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Limited duration of the effect of methylprednisolone on changes on MRI in multiple sclerosis*

F. Barkhof[1], M. W. Tas[1], S. T. F. M. Frequin[2], P. Scheltens[3], O. R. Hommes[2], J. J. P. Nauta[4], J. Valk[1]

[1] Department of Diagnostic Radiology, Free University Hospital, Amsterdam, The Netherlands
[2] Institute of Neurology, Academic Hospital, Nijmegen, The Netherlands
[3] Department of Neurology, Free University Hospital, Amsterdam, The Netherlands
[4] Department of the Theory of Medicine, Epidemiology and Biostatistics, Free University Hospital, Amsterdam, The Netherlands

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Abstract. Treatment with methylprednisolone reduces the duration and severity of clinical relapses in multiple sclerosis (MS), while reducing the number of gadolinium-enhancing lesions on T1-weighted MRI. We performed serial MRI imaging after methylprednisolone treatment to see whether suppression of enhancement persists and whether related abnormalities on T2-weighted images disappear at follow-up. Thirteen patients with definite MS received a total of 31 courses of methylprednisolone over an average period of 50 weeks. Gadolinium-enhanced MRI was obtained before and after treatment, then at monthly intervals, using a standardised repositioning and imaging protocol. Two experienced readers in conference defined the number of active (gadolinium-enhancing and new or enlarging nonenhancing) lesions. We detected 609 active lesions on 195 examinations. Directly after treatment the reduction in the number of enhancing lesions was 78 %, indicating restoration of the BBB and suppression of inflammation. It was uncommon for a lesion which stopped enhancing to show enhancement on a subsequent examination. No beneficial effect was observed on the rate of disappearance of related abnormalities on T2-weighted images, indicating persistent change such as oedema, cellular infiltration or demyelination. Moreover, in 89 % of cases, an increase in the number of active lesions was observed before new clinical activity, if any, was observed (on average 52 % earlier). MRI enabled us to demonstrate that the duration of the effect of methylprednisolone treatment is temporary (on average 9.7 weeks).

Key words: Multiple sclerosis – Magnetic resonance imaging – Corticosteroid – Gadolinium

Magnetic resonance imaging (MRI) in multiple sclerosis (MS) frequently reveals silent new disease activity, and is therefore well suited to evaluate the effect of therapy [1]. Corticosteroids are frequently given to decrease the severity and shorten the duration of relapses in MS [2–4]. Recent studies have shown that IV methylprednisolone reduces gadolinium (Gd) enhancement, while no significant effect on the corresponding abnormalities on T2-weighted images is observed [5–7], implying that methylprednisolone selectively suppresses the inflammatory component of lesions, which is accompanied by disruption of the blood-brain barrier.

Our purpose was to study disease activity assessed by MRI following methylprednisolone treatment, to see whether (1) suppression of Gd-enhancement is permanent (or if enhancement recurs); (2) the development of new Gd-enhancing lesions is suppressed (and if so, for how long); and (3) whether any changes occur in the abnormalities on T2-weighted images corresponding to areas of previous Gd-enhancement.

Patients and methods

We prospectively studied 13 patients with clinically (11) or laboratory supported (2) definite MS [8] and a relapsing-remitting disease course. Their mean age was 28 years (range 21–40). Most had disease of short duration (mean 3.1 yrs, range 0.5–13 yrs), and relatively moderate disability (median baseline expanded disability status scale [EDSS] 2.5, range 1.5–5). All but one had oligoclonal IgG bands in their cerebrospinal fluid (CSF) on isoelectric focussing.

Patients entered the study at the time of an acute clinical relapse (development of new or worsening of old symptoms for at least 24 h, not related to a period of fever or concurrent disease), for which high-dose IV methylprednisolone treatment was given (1000 mg/day for 10 days). Throughout the study, clinical examination and MRI were performed at the same time, before and after methylprednisolone therapy and then at monthly intervals. When new clinical relapses occurred, treatment was repeated. The study period for individual patients varied from 19 to 83 weeks (mean 50). All patients gave informed consent.

