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Triple stimulation technique findings in vascular Parkinsonism and Parkinson's disease

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HIGHLIGHTS

- Clinically, vascular Parkinsonism is difficult to diagnose clearly because this disease is very heterogeneous, and there are currently no biomarkers to diagnose vascular Parkinsonism.
- In triple stimulation technique, TST amplitude ratios reflecting upper motor neuron involvement were significantly different between vascular Parkinsonism and Parkinson's disease.
- The triple stimulation technique is an effective technique that may provide useful information for differentiating vascular Parkinsonism from Parkinson's disease.

ABSTRACT

Objective: One of the predominant clinical features that differentiates vascular Parkinsonism (VP) from Parkinson's disease (PD) is the pyramidal sign. The triple stimulation technique (TST) is one of the most sensitive methods for comparing upper motor neuron involvement in patients with VP and PD. This study aimed to evaluate the usefulness of the TST as a diagnostic tool for VP.
Methods: Thirteen VP patients, 18 PD patients and 10 age-matched healthy controls were enrolled in this study. We obtained basic participant demographic information and transcranial magnetic stimulation (TMS) parameters, including the TST amplitude ratio, from all participants. We compared the TMS parameters among the VP, PD and control groups.
Results: The TST amplitude ratio was significantly lower in the VP group than in the PD and control groups (71.59 ± 11.86 vs. 96.42 ± 5.11 and 97.70 ± 3.82, respectively; $p < 0.01$). The TST amplitude ratio was positively correlated with scores obtained on the United Parkinson's Disease Rating Scale-III, which reflects motor function.
Conclusions: The TST is an effective and easy technique that offers improved diagnostic sensitivity in patients with VP by assessing upper motor neuron involvement. The TST may also represent a useful monitoring tool for evaluating disease progression.
Significance: This study is the first to assess pyramidal involvement in patients with VP using the collision technique.

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1. Introduction

Critchley was the first to describe a syndrome characterised by hypokinetic-rigid Parkinsonism with arteriosclerosis and recurrent strokes (Critchley, 1929). This 'vascular Parkinsonism' (VP) has long been a controversial medical entity. Despite great advances in diagnostic methods, VP remains imprecisely defined and is considered a neuropathological diagnosis only after Lewy body disease and other neurodegenerative diseases related to Parkinsonism have been excluded (Murrow et al., 1990). Thus, differentiating VP from Parkinson's disease (PD) is extremely challenging because the vascular pathology can co-occur in patients with PD, such as basal ganglia infarction in PD with Lewy body pathology (Yamanouchi and Nagura, 1997).

Clinically, predominant bilateral symmetrical lower limb involvement, gait dysfunction, postural instability, falls, the absence of resting tremor and poor levodopa response are considered the hallmark features of VP (Gupta and Kuruvilla, 2011). Numerous previous studies have suggested that specific neuroimaging and other investigations may be helpful for distinguishing VP from PD. Presynaptic striatal dopamine transporter scanning is helpful in making differential diagnoses between VP and PD. Two prior studies reported that the striatal uptake ratio was reduced in patients with PD, whereas another study indicated that only the mean asymmetrical index was reduced in patients with VP (Gerschlager et al., 2002; Tzen et al., 2001; Zijlmans et al., 2007). In addition, magnetic resonance spectroscopy, transcranial Doppler sonography and cardiac metaiodobenzylguanidine (MIBG) scintigraphy have been proposed as potential adjuvant diagnostic tools (Kim et al., 2006; Tsai et al., 2007; Zijlmans et al., 1994). However, specific imaging protocols are limited as screening or monitoring tools because of the cost and time constraints associated with these techniques.

One clinicopathological study revealed that pyramidal signs were found in 63% of VP patients but that no pyramidal tract signs were observed in PD patients (Yamanouchi and Nagura, 1997). Recently, Glass et al. (2012) reported that 54.2% of patients with pathologically confirmed VP demonstrated pyramidal signs. Thus, we hypothesised that patients with VP may exhibit clinical or subclinical upper motor neuron (UMN) involvement, and UMN impairment may be a useful marker to differentiate between VP and PD.

