

Quantitative Cerebral MR in Rheumatoid Arthritis

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PURPOSE: To determine the presence of hyperintense white matter lesions and atrophy reflecting cerebral vasculitis in rheumatoid arthritis. **METHODS:** Thirty-three patients with rheumatoid arthritis and 48 control subjects were examined with MR. Mean age was 45.1 years (range, 26 to 55 years) for the patients and 42.2 years (range, 25 to 55 years) in the control group. To determine atrophy we measured the area of corpus callosum, the cerebrum, and the cerebellum on midline sagittal sections. On transverse images, the ventricle-to-brain ratio, the bifrontal ratio, and the bicaudate ratio were selected as atrophy parameters. Area and signal intensity were measured for the biggest and the smallest lesions in both groups. **RESULTS:** Nine patients (27%) had hyperintense lesions compared with 15 (31%) of the control subjects. Mean numbers of hyperintense lesions were 1.3 in patients and 2.1 in control subjects. Mean area of the largest lesion in each patient was 27.4 mm² for the patients and 29.8 mm² in the control group. In patients with long disease duration (>15 years) the mean ventricle-to-brain ratio was 0.09 compared with 0.08 in the control subjects. The midsagittal area of the cerebellum was 1349.8 mm² in the patients with long disease duration and 1573.3 mm² in the control group. No difference in number of hyperintense white matter lesions was detected between patients with long disease duration and the control subjects. Comparing the total group of patients with the control subjects, no significant differences in atrophy parameters or hyperintense white matter lesions were found. Also, there were no significant differences in relative signal intensity of the hyperintense lesions and corpus callosum between the two groups. We were not able to detect differences between treated versus untreated patients. **CONCLUSION:** This study indicates a tendency of more cerebral and cerebellar atrophy in patients with severe rheumatoid arthritis. The number and size of the white matter lesions were not significantly different in the two groups and do not support a higher frequency of even clinically silent infarcts caused by vasculitis in the patients with rheumatoid arthritis compared with control subjects.

Index terms: Arthritis; Brain, magnetic resonance

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A higher mortality rate in patients with rheumatoid arthritis compared with the general population is reported in several studies (1, 2). Infections and complications of the disease itself are the most important causes for this (3). Cerebral involvement in rheumatoid arthritis is uncommon and incompletely understood (4). Dural nodules (5), hyperviscosity syndrome (6),

and cerebral vasculitis (4) are some reported manifestations, but the reports are few and mostly uncontrolled. Minor psychiatric morbidity such as depression occurs more often in patients with rheumatoid arthritis (7), but cognitive impairment is less common in comparison with systemic lupus erythematosus (8). A negative association between rheumatoid arthritis and schizophrenia has been interpreted as a possible connection between rheumatoid arthritis and biochemical activity in the brain (9).

The present study was designed to test the hypothesis that patients with rheumatoid arthritis might have more subclinical cerebral damage than healthy control subjects and that there might also be an association between magnetic resonance (MR) abnormalities and disease du-

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ration activity of rheumatoid arthritis. Additionally, we present comparisons between drug-treated and untreated patients with rheumatoid arthritis.

Subjects and Methods

Thirty-three patients and 48 control subjects were included in the study. All were women. Mean age was 45.1 years (range, 26 to 55 years) for the patients and 42.2 years (range, 25 to 55 years) in the control group. The patients were randomly selected according to the 1987 American Rheumatism Association revised criteria for rheumatoid arthritis (10). The upper limit of 55 years was chosen to reduce the influence of age-related changes in the central nervous system (CNS). All patients listed as inpatients or outpatients treated at the Tromsø University Hospital living in the two northernmost counties in Norway were asked to participate. The clinical characteristics of the patients were described by the number of swollen joints (mean, 25.4 ± 11.9), the Ritchie index (11) (mean, 23.3 ± 14.6), and functional impairment classification (Steinbrocker's index, grade 1–4) (12). Laboratory parameters were erythrocyte sedimentation rate (mean, 21.4 ± 13.7 mm/h), C-reactive protein (mean, 13.6 ± 12.9), and rheumatoid factors (Latex-Waaler-Rose Test). Patients suffering from any chronic somatic or psychiatric disorder including alcoholism and patients with rheumatoid arthritis having atlantodental spaces larger than 0.5 mm radiologically were excluded.

