the bearer groups (in years) was 71.1 (SD 6.1) for *A2aAR* 1976C/C, 72.3 (SD 6.3) for 1976C/T and 72.6 (SD 6.2) for 1976T/T. The age at onset was not significantly different when comparing the three genotypic groups (p = 0.462).

In this study, we found no difference in *A2aAR* 1976T>C genotype distribution or allelic frequency when comparing AD patients with normal controls. From the analysis of age at AD onset, no significant difference was determined when comparing the three *A2aAR* 1976T>C genotype groups. Therefore, it is unlikely that the *A2aAR* 1976T>C polymorphism plays an important role in the pathogenesis of AD. In this study, the size of effect that could be detected with 80% power at the 5% significance level is odds ratio of 1.6 for AD. Since AD probably has multiple determinants, and if *A2aAR* is an uncommon disease locus or one of small effect, our power to detect a genetic effect would be reduced. Furthermore, negative findings for one polymorphism may not exclude the involvement of the locus as a whole. Before a role of the *A2aAR* gene in the etiology of AD can be definitely excluded, further studies using haplotype analysis to investigate multiple polymorphisms in the *A2aAR* gene in AD are needed.

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References

1 Guieu R, Dussol B, Halimi G, Bechis G, Sampieri F, Berland Y, Sampol J, Couraud F, Rochat H: Adenosine and the nervous system: Pharmacological data and therapeutic perspectives. Gen Pharmacol 1998;31:553–561.
2 Wojcik WJ, Neff NH: Adenosine measurement by a rapid HPLC-fluorometric method: Induced changes of adenosine content in regions of rat brain. J Neurochem 1982;39:280–282.
3 Maia L, de Mendonca A: Does caffeine intake protect from Alzheimer's disease? Eur J Neurol 2002;9:377–382.
4 Dall'Igna OP, Porciuncula LO, Souza DO, Cunha RA, Lara DR, Dall'lgna OP: Neuroprotection by caffeine and adenosine A2A receptor blockade of beta-amyloid neurotoxicity. Br J Pharmacol 2003;138:1207–1209.
5 Jin S, Fredholm BB: Adenosine A2A receptor stimulation increases release of acetylcholine from rat hippocampus but not striatum, and does not affect catecholamine release. Naunyn Schmiedebergs Arch Pharmacol 1997;355:48–56.
6 Auld DS, Kornecook TJ, Bastianetto S, Quirion R: Alzheimer's disease and the basal forebrain cholinergic system: Relations to beta-amyloid peptides, cognition, and treatment strategies. Prog Neurobiol 2002;68:209–245.
7 Deckert J, Nothen MM, Franke P, Delmo C, Fritze J, Knapp M, Maier W, Beckmann H, Propping P: Systematic mutation screening and association study of the A1 and A2a adenosine receptor genes in panic disorder suggest a contribution of the A2a gene to the development of disease. Mol Psychiatry 1998;3:81–85.
8 McKhann G, Drachman D, Folstein M, Katqman R, Price D, Stadlan EM: Clinical diagnosis of Alzheimer's disease: Reports of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. Neurology 1984;34:939–944.

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HIV-Associated Multiple Intracerebral Hemorrhages

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Introduction

Central neurological complications of HIV infection are common; however, its mechanisms of entry are still highly controversial. In 10–20% of symptomatic HIV infections, neurological disease is the first manifestation of AIDS. However, the presence of cerebrovascular disease in HIV has been rarely reported. Intracerebral hemorrhages (ICHs) seem to be less frequent than cerebral ischemia in HIV-positive individuals [1], and are often associated with thrombocytopenia or primary CNS lymphoma. In those with acute ICH, T_2-weighted gradient-echo MRI is a useful technique to determine additional older hemorrhages due to hemosiderin deposits.

We describe a 44-year-old HIV-positive man with multiple supra- and infratentorial hemorrhages.

Case Report

A 44-year-old man with chronic alcohol consumption (3–4 beers/day) was admitted to our hospital due to a first generalized seizure. Neurological examination revealed a left-sided facial paresis and a left-sided ataxia. The initial CCT showed an acute left cerebellar hemorrhage. MRI demonstrated, beside the acute cerebellar lesion (fig. 1), multiple older ICHs, located supra- and infratentorially (fig. 2). ECG, repeated EEG (alpha EEG), CSF and cardiac ultrasound revealed no major findings. Blood pressure was slightly elevated (140/80 mm Hg). Blood samples showed leucopenia (2.9×10^9/l), lymphopenia and an elevated creatine kinase of 827 U/l. The blood alcohol concentration upon admission was 1.18 g/l. INR, PTT and thrombocytes were within normal ranges. The first diagnosis of HIV-1 was confirmed by Western blot analysis. The CD4/CD8 ratio was below normal (0.74). There was no evidence of Kaposi's sarcoma. A cortical biopsy was not performed in the knowledge of the underlying disease. We started an anticonvulsive treatment with carbamazepine due to the symptomatic lesions. The seizure might have been additionally mediated by the patient's chronic alcohol consumption, as he developed an alcohol withdrawal syndrome, got delirious and was transferred to the psychiatric department for detoxication. There, he was treated for 1 week. Afterwards, he was retransferred to the neurologic department. Repeated CCT scans showed the cerebellar hemorrhage in regression. As the blood pressure was still slightly elevated, the patient was treated with metoprolol retard 95 mg/day. The outcome of the patient was without any deficit.

