Editorial

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Infections and the risk of relapse in multiple sclerosis

Immune dysregulation, likely to be autoimmune and organ-specific in essence, is a landmark in multiple sclerosis. Not surprisingly, physicians have always been concerned with a possible increase in the risk of multiple sclerosis relapse following an infection. Anecdotal reports have given consistency to this concern.

Several epidemiological studies sharing similar features have already addressed this issue. These were observational, prospective studies. Risk periods were defined as encompassing the onset of the clinical infection with the assumption that if a relapse was observed during the risk period, it could be regarded as being associated with the infection. Control periods were made of the non at-risk periods. The rate of relapses during the risk periods was systematically compared with that of control periods. In the pionneer study of Sibley *et al*. (1985), 170 patients with clinically definite multiple sclerosis were assessed at monthly intervals for a mean of 5.2 years regarding common viral infections and relapses. Risk periods were chosen as being the interval covering the 2 weeks prior infection to the 5 weeks afterwards. The rate of relapses was found to be 2.8-fold higher during the at-risk period by comparison with the control periods. This study provided strong evidence of an association between common viral infections and relapses in multiple sclerosis. However, in a more limited study of 60 patients with benign multiple sclerosis followed over a mean of 31 months (Andersen *et al*., 1993), the relative risk of relapses during the risk period by comparison with control periods was only 1.3, i.e. marginally significant ($P = 0.047$) when using a time-window of 4 weeks for the at-risk period. No significant association was found when using the 7-week time-window of Sibley *et al.* (1985). The results of the two other studies currently available deserve cautious interpretation (Panitch, 1994; Edwards *et al*., 1998). Numbers of enrolled patients were small, follow-up was limited, and studies were incorporated to a placebo-controlled trial of interferon-β, a drug which significantly affects the chance of relapse in multiple sclerosis patients. These studies showed a highly significant increase (2.5 and 2.1, respectively) in the rate of relapses during the risk period by comparison with the control periods.

In this context, the paper of Buljevac and colleagues in this issue of *Brain* is most welcome (Buljevac *et al*., 2002). The study design is similar to that of the above-mentioned studies. As many as 73 patients with exacerbating-remitting definite and active multiple sclerosis were enrolled in a prospective survey with systematic clinical assessments at 8-week intervals for a mean follow-up of 1.7 years. In case of symptomatic infection of any type or of relapse of multiple sclerosis, an extra visit was arranged within 3 days. Whenever the infection or the relapse was confirmed, another extra visit was arranged 3 weeks later. For confirmed infections, three serial MRI examinations at 3-week intervals with T_1-weighted sequences and gadolinium enhancement were also arranged. Relapses were graded as major or minor, according to the increase or the absence of change in the Expanded Disability Status Score (EDSS), and as short, long or sustained, according to the fact that the EDSS returned to baseline in <3 weeks, in >3 weeks or in >3 months. Main analysis was performed on the 7-week risk period previously defined by Sibley *et al.* (1985). A total of 167 infections and 145 relapses were recorded. By comparing risk and control periods, the relapse rate ratio was found to be 2.1 (95% CI 1.4–3.0; $P < 0.001$). A sensitivity analysis was performed by changing the location and the duration of the time-window encompassing the onset of the infection. It led to essentially similar results. Interestingly, the relapse rate ratio increased to 2.7 (95% CI 1.5–4.8; $P < 0.001$) when considering major long relapses only. It even reached 3.8 (95% CI 1.8–7.9; $P < 0.001$) for the subgroup of major sustained relapses.

