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Functional correlates of callosal atrophy in relapsing-remitting multiple sclerosis patients. A preliminary MRI study

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Abstract In multiple sclerosis (MS), periventricular lesions produce atrophy of the corpus callosum (CC), as evidenced by magnetic resonance imaging (MRI). We investigated whether CC atrophy in relapsing-remitting MS patients is related to functional deficits. We compared 14 mildly disabled (mean Expanded Disability Status Scale score 2.7) relapsing-remitting MS patients with 14 age- und sex-matched controls. CC size was determined using sagittal T1-weighted MRI. The function of the CC was studied using a neuropsychological battery and neurophysiological evaluation based on visual stimulation using a divided visual field paradigm. The total area of the CC in patients (mean 5.3 cm^2) was significantly (P=0.002) smaller than in controls (mean 6.6 cm^2). Patients showed left ear extinction using the dichotic listening test and impaired name learning, which was correlated with atrophy of the splenium. There were no differences in interhemispheric transfer time between patients and controls. Marked atrophy of the CC can be encountered in relapsing-remitting MS patients. The associated cerebral disconnection correlated with atrophy of expected regions of the CC, thus supporting topographical organization.

Key words Multiple sclerosis · Periventricular lesions · Callosal atrophy · MRI

Introduction

Multiple sclerosis (MS), one of the most common neurological disorders in young adults, is a disease that mainly affects the cerebral white matter. MS lesions characteristically cluster around the ventricles and periventricular white matter. Because the roof of the lateral ventricles is formed by the corpus callosum (CC), the major white matter tract between the two hemispheres, MS lesions will frequently be located in and around the CC and relate to atrophy of the CC [2].

Magnetic resonance imaging (MRI) clearly reveals periventricular and (sub-)callosal MS lesions [23]. In 93% of MS patients, lesions are found in the CC [5]. CC lesions can produce appreciable atrophy, although the exact relation between lesion volume and atrophy is not straightforward in the general MS population [2]. MRI provides the opportunity to investigate the size of the CC in vivo without the risk involved in invasive procedures or ionizing radiation and is, therefore, highly suitable for investigating callosal atrophy in various disease stages [5, 23, 24].

Neuropsychological studies indicate that mental deterioration occurs in 40–50% of MS patients [17] and that a

highly significant association exists between CC atrophy and impairment of mental functions [2, 7, 14, 17, 26]. The association between CC atrophy and neuropsychological dysfunction has mainly been established in patients with marked disability [7, 14]. Although CC atrophy is frequently observed, the functional consequences frequently remain unclear, and clinically appreciable disconnection syndromes are quite rare [22], while dementia in association with severe CC atrophy for the main part occurs in patients with severe physical disability [7].

The aim of the present study was to look for functional correlates of CC atrophy relatively early in the disease in relapsing-remitting MS patients. For this purpose, we correlated quantified magnetic resonance (MR) measurements of the CC with functional measures. The latter consisted of a neurophysiological test battery, including the dichotic listening test and the name learning test, both of which rely on callosal integrity and are impaired in MS patients [11, 12], together with a neurophysiological evaluation based on event-related potentials (ERPs) using a divided visual field paradigm (DVF). The DVF procedure involved presenting visual stimuli in one visual field so as to limit initial stimulation to one hemisphere before callosal transfer to the contralateral hemisphere. This enabled functional integrity of the CC to be measured in terms of interhemispheric transfer time (IHTT) for both ERPs and reaction time [3].

Patients and methods

Fourteen patients with relapsing-remitting definite MS [15] were included in this study: 11 female, 3 male; mean age 32 years (range 22–42); disease duration 1.5–13.0 years (median 4.5) The Expanded Disability Status Scale (EDSS) score [10] varied from 1.0 to 5.0 (mean 2.7). Because callosal size has been found to be dependent on age and sex [6, 9, 15, 27], we used a control group of 14 healthy students who were matched for age and sex (mean age 30 years, range 20–40). None of the subjects had relatives with MS or migraine. All subjects were right-handed [13] and had normal visual acuity.

