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The pathology of multiple sclerosis and its evolution

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The pathology of multiple sclerosis (MS) was defined more than a century ago as a chronic inflammatory process which is associated with widespread primary demyelination and glial scarring. In this short review we discuss controversial issues on (i) the relationship between inflammation and demyelination, (ii) the various possible mechanisms of myelin destruction, and (iii) axonal involvement in this disease. We suggest that the disease process of MS is more complex than previously believed.

Keywords: multiple sclerosis; pathology; immunology

1. HISTORICAL INTRODUCTION

The pathology of multiple sclerosis (MS) was defined more than a century ago. Following the first macroscopic illustrations of the lesions by Carswell (1838) and Cruveilhier (1841), early microscopic investigations described the perivenous distribution of the lesions associated with inflammation (Rindfleisch 1863) and the essential structural changes, such as demyelination and a variable extent of axonal destruction and scar formation (Rindfleisch 1863; Charcot 1868). The state of the art of MS pathology was then summarized by Frommann (1878) and Charcot (1880). Although these essential features of MS lesions have been known for many years, only recently, due to major achievements in basic neurobiology and immunology, have we started to understand the mechanisms which are responsible for their development. In the following short review recent developments in the field of MS pathology will be summarized (figure 1). It will be shown that as a consequence of more detailed knowledge of the disease process it is apparent that MS is a much more complex disease than originally thought.

2. MULTIPLE SCLEROSIS AS A CHRONIC T-CELL MEDIATED INFLAMMATORY DISEASE

The first notion of an inflammatory background in MS came from the study of Eduard Rindfleisch (1863) who noted that demyelinated lesions have in their centre a small vessel that is surrounded by a leucocyte inflammatory infiltrate. This view was later expanded by Dawson (1916), who described finger-like extensions of pre-existing lesions by sleeve-like demyelination around inflamed vessels that leave the plaques. It was already evident at the turn of the 20th century that the inflammatory infiltrates are mainly composed of small round leucocytes and macrophages (Frommann 1878). The latter were found in close contact with the disintegrating myelin sheath and contained intracytoplasmic, myelin-reactive

degradation products (Babinski 1885). Transformed into modern immunological terminology such a pattern of inflammation is consistent with a delayed-type hypersensitivity reaction.

Therefore, not surprisingly, immunohistochemical characterization of the inflammatory infiltrates revealed a dominance of T lymphocytes and macrophages (Traugott *et al.* 1983; Newcombe *et al.* 1994). During the stage of active myelin destruction, infiltrating macrophages, and in part the local resident microglia population, show signs of immunological activation (Ulvestad *et al.* 1994; Brück *et al.* 1995). Furthermore, a variety of different pro- and anti-inflammatory cytokines as well as their receptors have been detected within the lesion, although a clear pattern of their expression in relation to lesional activity is so far not established (Hofman *et al.* 1989; Selmaj *et al.* 1991; Woodroffe & Cuzner 1993; Bonetti & Raine 1997). Similarly, most immunological molecules that are associated with a T-cell-mediated inflammatory response, such as adhesion molecules (Sobel *et al.* 1990; Dore-Duffy *et al.* 1993; Washington *et al.* 1994; Cannella & Raine 1995), chemokines and their receptors (Sorensen *et al.* 1999), histocompatibility antigens (Traugott *et al.* 1983; Esiri & Reading 1987) or co-stimulatory molecules (Gerritse *et al.* 1996; Windhagen *et al.* 1995) have been reported to be expressed in MS lesions. In following the relevant literature one is struck by the impression that whatever is newly discovered in T-cell immunology is subsequently described as being expressed in or associated with active MS lesions. But what can we learn from all these reports?

