Abnormalities of Serum and Plasma Components in Patients with Multiple Sclerosis

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Qualitative and quantitative abnormalities in protein and non-protein components of serum and plasma in patients with multiple sclerosis have been the subjects of numerous reports. In this review many of the more recent observations are documented and evaluated. It is concluded that at present the welter of information that has been gathered does not contribute in any major, coherent way to our understanding of the etiology or pathogenesis of the disorder. Several of the abnormalities that have been observed may be future candidates for biochemical markers for multiple sclerosis; at present none is sufficiently reliable, distinctive or easily performed to warrant the status of a useful diagnostic or prognostic test.

Possible abnormalities of serum or plasma components in patients with multiple sclerosis (MS) have attracted the attention of many investigators. The impetus behind these studies is two-fold. First is the hope that a better understanding of the cause and pathogenesis of MS will emerge. Second is the search for sensitive and specific diagnostic and prognostic indicators. This review will attempt to document and evaluate many of the abnormalities in serum and plasma constituents that have been observed. A number of abnormalities in erythrocytes, white blood cells and cerebrospinal fluid in patients with MS have also been reported. These contributions to our understanding of the disorder are not covered in this review unless they relate directly to alterations in the composition of the serum or plasma. Because of the large number of publications touching on some aspects of the subject of this review, a process of selection was necessary. Many relevant articles published before 1980 have not been included. This policy was applied with particular stringency to reports concerning the immune responses in patients with MS—a topic which was comprehensively reviewed in 1980 by Iivanainen (1).

Non-protein components

I. LIPIDS

A. Cerebrosides

The cerebrosides of serum are normally mainly glucocerebrosides with a minor percentage of galactocerebrosides (2). The reverse is true for brain myelin and cerebrospinal fluid (CSF) where galactocerebrosides predominate (3). CSF cerebrosides were found to be consistently elevated at all stages of MS and this finding was more characteristic than were changes in a number of other individual lipids and lipid classes (4). The concept that an increase in the serum concentration of galactocerebrosides might reflect destruction of the central nervous system (CNS) has been investigated in a small number of patients and controls with conflicting results. Jones and co-workers (2, 5) were unable to demonstrate a difference in cerebroside composition or level either between pooled plasma from a large number of patients with MS and normal controls, or between individual samples from five patients and age-matched controls. Even in stroke patients, in whom relatively major destruction of the CNS occurs, the percent of total cerebrosides in plasma due to galactocerebrosides did not differ significantly from the percent found in controls. On the other hand, Baumann et al. (6) noted an elevation in the plasma level of galactocerebrosides in 4 of 12 patients with MS but in only 1 of 10 stroke patients. It can be tentatively concluded that the consistent increase in CSF galactocerebroside levels that has been observed in patients with MS is not as often accompanied by a comparable change in plasma levels.

B. Gangliosides

Gangliosides are also a major constituent of myelin (7) and elevated levels of ganglioside-derived N-acetyl-neuraminic acid have been found in the CSF of patients with MS (8). It has also been shown in the rabbit that gangliosides move rapidly from the CSF into the plasma (9). Sela et al. (10) reported a significant increase in the concentration of ganglioside-bound sialic acid in pooled serum from 20 patients with clinically definite MS (926 μg/100 mL) as compared to the concentration in pooled serum from the same number of

healthy blood donors (691 μg/100 mL). The pattern of individual gangliosides in the two pooled sera was identical. It was also found that peripheral blood lymphocytes from MS patients contained, on average, 39% more ganglioside than lymphocytes from the control group. These observations are of interest since gangliosides have been shown to alter the immune response of lymphocytes *in vitro* (11, 12). Further work is needed to assess what role, if any, blood or CSF gangliosides play in the altered immune response that is characteristic of many patients with MS (1, 12a).

C. Phospholipids

Although the early literature is contradictory with regard to the phospholipid composition of the serum in MS (reviewed in reference 13), later workers agree that neither the total nor the individual phospholipid content of serum from MS patients differs from normal (13–15). A reported increase in lysolecithin concentration in plasma of MS patients as compared with normal subjects (16) was probably a nonspecific consequence of illness since two groups could find no difference when MS patients were compared with patients with other neurological diseases (14, 15).

