Midsagittal MR Measurements of the Corpus Callosum in Healthy Subjects and Diseased Patients: A Prospective Survey

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PURPOSE: To determine quantitatively a possible corpus callosum (CC) involvement in normal aging and white matter diseases. **METHODS:** Midsagittal size and signal of CC were recorded prospectively from 243 routine MR brain examinations. A midline internal skull surface (MISS) and subcutaneous fat signal intensity were measured to calculate CC/MISS and CC/fat ratios. Four groups of subjects were studied: 124 apparently healthy subjects, 45 patients with multiple sclerosis, 13 patients with a noncerebral cancer under chemotherapy, and 37 AIDS patients. **RESULTS:** Mean surface area of CC in controls was 6.36 cm^2. It was significantly larger in men than in women ($P < .05$), but CC/MISS ratio was not. Elderly controls >70 years and AIDS patients displayed significant CC atrophy, as well as multiple sclerosis subjects with long-standing disease or with a severe chronic progressive form. **CONCLUSION:** CC substance loss identification should not be based on visual inspection or on absolute area, but by means of a CC/MISS ratio.

Index terms: Corpus callosum, abnormalities and anomalies; Brain, atrophy; Brain, measurements

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The corpus callosum (CC) is a major anatomical and functional commissure linking the two cerebral hemispheres. When disease affects a previously normal CC, interhemispheric disconnection symptoms occur that include visual, somesthetic, kinesthetic, auditory, and complex function impairment. Typical features of the callosal syndrome include unilateral ideomotor apraxia on the side of the dominant cerebral hemisphere, homolateral tactile dysnomia, contralateral hand difficulties, and homolateral ear and visual extinction on dichotic tests (1, 2). The introduction of magnetic resonance imaging (MR) has permitted the evaluation of CC abnormalities in vivo. Congenital involvement such as CC agenesis, dysgenesis, and hypoplasia are the most frequent callosal anomalies, and these malformations have been documented extensively with the use of MR (3–5). CC has also been measured on midsagittal MR in healthy subjects (5–8), and its size subjectively compared on visual inspection with patients suffering from multiple sclerosis (MS) (7, 8), trauma, vascular diseases or tumors (5). In these conditions, studies have provided information on CC atrophy as the result of insults from many causes (5). This atrophy was best demonstrated and compared with clinical status in MS (5, 7–10). However, only one of these studies (8) compared patients with normal subjects matched by age and sex.

Because MR also provides useful information concerning white matter involvement we undertook a prospective study of CC in healthy subjects and in patients with various diseases known to affect cerebral white matter (10–16), ie, MS, cerebrovascular diseases, tumors, chemotherapy (except for brain tumor), and infection. The rationale of this study was to determine, in each of these diseases, if CC atrophy was relevant, by comparing the mean surfaces of CC and the CC/midline internal skull surface (MISS) ratios measured on midsagittal MR plane; and to evaluate a possible

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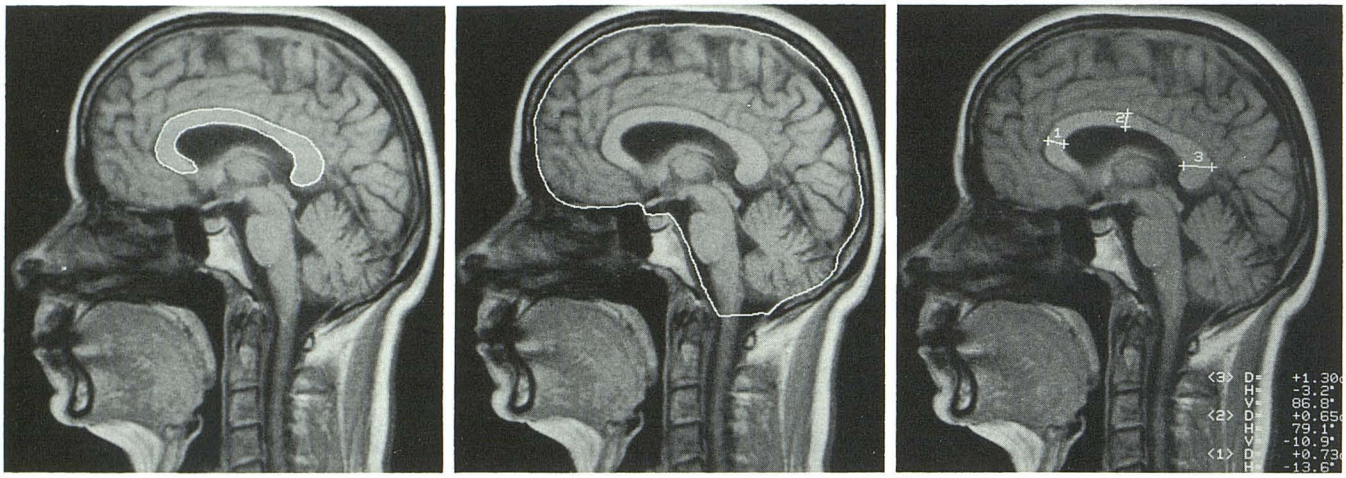

Fig. 1. Illustration of midsagittal image measurements: *A*, CC area; *B*, whole skull surface; *C*, CC thickness at genu, body, and splenium.

demyelination by means of a CC/subcutaneous fat signal intensity ratio.

Materials and Methods

This survey was prospectively undertaken in a series of 243 consecutive subjects, including 131 males and 112 females, ranging in age from 12 to 85 years (average, 44 years). The control population consisted of 124 subjects, including 63 males and 61 females ranging in age from 12 to 74 years (mean age, 37.5; SD, 15). Controls included 46 healthy volunteers and 78 patients referred for functional disorders, in whom neurologic, laboratory, and MR examinations were normal.

