Survey of progress

Immunological treatment of multiple sclerosis

Richard A. C. Hughes*

Department of Pathology, School of Medicine M-012, University of California, San Diego, La Jolla, California 92093, USA

Summary. Immunosuppressive treatment of multiple sclerosis (MS) is based on the autoimmune hypothesis for which the main evidence is the close histological similarity between the human disease and chronic relapsing EAE. Although controlled trials indicate that ACTH is effective in accelerating recovery from relapses, long term ACTH or oral steroids are ineffective. Two controlled trials have suggested a beneficial effect of azathioprine, but neither was conducted "blind" and neither was sufficiently convincing to cause the widespread adoption of azathioprine by neurologists. One controlled trial, also not blind, reported a beneficial effect of an intensive course of cyclophosphamide, but this hazardous treatment will not be widely adopted unless other trials confirm this result. The converse hypothesis that MS is due to a deficient immune response to a virus has led to trials of immunostimulation. Interferon and levamisole have proven ineffective so far, but transfer factor slowed disease progression in one well conducted trial.

Key words: Multiple sclerosis – Immunosuppression – Immunostimulation – Clinical trials – Treatment

Trial design

The 1980's have already produced so many therapeutic trials in multiple sclerosis (MS) that it is difficult to keep abreast of the latest developments. The variable prognosis and spontaneous tendency to remission combine to make the evaluation of treatment in MS extremely difficult. The need for controlled observations is widely accepted and there can scarcely be a place now for publication of data which do not include controls. The most powerful type of trial randomises contemporary patients between a test and control group [7]. Some trials, particularly

* Address for correspondence: Department of Neurology, Guy's Hospital, London SE1 9RT, England
from continental Europe have used the treated patients as their own controls, comparing disease course and relapse frequency and/or severity before and after treatment. Such a design is less satisfactory because of the tendency for relapse frequency to decline with the passage of years. The interpretation of the clinical features in MS is so subjective that a "double-blind" system of evaluation is necessary if the results are to be widely accepted. In some instances the treatment leaves an indelible mark, such as the alopecia caused by cyclophosphamide, which foils any attempt to "blind" the patient or observer. In others the personnel and financial resources of the investigating centre may have prevented the use of a double-blind strategy. The importance of double-blind observation is so great that grant-giving bodies must be urged to allow funding for such a design in future trials.

The objectives of any therapeutic trial govern its size. The trial design will differ according to whether acute exacerbations or relapsing-remitting or chronic progressive stages are being treated. The following comments are applicable to any of these. Criteria for preliminary, pilot and "full clinical" trials have been suggested [7]. The need for preliminary trials to establish dosage and the acceptability of side effects is not in dispute. The problem arises with pilot trials. Small trials are unlikely to detect anything less than a major effect on the course of the disease. For instance, if only 40 patients were available, 20 in each group, the tested treatment would have to reduce relapse frequency by an average of 80% if the trial were to have a 90% chance of detecting an effect. If we were interested, as we would be, in a drug which reduced relapse frequency by 50%, 122 patients would be needed with half in each group [7]. This consideration leads to the conclusion that the pilot trial has a very limited role. If we really want to investigate the usefulness of a drug in MS, we need to proceed from a preliminary trial to a full clinical trial. This requires a randomized controlled, double-blind design of sufficient power to satisfy any critics that it has detected, or failed to detect, a clinically important as well as statistically significant effect. It is doubtful whether trials with less than 50 patients in each group will produce answers so clear that their conclusions will be widely accepted. If the adequate trial of any new treatment has to be undertaken at such effort and cost the theoretical arguments in favour of such treatment need to be strong.

Evidence for autoimmunity

The histological similarity between experimental allergic encephalomyelitis (EAE) and MS remains the main evidence that MS is an autoimmune disease. The evidence has been enormously strengthened by the development of a chronic relapsing form of EAE, whose pathology closely mimics that of MS, as recently reviewed in this journal by Lassmann [24]. Nevertheless unlike some undoubtedly autoimmune diseases, such as myasthenia gravis, MS is not more frequently encountered in association with organ-specific immune diseases than would be expected by chance [3], although occasional examples, such as a patient with MS, myasthenia gravis and Graves' disease [26], are encountered. The main weakness of the autoimmune argument is that there have been no consistently confirmed