The patients were asked about their use of antirheumatic or other medications at the time of examination and for the last 3 months. Information on drug treatment was also extracted from the patients' medical records.

Neither the patients nor the control subjects included in the study scored more than 0 (maximum score was 4) on the widely validated alcoholic screening instrument, CAGE (Felt need to Cut down drinking? Ever felt Annoyed by criticism of drinking? Had Guilty feelings about drinking? Ever take morning Eye-opener?) (13). One of the control subjects scored 3 on this scale and was therefore excluded from the study. The control subjects were randomly recruited from a local occupational health center. The clinical examination was done by the same physician (S.I.B.).

Examination of the brain was performed in a 0.5-T magnet. Sagittal images were obtained with a T1 sequence (520/20/2 [repetition time/echo time/excitations]) followed by a second series of transverse images with a T2 sequence (2000/20/2, 90° flip angle). The section thickness was 5 mm with a section gap of 0.5 mm in all cases. The imaging matrix was 205×256 , and the field of view was 250 mm. All studies were performed using a circular, transmit-receive head coil. The patient's head was carefully positioned to obtain a median sagittal section along the interhemispheric fissure. The transverse images were obtained from the cranial base to the vertex. All sagittal and transverse images were transferred to a digital

image-analysis computer. The analyzed parameters of the corpus callosum (area and signal intensity), the cerebrum (area), and the cerebellum (area) were drawn on the mid-sagittal section (Figs 1 and 2). The area of the corpus callosum was related to the area of the cerebrum at the midline internal surface, giving a corpus callosum-to-cerebral ratio. The transverse T2-weighted images were used for calculating the ventricle-to-brain ratio (Fig 3), the bifrontal ratio, and the bicaudate ratio (Fig 4), and for quantitative evaluation of cerebral lesions (Fig 5). The ventricle-to-brain ratio was measured by dividing the area of the ventricle at the widest level by the total brain area on the same section (Fig 3). The widest distance between the frontal horns of the lateral ventricle divided by the total diameter of the brain at the same level created the bifrontal ratio. The bicaudate ratio was measured by dividing the minimum distance between the caudate indentations by the brain diameter along the same line (Fig 4). Subcutaneous fat served as the constant value in calculating the relative signal intensity of corpus callosum and cerebral lesions (14). The radiologist (C.P.J.) and the physician responsible for the study (S.I.B.) were not aware of the clinical and the serologic status of the patients when evaluating the images.

Statistical comparisons of MR measurements in patients, treated and untreated, and in healthy control subjects were performed with the Student's *t* test and the χ^2 test with continuity correction for qualitative variables. Changes in brain atrophy parameters during disease duration and disease activity parameters were analyzed by multiple linear-regression analysis.

Results

All patients and control subjects in the study were women. Mean age was 45.1 ± 7.4 years in the patients and 42.6 ± 8.8 years in the control group. Mean age at diagnosis was 37.8 ± 8.3 years, and mean time of disease duration was 7.0 ± 5.1 years. Eighteen (54%) of the patients were unable to work because of physical disability. Six of the patients were treated with prednisolone combined with other antirheumatic drugs. Eight patients were receiving methotrexate treatment; six patients were not medically treated. The others were treated with antimalarials, sulfasalazine, cytotoxic drugs, and nonsteroidal antiinflammatory drugs in monotherapy or in combinations. In the untreated subgroup of patients, the disease duration was 11.0 years compared with 11.8 years in the treated group. Mean numbers of arthritic joints were 32.7 in the treated group and 24.9 in the group without treatment.

The MR findings were essentially equal in the total group of patients and controls (Table 1). In