Exclusion criteria from the control group included periventricular high-signal areas in the elderly, and, for both groups, suboptimal scan quality, inadequate midsagittal images, and anomalous development of the CC (eg, callosal agenesis, dysgenesis, or hypoplasia; Chiari 1 or Dandy-Walker malformations; and sphenoidal encephaloceles). In the group of diseased patients, 119 individuals met inclusion criteria: 51 females and 68 males, ranging in age from 15 to 85 years (average, 52 years). From this diseased group of patients had been excluded all the patients known previously to have, or in whom MR depicted, space occupying diseases, whether those involved CC or not, including tumors, aneurysms, and arteriovenous malformations.

The final diagnosis was obtained in these diseased patients by the following criteria: 1) In MS, by a typical history of progressive neurologic deficits, alterations in evoked potentials, a positive cerebrospinal fluid (CSF) examination, and the absence of risk factors for other diseases. 2) In human immunodeficiency virus (HIV) carriers, patients with or without brain infection were included; when present, this disease was confirmed by imaging methods completed either by surgery, laboratory data, response under antitoxoplasmosis antibiotherapy, or from several sources. 3) In the mixed population under chemotherapy, patients having received brain irradiation or intrathecal chemotherapeutic agents at the time of MR examination were excluded. Only patients in whom MR examination was unremarkable (eg, without brain metastasis or white matter involvement) were incorporated. 4) The atrophic group was selected from a population of variously diseased patients, according to MR data. This population consisted in three Parkinson syndromes, six cerebrovascular diseases, four chronic alcohol abusers, two Alzheimer diseases, three posttraumatic, one brain radiation, two AIDS, and three MS cases. The AIDS and MS patients from this subgroup were not incorporated in the respective AIDS and MS corresponding subgroups of this study. Brain atrophy was confirmed, but not quantified, when it was subjectively suspected on axial T2 images (17). This confirmation was obtained by means of measurements extrapolated and simplified from those of Cala et al, and Meese et al (18, 19): bifrontal ventricular span at the level of the head of caudate nuclei and internal cranial diameter at the level of frontal horns for a ventricular/brain ratio (Evans index); width of the anterior portion of the interhemispheric fissure and of one of the two insular cisterns.

The MR scans of the 243 subjects were obtained with a 0.5-T imager (MR max; GE Medical Systems, Milwaukee, WI). All studies were performed using a circular, emitting-receiving polarized head-coil. The routine imaging sequences consisted of 7-mm thick contiguous sagittal gradient-echo 400/20 (TR/TE) sections with a flip angle of 90°, and noncontiguous (intersection gap of 1 mm) axial spin-echo 2000/50-100 images. Additional coronal acquisitions were obtained occasionally for further information. The matrix was 256 × 256 in the sagittal plane, 192 × 256 in the axial plane and the field of view was 250 mm. Two signal averages were used.

The following measurements were made on the midsagittal T1-weighted sections in each subject, by means of areas within irregular regions of interest, or with a cursor for determination of diameters (Fig. 1): 1) surface area of

TABLE 1: Average values in healthy subjects

	Healthy Subjects n = 124	Males n = 63	Females n = 61	Significance
Mean age	37.46 ± 15.50	37.30 ± 16.15	37.62 ± 14.92	NS
Mean CC surface (cm^2)	6.36 ± 1.19	6.54 ± 1.26	6.17 ± 1.07	$0.01 < P < .05$
Mean genu thickness (mm)	9.6 ± 1.9	9.8 ± 1.9	9.4 ± 1.9	NS
Mean body thickness (mm)	6 ± 1.1	6.2 ± 1.3	5.8 ± 1	$0.01 < P < .05$
Mean splenium thickness (mm)	10.8 ± 1.5	11 ± 1.7	10.6 ± 1.4	NS
Mean callosal length (cm)	7.06 ± 0.48	7.15 ± 0.33	7.01 ± 0.535	NS
Mean internal skull surface (cm^2)	143.19 ± 13.92	148.56 ± 13.56	137.66 ± 12.83	$P < .01$
CC/MISS ratio (%)	4.46 ± 0.78	4.45 ± 0.86	4.47 ± 0.71	NS
Mean CC signal	212 ± 33	209 ± 32	215 ± 35	NS
Mean subcutaneous fat signal	294 ± 51	301 ± 60	310 ± 41	NS
Mean CSF signal	61.69 ± 8.3	57.57 ± 8.1	65.95 ± 8.6	NS
CC/subcutaneous fat ratio (%)	69.4 ± 6	69.5 ± 6	69.3 ± 6	NS
CC/CSF signal ratio (%)	3.45 ± 0.5	3.63 ± 0.5	3.26 ± 0.5	NS

Note.—NS, nonsignificant ($P > .05$).

CC; 2) length of CC, from the anterior-most part of the genu to the posterior-most part of the splenium; 3) thickness of genu, corpus, and splenium; 4) mean signal intensity of the whole CC area, of the genu, and of the splenium; 5) midline internal skull surface (inner table, foramen magnum, clivus, sellar diaphragm, jugum sphenoidale); hyperostosis frontalis interna was not observed even in the elderly women, although the presence of this process, which tends to spare the midline, would have caused negligible or no effect on MISS measurement; 6) mean signal intensity of the subcutaneous fat at the level of the craniocervical junction. The background noise was also measured for each image on the right-hand side of the screen, behind the cranioservical junction, using a constant region of interest. Additionally, (CSF) signal intensity was recorded inside the fourth ventricle on T1 images in the last 130 subjects.

