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MR Imaging in Multiple Sclerosis: Comparison with Clinical, CSF, and Visual Evoked Potential Findings

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MR examinations of 136 patients with multiple sclerosis (MS) were evaluated to correlate the results with clinical, CSF, and visual evoked potential (VEP) findings. In addition, 22 of the 136 patients were studied several times during a 5-month follow-up period. It was demonstrated that MR is superior to CSF and VEP findings in establishing cerebral alterations in MS. A relationship between the results of CSF and VEP examinations and the MR results could not be detected. Negative CSF and VEP results corresponded to positive MR imaging and vice versa. In our series, five negative MR results were obtained in patients with clinically proved MS. The extent of alterations shown up by MR corresponds to the duration of the disease; in particular, more confluent abnormalities in the periventricular region were found in patients with long-standing disease. More plaques were found in patients with a primary relapsing/remitting course of the disease than with the primary chronic progressive form. The clinical course and the grade of disability did not correspond to differences in MR imaging. Follow-up demonstrated that most lesions remain unchanged (72–79%); increases and decreases in the size of the plaques seem to depend on the clinical course.

These results suggest that MR is the most sensitive technique for establishing the diagnosis of MS.

Despite published data concerning the value of MR imaging in patients with presumed multiple sclerosis (MS) there remain some questions that need to be answered. For example, it has yet to be determined whether negative MR results occur more often in patients with the diagnosis of probable MS. Another unanswered question is whether negative MR results tend to correlate with negative visual evoked potential (VEP) and CSF results. Articles on this matter have covered an insufficient number of patients [1–7].

Moreover, to gain an understanding of the alterations shown by MR, it is necessary to determine whether these alterations correlate in any way with clinical data on the duration of disease, the grade of impairment, and the course of disease. Many authors doubt that there is a correspondence; however, the issue has been studied only in a very small number of cases [1, 3, 5, 8–11].

One of the most interesting questions is whether MR can supply data on the activity of the disease. This would require criteria that can differentiate between acute inflammatory lesions and scars. Unfortunately, we are unable to say what the MR signal intensities represent; that is, which of the lesions represent demyelination and which are caused by edema. Attempts to differentiate between scar and acute inflammation by using T2 relaxation times have failed, because the differences in relaxation times between acute and chronic lesions were insufficient to differentiate between them [12].

To obtain answers to these questions we evaluated the results of our MR examinations of MS patients and correlated these data with the grade of certainty of the disease, the CSF laboratory and VEP results, the duration of disease, the grade of impairment, and the course of disease. To obtain more information about the character of the lesions on MR, a follow-up study was performed.

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Subjects and Methods

One hundred thirty-six patients were included in the study and evaluated with respect to MR results, certainty of diagnosis, CSF laboratory and VEP findings, duration of disease, index of impairment compared with the Kurtzke disability status scale [13], and clinical course. The MR scans were evaluated for signal abnormalities in the periventricular region, both hemispheres, the cerebellum, the brainstem, and the cervical spinal cord. To obtain semiquantitative results, we created an MR index (Table 1). In addition, we evaluated cerebral atrophy and differentiated between circumscribed or diffuse cortical atrophy and/or a subcortical atrophic process. Diffuse cortical atrophy was defined as the presence of more than five sulci with a width of 3 mm and greater. Subcortical atrophy was defined by the diameter of the ventricle bodies: The parietal diameter of the skull was measured and divided by the greatest outer width of the pars centralis of both ventricles. Ratios greater than 4 were considered normal.

Certainty of Disease

The certainty of clinical diagnosis was divided into five categories:

Group 1 included patients with proved MS on the basis of our criteria—relapsing/remitting course of disease only. The age of onset had to be between 20 and 50 years old; the duration of disease needed to be at least 2 years but no longer than 15 years. Two or more attacks with a definite remission of 1 month or longer were required. Pathologic VEP was required, as were pathologic CSF laboratory findings (including CSF oligoclonal bands and/or evaluation of intra-blood-brain IgG synthesis).

