Neuropsychological assessment in patients with relapsing-remitting multiple sclerosis and mild functional impairment: correlation with magnetic resonance imaging

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Abstract

Forty one moderately impaired patients with clinically confirmed multiple sclerosis (MS) and a relapsing-remitting course were submitted to a neuropsychological battery and magnetic resonance imaging (MRI) to correlate the neuropsychological performances with the degree of cerebral demyelination. The neuropsychological results were indicative of a very mild overall impairment. The patients were subdivided into two groups (extensive periventricular demyelination or discrete lesions on MRI) and the results of neuropsychological tests compared. Patients with extensive periventricular demyelination had an inferior performance on concept formation, non-verbal reasoning and verbal memory tests.

Magnetic Resonance Imaging (MRI) of the brain is a sensitive tool to detect demyelinating lesions in multiple sclerosis (MS). In clinically definite MS, MRI demonstrates lesions in a proportion ranging from 78%¹ to 99%² of cases; in suspected MS³ lesions have been found in 62% of patients.

The correlation of MRI findings with the clinical features report conflicting results. Some authors⁴⁻⁶ found no correlation with either the duration of illness or the disability score, while others^{7,8} reported a positive correlation between severity of MRI lesions and disability score. Moreover, recent serial studies in relapsing patients have documented changes on MRI unaccompanied by relevant new neurological symptoms or signs.^{9,10}

One relevant aspect of MS disability, which has been emphasised in recent years, is neuropsychological impairment. Cognitive deficits can be found in a substantial number of MS patients¹¹ and do not seem to be related either to length of illness or severity of the functional impairment.¹²⁻¹⁴ Studies investigating the relationship between neuropsychological deficits and structural brain damage are scanty. Rao *et al*¹⁵ found a relationship between CT-assessed ventricular enlargement and intellectual and memory dysfunction in 47 patients with chronic progressive MS. MRI has been employed by Medaer *et al*¹⁶ and Huber *et al*¹⁷ to investigate the extent of brain involvement

in patients with clinically and/or psychometrically assessed dementia, with different results: in the former study patients with cognitive impairment showed an overall greater degree of demyelination, while in the latter it was only the severity of corpus callosum atrophy that differentiated the demented patients.

The aim of the present research is to investigate the relationship between MRI involvement and neuropsychological performance in a group of outpatients with relapsing-remitting, clinically definite MS and mild overall functional impairment.

Material and methods

Patients

Forty one subjects were selected out of the patient population attending three MS clinics, on the basis of the following criteria:

- 1) Clinically definite MS according to Poser's criteria.¹⁸
- 2) Relapsing-remitting course.
- 3) Kurtzke disability score¹⁹ equal or inferior to 6.
- 4) Educational level of at least five years.
- 5) Right-handedness (Edinburgh Inventory score = 10)²⁰
- 6) Willingness to participate in the study.

The patients' characteristics are summarised in table 1.

Neuropsychological battery

The following tests were administered in the same sequence in a single session lasting approximately two hours. The patients had received no medication for at least two days before testing.

Token Test²¹ A sensitive test to detect auditory comprehension impairment. The score is the number of correct responses (range 0-36).

Judgment of Line Orientation²² A visuo-spatial matching task, sensitive to right hemisphere damage. The score is the number of correct responses (range 0-30).

Table 1 Patients' characteristics (N = 41)

Sex (Male/Female)	10/31
Age (years)	mean 34 (range 17-56)
Years of schooling	mean 11 (range 5-23)
Kurtzke Disability Status	
Score	mean 2 (range 0-6)
Time since onset of symptoms (years)	mean 6.8 (range 0.1-21)

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Table 2 Comparison (Mann-Whitney U-test) of demographic, clinical and neuropsychological data in patients without (Group 1) and with (Group 2) extensive periventricular demyelination. Mean (range)

	Group 1 (n = 19)	Group 2 (n = 22)	U	p
Age (years)	32 (17-56)	34.8 (20-56)	181.5	ns
Education (years)	12.3 (5-18)	10.1 (5-23)	146.5	ns
Kurtzke Score	2.3 (0- 6)	2.0 (0- 6)	188	ns
Zung Score	42.9 (24-79)	43.9 (24-74)	196.5	ns
Short Tale	15.7 (6-21)	12.6 (4-21)	123	0.012
Raven's PM	32.1 (20-36)	27.9 (12-36)	112	0.005
Corsi				
Supraspan	10.2 (4-18)	10.1 (3-18)	199.5	ns
Weigl	12.7 (9-15)	10.1 (0-15)	122.5	0.011
Benton	22.9 (18-29)	22.7 (10-30)	208	ns

Short Tale²³ A verbal memory test similar to the “logical memory” subtest of the Wechsler Memory Scale. The score is the mean number of items recalled immediately after presentation and 10 minutes later (range 0–28).

Raven’s Coloured Progressive Matrices²⁴ A non verbal reasoning test. The score is the number of correct responses (range 0–36).

Digit Span From the Wechsler Adult Intelligence Scale,²⁵ a verbal short term memory test. The score is the longest sequence recalled in correct order.

Corsi Span²⁵ A sequential block-tapping task, which is considered the visuo-spatial equivalent of Digit Span. Score as for digit span.

