Journal of the Neurological Sciences 401 (2019) 128–129

Contents lists available at ScienceDirect

Journal of the Neurological Sciences

journal homepage: www.elsevier.com/locate/jns

Letter to the Editor

Early diagnosis of Lewy body disease in elderly individuals with subjective cognitive decline

ARTICLE INFO

Keywords:
Parkinson's disease
Dementia with Lewy bodies
Alzheimer's disease
Differential diagnosis
REM sleep behavior disorder

Dear Editor

Many previous clinical trials, including anti-amyloid therapy, showed no benefit to patients with symptomatic Alzheimer's disease (AD). These results imply that therapies should be initiated during earlier stages of AD pathology. Thus, the research focus of identifying individuals with an underlying pathophysiology of AD is shifting to the prodromal or pre-mild cognitive impairment (MCI) stage, where cognitive performance levels are still in the normal range. Because subjective cognitive decline (SCD) has been suggested to be a possible first symptomatic manifestation of AD, research attention has been increasingly focused on SCD as a risk factor for incident AD dementia. The conceptual framework on SCD in pre-MCI was published by the International Working Group in 2014 [1], and a multicenter follow-up study of individuals with SCD has recently been reported. Although research criteria for SCD were defined in the context of prodromal AD, it is of note that approximately one-third of incident dementia in individuals with SCD has been ultimately diagnosed as non-AD in memory clinics based on findings of the multicenter study (mean follow-up period: 3.5 ± 2.3 years) [2]. Considering the disease heterogeneity underlying SCD, it is of considerable importance to identify the specific pathological basis in individuals with SCD in terms of the administration of disease-modifying therapeutics.

Dementia with Lewy bodies (DLB) is the second most common neurodegenerative disorder after AD, but its diagnostic sensitivity in clinical practice remains suboptimal. In 2017, the DLB clinical diagnostic criteria were modified to include the additional core feature of rapid eye movement (REM) sleep behavior disorder (RBD) and several suggestive features, such as olfactory dysfunction [3]. These clinical features often precede the onset of dementia by years or even decades [4]. In terms of early intervention during prodromal stages, DLB has some advantages compared to AD. First, the screening method to identify the specific pathological basis needs to be simple and non-invasive. Although only subtle cognitive/behavioral decline may lead us to suspect very early AD, a specific clinical sign has not been identified in prodromal AD. In contrast, various non-cognitive prodromal symptoms are useful for identifying prodromal DLB [4]. A community-based study reported that validated RBD questionnaires and olfactory testing might be helpful in defining target populations of future intervention trials [5]. Secondly, there are more practical biomarkers in prodromal DLB than in prodromal AD. It has been determined that AD can be identified during MCl stages using cerebrospinal fluid (CSF) profiles and amyloid positron emission tomography (PET) imaging, but previous studies reported that amyloid PET positivity was not always observed in patients with SCD. Only 88 (28%) of 318 participants who were aged 70–85 years with SCD exhibited amyloid PET positivity [6]. In the longitudinal follow-up study, there were no differences in Mini-Mental State Examination and Clinical Dementia Rating Scores at baseline and 30 months later between participants positive or negative for amyloid β. The authors mentioned that brain β-amyloidosis alone in individuals with SCD did not predict progression to prodromal AD within 30 months. In contrast, clinicopathological studies revealed a reasonably specific association between RBD and an underlying α-synucleinopathy in elderly patients, even before cognitive decline appears [4]. It is of considerable importance that RBD symptoms were confirmed by using indicative biomarkers in the revised DLB clinical diagnostic criteria: REM sleep without atonia on polysomnography and cardiac [^{123}I]-metaiodobenzylguanidine scintigraphy [3]. Third, phosphorylated α-synuclein, which is a major component of Lewy bodies, can be immunohistochemically identified in peripheral tissue biopsies and surgical tissue samples before autopsy confirmation. In the last few years, an increasing number of studies have been focused on the pathological confirmation of phosphorylated α-synuclein in the peripheral tissues of patients with Lewy body disease during their lifetimes [7]. The more reliably identifiable prodromal phase of DLB compared to that in AD in individuals with SCD provides a critical opportunity for potential intervention based on the specific pathological basis.