The measurements were made twice each by two radiologists in the first 20 subjects, and the results were reviewed. Intraobserver and interobserver variability was negligible, so that further measurements were only performed once in each patient; they were made without knowledge of clinical status. All these measurements were recorded on a computerized spreadsheet (Microsoft Excel), and CC/MISS, CC area/subcutaneous fat and CC/CSF signal intensity ratios were calculated for each subject.

Calculations (ANOVA) of average values were made for each item in normal and pathologic subcategories, as well as their standard deviations.

The Student's *t*-test for unpaired samples was then calculated to determine if significant differences were present between healthy and diseased subsets. Each subgroup proved to be homogeneous for sex and age ratios, respectively by χ^2 and Student's *t*-tests. 1) Average values for CC normal surface, diameters, and CC/MISS ratio were calculated for normal volunteers, and patients with normal clinical and MR evaluations, for each sex and age group. A preliminary validation that normal subjects and volunteers offered similar values needed to be obtained prior to further investigations. 2) Overall determination of significant differences between normal females and males, and for sex and age groups (Student's *t*-test), were performed. 3) Comparison between normal and pathologic subsets was conducted: i) For an available comparison, a subset of normal subjects statistically identical for age and sex to each pathologic group was preselected by the following criteria: mean age (Student's *t*-test for unpaired samples with $P > .3$); sex ratio (χ^2 with $P > .3$); ii) From these data, significant differences were calculated for: CC surface; CC/internal surface skull ratio. 4) Average measurements of CC/subcutaneous fat and of CC/CSF ratios were also performed in normal and pathologic cases to define indirectly a potential demyelination.

Results

Normal Subjects

Mean CC midsagittal surface area was 6.36 cm^2, and mean length was 7.06 cm. Mean diameters for the genu, the body, and the splenium were respectively 9.6, 6, and 10.8 cm. The MISS was 143.19 cm^2, and the CC/MISS ratio 4.46%. Average CC/subcutaneous fat ratio was 0.7 (SD, 0.06). CC/CSF ratio was 3.45 (SD, 0.5).

There was no difference in age or gender between volunteers and normal patients. No statistical differences were demonstrated in the measurements, so we could validate the appropriateness to combine these subgroups. Differences between males and females with their levels of significance are summarized in Table 1; they include surface area of CC ($.01 < P < .05$), diameter of the body ($.01 < P < .05$), the callosal length and MISS ($P < .01$), but not CC/MISS ratio (Fig. 2).

Similar comparisons between age subsets depicted differences in all measurements only for those groups more than 70 years in age: mean surface area of CC, splenium diameter, and CC/

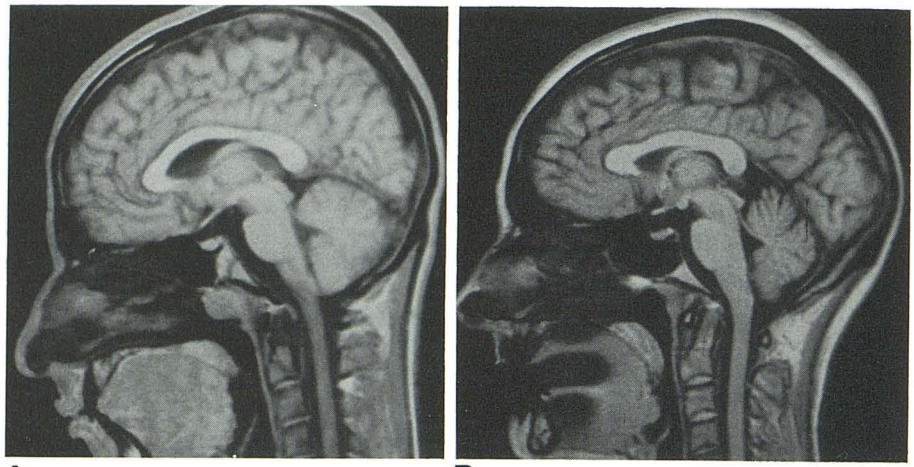

Fig. 2. This healthy 33-year-old man (*A*) has a 5% greater callosal area than that of this healthy 47-year-old woman (*B*). However, in both of them, there is an identical CC/MISS ratio of 4.5%.

MISS ratio ($P < .01$); genu and body diameter ($.01 < P < .05$). In fact, the mean surface area of CC and CC/MISS ratio showed a significant decrease only in males ($r = -.34$ and $-.004$, $P = .05$ and .02, respectively) (Fig. 3).

In each gender, the MISS did not differ with aging. So did callosal, subcutaneous fat, and CSF signal intensities, and hence, CC/subcutaneous fat and CC/CSF ratios. These measurements were validated on the hypothetical basis of a constant background noise; for comparison, this background noise was comprised in all the subjects between 5 and 13 arbitrary units (mean, 9.3; SD, 2.9).

Comparison with Diseased Patients

MS. The MS study group included 26 women and 19 men, ranging in ages from 23 to 65 years (mean, 40.55 years; SD, 12.16 years). The duration of disease ranged from 2 months to 14 years (15 had had initial symptoms for less than 6 months; eight patients had MS for less than 5 years, 12 between 5 and 10 years, and 10 more than 10 years). The group was homogeneous by age and sex with control subjects. No significant differences were demonstrated in any of the measures as compared to normal individuals (Table 2). Average CC/subcutaneous fat ratio was 0.64 (SD, 0.04).

