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Quantitative Determination of MS-Induced Corpus Callosum Atrophy In Vivo Using MR Imaging

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To quantitate the extent of corpus callosum atrophy in multiple sclerosis, midsagittal corpus callosum areas were determined in 48 controls with normal MR scans and 41 patients with definite multiple sclerosis. The mean midsagittal corpus callosum area was 601 mm^2 (range 405–791), 641 mm^2, and 561 mm^2 for all adult controls, for adult males, and for adult females, respectively. Control values were significantly greater than the means determined for all multiple sclerosis (MS) patients (508 mm^2, range 281–758), for MS men (528 mm^2), or for MS women (498 mm^2). The degree of corpus callosum atrophy paralleled the estimated volume of periventricular and corpus callosum high-signal lesions, suggesting a possible cause-effect relationship. The results indicate that corpus callosum atrophy occurs commonly in patients with typical clinical forms of multiple sclerosis.

MR imaging is more sensitive than CT in detecting cerebral multiple sclerosis (MS) [1–8]. By MR, most MS lesions cluster around the ventricle surface and periventricular white matter, which includes the corpus callosum. Previously, we reported that MR detected corpus callosum lesions in a high percentage of patients from our multiple sclerosis clinic [9]. In that report we described three types of lesions: diffuse corpus callosum atrophy, inner callosal-ependymal surface lesions, and focal lesions. The clinical significance and natural history of all such lesions are unknown.

To perform more precise radiologic studies, and to begin to study clinical correlations, a method for quantifying corpus callosum damage by MR is needed. Previously, cerebral atrophy has been reported in terms of ventricular and sulcal indexes by CT scan [10–12]. With MR, however, the midsagittal area of the corpus callosum can be determined directly, which makes it feasible to monitor atrophy within a single tissue and anatomic region. In this study, we report a quantitative method for determining corpus callosum atrophy in vivo and apply this technique to an analysis of corpus callosum atrophy in multiple sclerosis.

Materials and Methods

The study was based on an MS population of 41 patients (27 women and 14 men), who satisfied criteria for clinically or laboratory definite MS [13]. Patients ages ranged from 21 to 67 years (mean 41, standard deviation [SD] 11). The principal indication for MR examination in this group was confirmation of diagnosis. Patients with technically inadequate midsagittal images and patients with additional CNS diseases (e.g., infarction) were excluded.

The control population consisted of 48 subjects, including 25 males and 23 females ranging in age from 11 months to 64 years (mean age 29, SD 17). Controls included normal volunteers and patients with normal MR studies as determined by a neuroradiologist. Exclusion criteria from the control group included suboptimal scan quality, inadequate midsagittal images, periventricular high-signal areas in the elderly, and anomalous development of the corpus callosum (e.g., partial agenesis). Also excluded were subjects with a primary prescan diagnosis of MS or possible MS.

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All studies were at 1.5 T using a standard head coil (General Electric Signa, Milwaukee). Data were collected from the sagittal series using a partial saturation (PS) pulse sequence with pulse repetition time (TR) of 400 msec, echo delay time (TE) of 25 msec, and two excitations. The matrix was 128 × 256 or 256 × 256, and the field of view was 24 cm. Section thickness was 5 mm with acquisition at 7.5-mm intervals. Studies routinely included an axial spin-echo (SE) sequence with TR of 2000 msec, TE of 30 and 60 msec or 30 and 90 msec.

In a preliminary study [14], all midsagittal corpus callosum areas were determined from tracings of images projected from 35-mm slides. Callosal areas were then quantified by computerized planimetry, which was considered impractical for routine use. For this study, corpus callosum area was determined directly using standard Signa software version 2.0 (Fig. 1). All measurements were made by one investigator. The margins of the corpus callosum were occasionally estimated at the rostrum and adjacent to the body of the fornix where the corpus callosum was not always seen as a distinct tract. Additionally, some estimation of callosal margin was required in about 5% of the MS patients with severe disease when the inner callosal border was nearly isointense with CSF on the T1-weighted images.

Each study was subjectively graded for relative volume of lesions in the corpus callosum and in the noncallosal periventricular white matter on a scale designated as no lesion, mild, moderate, and severe volume of involvement. The assessments were based on the axial SE images.