MRI was performed on a 0.6-T machine (Teslacon II, Technicare, Solon, Ohio, USA) using a standard head-coil. Two pilot scans (transverse and coronal) were obtained to adjust for rotations of the head, to exclude artificially induced variation in CC size [18]. From those scout images, a midsagittal (double-oblique) short TR/short TE („T1-weighted") spin echo (SE) image was obtained (300/28/6) (TR/TE/excitations) for assessment of CC size. Then, 21 coronal long TR („T2-weighted") SE images (3025/60/2) were obtained in patients to assess the amount of hyperintense lesions. Throughout the scanning procedure, a slice thickness of 5 mm (1.25-mm interslice gap) was used with an in-plane resolution of 1×1.3 mm. The total acquisition time was 20 min.

Quantification of the CC was carried out from the midsagittal MR image using a dedicated computer program to measure various portions of the total callosal area. The outline of the CC was traced on a monitor, and according to a radial method six subregions in the CC were calculated [6]. All callosal measurements were corrected for the anterior-posterior (AP) length of the brain by multiplying CC size with ratio: individual AP diameter/mean AP diameter. The following CC areas (in cm2) were obtained for analysis: total callosal area and six CC subregions (A3 genu and rostrum, A2 anterior body, A1 anterior midbody, P1 posterior midbody, P2 posterior isthmus, P3 splenium). The reproducibility of this method has been reported previously as good [14]. The amout of white matter disease in MS patients was assessed on the coronal MR images using a semi-quantitative scoring system [21]. The number and size of the white matter lesions were scored in 5 discrete cerebral regions: frontal to the genu, at the level of the genu, at the level of the body of the CC, at the level of the splenium, occipital to the splenium. Furthermore, lesions within the CC itself were scored in the genu, corpus and splenium of the CC. Neuropsychological examination consisted of two tests intended to establish the general level of intellectual functioning (tests 1–2) and two tests designed to record behavioural effects of interhemispheric disconnection (tests 3–4): (1) Vocabulary was tested by choice of synonyms, using a subtest of a Dutch intelligence test [25]; the score was corrected for age. (2) The Raven standard progressive matrices [19], abbreviated to 3 series of 12 items (B, C and D). The sum of test 1 and 2 (maximum score 56) was employed as index of intelligence (this variable was normally distributed across subjects). (3) A dichotic listening tape was used to test the short-term verbal recall of dissimilar auditive stimuli, presented simultaneously to the right and left ear through headphones. Recall of 4 number pairs was tested in 16 trials in each of the two conditions. In the first condition (free recall), the subject was asked to report as many numbers as possible; in the second condition (ordered recall), the report started with the stimuli on the side that was specified by a preceding signal. Measurements were the traditional asymmetry score [100*(right–left)/(right+left)] for each condition, as well as the raw left score [12]. (4) Name learning is a paired-associate learning test, requiring the subject to learn a first name for four photographs of unfamiliar male faces, and is performed by measuring the number of correct responses in 28 trials.

During neurophysiological evaluation, subjects were comfortably seated using a chin rest. Recording was conducted in a light-dimmed, sound-attenuated room. Horizontal and vertical stimuli were presented on a monitor positioned 80 cm from the subject's eyes. Stimuli (duration 48 ms) consisted of square-wave gratings, subtending 1° of arc and presented at 4° eccentricity to the left and right of a central fixation point. Three experimental conditions were conducted, each with a total of 160 trials. First, subjects passively attended forty trials in each orientation and visual field. Second, subjects were instructed to respond as fast and accurately as possible by pressing micro-switches with their middle finger. Vertical bars, irrespective of visual field of presentation, were to be responded to with the right hand and horizontal stimuli with the left hand. The third condition was identical to the second, except that subjects responded with their arms crossed. Practice trials were presented in each condition to permit task familiarization. ERPs were recorded using tin electrodes, built into an electro-cap (10–20 system), referenced to linked earlobes. In this report, ERP data in the passive condition from latero-occipital (LO) leads only are reported, because subjects and patients were not actively engaged in any test during MR recording [20]. For correction purposes, an electro-oculogram (EOG) was

Table 1 Median surfaces (adjusted for head size) of callosal areas in cm^2

Callosal measure	Controls (n=14)	Patients (n=14)	P value[a]
Overall area	6.6	5.3	0.002
Subregions			
A3	1.94	1.63	0.03
A2	0.66	0.50	0.002
A1	0.77	0.59	0.007
P1	0.76	0.56	0.02
P2	0.75	0.51	0.002
P3	1.76	1.35	0.004