Long-standing and/or severe disease. Within the 45 MS cases included above, a subgroup of 14 patients suffered from long-standing and/or severe disease. The median age of this population was slightly higher than that of other MS subjects (44 years). 10 of these patients had MS for 10 or more years (long-standing disease) and were classified as having relapsing-remitting (secondary progressive) MS, while four patients suffered from severe chronic progressive (primary progressive) MS. These patients (Fig. 4A) exhibited significant CC atrophy and a low CC/subcutaneous fat ratio (Table 3).

Irregularities of the inner callosal arcuature were recognized in eight patients of this MS subgroup.

Chemotherapy. This group of cancer patients had no brain metastases. Three patients received chemotherapy for lung cancer, two for breast cancer, two for hepatic metastases from colorectal cancer, two for laryngeal cancer, two for mediastinal lymphoma, and two for melanoma. None had received chemotherapy intrathecally. There were four females and nine males, with a mean age of 39.8 years (SD, 12.7). Eleven subjects had completed their treatment within 1 year of the MR examination, and two subjects more than 2 years previously. Six had received one presumably neurotoxic drug, and two patients had received two (either methotrexate, cisplatin, cytararabin, or vinblastine sulfate). Although this sample was small, all measurements displayed significant differences when compared with normal individuals (Table 2).

Within this group moreover, two patients (one with breast carcinoma, one with lung carcinoma) underwent MR at 6- and 8-month intervals, respectively, during the course of chemotherapeutic regimens. They were examined using the same MR imaging parameters, the same field of view, and the same magnification each time. We observed that callosal area had decreased, as well by means of measurements as by the superimposition of the callosal images before and after treatment which revealed a noticeable callosal size reduction.

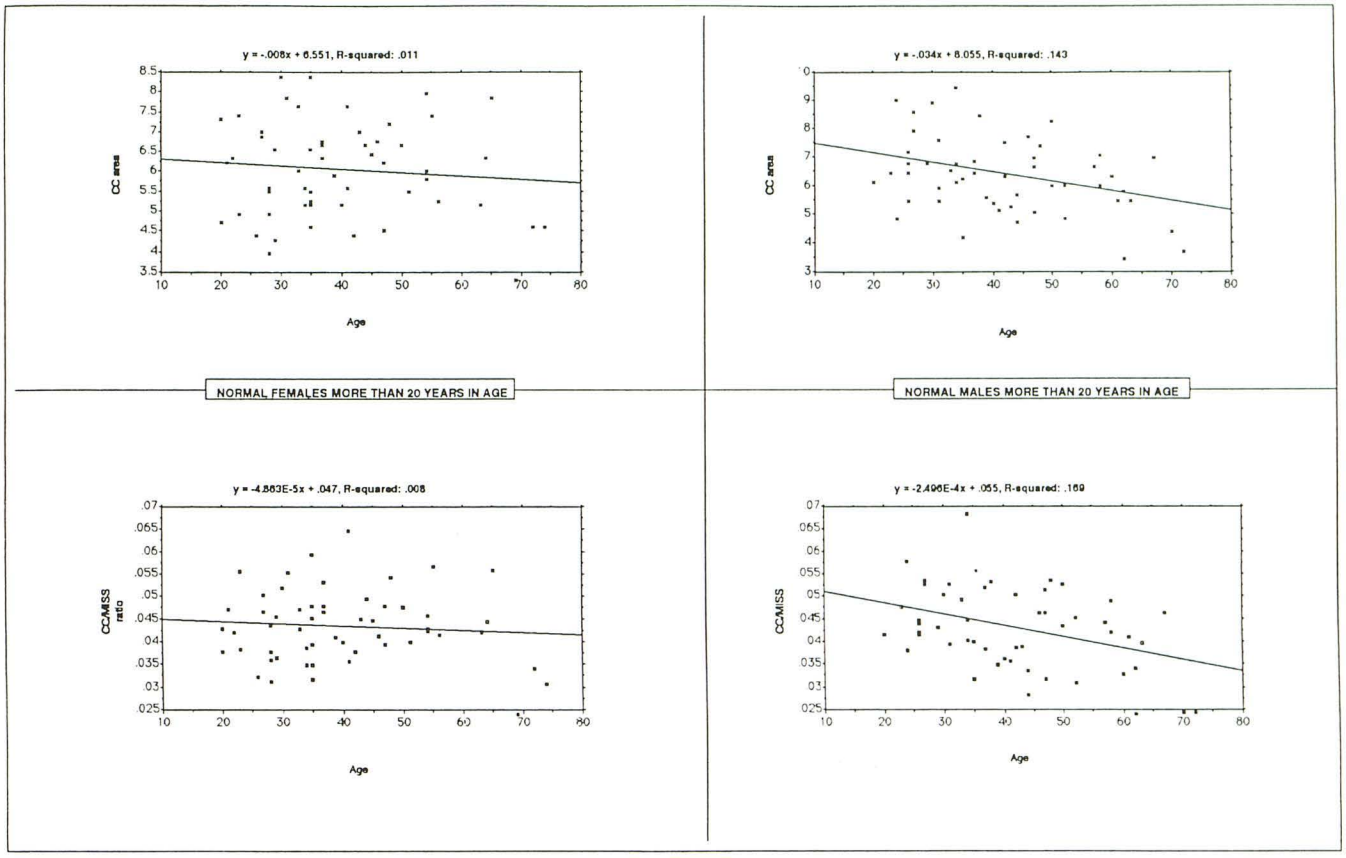

Fig. 3. Simple regression analysis curves of CC area (*upper panels*) and CC/MISS ratio (*lower panels*) as a function of age in healthy women (*left panel*) and men (*right panel*) more than 20 years of age. Absolute and relative callosal decrease are only significant in men.

