Journal of Neurology, Neurosurgery, and Psychiatry 1989;**52**:578–582

Antiviral IgM and IgG subclasses in varicella zoster associated neurological syndromes

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SUMMARY The varicella zoster virus (VZV) and herpes simplex virus (HSV) IgGl-4 subclasses were compared in serum and cerebrospinal fluid (CSF) of 22 patients with VZV-associated neurological symptoms, 12 patients with HSV-associated neurological symptoms and 14 controls. The clinical syndromes of the VZV-associated diseases comprised meningo-encephalitis, myelitis, myelopathies and polyneuropathies, mostly with a favourable outcome. A characteristic finding was an intrathecal synthesis of VZV IgGl and HSV-3. Commonly also IgG2 and 4 were seen in CSF of VZV patients. Their intrathecally synthesised HSV IgG was restricted to IgGl. VZV IgG3 occurred in serum and/or CFS together with VZV IgM in 14 cases and may be a marker of recent VZV replication. In patients with HSV-associated neurological disease, a multi-IgG subclass HSV response and concomitant VZV antibodies restricted to IgGl was found. Intrathecal synthesis of both HSV and VZV IgG occurred in 20 patients. Detection of two or more VZV or HSV specific IgG subclasses synthesised intrathecally identified the aetiological agent in 19 of these 20 cases.

Varicella zoster virus (VZV) causes chicken-pox in children and herpes zoster in the elderly. Overt neurological disease is less common but subtle findings of CNS involvement are readily detectable. Gibbs *et al* found an abnormal EEG in 22% of uncomplicated cases of varicella.[1] Neurological complications of varicella infections, primary and reactivated, include meningitis, encephalitis, myelitis and post-infectious polyradiculopathy.[2–5] Meningitis, encephalitis and some cases of myelitis are thought to reflect a viral CNS infection, while myelo-radiculopathy, late cerebellar signs (with prominent vertigo and ataxia) and polyneuropathy are post-infectious complications.[5,6] A rare complication of ophthalmic zoster associated VZV meningoencephalitis is an arteritis of the cerebral vessels that can cause ischaemic damage to the brain.[7,8]

In herpes simplex encephalitis (HSVE), the intrathecal herpes simplex virus (HSV) specific IgG is dominated by IgGl but almost all HSVE patients also have IgG3 and sometimes IgG4.[9] These patients often show a concomitant IgGl restricted intrathecal VZV IgG synthesis. The common finding of stimulated VZV and HSV IgG synthesis in HSV and VZV infections of the CNS warrants further studies to differentiate antigen specific and non-specific responses. For this reason we compared VZV and HSV IgM and IgG subclasses in serum and CSF and analysed them with regard to the clinical findings of patients with neurological symptoms linked to VZV infections or reactivations. For comparison, neurologically asymptomatic persons and HSV infected patients were analysed.

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Received 2 September 1988 and in revised form 8 December 1988. Accepted 19 December 1988

Material and methods

Patients (table)

Group I (VZV associated neurological disease)

Samples of serum and cerebrospinal fluid (CSF) from 22 patients were studied. Excluding the two varicella patients aged 12 and 11 years, the mean age was 68 years. Fourteen of the 22 patients were females. The patients were admitted to hospital because of VZV infection and/or neurological disease. A VZV infection was confirmed by conventional serology. Either a fourfold titre rise of VZV IgG antibodies, or specific IgM antibodies in serum or CSF, or a high titre of VZV IgG[10] antibodies and simultaneous VZV IgM antibodies was considered diagnostic. Six patients did not fulfil the criteria of IgM or a titre rise but had cutaneous

Table *Presentation of the patients with VZV intrathecal IgG synthesis, HSV intrathecal IgG synthesis and the healthy controls*

