Editorial

The value of natural history studies of multiple sclerosis

Since the description of the natural history of a disease underpins all scientific study of that disease, it is essential that the description is accurate. There have been many publications on the natural history of multiple sclerosis. Initially the databases of patients were derived from a clinical practice of individual clinicians interested in multiple sclerosis, notably McAlpine in the UK and Fog in Scandinavia. Valuable as these studies were they comprised a highly selected group of patients and therefore represented a non-random selection of the total cohort of multiple sclerosis cases. Subsequent studies were on broader based populations but these were still restricted, often to hospital based patients (Confavreux et al., 1980). To obtain a true sample from which to derive accurate information on the natural history of multiple sclerosis requires a geographically defined population. It is to this end that extensive databases have been developed, most notably in London, Ontario. Several studies from this Canadian group, and also from Scandinavia, have been published (Weinshenker et al., 1989a, b; Runmarker and Andersen, 1993); the current issue of this journal contains two further papers (Cottrell et al., 1999a, b). What is the value of such studies?

First, they have enabled reasonably accurate calculation to be made concerning trials of therapy designed to favourably alter the course of disease. Knowing the time course of a disease enables the statistician to calculate, within defined limits, the number of patients required in a trial to show effect of therapy of assumed efficacy, i.e. the likelihood of demonstrating a favourable effect. Thus, the data of Weinshenker et al. (Weinshenker et al., 1991) on relapsing–remitting multiple sclerosis were used to set up the various interferon trials and were found to be valid. The two papers in the current journal concern a large subset of patients with the infrequent, chronic progressive form of multiple sclerosis and show the number of subjects needed to demonstrate a significant effect in therapeutic trials—unfortunately the number is large unless the therapy is highly effective (Cottrell et al., 1999b).

Secondly, natural history studies help management of patients in defining the likely outcome given the symptoms and signs initially present. Thus, it is likely that the prognosis is poorer in patients with relapsing–remitting disease who have a large number of relapses within two years of the onset of symptoms, while in the chronic progressive cases an unfavourable course is more likely if the progression is rapid at onset and multiple systems of the CNS are affected initially. Conversely, good natural history studies can dispel incorrect, yet widely held, beliefs. For example, in the present papers, age at onset of chronic progressive disease did not affect the long-term prognosis, an observation that will surprise many clinicians. A good example of the use of databases on the course of multiple sclerosis concerns the effect of pregnancy. Many patients are understandably worried about the effect of pregnancy upon the course of their disease. Natural history studies have clearly demonstrated that relapses are less frequent during pregnancy and may be higher in the period immediately following birth than in the control population (Confavreux et al., 1998).

Thirdly, studies of natural history can define subsets of patients, indicating that an apparently single disease comprises multiple entities. Whether chronic progressive, relapsing–remitting and secondary progressive cases are a continuum is not yet known, but there are differences in laboratory parameters between these types of multiple sclerosis. Thus there is evidence of differences on MRI scanning of the brain, in pathology and there may be genetic differences between these groups (Thompson et al., 1991; Revesz et al., 1994; Van Lambalgen et al., 1986).

Finally, good natural history studies can give clues to the pathogenesis of a disease. Large databases enable detection of significant associations between different diseases, e.g. ulcerative colitis or ankylosing spondylitis and multiple sclerosis, suggesting common pathogenetic mechanisms. Similarly, one can extend studies of natural history to the effects of patients with multiple sclerosis upon other members of the population, especially with reference to inherited factors against acquired factors relevant to the disease. Numerous papers concerning the importance of genetic factors have been published, including one on biological and non-biological relatives in families with multiple sclerosis (Ebers et al., 1995). These demonstrate a clear genetic susceptibility while migration studies show environmental factors cannot be ignored (Kurtzke, 1993).

All the above are useful data for the patient, the clinician and the scientist, but their utility depends upon the validity of the clinical database. Clearly the greater the proportion of a population captured on a database, the greater the likelihood that the database will be of value. In the present study of chronic progressive patients the capture of cases diagnosed as having multiple sclerosis seems remarkably complete. There remains the problem of whether these data on the residents of Ontario can be useful in other populations. Given that multiple sclerosis is found most frequently in Northern Europe and North America and that most of the population...
of Canada, from which the cases in the current paper are culled, are derived from migrants from Northern Europe, it would be logical to assume that the Canadian population can be used for studies of the USA and European population—in essence inductive transposition is valid.

In conclusion, natural history studies such as the one published in this issue (Cottrell et al., 1999a) are a useful aid to our understanding of multiple sclerosis; the accompanying paper bears witness to the value in designing therapeutic trials (Cottrell et al., 1999b).

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References