TABLE 1: MR Index for Assessing Plaques of Multiple Sclerosis

A, Periventricular plaques:
- A0, No plaques
- A1, No more than five plaques, single plaque not larger than 8 mm, or one plaque larger than 8 mm and no more than three plaques; no confluence
- A2, More than five plaques, more than three plaques with one plaque larger than 8 mm, or two or more plaques larger than 8 mm; in addition or exclusively, there is periventricular confluence but the bodies of the ventricles are mainly unaffected
- A3, More than 12 plaques and/or periventricular confluence, including the bodies of the ventricles

B, Hemispheric plaques:
- B0, No plaques
- B1, No more than five plaques
- B2, More than five plaques

C, Cerebral atrophy:
- C1, White-matter atrophy
- C2, Focal cortical atrophy
- C3, Diffuse cortical atrophy
- C4, White-matter and cortical atrophy

D, Cerebellar plaques:
- D0, No plaques
- D1, One or more plaques

E, Brainstem plaques:
- E0, No plaques
- E1, One or more plaques

F, Spinal cord plaques:
- F0, No plaques
- F1, One or more plaques

Group 2 included patients who had proved MS on the basis of the criteria of Bauer [14]. Patients in this group had the relapsing/remitting *or* chronic progressive form of disease. The onset of symptoms was between the ages 10 and 50 years old. The relapsing and remitting course consisted of at least two bouts separated by no less than 1 month. Slow or stepwise progression of the disease extended over at least 6 months. In contrast to the first group, pathologic VEP was not obligatory. CSF laboratory had to be abnormal as in the first group.

Group 3 included patients with probable MS as defined by the Bauer criteria. These patients with a history of relapsing and remitting symptoms revealed signs suggestive of MS, but unequivocal signs of multifocal white-matter disease were not documented. Patients with a documented single bout of symptoms should have demonstrated signs of multifocal white-matter disease with good recovery, followed by variable symptoms and signs. Pathologic CSF alterations should be suggestive of MS, but a full-blown MS profile was not obligatory.

Group 4 included patients with negative CSF results, but well-documented and typical clinical signs of MS.

Group 5 included patients with symptoms and histories comparable to group 2; however, they did not undergo lumbar puncture for CSF laboratory or other studies.

Duration of Disease

Patients were divided into three groups on the basis of duration of disease: (1) up to 2 years, (2) 2–8 years, and (3) more than 8 years (Table 2).

Grade of Impairment

The Kurtzke disability status score was used to assess abnormalities of the various functional systems (pyramidal, cerebellar, brainstem, sensory, bowel and bladder, visual, cerebral total, cerebral-mentation). We divided the score into three groups: 1–2.5 (low impairment), 3–5.5 (moderate), and 6.0 or greater (severe). A score of 1.0 includes grade 1

TABLE 2: MR Alterations Relative to Duration of Disease

MR Category of Alterations	% of Total in Each Category		
	Up to 2 Years (n = 26)	2–8 Years (n = 65)	More Than 8 Years (n = 45)
A0 + A1	23	20	9
A2	54	43	44
A3	23	37	47
B0	4	8	4
B1	77	55	56
B2	19	37	40
D0	73	61	68
D1	27	39	32
E0	92	87.5	82
E1	8	12.5	18

abnormalities of one functional system, with the exception of cerebral; all other systems have to be grade 0. A score of 3.0 is limited to grade 3 abnormalities of one functional system or grade 2 of three or four functional systems; the other systems have to be of grade 0 or 1. A score of 5.5 required ambulation for 100 m without aid or rest. Other criteria included inability to work part time (about 4 hr/day) without special provisions. A score of 6.0 required assistance to walk about 100 m. Usual functional system-equivalents are combinations with more than two functional systems of grade 3 or more. We differentiated between patients with a primary chronic progressive form of disease and a primary relapsing/remitting course. Patients with a relapsing/remitting course were divided into "acute relapse" and "interval" groups.

Follow-up Studies

Twenty-two patients underwent a follow-up study. The criteria that determined a patient's inclusion in the study were (1) relapsing/remitting course of disease, onset of the disease between the ages of 20 and 50 years; and pathologic CSF laboratory and VEPs. The first examination was done during the acute relapse; afterward, cortisone therapy was begun. The second MR study was 4–6 weeks after the first one and the third 3 months after the previous one. The lesions in each section were counted, a distinction being made between the demarcated lesions and confluences. Care was taken to use the correct layer in repeat examinations. The head was positioned and the center of the field was fixed with reference to the first scan.

The initial MR examinations were done on either a 0.35 or 0.5-T system with a head coil. Because of the relatively low field strength, axial cuts were obtained with 10-mm slice thicknesses to achieve a sufficient signal-to-noise ratio in a reasonable time. Sagittal images were obtained for evaluation of the spinal cord with 6-mm sections. Spin-echo sequences had a repetition time (TR) of 1600 (0.35 T) and 2000 (0.5 T) msec and an echo time (TE) of 35 and 120 msec. The first 10 patients in the follow-up study were examined at 0.5 T; the remaining 12 patients at 1.5 T.

