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9. MULTIPLE SCLEROSIS

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9.1 Background

In multiple sclerosis (MS), one of the most common neurological causes of long-term disability, the myelin-producing oligodendrites of the CNS are the target of recurrent cell-mediated auto-immune attack. The lifetime risk of developing MS is about 1 in 800 in the western world, and in the UK the prevalence is 80 per 100,000 population. The incidence is higher in temperate climates and in people of European extraction, and the disease is slightly more prevalent in women (female: male ratio of 1.5:1).

9.2 Aetiology

Epidemiological evidence suggests an environmental influence on causation. The incidence varies with latitude, being low in equatorial areas and higher in the temperate zones of both hemispheres. A genetic influence is suggested by a 10-fold increase in risk in 10 degree relatives and from twin studies in which there is a higher concordance for MS in monozygotic twins compared to dizygotic twins. HLA tissue-typing has demonstrated an increased prevalence of the haplotypes: A3, B7, Dw2, and DR2, in affected patients in the UK, but different haplotypes are associated in other countries. An immune mechanism is suggested by increased levels of activated T-lymphocytes in the CSF, and increased immunoglobulin synthesis within the CNS. There are also increased levels of antibodies to some viruses, including measles virus, in the CSF, but this may be a result of the disease process rather than directly related to the cause. The relative importance of environmental, genetic, and immunological factors is unresolved. MS is likely to be multi-factorial in origin.

9.3 Pathology

An attack of CNS inflammation in MS begins with entry of activated T-lymphocytes through the blood-brain-barrier. These lymphocytes recognize myelin-derived antigens on the surface of the nervous system's antigen presenting cells, the microglia, and undergo clonal proliferation. The resulting inflammatory cascade releases cytokines and initiates destruction of the oligodendrcyte-myelin unit by macrophages. Histologically, the characteristic lesion is a plaque of inflammatory demyelination occurring most commonly in the periventricular regions of the brain, the optic nerves, and the subpial regions of the spinal cord. Initially, this is a circumscribed area of disintegration of the myelin sheath, accompanied by infiltration by activated lymphocytes and macrophages, often with conspicuous perivascular inflammation. After an acute attack gliosis follows, leaving a shrunken grey scar.

Much of the initial acute clinical deficit is caused by the effect of inflammatory cytokines upon transmission of the nervous impulse rather than structural disruptions of the myelin, which explains the rapid recovery of some of the deficits and probably the efficacy of the steroids in ameliorating the acute deficit. The myelin loss that results from the attack, however, reduces the safety factor for impulse propagation or causes complete conduction block, which lowers the efficiency of CNS functions. In established MS there is progressive axonal loss, probably due to direct damage to axonal integrity by the inflammatory mediators released during the acute attacks, including nitrous oxide. This is the cause of the phase of the disease where there is progressive and persistent disability.

9.4 Clinical Features

A diagnosis of MS requires the demonstration of lesions in more than one anatomical site at more than one time for which there is no other explanation. Around 80% of the patients have a relapsing and remitting clinical course of episodic dysfunction of the CNS with variable recovery. Of the remaining 20%, most follow a slowly progressive clinical course, with a tiny minority who have a fulminant variety leading to early death. The peak age of onset is in the fourth decade, onset before puberty or after 60 being quite rare.

The common presentations of MS include: optic neuritis, relapsing and remitting sensory symptoms, subacute painless spinal cord lesion, acute brain-stem syndrome, subacute loss of function of upper limb, and 6th cranial nerve palsy. Demyelinating lesions cause symptoms and signs that usually come on sub-acutely over days or weeks and resolve over weeks or months. Frequent relapses with incomplete recovery indicate a prro prognosis, while some presentations with purely sensory relapses have a poor prognosis.

9.5 Diagnosis and Investigations

There is no specific test for MS and the results of the investigations are taken in conjunction with the clinical picture in making a diagnosis of varying probability. The clinical diagnosis of MS can be supported by investigations that aim to exclude other conditions, provide evidence for an inflammatory disorder and identify multiple sites of neurological involvement.