Taking together all the published data it is safe to conclude that the inflammatory reaction in MS is consistent with that of a T-cell-mediated immune reaction, which secondarily leads to macrophage activation. It is also clear that activated macrophages or microglia cells are intimately involved in the process of myelin destruction. Unfortunately for modern immunology this view is not much different from that expressed by Joseph Babinski in 1885. What drives the inflammatory reaction is much less clear. The notion that MS is a Th-1 T-cell-driven

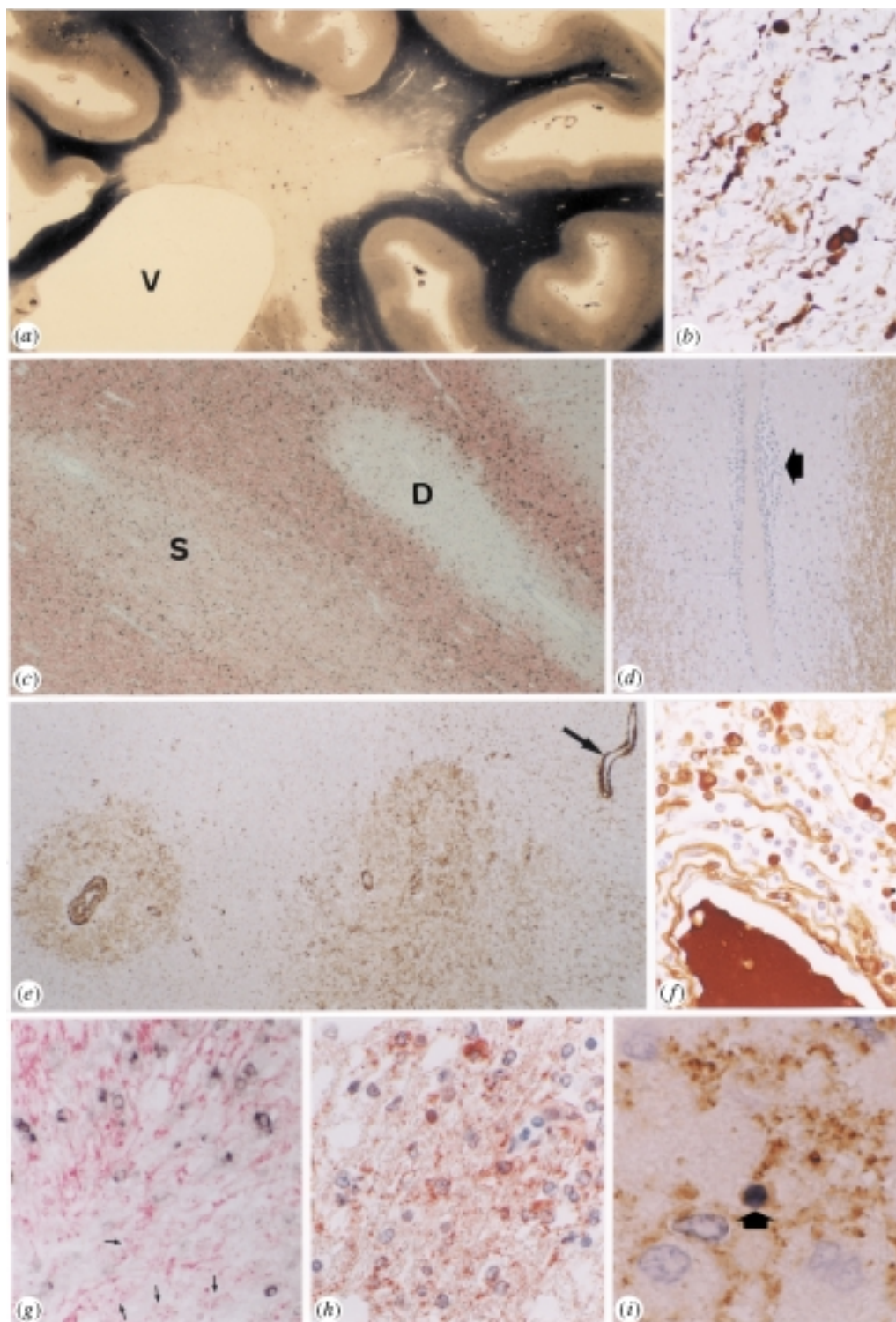


Figure 1. Pathology of MS. (a) Chronic MS; large periventricular demyelinated plaque with perivenous extensions into the adjacent white matter; extensive atrophy of the white matter with dilatation of the lateral ventricle (V); Heidenhein myelin stain, $\times 3$. (b) Actively demyelinating chronic MS lesion with numerous axonal spheroids as a sign of acute axonal injury; immunocytochemistry for phosphorylated neurofilament; $\times 500$. (c) Chronic MS with an inactive demyelinated (D) and a remyelinated shadow plaque (S). Oligodendrocytes (black cells) are lost in the demyelinated plaque, but present in the shadow plaque, although in reduced density; *in situ* hybridization for proteolipid mRNA (black) and immunocytochemistry for proteolipid protein red-brown $\times 30$. (d) Perivenous demyelination in chronic MS with focal inflammatory infiltrate (arrow); immunocytochemistry for myelin oligodendroglia glycoprotein, counterstained with haematoxylin; $\times 100$. (e) Actively demyelinating lesion in MS with plaque-like accumulation of lymphocytes (dark-brown stained cells) and macrophages (light-brown cells); perivascular inflammation is also present in the normal periplaque white matter (arrow); immunocytochemistry for CD45; $\times 30$. (f) Perivascular inflammatory infiltrate in chronic MS with high numbers of plasma cells; immunocytochemistry for IgG; $\times 350$. (g) Actively demyelinating lesion with numerous macrophages containing myelin-reactive degradation products (arrows); the oligodendrocytes (black cells) are reduced in the demyelinated area in

disease is mainly based on analogy with experimental models of autoimmune encephalomyelitis. To what extent Th-2 responses contribute to pathology, in particular in cases with pathogenic (demyelinating) antibodies, is unresolved. Completely unclear so far, also, is the role of CD8-positive T lymphocytes in MS. In that respect it has to be emphasized that in most MS lesions a dominance of CD8-positive over CD4-positive lymphocytes is found (Booss *et al.* 1983).

So far no aspect of inflammation in MS has been identified as being specific for the disease. In fact, a similar expression of immune-associated molecules is found in other T-cell-driven diseases of the nervous system, in particular in virus infections of the brain. Thus it seems rather unlikely that an MS-specific aspect of inflammation in the central nervous system will appear in the future. The explanation for that seems to be that the brain is surveyed by the immune system in a rather uniform way, which involves T-cell-mediated immune reactions, but avoids the diverse immune reactions operating in peripheral organs. Thus, an immunological attack in the brain, being directed against either foreign or auto-antigens, will follow very similar pathological patterns. The specificity of MS as a disease entity thus resides in the selective tissue damage, i.e. the demyelination, rather than the inflammatory process.

