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CASE REPORT

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Typical pathological changes of CADASIL in the optic nerve

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Abstract Visual impairment due to retinal and optic nerve changes in cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is more common than previously thought. Deposits of granular osmiophilic material (GOM) have been shown in the wall of retinal arterioles, though retinal infarcts and vascular occlusions have never been reported. Ischaemic optic neuropathy, on the other hand, has been reported in one case of CADASIL but no pathology reports of the optic nerve have been published. Here we report optic nerve morphological findings in the autopsy material of a 41-year-old woman with genetically assessed CADASIL. Longitudinal and transverse sections of optic nerves were examined. Classical histological methods (haematoxylin-eosin and Nissl) were performed. Diffuse pallor of myelin and rarefaction of optic nerve fibres were observed. Classical GOM was evident in the tunica media of vessels in the meninges and white matter. Arteriole lumina were slightly narrowed. In conclusion, the typical pathological changes of CADASIL occur in the optic nerve and may contribute to impairment of visual function in CADASIL.

Key words CADASIL • Optic nerve • Morphology • Immunocytochemical analysis

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Introduction

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is a hereditary late onset disorder characterised by transient ischaemic attacks, migraine, strokes and dementia [1]. The pathological hallmark of the disease is deposition of granular osmiophilic material (GOM) in the tunica media of small arteries and arterioles of the brain white matter and meninges [2]. Smooth muscle cells of arterial walls seem to be the pathological target [3]. Although clinical symptoms are restricted to the central nervous system, the pathological process also affects vessels in skin, muscle, peripheral nerves and internal organs [4]. In recent years, impairment of the visual system has been reported in CADASIL patients. In particular, ophthalmoscopic [5], haemodynamic [6] and electrophysiological [7] changes have been documented in the retina and GOM has been observed in retinal vessels. Beside the retina, the optic nerve may be involved, and ischaemic optic neuropathy was recently reported as a first symptom in a CADASIL patient [8].

Here we report optic nerve morphological findings in autopsy material (orbital, intracanalicular and intracranial portions) of a 41-year-old woman with genetically assessed CADASIL.

Case report

The clinical and neuropathological data of this patient have already been reported [9]. Briefly, at 34 years, episodes of migraine began. At 35 years she experienced right paresis which regressed in a few days. At 36 years, speech impairment associated with ataxia and progressive cognitive impairment were noted. At 40 years, her overall neurological condition deteriorated, leading to a comatose state and death at 41 years. Although she did no complain

of visual symptoms, optic nerves appeared diffusely pale and retinal vessels were narrowed on fundoscopy.

The diagnosis of CADASIL in this family was confirmed by molecular analysis (G437A substitution in exon 4 of the Notch 3 gene) and neuropathological findings.

Autopsy was performed about 18 h after death; the brain was fixed in formalin for 30 days. Longitudinal and transverse sections of chiasma and optic nerves (fragments from orbital, intracanalicular and intracranial portions) were embedded in paraffin and stained by routine histological methods (haematoxylin-eosin, Nissl, Woelcke).

Results

Woelcke stain showed diffuse pallor of myelin and fiber rarefaction in the optic nerves and chiasma (Fig. 1). Demyelination was irregular, without any precise distribution pattern. Meningeal and white matter arterial vessels showed thickened walls and classical deposits of granular eosinophilic and PAS-positive material in the tunica media (Fig. 2). The lumina of some vessels showed slight stenosis.

