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Early differentiation of dementia with Lewy bodies and Alzheimer's disease: Heart rate variability at mild cognitive impairment stage

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HIGHLIGHTS

- Differentiating between DLB and AD at MCI stage is often difficult.
- DLB patients exhibited lower levels of almost all HRV parameters than AD at MCI stage.
- HRV may be useful to differentiate DLB from AD at the early stage of disease.

ABSTRACT

Objective: Our study aimed to investigate whether heart rate variability (HRV) could be a useful diagnostic screening tool at MCI (mild cognitive impairment) stage of Dementia with Lewy bodies (DLB) from Alzheimer's disease (AD).
Methods: This retrospective study used a selected sample from Ajou neurological registry. We identified MCI patients who underwent HRV testing at baseline, and who developed probable DLB (MCI-DLB: n = 23) or AD (MCI-AD: n = 32).
Results: The MCI-DLB group exhibited significantly lower levels of almost all HRV parameters compared with the MCI-AD group. Fronto-executive function and visuospatial abilities were poorer in the MCI-DLB group, whereas the extent of verbal memory impairment was greater in the MCI-AD. Verbal memory score was negatively correlated with overall HRV parameters, and visuospatial function was positively correlated with the frequency domain of HRV. Receiver operating curve area under the curve (AUC) analysis revealed that the low frequency component was the best potential diagnostic marker (AUC = 0.88).
Conclusion: MCI-DLB patients exhibited greater cardiac autonomic dysfunction (as measured by HRV) and greater fronto-executive and visuospatial deficit compared with MCI-AD patients.
Significance: HRV may be useful method to differentiate DLB from AD in patients with MCI; this would facilitate early disease-specific intervention.

1. Introduction

Dementia with Lewy bodies (DLB) is the second most common type of degenerative dementia after Alzheimer's disease (AD). Mild cognitive impairment (MCI) is well-known as a precursor of AD, but often also precedes DLB (Ferman et al., 2013; Jicha et al., 2010; McKeith et al., 2016; Yoshizawa et al., 2013). Early differentiation of DLB from AD at MCI stage is crucial for early intervention and prognosis (Bergstrom et al., 2016; Sevigny et al., 2016). However, clinical diagnosis of DLB in the early stages can be difficult because few patients display all of the core clinical features, which leads to low sensitivity of current DLB criteria (Nelson et al., 2010).

To identify DLB at the MCI stage, various imaging methods including positron emission tomography (PET), cardiac iodine-123-meta-iodobenzylguanidine (MIBG) scanning, and MRI, have been suggested (Kantarci et al., 2016; Oda et al., 2013; Roquet et al., 2016), but simpler markers are also warranted to assist with the early identification of DLB.

Cardiac autonomic dysfunction occurs early in Lewy body disorders (LBD), including Parkinson's disease (PD), DLB, and REM sleep behavior disorder (RBD) (Cersosimo and Benarroch, 2012; Takahashi et al., 2015). Heart rate variability (HRV), measured by electrocardiography (ECG), is a simple and non-invasive method used to examine cardiac autonomic dysfunction. HRV is known

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to be reduced in Parkinson's disease or even in RBD, which is regarded premotor phase of LBD (Alonso et al., 2015; Valappil et al., 2010).

There has been increasing awareness regarding the association between cognitive impairment and HRV (da Silva et al., 2018). Impaired HRV could lead to blood pressure dysregulation or orthostatic hypotension resulting in cerebral hypoperfusion that contribute to the progression of cognitive decline (Bellelli et al., 2002; Kanemaru et al., 2001; Sloan et al., 1997a,b). In turn, neurodegenerative processes could influence cardiac autonomic dysfunction (Thayer et al., 2009; Thayer and Lane, 2009).

But, to the best of our knowledge, there is no direct study to compare reduction of HRV in patients with MCI preceding DLB and AD. Therefore, in the present study, we investigated HRV in patients with AD and DLB at MCI stage with detailed neuropsychological tests to verify the clinical usefulness of HRV for early differentiation between of these conditions.

2. Patients and methods

2.1. Patients

In this case-control study from Ajou neurological registry, 328 consecutive participants who underwent comprehensive neuropsychological evaluation, HRV testing and MRI (2012–2014) were initially selected. Of these, 132 were diagnosed with dementia and were excluded (81 had AD, 39 had vascular dementia, 12 had DLB), leaving 109 subjects with a diagnosis of MCI and 87 with normal cognition. From these 109 MCI subjects, patients who subsequently developed probable DLB (MCI-DLB; n = 23) after an average follow-up of 30 months were identified. In the same cohort, 46 patients with MCI who progressed to AD (MCI-AD) over a similar follow-up period were identified. From these 46 MCI-AD patients, 32 subjects frequency-matched based on age, sex, and education to DLB-MCI were selected. Among subjects excluded owing to normal cognition, a sample of age- and sex-matched individuals were selected as control group (n = 36).