Clinical disability was assessed using the EDSS [9]. The duration of clinical effect was defined as the period between the end of the

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Correspondence to: F. Barkhof, Department of Diagnostic Radiology, Free University Hospital, P. O. Box 7057, NL-1007 MB Amsterdam, The Netherlands

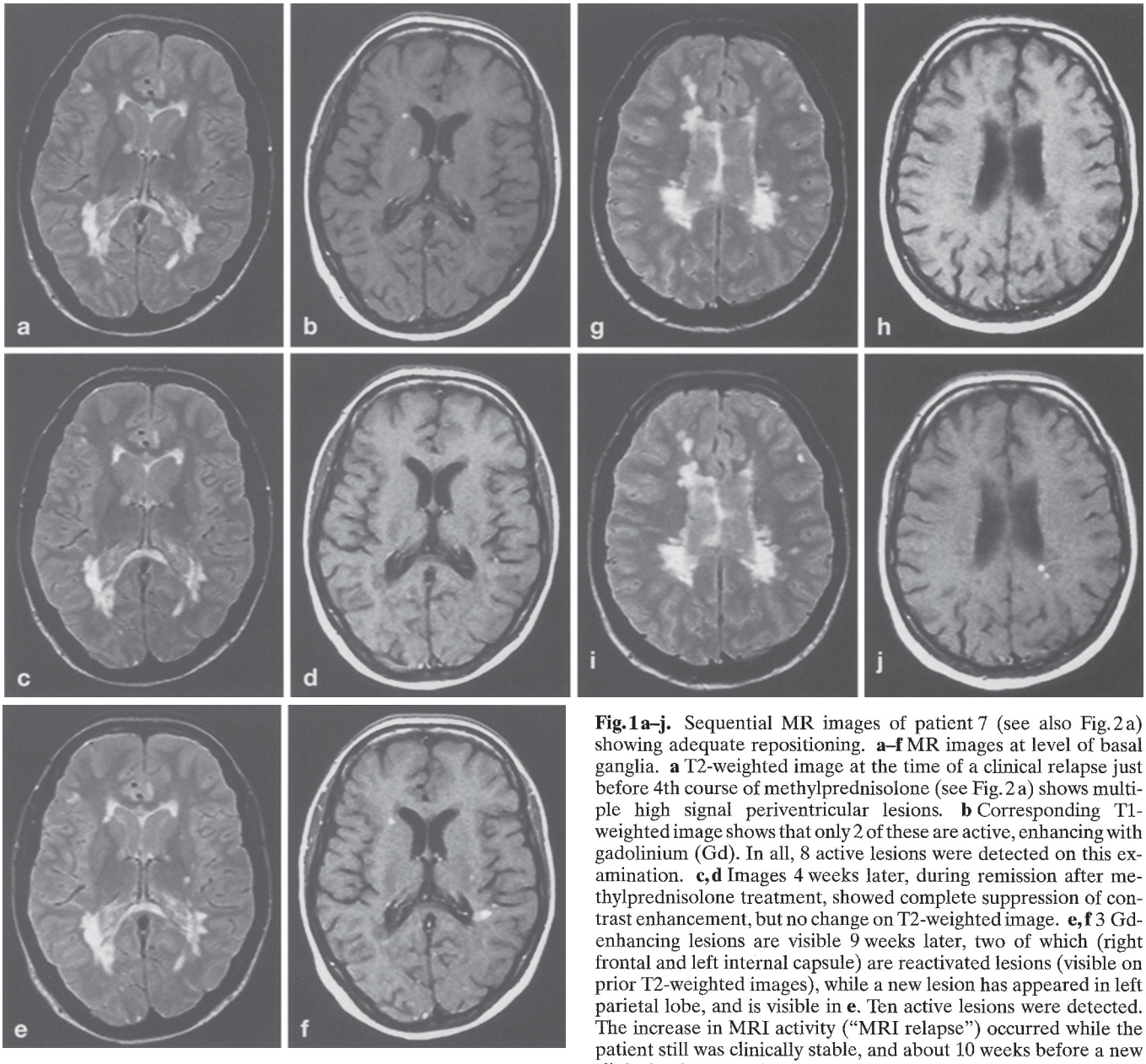

Fig. 1 a–j. Sequential MR images of patient 7 (see also Fig. 2 a) showing adequate repositioning. **a–f** MR images at level of basal ganglia. **a** T2-weighted image at the time of a clinical relapse just before 4th course of methylprednisolone (see Fig. 2 a) shows multiple high signal periventricular lesions. **b** Corresponding T1-weighted image shows that only 2 of these are active, enhancing with gadolinium (Gd). In all, 8 active lesions were detected on this examination. **c, d** Images 4 weeks later, during remission after methylprednisolone treatment, showed complete suppression of contrast enhancement, but no change on T2-weighted image. **e, f** 3 Gd-enhancing lesions are visible 9 weeks later, two of which (right frontal and left internal capsule) are reactivated lesions (visible on prior T2-weighted images), while a new lesion has appeared in left parietal lobe, and is visible in **e**. Ten active lesions were detected. The increase in MRI activity ("MRI relapse") occurred while the patient still was clinically stable, and about 10 weeks before a new clinical relapse. **g–j** Images at level of centrum semiovale. T2-weighted image (**g**) obtained at the same time as **a** shows multiple, confluent high-signal lesions, none of which enhances (in **b**). Four weeks later (compare with **c, d**), the T2-weighted image (**i**) is unchanged, while a T1-weighted image (**j**) reveals two new areas of enhancement; this activity would have been missed without Gd

treatment and the occurrence of signs or symptoms, leading to an increase in EDSS (clinical activity).

MRI was performed on a 0.6 Tesla system, using a standard head coil. A standard imaging protocol was employed. To ensure reproducibility (irrespective of the patient's position in the imager), we used two consecutive scout images (coronal, sagittal), the oblique scanning facility and internal landmarks of the brain. Axial (double oblique) images were obtained through a plane determined by the inferior