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Alzheimer's & Dementia: Diagnosis, Assessment & Disease Monitoring 1 (2015) 316-324

Alzheimer's & Dementia

Diagnostic Assessment & Prognosis

Improving the clinical detection of Lewy body dementia with the Lewy body composite risk score

James E. Galvin*

Department of Integrated Medical Sciences, Charles E. Schmidt College of Medicine, Florida Atlantic University, Boca Raton, FL, USA

Abstract

Introduction: Dementia with Lewy bodies (DLB) is a challenge to diagnose, particularly outside of expert centers with long delays in diagnosis leading to significant burden to patients and caregivers. Although consensus criteria have excellent specificity, there is no standardized way to assess symptoms reducing sensitivity. We developed the Lewy body composite risk score (LBCRS) from autopsy-verified cases to improve the ability to detect DLB in clinic and research populations.

Methods: The LBCRS was tested in a consecutive series of 256 patients compared with the clinical dementia rating and gold standard measures of cognition, motor symptoms, function, and behavior. Psychometric properties including floor and ceiling effects; concurrent, construct, and known-groups validity; and internal consistency of the LBCRS were determined. Receiver operator characteristic (ROC) curves assessed the ability of LBCRS to differentiate (1) DLB from Alzheimer's disease (AD), (b) DLB from all dementia, and (c) mild cognitive impairment (MCI) due to DLB from MCI due to AD. The LBCRS was completed independent of the clinical evaluation.

Results: Mean LBCRS scores were significantly different between DLB and AD (6.1 $\pm$ 2.0 vs. 2.4 $\pm$ 1.3, $P < .001$) and between MCI-DLB versus MCI-AD (3.2 $\pm$ 0.9 vs. 1.0 $\pm$ 0.8, $P < .001$). The LBCRS was able to discriminate DLB from other causes of dementia. Using a cutoff score of 3, areas under ROC for DLB versus AD = 0.93 (0.89–0.98) and for MCI-DLB versus MCI-AD = 0.96 (0.91–1.0).

Discussion: The LBCRS increases diagnostic probability that Lewy body pathology is contributing to the dementia syndrome and should improve clinical detection and enrollment for clinical trials.

Keywords: Lewy body dementia; Alzheimer's disease; Mild cognitive impairment; Clinical trials

1. Introduction

The Lewy body dementias, composed of two related disorders: dementia with Lewy bodies (DLB) [1] and Parkinson's disease dementia (PDD) [2], are a challenge to diagnose, particularly outside of expert centers [3]. One of the great challenges in differential diagnosis of neurodegenerative disorders is attributing clinical symptoms to specific pathologies to guide treatment choices and discuss prognosis and clinical course [4,5]. Although PDD provides a potentially easier route to diagnosis because the cognitive disorder begins in face of an established movement disorder [2] and criteria have defined a mild cognitive impairment (MCI) state [6], DLB is a more difficult entity to diagnose with delays in diagnosis approaching 18 months [7] leading to significant burden to patients and caregivers [8–10]. Patients with dementia are often misdiagnosed [7,11] with a neurologist finally establishing a diagnosis of DLB or PDD in 62% of cases [7]. Although consensus criteria for DLB [1] have excellent specificity (79%–100%) [12], there is no standardized way to assess or operationalize many of the cognitive and behavioral symptoms which markedly decrease sensitivity in clinical practice (range 12%–88%) [12,13].

*Corresponding author. Tel.: +1-561-297-4793; Fax: +1-561-297-0914.

E-mail address: galvinj@health.fau.edu

http://dx.doi.org/10.1016/j.dadm.2015.05.004

To address the difficulty in making DLB diagnosis and assist in the diagnosis of PDD, we developed the Lewy body composite risk score (LBCRS) [14] to improve the ability to detect DLB and PDD in clinic and research populations and increase the likelihood of determining whether Lewy bodies are contributing pathology to the cognitive diagnosis. The LBCRS was derived from clinical features in autopsy-verified cases of healthy controls, Alzheimer's disease (AD), DLB, and Parkinson's disease with and without dementia [15]. Features that predicted Lewy bodies at autopsy included extrapyramidal signs, cognitive fluctuations, hallucinations, and sleep disturbances [15]. The LBCRS was initially validated in a research sample with excellent psychometric properties demonstrating discrimination between AD and DLB cases with an area under the curve (AUC) of 96.8% (95% confidence interval [CI], 0.93–1.0) [14]. A cutoff score of 3 provided a sensitivity of 90% and a specificity of 87%. Here, we present the psychometric evaluation of the LBCRS in a well-characterized clinic sample.

