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Thalamic atrophy and cognitive impairment in clinically isolated syndrome and multiple sclerosis

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ABSTRACT

Background: Cognitive deficits worsen the quality of life in multiple sclerosis and may be predicted by deep gray matter atrophy, especially thalamic atrophy. This relationship has not been studied in the clinically isolated syndrome (CIS). The aims of this study were to assess cognitive deficits in patients with CIS and relapsing-remitting multiple sclerosis (RRMS) using neuropsychological testing, to search for thalamic atrophy on brain MRI, and to test for their correlations.
Methods: Forty-three patients (19 with CIS and 24 with RRMS) underwent brain MRI and neuropsychological testing involving multiple cognitive domains and the severity of depression. Thalamic volumes automatically segmented from MRI data were compared to 19 healthy controls. Correlations were sought between cognitive performance and thalamic volume.
Results: Cognitive impairment was detected in the majority of both CIS and MS patients, most affected in executive functions, auditory memory, lexical verbal fluency, distribution of attention and psychomotor speed. Cognitive impairment and depression were not significantly correlated to disease duration. Both CIS and MS patients demonstrated thalamic atrophy compared to controls, while many cognitive deficits correlated with thalamic volume in both patient groups.
Conclusion: Cognitive deficits in CIS resemble those found in the later stages of MS and may be directly related to the amount of thalamic damage.

1. Introduction

Multiple sclerosis (MS) patients, particularly in the later stage of the disease, are known to manifest cognitive deficits [1–6]. Cognitive deficit or impairment correspond to a decreased performance in one or more cognitive domains, such as memory encoding and recall, learning, attention, thought and understanding, psychomotor speed, and executive functions. The first mention of the failure of memory and thinking was included in Charcot's classical description of MS [7]. More recent studies have focused on early stage MS, including clinically isolated syndrome (CIS), and have demonstrated decreased cognitive performance in patients with CIS (deficits in memory, processing speed, information sorting, attention, and executive functions) [2,3,6,8–12].

The biological substrate underlying cognitive deficits in MS is likely to be gray matter atrophy; deep gray matter and especially thalamic atrophy have been described most consistently. Even when including other measures of brain damage such as T2 or T1 lesion load, thalamic atrophy seemed most strongly associated with the severity of cognitive deficits [13]. Thalamic atrophy has also recently been reported in the early stages of MS including CIS [14,15].

The first aim of this study was to identify and verify the presence of cognitive deficits in patients with CIS and relapsing-remitting multiple sclerosis (RRMS) using a battery of neuropsychological tests. The next aim was to confirm thalamic atrophy on brain MRI. The final aim was to explore the relationship between cognitive deficits and thalamic atrophy in the two RRMS subgroups and the subgroup with CIS.

2. Materials and methods

2.1. Patients

The study has been approved by the appropriate ethics committee and has therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and later

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amendments. All participants provided informed consent prior to inclusion in the study.CIS patients were consecutively recruited at the MS Centre at the Department of Neurology, University Hospital Olomouc, Czech Republic, over a period of 12 months. CIS patients had a history of a single neurological event consistent with an inflammatory/demyelinating lesion in the central nervous system, with symptoms lasting more than 48 hours. All CIS patients fulfilled the dissemination in space on MRI [16]. MS patients were selected based on disease duration (see below) from the patients followed at the MS Centre. All MS patients fulfilled McDonald's criteria [16]. Patients in acute relapse during the previous month or with severe visual impairment were excluded from the study. Disability was scored using the *Expanded Disability Status Scale* (EDSS) [17]. Neuropsychological tests were administered to 43 patients (29 women and 14 men). The CIS group included 12 women and 7 men; the MS5 group included patients with disease duration of 5 years (60–71 months) and had 11 women and 4 men; and the MS10 group of patients included patients with disease duration of 10 years (120–131 months) and had 6 women and 3 men. The average age (± standard deviation) for the groups was 36.4 ± 8.7 years (CIS), 35.2 ± 8.2 years (MS5), and 43.5 ± 8.7 years (MS10). The study groups did not significantly differ in age ($P = 0.214$, ANOVA) or gender ($P = 0.921$, Fisher's exact test). The average length of education was 13.1 ± 2.0 years (CIS), 13.7 ± 2.3 years (MS5), and 16.0 ± 2.7 years (MS10). All patients were tested in the morning to ensure the uniformity of testing conditions. Seventeen out of the 43 patients were taking antidepressant medication (SSRI).

For evaluations of thalamic integrity, patients were compared to an age- and education-matched control group, including 19 healthy volunteers, 5 men and 14 women, average age was 34.1 ± 6.9 (standard deviation) years. The control group did not significantly differ from the patient subgroups in either age ($P = 0.098$, ANOVA) or gender ($P = 0.921$, Fisher's exact test). The control group did not undergo psychological testing.