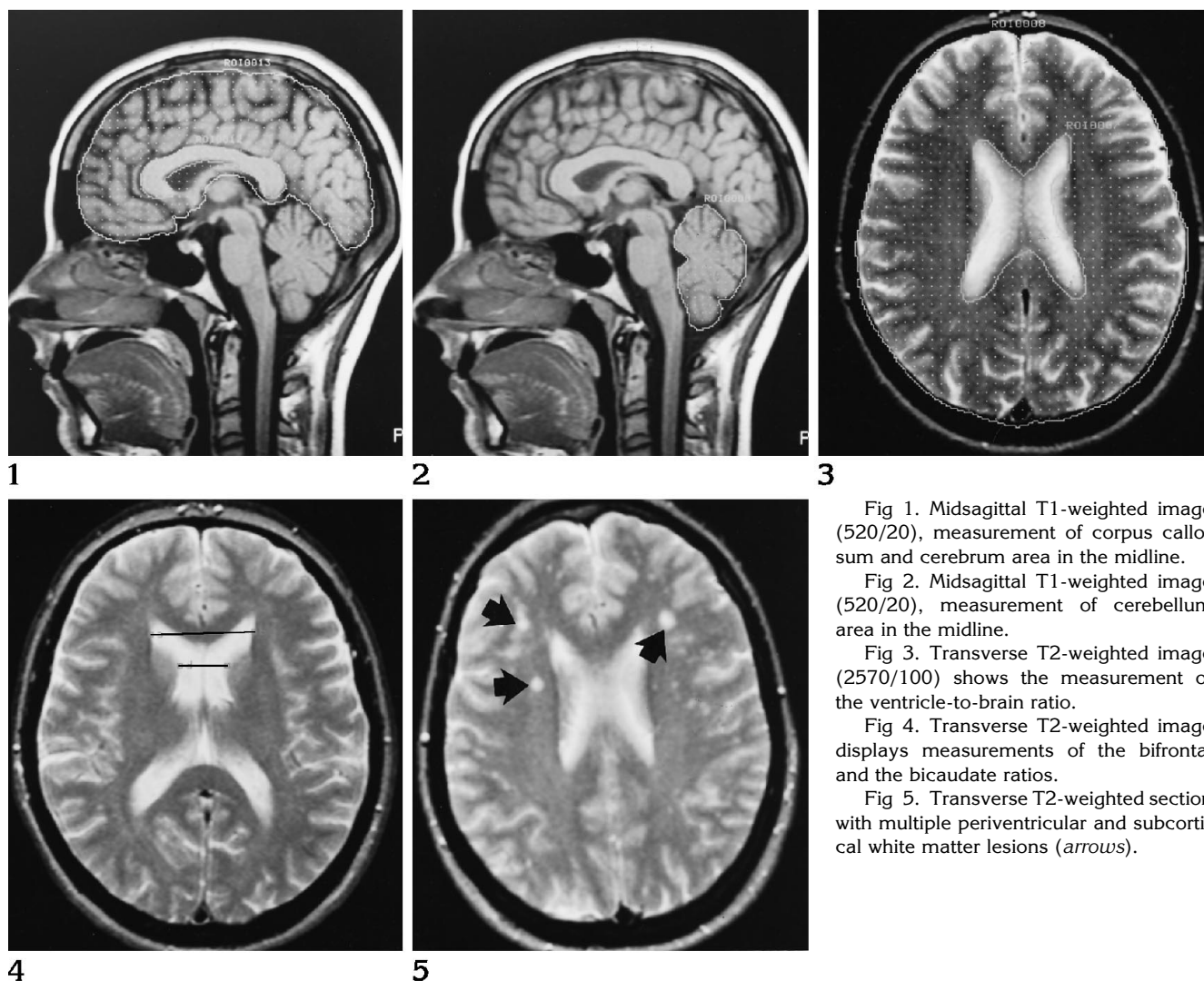


Fig 1. Midsagittal T1-weighted image (520/20), measurement of corpus callosum and cerebrum area in the midline.

Fig 2. Midsagittal T1-weighted image (520/20), measurement of cerebellum area in the midline.

Fig 3. Transverse T2-weighted image (2570/100) shows the measurement of the ventricle-to-brain ratio.

Fig 4. Transverse T2-weighted image displays measurements of the bifrontal and the bicaudate ratios.

Fig 5. Transverse T2-weighted section with multiple periventricular and subcortical white matter lesions (arrows).

nine patients with disease duration more than 15 years, the ventricle-to-brain ratio) was significantly increased compared with the control subjects (Table 2). In the same subgroup of patients with long-standing disease, the midsagittal area of cerebellum was significantly reduced compared with the control subjects (Table 2). Multiple regression analysis with cerebellar area as the dependent variable versus disease duration, number of arthritic joints, and Ritchie index (number of painful joints) as independent variables was performed. The explained variance was 35%, and a significant association between cerebellar atrophy and disease duration was detected ($P = .005$). The ventricle-to-brain ratio, bifrontal ratio, and bicaudate ratio as atrophy parameters measured on a transverse plane were almost identical in the two groups (Table 2). Except for a

slightly higher bicaudate ratio, no tendency of more cerebral involvement evaluated by MR in the drug-treated group was detectable (Table 3).

