scans of 23 adults (14 females, 9 males, mean age 47 $\pm$ 16 years).

### Neuropsychological evaluation

A comprehensive battery of neuropsychological tests was administered in order to assess verbal intelligence, attention, declarative memory and learning, as well as executive functions.

### Vascular risk factor profile

Data from patient's histories and laboratory tests were collected to establish the vascular risk factor profile of the patients.

**Table 1** Mean rating scores of severity and localization of diffuse white matter lesions (DWMLs), mean numbers and specific site of lacunar infarcts (LIs), and mean numbers and site of microbleeds (MBs), as was assessed separately by two investigators

| | Patient I | Patient II | Patient III |
|---|---|---|---|
| DWMLs | | | |
| fl | 3 | 3 | 3 |
| pl | 3 | 3 | 3 |
| tl | 1.5 | 2.5 | 2.5 |
| ol | 2 | 2 | 2 |
| pv | 1.5 | 2.5 | 3 |
| Mean | 2.4 | 2.6 | 2.7 |
| Lacunes | | | |
| pv | 1 | 0 | 4 |
| ci | 0 | 1 | 2 |
| cr | 2 | 0.5 | 2 |
| bg | 2 | 1 | 4.5 |
| th | 0 | 1 | 2.5 |
| bs | 2 | 0 | 3 |
| scwm | 0 | 0.5 | 1.5 |
| dwm | 0.5 | 3.5 | 3 |
| Other | 0 | 0.5 | 1 |
| Total | 7.5 | 8 | 23.5 |
| MBs | | | |
| fl | 0 | 0.5 | 0 |
| pl | 0 | 3 | 0 |
| tl | 1 | 1 | 1.5 |
| ol | 0 | 0.5 | 1 |
| cb | 0 | 3 | 3 |
| th | 0 | 0 | 4 |
| bg | 0 | 0 | 2 |
| pv | 0 | 0 | 1 |
| dwm | 0 | 0 | 0 |
| bs | 0 | 1 | 1 |
| Other | 0 | 0 | 0 |
| Total | 1 | 9 | 13.5 |
| Third ventricle (mm) | 8 | 8 | 8 |

DWMLs according to a simple 3-point scale (1 = mild, 2 = moderate, 3 = severe). Width of the third ventricle (mm) as a parameter for overall inner brain atrophy.

bg, basal ganglia; bs, brain stem; cb, cerebellum; ci, capsula interna; cr, corona radiata; dwm, deep white matter; fl, frontal lobe; ol, occipital lobe; pl, parietal lobe; pv, perinventricular white matter; scwm, subcortical white matter; tl, temporal lobe; th, thalamus.

## Results

### MRI

Table 1 summarizes the results of the MRI rating procedure. Agreement in rating was good ($\kappa = 0.6$). All three patients reached a maximum grade of CSVD. All major lobes and both hemispheres were affected, with preference of the frontal and parietal lobes, and the deep white matter. LIs were detected with nearly the same frequency in patients I and II (7.5 vs. 8) but their number was substantially increased in patient III (23.5). T2* GE-imaging revealed MBs in the subcortical white matter in all three patients. However, in patient I only a single MB was detected, whereas 9 MBs were present in patient II, and 13.5 in patient III. Infarcts suggesting large vessel disease or embolism were absent in all patients. The width of the third ventricle was identical in the three patients and was within normal limits. Overall cortical thickness (patient I: 3.28 mm left hemisphere, 3.27 mm right hemisphere; patient II: 3.3 mm left hemisphere, 3.5 mm right hemisphere; patient III 3.09 mm left hemisphere, 3.08 mm right hemisphere) did not differ from values obtained in 27 healthy individuals of different age groups [28].