Verbal Fluency²⁶ Assessing the timed production of words after phonemic and semantic cues. The score is the total number of acceptable responses.

Corsi Supra-span²⁷ A test of spatial non-verbal learning. The score is the number of trials to reach the criterion (three consecutive correct repetitions of an eight-block sequence) up to a maximum of eighteen trials.

Weigl Test²⁸ A sorting test assessing concept formation as well as “set shifting” abilities.

The score reflects the number of correctly identified categories (range 0–15).

Zung Depression Rating Scale²⁹ A self-administered questionnaire.

MRI study

All the MRI examinations were performed employing a 0.5 T superconductive unit (Philips Gyroscan S 5), capable of performing inversion recovery (IR) and spin echo (SE) sequences. In a standard examination multiple echoes (ME) were employed: pulse sequences had a repetition time (TR) varying from 500 to 800 ms with an echo time (TE) from 50 to 200 ms. Four images were usually obtained for each sequence. Pictures were acquired on 256 × 256 matrix. Slice thickness varied from 6 to 8 mm.

The routine examination consisted of axial slices from the foramen magnum up to the vertex and sagittal slices through the midline including the cervical spinal cord. Coronal slices were also frequently obtained in the pertinent position.⁵

All the patients had been submitted to MRI in a period from two days to six months before neuropsychological testing. Patients who had experienced new clinical symptoms or signs in the period between MRI and neuropsychological testing had a repeat MRI scan. This was carried out to improve clinical-anatomical correlation, even if it has been recently shown that MRI modifications may not be associated with clinical evidence.^{9 10}

The MRI films were scored using the method proposed by Ormerod,² which yields a numeric estimate of the severity of lesions in 15 discrete standardised areas of the brain. The evaluation of the MRI films was performed blindly to both the clinical conditions and the neuropsychological results for each patient.

Figure 1 (a and b) MRI of a patient with multiple isolated lesions (Group 1).

Figure 2 (a and b) MRI of a patient with extensive periventricular demyelination (Group 2).

Results

The scores on neuropsychological testing of MS patients were scrutinised using published norms.²¹⁻²⁸ Since none of the patients was impaired on the Token Test and the Digit and Corsi Span, these data were not analysed further.

Non-parametric correlations (Spearman rank correlation coefficients) were computed for the entire sample between the MRI abnormality index and scores (corrected for age, education and, when appropriate, sex) on selected tests (Raven, Weigl, Short Tale, Kurtzke disability score and Zung Depression Rating). The only significant correlation was between the severity of MRI involvement and performance on Weigl's Test ($p < 0.01$). Kurtzke and depression scores yielded no significant correlations with MRI involvement. Further correlations were attempted between severity of left or right hemispheric involvement and performances, respectively, on verbal fluency and on line orientation and supraspan spatial tests, with non significant results.

Patients were then subdivided into two groups, based on the presence of an extensive, irregular periventricular demyelination (a pattern of abnormality which has been suggested as characteristic of MS) ($N = 22$) or, alternatively, of single or multiple discrete lesions in the periventricular or extraperiventricular regions ($N = 19$). Figures 1 and 2 show an example of multiple isolated lesions and extensive periventricular demyelination respectively.

The two groups did not differ with respect to age, education, Kurtzke disability score and Zung depression score. The demographic and clinical data are shown in table 2, together with the results of neuropsychological tests. A significantly inferior performance in concept formation (Weigl's test), non-verbal reasoning (Raven's PM) and verbal memory (Short tale) tests was present in the patients with extensive periventricular demyelination.

Discussion

At variance with reports of other series¹²⁻¹⁴ the neuropsychological results showed a very mild

overall impairment in our group of multiple sclerosis patients. This apparent discrepancy is probably due to the characteristics of the present patient population. The majority of previous studies included patients with a wider range of physical disability. Moreover, with a few exceptions,^{15,30} it is often unclear whether the patients presented a chronic progressive or a relapsing-remitting course: this is particularly relevant since there is considerable evidence that cognitive dysfunction is particularly associated with a chronic/progressive disease course.^{30,31} The selection of patients in the ambulatory stage (Kurtzke score equal to or less than 6) and with a relapsing-remitting course may have excluded the majority of patients with MS-related dementia. Indeed, of the 41 patients only two had been considered by the attending neurologists as cognitively impaired on clinical grounds: both showed extensive periventricular demyelination.

Nevertheless, we found an inferior performance on abstract reasoning, concept formation and verbal memory tests in patients with evidence of extensive demyelination. Visuospatial performance and language were generally spared.

The pattern of neuropsychological impairment in MS patients is similar to the so called "subcortical dementias".¹¹ This group includes patients with different conditions, such as Huntington's chorea, progressive supranuclear palsy and even Parkinson's disease: intellectual slowing, attentional problems, impairment in abstract reasoning, problem solving and memory dysfunction are the hallmarks of this clinical picture.³² Studies, in particular from positron emission tomography,³³ suggest an association between "subcortical dementia" and a deactivation of the frontal lobes, due to widespread interruption of afferent connections coming from subcortical structures. The present study supports this hypothesis.

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