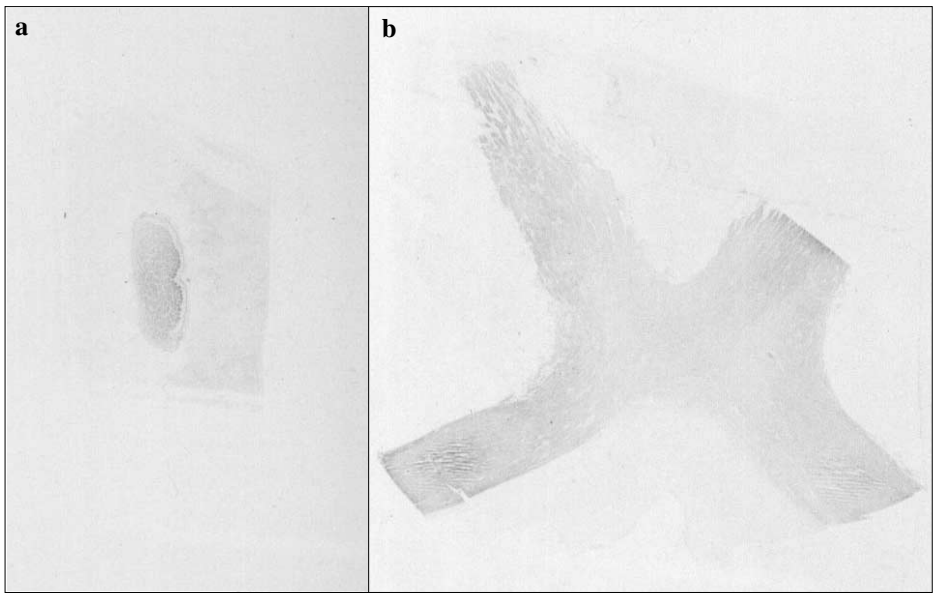

Fig. 1 (Woelcke stain) Macroscopic sections of (**a**) optic nerve (transverse section) and (**b**) chiasma (sagittal section) showing diffuse demyelination with irregular distribution

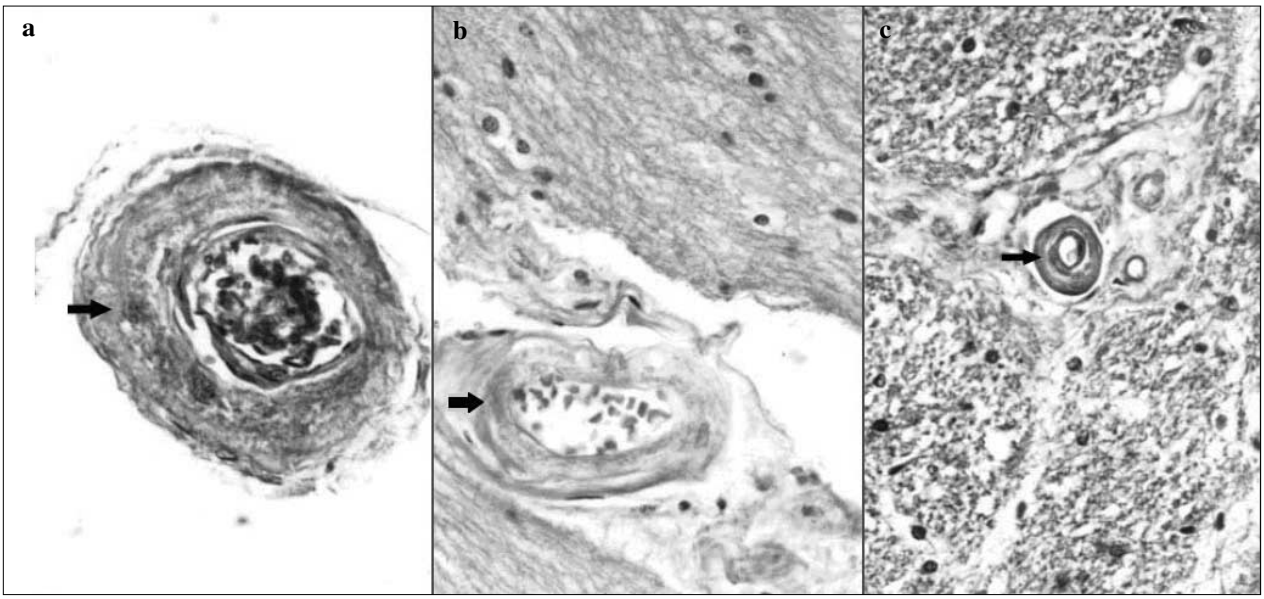

Fig. 2 (Optic nerve, H&E stain) of leptomeningeal (**a**, x600) and parenchymal (**b**, x500; **c**, x180) vessels, showing deposits of granular material in the walls (*arrows*). In **b** and **c**, rarefaction of white matter is also evident

Discussion

Recent reports underline impairment of visual function in CADASIL, mostly caused by retinal damage. This is to be expected, as retinal and cerebral arterioles have common anatomy and physiology. The presence of the pathological hallmark of the disease in retinal vessels was first demonstrated by Rouchoux et al. [10], who described an autopsy case of CADASIL in which GOM deposits greatly affected both brain and retina. The characteristic fundoscopic retinal findings observed are arteriole narrowing and sheathing, especially in the peripapillary region [11]. Vascular changes in the eye, however, are not limited to retinal vessels. Choroid vasculature may also be involved as demonstrated by Robinson et al. [5], who showed fluorescein angiographic evidence of irregular filling of the choroid.

Histopathological abnormalities have recently been reported in ocular blood vessels of CADASIL patients [12]. A significant loss of vascular smooth muscle cells (VSMC) was shown in retinal and optic nerve head vessels. Functional impairment of the retina was also documented in a visual electrophysiological study of patients with CADASIL. The authors showed abnormal responses in symptomatic and asymptomatic patients [13]. Another functional study, regarding haemodynamics of the superficial portion of the papilla, mostly supplied by retinal arterioles but partly by deeper optic nerve circulation, indicated a reduction in blood flow and volume [6].