border of the pituitary gland and the fastigium of the 4th ventricle for angulation and the inferior border of the splenium of the corpus callosum as Z-centre. This gives an acceptably small angulation error on serial studies [10]. T2-weighted spin echo images (2755/ 60, 120(reduced bandwidth)/ 2) [TR/TE/excitations] were obtained. Gd-DTPA was then given IV (0.2 mmol/kg), followed by 10 cc saline. T1-weighted spin-echo sequences were obtained (400/28/4) starting 5–10 min after Gd injection, with in-plane resolution 1.0×1.3 mm, and slice thickness 5 mm (gap 1.25 mm). The total investigation time was 45 min. Halfway through the study, the imaging protocol was adjusted, and Gd was injected at the outset, and T1-weighted images were then obtained before the T2-weighted series. The latter protocol reduces the investigation time to 35 min, precludes changes in repositioning during injection of Gd and does not reduce lesion conspicuity on T2-weighted images [11].

The images were analysed by two of the authors in conference. The number, not the size, of Gd-enhancing lesions was noted. All new lesions were assigned to one of seven anatomical regions. We assessed whether areas of enhancement were represented by abnormalities on T2-weighted images. In addition we looked for new unenhancing lesions. On each follow-up image, we analysed whether lesions persisted or had ceased to enhance, new areas of enhancement had occurred, new unenhancing lesions had appeared and whether lesions changed in size on serial T2-weighted images. Although meticulous efforts were made to ensure reproducibility,

Table 1. Distribution of (549 enhancing and 18 nonenhancing) new lesions

Location	Number of lesions (%)
Supratentorial	
Periventricular	92 (16%)
Cerebral cortex	29 (5%)
Junction cortex/white matter	44 (8%)
Deep white matter	
Frontal lobe	213 (38%)
Parietal lobe	73 (13%)
Occipital lobe	24 (4%)
Temporal lobe	51 (9%)
Internal capsula	4 (1%)
Basal ganglia	13 (2%)
Infratentorial	
Brainstem	11 (2%)
Cerebellum	13 (2%)
Total	567 (100%)

slight changes in positioning inevitably occurred, due to hardware and patient limitations. As a consequence, lesions sometimes changed in apparent size. Only marked changes in size were therefore recorded; disappearance of lesions (beyond the resolution of the imager) was assumed when a lesion was not visible on two consecutive images.