**Table 2** Summary of the applied neuropsychological tests and patient's performance

| Neuropsychological tests | Patient I | Patient II | Patient III |
|---|---|---|---|
| Years of education | 10 | 8 | 10 |
| MWT-B (IQ) | 93 | 95 | 112 |
| TAP-alertness/median (PR) | 1 | 5 | 93 |
| TAP-alertness/SD (PR) | 1 | 16 | 58 |
| Stroop/interference (PR) | < 1 | 16 | 30 |
| WMS-R: digit span forward/backward | 4.5/4 | 4.5/3.5 | 7.5/4.5 |
| Digit ordering test | 3.5 | 5.5 | 6 |
| WMS-R: memory quotient (index) | 83 | 81 | 81 |
| Verbal memory (index) | 92 | 70 | 82 |
| Visual memory (index) | 74 | 103 | 88 |
| Attention/concentration (index) | 62 | 80 | 103 |
| Delayed recall (index) | 51 | 107 | 99 |
| BADS (age corrected standard score) | 81 | 74 | 98 |
| MCST/categories | 4 | 4 | 5 |
| MCST/perseverative errors | 18/11 | 11/2 | 13/2 |

BADS, behavioural assessment of the dysexecutive syndrome; MCST, modified card sorting test; MWT-B, Mehrfachwahlworts-chatztest; PR, percentile; SD, standard deviation; TAP, Testbatterie zur Aufmerksamkeitsprüfung; WMS-R, Wechsler Memory Scale-revised.

### SPECT

All three patients showed a reduced regional cerebral blood flow (rCBF) in the cingulate cortex. Patient I showed decreased rCBF particularly in the temporal cortices of both hemispheres, whereas in patient II additional defects were found in the thalamic and fronto-parietal cortices. Patient III showed the most marked rCBF-reduction of all patients, and in particular the subcortical gray matter and the parietal cortices were affected.

### Neuropsychological testing

Table 2 summarizes the test performance of the patients. Premorbid intelligence was average in the three patients. Simple (visual) reaction times [29] were normal in patient III, and only mildly impaired in patient II, whereas patient I showed a severe slowing of information processing and a large variability of responses. In a Stroop-Task [30], interference was high only in patient I. Capacity of short-term memory was reduced in patients I and II. The memory quotient [31] was slightly reduced in all patients, but only patient I showed fast forgetting. Age-corrected standard scores of the 'Behavioural assessment of the dysexecutive syndrome' (BADS) [32] were borderline in patients I and II, and normal in patient III. In a modified cardsorting test [33] patient I made many perseverative errors.

### Laboratory tests, vascular risk factors

Patients I and III had hypercholesterolemia and homocysteinemia. Patient I was obese (BMI 33 kg/m$^2$) and

