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Impaired cognitive functions in adult-onset primary cranial cervical dystonia

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ABSTRACT

Background: Adult-onset primary dystonia is thought to be a purely motor disorder. Nevertheless, several studies provided evidence that sensory and psychiatric disturbances may contribute to the clinical spectrum of of dystonia, whereas evidence supporting cognitive impairment is still limited.
Methods: A set of neuropsychological tests was administered to non depressed, non demented patients with cranial-cervical dystonia and healthy control subjects. The test battery included *n*-Back Task, Wechsler Memory Scale, Trail Making Test version A and B, and Wisconsin Card Sorting Test.
Results: As compared with healthy control subjects of similar age, sex and socio-economic status, patients with cranial-cervical dystonia showed deficit on working memory functions revealed by *n*-Back task, impairment of mental control and visual reproduction subtests of Wechsler memory scale, deficit on information processing speed and set-shifting capacity revealed by Trail Making Test A and B.
Conclusion: Patients with cranial-cervical dystonia may have impairment in specific cognitive domains relative to working memory, processing speed, visual motor ability and short term memory. Probably, these deficits are not dependent on the clinical expression of dystonia but might rather reflect the cortical and subcortical changes highlighted by functional and VBM imaging studies in patients with different forms of dystonia.

1. Introduction

Adult-onset primary dystonia (AOPD) is considered the most common form of dystonia [1]. The general belief that AOPD is a purely motor disorder has been recently challenged by studies revealing that many AOPD patients carry other non-motor features [2]. This is not surprising given the grey matter abnormalities detected in non-motor brain regions of AOPD patients by functional imaging and voxel based morphometry (VBM) studies. Moreover, even the putative core abnormality in basal ganglia [3] might be expected to have non-motor consequences. In fact, the Basal Ganglia receive inputs from all cortical areas and throughout the thalamus project to several cortical areas, thus participating to circuits that have been linked to motor as well as sensory, emotional and cognitive functions [4,5].

Several studies provided convincing evidence that sensory and psychiatric disturbances should be included into the non motor spectrum of AOPD [6]. On the other hand, evidence supporting cognitive impairment in AOPD is still limited. Two earlier studies reported an attention deficit in patients with different forms of early- and late-onset of dystonia [7,8]. However, these studies might have been limited by the small size and the clinical heterogeneity of the examined samples, by concomitant therapy with dopaminergic and anti-cholinergic medication [7], and by possible distracting effects of dystonic spasms and depression [8]. A later study performed in a small sample of 20 patients with primary blepharospasm (BSP) and 17 healthy controls also observed that BSP patients were impaired on complex movements planning, motor dexterity, visual spatial working memory, and tactile object recognition [9]. These findings seemed to be independent of clinical expression of dystonia measured by symptom severity or duration.

In this study, we administered a set of neuropsychological tests to non depressed patients affected by the most frequent form of AOPD, cranial-cervical dystonia (CCD). Given that basal ganglia-thalamo-cortical circuits reveal functional subdivisions of the oculomotor, prefrontal and cingulated circuits that play an important role in executive functions, visual reproduction and visual-spatial coordination, working memory, attention, learning and potentiating behavioral-guiding rules [5]. We expect to find deficits in

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cognitive domains subserved by these circuits. Thus, our test battery included *n*-Back Task, Wechsler Memory Scale (WMS), Trail Making Test (TMT) version A and B (TMT-A and TMT-B), and Wisconsin Card Sorting Test (WCST).

2. Methods

2.1. Study subjects

Patients were selected among consecutive outpatients seen at the Movement Disorders Clinic of the Department of Basic Medical Sciences, Neuroscience and Sense Organs of the "Aldo Moro" University of Bari, Italy. Patients with primary adult-onset CCD (either focal or as part of a segmental/multifocal dystonia) diagnosed according with published criteria [10] were included in the study if they reported age at dystonia onset >26 years (to exclude, according with Bressman guidelines [11], dystonia associated with the DYT1 gene, and duration of disease >1. Exclusion criteria were other neurological disorders, with the exception of tremor associated with dystonia; features suggesting dopa-responsive dystonia, paroxysmal dystonia, and myoclonus-dystonia; a history of exposure to dopamine receptor–blocking agents before the onset of dystonia, as well as other causes of secondary dystonia; non-neurological (ophthalmological, psychogenic) causes of dystonia [10]; a diagnosis of depression (scoring > 9 on the Beck Depression Inventory [12]); and a diagnosis of dementia according to the Diagnostic and Statistical Manual IV.

