ASPECTS OF THE VIRAL ANTIBODY RESPONSE IN MULTIPLE SCLEROSIS

B.R. Ziola and A.A. Salmi

The Neurovirology Study Group, Department of Virology,
University of Turku
Turku, Finland

It has been suggested that the intrathecal synthesis of viral IgG antibodies indicates the presence of the corresponding viral antigen(s) in the central nervous system (CNS) of MS patients (6). Although measles virus has predominantly been implicated in such studies, intrathecal IgG synthesis to rubella, mumps and vaccinia virus has also been detected (4, 7). Intrathecal viral IgG antibody synthesis may, however, be a secondary, non-specific phenomenon in the pathogenesis of MS. Support for this idea comes from the fact that IgG antibodies against more than one virus are synthesized in the CNS of some MS patients (4). Moreover, not all MS patients have CNS IgG synthesis to a single virus i.e., measles virus (4) and of the oligoclonal IgG found in the CNS of MS patients, only a minor fraction is against a given virus i.e., measles virus (9).

Recently, we have analyzed MS patients for CNS IgG antibody synthesis to the human coronavirus OC43. A sensitive solidphase radioimmunoassay (RIA) was used (11). RIA determinations of respiratory syncytial virus-specific IgG were concurrently used to evaluate the integrity of the patients' blood-brain-barriers. Two MS patients, of 20 studied, were found to have CNS IgG synthesis to coronavirus OC43. Table 1 presents the data of some of the MS and control patients analyzed. A serum/CSF ratio of <80 is considered to be a clear indication of intrathecal antibody synthesis of a specific IgG (5). This demonstration of CNS IgG synthesis to yet another virus supports the contention that such antibody synthesis to viruses in MS patients may be more general than heretofore expected, and that the bulk of the oligoclonal IgG found in the CNS of MS patients is secondary to the MS disease process. This does not exclude, however, that some of the observed CNS oligoclonal IgG antibodies may have a pathological role in MS.

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Table 1. Analysis of viral IgG, total IgG, and albumin in paired serum (S) and cerebrospinal fluid (CSF) specimens.

	Coronavirus RIA IgG (log_2)		S/CSF ratio (virus IgG)		CSF/S ratio ($\times 10^{+3}$)	
Patient (diagnosis)*	S	CSF	Corona-virus	Respiratory syncytial virus	Albumin	IgG
MR (MS)	11.6	5.9	55	220	5.7	17.6
OP (MS)	9.3	4.2	35	335	3.6	4.2
RH (MS)	10.7	4.0	110	870	4.8	4.6
RB (MS)	11.2	2.6	385	205	8.0	21.1
VJ (MS)	10.2	1.7	360	230	3.5	5.9
KP (ALS)	9.6	$<1.0>$	500	1025	2.4	1.8

*MS = Multiple sclerosis; ALS = Amyotrophic lateral sclerosis

Virus specific IgM antibodies generally decline to undetectable levels following the convalescent phase of viral infections. Thus, the continued production of IgM antibodies long after convalescence may indicate a persistence of the viral infection. The human disease subacute sclerosing panencephalitis (SSPE) is known to occur months to years after a measles infection. Consequently, studies of measles IgM persistence in SSPE can be expected to provide useful background information for similar studies with MS patients, given the association of measles virus with most MS patients.

An immunofluorescence study (8) and an RIA study (13) have reported finding measles-specific IgM in SSPE patients. Studies conducted in our laboratories, also with an RIA designed to detect measles IgM antibodies (1), appeared to confirm that measles IgM is produced in at least some SSPE patients (2). Possible complications posed by IgM-class rheumatoid factor (RF), however, were not thoroughly taken into account in these studies. Therefore, in order to more fully investigate the possible persistency of measles IgM in SSPE patients, we developed a sensitive solid-phase RIA to test for low levels of RF. The RF RIA utilizes natural human IgG: antigen complexes on a solid-phase to bind RF which is then detected with ^{125}I-labeled antihuman-mu indicator antibodies (10). With the availability of the measles IgM RIA and the RF RIA, we then undertook an extensive study of sera and cerebrospinal fluid (CSF) from 19 SSPE patients. It was determined that what was originally believed to be measles IgM in the serum and CSF from some patients was, in fact, RF interference in the measles IgM RIA. No true measles IgM was found in the serum and CSF specimens from these 19 SSPE patients.

Similar techniques were then used to study 70 MS patients for the possible persistence of measles-specific IgM and not a single

patient with genuine measles IgM antibodies was found. These results indicate that, if there is continued production of measles IgM antibodies in the serum or CSF of MS patients, the levels are very low. It is not known at this time whether or not persisting IgM against other viruses is present in MS patients. Any such study, however, must clearly take into account low levels of RF which may be present.

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