[a] P values calculated using Mann-Whitney U-test

Table 2 Median number of hyperintense lesions in cerebral subregions in MS patients (*CC* corpus callosum)

Within CC		Outside CC		Total number of lesions[a]	
		Frontal to Genu	11		
Genu	2	At the level of the genu	11	Related to the genu	30
Body	3	At the level of the body	33	Related to the body	38
Splenium	1	At the level of the splenium	17	Related to the splenium	40
		Occipital to splenium	20		

[a] The total number of lesions is a summation of lesions within and outside the CC; since the provided figures are medians, the latter do not necessarily add up to the former

recorded in the horizontal plane and vertical plane. ERPs and EOG were sampled at a frequency of 200 Hz for each channel.

Statistical analysis was performed using the SPSSWIN software. Since the MRI data are not normally distributed, they were compared between groups using the Mann-Whitney U-test, and correlations between MRI and clinical variables examined using Spearman rank correlation coefficients (r). Neuropsychological and neurophysiological data were compared between groups using the t test, analysis of variance (ANOVA), multivariate analysis of variance (MANOVA), or covariance analysis (ANCOVA). P values smaller than 0.05 were considered statistically significant. The IHTT was calculated by subtracting the compatible from the incompatible reponse [averaged for left (L) and right (R) hands] in the uncrossed condition.

Results

MR imaging

The uncorrected total CC area for MS patients (median 4.9 cm^2; range 2.9–7.5 cm^2) was smaller than that of controls (median 7.1 cm^2; range 5.1–9.3 cm^2). The mean AP diameter of the skull of patients was 12.1 cm and for controls 12.6 cm (12.4 cm for the whole group, no significant difference between groups). The corrected total callosal area was significantly smaller in MS patients compared with controls, as was each of the six CC subregions (Table 1). The interquartile range (IQR) for corrected CC area was 4.60–5.48 cm^2 in controls. Three of the controlls fell below this IQR (i.e. had an „abnormal-sized CC"), while only two patients were within the IQR (i.e. had a „normal-sized CC") (χ^2, P=0.0008). The two patients with normal-sized CC both had a short disease duration (1.5 and 3 years). The IQR for size of the splenium (P3) was 1.58–2.03 cm^2 in controls, with 1 control falling below, but 9 patients falling within this range (χ^2, P=0.07).

Within the CC itself, most white matter lesions were found in the body of the CC, while most discrete matter lesions outside the CC were located at or beyond the level of the splenium of the CC (Table 2). A negative correlation between the overall number of lesions and the size of the CC was found (r=–0.20), but this correlation is not significant (P=0.48). Stronger correlations were found for subregions of genu (r=–0.37) and splenium (r=–0.36), but they too were not significant. No significant correlations were observed with either disease duration or EDSS.

Neuropsychology

Patients had significantly lower intelligence indices than controls (Table 3). The intelligence index was used as a covariate in examining group interactions for the other neuropsychology tests using ANCOVA. All P values for neuropsychology tests are, therefore, corrected for the influence of intelligence (no significant contribution found in any comparison). Using the dichotic listening test, the patients performed poorer in the first condition (free recall), which was significant for the raw left ear score, and showed a trend for the asymmetry score. Using the name learning test, patients performed significantly more poorly than controls (Table 3). None of the results changed when the analyses were performed according to the CC being „normal-" or „abnormal-sized".

To test the hypothesis that the splenium (P3) is the part of the CC most relevant for the tasks investigated, we calculated the correlation coefficient in the whole group between several CC areas and neuropsychology test results. There were significant correlations between P3 and name learning (r=0.45, P=0.02), while no such correlations were found for the toal CC size. In the group of MS patients, the number of lesions in the splenium correlated negatively with the score of the name learning test (r=–0.55, P=0.04). In patients, the size of the splenium correlated even more strongly with the name learning test (r=–0.67, P=0.009).