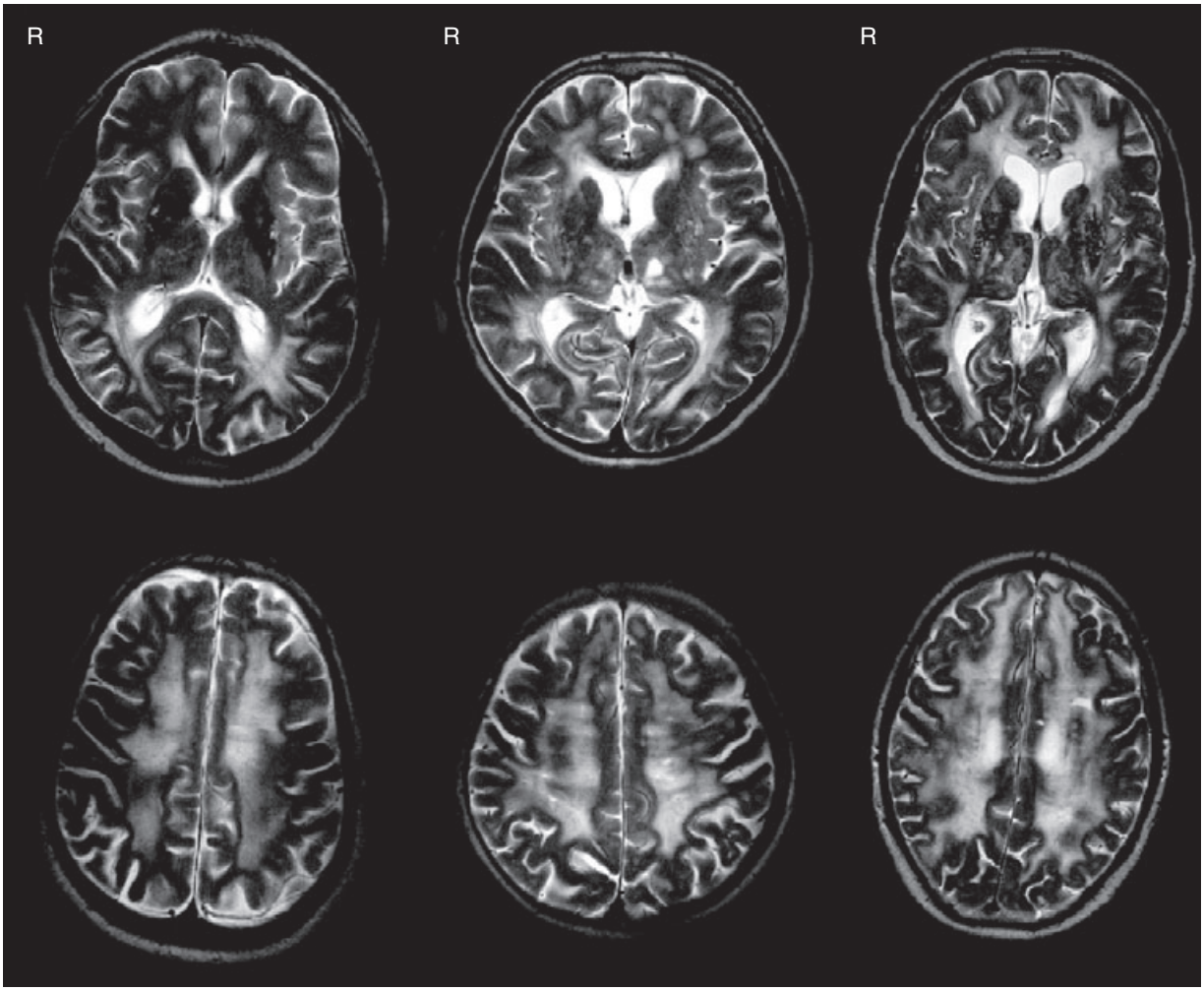


**Figure 1** Comparison of T2-weighted MR-images of patient I (left), patient II (middle), and patient III (right). Upper row: axial images at the level of the basal ganglia. Lower row: axial images at the level of the centrum semiovale. Confluent white matter lesions (WMLs) as well as lacunar infarcts are most pronounced in patient III. Note the marked involvement of the frontal white matter and the extension of the WMLs into the subcortical U-fibers in this patient.

had a history of tobacco abuse (20 pack years). Patient II was heterozygous for the factor V-Leiden mutation. Patient III had a history of arterial hypertension and hyperfibrinogenemia.

## Discussion

The main result of our study is a relative mismatch between neuroimaging findings and cognitive state. MRI depicted severe abnormalities in all three patients (Fig. 1). However, as was documented by the evaluation process of the MR-images by two independent readers, semiquantitative measurements of specific features (DWMLs, LIs, MBs) revealed substantial differences. The best cognitive performance was documented in the structurally most severely affected individual, and vice versa. Age differences are not responsible for this discrepancy. These should influence cognition in the