3. INFLAMMATION AND DEMYELINATION MAY OCCUR INDEPENDENTLY OF EACH OTHER IN MULTIPLE SCLEROSIS LESIONS

Another aspect of inflammation in MS that casts doubt on some of the modern immunopathogenetic concepts deals with the relationship between inflammation and demyelination or tissue damage. Overall, inflammation in MS is not restricted to demyelinated plaques, but affects the central nervous system tissue in a much more global sense. Thus inflammatory infiltrates are frequently present in the periplaque white matter as well as in the white and grey matter far distant from established demyelinated lesions. This is most impressively illustrated by the frequent occurrence of inflammation in the retina of MS patients, in a site which actually lacks myelin sheaths (Shaw *et al.* 1987). Furthermore, in contradiction to current belief in neuroradiology, inflammation in MS is not restricted to actively demyelinating plaques. Even in most inactive, burnt-out plaques perivascular infiltrates, composed of T cells, B cells and macrophages are a common finding. Although in general, inflammation is more pronounced in active compared with inactive lesions, these quantitative differences are relatively minor. The major difference between active and inactive lesions in MS resides in the local expression of macrophage activation antigens in the former (Brück *et al.* 1995).

In addition, the association of active myelin destruction with inflammation is in part controversial. Although it is

generally believed that demyelination occurs on a background of inflammation, in a recent systematic study Gay *et al.* (1997) concluded that the bulk of T-cell infiltration into the lesions follows the initial step of myelin destruction. Finally, active demyelination, in particular in patients under profound immunosuppressive treatment, can sometimes occur in the absence of overt perivascular inflammatory infiltrates (Guseo & Jellinger 1975). These observations have several implications: (i) the abundance of inflammation in the areas devoid of demyelination suggests that destruction of myelin sheaths in MS requires additional or even separate immunological mechanisms; (ii) ongoing active demyelination in the virtual absence of T-cell infiltrates in some (exceptional) cases suggests that the general view of a primary T-cell-mediated response being responsible for the formation of the lesions is not applicable to all cases; and (iii) the abundance of inflammation in completely inactive cases and lesions together with recent observations on the local production of neurotrophic factors by leucocytes in MS lesions (Kerschensteiner *et al.* 1999) indicates an additional role of invading leucocytes in regeneration and repair.