Neurophysiology

Reaction times (RTs) of patients were significantly longer for patients than for controls (F=9.5 [1, 26], P=0.005). There were slower RTs for left-hand responses, for incompatible responses and in the crossed-arm position (MANOVA, all P values ≤0.01), illustrating the appropriateness of the experimental design. However, no statistically significant group interactions (MANOVA) were found, indicating that the increase in RT associated the use of the left arm, incompatible response or crossed arms did not differ between patients and controls (Table 4).

The mean IHTT was 7.9 [standard error of the mean (SEM) 9.5] ms for controls and 21.4 (SEM 13.6) ms for patients. Although IHTT was longer for patients than for controls, the mean difference between the two groups

Table 3 Mean (SD) values per group in neuropsychological tests (*n.a.* not applicable)

Test	Controls (n=14)	Patients (n=14)	F value[a]	P value
Intelligence index	47.2 (3.3)	42.4 (4.3)	n.a.	0.002[b]
Dichotic listening				
Free recall, left ear	41.2 (7.7)	34.9 (9.7)	5.57	0.026[c]
Free recall, asymmetry score	2.7 (14.9)	11.3 (23.8)	3.18	0.086[c]
Ordered recall, left ear	42.1 (7.0)	40.1 (5.0)	0.26	0.61[c]
Ordered recall, asymmetry score	3.9 (7.2)	3.7 (9.9)	0.23	0.63[c]
Name learning	26.0 (2.1)	22.6 (5.2)	5.86	0.023[c]

[a] F value of ANCOVA only for main effects
[b] t test
[c] ANCOVA, using the intelligence index as a covariate (no significant contribution in any of the comparisons)

Table 4 Mean reaction time (SD) per group and condition

Condition	Controls (n=14)	Patients (n=14)	All subjects (n=28)	P value[a]
Compatible	565 (50)	645 (96)	605 (85)	0.01
Incompatible	588 (46)	672 (92)	629 (83)	0.006
Left	590 (45)	673 (103)	631 (88)	0.01
Right	563 (53)	643 (89)	603 (83)	0.007
Uncrossed	566 (47)	643 (92)	604 (82)	0.01
Crossed	587 (53)	674 (100)	631 (90)	0.008
All conditions	576 (47)	658 (94)	617 (84)	0.007

[a] Comparing controls and patients, P values calculated using ANOVA

(16.6 ms, 95% confidence interval –20.6 to 47.6) was statistically not significant (t=0.81, P=0.42). The same trend was observed for the individual hands, and although the SEMs of the IHTTs were smaller, the differences were again not statistically significant. For the whole group, the Spearman correlation between corrected CC size and IHTT was –0.13 (P=0.5); for the subgroup of MS patients, the correlation was more strongly negative (r=–0.39) but did not reach statistical significance (P=0.18). When groups with and without „normal" CC size were compared, again no difference in IHTT was found, indicating that CC size, independent of diagnosis, might not be important for IHTT.

ERPs are reported only for the passive condition. For P1 (Table 5), the direct hemisphere yielded the lowest amplitudes (85 vs 162 μV, t=–2.87, P=0.008) and shortest latencies (141 vs 154 ms, t=–3.77, P=0.001). However, the differences in latencies and amplitudes between the directly and indirectly stimulated hemisphere (Table 5) were not different between controls and patients (ANOVA, both P values >0.32), indicating that the experimental manipulation was successful but did not discriminate between groups. The N1 latency for direct stimulation was marginally delayed in patients compared with controls (ANOVA, F [1,26] 1.26, P=0.27), showing that the groups were well matched in terms of visual acuity. For N1, the direct hemisphere yielded the lowest amplitude (–269 vs –150 μV, t=–6.51, P<0.0001) and shortest latency (192 vs 197 ms, t=–4.56, P<0.0001). Again, the differences in latency and amplitude between the direct and indirect hemispheres (data not shown) were not different between controls and patients (ANOVA, both P values >0.65).

