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Comparative analysis of virus-specific antibodies and immunoglobulins in serum and cerebrospinal fluid of subacute measles virus-induced encephalomyelitis (SAME) in rats and subacute sclerosing panencephalitis (SSPE)

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Summary

The intrathecal humoral immune response was analysed in patients with subacute sclerosing panencephalitis (SSPE) and Lewis rats with subacute measles virus (MV)-induced encephalomyelitis (SAME). SSPE patients as well as SAME rats revealed oligoclonal, intrathecal antibody synthesis with MV specificity. SAME rats synthesized MV-specific antibodies intracerebrally to a higher extent than SSPE patients. Although a restricted isoelectric pattern of MV-specific antibodies was detected in the cerebrospinal fluid (CSF) of SSPE patients as well as of SAME rats, the heterogeneity within clusters of immunoglobulin bands was higher in the rat specimens. Increase in the blood–brain barrier permeability for albumin was exclusively detected in SAME rats but not in SSPE patients. These data suggest that the rat model offers excellent opportunities to study the initial humoral events in MV-induced encephalitides.

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Introduction

Measles virus (MV) is the agent responsible for the induction of subacute sclerosing panencephalitis (SSPE), a chronic central nervous system (CNS) disease process associated with a persistent MV infection in the CNS. The infection is virologically characterized by restricted envelope gene expression, the absence of infectious virus particle formation and a pronounced intrathecal antiviral immune response, which fails to overcome the infection (ter Meulen et al., 1983). So far, the pathogenic mechanism which leads to MV persistence is unknown, but it has been suggested that viral antibodies play an important role in the establishment and maintenance of this infection (Fujinami and Oldstone, 1984). In tissue culture, extracellular MV antibodies can cause an antigenic modulation, which results in persistence and interferes with viral replication (Barrett et al., 1985). Similar mechanisms may be of significance in SSPE, but these cannot be evaluated in this disease since the early state of CNS infection is clinically not detectable. Therefore, these aspects can only be studied in an experimental model.

Recently, we have established a model in which a persistent MV infection in the brain of weanling Lewis rats induces a subacute measles encephalomyelitis (SAME) after an incubation period of 3 weeks to 3 months (Liebert and ter Meulen, 1987). Like in SSPE, infectious measles virus cannot be reisolated from diseased brain areas by conventional methods and the virus cell interaction reveals a restriction of MV gene expression. In infected brain cells only measles virus nucleocapsid (N) and phosphoprotein (P) can regularly be detected, whereas the levels of hemagglutinin (H), fusion (F) and membrane (M) proteins are either drastically reduced or not detectable. Since the state of MV replication is similar to the one described in SSPE, it was the aim of this study to characterize the intrathecal immune response in SAME diseased rats in comparison to SSPE. The data obtained indicate that SAME in Lewis rats represents an excellent model to evaluate the role of the intracerebral immune response in subacute CNS diseases induced by MV.

Material and methods

Patients

Serum and CSF samples from five SSPE patients were obtained from the diagnostic laboratory of our institute. The permeability of the blood–brain barrier (BBB) was assessed by determination of CSF/serum ratios for immunoglobulin G (IgG) and albumin. To evaluate local antibody synthesis in the CSF, measles virus-specific antibodies were titrated by an enzyme immunoassay (EIA) and the clonal distribution of total as well as of MV-specific immunoglobulins was analyzed by affinity-mediated immunoblot (AMI).

Animals

A panel of 20 Lewis rats suffering from different stages of SAME after cerebral inoculation with measles virus strain CAM/RBH into the left hemisphere (25 μl,

1×10^4 tissue culture (TC) ID_{50}) were selected for this study. Animals were sacrificed at different intervals after infection and serum and CSF were taken to determine CSF/serum ratios of immunoglobulin (Ig), albumin and MV-specific antibody titers. Isoelectric distribution of Ig and MV-specific antibodies was visualized by affinity-mediated immunoblot. For histopathological evaluation brain and spinal cord were fixed in buffered paraformaldehyde, embedded in paraffin and stained with hematoxylin-eosin (HE) and Luxol fast blue for myelin. Adjacent regions were snap frozen in liquid nitrogen and the distribution of MV proteins was assessed by indirect immunofluorescence on acetone-fixed cryostat sections (Liebert et al., 1986).