Not only enhancing lesions (new areas of enhancement, recurrent enhancement in previously enhancing areas and persistently enhancing areas), but also new nonenhancing lesions, and enlarging lesions without enhancement were considered as lesions showing disease activity, and called "active" lesions. The duration of effect of methylprednisolone on the development of active lesions on MRI was defined as the period between the end of the therapy and an increase in the number of active lesions (MRI activity).

Results

Clinical

Four patients suffered no new relapse during the study and therefore were treated once only, at the beginning. All the others suffered clinical relapses, for which they received additional courses of methylprednisolone: 4 patients one, 2 patients two, 2 patients three, and 1 patient four. We thus gave a total of 31 courses of methylprednisolone. One patient was treated twice at the time of development of numerous new lesions on MRI, although she had minimal accompanying signs or symptoms. When 29 courses of methylprednisolone treatment were given on clinical grounds, clinical improvement was observed after 26 (90%), with a decrease in EDSS of 0.5 after 5 courses (18%) and of 1.0 or more points with 21 (72%).

Magnetic resonance imaging

Even with optimal repositioning, it is sometimes difficult to detect all changes on the T2-weighted images, and Gd-enhancement greatly facilitates this. In some cases new activity would have been missed completely on sequential T2-weighted images, especially when new areas of enhancement occurred within confluent abnormalities on T2-weighted images or when enhancement recurred (Fig. 1).

We performed 195 MRI examinations (7–24 per patient) and 549 new Gd-enhancing lesions were detected (enhancing lesions seen on the first examination were assumed to be new), 55 of which were not seen on the corresponding T2-weighted images (mean 41 per patient; range, 1–105); in addition, 18 new nonenhancing lesions (3% of all new lesions) were seen in 7/13 patients, and 4 enlarging lesions without enhancement (enlargement occurred far more often, but was usually accompanied by Gd-enhancement) were observed. Enhancement recurred in 38 lesions in 10/13 patients: in 12 it recurred on the second or third MRI examination (1 or 2 months after treatment), and in 26 it appeared independent of treatment (Fig. 1). Thus, 609 active lesions were detected during the study, 93 (15%) of which would have been overlooked without Gd-enhancement. Most of the new lesions (543, 96%) were supratentorial. The majority of those (365, 64%) lay in the deep white matter; 15% were related to grey matter (cortex, junction of cortex and white matter, or basal ganglia) (Table 1).

Before the courses of treatment, 293 active lesions were found. A decrease in the number of active lesions (Fig. 2) was seen after every course but the second in patient 12. After treatment 229 (78%) were no longer active, while 17 new nonenhancing lesions were detected and 1 lesion enlarged without enhancement; thus, 82 active lesions were seen after treatment. Without the use of Gd, the persistent enhancement in 60 lesions would not have been appreciated; 71% of persistent activity would not have been evident. The decrease in the number of active lesions from before treatment ranged from 0–100% for the individual courses. The percentage of decrease, per patient, ranged from 35 to 100%, mean 78%. The mean interval between pre- and post-treatment MRI was 22 days (SD 12 days). The last two courses in patient 11, given because of an increase in the number of active lesions, led to complete suppression of enhancement directly after treatment, but one month later a return to the pretreatment number of active lesions was observed.

Of the 567 enhancing and nonenhancing new lesions 103 (18%) eventually disappeared on the T2-weighted images. Of the 357 lesions first seen directly before methylprednisolone treatment was initiated, 87 (24%) eventually disappeared. Because lesions which developed before treatment had a longer follow-up period than lesions developing after treatment, lesions first seen on the pretreatment MRI study presumably had the same disappearance rate as those seen to develop after treatment. Lesions which persisted on follow-up T2-weighted images frequently became confluent with preexisting lesions, or could not be identified individually in the first place.