2.2. Neuropsychological testing

WCST: The Wisconsin Card Sorting Test focused on the quality of executive ability. The challenge was to deduce the rules under which picture cards are sorted, and sort them correctly [18]. The results included numbers, percentages, and percentiles of: categories achieved, trials, errors, and the perseverative errors (WCST_Pers_errors). For group comparisons, raw scores were used. Individual performance was also classified into the three commonly used success rate ranges (above average, average, below average/damage) using cutoffs specific for age and education.

TOL: The Tower of London examined the ability to solve problems and plan (executive function). The examinees attempted to move beads into stacks on the board according to a model in as few moves as possible [19]. Standard scores, adjusted for age, were calculated for Total Correct (TOL_correct), Total Moves (TOL_moves), Total Initiation Time, Total Execution Time (TOL_exec_time), and Total Time. All standard scores had higher value for better cognitive performance [19].

CWT: The Stroop Colour-Word Test measured psychomotor speed and working memory and the ability to move focused attention, to adapt to changing requirements (flexibility) and to suppress a habitual response in favour of an atypical one. The test had three parts. The first two depended on the quality of attention and psychomotor speed (part 1: for a given time period, read words as fast as possible, part 2: for a given time period, name the colours as fast as possible); the third part focused to the ability to suppress habitual response (the participant named the colours, regardless of what the words were) [20]. Test scores were adjusted for age.

BDI-2: Beck Depression Inventory scales resulted in a total gross score measuring the severity of depressive symptoms [21].

TMT: The Trail Making Test had two parts: A and B. Part A (connect the numbered dots) was used as an indicator of psychomotor speed. Part B (connect numbered and lettered dots in sequence) tested a wider range of mental abilities, such as recognizing letters and numbers, visual search, dividing attention, flexibility, working memory, and motor skills [22]. For group comparison, raw scores were used. For classification into performance classes, cutoffs used to classify performance reflected both age and education.

JLO: The Judgement of Line Orientation test focused on visuospatial perception. On the answer sheet, there was a pair of lines at different angles at the top and a set of 11 angled lines at the bottom. The task was to match the top pair to two of the 11 numbered lines shown at the bottom [23]. Raw scores were used for subsequent group comparisons and performance classification.

TTP: The Benton Test of Tactile Perception consisted of two parallel rows of 10 cards, each of which represented a geometric shape composed of fine sandpaper. The investigated person was instructed to use the right or left hand to palpate the test pattern (which was hidden from view under the table) and visually determine the corresponding design from a set of 12 drawings of geometrical figures in a slightly reduced size. The maximum time to explore each shape was 30 seconds, and the answer was required within 45 seconds [24,25]. Raw scores were used for subsequent group comparisons and performance classification.

VFT: The Verbal Fluency Test evaluated the ability to recall as many words as possible according to certain criteria during a fixed period of time (one minute). We investigated lexical verbal fluency using the letters N, K, and P, appropriate for the patients' language [26]. For group comparisons, raw scores were used.

PASAT: The Paced Auditory Serial Addition Test focused on deficits in attention and auditory memory. Participants added pairs of random numbers presented verbally in consecutive 3-second and 2-second intervals. The final scores were the numbers of correct responses for 3-second and 2-second versions of the task [27]. Raw scores were used for subsequent group comparisons.

BVMT-R: The Brief Visuospatial Memory Test – Revised measured visuospatial memory. For 3 consecutive 10-s intervals, participants were shown cards with six geometric shapes to be remembered and drawn. Total recall was the sum of scores across the three trials. After 30 minutes (delayed recall), the participants tried to draw the shapes again. At the end, the participants had to select from a presented set the shapes that were shown to them at the beginning of testing [28]. The calculated standardized scores (T-scores) included correction for age and education. Standardized scores were used both for group comparisons and for performance classification.

DSST: Digit Symbol Substitution Test: The booklet consisted of rows containing small blank squares, each paired with a randomly assigner number from one to nine. Above these rows was a printed key that paired each number with a different nonsense symbol. Following a practice trial on squares, the subject had to fill in the blank spaces with the symbol that is paired to the number above the blank space. The duration of the test was 90 s. The test score was the number of squares filled in correctly. Subjects were encouraged to perform the task as quickly and accurately as possible [20]. Age-adjusted weighted scores were used both for group comparisons and for performance classification.

All standardized tests were administered and evaluated according to their manuals, normative data was included with most of the tests.

2.3. MRI acquisition and post-processing

MR imaging studies were performed using a 1.5 Tesla Siemens Avanto scanner (Siemens Medical, Erlangen, Germany). For volume measurements, a three-dimensional magnetization-prepared fast gradient echo sequence (inversion recovery time TI, 500 milliseconds; TE, 5 milliseconds; TR, 30 milliseconds; 80 coronal slices 2.5 mm thick, inplane resolution 0.9 × 0.9 mm) was used. Thalamic and intracranial volumes were segmented automatically using the FSL toolbox (FMRIB's

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