Results

Of the 136 patients examined with MR, 90 (66%) were female and 46 (34%) male. Two percent were 20 years old or younger ($n = 3$), 33% were 21–30 ($n = 45$), 35% were 31–40 ($n = 47$), 18% were 41–50 ($n = 24$), and 12% were older than 50 ($n = 17$).

Location of Abnormalities

Periventricular lesions were seen in 96% of all patients; alterations in the hemispheres were found in 95%. Periventricular plaques were not seen in two patients, but lesions were found in other regions. In 34% of all examinations cerebellar plaques were seen and in 13% brainstem lesions were seen. Of 83 examinations of the cervical spinal cord 11% were abnormal. Circumscribed cortical atrophy was seen in nine cases, diffuse alterations in two. Gray- and white-matter atrophy was seen in 11 patients and atrophy of only white matter was seen in 22 cases. Forty-seven patients (35%) were classified as having atrophy in one form or another.

Certainty of Disease

Forty-nine patients were considered to be in group 1, 48 in group 2, nine in group 3, 13 in group 4, and 17 in group 5. Five MR images were negative; of those, four were of patients in group 2 and one in group 1.

MR vs VEPs and CSF

All five patients with negative MR images had positive CSF findings; three of these had pathologic VEP results and two had negative VEPs. All 13 patients with negative CSF results but typical clinical courses (group 4) had positive MR examinations. VEP examinations were negative in seven of these and positive in six. VEP examinations were negative in 23 patients; MR findings were positive in 21 of these and CSF results in 16.

Duration of Disease

Patients with a long duration of disease demonstrated more changes than patients with a short course (Table 2). In this group, more confluent periventricular lesions were identified, more plaques were seen in the white matter of both hemispheres, and more brainstem alterations were observed.

Grade of Impairment

We did not find a definite relationship between morphologic pattern and grade of impairment (Table 3).

TABLE 3: MR Alterations Relative to Grade of Impairment (Kurtzke Index)

MR Category of Alterations	% of Total in Each Category		
	1.0–2.5 ($n = 22$)[a]	3.0–5.5 ($n = 65$)	≥6 ($n = 46$)[b]
A0 + A1	27.3	12.3	15
A2	36.3	55.4	39
A3	36.3	32.3	46
B0	4	8	4
B1	73	58	57
B2	23	34	39
D0	71	58	76
D1	29	42	24
E0	95	82	89
E1	5	18	11

Note.—Grades of impairment are measured as low (1.0–2.5), moderate (3.0–5.5), and severe (≥6.0).

[a] There were 21 patients in categories D and E.

[b] There were 45 patients in categories D and E.

Forms of Disease

The primary chronic, progressive form of MS was found in 22 patients; a primary relapsing/remitting course was found in the other 114. Some differences were associated with the course of disease. Patients with the chronic, progressive form of disease showed less severe periventricular and brainstem lesions than patients with the primary relapsing/remitting form (Table 4). This pattern was not found with hemispheric and cerebellar lesions, however. No differences were seen between scans obtained during acute relapse and scans obtained in the interval of the relapsing/remitting form (Table 5).

Follow-up Studies

The results of the follow-up study are summarized in Table 6. Most plaques did not change at all (77.2 and 79.6%, respectively). The second MR study after the application of cortisone therapy showed that 10.2% of all plaques had enlarged, 4.9% had diminished, and 3.4% had vanished; there were new lesions in 4.3%. The third MR study in comparison with the second revealed that only 3.9% of all plaques had enlarged, 8.4% had decreased, 2.9% were new, and 5.2% had vanished.

The results in Tables 2–5 were analyzed for significance by using the chi-square test. Significant differences were not found.

TABLE 4: MR Alterations Relative to Course of Disease

MR Category of Alterations	% of Total in Each Category	
	Primary Chronic Progressive (n = 22)	Primary Relapsing/ Remitting (n = 114)[a]
A0	14	3.5
A1	18	11
A2	41	46
A3	27	39.5
B0	9	5
B1	55	61
B2	36	34
D0	68	65
D1	32	35
E0	100	84
E1	0	16

[a] There were 112 patients in categories D and E.