Results

Corpus Callosum Areas in MS and Controls

In controls, corpus callosum area increased from infancy through early adulthood in both males and females (Fig. 2). Beyond 18 years old there was no significant variation in corpus callosum area with age. For all females 18 years old and greater (17 subjects, average age 36, SD 15), the mean corpus callosum area was 561 mm (SD 91), the range was 405–715 mm^2. For males 18 years old and greater (17 subjects, average age 41, SD 8), the mean corpus callosum area was 641 mm (SD 94), the range was 496–791 mm^2. This sex-related difference was significant ($p < .05$).

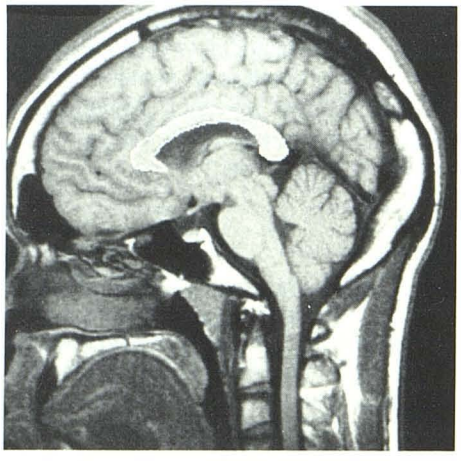

Fig. 1.—Technique for determining midsagittal corpus callosum area. Margins of corpus callosum were outlined on sagittal images and area determined within region of interest. Partial saturation pulse sequence with TR = 400 msec, TE = 25 msec.

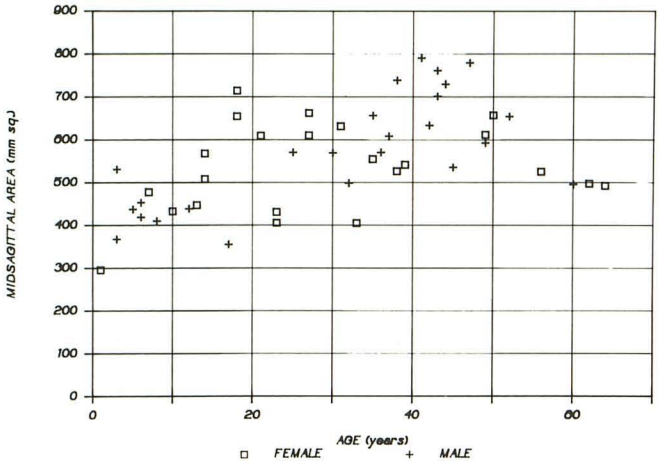

Fig. 2.—Midsagittal corpus callosum area in controls. All values represent mean of two or more determinations.

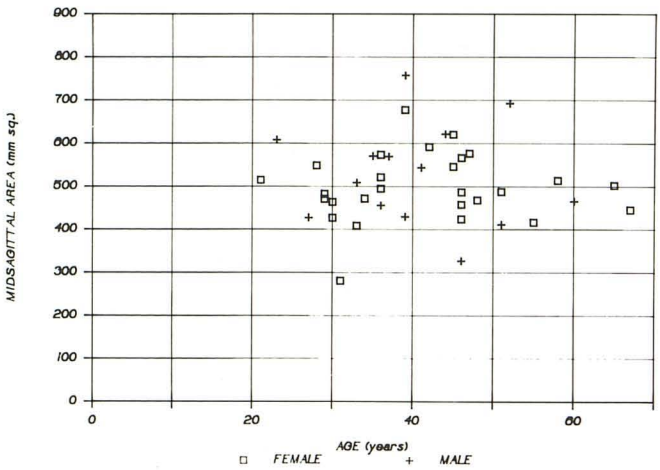

Fig. 3.—Midsagittal corpus callosum area in MS patients. All values represent mean of two or more determinations. In patients with more than one examination, only initial examination data are shown.

In the MS patients, there was no apparent change in midsagittal area with age (Fig. 3). The mean corpus callosum area was 498 (SD 77) for women (average age 41, SD 11), the range was 281–678. For men (average age 40, SD 9), the mean corpus callosum area was 528 (SD 114), the range was 327–758. The sex difference within the MS group was not significant.

Figure 4 compares the results of midsagittal area determinations in the MS patients with those in the controls. There was a significant difference in mean areas between controls aged 18 or older and MS patients ($p < .01$). This difference remained when male controls and male MS patients were compared ($p < .01$), and when female controls and female MS patients were compared ($p < .05$).