Virus

For infection of animals measles virus CAM/RBH was used as previously described (Liebert and ter Meulen, 1987). Viral antigen for use in EIA and AMI was prepared from Vero cells infected with the Edmonston strain of measles virus. Briefly, Vero cells showing strong cytopathic effect (CPE) 6 days post-inoculum (d.p.i.) were frozen at $-20\,^\circ$C, thawed and sedimented at $3000 \times g$ for 15 min. The supernatant (S1) was kept for purification of virus particles. The sediment was homogenized in NTE (0.1 M NaCl, 0.01 M Tris, 0.001 M EDTA) by ten strokes in a glass homogenizer and centrifuged at $3000 \times g$ for 15 min. The supernatant (S2) was pooled with supernatant S1 and loaded on a 25% sucrose cushion in NTE buffer, pH 7.4. After centrifugation (90 min, $76\,000 \times g$, 4 °C), the pellet was resuspended in NTE, homogenized with ten strokes and clarified by low-speed centrifugation (15 min, $3000 \times g$, 4 °C). The supernatant was centrifuged through 25% sucrose onto a 60% sucrose cushion (110 min, $73\,000 \times g$, 4 °C) and the visible, virus containing band on top of the cushion was collected by a syringe. To remove the sucrose, the virus band was diluted in NTE and viral antigens were pelleted for 90 min at $52\,000 \times g$. Pellets were resuspended in phosphate-buffered saline (PBS), homogenized with 20 strokes and kept at $-70\,^\circ$C until used as antigen in EIA and AMI.

Determination of albumin and immunoglobulin concentrations

Albumin concentrations were determined by rocket immunoelectrophoresis (Laurell, 1966). Immunoglobulin concentrations in serum and CSF from SSPE patients were determined by radial immunodiffusion (Mancini et al., 1964) and from rats by an EIA as described previously (Dörries et al., 1986).

State of the blood–brain barrier

The state of the blood–brain barrier was evaluated according to Reiber (1980). As a reference for the animal model CSF/serum ratios for albumin (A) and immunoglobulin (I) were determined in 19 healthy Lewis rats and the normal range was defined by adding 2 times the standard deviation to the mean values for A and I. For evaluation of the SSPE cases the normal range determined by Reiber (1980) was applied.

Enzyme immunoassay to detect measles virus-specific antibodies

A micro-enzyme immunoassay was used for determination of MV-specific titers in serum and CSF specimens from SSPE patients and diseased rats. MV antigen and Vero cell control antigen (25 µl, 100 µg protein/ml) were coated onto the surface of round-bottom microtiter plates (Immunoplates II, Nunc, Wiesbaden, F.R.G.) by overnight incubation at room temperature in coating buffer (0.05 M sodium carbonate buffer, pH 9.6). Unbound antigens were removed by washing the wells 3 times in 250 µl distilled water containing 0.1% Tween 20. Serial dilutions of serum and CSF from patients or rats in dilution buffer (0.1 M Tris-HCl, 0.4 m NaCl, 5% normal rabbit serum, 1% Tween 20, pH 7.5) were incubated in 25 µl aliquots/well for 60 min at 37°C. After a washing cycle as described MV-specific antibodies bound to the solid-phase antigen were detected by incubation with 25 µl per well of peroxidase-labeled rabbit anti-human immunoglobulin G (IgG) or rabbit anti-rat immunoglobulin fraction (Ig) antibodies (Dako Patts, Hamburg, F.R.G.) for 60 min at 37°C. After a final washing cycle peroxidase-labeled secondary antibodies were visualized by incubation at 100 µl of 0.1% *o*-phenylenediamine (OPD) and 0.03% hydrogen peroxide in 0.1 M citric acid-phosphate buffer, pH 5.0 per well for 30 min at room temperature. After stopping the enzyme reaction by addition of 50 µl of 3 M sulfuric acid, the absorbance (ABS) in each well was determined in a micro-colorimeter (Bio-Rad, Munich, F.R.G.) at 496 nm. The MV-specific titer was determined by the last dilution revealing a control antigen-corrected absorbance equal or higher than 0.2 ABS.

Calculation of specific antibody indices (AB index)

For determination of AB indices the procedure of Ukkonen et al. (1982) was followed. CSF/serum ratios of the reciprocal MV-specific antibody titers were divided by CSF/serum ratios of total IgG. Intrathecal MV-specific antibody synthesis was assumed if the AB index was equal or higher than 2.0.

Immunoblot to characterize the clonal distribution of antibodies and immunoglobulins

A modified procedure of the previously published AMI (Dörries et al., 1984) was applied to detect the distribution of total as well as MV-specific antibodies in serum and CSF.