TABLE 5: MR Alterations in Patients with Relapsing/Remitting Course of Disease Relative to Actual Clinical Situation

MR Category of Alterations	% of Total in Each Category	
	Acute Relapse (n = 53)	Interval (n = 60)
A0 + A1	17	12
A2	47	47
A3	36	41
B0	4	7
B1	62	60
B2	34	33
D0	63	68
D1	37	32
E0	85	83
E1	15	17

TABLE 6: Results of MR Follow-up Studies in Assessing Multiple Sclerosis Lesions in 22 Patients

MR Status of Lesions	No. of Lesions (%)	
	Second vs First MR Study	Third vs Second MR Study
Increased	48 (10.2)	19 (3.9)
Decreased	23 (4.9)	41 (8.4)
No change	363 (77.2)	387 (79.6)
Disappeared	16 (3.4)	25 (5.2)
Newly developed	20 (4.3)	14 (2.9)
Total	470 (100)	486 (100)

Discussion

MS is an inflammatory disease of the CNS, mainly of the white matter. The cause of MS has not been established, but an autoimmunologic process is presumed. The development of the MS is influenced by gender, age, and geographic variables. The female to male ratio is about 1.4/1; in some studies it is higher [15], as it was in ours (1.9/1). Most affected patients are 10–50 years old and live in northern Europe and the northern United States or, less often, in Japan and other Asian countries. About 16.8% of MS patients in a study by Sibley et al. [16] had a positive family history.

CT plays a role in establishing the diagnosis of MS. The sensitivity of CT has increased in recent years; with the introduction of better systems and the use of high doses of contrast media, the number of detected lesions has tripled [17–24].

The sensitivity of MR is superior to that of CT. In our study MR had a sensitivity of 96%, which agrees with the results of other investigators [2–6, 25, 26]. The typical MR pattern of MS, as seen in our patients, showed circumscribed or confluent plaques in the periventricular region, mainly at the anterior and posterior horns. Fewer abnormalities were found in other locations, mainly in the periphery of the white matter [27–31]. Although T2-weighting demonstrated lesions best, sometimes, particularly in the brainstem and cerebellum, proton-weighted images were superior. In agreement with some other authors, we believe that long TEs up to 100 or 120 msec are best at enhancing the affected regions [11, 32].

We evaluated whether a greater number of negative MR examinations would be found in patients with probable MS than in those with proved MS. To eliminate ambiguity between the degrees of certainty of diagnosis we studied only patients with a relapsing/remitting course of disease, because the diagnosis of the chronic progressive form is not clear cut.

Nonetheless, the certainty of diagnosis did not correspond to MR results; specifically negative MR findings were found in the first and second groups but not in the third and fourth groups. This may be explained by the fact that neuropathologic studies reveal only microscopic plaques [33]. Therefore, while all clinical criteria of MS may be fulfilled, plaques may not be visible on MR. Moreover, a spinal form of the disease exists in which no cerebral lesions are manifested. Sheldon et al. [31] correlated the grade of certainty with positive MR results. In their study 85% of all MR examinations were positive in patients with definite MS but only 11% were positive in patients with probable MS. Similar results were reported by Jackson et al. [12].

The results of MR imaging did not correspond to CSF laboratory or VEP findings. MR was negative when CSF or VEPs were positive and vice versa. This is another indication that the inflammation responsible for the pathologic results in VEPs or CSF laboratory may not be detected with MR. These results agree with the studies of Siddharthan et al. [6], Kirshner et al. [3], and Gebarski et al. [2]. When CSF is negative, it is worthwhile to perform an MR examination; if MR is negative, CSF and VEP examinations should be added. In our series there was no patient in whom all three examinations were negative. Since all negative MR scans were balanced by positive CSF studies, the need for VEPs is questionable. However, even though we had no cases in which MR and CSF were negative and VEP positive, we believe the VEP study is still necessary as it is the only of the three studies that supplies information about the status of the cranial nerves.

We were able to demonstrate that patients with a duration of disease of more than 8 years not only showed more changes, mainly periventricular confluence, but also showed more circumscribed lesions in the hemispheres than did patients with a short course (Fig. 1). However, the number of lesions gives no indication of the duration of the disease, since a short course may be accompanied by many circumscribed plaques (Fig. 2). If confluence with atrophy can be seen at the anterior and/or posterior horn, it is very likely that the duration of disease is long. On the other hand, larger plaques may be caused by edema, as is demonstrated in Figure 3.

MR alterations did not correspond to the grade of impairment. This may be explained by the fact that the Kurtzke score is based on clinical data and not on the morphologic pattern. A high score of impairment can be caused by few alterations in areas such as the brainstem or cervical spinal cord (Fig. 4). On the other hand, many lesions, including large ones, mainly in the periventricular region, do not cause clinical symptoms, and extensive alterations in the periventricular area may be accompanied by few clinical symptoms.