MRI is the most sensitive technique for imaging lesions in both brain and spinal cord and in excluding other causes of neurological deficit. The MRI appearances in MS may, however, be difficult to distinguish from those of cerebrovascular disease or cerebral vasculitis. Diagnosis depends on the clinical history and examination, taken together with investigative findings. It is

important to exclude other potentially treatable alternative conditions such as infections, Vit B12 deficiency, and spinal cord compression.

Following the first clinical event, investigations may help in confirming the disseminated nature of the disease. Visually evoked potentials can detect clinically silent lesions in up to 70% of patients, but auditory and somato-sensory evoked potentials are seldom of diagnostic value. The CSF may show a lymphocytic pleocytosis in the acute phase and oligoclonal bands of IgG in 70-90% of patients between attacks. Oligoclonal bands are not specific to MS but denote intrathecal inflammation and occur in a range of other disorders.

The MRZ reaction: The oligoclonal, intrathecally synthesized IgG, contains numerous specific antibodies and auto-antibodies. Antibodies are frequently found with specificities against: measles (78%); Rubella virus (70%), and Varicella zoster virus (62%), but seldom against the Herpes simplex virus (36%). The occurrence of one, two, or three of these antibodies is referred to as the MRZ reaction. The MRZ reaction is typical of MS as a chronically evolving immune process. The major diagnostic investigations in MS are the following (clinical sensitivity in parentheses): oligoclonal banding on iso-electro-focussing (98%); MRZ reaction (94%); activated B-lymphocytes (79%); local IgG synthesis - ratio diagram (73%).

The CSF changes are very constant and are present even in remissions. As is the case in all chronic inflammatory processes of the CNS, including MS, there is no relationship between the extent of the changes in the CSF and the severity or the progression of the disorder. Thus, marked local IgG synthesis may be related with only mild symptoms of the disease, while normal CSF changes may occur despite severe, progressive, disease.

In rare cases, the inflammatory demyelination process is limited to the hemispheres and psychiatric symptoms, such as endogenous or organic psychoses, changes in personality and dementia, might predominate. Epileptic seizures occur more frequently. In the encephalitic form of MS, more cases with pleocytosis of up to 200/µl and barrier dysfunction (leakage of protein into the CSF) with an albumin ratio of up to 20x10-3 are found.

If, in the case of monophasic disseminated encephalomyelitis, doubts remain about whether it represents a viral infection or the first flare-up of MS, the CSF should be re-examined a year later. If the local IgG synthesis is quantitatively unchanged, MS can be reliably confirmed. In cases of CNS involvement in systemic autoimmune disorders, such as lupus erythematosus or Sjorgen's syndrome, inflammatory changes in the CSF are usually present. In individual cases, however, MS cannot be differentiated from other conditions by the analysis of the CSF. Intrathecal DNA antibodies are found in MS while the MRZ reaction is found in systemic auto-immune disorders, although more rarely.

MS is associated with dysregulation of cytokine expression, especially in regard to TNF-a. These proteins, as well as some nucleic acids, can be used as markers of the immunologically mediated inflammatory process seen in MS. These markers include: TNF-a; ICAM-1; IL-10; sTNF-R. In MS these four markers are indicators of the course of the disease with intermittent remissions and relapses. Soluble ICAM-1 (sICAM-1) reflects the size of the lesions caused by MS presuming extracerebral endothelial activation can be excluded. Serum concentrations of these markers, followed over a long time period, are indicative for the activity of the inflammatory process.

9.6 Management and Complications

The management of MS involves treatment of the acute relapse, prevention of future relapses, and management of the patient's disability. In the acute relapse stage, high-dose steroids are the treatment of choice, but should not be given chronically. Interferon ß-1a/b reduces the number of relapses by about 30%, but other immune modulators do not seem to have a significant effect.

Complications of MS include: spasticity, ataxia, dysaesthesia, and bladder syndromes (incontinence, urgency and frequency of urination, as well as sexual dysfunction.

9.7 Prognosis

Prognosis is difficult to predict with confidence in any individual patient. Overall, after 10 years about 30% of patients are disabled to the point of needing help with walking, while after 15 years about 50% have this degree of disability.

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