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Vascular parkinsonism in a CADASIL case with an intact nigrostriatal dopaminergic system

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Sirs: Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukencephalopathy (CADASIL) is responsible for up to 5% of cerebral small vessel diseases manifesting mostly between the age of 40 and 60 years irrespective of vascular risk factors [1]. The clinical spectrum includes migraine, recurrent subcortical strokes, cognitive decline, and psychiatric manifestations [1, 2]. Here, we report for the first time a case of vascular parkinsonism and dementia showing functional integrity of the nigrostriatal dopaminergic system diagnosed as CADASIL by skin biopsy.

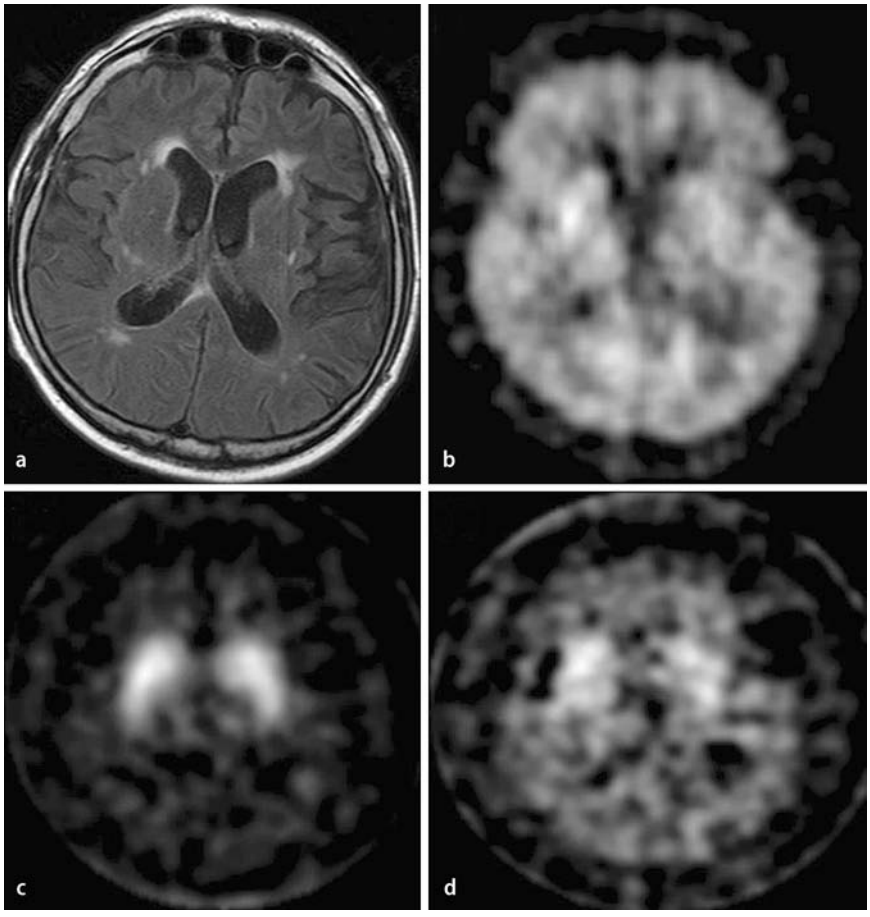

Fig. 1 Transverse images at striatal level. **A** MR T2w FLAIR image shows coalescent lesions in the white matter and subcortical atrophy suggestive for microangiopathic leukencephalopathy. We found a more extensive involvement of the superior frontal region and small lesions in the external capsule – involvement of these regions has a higher sensitivity and specificity for CADASIL **B** [^{18}F]FDG-PET of brain glucose metabolism is reduced in the thalamus and temporal cortex bilaterally as well as in the left striatum. **C** [^{123}I]FP-CIT SPECT of striatal dopamine transporter availability (left striatum 8.2, right striatum 8.0 – lower limit 4.6) and **D** [^{123}I]IBZM SPECT of striatal dopamine D2/D3 receptor availability (left striatum 2.2, right striatum 2.3 – lower limit 1.58) show normal values within the age range indicating functional integrity of the nigrostriatal dopaminergic system as described for vascular parkinsonism

A 55-year old male presented to our department with a two year history of reduced mobility, cognitive decline, chronic fatigue, and urinary incontinence. Previous diagnosis included major depression, however, the antidepressant therapy with mirtazapin was ineffective. Amisulpride had been administered due to hypochondric delusions. Hypertension and atrial fibrillation were treated adequately with metoprolol, digitoxin, and phenprocoumon, otherwise his

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past medical history was unremarkable. The family history remained uninformative.