4. PATTERNS AND IMMUNOLOGICAL MECHANISMS OF DEMYELINATION IN MULTIPLE SCLEROSIS ARE HETEROGENEOUS

Selective destruction of myelin with relative preservation of axons is the major hallmark of MS pathology. Macrophages are intimately attached to degenerating myelin sheaths (Babinski 1885) and are actively involved in their removal and degradation (Prineas *et al.* 1984). However, the events that initiate the destruction of myelin sheaths seem to be heterogeneous. Support for this concept comes from experimental studies. In autoimmune encephalomyelitis different immunological mechanisms, such as demyelinating antibodies or cytotoxic cytokines may be responsible for myelin destruction (Weissert *et al.* 1998; Eugster *et al.* 1999), depending upon the genetic background of the animals. Furthermore, closely similar inflammatory demyelinating lesions are present in certain virus-induced diseases (Rodriguez 1992).

In the majority of active MS plaques, precipitation of immunoglobulins and complement components can be found at the site of active myelin destruction (Prineas & Graham 1981; Gay *et al.* 1997). In particular, the local precipitation of C9neo antigen on degenerating myelin and oligodendrocytes strongly supports a role of demyelinating antibodies in myelin destruction (Storch *et al.* 1998a). This view is further supported by a recent observation describing local deposition of anti-myelin oligodendrocyte glycoprotein antibodies on dissolving myelin in active lesions (Genain *et al.* 1999). Thus in a subgroup of MS patients, demyelination appears to ensue by cooperation of T-cell-mediated inflammation with demyelinating antibodies in a similar way to that described in the

Figure 1. (*Cont.*) comparison with the periplaque white matter; *in situ* hybridization for proteolipid protein mRNA (black) and immunocytochemistry for proteolipid protein (red); $\times 500$. (*h*) Actively demyelinating lesion in MS with profound deposition of activated complement (C9neo-antigen); immunocytochemistry for C9neo; $\times 500$. (*i*) Actively demyelinating MS lesion with oligodendrocyte apoptosis, detected by nuclear condensation in a cell with cytoplasmic reactivity for cyclic nucleotide phosphodiesterase (CNPase, arrow); immunocytochemistry for CNPase with nuclear counterstaining with haematoxylin; $\times 1200$.

model of myelin oligodendrocyte glycoprotein-induced autoimmune encephalomyelitis (Storch *et al.* 1998b). However, not all cases of MS follow the pathway of antibody-mediated demyelination. Instead, in the latter, signs of oligodendrocyte dystrophy are apparent. They can be reflected by a disproportionate loss of myelin-associated glycoprotein (Itoyama *et al.* 1980), by degenerative changes in most distal oligodendrocyte processes ('dying back oligodendroglipathy'; Rodriguez & Scheithauer 1994), apoptosis of oligodendrocytes at the sites of active myelin destruction (Lucchinetti *et al.* 1996; Lassmann 1998), or degeneration of oligodendrocytes in a small rim of periplaque white matter, closely adjacent to the site of active myelin disintegration (Ozawa *et al.* 1994; Lucchinetti *et al.* 1996). Interestingly, within an autopsy specimen which contains multiple active plaques, the pattern of demyelination is homogeneous, the heterogeneity is manifested between different cases. It thus appears that different mechanisms of demyelination may operate in different subgroups of MS patients. So far it is unresolved whether these differences are due to the heterogeneous genetic background of the patients or reflect fundamental differences in disease-inducing triggers.