TABLE 2: Average values in diseased individuals: comparison with normal values

	MS n = 45	Significance	Infection n = 37	Significance	Chemotherapy n = 13	Significance	Brain Atrophy n = 24	Significance
Mean age	40.55 ± 12.16	NS	37.8 ± 10.41	NS	39.8 ± 12.73	NS	61.1 ± 18.9	
Mean CC surface (cm^2)	6.09 ± 1.49	NS	5 ± 0.92	$P < .01$	5.48 ± 0.98	$P < .01$	5.37 ± 1.65	$P < .01$
Mean genu thickness (mm)	9.2 ± 1.8	NS	7.66 ± 1.8	$P < .01$	8.48 ± 1.92	$.01 < P < .05$	7.4 ± 2.6	$P < .01$
Mean body thickness (mm)	5.7 ± 1.5	NS	4.73 ± 0.91	$P < .01$	5.07 ± 0.72	$.01 < P < .05$	4.8 ± 1.5	$P < .01$
Mean splenium thickness (mm)	9.9 ± 2.1	$.01 < P < .05$	9.38 ± 1.77	$P < .01$	9.98 ± 1.29	$.01 < P < .05$	8.7 ± 2.4	$P < .01$
Mean internal skull surface (cm^2)	143.64 ± 13.8	NS	46.83 ± 14.1	NS	139.38 ± 11.9	NS	143.9 ± 15.3	NS
Mean callosal length (cm)	7.02 ± 0.44	NS	7.1 ± 0.56	NS	7.04 ± 0.49	NS	7 ± 0.46	NS
CC/MISS ratio (%)	4.23 ± 1.1	NS	3.41 ± 0.6	$P < .01$	3.85 ± 0.71	$P < .01$	3.73 ± 1.09	$P < .01$
Mean CC signal	215 ± 41	NS	205 ± 49	NS	201 ± 38	NS	208 ± 34	NS
Mean subcutaneous fat signal	334 ± 66	NS	270 ± 73	NS	309 ± 62	NS	305 ± 74	NS
Mean CSF signal	62.3 ± 10.1	NS	60.92 ± 9.4	NS	54 ± 10	NS	64.89 ± 8.6	NS
CC/Subcutaneous fat signal ratio (%)	64.2 ± 5	NS	80 ± 2.3	$.01 < P < .05$	65 ± 4	NS	68 ± 4	NS
CC/CSF signal ratio (%)	3.45 ± 0.7	NS	3.09 ± 0.6	NS	3.71 ± 0.5	NS	3.34 ± 0.06	NS

Note.—NS, nonsignificant ($P > .05$). Determination of control subsets homogeneous for age and sex by χ^2 test.

Infection. Within this group of 37 AIDS patients, there were 26 males and 11 females, ranging in age from 16 to 60 years (mean age, 37.8 years; SD, 10.6). There were 23 HIV carriers and 14 AIDS-related complex or AIDS patients.

Twenty-one patients complained of subjective signs or were referred for brain examination because of diffuse inflammatory signs, while the

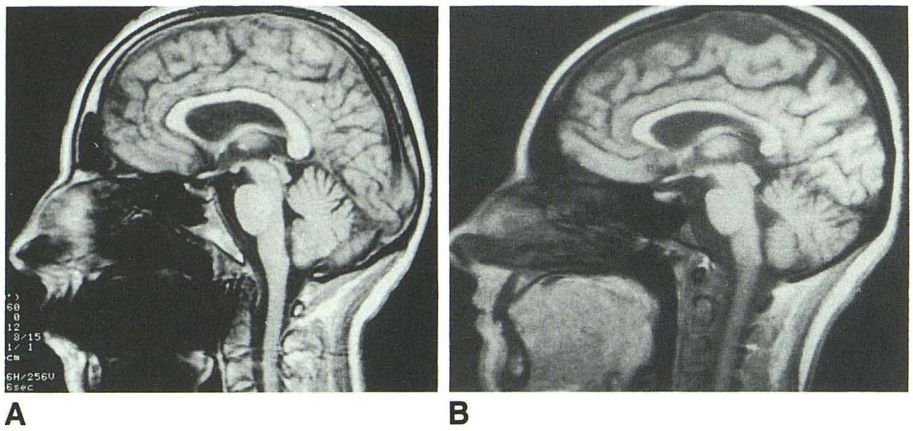

Fig. 4. *A*, Long-standing MS in a 63-year-old man: CC atrophy (CC/skull ratio 3.2%) without inner callosal irregularities, and possible CC demyelination (CC/subcutaneous fat ratio less than 0.6%).

B, HIV encephalitis in a 23-year-old woman: important CC atrophy is present (CC area is 3.8 cm^2, CC/skull ratio 3.5%). The signal of CC is visually normal, and there is a discordance between the CC/CSF and CC/subcutaneous fat ratios (3.2% and 0.8%, respectively).

TABLE 3: Measurements in longstanding and/or severe chronic progressive MS cases

		Significance[a]
Number of patients	14	
Mean age	43.86 ± 7	NS
Mean CC surface (cm^2)	4.74 ± 1.43	$P < .01$
Mean genu thickness (mm)	7.44 ± 1.56	$P < .01$
Mean body thickness (mm)	4.34 ± 1.14	$.01 < P < .05$
Mean splenium thickness (mm)	8.39 ± 2.19	$P < .01$
Mean internal skull surface (cm^2)	142.7 ± 14.2	NS
Callosal length (cm)	7.01 ± 0.49	NS
CC/MISS ratio (%)	3.3 ± 0.77	$P < .01$
CC/Subcutaneous fat signal ratio (%)	0.62 ± 0.04	NS
CC/CSF signal ratio (%)	3.16 ± 0.4	NS

Note.—NS, nonsignificant ($P > .05$).