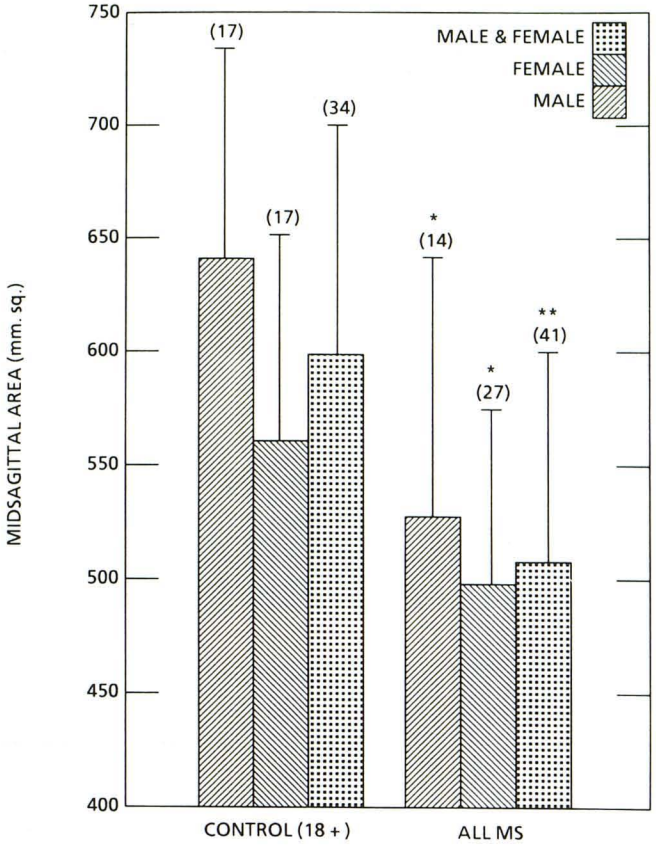

Fig. 4.—Comparison of midsagittal corpus callosum area in MS patients and controls aged 18 and older. Numbers in parentheses represent number of subjects in each group. Values are means ± standard deviation. Statistical significance of differences between each subgroup and the equivalent control by Student's t-test: * $p < .05$; ** $p < .01$.

Relationship Between Callosal Atrophy and High-Signal Lesions

Table 1 shows the relationship between the volume of high-signal corpus callosum lesions and periventricular (noncallosal) lesions in MS patients. In this series there were no patients without some degree of periventricular disease. Thirteen patients had periventricular lesions but no definite callosal lesions. Based on a collapsed chi-square analysis combining none and mild, and moderate and severe lesions, there was a highly significant relationship ($p < .05$) between volume of periventricular and corpus callosum lesions.

There was a positive correlation between periventricular disease as indicated by volume of periventricular high-signal lesions and corpus callosum atrophy (Fig. 5) and between high-signal corpus callosum lesions and corpus callosum atrophy (Fig. 6). Representative examples are shown in Figure 7. The decrease in corpus callosum area in patients with moderate and severe degrees of periventricular involvement achieved statistical significance. In both comparisons, there was a suggestion, though not statistically proven, that callosal atrophy occurred in cases with no visible callosal high-signal abnormalities and in patients with only mild degrees of periventricular disease.

TABLE 1: Relationship Between Corpus Callosum and Periventricular High-Signal Lesions*

Periventricular Grade	Callosal Grade			
	None	Mild	Moderate	Severe
None	0	0	0	0
Mild	10	11	0	0
Moderate	3	2	8	0
Severe	0	0	0	7

* Lesion volume was evaluated on a subjective basis using the axial SE images and then categorized into four relative grades as indicated. Values represent the number of multiple sclerosis patients in each category.

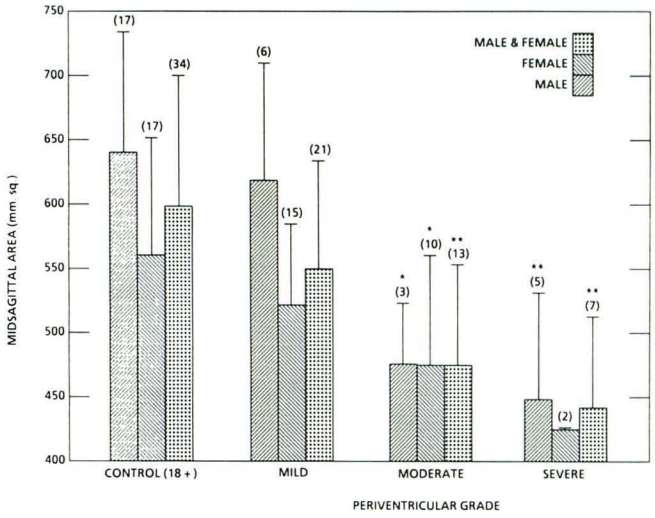

Fig. 5.—Relationship between volume of periventricular disease and mean midsagittal corpus callosum area. No patients were considered to be without any periventricular lesions. Details as per Fig. 4.