The strengths of this study are obvious. Regular survey visits at close intervals and, in case of any suspected infection or relapse, almost immediate additional visit have been systematically arranged to control for recall biases. Assessment of the infections and the relapses have therefore been done carefully. Infections of any kind (upper respiratory tract, gastrointestinal, urinary tract) have been taken into account. One could regret that attempts to confirm infection by serological testing have not been made. As a matter of fact, these have proven to be difficult, if not frustrating in this setting (Andersen *et al*., 1993; Panitch, 1994; Edwards *et al*., 1998). One may also argue that independent assessment of infections and relapses by two different assessors blind to each other would have increased the reliability of the measures. It is to be demonstrated that this could operate properly for addressing the present issue, notably when infection and relapse are present together. Another possible criticism is that infection could result in an apparent increase of relapses through pseudo-relapses related to fever or transient cytokines modifications (Coles *et al*., 1999). By definition, fever-related neurological episodes were not considered as a relapse in the study. Much more importantly, the more severe and long-lasting the relapse, the stronger the association with an infection was. This is precisely the reverse trend which could have been expected from pseudo-relapses. Overall, the results of this Buljevac *et al.* study render the likely association between infections and relapses in multiple sclerosis more convincing and add significantly to the available evidence in the literature. The biological plausibility of this association is straightforward. Induction by infectious agents of secretion of pro-inflammatory cytokines such as IFN-γ and interaction of the host immune system with viral superantigens are some of the mechanisms

which can result in immune activation leading to relapses of multiple sclerosis.

However, this is not that simple. MRI results in the Buljevac *et al.* study are indeed puzzling. When comparing the three serial scans performed following any confirmed infection, the percentage of active scans and the mean number of enhancing lesions per scan remained unchanged. This observation held whether the infection was associated with a relapse or not, whether the patient was receiving interferon-β therapy or not, and, in case of a relapse associated to the infection, whether methylprednisolone was administered or not. One may argue that the increase in MRI activity could have occurred prior to the first infection-related scan. The authors refer to a personal series of nine patients with multiple sclerosis and examined at monthly intervals during 8 months, again with no significant change in MRI activity related to the eight infections which occurred during the study period.

How is it possible to reconcile these seemingly contradictory clinical and MRI data? The authors propose that infections could lead to relapses through a mechanism which is independent of blood–brain barrier (BBB) dysfunction. Although multiple sclerosis lesions can be detected before overt BBB dysfunction (Filippi *et al*., 1998), it is still to be demonstrated that this applies to any lesion. Otherwise, correlation between clinical activity and MRI activity is presently strongly evidence-based in multiple sclerosis (Youl *et al*., 1991). The Buljevac *et al.* observation would therefore be the first instance of a dissociation between them. The interpretation of the authors can be accepted but it may also be hypothesized that, in that study, MRI tells the truth whereas clinical evaluation does not. There are possible sources of bias which could affect the clinical results significantly. It would have been interesting for example to learn from the authors whether the association between infections and relapses was also found when considering only the relapses with new neurological manifestations with respect to the past history of the patient, as such relapses are more likely to correspond to a new lesion of the nervous system. It would also have been interesting to assess, as difficult as this may be, duration and severity of infections. Infections are not operating as a single shot, by contrast to vaccination for instance. There is a possibility that longer infections could be associated with prolonged worsening of neurological symptoms and pseudo-relapses instead of true relapses. Interestingly, when the authors selected a risk period which was not overlapping the infection, no significant association was observed between infection and relapse. Lastly, a more sophisticated design, such as the case-crossover design (Confavreux *et al*., 2001), could provide more sensitive analyses by increasing the number of control periods.

Finally, the study of Buljevac *et al.* raises more questions than it provides definite answers. Had it been restricted to clinical results, it would be regarded as confirming perfectly the presently available evidence. Taking into account the MRI data raises uncertainties about a definite and clearcut conclusion. It remains to be understood why the increase in clinical activity of multiple sclerosis following an infection has no counterpart in conventional MRI activity and why infections and vaccinations have such opposite effects on the risk of relapse in multiple sclerosis whereas they share a similar absence of effect on conventional MRI activity.

The past months allowed us to improve our knowledge of putative precipitating factors of relapses in multiple sclerosis. Having to take a poll, I would say that the present evidence of an association of relapses of multiple sclerosis is strong for the post-partum period (Confavreux *et al*., 1998), is becoming possibly disputable for infections (Sibley *et al*., 1985; Buljevac *et al*., 2002), is minor, if any, for trauma (Goodin *et al*., 1999) and stress (Mohr *et al*., 2000), and is none for vaccinations, at least in patients free of relapse for >12 months (Confavreux *et al*., 2001).

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