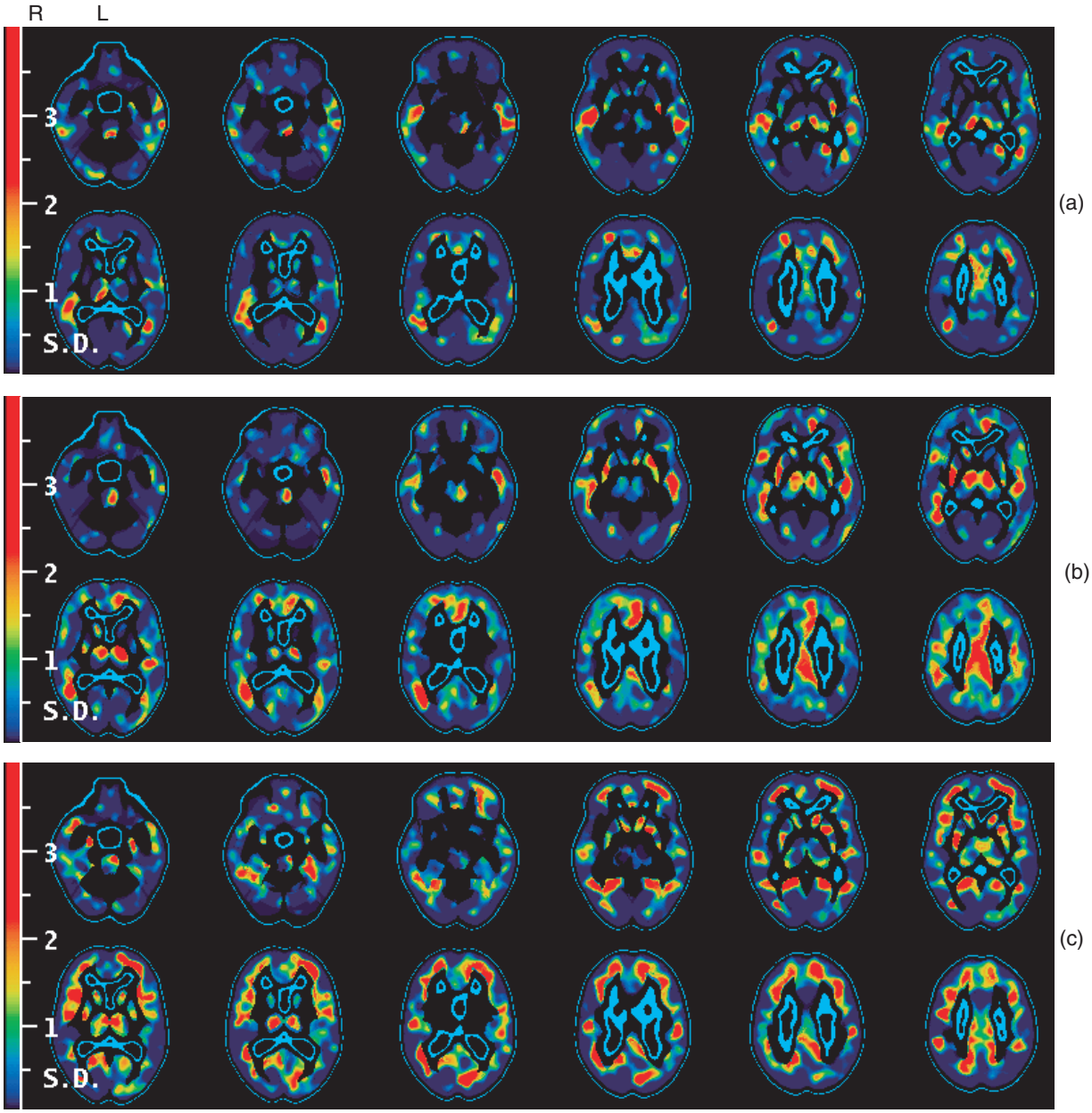


**Figure 2** Parametric images of rCBF-SPECT studies of patient I (a), II (b) and III (c). Axial slices show regional cerebral blood flow (rCBF)-reduction as pixelwise colorcoded *z*-scores (number of standard deviations from mean) resulting from an automated comparison of the individual SPECT studies with a normal template (software BRASS). Areas of significantly reduced rCBF are colored in red.

same direction, and not the other way round, as is the case in our patients, in whom the youngest fulfilled DSM-IV criteria of dementia [34].

Knowing about the limitations of studies with single subjects or small samples [35], our results qualify the results of several previously published studies concerning the correlation of MRI- and clinical findings in CADASIL [10,11,36]. The discrepancies may partly be explained by the insufficient sensitivity of the instruments used for the assessment of function. Scores like the Rankin scale [37], the EDSS score [38], or the Barthel Index [39] are determined mainly by motor functioning and are fairly rough. E.g. all three of our patients reached a score of 100 in the Barthel index and a score of 1 in the Rankin scale. The same applies to instruments for the evaluation of cognitive functioning like the MMSE or SIDAM [40,41]. A further explanation results from the limited validity of current MRI-morphometry [42].

Measurements of ventricular enlargement, as well as regional and overall cortical thickness were not helpful in our study. The latter finding may indicate that cortical hypometabolism could indeed be caused by remote effects because of functional disruption of subcortical fibers in CADASIL, and may not be a result of cortical atrophy itself [43]. However, in our patients, rCBF determined by SPECT did not correlate with cognitive performance, either. Patient III showed the most severe rCBF-reduction in 16/16 examined VOIs (Fig. 2). Nuclear medicine techniques have not often been used in the evaluation of CADASIL, and findings concerning the relationship between CBF and WMLs are inconsistent [43–47]. Our observations support the assumption of a positive correlation, but likewise indicate that neither CBF-measurement nor structural MRI are sufficient functional surrogate markers. In particular, our observations are contrary to the results of a previous study by one of the authors on subjects with CSVD [7]. Differences between the etiopathogenetic mechanisms underlying the cognitive decline in CADASIL and unspecified CSVD could therefore be hypothesized. However, further studies with more patients are necessary on that score.

