PAPER: ACCUMULATION OF IRREVERSIBLE DISABILITY IN MULTIPLE SCLEROSIS – LESSONS FROM NATURAL HISTORY STUDIES AND THERAPEUTIC TRIALS

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ABSTRACT

There is good evidence that relapses in multiple sclerosis (MS) are the clinical counterpart of acute focal inflammation of the central nervous system (CNS), whereas progression is that of chronic diffuse neurodegeneration. The classical view is to consider MS solely as an organ-specific auto-immune disease, i.e. inflammation is the cause of neurodegeneration. Recurring relapses eventually lead to accumulation of disability, and clinical progression could also result from subclinical relapses. Recent observations suggest that this classical concept should be challenged. In particular, striking results have come from the study of the natural history of MS in the Lyons MS Natural History Cohort.[1] Progression of irreversible disability from the assignment of a score of 4 on Kurtzke's disability status scale (DSS) to the assignment of a score of 6 or 7 is unaffected by the presence or the absence of a relapsing-remitting phase before the chronic progressive phase of MS. The same observation is true regarding the presence or absence of superimposed relapses during the progressive phase, either primary or secondary. Beta interferons lead to a 30% reduction in the relapse rate and to a more than 50% reduction in conventional magnetic resonance imaging (MRI) activity. Despite this effect on inflammation, the effect of interferons on disability is only marginal and this small effect may be relapse-reduction-driven. Administration of Campath-1H to MS patients with very active disease, results in a profound and prolonged lymphopenia, and the suppression of clinical and MRI activity. In spite of this, progression of clinical disability and cerebral atrophy still occurs. These observations support the view that in MS, relapses and focal inflammation do not influence the rate of progression of irreversible disability and diffuse neurodegeneration. They are consistent with what was shown in individual patients in the 1970s by performing serial quantitative neurological examinations over several years, and with what is emerging currently from early and serial structural brain MRI studies.

INTRODUCTION

The course of MS may be considered as an interplay between two clinical phenomena, relapses and progression, the latter being defined as a steady worsening of symptoms and signs over at least six months[2–4] or even 12 months according to the more recent definitions.[5, 6] It is also an interplay between two biological phenomena in the CNS; inflammation, which is focal, disseminated, acute and recurrent, and degeneration which is diffuse, early, chronic and progressive. There is strong evidence that relapses are the clinical counterpart of acute focal inflammation of the CNS.[7] There is also growing evidence that progression is the clinical counterpart of chronic and progressive neurodegeneration.[8, 9] One of the central issues with respect to outcome in MS is the mechanism of accrual of irreversible disability.[1, 9–10] It may be the result of relapses with sequelae (relapse-driven) as well as from progression (progression-driven). The question arises therefore of the respective contributions of relapses and progression, and of focal inflammation and diffuse degeneration, in this accumulation process. The classical view is that MS is an organ-specific auto-immune disease. This means that inflammation is responsible for the initiation of the degeneration of the CNS. Does this mean that inflammation is also responsible for the perpetuation and the progression of neurodegeneration? In this case, the relapses might be the major cause of the accumulation of the irreversible disability in MS.

RELAPSES ARE A MAJOR CAUSE OF IRREVERSIBLE DISABILITY

At first glance this assertion is attractive. Relapses may be an important cause of disability in MS. This is a landmark of borderline forms of MS like Devic's neuromyelitis optica, transverse myelitis, acute disseminated encephalomyelitis and Marburg disease, although it should also be noted, it is precisely because they are so devastating that they are not considered as typical MS. But relapse-driven irreversible disability may also be a feature of more classical cases of MS. Many clinicians will be familiar with individual cases in which there has been a complete and definitive neurological deficit brought about by a relapse. Among the 1,562 patients of the Lyons MS Natural History Cohort[1] with a relapsing-remitting onset, 274 (18%) did suffer from an initial relapse with irreversible incomplete recovery as defined by a score of 3 or more on the Kurtzke DSS scale. Among the 1,288 patients with a complete recovery – as defined by a Kurtzke DSS score of no more than 2 – after the initial relapse, 391 (30%) have experienced an incomplete recovery from a subsequent relapse.[11] A detailed analysis of pooled data from 224 patients with relapsing-remitting MS enrolled in the placebo arms of several randomised clinical trials has allowed the comparison of expanded DSS (EDSS) assessments prior to, at the time of and after a relapse of MS.[12] The baseline EDSS assessment was defined as the closest preceding the relapse. Comparing post-relapse and baseline evaluations, the net increase in