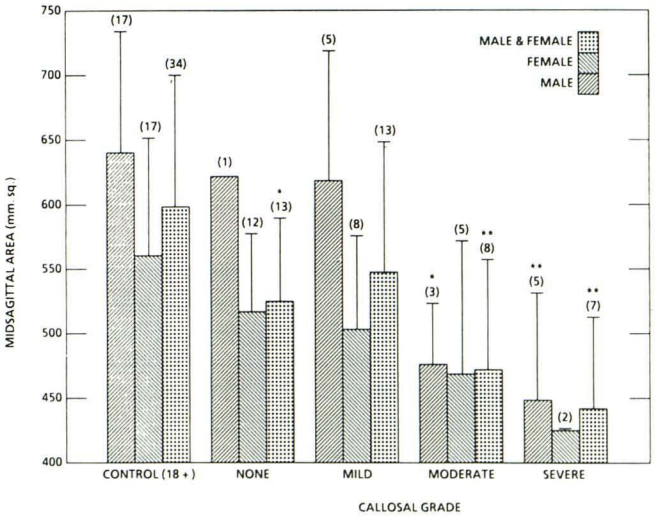

Fig. 6.—Relationship between volume of corpus callosum lesions and mean midsagittal corpus callosum area. Details as per Fig. 4.