We excluded subjects with (1) focal brain lesions, multiple lacunar infarctions or diffuse white matter hyperintensity, (2) clinical diagnosis with PD, (3) diabetic mellitus or cardiac diseases and (4) medications which was known to influence the cardiac autonomic functions, such as beta-blockers or thyroxine.

2.2. Neuropsychological tests

The diagnosis of MCI was based on Seoul Neuropsychological Screening Battery (SNSB). The SNSB assesses five domains: attention, verbal and visual memory, language, visuospatial function, and frontal/executive function. If at least one of five cognitive domains on the SNSB was abnormal, the patients were diagnosed with MCI (Ahn et al., 2010). The SNSB is comprehensive neuropsychological test and the most commonly used NP test in Korea. The specific tests used were the Seoul Verbal Learning Test (SVLT); the Rey Complex Figure Test (RCFT); the Controlled Oral Word Association Test (COWAT); the Korean version of the Boston Naming Test (K-BNT); Stroop color-word test. This study was approved by the local ethical committee at Ajou University Hospital and consent including information of study was obtained from all participants.

2.3. Follow-up

Subjects with MCI were followed-up at outpatient clinic, at least twice per year. Each of meeting, experienced movement disorder specialist (Y.J.H) evaluated the clinical status of patients and diagnosed the probable DLB or AD using the established criteria (McKeith et al., 2005; McKhann et al., 1984).

During follow-up, patients with probable AD were classified as MCI-AD, and patients with probable DLB were classified as MCI-DLB. 19 MCI patients with DLB underwent [18F]- fluoropropyl-CIT PET (FP-CIT PET) scans and every patient showed decreased dopamine transporter uptake in the posterior putamen.

2.4. Measurement of HRV

The ECG recordings of all subjects were performed in quiet conditions. Before the recording, all subjects were instructed to avoid alcohol or caffeinated beverages after 10 p.m. (22:00) at night and to avoid smoking 1 h before the recording. To control for diurnal variation, HRV was measured in the morning, between 8 a.m. (08:00) and 12 a.m. (12:00) using the SA-2000E model (Medi-core, Seoul, Korea) (Kim and Woo, 2011; Park et al., 2007). The subjects were asked to lie on a bed with electrodes placed on their wrists and left foot. The respiratory rate (RR) was measured. After arrhythmia and artifact removal, HRV was calculated for time and frequency domains using The SAP 2000E software ® (MEDICORE, Korea). The frequency domain parameters were obtained by the fast Fourier transforms technique, a widely used mathematical method for transforming time-dependent signals (e.g., RR intervals) to the frequency domain. Powers in the two frequency bands of HRV, low frequency (LF: 0.04–0.15 Hz), high frequency (HF: 0.15–0.4 Hz), and total spectral power (TP) were obtained. Time domain measure such as the standard deviation of the normal-to-normal interval (SDNN) and the root-mean square difference of successive RR intervals (RMSSD) was also calculated. This software was acknowledged as the first developer of eastern reference for HRV in the world. HRV clinical data were collected from 3600 people with 8 university hospital in Korea (Kim and Woo, 2011). HRV oriental reference is patented by Korean Industrial Property Office in 2005.

2.5. Assessment of nigrostriatal dopamine depletion

FP-CIT PET images of each patient were assessed according to a predefined visual grading method (Grade 0–3) (Benamer et al., 2000).

2.6. Statistics

Independent mean t-tests or one-way analysis of variance (ANOVA) were used to compare groups and Pearson's $\chi 2$ test to compare frequency of categorical variables, and these tests were followed by Bonferroni post hoc comparisons. A univariate analysis of covariance (ANCOVA) with age, gender, and education entered as covariates was performed to compare the raw scores of each neuropsychological score. The main and interaction effects were tested at a critical level of $\alpha = 0.05$. Partial correlations between HRV parameters and neurocognitive test scores were performed including age, gender, and education as confounders. To avoid inflated likelihood of error in multiple comparison in correlation analysis, an adjusted p-value was used to test for significance. To calculate this using Bonferroni's method, desired p-value (0.05) is divided by the number of comparison being conducted. The sensitivity and specificity differentiating MCI-DLB from MCI-AD were assessed using a receiver operating characteristic (ROC) analysis. To compare areas under the ROC Curves, DeLong's method was used. Statistical tests were performed using SPSS V.19. In all the analyses, significance was considered for $P < 0.05$.