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The relationship of leukoaraiosis and the clinical severity of vascular Parkinsonism

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ABSTRACT

Vascular Parkinsonism (VP) is referred to as secondary Parkinsonian syndrome. It occurs with lacunar state or subcortical white matter micro-angiopathy and is highly associated with vascular risk factors and leukoaraiosis, also known as cerebral white matter lesions (WML). This study aimed to assess the prevalence of different vascular risk factors and WML in patients with VP, and their impact on clinical features. Sixty-two consecutive VP patients (70.2 ± 9.2 years) were evaluated for clinical severity using the Unified Parkinson's Disease Rating Scale (UPDRS). WML was assessed and scored on fluid-attenuated inversion recovery T2-weighted (FLAIR) magnetic resonance imaging (MRI). Cerebro-vascular risk factors, WML severity, and the UPDRS for clinical disability were analyzed statistically. There were no associations between WML score and age, sex, hypertension, diabetes, previous stroke, cardiac disease, cigarette smoking, or serum levels of cholesterol and triglyceride. The WML score positively correlated with UPDRS part I ($p = 0.035$) and part III ($p = 0.041$) scores. After adjustments for age, gender, stroke history, and use of levodopa, the WML score was associated with the UPDRS total ($p = 0.020$), part I ($p = 0.012$), part II ($p = 0.039$), and part III ($p = 0.019$) scores. The severity of WML is not associated with conventional vascular risk factors in VP patients but is significantly correlated with the UPDRS total and all sub-scores, which suggests that disruption of the cortico-sub-cortical circuits may lead to impaired mentation, behavior and mood, activities of daily living, and motor performance in these patients.

1. Introduction

Vascular Parkinsonism (VP) described by Critchley in 1929 as "arteriosclerotic Parkinsonism", is one of the most important causes of secondary Parkinsonism. Compared to Parkinson's disease (PD), VP is characterized by older onset age, shorter disease duration, earlier gait disorder, less resting tremor, and less responsiveness to levodopa [1–3]. Moreover, it affects the lower limbs more than the upper ones, i.e., lower-body Parkinsonism, and is often associated with pseudo-bulbar palsy, cerebellar signs, and cognitive impairment [4–6]. Findings by magnetic resonance imaging (MRI) include white matter changes, multiple lacunar infarctions in the basal ganglia, or rarely, a solitary vascular lesion involving the basal ganglia [4].

Leukoaraiosis, also known as white matter lesion (WML), has been coined as the radiologic appearance of patchy or diffuse abnormalities in the deep white matter that appear as low attenuation on computed tomography (CT) or high intensity signal on T2-weighted MRI. Arteriosclerosis of the penetrating arteries is fundamental to the mechanism of the white matter changes and is due to hemodynamic ischemia rather than infarction from thrombo-embolic occlusion of arterioles [7]. Arterial hypertension, hyperlipidemia, diabetes mellitus, cardio-vascular diseases, and smoking are classic risk factors for atherosclerosis, which is not only related to cerebrovascular disorders but also to cerebral white matter abnormalities [8].

Leukoaraiosis per se may underlie the intellectual impairment in the elderly, as well as of the slowing of distinct motor and attention functions [9]. WML is correlated with cognitive changes in aged persons [10–12], and PD patients [13]. To date, no study has explored the relationship of clinical manifestations of VP and WML. This study hypothesizes that the clinical severity of patients with VP may be positively correlated with WML.

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2. Materials and methods

The study was approved by the Institutional Review Board of Kaohsiung Chang Gung Memorial Hospital (No. 97-057B) and all subjects gave written informed consent.

2.1. Patients

Consecutive patients were collected between September 2008 and March 2009 in the Neurology Department of Kaohsiung Chang Gung Memorial Hospital. Patients with Parkinsonism (the presence of hypokinesia/bradykinesia and at least one of the following: tremor, rigidity, and postural instability) and a vascular score of ≥2 diagnosed as VP according to the criteria proposed by Winikate and Jankovic [6] were included in this study. Vascular disease was assessed using a vascular rating scale as follows: two points for pathologically or angiographically proven diffuse vascular disease, 1 point for onset of Parkinsonism within 1 month of clinical stroke, 1 point for history of two or more strokes, 1 point for history of two or more risk factors for stroke, and 1 point for neuro-imaging evidence of vascular disease in two or more vascular territories [6]. To prevent a coincidence of vascular changes in some patients with PD, we excluded patients who met the UK Parkinson's Disease Society Brain Bank criteria [14] for idiopathic PD and subsequent cerebro-vascular disorders. Besides, we excluded patients with MRI showing significant hydrocephalus and those with disabling stroke with modified Rankin score >3.

Demographic and clinical data, including age, gender, previous stroke, use of levodopa, and cerebro-vascular risk factors like hypertension, diabetes mellitus, cardiac disease, smoking status, and lipid profiles were recorded. Serum levels of total cholesterol and triglyceride (TG) were measured after 12-h fasting.

2.2. Cognitive function and motor performance evaluation

An experienced movement disorder specialist (Chang YY) assessed the VP patients in using the UPDRS. The UPDRS part I evaluated mentation, behavior and mood, part II activities of daily living, and part III motor performance. The total UPDRS was the sum of parts I, II and III scores.

