NOTE

ANTERIOR CORPUS CALLOSUM ATROPHY AND VERBAL FLUENCY IN MULTIPLE SCLEROSIS

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Introduction

MRI of Corpus Callosum (CC) atrophy may be an useful predictor of cognitive impairment in patients with Multiple Sclerosis (MS) (Huber et al., 1987), particularly of those functions as mental processing speed and rapid problem solving that depend on precisely timed interhemispheric communication (Rao et al., 1989). Since other MRI measures (i.e. periventricular burden, total weighted lesion score) proved also to be sensitive indicators of cognitive dysfunction in MS (Medaer et al., 1987; Franklin et al., 1988; Callanan et al., 1989; Rao et al., 1989; Anzola et al., 1990) it remains to be extablished whether CC atrophy itself is related to cognitive dysfunction or it is simply an other marker of the extent of total cerebral involvement.

Significant differences in callosal configuration were recently found in relation to gender and cerebral dominance (DeLacoste-Ultramsing and Hollway, 1982; Witelson, 1989) supporting the notion that anatomical callosal variations are not random but may have functional consequences. Smaller size in a portion of the CC may indicate less callosal fibers and decreased interhemispheric callosal transfer between homologous cortical structures. There is some previous suggestion that the anterior portion of the CC may be involved in higher cognitive operations, whereas the posterior callosum plays an important role in the sensory motor interhemispheric integration (Risse et al., 1989).

The aim of the present study was twofold: (1) to examine whether the relationship between CC atrophy and cognitive dysfunction is independent of the effect of cerebral lesions; (2) to explore the hypothesis that the anterior and posterior CC atrophy have a different influence on cognitive performance.

Material and Method

Patients

This study was based on 18 right-handed females, who satisfied criteria for clinically or laboratory definite MS (Poser et al., 1983). Left handers were excluded in order to reduce callosal configuration variability. Patients were rated with regard to disease duration and physical disability (Kurtzke Expanded Disability Status Scale) (Kurtzke, 1983). All patients had a relapsing-remitting form of MS and they were in clinical remission at the time of the study.

Neuropsychological Assessment

Neuropsychological tests of general and specific cognitive function were administered (Lezak, 1987). The examiners (DP and AP) had no prior knowledge of the results of patients' MRI scans. The severity of global cognitive impairment was rated by using the Mini-Mental State Examination.

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Tests of abstract/conceptual reasoning skills consisted of the Standard Raven Progressive Matrices and Wisconsin Card Sorting Test. The assessement of expressive language abilities included Boston Naming Test, Controlled Oral Word Association Test for broad phonemic categories (F-A-S version) and restricted semantic categories (Set test for animals and furnitures). Visuoconstructional skills were assessed with the Rey-Osterrieth Complex Figure Copy.

The memory verbal tests consisted of the WMS Digit Span Subtest, Babcock Short Story Italian Version and Rey Auditory Verbal Learning Test. Visuospatial memory was assessed by the Corsi Tapping Test and Rey-Osterrieth Complex Figure Delayed Memory.

MRI

MRI studies were performed with a 1.5 Tesla superconductive unit (Philips, Gyroscan S-15). Sagittal T1 weighted spin-echo sequences (TR 350, TE 30) on sagittal plane and both axial and coronal T2 weighted spin-echo sequences (TR 2300, TE 30, 120) were obtained from each patient. The MRI scans were evaluated by two neuroradiologists (SB, LB) without knowledge of the clinical and neuropsychological findings.

All measurements were performed two times and a mean was calculated for use in analysis.

Hyperintense demyelinating lesions which were periventricular in part and extended out into the brain parenchima were considered "periventricular" (PVL), while lesions which were apparently separate from the ventricles were designated "subcortical" lesions (SCL). Weighted lesions scores were developed based on the number and size of the lesions. We assigned the following weights according to lesion size: 1 = < 8 mm; 2 = 8-20 mm; 3 = > 20 mm. PVL and SLC scores were obtained by summing the weighted score for each lesion in the respective areas.

In the midsagittal T1 weighted planes, measures of the CC and brain areas were taken from the same image. The outlines of these structures were traced on monitor screen with a cursor and their areas were then calculated by means of a computerized graphic table.

Brain size correction was obtained by for each subject by dividing the midsagittal CC area with the respective brain area (CC/brain) (Reinars et al., 1988). The maximal antero-posterior length of the CC was measured and divided into anterior and posterior halves according to Witelson (1989). The anterior half area (Ant. CC) corresponded to the head, genu and rostral callosal body; the posterior half area (Post. CC) corresponded to the posterior callosal body, isthmus and splenium.

Measurements of Ant. CC, Post. CC and CC/brain were also obtained in 18 age-matched healthy females who served as normal controls subjects.

Statistical Analysis

Control CC measures were contrasted with those of patients with MS using Student's t test for unpaired data (two tailed).

With regard to the performances on each neuropsychological test, a multiple regression analysis was carried out using the following measures: Ant. CC, Post. CC, PVL and SCL.

The effects exerted on each neuropsychological test by Ant. CC and Post. CC, adjusted for PVL and SCL, have been tested first together, then one by one, and compared with each other by using the Scheffè post hoc test.

Results

Demographic and clinical characteristics of the MS sample are shown in Table I.