The multicenter follow-up study of individuals with SCD also reported that apolipoprotein E (*APOE*) ε4 increased the risk of dementia [2]. Although the strong association between *APOE* ε4 and the incident risk of AD is well known, the most replicated genetic risk factor for DLB is also the *APOE* ε4 allele [8]. In patients with DLB, abundant cerebral amyloid deposition is common, and the link between low CSF amyloid beta 1–42 and subsequent cognitive decline has been reported [9,10]. Although the link between *APOE* ε4 and DLB through an amyloid cascade hypothesis can be postulated, a recent pathological study demonstrated that *APOE* ε4 is associated with the severity of Lewy body pathology independent of Alzheimer pathology [8]. These findings

https://doi.org/10.1016/j.jns.2019.05.004
Received 13 April 2019; Received in revised form 4 May 2019; Accepted 6 May 2019
Available online 07 May 2019
0022-510X/

suggest that it is crucial to carefully interpret AD-related biomarkers in individuals with SCD. In terms of the administration of disease-modifying therapeutics targeted at specific pathologies, differentiating prodromal DLB from AD could be a first step toward defining the distinct prognostic subgroup that is at great risk of incident dementia.

Conflict of interest

H. Fujishiro reports no disclosures.

Author contributions

H. Fujishiro participated in designing the study and wrote the paper.

Acknowledgements

This study was supported in part by a Grant-in-Aid for Scientific Research (C) 15K09824 from the Ministry of Education, Culture, Sports, Science and Technology in Japan.

References

[1] F. Jessen, R.E. Amariglio, M. van Boxtel, M. Breteler, M. Ceccaldi, G. Chételat, et al., A conceptual framework for research on subjective cognitive decline in preclinical Alzheimer's disease, Alzheimers Dement. 10 (2014) 844–852, https://doi.org/10.1016/j.jalz.2014.01.001.

[2] R.E.R. Slot, S.A.M. Sikkes, J. Berkhof, H. Brodaty, R. Buckley, E. Cavedo, et al., Subjective cognitive decline and rates of incident Alzheimer's disease and non-Alzheimer's disease dementia, Alzheimers Dement. 15 (2019) 465–476, https://doi.org/10.1016/j.jalz.2018.10.003.

[3] I.G. McKeith, B.F. Boeve, D.W. Dickson, G. Halliday, J.P. Taylor, D. Weintraub, et al., Diagnosis and management of dementia with Lewy bodies: fourth consensus report of the DLB consortium, Neurology 89 (2017) 88–100, https://doi.org/10.1212/WNL.0000000000004058.

[4] H. Fujishiro, S. Nakamura, K. Sato, E. Iseki, Prodromal dementia with Lewy bodies, Geriatr Gerontol Int 15 (2015) 817–826, https://doi.org/10.1111/ggi.12466.

[5] P. Mahlknecht, K. Seppi, B. Frauscher, S. Kiechl, J. Willeit, H. Stockner, et al., Probable RBD and association with neurodegenerative disease markers: a population-based study, Mov. Disord. 30 (2015) 1417–1421, https://doi.org/10.1002/mds.26350.

[6] B. Dubois, S. Epelbaum, F. Nyasse, H. Bakardjian, G. Gagliardi, O. Uspenakaya, M. Houot, et al., Cognitive and neuroimaging features and brain β-amyloidosis in individuals at risk of Alzheimer's disease (INSIGHT-preAD): a longitudinal observational study, Lancet Neurol. 17 (2018) 335–346, https://doi.org/10.1016/S1474-4422(18)30029-2.

[7] K. Doppler, H.M. Jentschke, L. Schulmeyer, D. Vadasz, A. Janzen, M. Luster, et al., Dermal phospho-alpha-synuclein deposits confirm REM sleep behaviour disorder as prodromal Parkinson's disease, Acta Neuropathol. 133 (2017) 535–545, https://doi.org/10.1007/s00401-017-1684-z.

[8] D.W. Dickson, M.G. Heckman, M.E. Murray, A.I. Soto, R.L. Walton, N.N. Diehl, et al., *APOE* ε4 is associated with severity of Lewy body pathology independent of Alzheimer pathology, Neurology 91 (2018) e1182–e1195, https://doi.org/10.1212/WNL.0000000000006212.

[9] O. Bousiges, S. Bombois, S. Schraen, D. Wallon, M.M. Quillard, A. Gabelle, et al., Cerebrospinal fluid Alzheimer biomarkers can be useful for discriminating dementia with Lewy bodies from Alzheimer's disease at the prodromal stage, J. Neurol. Neurosurg. Psychiatry 89 (2018) 467–475, https://doi.org/10.1136/jnnp-2017-316385.

[10] C. Abdelnour, I. van Steenoven, E. Londos, F. Blanc, B. Auestad, M.G. Kramberger, et al., Alzheimer's disease cerebrospinal fluid biomarkers predict cognitive decline in Lewy body dementia, Mov. Disord. 31 (2016) 1203–1208, https://doi.org/10.1002/mds.26668.

Hiroshige Fujishiro
Department of Psychiatry, Kawasaki Memorial Hospital, 20-1 Shiomidai, Miyamae, Kawasaki, Kanagawa 216-0013, Japan
E-mail address: fujishiro17@hotmail.co.jp.