Prior to isoelectric focusing (IEF) in an 0.5 mm agarose gel (1% IEF agarose, 6.25% Pharmalyte pH 3.0–10.0, 12% sorbitol, 1% NP-40), serum specimens were diluted to contain the same amount of Ig as the corresponding CSF sample. Focusing of 20 µl specimens, usually containing 100 ng of Ig, took place for 1000 Volthours (Vh) with a starting voltage of 500 V. The established pH gradient was monitored with a marker protein solution (Pharmacia, Freiburg, F.R.G.). After focusing any visible moisture on the gel was removed by blotting with a cellulose acetate foil for a few seconds. Subsequently the gel-fractionated antibodies were transferred to nitrocellulose strips coated either with measles virus antigen or the IgG fraction of rabbit anti-rat Ig or anti-human IgG immunoglobulins. These strips were coated overnight on a rocker platform at room temperature, usually with a protein concentration of 100 µg/ml and 1 ml/10 cm^2 of nitrocellulose area in the

case of the anti-immunoglobulin or with 500 μg MV proteins/ml and 1 ml/10 cm^2 of filter area in PBS. After coating the strips were blocked by 5% Tween 20 for 1 h at room temperature, washed briefly in PBS and used for blotting. After transfer of the antibodies to nitrocellulose by an incubation of 1 h at room temperature, the strips were removed from the gel, washed in PBS, PBS-Tween 20 (0.1%) and PBS (10 min each) and incubated in peroxidase-labeled rabbit anti-rat Ig or anti-human IgG antibodies (1 ml/10 cm^2 of filter area) diluted 1 : 100 in PBS-Tween 20 (0.1%) containing 5% of normal rabbit serum. To visualize transferred antibody clones, filters were washed as described and developed in 4-chloro-naphthol.

Results

Clinical and neuropathological findings in diseased Lewis rats

The animals exhibited various degrees of clinical disease characterized by a weight loss of 10–20%, unsteadiness, abnormal posturing and in some cases a mild paresis of one or more limbs. None of the animals reached a moribund stage. Animals 2, 3, 8 and 13 survived a mild clinically apparent subacute disease by 7–31 days. In animals 4, 9, 18 and 19 no overt clinical signs were observed (Table 1).

Histopathologically, all animals revealed a subacute measles encephalomyelitis (SAME) of varying degree characterized by perivascular lymphomonocytic infiltrations in the gray and white matter. Demyelination was not observed. Viral antigen was demonstrated using a human serum containing high titers of MV-specific antibodies specific for all viral structural proteins. Animals 7, 11, 15 and 18 showed the presence of brightly fluorescing cells in the cortex and the basal ganglia, probably large neurons and probably some glia cells. In animals 5, 13 and 14 only few weakly staining cells were detected while in the remainder of animals no measles virus-specific antigen could be seen in the sections studied. However, the failure to localize MV antigen in some animals does not exclude the presence of MV antigen, since not the entire brain was available for this analysis.

MV-specific antibodies

Serum and CSF specimens of Lewis rats or SSPE patients were tested for the presence of virus-specific antibodies by micro-enzyme immunoassay. As can be seen in Table 2, 19 out of 20 rats developed MV-specific antibodies in the serum and in 16 out of 20 animals MV-specific antibodies were detectable in the CSF. There was no correlation between the presence or titer of antibodies and the severity of the disease. All five of the SSPE patients had MV-specific antibody titers in serum as well as in the CSF and these were much higher than those of the rats (Table 3).

In SSPE it is known that most of the CSF-derived MV-specific IgG is produced intrathecally (Vandvik et al., 1976). To enable direct comparison of the SAME diseased animals with the SSPE cases, CSF/serum ratios of MV-specific antibody titers (AB_{MV}) and immunoglobulin (I) were used to calculate MV-specific antibody indices (AB index) in both groups.

TABLE 1

HISTOLOGICAL AND CLINICAL FINDINGS IN LEWIS RATS INFECTED INTRACEREBRALLY WITH MEASLES VIRUS CAM/RBH

Rat No.	Collection of specimens (d.p.i)	Clinically diseased	Histological diagnosis	Viral antigen in brain
1	87	±	SAME 1+	–
2	87	–	SAME 1–	
3	58	–	SAME 1+	
4	46	–	SAME 1+	–
5	27	±	SAME 1–	±
6	50	–	SAME 1+	–
7	21	+	SAME 2+	+
8	60	–	SAME 2+	–
9	25	–	SAME 2–	–
10	31	±	SAME 2+	–
11	31	+	SAME 3+	+
12	31	±	SAME 3–	–
13	47	–	SAME 3–	±
14	21	+	SAME 3+	±
15	27	±	SAME 3+	+
16	35	+	SAME 3+	ND
17	23	+	SAME 3+	
18	28	–	SAME 3+	+
19	25	–	SAME 3+	–
20	27	+	SAME 3+	–

Key: + = yes, ± = borderline, – = no, 1+ = mild, 2+ = moderate, 3+ = severe. ND = not done.