D. Fatty acids

Reports of a decrease in the percentage of total serum fatty acids due to linoleic acid in MS patients (especially during exacerbations) go back at least to 1964 (17). A relative decrease in cholesterol linoleate and an increase in tri- and tetra-unsaturated fatty acid esters of cholesterol were also observed in MS patients, especially during the progressive stage of the disease (18). Love and co-workers (19) found a decrease in linoleic acid content of serum lipids to be a general phenomenon in ill patients and not specific for MS. Several other groups were also unable to find a characteristic abnormality in total or cholesterol-esterified linoleic acid concentration in MS serum (20–22). MS patients apparently do show a consistent decrease in the levels of linoleic and arachidonic acids in CSF (23), however the pathophysiological significance of this finding is unclear. Possible abnormalities in linoleate metabolism in MS patients have attracted considerable interest because of the controversial diagnostic test for MS which depends on a characteristic decrease in the electrophoretic mobility of erythrocytes from MS patients in the presence of linoleic acid (24) and because of the possible therapeutic value of linoleate supplementation of the diet (25, 26).

II. TRACE METALS

A. Zinc

The results of studies on the concentration of zinc in the peripheral blood of patients with multiple sclerosis are conflicting (Table 1). The most obvious explanation for the discordant results is that different types of samples were analyzed, namely, serum, plasma, erythrocytes and whole blood. Until more data are obtained,

TABLE 1

Zinc Concentration in the Blood of MS Patients and Patients With Other Neurological Disease (OND) Compared With Levels in Normal Subjects

Blood fraction	MS	OND	Reference
Serum	Decreased		(27)
Plasma	Decreased	Slightly decreased	(28)
	Slightly increased	Increased	(29)
Erythrocyte	Increased	No difference	(29)
Whole blood	Increased	Increased	(30)

no definite conclusions can be reached concerning zinc status and compartmentalization in MS patients.

B. Copper

Recent studies have suggested that the concentrations of copper in serum (27) and whole blood (30) are normal in MS patients.

III. AMINO ACIDS

Reports of increased plasma concentrations of alanine and arginine (31) and decreased plasma concentrations of tryptophan, leucine, isoleucine, valine, tyrosine and phenylalanine (32) in MS patients were not confirmed by a third group who used serum (33). The latter investigators observed an elevation in serum glutamate concentration which was most striking during relapses. Geographical factors may have contributed to the disparate results since the reports originated from Japan, Italy and the United States, respectively. Furthermore, it is known (33a) that the concentrations of glutamine and asparagine are decreased and the concentrations of aspartate and glutamate increased in serum relative to plasma.

IV. VITAMINS

Serum folate levels were found to be significantly lower in patients with MS than in a group of patients with non-neurological diseases (34). It has been reported, however, that variable degrees of folate deficiency may accompany a variety of chronic neurological diseases (35). Serum vitamin E levels in MS patients were found to be normal (36).

Proteins

I. PROTEINS OTHER THAN ENZYMES AND IMMUNOGLOBULINS

A high incidence of abnormal patterns in paper chromatograms of serum proteins from patients with MS was reported many years ago (37). The abnormal patterns tended to recur in cycles of 1–3 months and were not clearly related to the clinical activity of the disease. The significance of these findings is unclear, not only because the proteins were not specifically identified, but also because similar but less marked cyclical abnor-

malities in the protein patterns were also observed in the sera from normal subjects.

In another study of serum protein patterns, a procedure for staining electrophoretically-separated glyco- and lipoproteins was used to compare sera from patients with MS, patients with herniated vertebral discs, and normal subjects (38). An increase in the β-lipoprotein fraction and/or a decrease in the α-lipoprotein fraction were found in about 60% of MS patients. A large number of the patients with herniated discs showed similar abnormalities so that the findings were considered non-specific for MS.

Wu and co-workers (39) subjected serum to gradient polyacrylamide gel electrophoresis and observed 3 distinct protein bands in 11 of 15 MS specimens which were not present in 10 control sera. The distinctive bands were not demonstrable by electrophoresis on uniform 5% of 7% gels. The 3 proteins were purified to homogeneity and molecular weights of 398000, 363000 and 302000 were assigned. Confirmation and extension of these studies are awaited with interest.