the EDSS score was 0·27 ± 1·04 (mean ± SD; median = 0). This corresponds to 42% of the patients with a score of 0·5 or more and 28% with a score of 1·0 or more EDSS point increase. In this study however, the median time between evaluations performed during and after the relapse was only 63 days, with a minimum of 32 days and a maximum of 140 days.

Similarly, the assessment of the possible effect of the degree of recovery from the initial relapse; of the time from the initial relapse to the second relapse; and of the number of relapses during the first years of the disease (on the disability accrual process) leads to consistent results in natural history MS cohorts. An incomplete recovery from the initial relapse, a short interval between the first two relapses, and a high number of relapses during the first years of the disease are associated with a rapid accumulation of irreversible disability.[11, 13–15]

Furthermore, brain MRI studies on recent cases of MS, or on first neurological episodes suggestive of MS, consistently show tissue destruction with axonal loss in acute lesions. Recent pathological studies on MS brain tissue have provided convincing evidence of the causal effect of relapses on accumulation of irreversible disability. Focal inflammation can indeed lead to focal tissue destruction with demyelination, astrocytic gliosis and, more importantly, axonal transsection.[16, 17]

RELAPSES ARE NOT THE MAJOR CAUSE OF IRREVERSIBLE DISABILITY

The real contribution of relapses to disability accumulation is not that simple, however. Inflammation has also some beneficial effects, the most natural evidence being that remission is the rule following a relapse. Some experimental data have also shown a neuroprotective effect of inflammation.[18] Another line of evidence comes from the primary progressive forms of MS. In these cases, progression of irreversible disability occurs without superimposed relapses[19] and without clearcut inflammation at the pathological and MRI levels. In these cases of MS the rate of the progression of disability is similar to that of the progressive-relapsing forms of MS.[1, 20, 21]

Instructive observations have been made on pooled data from 313 patients with relapsing-remitting MS enrolled in the placebo arms of two large phase III trials of interferon beta-1a[22] and glatiramer acetate,[23] assessed at three-month intervals with a two-year follow-up.[24] Analyses were performed on the 289 patients with complete two-year data on EDSS assessments. According to the observed course of their EDSS score throughout the two years of follow-up, 29% of the patients could be classified as progressors in the trial with a confirmation at three months but, among these progressors, the EDSS increase was still present at the end of the follow-up period in about half of them only. These results clearly show that an increase in disability confirmed at three or even six months must not be considered as equivalent to an irreversible increase in disability. Interestingly, Lublin *et al.*[12] also found from similar material a 1·0 or more EDSS point increase relative to baseline in 28% of their patients at a median of 63 days after a relapse. This suggests that, in the available placebo cohorts of relapsing-remitting MS patients, the confirmed disability increases were mainly relapse-driven. Clearly, short-term confirmed increase in disability is often relapse-driven and reversible.

Totally different is the issue of the long-term irreversible progression of disability. For the statistical analysis of the 1,844 patients of the Lyons MS Natural History Cohort,[1] focus was placed on robust landmarks of disability that could be easily identified through successive neurological assessments as well as through retrospective interviews with patients whenever necessary. They were rated as DSS 4, defined as walking without aid and a limited walking distance but exceeding 500 metres without rest; DSS 6, walking with unilateral support and a walking distance not exceeding 100 metres without rest; and DSS 7, home restriction with a few steps still possible while holding onto a wall or furniture but not exceeding ten metres without rest. Disability was defined as irreversible when a definite rating had been reached and had persisted for at least six months, excluding any transient worsening of disability related to relapses. This irreversibility would be confirmed at any subsequent assessment during the follow-up of the patient which could be up to a year later. From this cohort, the well-known difference between the patients with a relapsing-remitting onset and the patients with a progressive onset has been observed: median time from the onset of MS to assignment of a score of 4 of irreversible disability on Kurtzke's DSS scale was significantly longer in the relapsing-remitting onset cases than in the progressive onset cases (Figure 1). The same observation was made for time of onset of MS to assignment of a score of 6 or 7. This is in agreement with earlier analyses on this cohort[25] and with the results from many other series.[14, 15, 26–32] In spite of this, progression of irreversible disability from the assignment of a score of 4 to the assignment of a score of 6 was similar in cases with a relapsing-remitting onset and in cases with a progressive onset (Figure 1). This was also true for progression of disability from a score of 4 to a score of 7, and from a score of 6 to a score of 7.[1] This could be interpreted as the rate of progression of irreversible disability from the assignment of a score of 4 not being affected by the presence or absence of relapses, i.e. of a relapsing-remitting phase, before the chronic-progressive phase of MS.