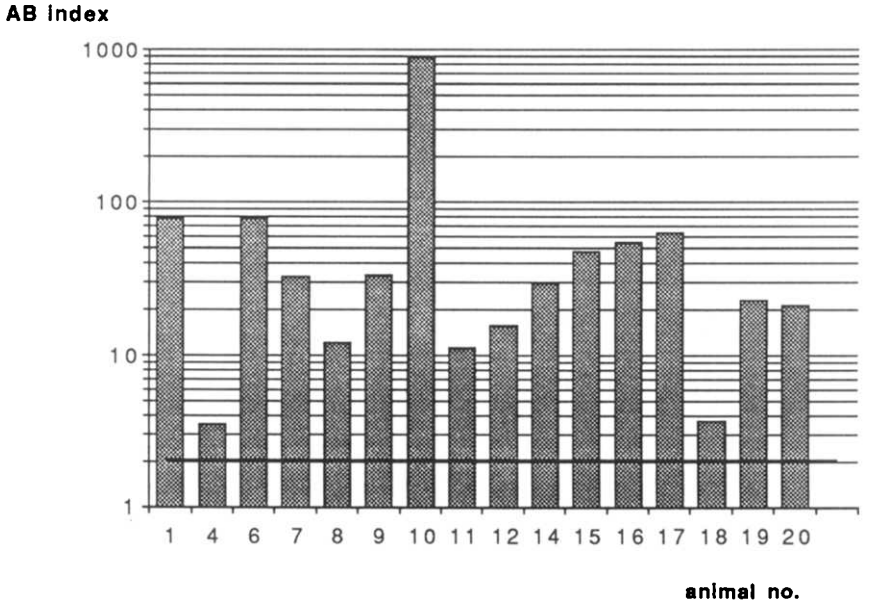

Fig. 1. Antibody indices in 20 SAME-diseased Lewis rats. The horizontal black bar indicates the cut-off value for intrathecal MV-specific antibody synthesis.

TABLE 2

VIRUS-SPECIFIC ANTIBODY TITERS IN PAIRED SERUM AND CSF SPECIMENS FROM LEWIS RATS INFECTED INTRACEREBRALLY WITH MEASLES VIRUS CAM/RBH

Rat No.	Reciprocal of EIA titers	
	Serum	CSF
1	800	40
2	200	< 10
3	200	< 10
4	3200	80
5	< 100	< 10
6	3200	640
7	400	20
8	12800	160
9	1600	640
10	400	1280
11	6400	640
12	3200	640
13	400	< 10
14	1600	640
15	1600	1280
16	1600	320
17	1600	640
18	3200	80
19	800	160
20	3200	1280

As can be seen in Figs. 1 and 2, all animals with MV-specific antibody titers in the CSF and all SSPE patients synthesized these antibodies to a significant extent intrathecally. It is remarkable that in the animal model the AB indices are much higher than in the SSPE cases, pointing to a stronger intrathecal MV-specific antibody synthesis in the animals compared to the patients.

TABLE 3

VIRUS-SPECIFIC ANTIBODY TITERS IN PAIRED SERUM AND CSF SPECIMENS FROM SSPE PATIENTS

Patient No.	Reciprocal of EIA titers	
	Serum	CSF
1	102400	10240
2	25600	640
3	25600	640
4	102400	10240
5	102400	10240

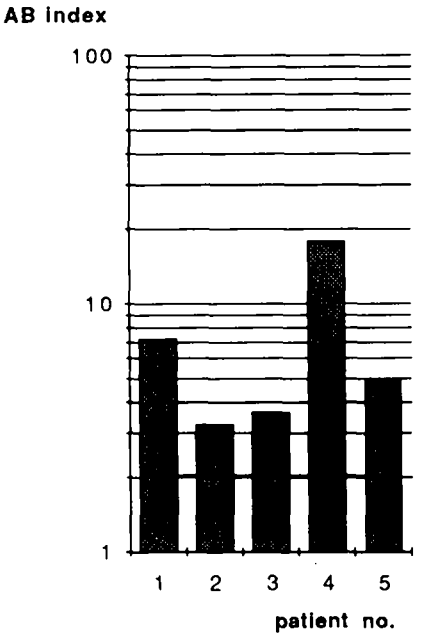

Fig. 2. Antibody indices in five SSPE-diseased patients. The horizontal black bar indicates the cut-off value for intrathecal MV-specific antibody synthesis.