Optic nerve dysfunction has been the subject of little study in CADASIL, and pathology reports have not focused on this problem. Although no retinal infarcts or vascular occlusions have been shown in symptomatic CADASIL patients, we recently reported a case of acute and permanent visual loss due to optic nerve ischaemia [8].

In the present study we found the characteristic lesions of CADASIL in arterial vessels of the optic nerve. We also found slight demyelination and fibre rarefaction. These lesions may explain abnormalities of the visual system detected in previous studies.

In conclusion, our study demonstrates GOMs in arteriolar walls of the optic nerve, associated with demyelination, fibre rarefaction and, sometimes, vessel lumen narrowing. These findings suggest that optic nerve damage may contribute to impairment of visual function in CADASIL.

Sommario *Il coinvolgimento visivo nel "Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy" (CADASIL) è più comune di quanto inizialmente riportato. Oltre alle note alterazioni retiniche, sono state riscontrate recentemente alterazioni a carico del nervo ottico. In particolare è stata descritto un caso di ischemia del nervo ottico come primo sintomo di CADASIL. I caratteristici depositi di materiale granulare osmofilico (GOMs) nella parete delle arteriole retiniche è stata precedentemente documentata. In questo lavoro dimostriamo che anche il nervo ottico presenta le caratteristiche alterazioni morfologiche della malattia, in più è presente una rarefazione delle fibre e della mielina. Questi dati suggeriscono che un danno a carico del nervo ottico può contribuire ad una alterazione della funzione visiva nel CADASIL.*

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References

1. 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
2. Baudrimont M, Dubas F, Joutel A, Tournier-Lasserve E, Bousser MG (1993) Autosomal dominant leukoencephalopathy and subcortical ischemic stroke. A clinicopathological study. Stroke 24:122–125
3. Joutel A, Andreux F, Gaulis S, Domenga V, Cecillon M, Bettail N, Piga N, Chapon F, Godfrain C, Tournier-Lasserve E (2000) The ectodomain of the Notch3 receptor accumulates within the cerebrovasculature of CADASIL patients. J Clin Invest 105:597–605
4. Goebel HH, Meyermann R, Rosin R, Schlote W (1997) Characteristic morphologic manifestation of CADASIL, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy, in skeletal muscle and skin. Muscle Nerve 20:625–627
5. Robinson W, Galletta SL, McCluskey L, Forman MS, Balcer LJ (2001) Retinal findings in cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL). Surv Ophthalmol 45:445–448
6. Rufa A, Dotti MT, Frezzotti P, De Stefano N, Caporossi A, Federico A (2004) Hemodynamic evaluation of the optic nerve head in CADASIL. Arch Neurol 61:1230–1233
7. Parisi V, Pirrelli F, Malandrini A, Carrera P, Olzi D, Gregori D, Restuccia R, Parisi L, Fattaposta F (2000) Visual electrophysiological responses in subjects with cerebral autosomal arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL). Clin Neurophysiol 111:1582–1588
8. Rufa A, De Stefano N, Dotti MT, Bianchi S, Sicurelli F, Stromillo ML, D'Aniello B, Federico A (2004) Acute unilateral visual loss as the first symptom of cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy. Arch Neurol 61:577–580
9. Malandrini A, Carrera P, Palmeri S, Cavallaro T, Fabrizi GM, Villanova M, Fattapposta M, Vismara L, Brancolini V,

Tanganelli P, Cali A, Morocutti C, Zeviani M, Ferrari M, Guazzi GC (1996) Clinicopathological and genetic studies of two further Italian families with cerebral autosomal dominant arteriopathy. Acta Neuropathol 92:115–122

10. Ruchoux MM, Guerouaou D, Vandehaute B, Pruvo JP, Vermersch P, Leys D (1995) Systemic vascular smooth muscle cell impairment in cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy. Acta Neuropathol 80:500–512
11. Haritoglou C, Rudolph G, Hoops JP, Opherk C, Kampik A, Dichgans M (2004) Retinal vascular abnormalities in CADASIL. Neurology 62:1202–1205
12. Haritoglou C, Hoops JP, Stefani FH, Mehraein P, Kampik A, Dichgans M (2004) Histopathological abnormalities in ocular blood vessels of CADASIL patients. Am J Ophthalmol 138:302–305
13. Parisi V, Pirrelli F, Fattaposta F, Bianco F, Parisi L, Restuccia R, Malandrini A, Ferrari M, Carrera P (2003) Early visual function impairment in CADASIL. Neurology 60:2008–2010