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Letter to the editor

Alcohol misuse can mimic frontotemporal degeneration in Alzheimer's disease patients

To the editor,

We would like to report the case of a 64-year-old Caucasian male, referred to our memory clinic in 2015 for investigation of a cognitive disorder which had been evolving progressively over the previous year. Severe memory loss was in the foreground, associated with behavioral change characterized by aggressiveness and irritability. The patient had a history of alcohol misuse, with daily consumption of alcohol (several glasses of whisky and beer), several drunken episodes, and a recent stay in the emergency department with a 2.4 g/L blood alcohol level. The physical examination was unremarkable and preliminary cognitive evaluation found an MMSE score at 15/30 and an amnesic syndrome at routine testing. The diagnosis of Alzheimer's disease (AD) was first evoked due to severity of the amnestic syndrome and progressive presentation. Neuropsychological testing confirmed severe memory impairment (free and total recall equal to 0 on the Free and Cued Selective Reminding Test), with a dysexecutive syndrome (Frontal Assessment Battery: 7/18) and a marked deficit in emotion recognition (Mini-SEA: 15/35). Brain magnetic resonance imaging (MRI) found global atrophy that was predominant in the frontal area with relative preservation of parietal cortex (Fig. 1A), and a moderate hippocampal atrophy, Scheltens 2 (Fig. 1B). The brain flurodeoxyglucose positron emission tomography (FDG PET) found severe and asymmetric hypometabolism, predominant in the left frontal

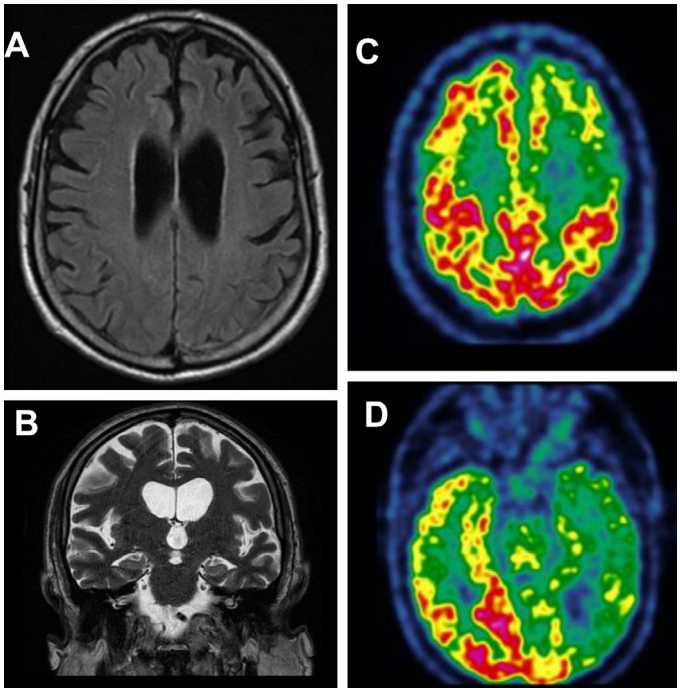

Fig. 1 – Brain MRI and FDG-PET of the patient. The MRI shows global atrophy predominating in the frontal lobe (A) and a Scheltens score at 2 (B). The FDG-PET shows severe and asymetric brain hypometabolism, in the left frontal (C) and temporal (D) lobes, with relative respect of the parietal cortex (C).

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and temporal lobes (Fig. 1C and D) involving both anterior (anterior cingulate and prefrontal cortex) and posterior (precuneus, posterior cingulate cortex) areas. AD biomarkers in the cerebrospinal fluid (CSF) found a decreased level of CSF Aβ42 (532 pg/mL, normal >815) but normal values of total tau (258 pg/mL, normal < 300) and phosphorylated tau (45 pg/mL, normal < 58) and were interpreted as not suggestive of AD. Despite alcohol abstinence, the patient's cognitive function continued to decline, and the diagnosis of possible frontotemporal dementia was retained, after confrontation of the clinical presentation, imaging findings, and biomarker results. The patient died in 2020 in intensive care, following post-traumatic hemorrhagic shock. A diagnostic autopsy was performed, revealing extensive deposits of neurofibrillary tangles (Braak stage V, Fig. 2A) and β-amyloid peptide (Thal phase 5, Fig. 2B) without significant co-pathology, in particularly no lesions that would have been suggestive of alcoholic encephalopathy. The final diagnosis was a pure form of Alzheimer's disease with early onset.