[a] Determination of control subsets homogeneous for age and sex by χ^2 test.

remaining had neurologic impairment. Nine patients had brain toxoplasmosis; four of them were under treatment or exhibited sequelae. One patient exhibited typical clinical and MR features of progressive multifocal leukoencephalopathy. Twenty MR examinations were unremarkable, while the latter seven exhibited focal high signal intensity areas within the deep white matter.

Overall CC atrophy (confirmed by CC/internal skull surface ratio), as well as reduction in all CC diameters, was highly significant. One 28-year-old HIV female patient had two normal MR examinations at 1-year intervals, with the exception of a decrease in CC area of 28%.

The relative hyperintensity of CC in AIDS patients was significant also, 16% higher than that of the normal subgroup (Table 2). Mean CC/subcutaneous fat ratio was 0.81 (Fig. 4C). However, this group displayed a mean signal intensity of subcutaneous fat 15% lower than that of the control group, in contrast with equivalent CSF and background noise signal intensities. Furthermore, the CC/CSF signal ratio was not significantly different from that of normal subjects. Thus, this abnormal CC/subcutaneous fat ratio was not significant. Irregularities of the external callosal arcuature were observed in six patients.

Brain atrophy. Among the mixed cases of diseased patients, 24 (nine females, 15 males) had moderate to severe generalized brain atrophy. This group included three patients with MS, 18 with vascular diseases, one with a tumor, and four with AIDS. Measurements exhibited a significant callosal atrophy (Table 2), compared to normal subjects.

Discussion

CC is the major pathway for association fibers between the two cerebral hemispheres. The anatomy and embryology of this commissure have been studied extensively (3, 4, 20).

Normal Subjects

The size of CC has variably been evaluated in vivo on midsagittal MR (5–8), either in normal individuals, or in pathologic conditions. This measurement was compared with brain size in some studies (5, 6), but never with skull size. These studies provided varying results in the measurements of normal subjects, owing to the mode of calculations (whether on a hard copy, by slide projection, or by means of the imaging system software) and, to a lesser degree, to differences in age of the population selected. The mean CC surface was 7.2 cm^2 in one study (6), and 6.01 cm^2 in another (8). Both included con-

trols aged more than 18 years. In the present group of 124 controls, all measurements were determined directly using standard MR max software.

We are aware of some criticisms that the methodology of the present study may provoke. Indeed, our measurements incorporated patients with "functional" disorders (dizziness, headaches, migraine, visual, or ear disturbances); whether such patients have normal CCs or not is controversial. The interindividual comparison in this subgroup did not display any difference between the controls and these normal subjects; however, this can represent a potential pitfall in our study.

The choice of a CC/MISS ratio for the evaluation of callosal atrophy was preferred to that of CC/brain ratio as measurements are easier along the inner table, and brain atrophy is neglected. By chance, we did not observe hyperostosis frontalis interna in elderly women, which could have affected this ratio, although this abnormality seldom affects the midline. More controversial is the effort to identify a potential callosal demyelination by means of a CC/subcutaneous fat and a CC/CSF signal ratio. Each have their advantages and drawbacks. The subcutaneous fat signal was measured peripherally in the head coil, while CSF signal was measured close to the CC. Despite these different measurement locations, neither of these two ratios differed significantly between controls and patients. The background noise was quite constant, and did not thus represent a bias in these results.

We did not compare the CC sizes of left- and right-handers, a controversial subject at the origin of numerous papers. The first author who raised the possibility of a difference in callosal area was Witelson, based upon her work on autopsy specimens (21). Her work included three parameters: the degree of hand preference, age, and gender. More recent results from MR measurements exhibit no significant differences between these two subgroups, but most of them were based on the side of handedness or, more simply, the writing hand, so that no comparison is available at the present time (5, 6). Thus, sufficient data have not yet been collected to determine if an increased callosal connectivity is present in left-handers.

Comparisons between female and male callosum have also been performed using MR. Some studies (5, 8) have seemed to favor the hypothesis that CC carries a different number of fibers because of a bigger callosum in males. These differences are contradicted by results obtained in another study of 104 normal adults (6). Our data appear to agree with the latter study, since the CC/MISS ratios of the two genders were identical because of a smaller skull size in females.

In elderly subjects, brain atrophy is common (19, 22). CSF spaces with large ventricles and sulci are the indirect witnesses of neuron loss in normal aging. Involvement affects primarily superior frontal and temporal gyri, precentral gyrus, striatum, and basal ganglia (17, 22). However, these changes have not been widely documented with special concern for CC. The decrease of callosal size we observed with aging, without associated brain atrophy, is a somewhat interesting data. It is suggested that callosal decline predominantly affects elderly men, in the absence of brain atrophy; one could hypothesize, like Witelson (21), that callosal size is under hormonal control.

MS

Dietemann et al (9) subjectively evaluated the size and morphology of CC in MS, and correlated the involvement of CC with the duration and severity of the disease. Simon et al found significant differences between controls and MS patients, in both the mean thickness of CC (7), and its area (8). The association of MS (5–8) and callosal atrophy has been described with a prevalence ranging from 2% to more than 50%. This atrophy has essentially been determined visually, however. We demonstrated quantitatively, following the works of Dietemann et al, that CC atrophy occurs mainly in long-standing MS cases, after 10 years of evolution. In more recently affected patients, no significant callosal difference with controls was identified, except in those patients with severe progressive MS.