5. OLIGODENDROCYTE PATHOLOGY AND ITS CONSEQUENCES FOR REMYELINATION

In principle, two patterns of oligodendrocyte pathology can be found in MS lesions (Lucchinetti *et al.* 1999). The first is characterized by a variable reduction of oligodendrocyte density at sites of active demyelination with rapid reappearance of oligodendrocytes, which are likely to be recruited from progenitor cells, in inactive plaque areas. In such cases repeated demyelination of previously remyelinated areas may lead to an exhaustion of the progenitor pool, which results in persistently demyelinated plaques (Prineas *et al.* 1989, 1993). The pathology of such cases is therefore characterized by a coexistence of active plaques, demyelinated plaques and remyelinated shadow plaques. This pattern is found in cases with antibody involvement in the demyelinating process (Storch *et al.* 1998a) and is closely similar to that in myelin oligodendroglia glycoprotein-induced autoimmune encephalomyelitis (Storch *et al.* 1998b). In other cases, however, oligodendrocytes are lost at the site of active demyelination and there is no major evidence for reappearance of new myelinating cells within inactive lesional areas (Lucchinetti *et al.* 1999). Not surprisingly, remyelination is sparse or absent in such cases. This second pattern of oligodendrocyte pathology is mainly found in cases which reveal signs of oligodendrocyte dystrophy at sites of active myelin destruction.

6. AXONAL PATHOLOGY IS PROMINENT IN MULTIPLE SCLEROSIS LESIONS AND REPRESENTS THE MAJOR PATHOLOGICAL CORRELATE OF PERMANENT FUNCTIONAL DEFICIT

MS is a demyelinating disease with relative sparing of axons. However, as stressed already by Marburg (1906) emphasis has to be laid on the term 'relative'. Significant axonal destruction was noted even in the earliest histological descriptions of MS pathology by Frommann

(1878), Charcot (1880) and Marburg (1906). These and later studies also revealed that acute axonal injury mainly occurs in active MS lesions and results in axonal swellings within the course of axons as well as terminal axonal end-bulbs (Marburg 1906; Doinikow 1915). Recently the topic of axonal injury has been reintroduced and additional quantitative data on the extent of axonal injury have been provided (Ferguson *et al.* 1997; Trapp *et al.* 1998; see also Perry & Anthony, this issue). There is now good agreement that axonal injury occurs mainly at the time when myelin sheaths are actively destroyed and thus may occur very early in disease development (Ferguson *et al.* 1997; Trapp *et al.* 1998). The extent of acute axonal injury apparently correlates with the degree of macrophage infiltration (Ferguson *et al.* 1997) and injured axons are frequently found in contact with macrophages (Trapp *et al.* 1998). In a recent study we further investigated axonal pathology in MS and found that even in the chronic stage of the disease, in completely inactive plaques, acute axonal injury continues as a slow-burning process. This could explain why clinical deterioration in chronic progressive MS may occur in the absence of fresh, gadolinium-enhancing lesions. Interestingly, progression of acute axonal injury was absent in remyelinated shadow plaques (B. Kornek, M. Storch, R. Weissert, E. Wallstroem, A. Stefferl, T. Linington, M. Schmidbauer and H. Lassmann, unpublished observations). As will be discussed in another paper of this issue, recent neuro-radiological studies suggest that axonal degeneration is a much better correlate for permanent clinical deficit than demyelination.

7. LESSONS FROM MS PATHOLOGY FOR MANAGEMENT AND TREATMENT OF MULTIPLE SCLEROSIS PATIENTS

There are two main therapeutic consequences emerging from the findings described above. First, all current data agree that significant tissue damage has already occurred very early in the development of the disease. This is particularly evident for axonal injury, which is an irreversible phenomenon and occurs at any time when new lesions arise. In addition, remyelination in the majority of cases is prominent at early disease stages, but its capacity decreases with the time of disease evolution. All these aspects argue in favour for early treatment of the disease. Second, the data coming from pathological studies strongly argue for a pathogenetic heterogeneity of the disease. Different cells and molecules of the immune system are involved in the induction of the lesions and different targets in the central nervous system, such as myelin, oligodendrocytes and axons are affected. Thus, simple immunomodulatory or anti-inflammatory strategies alone will not be sufficient to give satisfactory therapeutic responses. Future MS therapies will have to take into account the interindividual heterogeneity of the disease and will have to be directed against various different components of the immune system in conjunction with strategies to prevent axonal degeneration and to stimulate remyelination and repair.

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