It seems probably that CADASIL primarily restricts cognition [14,48–50]. As long as there are no imaging procedures, which are more sensitive for subtle functional impairments, detailed neuropsychological testing may be the best instrument for the assessment of disease severity and progression. This is particularly important in early stages and for the evaluation of potential preventive therapies in CADASIL. However, as recent studies suggest that the measurement of water diffusion over time could be a useful marker for the progression of tissue damage, the role of diffusion tensor imaging needs to be examined further in this respect [12,13].

The vascular risk factor profiles of our patients are heterogeneous and specific interrelations regarding cognition are not to be assumed. Noteworthy, the clinically most affected patient was the only one with a history of smoking. Smoking has been reported to be correlated with onset of stroke/transient ischemic attack [19]. It therefore could be speculated that tobacco abuse might have a particular negative pharmacodynamic effect in CADASIL.

An additional interesting, but with respect to the aim of our study not further considered finding is the sensorineural hearing loss of which all three patients were suffering from. Hearing loss has repeatedly been reported in CADASIL patients [16,51–53]. However, there is no information about its etiology and significance. Further studies are therefore needed to clarify if neurosensory hearing loss might not only be associated but might be caused by CADASIL, and if it could be an early clinical marker of the disease.

## Acknowledgement

We thank patient II for participation.

## References

1. Tournier-Lasserve E, Joutel A, Melki J *et al.*, Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy maps to chromosome 19q12. *Nature Genetics* 1993; **3:** 256–259.
2. Joutel A, Corpechot C, Ducros A *et al.*, Notch3 mutations in CADASIL, a hereditary adult-onset condition causing stroke and dementia. *Nature* 1996; **383:** 707–710.
3. Pantoni L, Garcia JH. Pathogenesis of leukoaraiosis: a review. *Stroke* 1997; **28:** 652–659.
4. Auer DP, Putz B, Gossl C, Ebel G, Gasser T, Dichgans M. Differential lesion patterns in CADASIL and sporadic arteriosclerotic encephalopathy: MR imaging study with statistical parametric group comparison. *Radiology* 2001; **218:** 443–451.
5. O'Sullivan M, Jarosz JM, Martin RJ, Deasy N, Powell JF, Markus HS. MRI hyperintensities of the temporal lobe and external capsule in patients with CADASIL. *Neurology* 2001; **56:** 628–634.
6. Román GC. From UBOs to Binswanger's disease: impact of magnetic resonance imaging on vascular dementia research. *Stroke* 1996; **27:** 1269–1273.
7. Sabri O, Ringelstein EB, Hellwig D *et al.*, Neuropsychological impairment correlates with hypoperfusion and hypometabolism but not with severity of white matter lesions on MRI in patients with cerebral microangiopathy. *Stroke* 1999; **30:** 556–566.
8. de Groot JC, de Leeuw FE, Oudkerk M *et al.*, Cerebral white matter lesions and cognitive function: The Rotterdam Scan Study. *Annals of Neurology* 2000; **47:** 145–151.
9. Smith CD, Snowdon DA, Wang H, Markesbery WR. White matter volumes and periventricular white matter