State of the blood–brain barrier

In order to correlate intrathecal synthesis of MV-specific antibodies and the state of the blood–brain barrier, a graphical analysis according to Reiber (1980) was performed. Disturbances of the BBB permeability for albumin could be observed frequently in the rat group (Fig. 3). Increased permeability was detectable with normal Ig ratio (rats No. 5 and 6) or proportional increase of the Ig ratio (rats No. 7 and 16), as well as in relation to disproportional increase of the Ig ratio (rats No. 17 and 20). Intrathecal synthesis of Ig and increased permeability for albumin was found in five rats (Nos. 4, 11, 14, 15 and 18). Together, almost 50% of the animals (9/20) revealed a dysregulated BBB. Rats No. 9, 10, 12 and 19 synthesized Ig intrathecally with a normal BBB permeability, whereas rats No. 1, 2, 3, 8 and 13 were within the normal range of CSF/serum ratios for albumin and immunoglobulin. Interestingly, two of these animals (Nos. 1 and 8) produced MV-specific antibodies in the CSF, a fact which did not result in an increase of the CSF/serum ratio for Ig. No animals were observed with an intrathecal Ig synthesis in the absence of MV-specific antibody production in the CSF. As expected, all of the SSPE patients did show intrathecal increases in total IgG and intact diffusion control by the BBB (Fig. 4).

Isoelectric patterns of total and MV-specific antibody clones

One of the most prominent immunological markers of SSPE is the marked oligoclonal distribution of MV-specific antibodies in the CSF. To analyze this

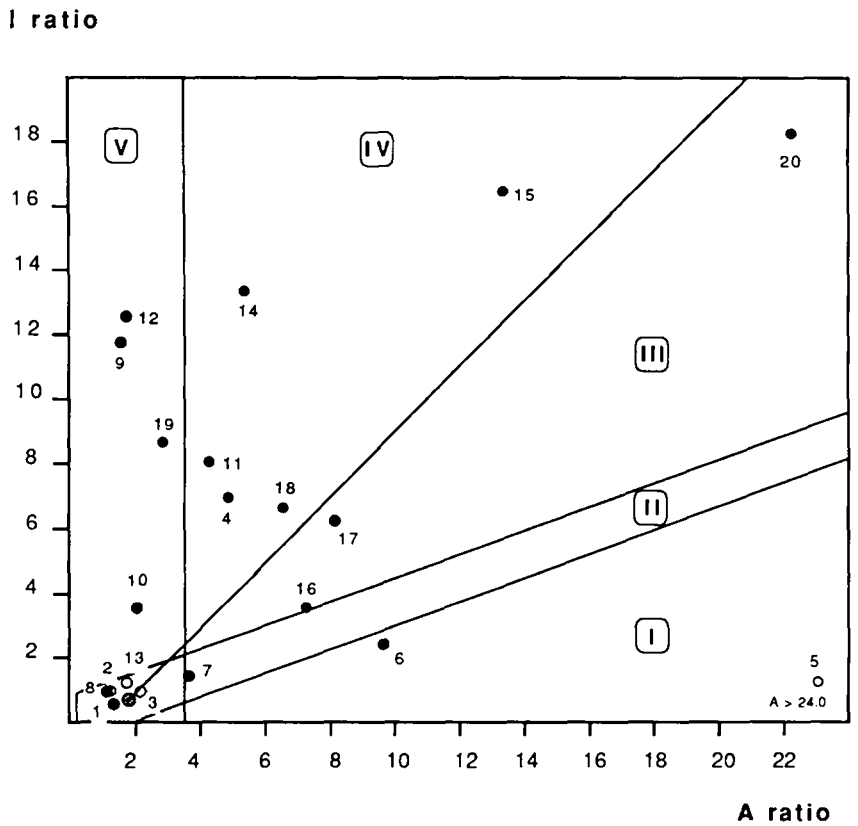

Fig. 3. CSF protein profile of 20 Lewis rats infected intracerebrally with measles virus CAM/RBH. A = CSF/serum ratios for albumin $\times 10^3$; I = CSF/serum ratio for immunoglobulin $\times 10^3$; area I = disproportional increase of the BBB permeability for albumin; area II = proportional increase of the albumin and immunoglobulin permeability; area III = increased permeability for albumin either in conjunction with intrathecal Ig synthesis or disproportional increase of the Ig diffusion; area IV = increased permeability for albumin and intrathecal Ig synthesis; area V = normal permeability for albumin and intrathecal Ig production; ● = intrathecal MV-specific antibody synthesis; ○ = no intrathecal MV-specific antibody synthesis.

aspect an affinity-mediated immunoblot (Dörries et al., 1984) was applied. Two representative patterns are shown in Figs. 5 and 6.