2.3. MRI study

According to facility availability, the patients were examined with one of the two MRI systems, either 1.5 T or 3.0 T scanner (GE Medical Systems, Milwaukee, WI). With the 1.5 T unit, the imaging protocol included axial T1-weighted (TR/TE/excitation [NEX], 475/min full/2), T2-weighted (TR/TE/NEX, 4000/96/3, echo train length [ETL]: 14), and FLAIR (TR/TE/inversion time [TI], 9000/133/2000). With the 3.0 T unit, the imaging protocol included axial T1-weighted (TR/TE/NEX, 500/min full/2), T2-weighted (TR/TE/NEX, 4200/102/2, ETL: 18), and FLAIR (TR/TE/TI, 8000/100/2000). The images were obtained with a 5-mm section thickness and a 2-mm gap, a 192 × 224 matrix, and a 20–24 cm field of view.

2.4. Total white matter lesions (WML) score

An experienced neurologist (Lan MY) rated the hyper-intensity lesions in the white matter on FLAIR MRI using a visual rating scale modified from that proposed by Fazekas et al. [15] in the peri-ventricular (PV) area and centrum semiovale (CS). The PV hyper-intensity was graded as 0 for absence, 1 for "caps" or pencil-thin lining, 2 for smooth "halo", and 3 for irregular PVH extending into the deep white matter. Separate CS hyper-intense signals were rated as 0 for absence, 1 for punctuate foci, 2 for beginning confluence of foci, and 3 for large confluent areas (Fig. 1).

The WML score was calculated by summing up the scores in the bilateral PV and CS areas, with a range theoretically from 0 to 12 points. Hyper-intensity caused by focal infarction was omitted in the scoring. For a region containing a large sub-cortical infarction that was difficult to rate, the corresponding area in the contralateral cerebral hemisphere was scored.

2.5. Statistical analyses

Data of continuous variables were presented as mean ± standard deviation unless otherwise specified. The *T*-test and x^2-test were performed to compare demographic and clinical characteristics of the patients with respect to the MRI system. For the study population, data of WML and UPDRS scores were obviously skewed from the normal distribution. Thus, the association of WML score with demographic and clinical characteristics and UPDRS scores was analyzed using Spearman's non-parametric correlation test or the Mann–Whitney *U* test. Multiple linear regression analysis was performed to identify independent determinants for the UPDRS scores. The covariates included age, sex, previous stroke, use of levodopa, and WML score. A $p < 0.05$ was considered statistically significant. All data were analyzed using the Statistical Package for the Social Sciences (ver. 10) software (Chicago, Illinois).

3. Results

Sixty-two patients with VP (mean age 70.2 ± 9.2 years, range 44–92 years; males, 66.1%) were recruited. Among them, 82.3% had hypertension, 33.9% had diabetes, 72.6% had previous strokes, 17.7% had cardiac disease, 43.5% were cigarette smokers, and 43.5% received levodopa treatment. The total UPDRS score was 60.3 ± 24.1 (median, 60.5; range, 22–132). Clinically, relative symmetry of motor symptoms with lower body predominance, gait disorder, postural instability, and falling was common in our patients. Besides, less resting tremor, and less responsiveness to levodopa could be identified.

For brain MRI study, 41 patients (66.1%) were examined with the 1.5-T system and the rest by the 3.0-T system. The WML score was 24.1 ± 4.6 (median, 24; range, 13–35). Patients examined by the 1.5-T MR system had more stroke history (85.4% vs. 47.6%, $p = 0.002$) and fewer cigarette smokers (2.4% vs. 19.0%, $p = 0.023$) than those examined by the 3.0-T system. Aside from this, there was no difference in the other demographic and clinical data, WML score, and UPDRS (total and parts) scores between the two groups of patients (Table 1).

As regards similarities in clinical characteristics, the patients examined by the 1.5-T system and those by the 3.0-T system were combined for subsequent analyses. There were no associations between WML score and age, sex, hypertension, diabetes, previous stroke, cardiac disease, cigarette smoking, or serum levels of cholesterol, triglyceride, and homocysteine (Table 2).

There were positive correlations of WML score with the UPDRS part I and III scores (part I, correlation coefficient = 0.268, $p = 0.035$; part III, correlation coefficient = 0.260, $p = 0.041$) (Table 2). The WML score was associated with the UPDRS total (R2 variance = 0.092, $p = 0.020$), part I (R2 variance = 0.112, $p = 0.012$), part II (R2 variance = 0.073, $p = 0.039$), and part III (R2 variance = 0.094, $p = 0.019$) scores after adjusting for age, gender, stroke history, and use of levodopa (Table 3).

4. Discussion

Hypotheses on the pathogenesis of WML in the elderly have been focused on the ischemia paradigm. Most risk factors involved with WML are similar to cerebro-vascular risk factors, such as hypertension, diabetes, oxidative stress, or hyper-homocysteinemia [8]. In the current study, nevertheless, age, hypertension and other cerebro-vascular risk factors are not significantly correlated with the WML score. This can be mainly attributed to the relatively small sample sizes in our cohort, due to low prevalence of VP clinically with the difficulties in the case

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