Discussion

ICH is a seldom entity in young individuals as well as HIV-positive patients. The coexistence of these two disorders and the

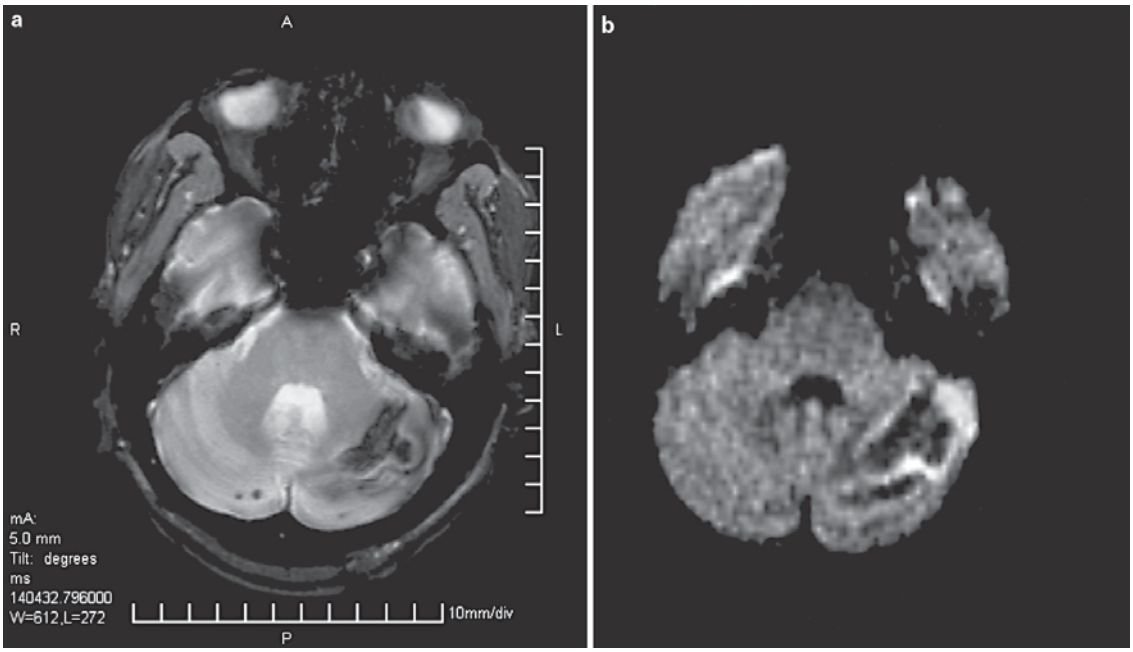

Fig. 1. a Gradient-echo MRI showing acute symptomatic hemorrhage in the left cerebellum and two older small hemorrhages in the right cerebellum. **b** Diffusion-weighted imaging showing left-sided lobar hemorrhage. The core of the hemorrhage appears diffusion negative, whereas the border of the bleeding becomes diffusion positive. The two older lesions in the right cerebellum are not visible on diffusion-weighted imaging.