Mean values for Ant. CC, Post. CC and CC/brain in MS patients and control group are presented in Table II. Significant group differences ($p < 0.001$) by using Student's t test were found for both Ant. CC and Post. CC as well as for CC area controlled for sagittal brain

TABLE I

Demographic and Clinical Characteristic of MS Sample (N = 18)

Age (years ± SD)	31.9 ± 9.9 (range, 19-53)
Education (years ± SD)	13.1 ± 1.7 (range, 8-17)
Disease Duration (years ± SD)	6.0 ± 4.6 (range, 2-18)
Expanded disability status scale	1.6 ± 1.1 (range, 1-4)
Mini mental state examination	28.3 ± 1.3 (range, 23-30)

TABLE II

Mean Callosal Areas and Callosal-Brain Ratio in Patients with Multiple Sclerosis and Age Matched Healthy Controls

Callosal measures	Controls Mean (SD) N = 18	MS Mean (SD) N = 18	p*
Ant. CC (mm 2)	408 (49)	343 (44)	< .001
Post. CC (mm 2)	388 (51)	319 (61)	< .001
CC/Brain (%)	9.8 (0.8)	8.1 (1.1)	< .001

* Derived from unpaired t test (two tailed).

size. In addition no linear correlation was found in MS patients between CC and sagittal brain areas.

We found a significant association between verbal fluency as measured by Control Oral Word Association Test and Ant. CC area, which was independent of the effect of PVL and SCL. When analyzed together using a confidence level of 0.90 both Ant. and Post. CC significantly influenced the performance on verbal fluency ($F = 11.13$; d.f. = 2, 13; $p < 0.0015$). Only the effect of Ant. CC was, however, statistically significant ($F = 8.33$, d.f. = 1, 13, 2; $p < 0.0045$) when the two portions of the CC were evaluated one by one. Furthermore, when Ant. CC and Post. CC were compared with each other, Ant. CC proved to be superior to Post. CC ($F = 11.01$; d.f. = 1, 13, 2; $p < 0.0016$) in affecting the performance on verbal fluency.

No others cognitive test performances were specifically influenced by the presence of Ant. or Post. CC atrophy.

Discussion

A significant reduction of entire callosal size has been previously reported in MS patients (Simon et al., 1987) and also found to be related with selective cognitive disturbances (Rao et al., 1989). Our study, however, examines the different portions of CC and their relationship with cognitive performances.

This study shows that relapsing-remitting MS patients with mild dysability, when compared with control subjects, exhibited a statistically significant decrease in both Ant. CC and Post. CC as well as in CC area controlled for sagittal brain size. Therefore CC atrophy area may not be simply considered as an element of diffuse brain atrophy but as an early sign of disease process.

Our data demonstrate a specific association between the degree of Ant. CC area and performance on verbal fluency task, which was independent of the effect of focal cerebral lesions.

Anatomic studies describing the projection areas for fibers in CC have demonstrated that Ant. CC reciprocally interconnects frontal areas of the two hemispheres while fibers arising from the temporoparietal-occipital regions are believed to course through the splenium and caudal portion of the body (Post. CC) (Pandya and Seltzer, 1986). Previous studies have implicated both left and right frontal lobes as strategic in the mediation of cognitive processes associated with verbal fluency (Benton, 1968; Miller, 1984; Knopman et al., 1984). At this regard, Benton (1968) reported that patients with left frontal lobe lesions produce significantly fewer words than patients with right frontal lesions, but the worst performance was obtained by those patients with bilateral frontal lesions. In addition, there is strong evidence that a significant association between frontal dysfunction and verbal fluency is independent of more generalized cognitive processing deficiencies (Miller, 1984).

However, it must be stressed out that these previous studies included patients with cortical involvement, whereas MS patients did not typically show any evident cortical abnormalities. Our results support the assumption that fibers of specific portions of the CC transfer particular kinds of informations (Risse et al., 1989) and suggest that a normal interhemispheric transfer between the frontal cortex of the two hemispheres is a necessary requirement for an adequate performance on verbal fluency task.

There is recent evidence that Ant. CC plays a role in the interaction between cognitive rather than sensory systems in each hemisphere. Sidtis et al. (1981), in fact, described a patient in whom after initial posterior callosal section, there was no evidence of interhemispheric sensory transfer, although the left hemisphere did have access to stimulus-related semantic and episodic information from the right hemisphere. After the callosum was completely sectioned, this exchange was no longer observed. More recently, in patients who underwent partial or total commissurotomy, Sass et al. (1990) reported significant language impairments that were not present prior to the operation. Two of their patients who underwent posterior section first, did not have speech impairments until the section was completed. All language deficits involved primarily verbal output including measures of cued word production (Controlled Word Fluency Test). Although a transient postcallosotomy mutism is a common event (Bogen, 1985), permanent language deficits are reported only in patients with crossed or bilateral speech dominance (Sass et al., 1990; Rayport, Ferguson and Corrie, 1984).

Future investigations are required to evaluate whether the relation between an impairment in verbal fluency and Ant. CC atrophy is specific of MS or it could be extended to other neurological diseases such as Alzheimer's dementia where a selective decrease of nerve fibers in the Ant. CC has been also reported (Yamanouchi, Sugiura and Shimada, 1989).

Abstract

To determine whether different portions of the corpus callosum (CC) are responsible for transferring the information of specific cognitive modalities, eighteen females with relapsing-remitting Multiple Sclerosis (MS) were studied using neuropsychological procedures and Magnetic Resonance Imaging (MRI).

Measures of both anterior and posterior CC areas were obtained in patients with MS as well as in eighteen age and sex matched healthy controls. MRI scans were additionally analyzed for each patient in order to evaluate the extent of demyelinating lesions in both periventricular and subcortical areas.

Patients with MS exhibited a significant decrease in both the anterior and posterior CC areas compared with normal subjects.

The results of statistical analysis showed that, even when the effect of demyelinating lesions was taken into account within a regression equation, the atrophy of anterior CC area strongly affected the performance on verbal fluency task.

These data emphasize the importance of the anterior CC area for the interhemispheric transfer of cognitive information associated with verbal fluency.

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