Distinct differences were noticeable between oligoclonal antibody patterns of serum and CSF specimens obtained from SAME Lewis rats (Fig. 5) and SSPE patients (Fig. 6). MV-specific antibody clones focus more cathodically and individual bands are more prominent in the SSPE cases than in the SAME rat samples. However, clusters of antibody bands were observed in both diseases. Moreover, fainter staining of antibody bands in the paired serum specimen as compared to the CSF, verified intrathecal synthesis of MV-specific antibodies in SAME rats and SSPE patients, also demonstrated above by calculation of AB indices (Figs. 1 and

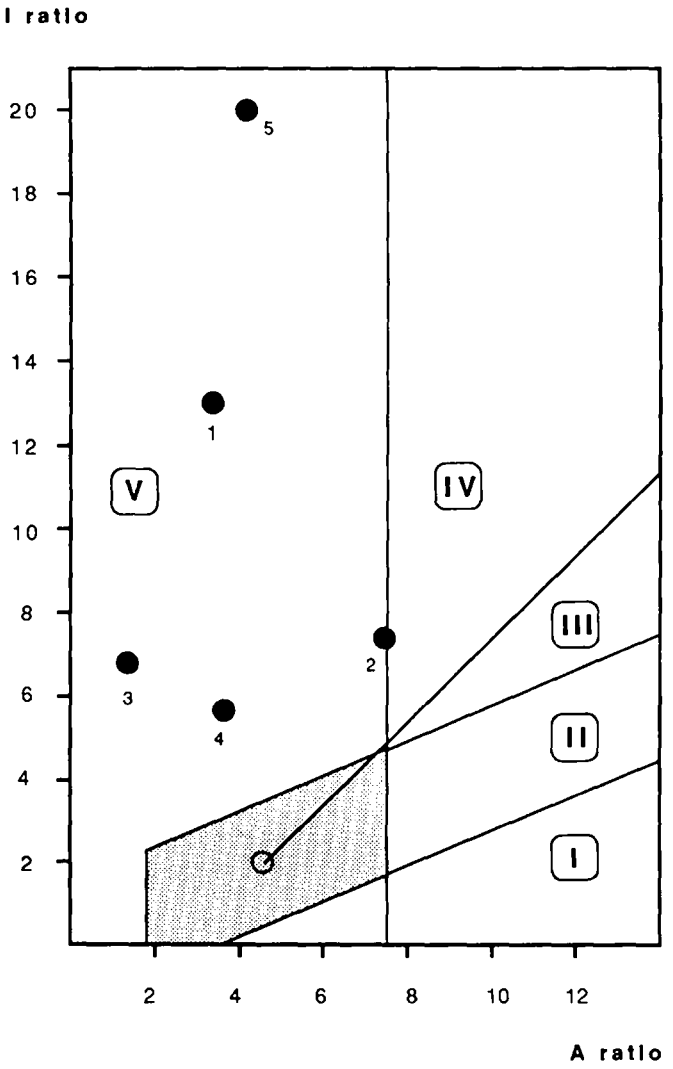

Fig. 4. CSF protein profile of five SSPE patients. A = CSF/serum ratios for albumin $\times 10^3$; I = CSF/serum ratio for immunoglobulin $\times 10^3$; area I = disproportional increase of the BBB permeability for albumin; area II = proportional increase of the albumin and immunoglobulin permeability; area III = increased permeability for albumin either in conjunction with intrathecal Ig synthesis or disproportional increase of the Ig diffusion; area IV = increased permeability for albumin and intrathecal Ig synthesis; area V = normal permeability for albumin and intrathecal Ig production; ● = intrathecal MV-specific antibody synthesis.

2). The focused Ig patterns detected in clinically severely diseased rats were not distinguishable from those with a mild disease or from clinically healthy, but histopathologically severely diseased animals.

