A comparison of neuropsychological deficits in primary and secondary progressive multiple sclerosis

Introduction

Cognitive impairment is well recognised in multiple sclerosis (MS) and has been reported to be more severe in patients with a chronic progressive course than in those with a relapsing/remitting one [2, 5]. Two forms of chronic progressive MS have been clinically defined, namely, primary progressive (PP) in which there is steady deterioration from the outset and secondary progressive (SP) in which progressive deterioration follows an initial period of relapses and remissions. More severe neuropsychological and magnetic resonance imaging (MRI) abnormalities have been reported in SP than in PP MS in relation to the size and number of lesions [15], extent of inflammation [10] and rate of new lesions [16]. Thompson et al. [15] reported that lesions are more frequent and larger in SP than in PP patients. In this exploratory study only subtle differences in cognitive impairment were detected between SP and PP patients matched for physical disability and relevant illness features. The results also suggest that the severity of cognitive impairment cannot be fully explained by the extent of abnormalities detected on conventional T2-weighted magnetic resonance images, and that other pathological abnormalities such as in normal-appearing white matter are likely to be involved.

Abstract

Neuropsychological deficits and the relationship to brain pathology were examined in 13 primary progressive (PP) and 12 secondary progressive (SP) multiple sclerosis patients with a similar duration of the progressive phase and comparable physical disability. A battery of neuropsychological tests to assess attention, short-term and working memory was administered to the patients, and their performance was compared to that of 20 healthy controls matched for age and premorbid IQ. Total cerebral lesion load on T2-weighted magnetic resonance imaging was measured in the patients. Both PP and SP patients performed significantly worse than controls in most of the neuropsychological tests. There were only subtle differences between SP and PP on the working memory task although magnetic resonance imaging lesion load was significantly higher in SP than in PP patients. In this exploratory study only subtle differences in cognitive impairment were detected between SP and PP patients matched for physical disability and relevant illness features. The results also suggest that the severity of cognitive impairment cannot be fully explained by the extent of abnormalities detected on conventional T2-weighted magnetic resonance images, and that other pathological abnormalities such as in normal-appearing white matter are likely to be involved.

Key words Multiple sclerosis · Neuropsychological · Cognitive · Magnetic resonance imaging · Lesion load
there is evidence that cognitive impairment is progressive over time [6]. We used a battery of neuropsychological tests shown to be sensitive to cognitive deficits in MS from our previous studies [2, 3].

Methods

Subjects

We recruited 25 patients with MS: 13 with PP (5 men, 8 women; mean age 44.08 years) and 12 with SP (7 men, 5 women; mean age 44.08 years). All patients had a diagnosis of clinically definite MS according to the criteria of Poser et al. [9]. Patients were classified as PP if they had had a progressive course since the onset of MS without any relapses or remissions, and as SP if progression had followed an initial course of relapses and remissions. PP and SP patients were matched as closely as possible with respect to duration of the progressive phase. While there was a significant difference in the duration of illness between PP patients (mean 9.15 years) and SP patients (15.09 years, P < 0.01), the mean duration of the progressive phase in the SP patients (7.58 years) did not differ significantly from that of the PP group (9.15 years). Patients were excluded if their corrected visual acuity was less than 6/12, or if there was motor impairment that would interfere with using a computer touch screen accurately. All MS patients had a neurological examination and physical disability was assessed using Kurtzke’s Expanded Disability Status Scale [7]. Differences in mean Extended Disability Status Score were not significant between PP patients (5.42) and SP patients (6.00).

Twenty healthy controls (9 men, 11 women; mean age 40.55 years, NS) were selected to match the patients as closely as possible with respect to age and estimated premorbid IQ (PP 112.23, SP 111.08, controls 115; National Adult Reading Test [8]). Informed consent was obtained from all subjects. The following battery of neuropsychological tests was administered to each subject to assess attention, short-term and working memory.

Tests of attention

To test simple reaction time an arrow in a centre square is presented on the computer screen at random intervals (0, 0.2, 0.8 and 1.6 s) prior to the square in the direction of the arrow lighting up. The subject presses either the right or the left button on a button box depending on which square lights up. Each hand was tested independently. The mean response time for the two hands at each interval was used as the score.

For choice reaction time the same stimulus is used as in the simple reaction time. A mixture of warned and cued trials is used. In the warned trials a cross appears in the centre square, which indicates that a box will light up but not which side. In the cued trials the arrow appears pointing in the direction of the square that will light up. The cross and arrow appear at random intervals (0, 0.2, 0.8, 1.6 s) prior to the square lighting up. The mean response time for the two hands at each interval of the cued and warned trials was used as the score.

On the symbol digit substitution test [13] the subject names numbers represented by nine different symbols according to a code shown on the computer screen. Eight trials were presented and the mean time taken per trial was recorded.

The Stroop [14] test presents names of colours printed in different colours on a computer screen. The score was the time which the subject took to name the colours in which the words were printed.

Tests of short-term and working memory

These included the following tests:

- Digit span (forward) [17]: the longest sequence of digits that the subject could recall.
- Digit span (backward) [17]: the longest sequence of digits that the subject could recall in reverse.
- Spatial span test: the longest sequence of squares lighting up on the computer screen that the subject could recall accurately (from the Cambridge Neuropsychological Test Automated Battery, CANTAB [12]).
- Spatial working memory: the subject searches for blue tokens hidden within a number of boxes on the screen by touching the boxes in turn until the token is located; subjects were instructed that the blue token would not be hidden in the same box in which it had been located previously. Two types of error were recorded: returning to a box in which a blue token had previously been located (‘between error’) and returning to a box previously shown to be empty during the same search (‘within error’). The ‘between errors’ is considered to be a more stringent measure. Four trials were presented at each level of difficulty (4, 6, 8 box problems). (Also from CANTAB)

Magnetic resonance imaging

MRI was performed in the MS patients using a 1.5-T GE Signa System. Axial slices were obtained using a pulse sequence VEMP 35/90/2400. A series of 36 contiguous, axial slices (3 mm thick) with a TR of 2400 ms and TE of 35 ms was selected for measurement of lesion load. A neuroradiologist (W.K.C.) delineated the lesion areas on hard copies. With reference to these, one rater (L.R.) obtained measurements of total lesion load using a semi-automated contouring technique to mark the lesions on images displayed on a SUNSPARC station and a software lesion volume measurement programme similar to that used in our previous study [3].

Statistical analysis

We used the t test and analysis of variance to examine group differences. Multivariate logistic analysis was used to determine whether neuropsychological performance could predict disease subgroup. Correlation analysis was performed using Spearman’s correlation coefficient.

Results

There were significant differences between MS patients as a group (PP plus SP) and controls in most tests of attention and memory, namely reaction time, symbol digit substitution, Stroop, reversed digit span and spatial working memory tests (Table 1). Neuropsychological performance was compared between the two patient subgroups, and the raw scores suggested that SP patients performed worse than PP patients in most of the neuropsychological tests; however, these differences reached statistical significance only for the ‘between errors’ score on the CANTAB spatial working memory test (F = 6.40, df = 1, P < 0.02).

In order to compare the severity of cognitive impairment in the two patient groups, a grading system was established for the tests in which patients were significantly impaired compared to controls, namely, symbol digit sub-