Clinical and MRI correlation

Figure 2 shows the relation between the number of active lesions and the EDSS as a function of time for patients 7, 8 and 9.

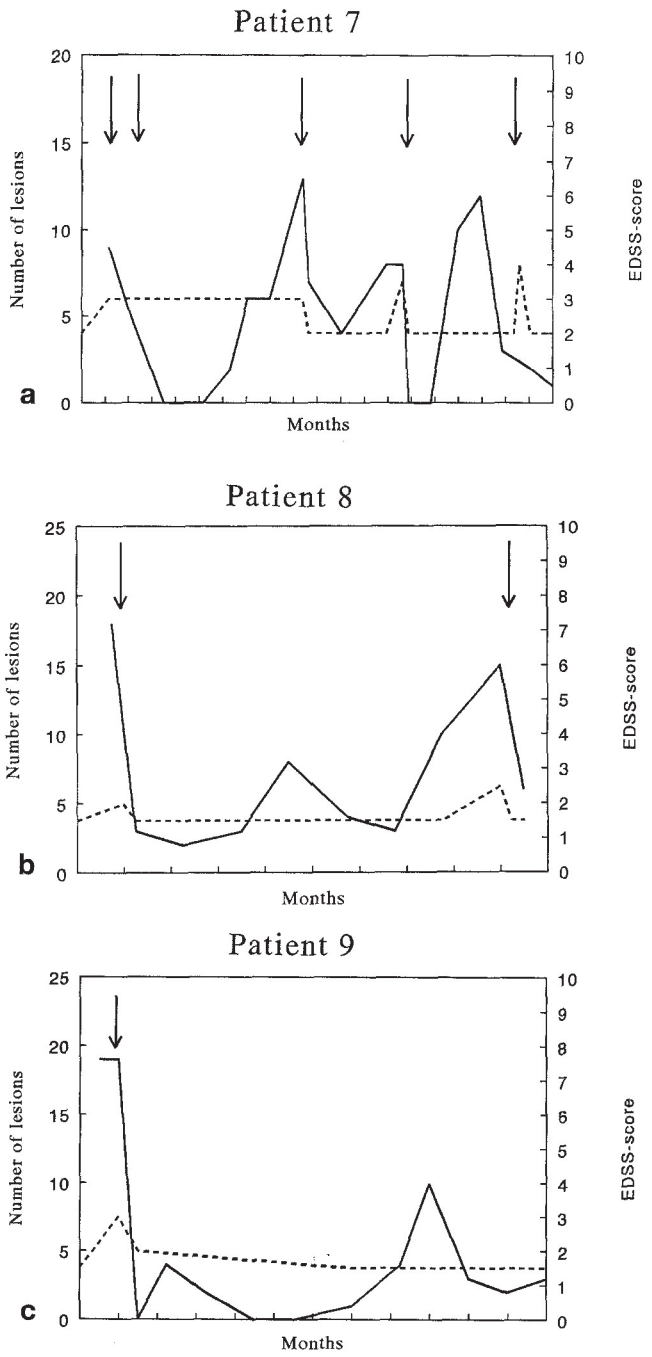

Fig. 2a–c. Comparison of clinical and MRI disease activity in 3 patients. Relation between the number of active lesions (continuous lines and left Y-axis) and EDSS score (dotted lines and right Y-axis) as a function of time (X-axis, stacks at monthly intervals). While the right Y-axis has a fixed scale, the scales of the left Y-axis and the X-axis vary. After most methylprednisolone courses MRI activity is suppressed, but than an increase in MRI activity ("MR relapse") occurs in all cases, and far precedes clinical relapses, if any (see also Fig. 3). *Arrows*, courses of methylprednisolone

After two courses of methylprednisolone (the last courses for patients 7 and 8) no adequate follow-up was available. Only following one course (patient 10) was the clinical effect shorter than the MRI effect (although the MR images were never completely negative after methylprednisolone), while after three courses (patients 2, 6 and 13) neither clinical nor MRI activity was detected before the end of the follow-up period. With most courses (89%), however, the effect on MRI lasted for a shorter period than the clinical effect. After 11 courses new MRI activity was detected without any new clinical activity during follow-up, whereas after the 12 courses in which any new clinical activity was detected, new MRI activity was detected first (Fig. 2). When new MRI activity was detected, usually more than one new lesion (an "MRI relapse") appeared; new incidental lesions were sometimes detected slightly earlier (1 week on average) than such "MRI relapses".