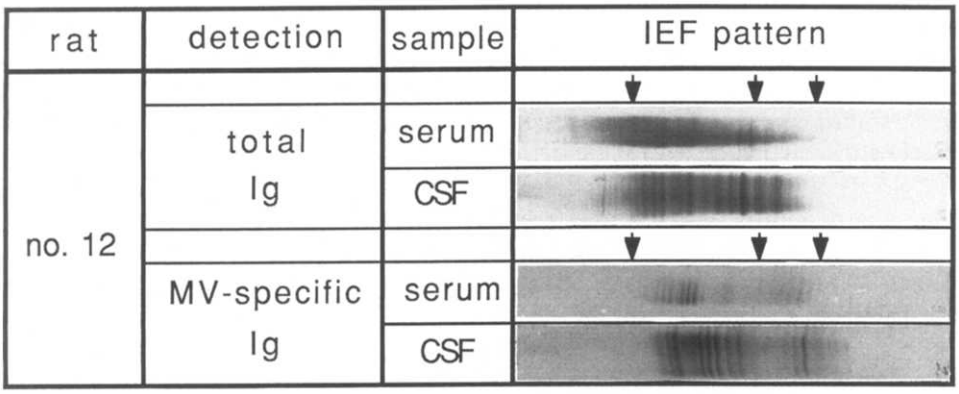

Fig. 5. Affinity-mediated immunoblot of immunoglobulin and MV-specific antibodies in the CSF and serum of an SAME-diseased Lewis rat. Arrows indicate the established pH gradient, from left to right: pH 6.6, 8.2, 8.7. Amount of Ig focused: 100 ng of serum or CSF-derived Ig per track to develop the total Ig pattern and 200 ng of serum or CSF-derived Ig per track to develop the MV-specific antibody pattern.

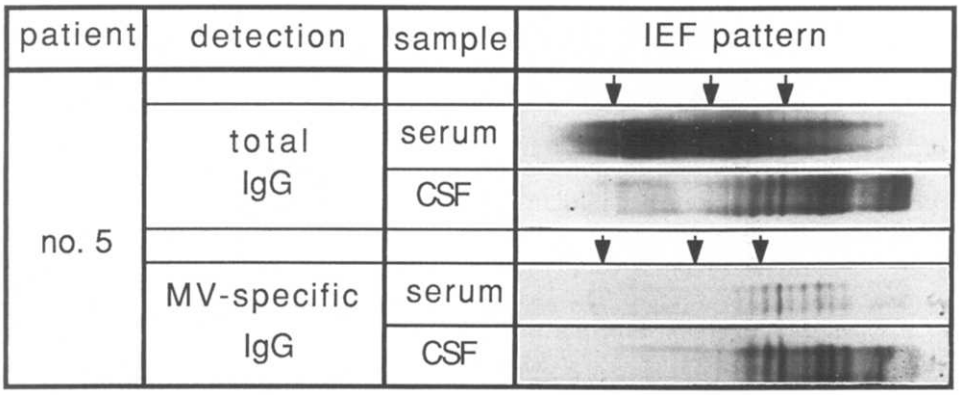

Fig. 6. Affinity-mediated immunoblot of immunoglobulin and MV-specific antibodies in the CSF and serum of an SSPE patient. Arrows indicate the established pH gradient, from left to right: pH 6.6, 8.2, 8.7. Amount of Ig focused: 100 ng of serum or CSF-derived Ig per track.

Discussion

In this study, paired serum and CSF samples were used to compare measles virus-induced subacute encephalomyelitis of Lewis rats (SAME) and SSPE. The state of the BBB was analyzed and MV-specific antibodies were characterized with respect to titers, site of synthesis and isoelectric distribution.

MV-specific antibody titers in patients suffering from SSPE were extraordinary high in serum as well as CSF, a finding which is well known (ter Meulen et al., 1983). A similar phenomenon occurred in MV-infected rats. Almost all SAME rats developed significant MV-specific titers in serum and CSF, but not to the same high levels as observed in SSPE samples. However, with respect to MV-specific AB

indices, rats revealed much higher ratios than SSPE patients, indicating a very strong intrathecal synthesis of MV-specific antibodies in the animals. This result suggests that SAME in rats represents probably the early events of a subacute MV-induced encephalitis, whereas SSPE reflects the late consequences of a subacute encephalitis, characterized by the presence of a few CNS-residing, antibody-secreting B cell clones, highly selected over the years by the persistent presence of a restricted pattern of MV-specific proteins in brain cells.