The involvement of the CC described in severely affected MS brains is usually described as focal, extensive CC demyelination (7, 8). CC/subcutaneous fat ratio seems to be an interesting measure for evaluating this demyelination, as it demonstrated a diminution in both long-standing and severe progressive MS, compared to controls as well as to recent MS cases (with a significance of only $P < .05$, probably due to the small sample). It is obvious that demyelination is best observed on T2-weighted sagittal images, as described by Gean-Marton et al (10).

The focal lesions of the CC depicted by MR techniques, such as low signal intensity areas or inner callosal arcuatures, probably represent re-

gions of demyelination and/or gliosis. The similar signal intensity of these lesions compared with that of other noncallosal periventricular lesions suggests a common underlying neuropathologic basis (eg, demyelination and/or gliosis), or MR changes in tissue water content as a result in myelin loss and decreased brain volume (8). However, the elective localization of MS plaques to the inner callosal arcuature seems specific to this disease: focal lesions radiate from the ventricular surface into the overlying CC, thus creating an irregular inferior margin (10). Patients with MS seldom exhibit brain atrophy without CC atrophy, while CC atrophy may occur with or without even mild brain atrophy (9). This was the case in all the long duration MS cases we observed, except two. This atrophy in MS seems, then, to be the direct consequence of the demyelinating and destructive process itself, and of the loss of callosal axons and wallerian degeneration (8–10, 23). This is particularly noticeable in those cases of patients with atrophy of CC related to direct involvement from the demyelination: the CC appears with some inner irregularities (8–10). In fact, only patients with contiguous white matter plaques exhibited inner callosal irregularities within our MS group.

In particularly severe cases, the inner callosal border can be nearly isointense with CSF on the T1 images, making it difficult to obtain a precise measurement (8). This is the reason for which exploration of the CC on T2-weighted spin-echo, sagittal sections, is recommended; the long TR/short TE delineates best callosal lesions from fluid at its junction with the septum pellucidum and from the adjacent ventricular system (10). We did not observe such cases in our patient population.

This study supports the results of previous studies which found that significant atrophy of the CC occurs in long-standing MS, and that CC atrophy occurs earlier than brain atrophy in the course of the disease.

Chemotherapy

Leukoencephalopathy has been described in relation with several chemotherapeutic drugs (methotrexate, cisplatin, arabinosyl cytosine, carmustine, and thiotepa), and with radiotherapy. Among them, methotrexate treatments seem to be the most responsible for white matter involvement. MR easily depicts such lesions, even in patients without neurologic impairment (16).

Two forms have been described: high signal intensity patchy lesions of the white matter that seem to be reversible soon after the completion of the treatment (16); and brain atrophy without signal abnormalities at a later stage, which are hypothesized to be nonspecific sequelae (15).

In the series of Lien et al (16) of 22 neurologic symptom-free patients treated by methotrexate and cisplatin for bone osteosarcoma, five exhibited a callosal involvement, while 12 had white matter lesions.

AIDS

AIDS is a great concern. Brain atrophy, although not the most frequent, is one of the most common imaging findings seen in these patients, whether associated or not with focal high signal intensity areas within the white matter (14).

HIV enters the central nervous system in a very early stage of infection. HIV encephalopathy affects 60% of AIDS cases; it is far more frequent than progressive multifocal encephalopathy, another cause of CC involvement (24). HIV encephalopathy is attributed to direct infection of the central nervous system with HIV (12, 14). It involves primarily the deep white matter of the frontal lobes in a bilateral, but not always symmetric, manner.

The areas of demyelination that occur in the course of the disease have been studied microscopically on autopsy specimens; they are variably associated with gliosis, macrophage infiltration, and multinucleated giant cells (12). At the initial stage of myelin pallor, cerebral atrophy is usually absent. It is thought that this atrophy is probably the consequence of a loss of white matter. As deep white matter is the most prominent site of involvement, the associative myelinated fibers of the CC are at great risk of involvement as well. This atrophy is far less frequently seen by neuropathologists than by neuroradiologists in vitro, so the question of intercurrent factors such as dehydration secondary to alcoholism (25), and chronic drug abuse (26), is raised. In a series of 17 patients, autopsy revealed specific involvement of CC in seven, all had HIV encephalopathy (13).

In AIDS dementia complex (ADC) studied with ^{31}p nuclear magnetic resonance spectroscopy (27), it has been demonstrated that phosphate metabolite deficiency was present, consistent with the hypothesis that brain cell function was affected by a direct, generalized HIV-associated

toxic process; this phenomenon was not in relation with brain atrophy. Despite the absence of neurologic symptoms in the majority of the AIDS patients (except one with ADC) analyzed in the present series, a significant CC atrophy was present, while brain atrophy was visually present in only two cases. Consequently, this atrophy seems to be relatively independent of brain atrophy that occurs later in the course of the disease, usually when ADC is already present.

The mean high signal intensity of the CC probably remains normal during the course of this disease. The abnormally high CC/subcutaneous fat ratio is indeed a poor witness of callosal myelination, owing to a decrease in signal intensity of the subcutaneous fat; it is well known that energetic resources in AIDS patients decrease during the course of this disease. Thus, CC/CSF ratio, similar in normal subjects and those patients, seems to be the best indicator of the absence of CC demyelination.

From this analysis, it may be suggested that CC atrophy can permit an early detection of the involvement of the CNS by HIV.