Minchin et al. (40) measured the concentration of 11 well-characterized serum proteins by quantitative immunoelectrophoresis and found no difference between MS patients and normal subjects. Dowling and Cook (41) did observe transient elevations in the serum concentrations of several acute-phase reactants—C3 proactivator, C-reactive protein and orosomucoid—in MS patients during exacerbations. It was later reported by the same group (42) that the concentration of the fourth component of the classical complement pathway (C4) was also elevated in some MS patients during relapse, whereas C3 was not. Mar et al. (43) found the level of C3 to be significantly higher in the serum of MS patients with stable disease. In 9 out of 12 patients with a fluctuating clinical course the C3 concentrations fell to normal levels during relapse or within 4 weeks afterwards. Serum C2 hemolytic activity was found to be normal in 46 MS patients, whereas the activity in the CSF was substantially decreased in patients with severe active disease (44). Despite these observations, the suggestion (41) that measurements of selected acute-phase proteins might be of value in assessing disease activity in MS patients has not received widespread acceptance.

An early report (45) that serum ceruloplasmin levels (measured as oxidase activity) were elevated in patients with MS was not confirmed when immunoelectrophoresis was used (40).

Rastogi and co-workers (46, 47) reported an abnormality in serum $α_2$-macroglobulin in 22 of 26 patients with definite or probable MS. Crossed immunoelectrophoresis resulted in an asymmetric immunoprecipitate which suggested the presence in MS serum of two species of $α_2$-macroglobulin with slightly different electrophoretic mobilities but very similar antigenicity. The sera of 4 of 24 patients with neurological diseases other than MS also showed the abnormal $α_2$-macroglobulin immunoprecipitate. Isoelectric focusing of $α_2$-macroglobulin isolated from MS sera revealed an extra band with an isoelectric point of 4.5. $α_2$-Macroglobulin is able to bind to and alter the catalytic specificity of a number of circulating proteases. The authors

speculated that their findings might somehow be related to the increased acid protease activity which they (48) and numerous others have observed in plaques and white matter of patients with MS.

The findings of Rastogi et al. have been questioned by Bridges and co-workers (49) who suggested that the procedure used to demonstrate the abnormal $α_2$-macroglobulin species may have led to artifacts. Furthermore, Bridges and co-workers found no difference between normal and MS subjects with regard to the ability of $α_2$-macroglobulin to bind to trypsin or the ability of the trypsin-$α_2$-macroglobulin complex to hydrolyse an artificial substrate. It was pointed out that even if the findings of Rastogi et al. were confirmed, the significance of such an abnormal species of $α_2$-macroglobulin to the individual with MS was not clear since protease binding by $α_2$-macroglobulin in MS serum appeared to be normal.

Although the mean level of prealbumin in CSF of MS patients was found to be twice that of controls, no significant difference was found in the serum concentration (50).

Elevated serum titres of interferon have been reported in 22 of 36 patients with definite MS and in 5 of 9 children with acute encephalitis (51). Only 3 of 59 patients with non-inflammatory nervous system disease and 8 of 50 presumably healthy blood donors had significant blood titres. Significant interferon titres in CSF were regularly associated with significant titres in serum, but very high serum titres were detected without detectable CSF titres. No quantitative correlation was found between interferon levels in serum and CSF in individual cases. The authors suggested that MS might in some way be linked to virus infection or to one of the other agents known to stimulate the production or release of interferon. However, others (52) have found reduced interferon production in vitro by lymphocytes from MS patients. A number of types of interferon are recognized (53) and different results may be explained by the fact that serum interferon was measured by viral induction whereas the in vitro study assayed mitogen-induced interferon production.

II. ENZYMES

Rieder et al. (54) reported that about one-third of a group of MS patients had moderately elevated levels of γ-glutamyltransferase activity in their sera. Alcohol intake as a cause was unlikely in these subjects. The difficulties in establishing reference ranges for γ-glutamyltransferase activity and the many factors that can affect its activity (including neurological disorders) have been reviewed (55). The significance with regard to MS of the findings of Rieder and co-workers is, therefore, questionable. For example, the authors found higher levels of activity in older MS patients and it is known (56) that the reference range for γ-glutamyltransferase activity increases with age.