The same material allowed an assessment of the possible influence of the presence or absence of

superimposed relapses during the progressive phase, either primary or secondary.[1] Progression of irreversible disability from the assignment of a DSS score of 4 to the assignment of a DSS score of 6 in cases with a primary progressive course was similar whether relapses were superimposed or not on the progressive phase of the disease (Figure 2). Similarly, the progression of irreversible disability from the assignment of a score of 4 to the assignment of a score of 6 in cases with a secondary progressive course was similar whether relapses were superimposed or not on the progressive phase of the disease (Figure 3). It could be concluded that, at the level of population studies, the rate of irreversible progression of disability from the assignment of a score of 4 is unaffected by the presence or the absence of superimposed relapses during the progressive phase, either primary or secondary. A dissociation between relapses and progression does therefore exist in MS. These results are in accordance with, and extend, those from other large studies on the natural history of MS.[20, 21, 33]

The results of the Lyons MS Natural History Cohort study[1] were obtained by considering relapses as either present or absent, in a binary way. When analysing the possible influence of relapses at the onset and during the early years of the disease with respect to their degree of recovery, the time to the second relapse, and their number and frequency, similar results could be reached. For instance, a shorter time interval to a second neurological episode was correlated with shorter median times from onset of MS to assignment of a DSS score of 4, 6, or 7 (Figure 4).[11] Similar observations have been made in many other series.[25, 27, 29, 30, 34–49] The originality of the Lyons study[1] is that it assessed the possible influence of the same clinical variables on the progression of irreversible disability from the time of assignment of a score of 4 to a score of 6, but also from a score of 4 to a score of 7, or from a score of 6 to a score of 7. None of these variables remained predictive of the time course of disability past this point (Figure 4), which is in accordance with the results seen in primary progressive MS.[20] Progression to irreversible disability is seemingly unrelated to the clinical characteristics of the relapses which have occurred during the initial stages of the disease.

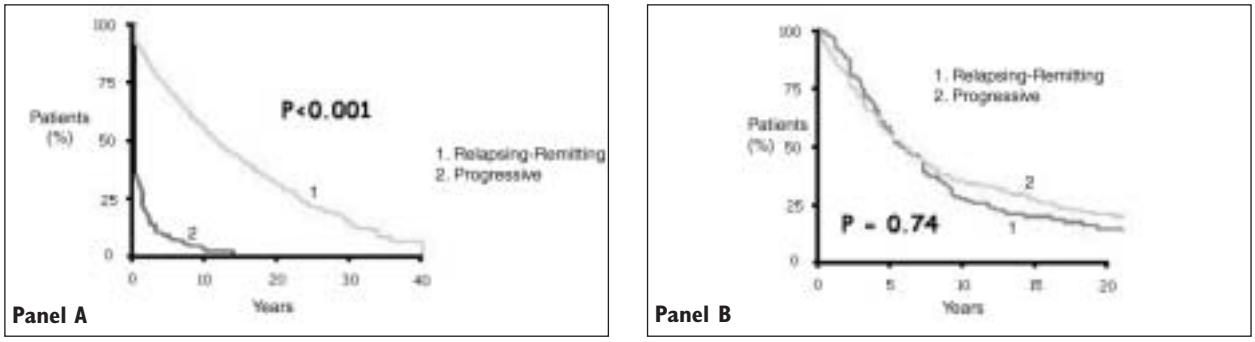

FIGURE 1

Kaplan-Meier estimates of the time from the onset of MS to the assignment of a score of 4 on the Kurtzke DSS (panel A), and the time from the assignment of a score of 4 to a score of 6 (panel B) among 1,844 patients with MS, according to the initial course. (Confavreux *et al.,* 2000.[1] Copyright © 2000 Massachusetts Medical Society. All rights reserved. Reproduced with permission from the *New England Journal of Medicin*e.)