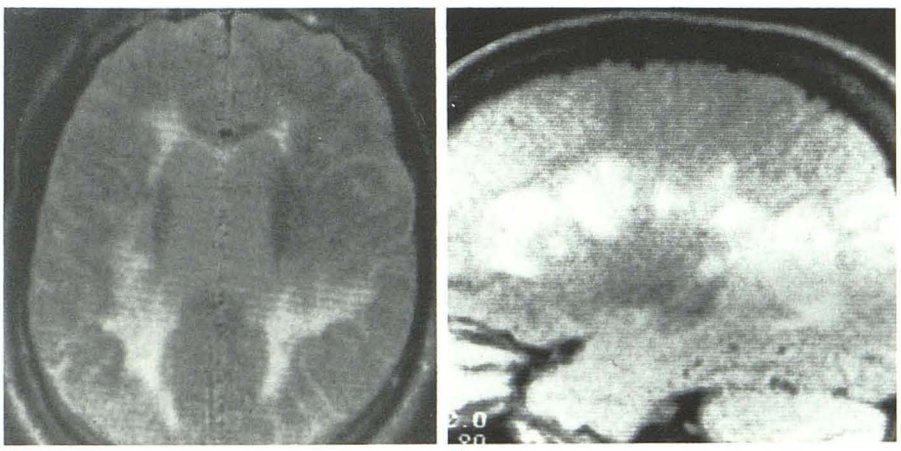
We were able to demonstrate differences in the morphologic pattern between patients with a chronic progressive form of disease and a relapsing/remitting course. The latter revealed more alterations, both periventricular and in the brainstem. It has been established that patients with a relapsing/remitting course often have more severe clinical symptoms than other patients, especially during acute relapse. More alterations could be expected to be revealed by MR in patients experiencing acute relapse than in patients in remission; however, our data did not indicate this.

Some other authors have wondered whether there is a correlation between clinical data and extent of alterations as seen with MR imaging. Crisp et al. [1] examined 43 patients and found no correlation between the number of lesions and the disability score or clinical course. Similar results were reported by Kirshner et al. [3]. However, Sheldon et al. [31] reported that more examinations were positive in patients scanned during acute relapse (93%) than in patients examined during remission (82%).

If one compares the neuropathologic description of morphologic changes with what can be seen with MR, there is a lack of agreement between the overall pathologic pattern and what MR can demonstrate. Lumsden [33] reported one case with 48 cerebral plaques, of which only 13 were macroscopically visible, the others being seen with a hand lens or low-power microscope. In one patient more than 200 plaques could be counted, and in another case 465 gyral plaques

Fig. 1.—Duration of disease = 13 years. MR image (TR = 2000 msec, TE = 120 msec) shows large confluent periventricular lesions. Note lack of cortical and subcortical atrophy.

Fig. 2.—Many plaques seen on MR (TR = 2000 msec, TE = 120 msec) during first bout of MS. Number of plaques alone gives no indication as to duration of disease.



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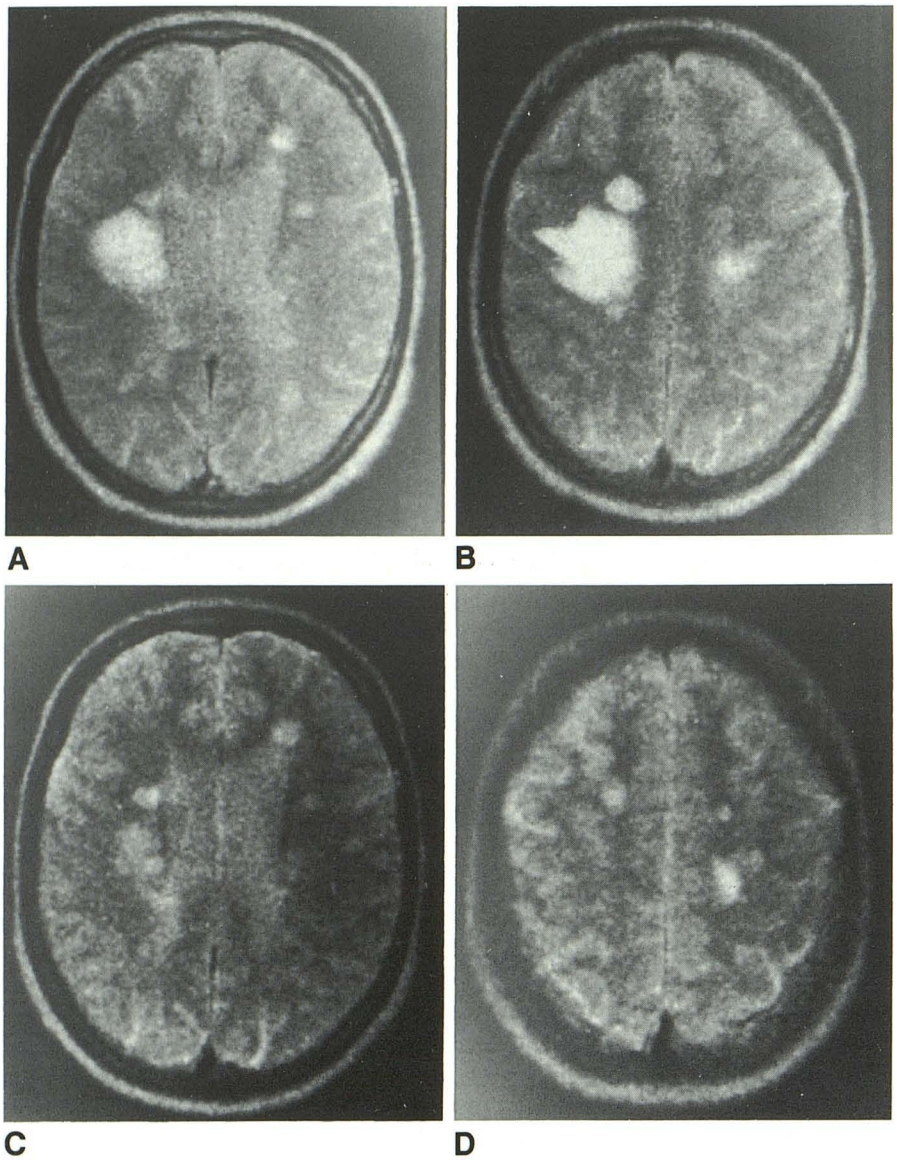

