European DLB consortium: diagnostic and prognostic biomarkers in dementia with Lewy bodies, a multicenter international initiative

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As the population ages, the incidence of chronic diseases such as dementia increases. Dementia with Lewy bodies (DLB) is the second most common neurodegenerative dementia after Alzheimer's disease (AD) and even though both diseases are clinically separate entities [1,2], diagnosing DLB can be challenging. Despite validated diagnostic criteria for DLB [3–5], only one in three cases are correctly identified [6]. Hence, the biggest challenges in the diagnosis of DLB at present are reaching an early diagnosis and differentiating DLB from AD [7]. The current consortium diagnostic criteria for DLB have low sensitivity. Sensitivity and specificity were reported as 32 and 95%, respectively against autopsy-confirmed diagnosis [8]. In addition, differential diagnosis is still a concern, particularly in early stages of the disease due to great clinical and neuropathological overlap mainly among DLB, AD and Parkinson's Disease Dementia (PDD). Reaching an accurate diagnosis is essential to personalize management to the very specific challenges DLB patients face. Besides, administering medication without a clear indication increases potential risk for patients as well as the economic burden for healthcare systems [9].

More specific biomarkers for DLB are urgently required in order to achieve better clinical therapeutic decisions. Additionally, prognostic markers are not routinely available. DLB leads to poor outcomes on key indicators including quality of life, caregiver burden, nursing home admission, hospitalization and mortality [10]. However, there is huge variability within DLB, with some patients having a very rapid decline and short survival and other patients having less rapid decline. Therefore, early discrimination between different types of patients is crucial in order to optimize management strategies and disease monitoring. There are no disease-modifying treatments available for DLB yet. However, scientific societies agree that once available, treatments should be initiated at an early disease stage, in other words, when there are still functioning neurons to salvage [11]. Early diagnosis is also crucial for clinical trials of potential novel drugs. Therefore, there is a need for identifying new biomarkers for

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improving the early detection of DLB as well as our ability to distinguish between different neurodegenerative diseases.

The European DLB consortium (E-DLB) is a multicenter and global effort concieved by leaders from the contributing centers and leading scientists in different areas of DLB research and was established in 2015. Main ambitions of the E-DLB consortium is to establish an international consensus on diagnostic criteria for DLB as well as to collect representative and high quality biomarkers data from DLB patients as part of the E-DLB study. The study has been conducted throughout an inception retrospective phase, and currently also involves the ongoing prospective phase.

Retrospective E-DLB data collection

From the E-DLB initiative, initially retrospective data from more than 1000 patients from 40 European centers with DLB data was collected, one of the largest DLB cohorts worldwide [12]. Patients were referrals from outpatient memory, movement disorders, geriatric medicine, psychiatric and neurology clinics. Local institutional ethics committee approvals were available for all centers, including the transfer of neuroimaging data. Out of this initiative, important scientific contributions have been done. Biundo *et al.* compared MMSE and MoCA as tools for measuring cognitive impairment on 265 patients with Lewy body diseases (LBD) and showed that both tests are comparable in measuring the rate of cognitive change over time. However, in patients with Parkinson's disease without dementia the MoCA was found to be a better measure of cognitive status as it lacks both ceiling and floor effects [13]. van Steenoven *et al.* evaluated the prevalence of abnormal cerebrospinal fluid (CSF) AD biomarkers across the spectrum of LBD. A CSF AD profile was more common in DLB (N = 375) compared with PDD (N = 55) and PD (N = 164), and it was associated with more severe cognitive impairment in DLB [14]. Abdelnour *et al.* reported that reduced levels of CSF amyloid β 1–42 were associated with a more rapid cognitive decline in LBD (N = 100) [15]. Kramberger *et al.* showed that the average annual cognitive decline measured by MMSE was approximately two points in DLB patients (N = 835) using a linear mixed effects analyses, but this annual decline was not significantly different from that of AD or PDD patients [16]. Bonnani *et al.* validated quantitative electroencephalogram (EEG) as a tool for differential diagnosis between DLB (N = 79) and AD (N = 133) patients from the E-DLB cohort showing 90 and 64% correct classification for DLB and AD, respectively. Additionally, discriminant analysis was performed to establish cutoff values for each EEG mathematical descriptor [17]. Oppedal and Ferreira *et al.* showed that DLB (N = 333) patients had more overall cortical atrophy on MRI measured by visual rating scales as compared with normal controls (N = 233) and less atrophy in the medial temporal lobe than AD (N = 352). Additionally, a signature hippocampal-sparing atrophy pattern was observed in DLB patients [18]. Morbelli *et al.* found that even though regions with preserved metabolism measured by fluorodeoxyglucose-positron emission tomography (FDG-PET) in 171 patients from the E-DLB cohort are relatively consistent across the DLB spectrum, core DLB features such as parkinsonism, visual hallucinations, rapid eye movement sleep behavior disorder and cognitive fluctuations were associated with hypometabolism in specific regions suggesting a close clinical-imaging correlation in DLB patients [12]. Rongve *et al.* reported two susceptibility *loci* for DLB at genome-wide significance including 828 DLB patients and 82,035 normal control, highlighting the complex relationship between the genetic architecture of DLB and other neurodegenerative disorders [19]. Di Censo *et al.* showed that tau pathology (increased t-tau and p-tau in CSF) in 171 DLB patients was associated with less typical clinical DLB presentation with lower occurrence of Parkinsonism and lower number of concurrent core DLB features indicating a complex molecular relationship between Lewy body and AD-type pathology [20].