Cerebral hyperintense lesions were identified in 9 patients (27%), multifocal in 4 (12%), and single in 5 (16%). Fifteen of the control subjects (31%) had hyperintense lesions; of them, 12 were (25%) multifocal and 3 (6%) single. Their shape was either round or ovoid and bilaterally distributed in both groups. The size and signal intensity of the biggest lesion were not significantly different in patients compared with control subjects (Table 2), and all lesions were identified on the T2-weighted images. No lesions were found in the corpus callosum, the cerebellum, or the brain stem. Also, no additional lesions were found in the group of patients with long disease duration. We found no rela-

TABLE 1: MR characteristics in patients with rheumatoid arthritis and in control subjects (mean \pm SD)

	Rheumatoid Arthritis (n = 33)	Control Subjects (n = 47)	95% Confidence Interval	P Value
Cases with lesions (%)	9 (27%)	15 (31%)84
Number of lesions	1.3 \pm 3.29	2.1 \pm 7.1153
Area of the biggest lesion, mm ²	27.4 \pm 15.0	29.8 \pm 22.8	-6.54, 11.34	.77
Relative signal intensity biggest lesion	0.53 \pm 0.17	0.49 \pm 0.24	-0.04, 0.12	.67
Cerebrum surface area, midsagittal section, mm ²	9756.5 \pm 789.7	9834.3 \pm 1664.7	-537.1, 693.3	.80
Cerebellum surface area, midsagittal section, mm ²	1586.9 \pm 274.8	1573.3 \pm 247.1	-102.2, 129.4	.81
Corpus callosum area, midsagittal section, mm ²	749.2 \pm 141.2	797.3 \pm 117.5	-9.1, 105.3	.10
Corpus callosum relative signal intensity	0.43 \pm 0.16	0.46 \pm 0.15	-0.03, 0.09	.39
Ventricle-to-brain ratio	0.08 \pm 0.02	0.08 \pm 0.0226
Bifrontal ratio	0.33 \pm 0.02	0.33 \pm 0.0350
Bicaudate ratio	0.11 \pm 0.02	0.12 \pm 0.0270

TABLE 2: MR characteristics in patients with longstanding rheumatoid arthritis and in control subjects (mean \pm SD)

	Patients with Rheumatoid Arthritis Duration of at Least 15 Years (n = 9)	Control Subjects (n = 47)	P Value
Number of lesions	0.44 \pm 0.53	2.17 \pm 7.11	.47
Cerebrum surface area, midsagittal section, mm ²	9892.34 \pm 700.3	9834.3 \pm 1664.7	.91
Cerebellum surface area, midsagittal section, mm ²	1349.8 \pm 243.3	1573.3 \pm 247.1	.015*
Corpus callosum area, midsagittal section, mm ²	729.7 \pm 113.0	797.3 \pm 117.5	.11
Corpus callosum relative signal intensity	0.42 \pm 0.2	0.46 \pm 0.15	.48
Ventricle-to-brain ratio	0.09 \pm 0.02	0.08 \pm 0.02	.026*
Bifrontal ratio	0.32 \pm 0.02	0.33 \pm 0.03	.26
Bicaudate ratio	0.11 \pm 0.03	0.12 \pm 0.02	.58

* $P < .05$.TABLE 3: MR parameters in medically treated and untreated patients with rheumatoid arthritis (mean \pm SD)

	Medically Treated (n = 6)	Untreated (n = 27)	P Value
Number of lesions	1.1 \pm 2.9	1.8 \pm 4.4	.64
Cerebrum surface area, midsagittal section, mm ²	9679.3 \pm 796.9	10043.2 \pm 747.1	.28
Cerebellum surface area, midsagittal section, mm ²	1598 \pm 297.4	1542.3 \pm 177.4	.63
Corpus callosum area, midsagittal section, mm ²	749.3 \pm 145.7	748.6 \pm 133.8	.99
Corpus callosum relative signal intensity	0.44 \pm 0.17	0.38 \pm 0.14	.45
Ventricle-to-brain ratio	0.08 \pm 0.01	0.07 \pm 0.01	.41
Bifrontal ratio	0.33 \pm 0.01	0.32 \pm 0.02	.69
Bicaudate ratio	0.11 \pm 0.02	0.09 \pm 0.01	.052

tionship between number of lesions and atrophy score on either sagittal or transverse sections in the two groups. No correlation was detected between age and any of the quantitative MR parameters.