2. Methods

2.1. Study participants

Participants were drawn from a consecutive series of 256 referrals to the Pearl I. Barlow Center for Memory Evaluation and Treatment, a dementia specialty practice at NYU Medical Center, from September 2013 to December 2014. Assessments were completed by a transdisciplinary team of a neurologist, geriatric nurse practitioner, social worker, and psychometrician, and all components of the assessment were part of standard of care at our center [16]. The LBCRS was completed by the author after the entire evaluation was performed. During the 75–90 minute office visit, the patient and caregiver underwent a comprehensive evaluation including the clinical dementia rating (CDR) and its sum of boxes (CDR-SB) [17], mood, neuropsychological testing, caregiver ratings of behavior and function, and caregiver burden and depression. This study was approved by the NYU Langone Medical Center Institutional Review Board.

2.2. Clinical assessment

Independent semi-structured interviews were conducted with the patient and a collateral source. The CDR [17] was used to determine the presence or absence of dementia and to stage its severity. The CDR rates cognitive function in six categories (memory, orientation, judgment and problem solving, performance in community affairs, home and hobbies, and personal care); a global CDR 0 indicates no dementia; CDR 0.5 represents MCI or very mild dementia; CDR 1, 2, or 3 corresponds to mild, moderate, or severe dementia. Diagnoses were determined using published clinical criteria for MCI due to AD [18], AD [19], DLB [1] frontotemporal degeneration (FTD) [20,21], and vascular dementia (VaD) [22]. Research criteria were used for defining MCI due to DLB [22–25]. Extrapyramidal features were assessed with the Movement Disorders Society-Unified Parkinson's Disease Rating Scale, motor subscale part III (UPDRS) and a modified Hoehn and Yahr stage was assigned [26]. The Charlson comorbidity index [27] was completed to assess the potential impact of comorbid medical conditions on the patient's cognitive status.

2.3. Caregiver evaluation

Caregivers completed evaluations to determine the presence and severity of noncognitive symptoms observed in the patient and their impact on the caregiver. The neuropsychiatric inventory (NPI) [28] assessed behavior, Mayo fluctuation questionnaire (MFQ) [29] assessed presence of cognitive fluctuations, and Epworth Sleepiness Scale (EES) [30] assessed daytime sleepiness. The Mayo sleep questionnaire (MSQ) [31] assessed the presence of parasomnias, particularly rapid eye movement sleep behavior disorder (RBD). A caregiver rating of daytime alertness was collected using a 1-10 Likert scale [31]. The functional activities questionnaire [32] was used to rate performance of activities of daily living. The Zarit burden inventory [33] evaluated caregiver burden and the personal health questionnaire [34] assessed caregiver depression.

2.4. Neuropsychological evaluation

Each patient was administered a 30-minute test battery at the time of the office visit to assess their cognitive status. The psychometrician was unaware of the diagnosis, CDR stage, or LBCRS. A brief global assessment was performed using the mini mental state examination (MMSE) [35]. The battery included measures of episodic memory (Hopkins verbal learning task) [36]; semantic memory (animal fluency) [37] and 15-item Boston naming test [38]; and working memory (letter-number sequencing) [39]. Two-timed measures addressed psychomotor and executive abilities: trail making A and trail making B [40]. Construction was assessed with the clock drawing task [41]. Mood was assessed with the hospital anxiety depression scale [42] providing subscale scores for depression (HADS-D) and anxiety (HADS-A).

2.5. Completion of the LBCRS

The LBCRS (Table 1) was not considered during the clinical assessment or diagnosis. The LBCRS was completed after all other rating scales were scored and the diagnosis presented to the patient and family. Data were taken from the patient charts to complete the LBCRS with questions 1–4 taken from the UPDRS, question 5 from the ESS, questions 6–7 from the MFQ, question 8 from the NPI, question 9 from the MSQ, and question 10 from physical findings and complaints of the patient. The operationalization of physical findings as being present for at least 6 months or symptoms occurring at least three times over the past 6 months