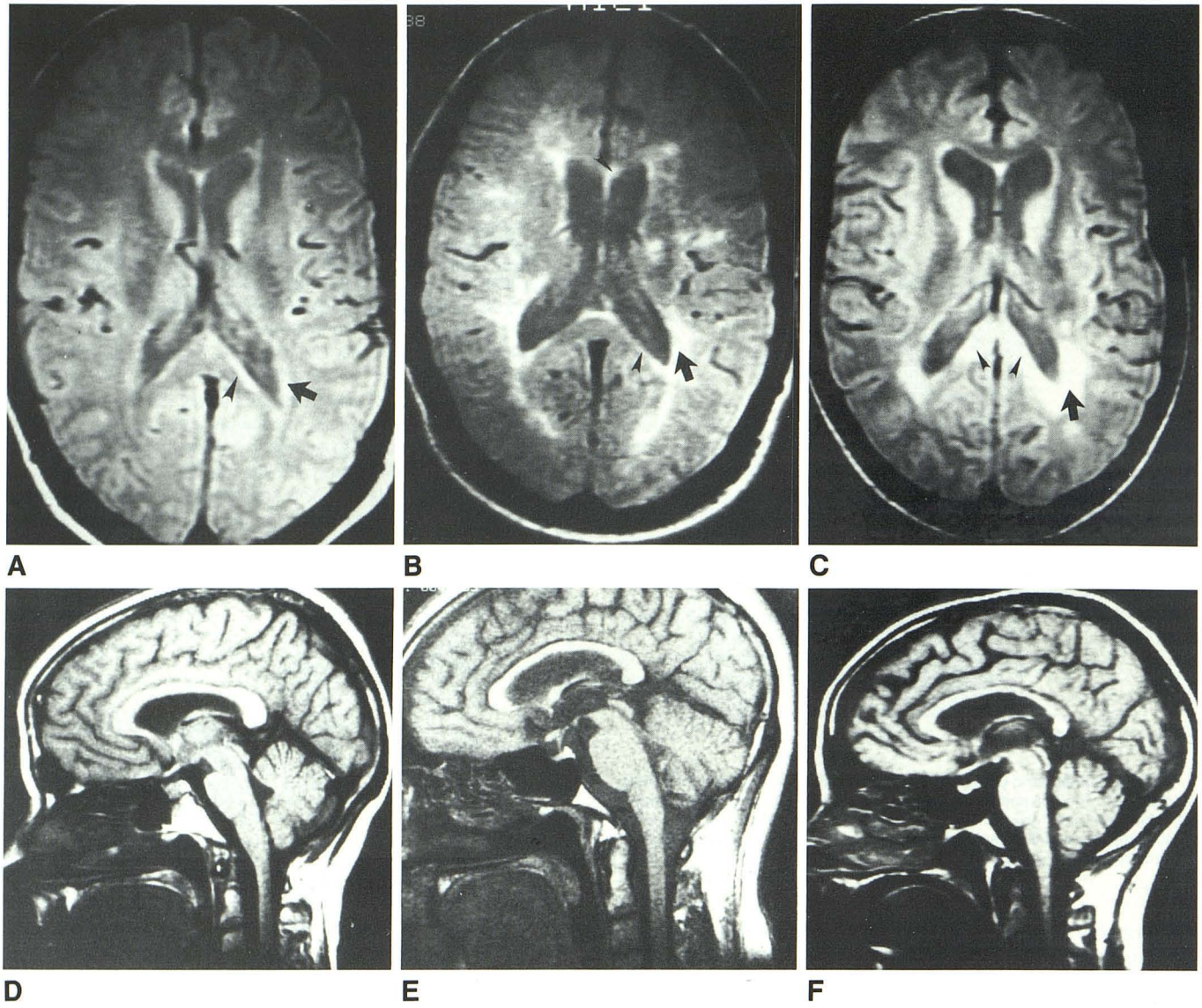

Fig. 7.—Increasing grades of corpus callosum and noncallosal high-signal periventricular lesions and corresponding sagittal images. Typical examples of mild (*A*), moderate (*B*), and severe (*C*) volume of involvement of corpus callosum and noncallosal periventricular white-matter lesions. Axial SE sequence with TR = 2000 msec, TE = 30 msec. *Arrowheads* show examples of corpus callosum lesions. *Arrows* show noncallosal periventricular lesions. Corresponding sagittal partial saturation pulse sequences with TR = 400 msec, TE = 25 msec (*D–F*). Mean midsagittal corpus callosum areas were 678 mm² (*D*), 544 mm² (*E*), and 424 mm² (*F*), respectively.

Discussion

Studies have shown that MS has a predilection for periventricular white matter [15, 16]. Little is known, however, about how the disease affects the corpus callosum, a structure that makes up a large fraction of the periventricular tissues [17].

This study, using quantitative measures, confirms previous in vivo [9] and postmortem studies [18, 19] that describe corpus callosum atrophy in MS. The MS group exhibited a statistically significant decrease in mean corpus callosum area, which was independent of age and sex. The spectrum of corpus callosum involvement in MS ranged from no detectable change in signal intensity or midsagittal area to major tissue losses approaching 50% of expected.

The cause of corpus callosum atrophy remains speculative. Autopsy series show that MS plaques are classically associated with local volume loss, due principally to decreased myelin in the axon sheath. Some contribution to local atrophy may be made from direct axon loss, which is relatively minor in MS, and from Wallerian degeneration [16, 19]. In a series of 20 MS brains reported by Barnard and Triggs [18], corpus callosum atrophy was accompanied by both demyelination and axon loss, but the relative contributions of these factors were not determined. That study did not distinguish between