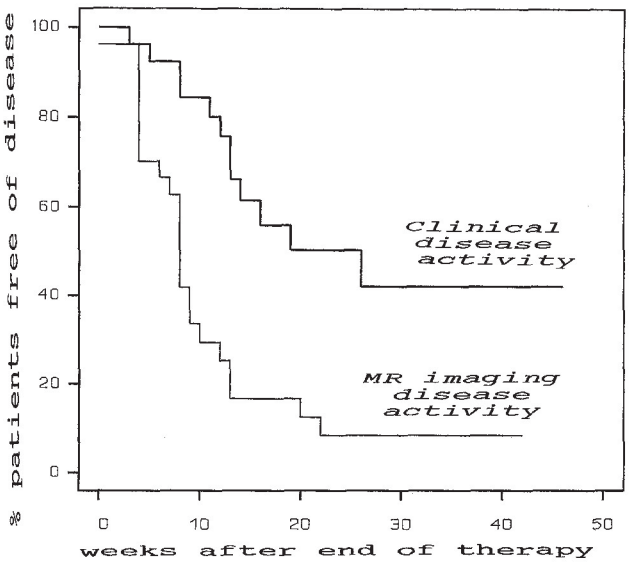

Fig. 3. Kaplan-Meier curve shows percentage of patients free of disease activity on clinical and MRI grounds against time. The percentage of patients free of new MRI disease activity decreases more rapidly than that of patients free of new clinical disease activity

Suppression of MRI activity by methylprednisolone treatment had a mean duration of 9.7 weeks, while the clinical effects lasted 17.1 weeks. Thus, MRI showed new activity on average 7.4 weeks earlier than new clinical activity was recorded; this is probably an underestimate, as in all but two courses new MRI activity was detected before the end of follow-up, while after most courses no new clinical activity was detected. In other words, with regard to new clinical activity, the observation time had been censored. The actual duration of the clinical effect can be estimated statistically by the maximum likelihood estimation for censored observations [12]. Assuming that the distribution of the duration of the clinical effect is approximately Gaussian, the actual average duration of the clinical effect can be estimated at 20.3 weeks, indicating that the MRI effect was on average 10.6 weeks shorter. A Kaplan-Meier curve (Fig. 3) shows that the percentage of patients free of disease activity is clearly lower if assessed by MRI then by clinical examination.

Discussion

Corticosteroids and most other drugs used to treat MS are employed because of their immunosuppressive effect. As blood-brain barrier disruption in MS indicates active inflammation, Gd-enhancement is well suited to monitor immunosuppressive treatment, such as methylprednisolone. In our study "active" lesions also included new or enlarging nonenhancing lesions. Our rationale was that such lesions represent progression of the disease, even in the absence of (detectable) blood-brain barrier disruption. By combining enhancing (96 %) and nonenhancing (4 %) active lesions, every type of progression of the disease on MRI is included.

The beneficial short term clinical effect of methylprednisolone is well established [2–4], and the drug is widely used to shorten the duration and reduce the intensity of relapses. The effect is associated with an improved integrity of the blood-brain barrier [5–7, 13]. There is a correlation between clinical improvement, suppression of Gd-enhancement and decrease in myelin breakdown products in the CSF [14]. It therefore may be assumed that restoration of the blood-brain barrier plays an important role in clinical improvement, by reducing cellular infiltration, oedema, the effects of cytokines or complement [7] or by reducing demyelination [14]. Whether methylprednisolone has any long term beneficial effect on the clinical course is debatable [15–17]. We showed with MRI that the effect of treatment is temporary and probably will have little long term consequences.