Discussion

In the present study, the prevalence of cerebral lesions in the group of patients with rheumatoid arthritis was not different from that in the control subjects. The ventricle-to-brain ratio was increased, and the midsagittal area of the cerebellum was significantly lower in a subgroup of patients with long disease duration, but

not in the total group. The other morphometric measurements of atrophy were not different between the two groups.

Although rare, cerebral vasculitic infarcts in rheumatoid arthritis occur (15). The lower prevalence of multiple hyperintense cerebral lesions in rheumatoid arthritis might be a coincidence. Epidemiologic studies show a higher mortality rate in rheumatoid arthritis compared with the general population (2, 16). Cardiovascular disease is the most common cause of death in rheumatoid arthritis and in the general population, but diseases in the CNS are reported to cause up to 18.6% of deaths in rheumatoid arthritis (17). The explanation for a reduced ven-

tricle-to-brain ratio and cerebellar area in the small group of patients with disease duration more than 15 years is not obvious. Although alcoholism was excluded, we cannot be sure that some use of alcohol may have been a confounding variable in this study. Rheumatoid arthritis might be more prevalent and less severe in the community (18), suggesting most of the hospital-based patients participating in the present study to have more severe disease than rheumatoid arthritis in general. Therefore, it is reasonable to suggest that the findings in our study are probably not overestimated. A tendency of more atrophy in patients with longstanding disease indicates an association between rheumatoid arthritis and CNS disease, although a nonsignificant tendency of more hyperintense white matter lesions was detected in the control subjects.

Rheumatoid factor, which is regarded as a negative prognostic factor in rheumatoid arthritis (19), was not associated with cerebral findings, indicating such changes not to be of prognostic value. A positive association of corticosteroid treatment with cognitive impairment (20) and cerebral vasculitis (21) has been suggested. Only six of our patients were on corticosteroid treatment, and we could not detect more lesions or atrophy in these patients. No consistent conclusions can be given for any treatment subgroups, possibly because of the small samples. Adverse effects on the CNS has been shown for high-dose intrathecal methotrexate therapy (22), but not in rheumatoid arthritis or in other patients treated with low-dose methotrexate (23). No abnormal findings were recorded by electroencephalographic examination in seven methotrexate-treated patients with psoriasis (24). Mixed treatment and frequent changes in medication, in addition to the small sample, may explain the similar results of treated and untreated patients in this study.

In one recent study (25), 33% of asymptomatic persons had hyperintense lesions, which is similar to our results. Age and antihypertensive medications were positively associated with the MR findings, suggesting the lesions to be of vascular origin (25). In our study, age was not correlated with MR changes, and the lesions had similar characteristics (shape, location, and signal intensity) in both groups, supporting the hypothesis of a common cause of these lesions. The tendency of hyperintense lesions to occur more often in healthy persons older than 50

years is reported by others (26). The pathologic differential diagnosis existing for multiple white matter lesions in the CNS is divided mainly into vascular and inflammatory conditions (27). Normal aging and white matter ischemic lesions are reported as common causes of high signal in the CNS (27). On T2-weighted images in our study, lesions might have been underevaluated because no T2 sagittal sections were obtained. Also, we did not use intravenous contrast (gadolinium) in our MR series.

The cerebrum-to-corpus callosum ratio was not related to the number or size of the hyperintense lesions in either group. Others have reported a correlation between the volume of multiple sclerosis lesions and atrophy of the corpus callosum (28). Hence, in patients with multiple sclerosis, atrophy of the brain seldom occurs without atrophy of the corpus callosum; on the other hand, isolated atrophy of the corpus callosum might be present (29).

In conclusion, we found that hyperintense lesions in the cerebral hemispheres were common, but were not more prevalent in patients with rheumatoid arthritis than in control subjects. Patients with long disease duration had increased ventricle-to-brain ratios and decreased midsagittal cerebellar areas indicating an association between cerebral and cerebellar atrophy and rheumatoid arthritis.

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