On neurological examination the patient displayed a symmetric hypokinetic-rigid parkinsonian syndrome with mild upward gaze palsy, moderate dysarthrophonia and hypomimia, marked limb rigidity, severe impairment of fine motor skills of finger and hand movements as well as moderately impaired diadochokinesia and leg agility. Arising from a chair was possible without assistance, his gait and postural reflexes were mildly impaired with retropulsion but unaided recovery. Administration of levodopa (200 mg p. o. plus benserazide) did not result in any improvement of his United Parkinson's Disease Rating Scale motor score (UPDRS part III: 45 points). Hyperreflexia, urinary incontinence, and a pathological decrease of pulse frequency following standing up suggested additional lesions of the pyramidal tract and the autonomous nervous system. In the Mini-Mental State Examination (14 points) he showed no orientation in time, a reduced short-term memory, and lacked the ability to calculate serial sevens. The patient fulfilled the diagnostic criteria for vascular dementia (DSM-IV). After admission, neuroleptic pharmacotherapy with amisulpride (600 mg/day, half life 12 h) was discontinued at once; however, only his limb rigidity and fatigue syndrome improved slightly during the next few days. Levodopa was increased gradually to 800 mg/day without beneficial effects and, therefore, subsequently reduced to 300 mg/day. We initiated administration of rivastigmin and treated a newly diagnosed hyperlipidaemia with atorvastatin. In follow-up examinations up to ten months later the patient displayed a similar parkinsonian syndrome (UPDRS part III: 38 points) without neuroleptic pharmacotherapy. Thus, we concluded that amisulpride had not been responsible for the parkinsonism.

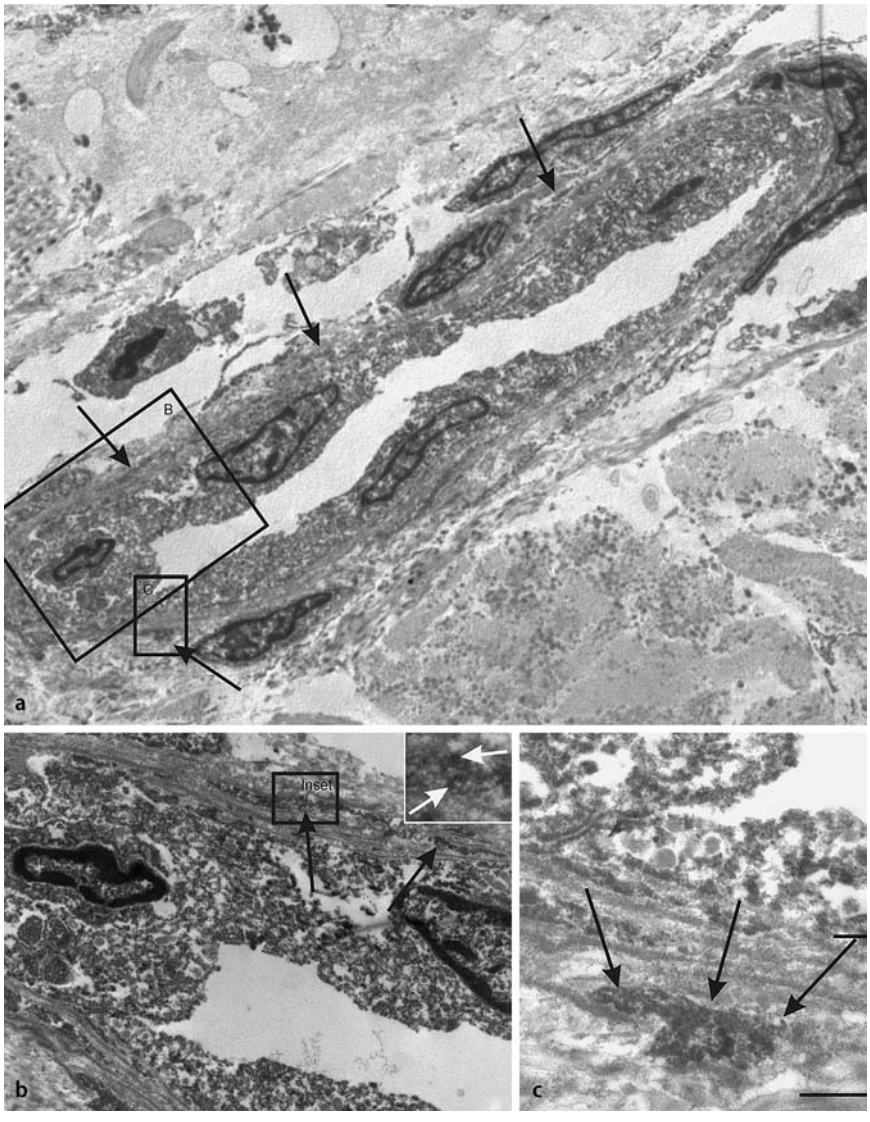

Fig. 2 Skin biopsy revealed multiple granular osmiophilic material along the basement membrane of small arteries (indicated by arrows in **A**). **B** shows a higher magnification of this vessel (boxed area in **A** indicated as **B**) exhibiting multiple lesions with osmiophilic material in the vessel wall, whereby some of these deposits appear to have a granular character (inset in **B**, arrows). The higher magnification of another part of this artery (boxed area in **A** indicated as **C**) demonstrates the granular and osmiophilic character of the deposits in a second part of the artery (arrows). Calibration bar: **A** = 2500 nm; **B** = 1000 nm; inset-**B, C** = 300 nm