Although Gd-enhancement is transient, its disappearance is accelerated by methylprednisolone [5–7]. The suppression by methylprednisolone of Gd-enhancement seen prior to treatment seems to be effectively permanent, as enhancement recurred in only 12 of 293 lesions (4 %) active before treatment with the dose used. If a lower dose of is used (e. g. 1 g for 3 days) enhancement may recur more often (39 %) [7], although the timing of the treatment and MRI examinations in other studies differed from ours. Unfortunately, the rather effective suppression of Gd-enhancement does not lead to increased disappearance of related abormalities on T2-weighted images, when compared to the disappearance rate of lesions developing after treatment or to the natural disappearance rate in studies of untreated patients [10, 18]. Thus, although inflammatiom is suppressed, the vast majority of lesions cause persistent T2-abnormalities. Apparently, the temporary opening of the blood-brain barrier has already been accompanied by considerable tissue changes. Alternatively, the suppression of Gd-enhancement may be the result of reduced cytokine production by inflammatory cells, while the inflammatory process inside the blood-brain barrier continues.

The most important indication that there is no long term effect of methylprednisolone is that an increase in new lesions ("MRI relapse") occurs at some stage in most patients after cessation of therapy. Given sufficient follow-up, new MRI activity preceded new, if any, clinical activity after all courses but one. MRI showed an average reduction in duration of effect of 52 % compared to clinical criteria. The reduction in the percentage of patients free from disease activity on MRI as compared to clinical assessment is shown in Fig. 3. One could argue that the effect of methylprednisolone could be prolonged by adding a tapering oral dose, or by prophylactic monthly intravenous pulse doses [19, 20].

What is the clinical implication of new clinically silent brain lesions on MRI? First, disability shows a varying but usually positive correlation with overall extent of MRI abnormalities [21]. A closer correlation can be observed for individual symptoms scores with specific brain areas [22]. Secondly, follow-up revealed a significantly higher number of new MRI lesions in patients with clinical relapses than in those without [23]. Apparently, not all new lesions increase clinical disability, as they are at nonstrategic sites (but do correlate with neuropsychological impairment [24]). The EDSS, for example, evaluates mainly motor function, which probably correlates best with the presence of spinal lesions. Thirdly, postmortem MRI findings correlate well with pathological findings, indicating that brain lesions on MRI do represent the demyelinated plaques characteristic of MS [25, 26], although Lumdsden [27] notes a poor correlation of pathological findings with the clinical picture. Thus, new brain lesions on MRI indicate progression of the disease, although their exact relation to clinical disability remains to be elucidated. Our finding of MRI relapses relatively soon after cessation of methylprednisolone treatment, indicates clinically silent, but nevertheless significant progression of the disease.

Serial MRI studies frequently detect clinically silent disease activity in patients with relapsing-remitting MS [1]. Therefore, the criteria in this study for the duration of effect on MRI have been rather strict: it was defined as the disease-free period before an increase in the number of active lesions ("MRI relapse"). After 7 courses, however, the MR images were never without active lesions, although fewer lesions were seen than before treatment. If any new clinical activity was detected it was usually preceded by an increase in MRI activity. The latter apparently leads to clinical worsening only if enough active lesions are present, or if active lesions develop in strategically important sites (internal capsule, brainstem, cerebellum, or spinal cord). These observations underline the value of serial MRI in assessing disease activity.

Most relapses are self-limiting in relapsing-remitting MS; after an exacerbation, a remission phase will set in by definition. Perhaps methylprednisolone is even less effective then we believe; in two courses given solely because of an increase in enhancing lesions its effect was extremely short. If we accept that MRI activity and clinical activity are comparable measures, this observation shows that disease activity is actually tempered for only a very short time, and that clinical improvement in most cases will be the result of (acceleration of) the natural course. It would be of particular interest to study in a placebo-controlled fashion whether steroids, given not on clinical grounds, but on MRI criteria, could alter the evolution of the MRI pattern and subsequently the clinical course.

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