A deficit in the intestinal isozyme of alkaline phosphatase was observed in the sera of MS patients in Northern England (57). This was particularly striking in patients with the O blood group, of whom only 52% displayed the intestinal isozyme as compared with 83%

of the O blood group controls. The presence or absence of the intestinal isozyme in normal subjects is known to be related to the ABO blood group of the subject. A significantly increased incidence of type O among MS patients in Northern England was also found (58), but was not found in a large group of patients in the United States (59). It was suggested that the population of the North of England might be characterized by a high frequency of blood group O and might also be characterized by a predisposition to MS for some unrelated reason.

Plasma and erythrocyte glutathione peroxidase activity was found to be similar among patients with MS, patients with other neurological diseases and normal subjects (60). The results of this study, conducted in Great Britain, differed from the significantly lower levels of enzyme activity observed in MS patients in Denmark (61) and Israel (62). Glutathione peroxidase is a selenium-containing enzyme and in animals its activity is affected by selenium intake. Whatever the reasons for the difference in results obtained in the three countries, it is doubtful that deficiency of either selenium or glutathione peroxidase activity contributes to the etiology or pathogenesis of MS. Mehlert et al. (60) point out that decreased levels of glutathione peroxidase activity have been reported in several areas of the world without associated pathological conditions.

III. IMMUNOGLOBULINS

Al-Agidi and Roberts (63) measured the serum levels of immunoglobulin classes in a large group of MS patients and controls in Orkney, an island with an extremely high incidence of MS. Aside from a slight increase in the mean concentration of IgE in patients from rural areas, no significant differences were found. Pandey et al. (64) observed a difference between MS patients and controls in the frequency of IgG heavy chain allotypes in serum. The Gm genes encode for either of two allelic heavy chains within each IgG subclass in humans. Caucasians with the Gm 1,17;21 phenotype were almost four times more likely to develop MS than those without it. It was suggested that this finding was further evidence (in addition to the predominance of certain HLA phenotypes in MS patients, for example) of an abnormality in the immune response in patients with MS.

A. Rickettsial and viral antibodies

Rickettsial antibodies were found in the sera of many patients with MS in uncontrolled studies in France (65); however, controlled investigations in the United Kingdom did not substantiate this finding (66, 67). The possibility that rickettsial infection may in some way be involved in the pathogenesis of MS was again raised when it was reported from Hungary (68) that the sera of 42 of 56 MS patients but only 8 of 42 age- and sex-matched controls contained rickettsial-specific antibodies. Most positive sera contained antibodies against R. mooseri. It is possible that patients with MS may be more susceptible to rickettsial infections in areas where rickettsia are indigenous, or that MS causes a non-specific stimulation or de-regulation of previously acquired antibody-producing cells.

Reports of elevated levels of measles antibody in the sera of patients with MS (69) continue to appear (70–78). Whether the level of antibody titre against measles virus is (74) or is not (72, 73) influenced by the HLA type of the individual patient is a subject of disagreement. Some studies have failed to find a significant difference in measles antibody titres between MS patients and control groups (79, 80). Poskanzer et al. (79) carried out a serologic survey of antibody titres against 17 viruses, including measles, among inhabitants of the Orkney and Shetland Islands, an area of extremely high incidence of MS. No consistent pattern of antibody levels or of the presence or absence of antibodies was found in MS patients when compared with two control groups. Because of the isolation of the islands, the mean age of acquisition of childhood viral infections, including measles, is older than that of inhabitants of many other parts of the world. It was of interest that 6 patients contracted clinical measles 2–9 years after the onset of MS. The authors concluded that the results failed to incriminate any of the viruses tested in the etiology of MS.

Because of a possible association between exposure to household pets and MS, a number of investigators have measured serum antibody titres against canine distemper virus. Cook and co-workers (75) and Madden et al. (76) found elevated levels of antibodies against both measles and distemper viruses in MS patients as compared with age- and sex-matched controls. Measles and canine distemper viruses are highly related antigenically. Based on an inability to demonstrate specific canine distemper virus antibodies in the sera of MS patients, it has been suggested (77, 81) that reactivity of measles antibodies in the assays for canine distemper virus antibodies explains the results of studies which showed elevated titres against the latter virus and that canine distemper virus is unlikely to be involved in the etiology of MS.