Fig. 3.—MR images (TR = 2000 msec, TE = 120 msec).

A and *B*, Follow-up images show large periventricular plaque (*A*) and plaque in centrum semiovale (*B*) on left side.

C and *D*, Second MR study 6 weeks later shows nearly complete disappearance of lesion, which was caused by edema.

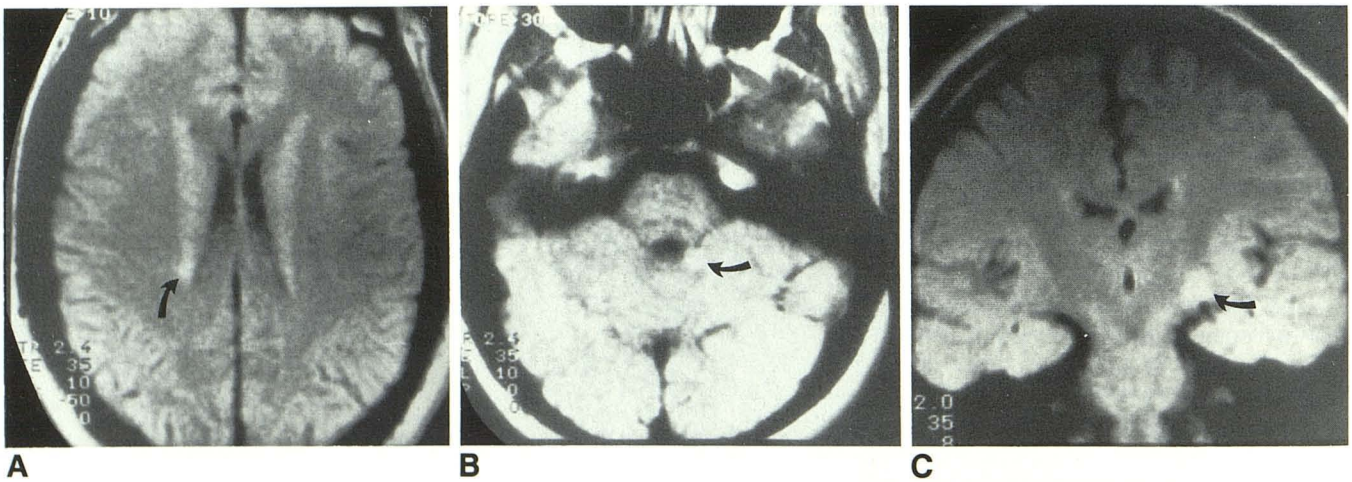

Fig. 4.—MR images (TR = 2000 msec, TE = 120 msec) in patient with severe physical disabilities and seizures. Only three plaques were found, one periventricular (*A*), one in cerebellar peduncle (*B*), and one at mesencephalon (*C*) (*arrows*).

were found. Compared with the periventricular patches, each peripheral gyral alteration was usually only about 1–3 mm in diameter. Thus, it is understandable that MR imaging does not agree fully with the clinical data and the course of disease. Neuropathologists are convinced that the degree of morphologic alteration corresponds well to the grade of severity of the disease, and Lumsden [33] described how the grade of atrophy is dependent on the duration of disease.

