Measles Virus-Specific IgG in Cerebrospinal Fluid in Multiple Sclerosis

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Summary

The prevalence of measles virus-specific IgG in cerebrospinal fluid (C.S.F.) of patients with multiple sclerosis (M.S.) has been compared with that in fluids from patients with other neurological diseases and from normal control subjects. The prevalence in the three groups was 58·1%, 24·1%, and 0% respectively. Fivefold concentration of the specimens increased the prevalence in the first two groups to 80·6% and 34·5% respectively, while measles IgG was not detected in any fluids of the normal control group, even after concentration.

Introduction

Since Adams and Imagawa (1962) first reported a slightly increased average titre of antibody against measles virus in the serum of patients with multiple sclerosis (M.S.) many workers, using a variety of different techniques, have confirmed this finding (Brody *et al.*, 1972). In a few studies a higher prevalence of antibody to measles virus has been detected in cerebrospinal fluids (C.S.F.) from patients with M.S. compared with patients with other neurological diseases. Using the sensitive mixed haemadsorbing antibody technique Brown *et al.* (1971) found 79% of 119 patients with M.S. had measles antibody in C.S.F. compared with 45% of a control group of 112 patients with other neurological diseases, while Salmi *et al.* (1974) found increased incidence of antibodies against three structural components of measles virus compared with controls.

The frequency of relatively increased IgG in the C.S.F. (Link and Müller, 1971) and the demonstration in the C.S.F. of a few patients with M.S. of IgG which contained measles antibody (Salmi *et al.*, 1972; Panelius and Salmi, 1973) encouraged us to examine a larger number of C.S.F.s from M.S. patients for virus-specific IgG antibody. Though we have found IgG antibody specific for several viruses in the C.S.F. of M.S. patients measles virus-specific IgG has predominated (Haire *et al.*, 1973 a, b), and in separate studies the prevalence has been consistent (table I).

We now present the findings of a further study in which we examined the effect of concentration of C.S.F. on the prevalence and titres of measles virus-specific IgG antibody.

Patients and Methods

C.S.F. was obtained from 31 patients with M.S., 29 patients suffering from other well-defined neurological diseases, and 15 patients undergoing myelography for suspected prolapsed intervertebral disc.

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TABLE I—*Prevalence of Measles Virus-specific IgG Antibody in C.S.F. of Multiple Sclerosis Patients in Three Study Groups*

Measles Virus IgG Antibody	Published Data: Haire *et al.* (1973 a)	Published Data: Haire *et al.* (1973 b)	Unpublished Data	Total
No. positive/No. tested	16/25	19/30	15/22	50/77
Percentage positive	64·0	63·3	68·2	64·9

The last group formed our "normal' control group. In the neurological control group there were four cases of motor neurone disease, three of neurosyphilis, three of dementia, three of polyneuropathy, three of secondary carcinomata, two of Chiari syndrome, two of syringomyelia, two of spondylosis, two of myelitis, and one of each of the following: Friedrich's ataxia, epilepsy, cerebrovascular disease, diabetic amyotrophy, and pseudobulbar palsy. The fluids were from consecutive patients from whom sufficient was available for concentration.

Specimens were stored at −20°C and were thawed once for concentration, by means of an Amicon 8-MC ultrafiltration unit with a PM-30 membrane. Each specimen was concentrated fivefold and an aliquot of the orginal material was retained for testing. Samples were refrozen and were finally tested in large experiments under standard conditions. They were examined by means of the indirect immunofluorescent technique for measles virus-specific IgG using acetone-fixed virus-infected HEp_2 cells as antigen, as previously described (Haire and Hadden, 1970; Millar *et al.*, 1971; Haire *et al.*, 1973 a). These assessments were made without knowledge of the patient's group.

To determine if measles virus-specific IgG antibody was associated with either the age or sex of the patient a study was made of the titres of measles IgG in serum from normal healthy adults, 46 men and 45 women.

Results

Though the M.S. patients and the normal control subjects were of similar average age the neurological control patients were on average significantly (at $P < 0{\cdot}05$, used throughout this report) older than either of the two other groups (table II). Though not technically significant ($\chi^2 = 5{\cdot}29$; D.F. = 2; $0{\cdot}1 > P > 0{\cdot}05$) the percentage of men was greater in the two control groups than in the M.S. group. It therefore seems reasonable to conclude that the three groups of patients were dissimilar with resepect to both average age and sex ratio. Therefore, the comparison of the results of antibody tests on the C.S.F. is valid only if measles virus-specific IgG in serum is not associated with either the age or sex of the patient. From analysis of the titres of measles IgG in 91 normal healthy adults (table III) it seems that the titre distribution did not

TABLE II—*Age and Sex of Patients in Three Study Groups*

	Multiple Sclerosis Patients	Neurological Control Patients	Normal Control Subjects
No. of patients	31	29	15
Mean age (years) ± S.E.	39·0 ± 1·85	52·1 ± 2·53	35·9 ± 3·35
Percentage men	45·2	62·1	80·0

TABLE III—*Titres of Measles Virus-specific IgG Antibody in Sera from Normal Subjects (Mean Age ± S.E. is Given in Parentheses)*