Bray et al. (80) observed that MS patients displayed a significantly higher incidence of seropositivity to Epstein-Barr virus (99% as compared to 89% in controls) and a lower incidence of seropositivity to cytomegalovirus (47% as compared to 57% for controls). Two groups (82, 83) have reported no significant difference between MS patients and controls in serum antibody titres to several mouse and human coronaviruses.

In summary, many but not all patients with MS have a significantly higher serum antibody titre against measles virus than do controls. This finding is usually explained as a manifestation of loss of control or nonspecific stimulation of the immune response. If so, the abnormal immune response is very limited, at least as judged by examination of serum, since most studies have found that antibody titres against a large number of viruses other than measles are usually not elevated in MS patients as compared with controls (70). It is true that a wider range of antiviral antibodies can be detected in the CSF of MS patients (1, 70).

B. Anti-brain antibodies

Complement-fixing IgG antibodies against antigens

in homogenates of grey or white matter have been reported to occur frequently in MS patients (84). Although titres are usually higher in CSF, similar antibodies have been found in serum (85). Because of the wide range of titres in paired CSF and serum samples from the same patient, it was suggested that the synthesis of the antibodies occurred both intra- and extra-thecally. The anti-brain antibodies have been characterized by bacterial absorption and found to be primarily of the IgG_1 and/or IgG_2 subclasses (86). In some MS patients anti-brain antibodies cannot be demonstrated and this is apparently not due to the presence of a serological inhibitor (87). Anti-brain antibodies were present in 40% of the serum and 88% of the CSF samples from patients with clinically definite MS; the corresponding figures were 21% and 73% for probable MS, and 11% and 6% for controls (88). Although anti-brain antibody titres in serum were higher in patients with a more malignant course, there was no consistent correlation between remissions and exacerbations in the clinical course and changes in antibody titres (89). Others (90), using a different assay, were unable to demonstrate a difference between MS patients and controls in the binding of serum immunoglobulins to homogenates of brain. Ryberg (85) claims that in such assays nonspecific binding of IgG obscures the increase in anti-brain antibody titres in MS serum which is detected by his complement fixation technique.

Clausen (91) observed the binding of the $F(ab)_2$ moiety of serum IgG from MS patients and normal subjects to subcellular fractions of brain tissue obtained at autopsy from patients with and without MS. Binding of antibodies from MS serum to cytosol proteins from MS brains was about twice as great as the binding of the same antibodies to cytosol proteins from non-MS brains, and was about 50% greater than the binding of antibodies from normal sera to MS cytosol proteins. Antibodies from MS patients and normal subjects bound equally well to control cytosol proteins and to particulate fractions from all brain tissue. These results and others using crossed immunoelectrophoresis suggested that the MS serum contained antibodies to up to 3 antigens in the cytosol of the MS brain tissue.

Arnon and co-workers (92) prepared liposomes containing purified gangliosides and observed that the serum from 30%–40% of patients with definite MS caused complement-dependent lysis of the liposomes. Liposomes containing GM_4, the major myelin ganglioside, and GM_1, the major brain ganglioside, were lysed to the greatest extent. Sera from normal subjects did not cause significant lysis. A correlation between the extent of lysis and the severity of MS could not be definitely established. Mullin et al. (93), on the other hand, were unable to demonstrate a significant ($p < 0.05$) difference in the lysis of GM_1-containing liposomes between MS and control sera. Also, release of gangliosides by MS sera did not seem to be complement-dependent. The conflicting results of these two studies may be due to the fact that different assays were used to assess liposome lysis.

Frick and Stickl (94) observed that serum from MS patients stimulated antibody-dependent lymphocyte cytotoxicity against erythrocytes in the presence of myelin basic protein, cerebrosides, gangliosides or encephalitogenic peptide. The latter peptide represents that region of myelin basic protein which, on administration to susceptible animals, is followed by experimental allergic encephalomyelitis. Lysis in the presence of the encephalitogenic peptide, but not the other three substances, was highly specific for MS (1% false positive rate in patients with other neurological diseases) and also sensitive (70%–98% of MS patients giving a positive result depending on disease activity). The high degree of specificity and sensitivity of the lytic response in the presence of the peptide led the authors to suggest that the reaction might have a pathogenetic role in MS.