Brain MRI (Fig. 1a) showed a subcortical enhanced atrophy and microangiopathic leukencephalopathy compatible with small vessel disease. Brain glucose metabolism (18F-FDG-PET, Fig. 1b) was decreased in the temporal cortices, thalami, and in the left striatum. The imaging of striatal dopamine transporters (FP-CIT-SPECT, Fig. 1c) and dopamine D2/D3 receptors (IBZM-SPECT, Fig. 1d), performed as described previously [3], showed ratios for specific uptake well within the range of healthy subjects indicating functional integrity of the nigrostriatal dopaminergic system.

Despite predominance of upper extremity parkinsonism these neuroimaging data suggested a vascular aetiology. Histopathological

evaluation of a skin biopsy using electron microscopy (Fig. 2) revealed numerous small arterioles with granular osmiophilic material in association to the basal lamina as described for CADASIL [4]. Genetic analysis did not show any pathogenic mutations in the exons 2–24 of the Notch3 gene. However, genetic testing in biopsy-proven CADASIL is associated with a nameable proportion of negative results [5]. Besides genotyping, electron microscopic analysis of tissue derived from skin biopsies seems to be equally specific favouring a diagnosis of CADASIL in our patient [5, 6].

So far, one case of progressive supranuclear palsy showing a brain MRI and skin biopsy consistent with CADASIL has been described [7]. In contrast to progressive supranuclear palsy and Parkinson's disease a normal striatal dopamine transporter and dopamine D2/D3 receptor binding as seen in our patient was shown for vascular parkinsonism [8–10]. Our case suggests that vascular parkinsonism and CADASIL should be considered in patients presenting with an atypical parkinsonian syndrome and functional integrity of the nigrostriatal dopaminergic system.

Competing interests JS has been reimbursed by GE Health Care, the manufacturer of DaTSCAN, for running educational programmes and consulting.

Abbreviations

CADASIL	cerebral autosomal dominant arteriopathy with subcortical infarcts and leukencephalopathy
MRI	magnetic resonance imaging
PET	positron emission tomography
SPECT	single photon emission computed tomography

References

1. Ringelstein EB, Nabavi DG (2005) Cerebral small vessel diseases: cerebral microangiopathies. Curr Opin Neurol 18:179–188
2. Dichgans M, Mayer M, Uttner I, Bruning R, Muller-Hocker J, Rungger G, Ebke M, Klockgether T, Gasser T (1998) The phenotypic spectrum of CADASIL: clinical findings in 102 cases. Ann Neurol 44:731–739
3. Günther P, Storch A, Schwarz J, Sabri O, Steinbach P, Wagner A, Hesse S (2004) Basal ganglia involvement of a patient with SCA 17 – a new form of autosomal dominant spinocerebellar ataxia. J Neurol 251:896–897
4. Ruchoux MM, Guerouaou D, Vandenhaute B, Pruvo JP, Vermersch P, Leys D (1995) Systemic vascular smooth muscle cell impairment in cerebral autosomal dominant arteriopathy with subcortical infarcts and leukencephalopathy. Acta Neuropathol (Berl) 89:500–512
5. Peters N, Opherk C, Bergmann T, Castro M, Herzog J, Dichgans M (2005) Spectrum of mutations in biopsy-proven CADASIL: implications for diagnostic strategies. Arch Neurol 62:1091–1094
6. Markus HS, Martin RJ, Simpson MA, Dong YB, Ali N, Crosby AH, Powell JF (2002) Diagnostic strategies in CADASIL. Neurology 59:1134–1138
7. Van Gerpen JA, Ahlskog JE, Petty GW (2003) Progressive supranuclear palsy phenotype secondary to CADASIL. Parkinsonism Relat Disord 9:367–369
8. Thanvi B, Lo N, Robinson T (2005) Vascular parkinsonism–an important cause of parkinsonism in older people. Age Ageing 34:114–119
9. Gerschlager, W, Benesits G, Pirker W, Bloem BR, Asenbaum S, Prayer D, Zijlmans JC, Hoffmann M, Brucke T (2002) [123I]beta-CIT SPECT distinguishes vascular parkinsonism from Parkinson's disease. Mov Disord 17: 518–523
10. Plotkin M, Amthauer H, Klaffke S, Kuhn A, Ludemann L, Arnold G, Wernecke KD, Kupsch A, Felix R, Venz S (2005) Combined 123I-FP-CIT and 123I-IBZM SPECT for the diagnosis of parkinsonian syndromes: study on 72 patients. J Neural Transm 112:677–692