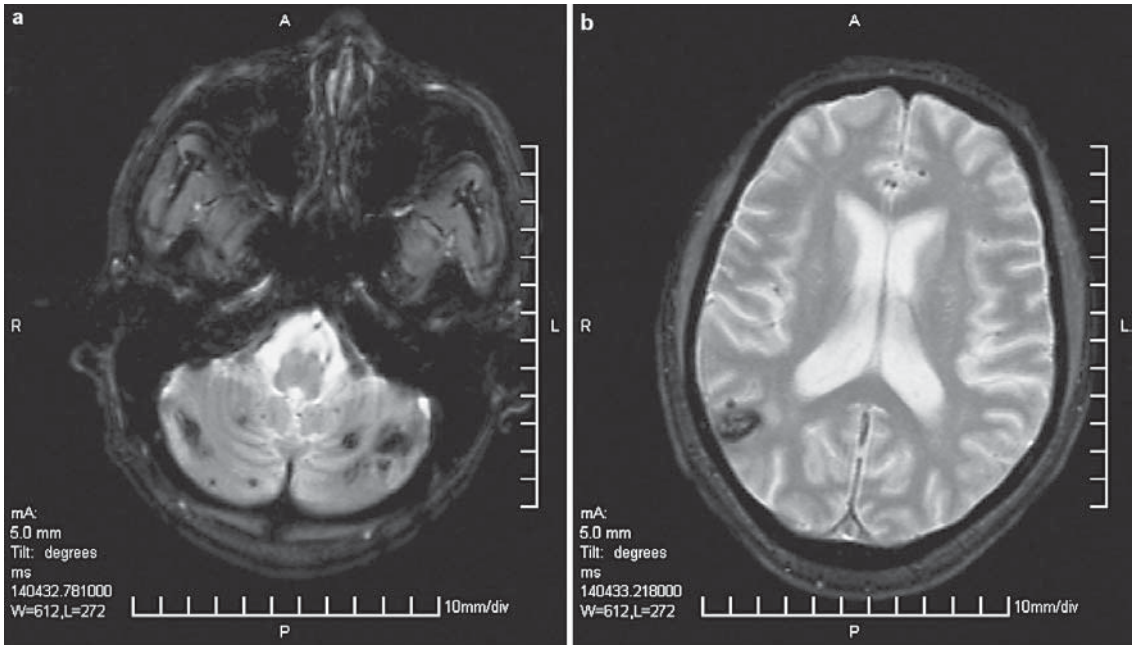

Fig. 2. Gradient-echo MRI demonstrating multiple bilateral hemorrhages in the cerebellum (**a**), and lobar hemorrhage in the gyrus angularis of the right side (**b**).

Table 1. Boston criteria for diagnosis of CAA-related hemorrhage

Definite CAA
Full postmortem examination demonstrating:
Lobar, cortical, or corticosubcortical hemorrhage
Severe CAA with vasculopathy
Absence of other diagnostic lesion
Probable CAA with supporting pathology
Clinical data and pathologic tissue
(cortical biopsy or evacuated hematoma) demonstrating:
Lobar, cortical or corticosubcortical hemorrhage
Some degree of CAA in specimen
Absence of other diagnostic lesion
Probable CAA
Clinical data and MRI or CT demonstrating:
Multiple hemorrhages restricted to lobar, cortical, or corticosubcortical regions (cerebellar hemorrhage allowed)
Age ≥ 55 years
Absence of other cause of hemorrhage
Possible CAA
Clinical data and MRI or CT demonstrating:
Single lobar, cortical or corticosubcortical hemorrhage
Age ≥ 55 years
Absence of other cause of hemorrhage

lack of opportunistic infections in our case may implicate a role of HIV-induced amyloid deposition in cerebral vessels. This hypothesis is supported by one neuropathological study, where perivascular amyloid deposition was frequently found in young HIV-positive individuals [2]. It is well known that amyloid deposition in cerebral vessels increases the risk of ICH manifold [3]. This was shown for cerebral amyloid angiopathy (CAA), which is a common reason for recurrent lobar ICH, especially in older age [4]. With widely available new MRI techniques, including T_2-weighted gradient echo, the frequency of multiple ICHs and probable CAA diagnosis has increased rapidly during the last years.

On the one hand, our case showed several criteria for the diagnosis of CAA, i.e. multiple ICHs restricted to corticosubcortical regions. On the other hand, especially due to the relatively young age of our patient, a diagnosis of probable CAA according to the Boston criteria could not be made (table 1) [4], as the age of the patient is required to be >55 years. We were aware of the problem, and we did not perform a cortical biopsy to prove the relationship between amyloid deposition and the occurrence of the ICHs. Since the patient had no evidence of opportunistic infections, the therapeutic benefit from a cortical biopsy for the patient might be questioned. Unquestionably, moderate to high alcohol intake increases the risk of ICH [3]; therefore, we cannot exclude the possibility that the chronic alcohol consumption of the patient might be an alternative cause of the hemorrhages; however, alcohol-mediated ICH typically does not appear like CAA-related ICH.

This case appears to be unique because of multiple, morphologically CAA-typical infra- and supratentorial lobar hemorrhages in a rather young, 44-year-old man. As the availability of T_2-weighted gradient-echo MRI is increasing, we suggest that atypical lobar hemorrhages, especially in young individuals be examined for additional older ICHs, and that HIV be considered in the spectrum of underlying causes.

References

1 Pinto AN: AIDS and cerebrovascular disease. Stroke 1996;27:538–543.
2 Izycka-Swieszewska E, Zoltowska A, Rzepko R, Gross M, Borowska-Lehman J: Vasculopathy and amyloid beta reactivity in brains of patients with acquired immune deficiency (AIDS). Folia Neuropathol 2000;38:175–182.
3 Ariesen MJ, Claus SP, Rinkel GJ, Algra A: Risk factors for intracerebral hemorrhage in the general population: A systematic review. Stroke 2003;34:2060–2065.
4 Greenberg SM, Briggs ME, Hyman BT, Kokoris GJ, Takis C, Kanter DS, Kase CS, Pessin MS: Apolipoprotein: E epsilon 4 is associated with the presence and earlier onset of hemorrhage in cerebral amyloid angiopathy. Stroke 1996;27:1333–1337.

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