Journal of NeuroVirology (2000) 6, Suppl 2, S1–S3

www.jneurovirol.com

Introduction

The puzzling natural history of multiple sclerosis: a challenge for the research and care

Pasquale Ferrante*,[1]

[1]*Chair of Virology, Department of Preclinical Sciences, and Don C. Gnocchi Foundation, IRCCS, via Capecelatro 66, 20148, Milan, Italy*

Journal of NeuroVirology (2000) **6,** S1–S3.

Keywords: multiple sclerosis; natural history; multiple sclerosis genetics; epidemiology; immunology; neuroimaging; rehabilitation

Multiple sclerosis (MS) is a human inflammatory demyelinating disease of the central nervous system with a relatively low incidence and prevalence, but, although it can be considered a rare disease, it is of great interest to the scientists involved in various research fields. For a long time numerous studies have been devoted to the polymorphic aspects of this disease with the continuous publication of high level scientific papers and the frequent organization of meetings and symposia.

However, despite the employment of large resources and the involvement of several leading Institutions around the world, and although MS was clinically recognized already in the 19th century by the French neurologist Charcot, there are still numerous points to be clarified regarding the etiology, the pathogenic mechanism and the treatment of this disease.

Perhaps also owing to its vagueness, the most commonly accepted concept is that MS is a disease caused by destruction of the myelin sheet through an autoimmune process that originates in subjects with genetic predisposition as a consequence of the intervention of largely unknown exogenous factors.

Although many aspects of MS both in the central nervous system and in the peripheral system are clearly due to inflammatory phenomena, MS is not an acute disease, but due to its characteristics, MS has a natural course resembling that of chronic degenerative diseases, and thus it can be subdivided into five phases: susceptibility, induction, the preclinical phase, the degenerative phase, and rehabilitation.

*Correspondence: P Ferrante

In this supplement of *Journal of Neurovirology* are published the views that some of the most important scientist in this field gave during the 'International Symposium on Multiple Sclerosis Research and Care', organized in Milan from May 6th to 9th, 1999, from the Don C Gnocchi Foundation, IRCCS. The topics and the speakers were essentially selected taking into account the model of natural history of chronic degenerative disorders and that can also be proposed for MS.

Susceptibility to multiple sclerosis

MS susceptibility is under a polygenic control and thus, besides the well known involvement of hystocompatibility lymphocyte antigens (HLA), that has been studied in the past, other genes, including both those coding for immunologically active molecules, such as cytokines, and antigens suspected of being an important target of the immune process, such as myelin basic protein, are thought to be relevant (Compston, 1997; Ebers and Sadovnick, 1994; Olerup and Hillert, 1991; Sciacca *et al*, 1999). In this issue of *Journal of NeuroVirology* several papers dealing with the various puzzling aspects of MS genetics are included. Some of them give an inside view of the current trend in the genetic research on MS in different countries of the world, like those from Compston, Hillert, and D'Alfonso. Others, including Rasmussen and Guerini, report original and innovative findings about the possible role of new genetic elements like the endogenous retroviruses in the susceptibility to the disease.

The induction of multiple sclerosis

As shown by epidemiological studies (Kurtzke, 1980; Martin and Gale, 1997), the period of

susceptibility to MS begins in early infancy and ends in adulthood, thus it is postulated that one or more events occurring during the susceptibility period, lead to the induction of the disease. Induction is an unidentifiable point in time, probably because it coincides with biological alterations which are not perceptible by clinical examination or testing. Epidemiological studies are thus fundamental for the understanding of the induction time and to have suggestion about the possible triggering factors, and in the epidemiological papers published in this issue from Kurtzke, Granieri, Casetta and Boiko, complete, convincing evidence is given in favour of the role of exogenous, environmental factors.

Among the environmental factors, for a long time viruses are suspected of playing an important role in the triggering of MS (Dalgleish, 1997), and the possible role of human herpes virus 6 (HHV6), Epstein-Barr virus (EBV), retroviruses are largely discussed in the papers from Berti, Rotola, Haahr, Rasmussen and Perron. Moreover a careful review of the molecular characteristics of JC virus, of its demyelinating capability *in vivo* and *in vitro*, and of its possible role in the etiology of MS is contained in a group of papers of leading scientists in this field such as Khalili, Major and Stoner.