hyperintensities in aging and dementia. *Neurology* 2000; **54:** 838–842.
10. Dichgans M, Filippi M, Brüning R *et al*., Quantitative MRI in CADASIL. Correlation with disability and cognitive performance. *Neurology* 1999; **52:** 1361–1367.
11. Yousry TA, Seelos K, Mayer M *et al*., Characteristic MR lesion pattern and correlation of T1 and T2 lesion volume with neurologic and neuropsychological findings in cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL). *American Journal of Neuroradiology* 1999; **20:** 91–100.
12. Molko N, Pappata S, Mangin JF *et al*., Monitoring disease progression in CADASIL with diffusion magnetic resonance imaging: a study with whole brain histogram analysis. *Stroke* 2002; **33:** 2902–2908.
13. O'Sullivan M, Singhal S, Charlton R, Markus HS. Diffusion tensor imaging of thalamus correlates with cognition in CADASIL without dementia. *Neurology* 2004; **62:** 702–707.
14. Taillia H, Chabriat H, Kurtz A *et al*., Cognitive alterations in non-demented CADASIL patients. *Cerebrovascular Diseases* 1998; **8:** 97–101.
15. Trojano L, Ragno M, Manca A, Caruso G. A kindred affected by cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL). A 2-year neuropsychological follow-up. *Journal of Neurology* 1998; **245:** 217–222.
16. Dichgans M, Mayer M, Uttner I *et al*., The phenotypic spectrum of CADASIL: clinical findings in 102 cases. *Annals of Neurology* 1998; **44:** 731–739.
17. Opherk C, Peters N, Herzog J, Luedtke R, Dichgans M. Long-term prognosis and causes of death in CADASIL: a retrospective study in 411 patients. *Brain* 2004; **127:** 2533–2539.
18. Pantoni L, Sarti C, Pescini F *et al*., Thrombophilic risk factors and unusual clinical features in three Italian CADASIL patients. *European Journal of Neurology* 2004; **11:** 782–787.
19. Singhal S, Bevan S, Barrick T, Rich P, Markus HS. The influence of genetic and cardiovascular risk factors on the CADASIL phenotype. *Brain* 2004; **127:** 2031–2038.
20. Norris DG. Reduced power multislice MDEFT imaging. *Journal of Magnetic Resonance Imaging* 2000; **11:** 445–451.
21. Fazekas F, Barkhof F, Wahlund LO *et al*., CT and MRI rating of white matter lesions. *Cerebrovascular Diseases* 2002; **13**(suppl. 2)**:**31–36.
22. van Swieten JC, Hijdra A, Koudstaal PF, van Gijn J. Grading white matter lesions on CT and MRI: a simple scale. *Journal of Neurology, Neurosurgery and Psychiatry* 1990; **53:** 1080–1083.
23. Hund-Georgiadis M, Ballaschke O, Scheid R, Norris DG, von Cramon DY. Characterization of cerebral microangiopathy using 3 Tesla MRI: correlation with neurological impairment and vascular risk factors. *Journal of Magnetic Resonance Imaging* 2002; **15:** 1–7.
24. Fazekas F, Kleinert R, Roob G *et al*., Histopathologic analysis of foci of signal loss on gradient-echo T2*-weighted MR images in patients with spontaneous intracerebral hemorrhage: evidence of microangiopathy-related microbleeds. *American Journal of Neuroradiology* 1999; **20:** 637–642.
25. Dichgans M, Holtmannspötter M, Herzog J, Peters N, Bergmann M, Yousry TA. Cerebral microbleeds in CADASIL. A gradient-echo magnetic resonance imaging study. *Stroke* 2002; **33:** 67–71.
26. Cohen J. A coefficient of agreement for nominal scales. *Educational and Psychological Measurement* 1960; **XX:** 37–46.
27. Lohmann G, Preul C, Hund-Georgiadis M. Morphology-based cortical thickness estimation. *Information Processing in Medical Imaging* 2003; **18:** 89–100.
28. Preul C, Lohmann G, Hund-Georgiadis M, Guthke T, von Cramon DY. Morphometry demonstrates loss of cortical thickness in cerebral microangiopathy. *Journal of Neurology. Stroke* 2005; **252:** 441–447.
29. Zimmermann P, Fimm B. *Testbatterie zur Aufmerksamkeitsprüfung (TAP)*. Psytest, Herzogenrath, 1994.
30. Wolfram H, Neumann J, Wieczorek V. *Psychologische Leistungstests in der Neurologie und Psychiatrie. Methoden und Normwerte*. Thieme, Leipzig, 1986.
31. Härting C, Markowitsch HJ, Neufeld H, Calabrese P, Deisinger K, Kessler J (eds) (*WMS-R. Deutsche Adaptation der revidierten Fassung der Wechsler Memory Scale*. Verlag Hans Huber, Bern Göttingen Toronto Seattle, 2000.
32. Wilson BA, Alderman N, Burgess PW, Emslie H, Evans J. *Behavioural Assessment of the Dysexecutive Syndrome*. Thames Valley Test Company, Bury St. Edmunds, 1996.
33. Drühe-Wienholt CM. Der veränderte Wisconsin Kartensortiertest und seine Relevanz für neuropsychologische Diagnostik und Therapie. *Deutsche Hochschulschriften*, 2322. Hänsel-Hohenhausen, Egelsbach, 1996.
34. American Psychiatric Association (*Diagnostic and Statistical Manual of Mental Disorders*, 4th edn. American Psychiatric Association, Washington, DC, USA, 1994.
35. Robey RR, Schultz MC, Crawford AB, Sinner CA. Single-subject clinical-outcome research: designs, data, effect sizes, and analyses. *Aphasiology* 1999; **13:** 445–473.
36. Desmond DW, Moroney JT, Lynch T *et al*., CADASIL in a North American family. Clinical, pathologic, and radiologic findings. *Neurology* 1998; **51:** 844–849. Comment in: Neurology 1999; 52:1518–1519.
37. van Swieten JC, Koudstaal PJ, Viser MC, Schouten HJA, van Gijn J. Interobserver agreement for the assessment of handicap in stroke patients. *Stroke* 1988; **19:** 604–607.
38. Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). *Neurology* 1983; **33:** 1444–1452.
39. Mahoney FI, Barthel DW. Functional evaluation: the Barthel index. *Maryland State Medical Journal* 1965; **14:** 61–65.
40. Folstein MF, Folstein SE, Mc Hugh PR. Mini-mental state. A practical method for grading the cognitive state of patients for the clinician. *Journal of Psychology Research* 1975; **12:** 189–198.
41. Zaudig M, Mittelhammer J, Hiller W *et al*., SIDAM – a structured interview for the diagnosis of dementia of the Alzheimer type, multi-infarct dementia and dementias of other aetiology according to ICD-10 and DSM-III-R. *Psychological Medicine* 1991; **21:** 225–236.
42. Tittgemeyer M, von Cramon DY. Morphometry using magnetic resonance imaging (German). *Nervenarzt* 2004; **75:** 1172–1178.
43. Tatsch K, Koch W, Linke R *et al*., Cortical hypometabolism and crossed cerebellar diaschisis suggest subcortically induced disconnection in CADASIL: a $^{18}$F-FDG