Our MR follow-up results demonstrate that plaques do not vary much in size and are almost constant in total number. However, one discernible trend is that about 6 weeks after the beginning of corticosteroid therapy, more lesions enlarge than diminish, and more lesions develop than vanish. The opposite situation is seen when the third MR study is compared with the second. Obviously, the pattern in MR imaging is more dependent on the course of disease than on corticosteroid therapy. All patients were in remission when the third MR study was done. Thus, the reduction in the size and number of plaques is understandable (Figs. 5 and 6). Why do so few lesions change? The reason could be that most of the plaques seen on MR represent scars and not edema. Another reason could be that the inflammation cannot be influenced much by corticosteroids; despite therapy, it continues to develop very slowly.

Can we distinguish between acute inflammatory lesions and scars with MR? Regarding signal intensity in the T2-weighted images, differentiation is not possible. However, confluent areas in the periventricular region mainly represent scars, whereas at the periphery of these confluences the inflammation may continue. Neuropathologists know that smaller plaques can also consist of scars [33]; however, T1-weighted MR may offer a means of distinguishing scars from inflammation. When T1-weighted MR images have been obtained, scars were seen as regions with very low signal intensity similar to that of lacunae, whereas acute inflammation was not distinguishable from healthy tissue (Fig. 7).

CT can provide information about acute inflammation because inflamed regions display contrast enhancement when a delayed scan is obtained after injection of a high dose of contrast material [22, 24, 30, 34]. Similar effects were noted for MR imaging by Grossman et al. [35] after the injection of gadolinium DTPA; however, this is not consistent with our experience [36]. It may be that the higher field strength of the system used by Grossman et al. is the reason for the discrepancy.

What would be the indication for MR imaging in cases of suspected MS. If clinical symptoms are typical and the patient is 20–50 years old, one should try to establish the diagnosis with CSF laboratory and VEP studies. If that does not work, MR is indicated. It is not advisable to perform MR first because of the expense of the examination and the relatively few installed units in some areas. Moreover, the alterations demonstrated with MR are not specific to MS. The differential diagnoses of multiinfarct syndrome, Binswanger disease, other forms of encephalitis, Boeck sarcoid, lupus erythematosus, and vitamin B_{12} deficiency have to be considered [37, 38].

In conclusion, we found MR imaging to be the most sensitive method of diagnosing MS. In the few negative examinations, the diagnosis was proved by other studies together with typical clinical signs. Negative results in CSF laboratory and VEP studies did not coincide with negative MR scans, and vice versa. Therefore, all methods should be used if a diagnosis cannot be established in any other way. MR imaging shows that the more lesions there are the longer the disease has existed. But a correlation could not be found between the number and size of plaques and the grade of impairment (index of Kurtzke). Patients with a relapsing/remitting course of disease revealed more and stronger alterations, mainly in the periventricular region and brainstem, than patients with a primary chronic progressive course. On the other hand, patients examined during acute relapse did not display more plaques than those scanned during remission. Somewhat surprisingly, corticosteroids did not have a reliable effect on the size and number of plaques in MR, as demonstrated by follow-up studies. Most alterations remained unchanged; however, the number and size of the plaques seemed to depend on the clinical course.

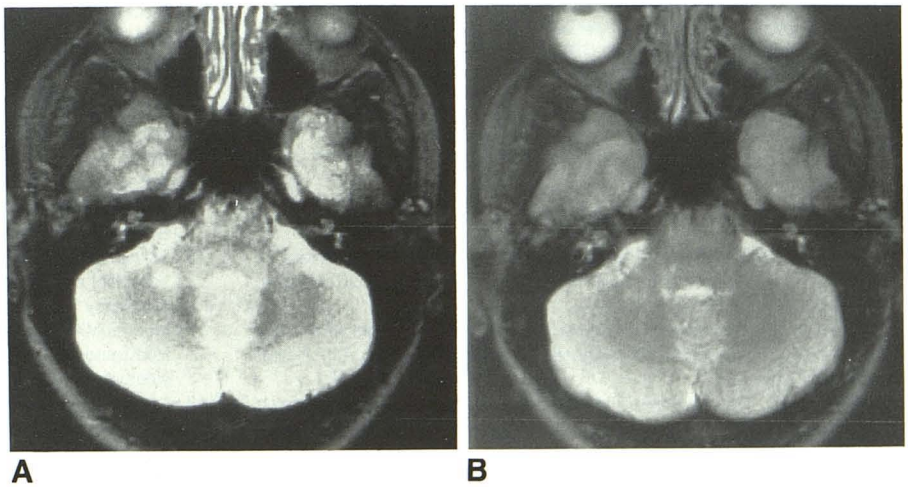

Fig. 5.—MR images (TR = 2000 msec, TE = 90 msec).