Two recent studies found that substantial numbers of both MS patients and control subjects possess serum antibodies against myelin basic protein and that the incidence and titre of such antibodies do not distinguish between the two groups (95, 96). The earlier, conflicting results obtained by investigators with regard to the titre or even the presence of such antibodies are summarized by Ruutiainen et al. (95). They point out that differences in the antigen preparations used, differences in the MS populations studied, differences in the populations used as controls and differences in the antibody assays used may all have contributed to the variations in the results that have been reported. A similar set of explanations can be put forward for many of the other conflicting observations that have been reported in patients with MS.

Paterson and co-workers (97) reported the presence in serum of MS patients and controls of substances which combine with varying affinities with antibodies against myelin basic protein. Anti-myelin basic protein antibodies with varying affinities for myelin basic protein were also detected in MS and normal sera. The affinities of the substances were usually lower and the affinities of the antibodies usually higher in patients with active MS than in normal subjects. The authors suggested that the circulating substances might function to restrict potentially injurious myelin-basic-protein-reactive lymphoid cell clones.

A number of investigators now believe that the binding of serum immunoglobulins to oligodendrocytes and glial cells is nonspecific, as usually studied, and is not a distinguishing feature of MS (98–101). Indirect studies indicated that the binding reactions were due to the presence of Fc receptors on the oligodendrocytes and that the reactions were, therefore, nonspecific. Furthermore, it has been pointed out (101) that the use of bovine oligodendrocyte preparations to demonstrate antibodies in human sera directed against human oligodendrocytes may result in failure to identify specific and pathogenetically relevant immune responses in MS patients because of interspecies differences in cell surface characteristics. Two groups consider their assay system to be specific with regard to both the antibody and the glial cell. Singh and Mashal (102) found glial-cell-binding antibodies in 43% of MS sera examined. They claimed the reaction was specific for the glial cell in their culture system and that no binding occurred when sera from normal subjects or patients with other neurological diseases were used. Mar (103)

TABLE 2
Antibodies and Factors in the Serum or Plasma of MS Patients

Antibody or factor	Frequency or level of titre compared with control groups	Reference
Anti-HLA-B8	Increased	(112)
Anti-thyroid (microsomal)	Increased	(113)
Anti-staphylococcal lipoteichoic acid	Decreased	(114)
Anti-smooth muscle	No difference	(115)
Anti-nuclear	No difference	(115)
	Increased	(116)
		(117)
Rheumatoid factor	Increased	(118)
Leukocyte adherence-inhibiting factor	Increased	(119)
	Slightly increased	(120)

reported that the serum of MS patients was capable of initiating a specific, antibody-dependent, lymphocyte-mediated cellular toxicity against a rat glial tumour cell line. The gliotoxic-stimulating activity was found to be significantly higher in MS sera than in normal sera or sera from patients with other neurological diseases. The gliotoxic activity was tissue-specific for glial cells and was greatest in patients with chronic progressive MS and least in those with stable disease.

Do any of these various anti-brain antibodies play a role in the pathogenesis of MS? A strong case can be made that MS is a disease of immune regulation (12a). If this hypothesis is true, a principal question that must be answered concerns the nature of the neural antigens involved. At present, no clearcut answers to this question are available. Some reasons have been given above for the inconclusive results that have thus far been obtained. An especially telling argument against a pathogenetic role for any of the anti-brain antibodies that have been described is that in each instance a substantial proportion of patients with MS do not appear to have the antibody or it is present in normal subjects or in those with other neurological diseases.

C. Lymphocytotoxic antibodies

Many workers have searched for lymphocytotoxic antibodies in the serum of MS patients. Schocket et al. (104) found the incidence of cold-reactive lymphocytotoxic antibodies to be significantly increased in MS patients (46%) as compared with their siblings (18%), patients with other neurological diseases (5%) and normal subjects (13%). The levels correlated significantly with serum measles antibody titres but not with the clinical course. Other workers (105–108) have confirmed that cold-reacting lymphocytotoxic antibodies are found more frequently in MS patients than in controls. Scott et al. (107) absorbed sera with pooled human platelets in an attempt to remove interfering anti-HLA antibodies. After absorption 8 of 32 MS sera, but only 1 of 20 control sera, remained lymphocytotoxic. The cytotoxicity was greatest towards suppressor T cells, as defined by a monoclonal antibody. All MS sera positive for lymphotoxins were from patients with active or progressive disease. Tsukamoto and co-workers (108)

also observed a marked increase in the incidence of these antibodies in MS patients during periods of increased disease activity (83% of patients positive); others (104, 106) did not observe such a correlation. It is suggested that these antibodies may be markers for viral infection associated with MS or may play a role in modulating the immune response, or both.