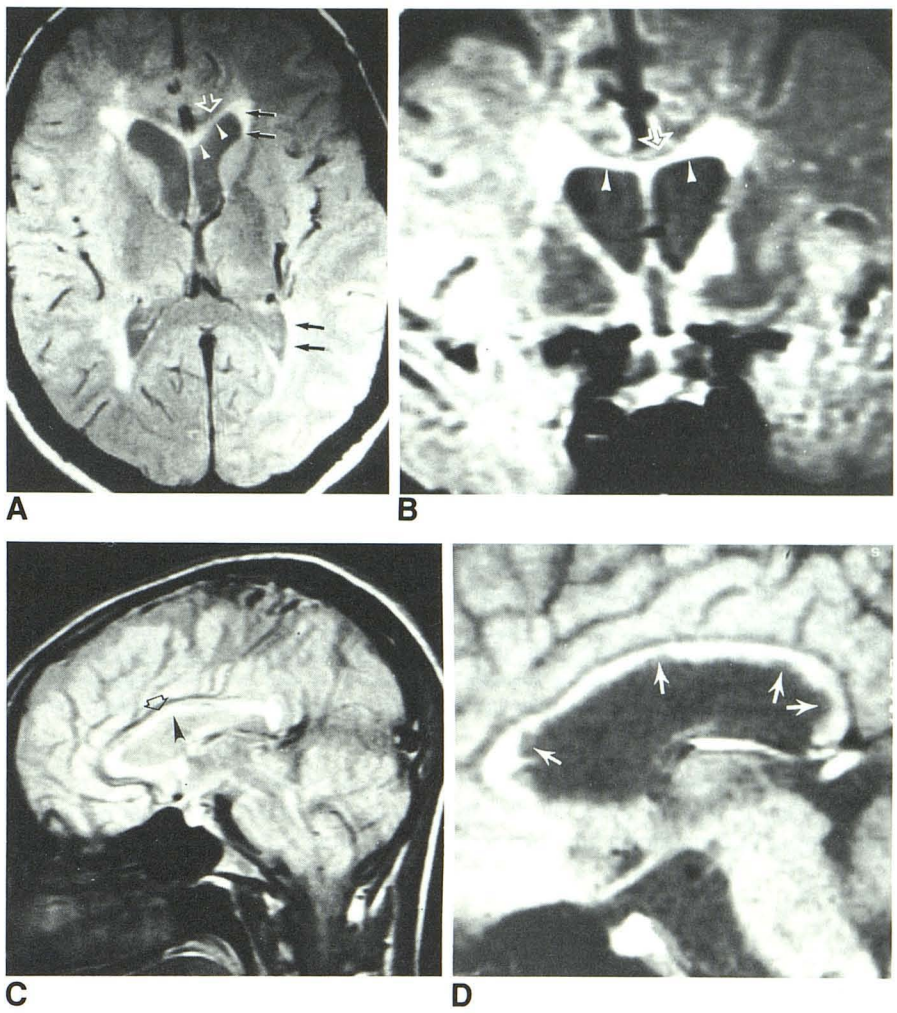

Fig. 8.—Typical corpus callosum lesions in MS. Axial (*A*) and coronal (*B*) SE sequence with TR = 2000, TE = 30. Note inner callosal distribution of lesions (*arrowheads*), which are inseparable from ependyma but penetrate into substance of corpus callosum. *Open arrow* indicates outer border of corpus callosum. *Closed arrows* show examples of periventricular lesions considered to be noncallosal for the purpose of this study.

***C*, Sagittal image, same sequence, in a patient with corpus callosum atrophy. Sagittal image shows long extent of inner callosal lesion (*arrowhead*) with relative sparing of mid and outer fibers (*open arrow*).**

***D*, Sagittal image, partial saturation sequence with TR = 400 msec, TE = 25 msec. Atrophy of corpus callosum is determined better by visual and quantitative criteria on the more T1-weighted images. Note low signal intensity inner callosal lesions (*arrows*) and atrophy in this severe case.**

axon loss from local (callosal) lesions separate from loss secondary to more peripheral disease.

Our results indicate that in the MS population corpus callosum atrophy parallels the extent of periventricular and callosal high-signal lesions, but in individual cases the relationship is not straightforward. One may hypothesize that the inner callosal high-signal lesion reflects some stage in tissue damage that seems to progress outward from the inner callosal-ependymal surface [9], ultimately resulting in callosal atrophy (Fig. 8). Alternatively, callosal atrophy may be secondary to axonal loss related to the adjacent ventricle angle lesions, which tend to be relatively large and early lesions, or secondary to more distant lesions.

The relevance of subject age to our measures of callosal volume is also of interest. Recent postmortem studies have suggested that handedness [20] and sex [20, 21] may be significant variables, but age was not evaluated in detail. Our data indicate that at least in the earliest age groups, age can be an important variable. After adolescence, no obvious relationship could be seen between age and callosal area. By excluding non-MS patients with periventricular high-signal lesions from the control group, we may have selected for adults with lesser degrees of atrophy. However, exclusion of controls with periventricular "lesions" should not affect the conclusions of this study, since these high-signal regions are relatively rare before the age of 45 years [22].

Clinical correlations of corpus callosum lesions are not yet certain, but may include apraxia [23], abnormalities detected by dichotic listening tests [24], and cognitive dysfunction [18]. Recent studies have in fact suggested that corpus callosum atrophy may be a predictor of disability and intellectual impairment in patients with MS [25].

In conclusion, quantitative analysis of corpus callosum area in MS patients compared with age-matched controls confirms the observation of frequent major callosal atrophy in MS patients in vivo. This technique may be applicable to prospective studies of the natural history and pathophysiology of MS.

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