Reciprocal of Antibody Titre	Men	Women
320	-	1
160	-	1
80	8	5
	8 (41·4 ± 5·44)	7 (41·1 ± 5·02)
40	10 (34·1 ± 3·54)	7 (41·1 ± 5·16)
20	10 (45·6 ± 3·49)	14 (38·0 ± 3·03)
10	10 (34·1 ± 2·75)	10 (47·5 ± 5·05)
5	8	6
<5	0	1
	8 (39·4 ± 2·82)	7 (35·6 ± 3·37)
Total	46 (38·8 ± 1·70)	45 (40·7 ± 1·93)

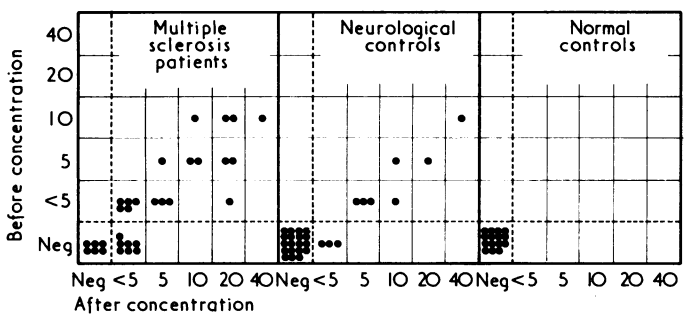
$\chi^2 = 1{\cdot}32$; D.F. = 4; $0{\cdot}90 > P > 0{\cdot}80$.

differ significantly ($\chi^2 = 1{\cdot}32$; D.F. = 4; $0.90 > P > 0{\cdot}80$) between the sexes. There was also no obvious trend in mean age within each sex in spite of the fact that there were significant differences between some of the mean ages.

The prevalence of measles IgG in the C.S.F. in the three groups both before and after concentration is shown in table IV, while the titres of antibody are shown in the diagram. The results of statistical analysis on these figures were as follows: before concentration multiple sclerosis *v.* neurological controls: $\chi^2 = 5{\cdot}77$; D.F. = 1; $0{\cdot}02 > 0{\cdot}01$. Multiple sclerosis *v.* normal controls: $P < 0{\cdot}001$. Neurological controls *v.* normal controls: $P = 0{\cdot}0765$. After concentration multiple sclerosis *v.* neurological controls: $\chi^2 = 11{\cdot}31$; D.F. = 1; $P < 0{\cdot}001$. Multiple sclerosis *v.* normal controls: $P < 0{\cdot}001$. Neurological controls *v.* normal controls: $P = 0{\cdot}0092$.

TABLE IV—*Prevalence of Detectable Measles Virus-specific IgG Antibody in C.S.F. before and after Concentration*

Patient Group	No. in Group	Measles IgG Antibody Detected: Before Concentration	After Concentration
Multiple sclerosis ..	31	18 (58·1%)	25 (80·6%)
Neurological control ..	29	7 (24·1%)	10 (34·5%)
Normal control ..	15	0	0



Reciprocal titres of measles IgG in C.S.F. in three study groups before and after concentration.

Before concentration the percentage of C.S.F.s with detectable measles IgG in the M.S. group (58·1%) significantly exceeded that in either the neurological control group (24·1%) or normal control group (0%). The difference between the two control groups just failed to reach significance at the 5% level ($P = 0{\cdot}0765$). After concentration the percentage of C.S.F.s with detectable measles IgG in the M.S. group (80·6%) significantly exceeded that of the neurological control group (34·5%), which in turn significantly exceeded that in the normal control group (0%). The increase in the prevalence of measles IgG in the C.S.F. of M.S. patients after concentration was significantly more than would have been expected by chance ($P = 0{\cdot}016$). A similar, but much less marked, trend occurred in the neurological control group ($P = 0{\cdot}25$).

Discussion

While other workers have found higher levels of measles antibody in women than in men in groups of M.S. patients, in their siblings, and in normal control people resident in the same area (Henson *et al.*, 1970; Salmi *et al.*, 1973), we did not show a sex difference of measles IgG in the serum of normal controls. Though the numbers in our study groups were small we feel that the differences in average age between our three groups of subjects did not invalidate our results.

We report now a prevalence of measles IgG in the C.S.F. of patients with M.S. of 58·1%, a rate consistent with our previous findings (see table 1). In this study, however, the prevalence of measles IgG in the C.S.F. of patients with other neurological diseases was higher than we found before, 24·1% compared with 6·7% (Haire *et al.*, 1973 b). We cannot offer an explanation but because of the small numbers the possibility that this is a chance difference cannot be overlooked. The diagnoses in the group were rather similar to those in our earlier study (Haire *et al.*, 1973 b) and we did not have a "concentrate" of patients with one clinical condition.

The significantly high increase in prevalence of measles IgG in the C.S.F. of M.S. patients as a result of the fivefold concentration compared with a lower rate of increase in the neurological control group may result from a qualitative difference between the immunoglobulins in the fluids. This may be due to the oligoclonal pattern of the IgG in the C.S.F. of the M.S. patients (Link and Müller, 1971).

Panelius and Salmi (1973) have shown measles complement-fixing and haemagglutinating-inhibiting antibody in electrophoretically separated immunoglobulin fractions of such IgG in the C.S.F. from one patient with M.S. Additional findings of this nature, including precise knowledge about the viral components responsible for the antigenic stimulus, might give further clues concerning the role of measles virus in the pathogenesis of M.S.

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