Armentrout et al. (109) reported the presence in MS serum of a factor (not necessarily an antibody) that inhibited the mitogen-induced blast transformation of human lymphocytes. T cells were most sensitive to the inhibitory factor and the degree of inhibition produced by a patient's serum was correlated with the level of clinical disease activity. Contrary results were reported by Mogensen and co-workers (110) who found that serum from patients with MS was less inhibitory for mitogen-stimulated lymphocyte transformation than was serum from patients with other neurological diseases. The issue is an important one since considerable evidence has accumulated that abnormalities of immunoregulatory T lymphocytes occur in MS, as in a number of other neurological disease states (111, 12a).

D. Other antibodies and factors

Many other antibodies and factors have been assayed in sera from MS patients (Table 2). Of the results listed in Table 2, the abnormality found most consistently in MS sera was the inhibition of leukocyte adherence. Positive results were observed in 53 of 58 patients with MS (91%) and in only 3 of 75 control subjects (4%). However, this unusual sensitivity and specificity of the leukocyte adherence inhibition assay for MS was not confirmed by other workers (120).

E. Oligoclonal bands

Oligoclonal bands demonstrably or presumably of IgG, have been observed in the serum of patients with MS by a number of investigators (121–130). Olsson and Nilsson (121) subjected serum and CSF to isoelectric focusing and found that bands in serum corresponding to those in CSF were present in 10% of MS patients. Because the bands in serum were fainter, the authors suggested that they were derived from the CSF. This

report confirmed earlier work by Laurenzi and Link (122) who observed oligoclonal bands in the serum of 41% of MS patients. Oligoclonal bands in serum are only rarely demonstrated by agarose gel electrophoresis which is less sensitive than isoelectric focusing (123). Mehta et al. (126) reported that 70% of MS patients had oligoclonal bands of IgG in their sera after isoelectric focusing. The banding pattern was generally similar to that of the CSF. Later work by the same group (127), however, showed that in the individual MS patient the majority of oligoclonal bands in serum differed with respect to number, isoelectric point and light chain type from the bands seen in the patient's CSF.

Nagelkerken et al. (128, 129) prepared antisera which reacted specifically with CSF oligoclonal IgG. In the CSF, antigenic oligoclonal IgG was enriched relative to total IgG which suggested its intrathecal synthesis. However, the absolute concentration of the antigenic IgG was higher in serum than in CSF, which suggested that at least a portion was synthesized outside the CNS. The investigators were unable to demonstrate cross-reactivity between the IgG bands of different patients which supported the view that at least some of the oligoclonal bands were antibodies unique to each individual. Cross-reactivity between bands in the serum and CSF of the same patient was observed. Findings similar to those of Nagelkerken et al. (128, 129) were reported by Baird and co-workers (130) who also noted that the unique idiotypic IgG of a patient with MS persisted over a five-year period. This finding suggested that continuous stimulation by an unknown antigen was occurring.

Vartdal et al. (124), using a highly sensitive electroimmunofixation method, found no notable difference between MS patients and age- and sex-matched controls in the frequency of oligoclonal serum antibodies against a variety of bacterial and viral antigens. These oligoclonal antibodies were not associated with the oligoclonal bands of IgG demonstrable in serum and CSF by isoelectric focusing.

F. Immune complexes

Circulating immune complexes were found in the sera of one-third of 138 MS patients by Patzold and co-workers (131) but only in 19% of CSF samples. The immune complexes were observed with equal frequency during acute exacerbations and in stable phases of the disease, and were more frequent in patients with long-standing disease. Patients with immune complexes tended to exhibit a more rapid clinical deterioration. This latter observation was confirmed by Jans et al. (132). Trouillas and co-workers (133) detected immune complexes in the sera of 43% of patients with MS and in 52% of their first degree relatives, but could find no association between the clinical course of MS and the presence or absence of the complexes. Haile et al. (134) confirmed the high incidence of immune complexes in the sera of MS patients and their unaffected relatives. The finding suggests that elevated levels in MS patients may be a familial phenomenon related to common environmental or genetic factors.