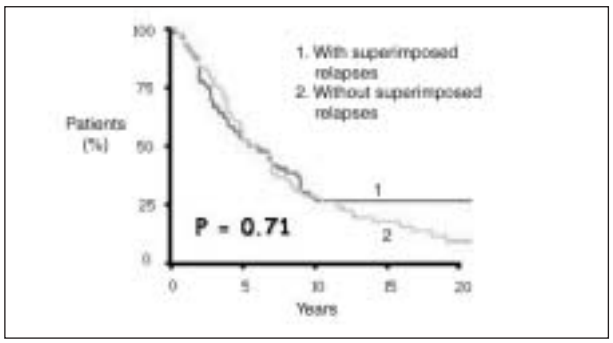

FIGURE 2

Kaplan-Meier estimates of the time from the assignment of a score of 4 on the Kurtzke DSS to the assignment of a score of 6 among 282 patients with a progressive onset of MS. (Confavreux *et al.,* 2000.[1] Copyright © 2000 Massachusetts Medical Society. All rights reserved. Reproduced with permission from the *New England Journal of Medicin*e.)

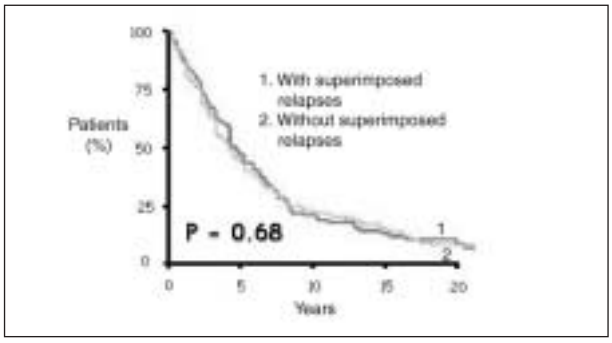

FIGURE 3

Kaplan-Meier estimates of the time from the assignment of a score of 4 on the Kurtzke DSS to the assignment of a score of 6 among the 496 patients with the secondary progressive type of MS. (Confavreux *et al.,* 2000.[1] Copyright © 2000 Massachusetts Medical Society. All rights reserved. Reproduced with permission from the *New England Journal of Medicin*e.)

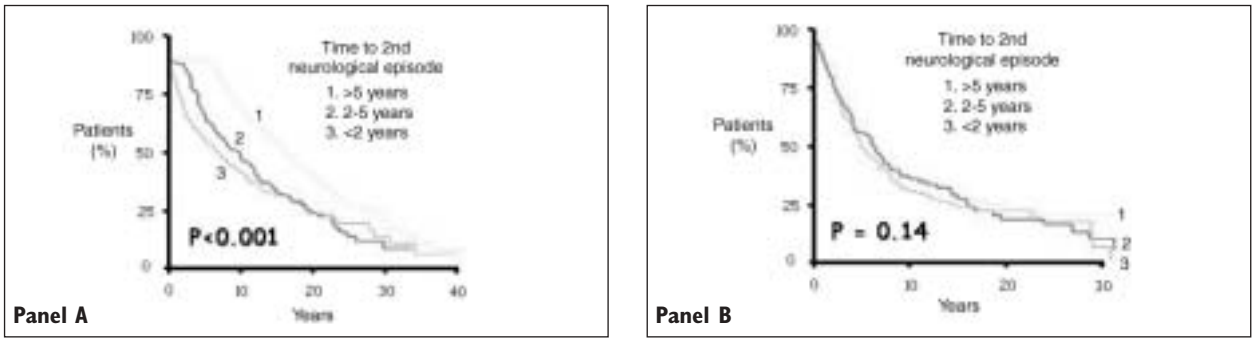

FIGURE 4

Kaplan-Meier estimates of the time from the onset of multiple sclerosis to the assignment of a score of 4 (panel A) and from the assignment of a score of 4 to the assignment of a score of 6 (panel B) on the Kurtzke DSS among 1,844 patients with multiple sclerosis, according to the time from the onset of multiple sclerosis to the second neurological episode. (Data source: Confavreux e*t al.*[11])