Transcranial magnetic stimulation (TMS) is widely used to evaluate the integrity of the motor pathway in various diseases (Chen et al., 2008). A collision technique known as the triple stimulation technique (TST) has proven to be more sensitive in assessing UMN impairment than other conventional TMS parameters (Magistris et al., 1998). Numerous studies have been published using the TST as a diagnostic and monitoring tool in amyotrophic lateral sclerosis (ALS) and stroke (Rosler and Magistris, 2004; Rosler et al., 2000; Tan et al., 2013). In previous movement disorder studies, the TST has been identified as a potentially useful measure to make differential diagnoses between PD and multiple system atrophy by assessing UMN impairment (Eusebio et al., 2007). The TST may also be helpful in diagnosing spinocerebellar ataxia type 6 (SCA6), which involves the corticospinal tract (Sakuma et al., 2005). However, to the best of our knowledge, no previous study has assessed pyramidal involvement in VP using the TST.

The purpose of this study was to evaluate UMN impairment in patients with clinically diagnosed VP using the TST method and to determine whether the assessment of UMN impairment using this technique was effective in differentiating VP from PD.

2. Patients and methods

2.1. Subjects

We recruited 13 patients with VP who satisfied Zijlmans' proposed diagnostic criteria (Zijlmans et al., 2004), 18 patients with PD and 10 age-matched healthy control subjects from the Gangneung Asan Hospital Neurology clinics in Gangneung, South Korea. All PD patients were diagnosed using the United Kingdom Parkinson's Disease Society Brain Bank criteria (Hughes et al., 1992). Disease severity was assessed according to the 'on' state of the United Parkinson's Disease Rating Scale-III (UPDRS-III) and the Hoehn and Yahr (H&Y) stage. The vascular rating scale proposed by Winikates and Jankovic (1999) was also used to evaluate VP patients. Basic demographic and clinical information was obtained from all VP and PD patients, including symptom duration, presence of tremor, gait disturbance, low body predominance, freezing, falls and pyramidal signs. Levodopa response was also assessed in all VP and PD patients. Good responsiveness to levodopa was defined as an improvement of >20% on the UPDRS-III score compared with baseline. Magnetic resonance imaging (MRI) of the brain was performed on all patients. For PD patients, abnormalities on the MRI precluded enrolment, except for minimal evidence of small vessel disease (other than in the basal ganglia) that the radiologist determined to be relatively age appropriate. Previous history of stroke was an exclusion criterion for PD patients. Individuals in the control group had no significant medical history or MRI abnormalities (i.e., severe white matter lesion and space-occupying lesion) that could affect the TMS parameters. Lesions visualised via MRI in VP patients were categorised into five groups: juxtaventricular, periventricular white matter lesions, deep white matter lesions, juxtacortical lesions and lacunar infarctions. We also excluded subjects with a history of neuropathy or other conditions that could affect the conventional TMS parameters and TST amplitude ratio.

Informed consent was obtained from all patients according to the Helsinki Declaration, and this study was approved by the Institute of Gangneung Asan Hospital Ethics Committee.

2.2. Conventional TMS study

Conventional TMS was performed using a Magstim magnetic stimulator (Magstim Company, Dyfed, UK) on the contralateral hand-associated motor cortex using a circular coil. First, the compound motor action potential (CMAP) recording was assessed from the abductor digit minimi (ADM) muscle on the ipsilateral side, using a supramaximal stimulus performed on the ulnar nerve at the wrist. All subjects were comfortably seated in a chair with the surface Ag/AgCl electrode located over the ADM. The resting motor threshold (RMT) was determined as the lowest stimulation intensity that could induce a motor-evoked potential (MEP) of 50 μV amplitude measured peak to peak from the ADM in five of 10 trials. After the RMT was obtained, five MEPs were elicited using 130% of the RMT stimulus intensity. Next, the MEP amplitude ratio (MEPAR) was calculated as a ratio of the obtained CMAP amplitude (baseline-to-peak) to baseline-to-peak amplitude of the MEP. Latencies of the cortical and cervical root evoked potentials were assessed to obtain the central motor conduction time (CMCT). A circular coil was placed over the frontoparietal region to stimulate the ADM. Stimulus pulses of increasing intensity were administered to each participant (maximum intensity: 130% of RMT). When the stimulus intensity was greater than the threshold, the onset latency of the MEP was obtained. The onset latency was defined as the shortest latency from the MEP out of 10 trials. Next, the magnetic stimulation was applied to the C7 overlying proximal