PET study. *Journal of Nuclear Medicine* 2003; **44:** 862–869.
44. Chabriat H, Bousser MG, Pappata S. Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy: a positron emission tomography study in two affected family members [letter]. *Stroke* 1995; **26:** 1729–1730.
45. Mellies JK, Baumer T, Muller JA *et al*., SPECT study of a German CADASIL family: a phenotype with migraine and progressive dementia only. *Neurology* 1998; **50:** 1715–1721.
46. Tuominen S, Juvonen V, Amberla K *et al*., Phenotype of a homozygous CADASIL patient in comparison to 9 age-matched heterozygous patients with the same R133C Notch3 mutation. *Stroke* 2001; **32:** 1767–1774.
47. van den Boom R, Lesnik Oberstein SA, Spilt A *et al*., Cerebral hemodynamics and white matter hyperintensities in CADASIL. *Journal of Cerebral Blood Flow and Metabolism* 2003; **23:** 599–604.
48. Desmond DW, Moroney JT, Lynch T, Chan S, Chin SS, Mohr JP. The natural history of CADASIL. A pooled analysis of previously published cases. *Stroke* 1999; **30:** 1230–1233.
49. Harris JG, Filley CM. CADASIL: neuropsychological findings in three generations of an affected family. *Journal of the International Neuropsychological Society* 2001; **7:** 768–774.
50. Amberla K, Waljas M, Tuominen S *et al*., Insidious cognitive decline in CADASIL. *Stroke* 2004; **35:** 1598–1602.
51. Mayer M, Straube A, Bruening R *et al*., Muscle and skin biopsies are a sensitive tool in the diagnosis of CADASIL. *Journal of Neurology* 1999; **246:** 526–532.
52. Joutel A, Favrole P, Labauge P *et al*., Skin biopsy immunostaining with a Notch3 monoclonal antibody for CADASIL diagnosis. *Lancet* 2001; **358:** 2049–2051.
53. Lopera F, Rivera N, Arboleda J, Restrepo T, Arcos-Burgos M. Analysis of complex segregation in a large family with hereditary cerebrovascular disease in Antioquia, Colombia (Spanish). *Revista de Neurologia* 2001; **32:** 222–225.