Discussion

MRI provides an accurate tool for the study of the size and shape of the CC in vivo, and the callosal area observed in our control sample is comparable with that observed in previous MR studies [14, 24]. Atrophy of the CC is frequently observed in patients with MS [4], as is manifested by our findings of significant callosal atrophy (overall 20% reduction in adjusted CC area) in relapsing-remitting MS patients with relatively mild disability [16]. CC atrophy is probably caused by lesions in and around the CC owing to focal areas of demyelination, decrease in number of axons or through Wallerian degeneration [24]. We are not able to demonstrate an association between the number of lesions and the degree of atrophy of the CC, although the negative sign of the correlation coefficient indicates that with increasing numbers of lesions, CC size decreases [23, 24]. A recent paper [14] reported data from 90 patients and 25 controls, and a slightly stronger correlation (r=0.49, P=0.001) was reported. Apparently, the association is weak; even in a larger sample, the variance in CC size is only partly explained by lesion load ((r^2=0.24). Also in the study by Dietemann et al., the relationship between white matter lesions and CC atrophy was weak [4]. The histopathological heterogeneity of lesions, as observed by MRI, possible accounts for this discrepancy.

Notwithstanding the clear reduction in CC size in our group of relapsing-remitting patients, we were not able to demonstrate a functional deficit that could be attributed to

Table 5 Mean values (SD) for P1 (uncrossed condition) [a]

	Latency (SD) in milliseconds		Amplitude (SD) in microvolts	
	Controls	Patients	Controls	Patients
Direct	139 (23)	144 (21)	92 (197)	80 (184)
Indirect	148 (20)	160 (16)	188 (206)	138 (192)
Difference*	9 (17)	16 (19)	96 (143)	58 (142)
*ANOVA	F [1, 26]=1.04, P=0.31		F [1, 26]=0.64, P=0.43	

[a] All data were recorded at the latero-occipital electrode

atrophy of the CC using neurophysiological measures. In controls, we found a mean IHTT of 8 ms, which is similar to what has been previously reported using a simple manual RT task [3]. As expected, reaction times were longer in MS patients, compared with controls, but the IHTT was not significantly different. Several explanations of this discrepancy are possible. First, the number of axons in the CC (about 200 million) in normal subjects is high [1], and a 20% reduction might not be significant in functional terms (especially if plasticity of CC allows information to be passed via collateral axons). Second, atrophy of the CC could be produced by thinning of myelin sheaths, which continue to function. Third, the delay in IHTT is modest in comparison with the sampling time (5 ms) used in the present study (whether delays in IHTT of about 10 ms are at all relevant in functional terms in relation to the mean reaction time remains to be elucidated). Fourth, the size of the CC is not important in determining IHTT; Jäncke and Steinmetz [8] found no relation between CC size and IHTT in normal controls. Finally, given the high standard deviations in IHTT and the small sample size in this preliminary study, the absence of a statistically significant prolongation of IHTT could also be caused by a type-I error.

Neuropsychology tests, however, revealed several mild functional deficits. Intelligence is supposed not to be severely affected in relapsing-remitting MS patients, and we assume that it was higher in the control group owing to unfortunate matching. In subsequent analyses, IQ was therefore used as a covariate. As expected, speed was lower for patients, indicating a generalized slowing with the disease. The two tests included to detect interhemispheric disconnection (tests 3 and 4) both indicated mild abnormalities. Our results further support the concept that the splenium is the relevant part of the CC for these tasks and indicate that the level of atrophy of the splenium is associated with poorer performance in the two tasks for detecting cerebral disconnection.

Our results with the dichotic listening tests are in accordance with two previous studies. In patients with longstanding secondary progressive disease, Lindeboom and ter Horst [12] established left ear suppression; in our study, this was slightly more obvious in the free recall condition. In contrast to the present study, that study found a strong right ear advantage, probably related to the much longer disease duration of their patients. In another study, Pelletrier et al. [14] established that such left ear suppression is associated with atrophy of the splenium. In their study, patients had a longer disease duration (mean 7.7. years), a higher EDSS (mean 3.9), while 30% of patients had a progressive disease course; also, the degree of CC atrophy (25%) was slightly higher than in our group (20%). All this evidence supports the concept of topographical organization of fibres within the CC, as can be deduced from the relation between atrophy of the anterior part of the CC and verbal fluency [16].

In conclusion, marked atrophy of the CC was found in relapsing-remitting MS patients. Although IHTT was not prolonged in MS patients, cerebral disconnection was evidenced by neuropsychological tests and was associated with atrophy of relevant parts of the CC.

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