Neuroscience Letters 534 (2013) 155–159

Contents lists available at SciVerse ScienceDirect

Neuroscience Letters

journal homepage: www.elsevier.com/locate/neulet

TMS follow-up study in patients with vascular cognitive impairment-no dementia

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HIGHLIGHTS

- Vascular cognitive impairment-no dementia (VCI-ND) is an at risk state for dementia.
- We aimed to detect measures of cortical excitability related to disease progression.
- After a follow-up period, the resting motor threshold decreased in VCI-ND patients.
- The observed change might be a plastic mechanism compensatory to VCI progression.
- TMS enhances the understanding of VCI-ND process and its progress.

ARTICLE INFO

Article history:
Received 30 August 2012
Received in revised form
29 November 2012
Accepted 12 December 2012

Keywords:
Vascular cognitive impairment-no dementia
Transcranial magnetic stimulation
Motor threshold
Executive dysfunction

ABSTRACT

Vascular cognitive impairment-no dementia (VCI-ND) is a condition at risk for future dementia and should be the target of preventive strategies. Recently, an enhanced intracortical facilitation observed in VCI-ND patients was proposed as a candidate neurophysiological marker of the disease process. The aim of this study was to monitor the excitability of the motor cortex and the functioning of excitatory/inhibitory intracortical circuits in patients with VCI-ND after a follow-up period of approximately 2 years, in order to pick out early markers of disease progression into dementia. Nine patients and 9 age-matched controls were re-evaluated for single and paired pulse TMS measures of cortical excitability, as well as for neuropsycological and functional assessment. Compared to the first evaluation, patients showed a decrease of the median resting motor threshold (rMT). Patients exhibited a significant worsening at Stroop Color-Word Test Interference scores without substantial functional impairment. Our study represents the first evidence of a decrease of rMT in VCI-ND patients during the progression of cognitive impairment. This result might be considered an index of motor cortex plasticity and interpreted as a compensatory mechanism for the loss of motor cortex neurons.

1. Introduction

The term vascular cognitive impairment-no dementia (VCI-ND) describes a group of individuals with cognitive loss of presumed vascular origin without substantial functional impairment [19]. Although not yet well defined, there is a growing body of literature that highlights the relevance of this concept as a target for preventive interventions on vascular dementia. In the Canadian Study of Health and Aging, VCI-ND was the most prevalent form of VCI among people aged ≥65 years [33]. Clinically, executive dysfunction associated with poor performance on other measures of cognition and with worse short-term outcome and mood and behavioral disorders are its most prominent cognitive features [19,20,22]. Moreover, it has been shown that even a mild form of VCI-ND is associated with an adverse outcome, probably as a consequence of early motor impairment (such as gait and

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http://dx.doi.org/10.1016/j.neulet.2012.12.017

balance disturbances, postural instability, urinary complaints) or early impacts on executive function [12].

Although cross-sectional evidence seems to suggest that VCI-ND might be a benign condition, lying between normal cognition and vascular dementia [37], a 5-year follow-up study on progression of cognitive and functional impairment showed that 52% of VCI-ND patients died and 46% developed dementia [38]. Moreover, VCI-ND confers an increased risk of death and institutionalization [33] and carries an high risk of post-stroke dementia [36].

However, unlike degenerative dementias, VCI can be counteracted by a careful prevention strategy and a close monitoring of vascular risk factors. Therefore, the identification of patients with VCI-ND or at an early stage of dementia, by means of specific clinical and biological markers, would be desirable in an attempt to stop the progression of vascular dementia. To date, the exact mechanisms leading to dementia or to preserved cognition are not well understood, although endogenous compensatory mechanisms, at both cellular and network levels, have been proposed [25].

In a recent study using Transcranial Magnetic Stimulation (TMS), we observed an enhanced motor cortex facilitation (ICF) in a group of 10 elderly patients with subcortical vascular disease and a neuropsychological picture of VCI-ND, compared to age-matched controls [4]. This finding first provided an electrophysiological support to the hypothesis that age-related white matter lesions might result in functional changes of intracortical excitatory neuronal circuits, even in the absence of modification of resting motor threshold (rMT). A compensatory role in response to vascular damage of the frontal cortical–subcortical circuits was also suggested in elderly patients with vascular depression [3], in whom a trend toward an enhancement of intracortical facilitation was found.