Several conclusions can be drawn from this clinical case. The clinical determination of the etiology of a dementia syndrome is complex and remains probabilistic most of the time, except in the rare case of identification of a genetic cause. A recent large-scale French neuropathological study highlighted that amnesia is far from being specific to AD pathophysiology, and should rather be considered as a common symptom of neurodegenerative disease [1]. Amnestic forms of frontotemporal dementia (FTD) have been reported, as well as dysexecutive presentation of AD, especially in early-onset patients [2]. In this context, clinicians increasingly rely on biological and imaging biomarkers to confirm diagnosis. A French national survey has shown that in case of discrepancy between the initial diagnosis based on clinical presentation and the results of CSF biomarkers, clinicians base their final diagnosis on the results of the biological profile rather than the initial clinical diagnosis in 75% of cases [3]. However, the sensitivity of biomarkers is far from perfect and our clinical case illustrates that levels of tau and phosphorylated tau in the CSF can be in the normal range despite extensive deposits of neurofibrillary tangles in the brain. Results of the brain MRI and FDG PET in this case suggested possible FTD, due to the predominance of abnormalities in the frontal and temporal area and the relative preservation of the posterior area. We think that alcohol consumption may have played a role in this misdiagnosis, as we recently showed that frontal hypometabolism is commonly observed in alcohol-related cognitive impairment [4], as well as behavioral disturbances which could mimic FTD. Whether alcohol consumption played a role in the lower than expected levels of CSF tau and phosphorylated tau that we found in this patient remains open to question. To note, in a recent animal model study, high-dose alcohol is thought to have acutely reduced the brain's glymphatic function [5], and may therefore play a role in determining the levels of CSF AD biomarkers.

We would like to propose the following mnemonic "AD + OH = FTD" to keep in mind that some patients with FTD-like presentation may be due to AD pathology associated with excessive alcohol consumption, due to the potential impact of alcohol on symptoms as well as on the brain imaging findings [4]. The effect of alcohol in CSF AD biomarker levels remain largely unknown and deserve further investigation.

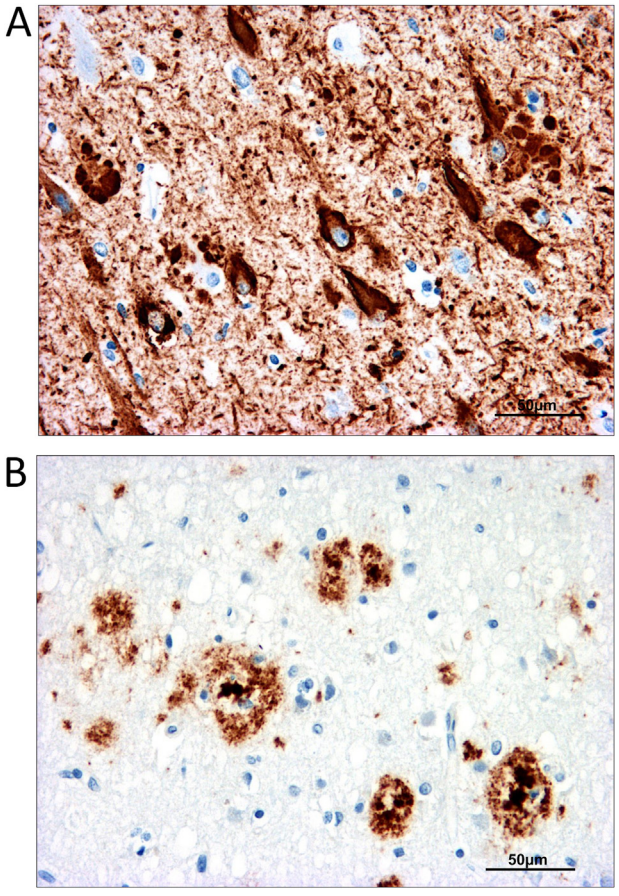

Fig. 2 – Alzheimer disease neuropathological changes at the post-mortem examination of the patient's brain, showing extensive intraneuronal deposits of neurofibrillary tangles (A) and extracellular β-amyloid plaques (B). A. CA1 of the hippocampus. B. Frontal cortex. Immunohistochemistry in (A) anti-phospho-tau (pS202, pT205): clone AT8, in (B) anti-A antibody: clone 6F/3D.

Disclosure of interest

The authors declare that they have no competing interest.

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REFERENCES

[1] Bertoux M, Cassagnaud P, Lebouvier T, Lebert F, Sarazin M, Le Ber I, et al. Does amnesia specifically predict Alzheimer's pathology? A neuropathological study. Neurobiol Aging 2020;95:123–30.

[2] Townley RA, Graff-Radford J, Mantyh WG, Botha H, Polsinelli AJ, Przybelski SA, et al. Progressive dysexecutive syndrome due to Alzheimer's disease: a description of 55 cases and comparison to other phenotypes. Brain Commun 2020;2(1) [fcaa068].
[3] Mouton-Liger F, Wallon D, Troussière AC, Yatimi R, Dumurgier J, Magnin E, et al. Impact of cerebro-spinal fluid biomarkers of Alzheimer's disease in clinical practice: a multicentric study. J Neurol 2014;261(1):144–51.
[4] Clergue-Duval V, Questel F, Azuar J, Paquet C, Cognat E, Amami J, et al. Brain 18FDG-PET pattern in patients with alcohol-related cognitive impairment. Eur J Nucl Med Mol Imaging 2020;47(2):281–91.
[5] Lundgaard I, Wang W, Eberhardt A, Vinitsky HS, Reeves BC, Peng S, et al. Beneficial effects of low alcohol exposure, but adverse effects of high alcohol intake on glymphatic function. Sci Rep 2018;8(1):2246.

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