# CORONAVIRUS ANTIBODIES IN PATIENTS WITH MULTIPLE SCLEROSIS

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## INTRODUCTION

Several strains of murine coronavirus are able to induce a demyelinative disease in laboratory animals. The disease is characterized by a chronic course with relapses after the initial phase of acute encephalitis (Herdon et al., 1975; Holmes et al., 1980). Recently a coronavirus has also been implicated in human demyelinative disease, multiple sclerosis (Burks et al., 1980). In order to determine whether a coronavirus etiology for MS could be demonstrated in analogy to the role of measles virus in SSPE, we have studied the occurrence of coronavirus antibodies in two collections of clinical material.

## MATERIAL AND METHODS

The antibody levels for three different coronaviruses, OC43, 229E and A59 (a murine strain) were compared in 56 patients with multiple sclerosis (MS) in a clinically stable phase and their carefully matched controls (Madden et al., 1980). In the other collection we analyzed the levels of OC43 antibodies in a series of patients with acute clinical disease. Eighteen had MS, 8 had optic neuritis (ON), 27 had other neurological diseases (OND) and 88 were judged as controls without neurological disease by a careful clinical follow-up for more than a year after the samples were taken (Leinikki et al., 1980).



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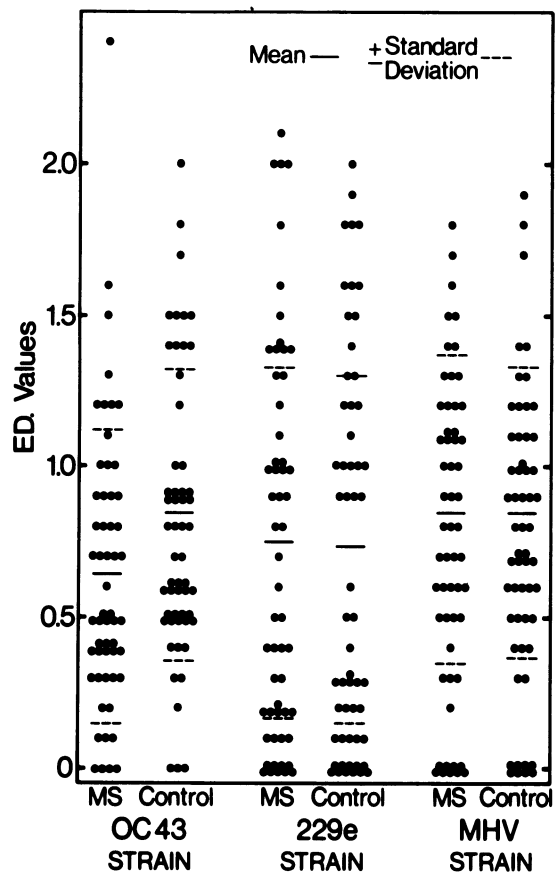


Figure. Occurrence of coronavirus $OC_{43}$, 229e and A59 antibody in 56 multiple sclerosis (MS) patients and matched controls.

The antibody assays were made by using ELISA as described (Leinikki and Pässilä, 1976). Tissue culture derived 229E and A59 viruses and mouse brain derived $OC_{43}$ viruses were used for the sensitization of polystyrene cuvettes. Sera or cerebrospinal fluid (CSF) were incubated in the cuvettes and the amount of fixed IgG was determined by using alkaline-phosphatase conjugated anti-IgG. The results were calculated by comparing the optical density given by the sample with that of a standard curve and expressed as logarithmic ED-values (Leinikki and Pässilä, 1977).

## RESULTS AND DISCUSSION

In the 56 MS patients with stable disease no difference was found in the distribution of antibody activities when compared to the controls with any of the three coronavirus antigens. (Figure). According to the ED-values, a very high number of patients and controls had various coronavirus antibodies. However, in a sensitive assay like ELISA the cut-off for seronegativity is often difficult to determine before a large clinical material has been analyzed. It is possible that part of the samples with low ED actually should be regarded as seronegatives. This however, does not alter the interpretation of the data from figure 1; the distribution of both high and low ED-values is quite similar for MS and controls. The high incidence of A59-antibodies both in MS and in controls suggest a strong cross reaction between murine and human coronavirus strains.

Table 1. Mean Values (ED±SD) of Serum Antibody Levels in different Patients Groups

| | PATIENT GROUP | | | |
|---|---|---|---|---|
| VIRUS | MS | ON | OND | CONTR |
| CORONA | 0.6±0.3 | 0.6±0.2 | 0.7±0.4 | 0.8±0.4 |
| MEASLES | 1.9±0.6 | 1.7±0.2 | 1.8±0.5 | 1.7±0.5 |
| RUBELLA | 1.6±0.4 | 1.6±0.5 | 1.9±0.6 | 1.7±0.5 |
| VACCINIA | 0.6±0.7 | 0.5±0.2 | 0.7±0.4 | 0.7±0.3 |
| MUMPS | 0.9±0.3 | 1.3±0.3 | 1.0±0.3 | 1.1±0.5 |

In the patients with acute disease the mean titres of serum antibodies were quite similar in the different study groups (Table 1). On the contrary, CSF antibody levels were significantly elevated in MS as judged from serum/CSF-antibody ratios (Table 2). However, a similar increase was found with several different viral antigens such as measles, rubella, vaccinia and mumps. Also the amount of increase of these unrelated viral antibodies was very similar in many individual patients. No correlation was found between the antibody levels and parameters for blood-brain-barrier condition such as serum and CSF albumin, IgG and total protein as measured by standard nephelometric techniques indicating that the antibodies are synthesized within the central nervous system.

The results indicate that seroepidemiologically no significant difference can be detected between MS and other patient groups or controls in their relationsip with coronaviruses. They also suggest that the elevation of coronavirus antibodies in CSF of MS patients

Table 2. Mean (±SD) of Serum/CSF Virus Antibody Ratios (ED serum - ED CSF) in Various Patient Groups

| VIRUS | PATIENT GROUP MS | (N)[a] | ON | (N) | OND | (N) | CONTR | (N) |
|---|---|---|---|---|---|---|---|---|
| CORONA | 1.5±0.1 | (4) | - | (0) | 2.1±0.2 | (9) | 2.3±0.2 | (8) |
| MEASLES | 1.6±0.2 | (17) | 2.0±0.3 | (8) | 2.2±0.3 | (27) | 2.5±0.2 | (78) |
| RUBELLA | 1.6±0.3 | (18) | 2.1±0.3 | (6) | 2.4±0.2 | (26) | 2.5±0.2 | (74) |
| VACCINIA | 1.3±0.7 | (4) | 1.5±0.2 | (2) | 2.2±0.3 | (6) | 2.3±0.2 | (8) |
| MUMPS | 1.8±0.1 | (9) | 2.1±0.2 | (6) | 2.3±0.1 | (7) | 2.5±0.3 | (31) |
| ALL VIRUSES | 1.6±0.3 | (18) | 2.1±0.2 | (8) | 2.3±0.3 | (27) | 2.5±0.2 | (87) |

[a]Number of patients with detectable CSF antibody levels.

in acute stage is caused by nonspecific stimulus which also increases the synthesis of several other viral antibodies within the central nervous system of these patients. These antibodies reflect an immunological disturbance rather than etiological relationship.

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