To further clarify the impact of subcortical vascular lesions on motor cortex excitability and to define the meaning of the observed enhancement of ICF in a population at risk for vascular dementia, we re-evaluated, after about a 2-years follow-up period, subjects who were diagnosed at the entry to the study as VCI-ND. Given that rMT is stably affected in dementing processes [29,30], we hypothesized that VCI-ND patients who progress into dementia would exhibit a pattern of cortical hyperexcitability.

2. Materials and methods

2.1. Subjects

Of the original cohort of 10 VCI-ND patients, 1 was no more eligible to perform TMS because of a permanent pacemaker implantation due to a severe bradyarrhythmia; nevertheless, the patient was re-evaluated for the neuropsychological profile. Of the 10 controls previously enrolled 1 was lost to follow-up. Nine patients (median age 70 years; range 66–84 years) and 9 age-matched controls (median age 67 years; range 65–88 years) were finally re-evaluated after a follow-up of approximately 2 years (22.1 ± 3.5 months).

At the entry of the study patients did not meet all the DSM-IV criteria for dementia and fulfilled the brain imaging criteria for subcortical vascular disease (SVD) [9].

Major psychiatric disorders, other neurological disease (i.e. stroke, epilepsy, movement disorders, inflammatory demyelinating disease, head trauma), chronic medical illness affecting cognitive functions, alcohol abuse or drug acting on the cerebral nervous system were exclusion criteria.

The study was approved by the local ethics committee and informed consent was obtained from all subjects.

2.2. Assessment

None of the eligible participants developed neurological deficits or other medical complications over the follow-up period. All patients and controls were retested with the same neuropsychological and functional assessment, including the evaluation of global cognitive status, frontal lobe abilities, mood and behavior symptoms, basic and instrumental activities of daily living, for details see Bella et al. [4], and TMS protocol performed at the entry of study.

At baseline in VCI-ND patients the severity of the white matter lesions was rated by the visual Fazekas scale. Neuroimaging of the brain was not repeated since none of the patients complained of new neurological symptoms with respect to the baseline evaluation and general and neurological exams did not show other pathological findings with respect to the first examination.

2.3. Transcranial magnetic stimulation

TMS was performed using a High-power Magstim 200 magnetic stimulator (Magstim Co., Whitland, Dyfed, UK). A 70 mm figure-of-eight coil was held over the motor cortex at the optimum scalp position to elicit motor responses in the right and the left First Dorsal Interosseous (FDI) muscles. The induced current flowed in a posterior–anterior direction. Electromyographic (EMG) activity was recorded from a silver/silver-chloride surface active electrode placed over the motor point of the target muscle with the reference electrode placed distally at the metacarpophalangeal joint of the index finger. Motor responses were amplified and filtered (bandwidth 3–3000 Hz) using a Medelec Synergy (Oxford Instruments) system with gains of 100 μV and 5 mV/div. Resting motor threshold and amplitude of MEP, central motor conduction time (CMCT), silent period duration, the short latency intracortical inhibition and intracortical facilitation to paired TMS. Resting Motor Threshold (rMT) was defined as the lowest stimulus intensity able to elicit MEPs of an amplitude >50 μV in at least 5 of 10 trials, with the muscle at rest. CMCT was calculated by subtracting the peripheral conduction time from the spinal cord to muscles from the latency of responses evoked by cortical stimulation. The Cortical Silent Period (CSP) was determined with an approximately 50% of maximum tonic voluntary contraction of the FDI muscles, induced by single TMS pulses delivered at 130% of rMT. The mean CSP duration of ten rectified trials was calculated. Short latency intracortical inhibition (SICI) and intracortical facilitation were studied using a paired pulse magnetic stimulation paradigm [14]. Two magnetic stimuli were given through the same stimulating coil, using a Bistim module connected to a CED micro 1401 interface (Cambridge Electronic Design, Cambridge, UK), over the motor cortex, and the effect of the first (conditioning) stimulus on the second (test) stimulus was investigated. The conditioning stimulus (CS) was applied at 80% of the subject's rMT, and the intensity of the test stimulus (TS) was set at 130% of the rMT. The Interstimulus Intervals (ISIs) tested were 1, 3, 5, 7, 10 and 15 ms. Ten trials for each ISI, for the conditioning stimulus alone and for test stimulus alone, were recorded in a random way with an 8-s interval among each trial. The responses were expressed as the ratio of the MEP amplitude produced by paired stimulation to that produced by test stimulation alone. The subjects were seated in a comfortable chair and were given audiovisual feedback at high gain to assist in maintaining complete relaxation.

2.4. Statistical analysis

All changes observed for the different parameters taken into account in this study were first quantified as the difference between