All patients were receiving botulinum toxin type A injections every 3–4 months but none of them received concomitant therapy with dopaminergic and anti-cholinergic medication. Cognitive assessments were carried out 4–5 weeks after the new treatment session when botulinum toxin reaches its peak of efficacy; all patients were optimally treated and had no visual or other functional impairment secondary to dystonia.

Control subjects recruited among relatives of outpatients suffering from neurological conditions other than dystonia were frequency matched to case patients by age (±3 years) and sex. All participants gave their written informed consent to the study (approved by the local ethics committee) according to the Declaration of Helsinki.

2.2. Neuropsychological assessment

The tests were given under the same environmental conditions to all subjects. The scoring in both case and control subjects was obtained by an experienced evaluator (RR) who was not blinded to patients and control subjects because it is difficult to blind case patients with CCD and healthy subjects. In both case and control groups, parental social-economical status (Hollingshead Scale) [13], and intelligence quotient (IQ). Estimates of premorbid IQ were obtained using the Italian version of the Wide Reading Achievement Test – revised (TIB) [14]. Subjects who did not reach an IQ > 80 were excluded.

The test battery included *n*-Back Task (0-Back, 1-Back, 2-Back conditions), WMS, TMT-A and TMT-B, and WCST.

n-Back Task is a parametric working memory (WM) task providing increasing working memory load [15]. Test stimuli are numbers (1–4) shown in a random sequence and displayed at the corners of a diamond-shaped box. The task has a non-memory guided control condition (0-Back) that requires subjects to identify the stimulus currently seen. As memory load increased, the task requires to recall a stimulus seen one stimulus (1-Back) or two stimuli earlier (2-Back) while continuing to encode other incoming stimuli. Performance data were recorded as percent of correct responses (accuracy) and reaction time (RT) expressed in msec [15].

WMS measures different memory functions by several subtests, including information on general knowledge, orientation in time and place, mental control (testing the ability to repeat sequences such as the alphabet), logical memory (immediate repetition of short stories presented orally), digits forwards and digits reversed (the conventional digit span tests), visual reproduction (drawing reproduction of three simple designs, each presented individually for 10 s), and associate learning (the patient is given three trials to learn 10 pairs of words, six are obvious – up-down, and four difficult – cabbage-pen –)[16].

TMT requires a subject to 'connect-the-dots' of 25 consecutive targets on a sheet of paper [17]. The test includes two parts: TMT A, in which the targets are all numbers (1, 2, 3, etc.) and the test taker needs to connect them in sequential order; and TMT-B, in which the subject alternates between numbers and letters (1, A, 2, B, etc.). The goal of the test is to finish part A and part B as quickly as possible. Error rate is not recorded because it is assumed that if errors are made it will be reflected in the completion time. Although both TMT-A and TMT-B reflect attention, visual scanning, and visual-spatial coordination, TMT-B requires more cognitive flexibility, and/or maintaining sets. In addition, TMT B-A differences or TMT B/A ratio scores were calculated as indicators of executive control function [17].

WCST [18] is a well-established measure of general executive function evaluating several "frontal" lobe functions including strategic planning, organized searching, utilizing environmental feedback to shift cognitive sets, directing behavior toward achieving a goal, and modulating impulsive responding. The test uses stimulus and response cards (64-card scoring version) characterized by various forms, colors and numbers [18]. The participant is told to match the cards, but not how to match them; however, the subject is told whether a particular match is right or wrong. As the test progresses, there are unannounced shifts in the sorting principle which require the subject to alter her/his approach. Performance data are recorded as number of correct categories and number of perseverative errors.

2.3. Statistical analysis

Statistical analysis was performed by STATISTICA (StatSoft, Tulsa, Okla). Data were expressed as mean ± SD unless otherwise indicated. Differences between groups were analyzed using the Student's *t*-test for independent samples and chi square test, as appropriate. With regard to *n*-Back task, accuracy and RT were analyzed by means of two different analysis of variances (ANOVAs) with repeated measures. Since RT and accuracy are separate measures of patients' performance, no correction for multiple ANOVAs was made. Each ANOVA had one between subjects factor: group (CCD patients vs. control subjects); one within-subjects factors: memory load (0-Back, 1-Back, and 2-Back); and an interaction factor between diagnosis and memory load. Post hoc comparisons were carried out by means of HSD Tukey Test.

Raw scores from all neuropsychological tests were transformed into z scores and averaged to obtain an overall composite score. For all the above analyses, p values < 0.05 were considered to be significant.

The Spearman correlation coefficients (with Bonferroni correction) were used for assessing the possible relationships between impaired cognitive measures and relevant demographic/clinical variables. To take into account possible confounding by age, multivariable linear regression analysis was also performed.

3. Results

During the study period, 45 right-handed patients with primary adult-onset CCD were recruited. Dystonia presented with BSP in 28