Other evidence comes from the use of disease-modifying drugs. For instance, treatment with beta interferons leads to a 30% reduction in the relapse rate and to a more than 50% reduction in conventional MRI activity. Despite this strong effect on inflammation, the effect of interferons on disability and brain atrophy is only marginal.[22, 50–3] Administration of potent immunosuppressive agents has also proven very informative. Campath-1H is a humanised monoclonal antibody with a powerful lymphocyte-depleting activity. Its administration to MS patients with high relapse rates, rapid accumulation of disability, and high MRI activity resulted in a profound and prolonged lymphopenia, and the suppression of clinical and MRI activity.[54] In spite of this, clinical disability and cerebral atrophy still progressed.[55] Similar conclusions can be derived from the use of mitoxantrone and cyclophosphamide. Their efficacy in very active MS with repeated relapses at close intervals and accumulating disability has been well demonstrated.[56, 57] Despite this high and effective anti-inflammatory activity in the suppression of relapses and the reduction of relapse-driven disability, it is not unusual to observe in these patients a secondary progression of disability a few years later. Furthermore, in our experience and that of others, administration of these drugs in progressive MS with a standard relapse rate or no superimposed relapse at all, is not very helpful.

All of these observations have been collected using statistical analysis of groups of patients with MS. They are consistent with what has been shown at the individual level in the 1970s. By performing serial quantitative neurological examinations over several years, it has been shown in the majority of MS patients that progression of neurological abnormalities followed, after regression analysis, either a linear curve or a curvilinear curve with only a small inflexion, even in cases with a relapsing-remitting course or with superimposed relapses during the progressive phase of the disease.[38, 58]

IS THERE A DISSOCIATION BETWEEN RELAPSES AND PROGRESSION OF DISABILITY, AND BETWEEN FOCAL INFLAMMATION AND DIFFUSE NEURODEGENERATION?

These observations are puzzling. As clinicians, we all learn directly from our patients and naturally our minds tend to retain our most striking experiences. Most neurologists have been struck at one time or an other by a patient with MS who has developed a relapse with a complete and definitive deficit. There are many instances in medicine in general and in MS in particular of anecdotal clinical impressions that have been clearly refuted by appropriate large-scale epidemiological studies. With respect to MS, the influence of pregnancy[59] or of vaccinations[60] on the course of the disease are highly illustrative. The single tree in the foreground must not mask the forest in the background. Therefore, no matter how puzzling the hypothesis, it must be concluded from the population studies and from statistical analysis, that relapses are not so important in determining the progression of irreversible disability in MS. Although MS is an auto-immune disease, focal inflammation may have only a limited effect on the course of the diffuse neurodegeneration. Once triggered by focal inflammation, subsequent progression of diffuse neurodegeneration becomes a seemingly self-perpetuating process, independent of inflammation.

CONCLUSION

Does this mean that inflammation and relapses do not deserve consideration? Obviously not. Supposing that the disease could be detected at the very beginning of the auto-immune process, immunoactive drugs might be urgently needed and could presumably show a dramatic efficacy. Unfortunately, when MS becomes clinically overt, the disease, in the majority of the cases, is already well-established from a biological point of view. Currently approved immunoactive drugs can serve to control inflammation and relapses. It must be kept in mind, however, that even with powerful agents such as campath-1H or mitoxantrone, this strategy

does not prevent subsequent accrual of irreversible disability and neurodegeneration. Therefore, in the forthcoming years, in addition to the well acknowledged anti-inflammatory strategies, major efforts must concentrate on the development of powerful tools to protect the CNS from degeneration and enhance its repair.[61–3]

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