Correlation of these data to the graphic analysis of the state of the BBB revealed that in SAME rats as well as in SSPE patients no increase of the CSF/serum ratio for Ig could be detected in the absence of an increased ratio for MV-specific antibody titers. For SAME rats this observation holds true whether the animals had an intact or disturbed BBB permeability. This observation seems to rule out the possibility that beside MV-specific antibodies, non-virus-specific antibodies have been produced in significant amounts in the CNS. This is in contrast to coronavirus JHM-induced encephalomyelitis in Lewis rats. In this model, JHM virus causes extensive primary demyelination in the CNS which is sometimes accompanied by an intrathecal synthesis of non-virus-specific immunoglobulins of restricted heterogeneity in the absence of JHM-specific antibody clones (Dörries et al., 1986). Whether these non-viral antibodies are directed against brain antigens as described in canine distemper virus-induced demyelinating encephalitis of dogs (Krakowa et al., 1973; Vandevelde et al., 1982a, b) or Theiler's virus encephalomyelitis in mice (Rauch et al., 1987) is presently unknown.

An intrathecal MV-specific antibody response of oligoclonal nature has also been reported in another animal model of MV-induced subacute encephalitis in ferrets (Thormar et al., 1983, 1985; Mehta and Thormar, 1986). However, the development of this subacute encephalitis could only be detected in animals which were pre-immunized with an MV vaccine. The necessity for pre-immunization in order to obtain a persistent MV infection of brain tissue is surprising, since SSPE has never been observed in children after MV vaccination (ter Meulen et al., 1983). On the contrary, MV immunization seems to prevent this chronic human CNS disease (Halsey et al., 1978).

Another interesting aspect is the observation that the intrathecal production of MV-specific antibodies in SAME rats is not always connected with an increase of the CSF/serum ratio for total Ig, a finding shared with mumps meningitis in man (Link et al., 1981; Ukkonen et al., 1981) and coronavirus-induced encephalomyelitis in Lewis (Dörries et al., 1986) and BN rats (Dörries et al., 1987). Obviously the amount of virus-specific antibody produced is not sufficient to result in an increase of the CSF/serum ratio of total Ig. Therefore, an intact BBB and a normal CSF/serum ratio for total Ig does not exclude the possibility of intrathecal synthesis of virus-specific antibodies in persistent CNS infections.

Analyzing the isoelectric distribution of Ig and MV-specific antibodies in serum and CSF samples, SSPE-derived specimens revealed the typical oligoclonal banding of IgG in the alkaline region of the pH gradient. According to the classification of Tourtellotte (1983) these bands would be assigned to area III (pH 8.2–9.3) of the pH gradient. This is the area where oligoclonal IgG bands from most inflammatory

disorders of the CNS in man are detected. To date, there is no satisfying explanation for this clustering of oligoclonal bands in the alkaline area of the pH gradient. As discussed by Walsh et al. (1987), the passage of proteins through the blood–brain barrier in man might be facilitated largely by a strong negative net charge. This could favor the entry of those B cell clones into the CNS, which carry surface immunoglobulins with alkaline isoelectric points.

Most, if not all, of the oligoclonal bands could be characterized in SSPE as MV-specific and parallel focusing of the same amount of serum and CSF-derived IgG verified that MV-specific Ig clones were synthesized for the major part in the CSF. Although SAME rats showed similar results, subtle differences were detectable concerning the isoelectric distribution of MV-specific bands. As in SSPE, clusters of focused bands were detectable, but the heterogeneity within these clusters seems to be higher in CSF of SAME rats. This again supports the interpretation that SAME in rats is reflecting the early stages of a subacute encephalitis, where infiltrating B cell clones are not yet selected as in SSPE. Moreover, CSF clones in rats were detected predominantly in area II (pH 7.3–8.2) of the gradient. Since the same observation has been made in coronavirus-induced subacute encephalomyelitis in Lewis and BN rats (Dörries et al., 1986, 1987), and Ig clones from serum usually do not focus at higher pH values, it seems that rat immunoglobulins are confined to a narrower pH band than human antibodies.

In conclusion, SAME in Lewis rats appears a promising model for the study of the intrathecal, humoral immune response during the course of an MV-induced subacute encephalomyelitis. In view of similarities between SAME and SSPE with respect to the virus-specific CNS-resident antibody response and the restriction of expression of MV-specific genes in the infected brain tissue, this animal model will provide the opportunity to obtain insight into the potential role of the MV-specific antibody response in the CNS as a modulating factor in chronic persistent MV infection of the brain cells.

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