The pre-clinical phase

A large body of evidence suggests that after the induction, due to exogenous factors, an immunological process begins and produces the nervous system damage that initiates the pre-clinical phase. The nature of the immunological abnormalities that induce the pathogenic process of MS has been widely studied for many years, and the presence of autoreactive lymphocyte cells, the imbalance of the Th1/Th2 cytokine profile, the alteration of the apoptotic process, the over-expression of adhesion molecules, the restricted T cell receptor usage and perhaps the intervention of superantigens are just part of the enormous number of data produced in the field of neuroimmunology of MS. Some of these aspects are treated, in an innovative way, in the papers of Sciacca, Trabattoni, Pinter, Uccelli and Speciale.

It should also be pointed out that even at the start of the pre-clinical phase it is difficult to determine and it is probable that a clear-cut borderline does not exist between the induction and the pre-clinical phases of MS. Yet, the pre-clinical phase does take on considerable importance as a target of laboratory testing because the development of techniques permitting the detection of lesions when clinical signs of MS are still not evident, will lend greater weight to laboratory investigations in terms of our understanding of the etiology of MS. Under this point of view in recent times, as a consequence of the improvement of the neuroimaging technologies, we are facing an almost revolutionary way of thinking about the time in which classical demyelinating lesions or pathologic involvement of the normally appearing white matter are detectable in the brain of MS patients, while they are clinically asymptomatic (Filippi and Miller, 1996). An inside view on the use of magnetization transfer, proton magnetic resonance imaging and other updated neuroimaging methods for the understanding of the pathogenic mechanism of MS and of other brain white matter diseases, both of the brain and of the spinal cord, is given from the papers of Bastianello, De Stefano and Filippi.

The clinical phase and the rehabilitation

The new neuroradiological techniques, and updated laboratory methods have also modified the time period which is needed to define the diagnosis of MS. Clearly this is carried out earlier in the life of the patients than it was years ago. When diagnosed, MS can have different clinical courses that are classically defined as relapsing-remitting, primary chronic progressive and secondary chronic progressive MS, with several patients that during their life can switch from the first form to the latter one. Moreover the disease course can be particularly aggressive, or, on the contrary have a benign evolution. Thus it is evident that the challenge of having efficient therapy for MS treatment is a very complex point, but it is clear that the possibility of establishing MS diagnosis earlier can be seen as a great opportunity to intervene with therapy, thus having an increased chance of success. In this supplement a little space is devoted to the therapy, and in their papers Speciale and Trojano present interesting data about the immunological effects of beta interferon therapy in MS patients. Due to the mission of the Don Gnocchi foundation, in the Symposium organization a large space was devoted to the problems of the cognitive and physical impairment, to their relationship with the life style of the patients and with neuroimaging alterations, and to their updated rehabilitative approach. Finally the psychological changes and the impact of this disease on the patients, their families and on the social environment is discussed in the papers of Minden, Landoni, Cutajar and Battaglia.

We hope that this special issue on MS research and care will be of interest to the readers of the Journal of Neurovirology and will stimulate further discussion and research toward the understanding of the various aspects of MS, and in particular that other neurovirologist could be involved in this research field.

Acknowledgements

I would like to thank the authors for their contributions and the editorial staff of *Journal of Neurovirology* particularly June Vieth and Jennifer Gordon.

References

Compston A (1997). Genetic epidemiology of multiple sclerosis. *J Neurol Neurosurg Psych* **62:** 553–561.

Dalgleish AG (1997). Viruses and multiple sclerosis. *Acta Neurol Scand* **169** (Supp): 8–15.

Ebers GC, Sadovnick AD (1994). The role of genetic factors in multiple sclerosis susceptibility. *J Neuroimmunol* **54:** 1–17.

Filippi M and Miller DH (1996). MRI in the differential diagnosis and monitoring the treatment of multiple sclerosis. *Curr Opin Neurol* **9:** 178–186.

Kurtzke JF (1980). Epidemiological contribution to multiple sclerosis. An overview. *Neurol* **30** (suppl 2): 61–79.

Martyn CN, Gale CR (1997). The epidemiology of multiple sclerosis. *Acta Neurol Scand* **169** (suppl): 3–7.

Olerup O, Hillert J (1991). HLA class II-associated genetic susceptibility in multiple sclerosis: a critical evaluation. *Tissue Antigens* **38:** 1–15.

Sciacca FL, Ferri C, Vandenbroeck K, Vegli F, Gobbi C, Martrinelli F, Franciotta D, Zaffaroni M, Marrosu M, Martinelli V, Comi G, Canal D, Grimaldi LM (1999). Relevance of interleukin 1 receptor antagonist intron 2 polymorphism in Italian MS patients. *Neurol* **10:** 1896–1898.