Conclusion

When CC involvement is suspected, it should not be estimated on visual inspection alone, but by means of several measurements including a CC/MISS ratio. This study does not address the question of specificity of CC lesions encountered in this panorama of diseases. In MS and infection, atrophy seems to evolve in parallel with the severity of the disease and/or its duration. Morphologic alterations are not specific. This CC substance loss (as determined by measuring (area of CC)/(MISS) ratios) is a significant but nonspecific finding. Measuring both CC/MISS, T1 (and perhaps T2-weighted) CC/CSF ratios may help to distinguish between axon loss and demyelination. One could hypothesize that CC atrophy without abnormal signal intensity would predict axonal loss only: on the opposite, abnormal signal intensity without CC atrophy would witness alterations of myelination alone, while signal involvement associated with CC atrophy would indicate both axon loss and demyelination. This hypothesis, however, remains yet speculative. Further MR imaging studies are required to determine if signal intensity measurements have a real diagnostic value, and to improve our comprehension upon callosal involvement.

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References

1. Habib M, Ceccaldi M, Poncet M. Callosal disconnection syndrome caused by left hemisphere infarction (in French). *Rev Neurol (Paris)* 1990;146:19–24
2. Risse GL, Gates J, Lund G, Maxwell R, Rubens A. Interhemispheric transfer in patients with incomplete section of the corpus callosum: anatomic verification with magnetic resonance imaging. *Arch Neurol* 1989;46:437–443
3. Barkovich AJ, Norman D. Anomalies of the corpus callosum: correlation with further anomalies of the brain. *AJNR* 1988;9:493–501
4. Atlas SW, Zimmerman RA, Bilaniuk LT, et al. Corpus callosum and limbic system: neuroanatomic MR evaluation of developmental anomalies. *Radiology* 1986;160:355–362
5. Reinarz SJ, Coffman CE, Smoker WRK, Godersky JC. MR imaging of the corpus callosum: normal and pathologic findings and correlation with CT. *AJNR* 1988;9:649–656
6. Kertesz A, Polk M, Howell J, Black SE. Cerebral dominance, sex, and callosal size in MRI. *Neurology* 1987;37:1385–1387
7. Simon JH, Holtas SL, Schiffer RB, et al. Corpus callosum and subcallosum periventricular lesions in multiple sclerosis: detection with MR. *Radiology* 1986;160:363–367
8. Simon JH, Schiffer RB, Rudick RA, Herndon RM. Quantitative determination of MS-induced corpus callosum atrophy in vivo using MR imaging. *AJNR* 8;1987:599–604
9. Dietemann JL, Beigelman C, Rumbach L, et al. Multiple sclerosis and corpus callosum atrophy: relationship of MRI findings to clinical data. *Neuroradiology* 1988;30:478–480
10. Gean-Marton AD, Vezina LG, Marton KI, et al. Abnormal corpus callosum: a sensitive and specific indicator of multiple sclerosis. *Radiology* 1991;180:215–221
11. Brant-Zawadski M. MR Imaging of the brain. *Radiology* 1988;166: 1–10
12. Balakrishan J, Becker PS, Kumar AJ, Zinreich SJ, McArthur JC, Bryan RN. Acquired immunodeficiency syndrome: correlation of radiologic and pathologic findings in the brain. *Radiographics* 1990; 10:201–215
13. Post DMJ, Tate LG, Quencer RM, et al. CT, MR and pathology in HIV encephalitis and meningitis. *AJNR* 1988;9:469–476
14. Jarvik JG, Hesselink JR, Kennedy C, et al. Acquired immunodeficiency syndrome: magnetic resonance patterns of brain involvement with pathologic correlation. *Arch Neurol* 1988;45:731–736
15. Ebner F, Ranner G, Slavc I, et al. MR findings in methotrexate-induced CNS abnormalities. *AJNR* 1989;10:959–964
16. Lien HH, Blomlie V, Saeter G, Solheim O, Fossa SD. Osteogenic sarcoma: MR signal abnormalities of the brain in asymptomatic patients treated with high-dose methotrexate. *Radiology* 1991;179: 547–550
17. Drayer BP. Imaging of aging brain. II. Pathologic conditions. *Radiology* 1988;166:797–806
18. Cala LA, Thickbroom GW, Black JL, Collins DWK, Mastaglia FL. Brain density and cerebrospinal fluid space size: CT of normal volunteers. *AJNR* 1981;2:41–47
19. Meese W, Kluge W, Grumme T, Hopfenmuller W. CT evaluation of the CSF spaces of healthy persons. *Neuroradiology* 1980;19: 131–136
20. Rakic P, Yakovlev PI. Development of the corpus callosum and cavum septi in man. *J Comp Neurol* 1968;132:45–72
21. Witelson SF. The brain connection: the corpus callosum is larger in left-handers. *Science* 1985;229:665–668

22. Drayer BP. Imaging of aging brain. I. Normal findings. *Radiology* 1988;166:785–796
23. Kuhn MJ, Johnson KA, Davis KR. Wallerian degeneration: evaluation with MR imaging. *Radiology* 168;1988:199–202
24. Mark AS, Atlas SW. Progressive multifocal leucoencephalopathy in patients with AIDS: appearance on MR images. *Radiology* 1989; 173:517–520
25. Schroth G, Naegele T, Klose U, et al. Reversible brain shrinkage in abstinent alcoholics measured by MRI. *Neuroradiology* 1988;30: 385–389
26. Tumeh SS, Nagel JS, English RJ, Moore M, Holman BM. Cerebral abnormalities in cocaine abusers: demonstration by SPECT perfusion brain scintigraphy. *Radiology* 1990;176:821–824
27. Bottomley PA, Hardy CJ, Cousins JP, Armstrong M, Wagle WA. AIDS dementia complex: brain high energy phosphate metabolic deficits. *Radiology* 1990;176:407–411