The common conclusion from all these published papers from the E-DLB initiative are the urgent need for future prospective studies with larger samples, centralized biomarker and neuroimaging analyses and longer follow-up leading to the prospective initiative.

Prospective E-DLB data collection

Currently, also as part of the E-DLB initiative, prospective/longitudinal data are being collected coordinated by Professor Dag Aarsland (King's College London, UK). The study is built in close collaboration with prestigious institutes not only in Europe, but also in America and Asia. One of the principal aims is to explore the utility of combinatorial biomarkers to improve diagnostic accuracy and the available methods for an early detection of the disease. Very few longitudinal studies have been reported to the present date, and no longitudinal multicenter studies with across-center harmonization of diagnostic procedures have been reported to date.

As of today, the current consortium centers contributing to the prospective E-DLB study are: Fundació ACE (Barcelona, Spain), CMRR Strasbourg (France), Alzheimer Center (Amsterdam, The Netherlands), Memory Clinic Malmo (Malmo, Sweden), Charles University (Prague, Czech Republic), Leuven University Hospital (Leuven, Belgium), Landspitali University Hospital (Reykjavík, Iceland), University of Genoa and University of Chieti-Pescara (Italy), University Medical center Ljubljana, (Ljubljana, Slovenia), United Kingdom network – ENLIST study (5 centers, + more), Karolinska Institutet, Stockholm (Sweden), Stavanger University Hospital, Haugesund Hospital and Betanien Hospital in Bergen, (Norway). For a total of 623 patients with a diagnosis of probable DLB, available data are as follows: MRI = 494, Blood = 383, FDG-PET = 88, Dat-scans = 159, CSF = 22, EEG = 216 (report corresponding to July 2019).

Additionally, centers in other parts of the world have joined the initiative, in China; Kangning Hospital, Peking University Institute of Mental Health and Xuan Wu Hospital (now recruiting). Representing Latin America, Hospital Universitario San Ignacio and Fundación Valle del Lili, both centers in Colombia (waiting for protocol approvals). Collaborative studies with Mayo Clinic in United States are also ongoing [21].

This project, collecting data from across Europe and the world, will make efforts to answer an urgent unmet need regarding diagnostic and prognostic markers of a disease with poor prognosis by using innovative methods and equipment.

Many scientists from different nationalities and institutions will be working with the same cooperative data. For this reason, a global representation of a disease can be achieved, also allowing international comparisons between the participating centers. The E-DLB study is certainly novel and necessary. Findings from this global initiative may set a difference in the way we currently see, diagnose and treat DLB.

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