***A*, Follow-up study 6 weeks after beginning corticosteroid therapy. Plaque on right side in cerebellar peduncle had not been seen on first MR study before starting therapy.**

***B*, 6 months after acute relapse, and 4 months after corticosteroid therapy, plaque has diminished.**

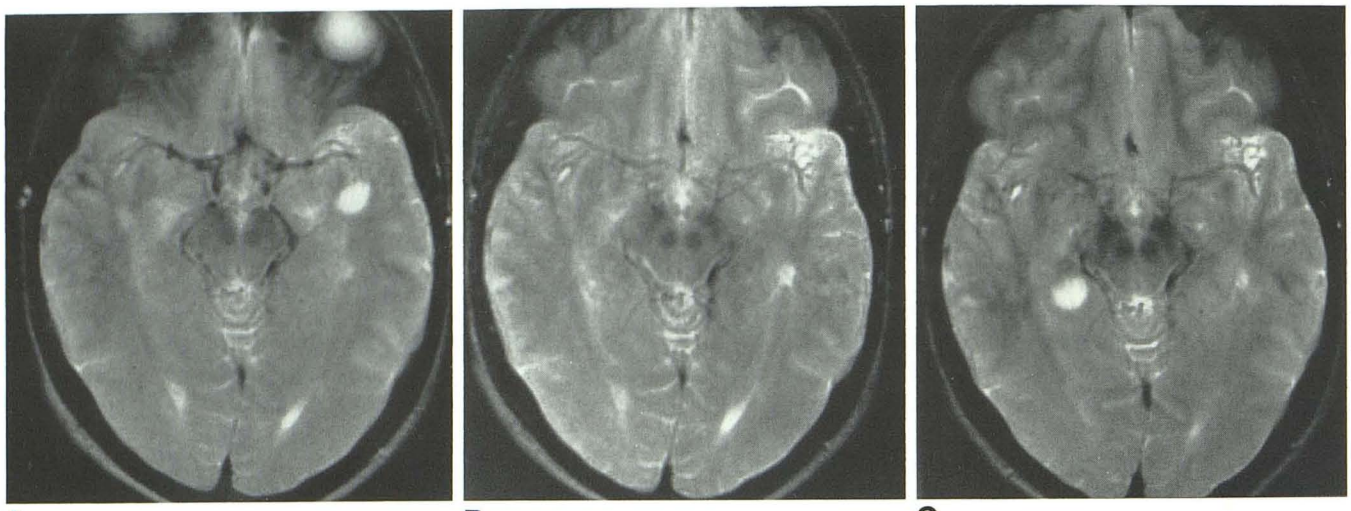

Fig. 6.—MR images (TR = 2000 msec, TE = 90 msec).
***A*, Follow-up study during acute relapse before beginning therapy. Plaque is on left side in temporal lobe.**
***B*, 6 weeks later. Plaque has vanished.**
***C*, 6 months after first MR study. Another plaque has arisen on right side in area of corpus geniculatum.**

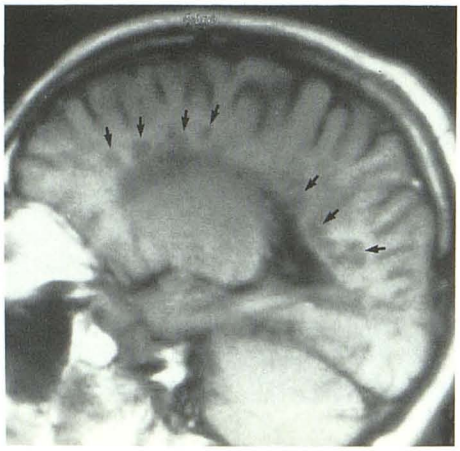

Fig. 7.—T1-weighted image (TR = 500 msec, TE = 30 msec) in patient whose duration of disease was more than 8 years shows periventricular lacunae expressing scars filled with CSF. Sharply demarcated lesions (*arrows*) show very low signal intensity; however, inflammation is often hardly visible on T1-weighted sequences.

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