Arnadottir and co-workers (135) carried out an ex-

tensive longitudinal study of serum and CSF immune complexes in MS patients and were unable to discern a clear correlation between the presence, quantity or fluctuation of the complexes and the clinical course of the disease. It was concluded that the complexes were not precipitating factors in the pathogenesis of MS. These workers went on to characterize further the immune complexes in MS patients by an antigen-specific immune complex radioimmunoassay which detected the presence of myelin membrane-related antigens (136). A significant correlation was observed between the serum levels of immune complexes detected by a standard method (C1q reactivity) and by myelin membrane-related antigenicity. The buoyant density of the antigenic complex on sucrose gradient centrifugation suggested that it contained lipid. Further work will be required to establish a role for these specific immune complexes in MS. Obviously, it is hoped that characterization of the antigenic moiety of the complex will lead to an understanding of the neural antigen(s) important in the pathogenesis of MS as a disease of autoimmunity.

Dasgupta and co-workers (137) and Noronha et al. (138) observed a significantly higher incidence of immune complexes in serum of MS patients during active disease as compared with those in remission. These results, which differ from many earlier studies and suggest a pathogenetic role for immune complexes, were explained as being due to the application of more sensitive assays than had been previously used.

Demyelinating factors and neuroelectric blocking factors

Conflicting results have been reported concerning the incidence, specificity and pathogenetic importance of substances in the CSF and serum of MS patients, which demyelinate nerves or inhibit their electrical conductance. Bornstein and co-workers (139–141) claimed that the serum of 64% of patients with active MS produced demyelination of cultured CNS tissue. The major portion of the demyelinating activity was not associated with the serum immunoglobulins. Ulrich and Lardi (142) reported that 51% of sera from patients with a variety of neurological diseases other than MS but only 14% of MS patients were positive for demyelination activity. Seil et al. (143) found only 16% of serum samples from MS patients to be demyelinating. In agreement with the results of Bornstein and co-workers, a correlation was observed between serum demyelinating activity and disease activity. The authors speculated that serum demyelinating activity is an epiphenomenon not directly related to the pathogenesis of MS.

The suggestion that neuroelectric blocking factors are present in the serum or CSF of MS patients is attractive since it offers an explanation for the transient neurological defects that occur. The brevity of these fluctuations in neurological signs and symptoms is often incompatible with the time required for demyelination followed by remyelination. Schauf and Davis (144) used as a test system the isolated spinal cord of frogs. Although they were unable to demonstrate any

effect of MS sera on the conduction of either normal or demyelinated nerves, they did observe blockade of ventral root responses by serum from MS patients. The level of such neuroelectric blocking activity correlated with variations in the course of the disease. It was not present in normal serum but was observed in serum from patients with amyotrophic lateral sclerosis. On the other hand, Seil and co-workers (reviewed in reference 145) concluded that there was no evidence to indicate that neuroelectric blocking factors play a role in human neurological diseases. These investigators used mouse cerebral neocortex cultures as the test system. They found that neuroelectric blocking factors were not specific for demyelinating diseases and that such factors were present in a high proportion of normal sera.

Conclusions

A large number of observations have been made concerning the presence and absence of abnormalities in the serum and plasma of patients with MS. Unfortunately, this extensive collection of information has not contributed in any major, coherent way to our understanding of the etiology and pathogenesis of the disorder. As a clearer picture of the cause of MS emerges, perhaps we will recognize the importance of certain abnormalities which are currently regarded as nonspecific or epiphenomena. Furthermore, none of the reported changes has proved to be sufficiently reliable and distinctive to gain the status of a diagnostic or prognostic test. It may be that the sensitive and specific abnormalities associated with MS are more subtle than suspected or do not appear to an appreciable extent in serum or plasma. Alternatively, MS may have multiple etiologies and pathogeneses which, although producing a recognizable clinical picture, do not lead to a single characteristic abnormality in serum or plasma.

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