Patient no	*Neurological symptoms*	*Age*	*sex*	*IgM (VZV)*	*VZV IgG 1*	*2*	*3*	*4*	*HSV IgG 1*	*2*	*3*	*4*
VZV IgG associated disease (GROUP I)												
1	T8 zoster local myelopathy	57	M	—	++	0	++	++	+	0	0	0
2	C6 zoster local myelopathy	62	M	s, csf	+	++	+	+	0	0	0	0
3	Polyneuropathy	75	F	—	++	++	++	+	++	++	++	+
4	T10 zoster polyneuropathy	80	F	—	++	++	+	++	+	0	+	+
5	VZV-meningitis	11	F	s, csf	++	0	+	0	0	0	0	0
6	VZV-meningitis	71	M	s, csf	++	0	++	++	++	0	+	0
7	VZV-meningitis	76	F	s, csf	++	0	+	++	++	0	+	0
8	VZV-meningitis and N VII palsy	25	M	s, csf	++	0	++	+	0	0	0	0
9	Facial zoster encephalitis, later ataxia and vertigo	75	M	s, csf	++	++	+	+	++	0	0	0
10	Facial zoster encephalitis, later polyneuropathy, ataxia, vertigo	74	M	s, csf	++	++	+	+	++	0	0	0
11	Facial zoster encephalitis	73	F	s, csf	++	+	++	+	++	0	0	0
12	Facial zoster encephalitis	81	F	s, csf	++	0	++	0	++	0	0	0
13	Retinal necrosis encephalitis	50	M	s, csf	++	0	+	++	0	0	+	+
14	Retinal necrosis meningitis	57	F	s, csf	++	0	++	++	+	0	0	0
15	Meningoencephalitis lumbar zoster	41	F	—	+	0	+	0	+	+	+	+
16	Meningoencephalitis zoster (NV:3)	67	F	—	++	0	0	0	+	0	+	0
17	Meningoencephalitis zoster (NV:1), cortisone	76	M	s, csf	++	0	0	0	+	+	0	+
18	Meningoencephalitis zoster (NV:1)	87	F	s, csf	++	++	++	0	+	0	+	0
19	Meningoencephalitis zoster (NV:1)	83	F	—	++	+	++	0	++	0	+	0
20	Meningoencephalitis zoster, (NV:1), fatal outcome	78	M	s	++	++	++	+	+	0	+	+
21	Meningoencephalitis zoster oticus, later ataxia and vertigo	73	F	s, csf	++	++	++	0	+	0	+	+
22	VZV meningitis	12	F	s	+	—	—	—	—	—	—	—
HSV IgG associated neurological diseases (GROUP II)				*HSV IgM*								
21	Myelitis	56	M	s	++	0	0	0	++	0	++	+
22	Meningitis	9	F	—	+	0	0	0	++	0	++	++
23	Encephalitis	68	M	s	0	0	0	0	++	++	++	++
24	Encephalitis	63	F	s	++	0	0	0	++	++	++	++
25	Encephalitis	68	M	—	++	0	0	0	++	0	++	++
26	Encephalitis	67	F	—	++	0	0	0	++	0	+	++
27	Encephalitis	48	M	—	++	0	0	0	++	++	++	++
28	Encephalitis	46	F	s	++	0	0	0	++	0	++	0
29	Encephalitis	57	M	s	++	0	0	0	++	++	++	++
30	Encephalitis	45	F	s, csf	++	0	0	+	++	0	++	0
31	Encephalitis	20	F	s	++	0	0	0	++	0	++	++
32	Encephalitis	57	F	s	++	0	0	0	++	0	++	0
Controls n = 14, 6 M, age all VZV and HSV seropositive No of respective +, no ++ found					14	0	12	8	9	0	0	1

The diagnosis are summarised; age is given as is sex. M denotes males and F females.
Detected IgM in serum (s) and cerebrospinal fluid (csf) is shown. HSV IgM was not found in patients 1–14 and VZV IgM was not found in patients 15–27.
Intrathecal IgG synthesis of a specific antiviral IgG subclass is denoted by ++, mere detection without intrathecal synthesis demonstrated by +. 0 implies that a particular subclass was not detected.
All patients in group I had intrathecal VZV IgG synthesis of total IgG and very high VZV IgG titres. VZV IgM was found in some patients. In group II all patients except patient 27 had total HSV IgG synthesis intrathecally. Significant titre rises for HSV were seen in all group II patients. HSV IgM was detected in one CSF sample and in 9 sera. HSV antigen was demonstrated by immunofluorescence in brain biopsies from patients 17, 25 and 26.

manifestations typical of VZV reactivation in addition to high VZV IgG titres. Altogether, a majority of the patients had a history of recent varicella (two patients) or herpes zoster (15 patients). The time between the initial cutaneous manifestations and the debut of neurological symptoms was 1–20 days. Samples of serum and CSF were usually collected within 3 weeks after onset of neurological symptoms. In three patients (nos 1, 3 and 4) the time interval was 1 to 6 months.

Patient no 17 received cortisone for rheumatoid arthritis and patient no 15 was treated with azathioprim for systemic lupus erythematosus. These two patients and patient no 2 received therapy with acyclovir during the course of the acute zoster infection. The other patients were not immunocompromised.

Twelve patients developed meningoencephalitis following herpes zoster, usually with cranial localisation, and two during the course of varicella. In two patients with meningoencephalitis, no zoster eruption had been observed (no 6 and 7). The CNS symptoms ranged from meningeal irritation and confusion to coma (no 20). Cerebellar signs with vertigo and ataxia were detectable in seven patients. Most patients returned to their previous lives with no or minimal deficits. Patients no 6 and 10 developed myelitis and cerebellar degeneration respectively during the convalescence and

became dependent on assistance. Patient no 20 died from the acute encephalitis. A myelitis and/or polyneuropathy was the presenting clinical picture in patients no 1–4. Clinical signs were detected 20 days to 3 months after a herpes zoster. The outcome was excellent in two patients, while moderate disability remained in two. The initial disease manifestation of two patients was a retinal necrosis, 13 and 18 days before debut of meningoencephalitis. Their vision remained impaired and patient no 14 was left with a moderate hemiparesis.

Group II (HSV associated neurological disease)
Samples of serum and CSF were also obtained from 12 patients with HSV associated neurological disease. The mean age was 50 years. Seven patients were females. Ten patients had a focal frontotemporal encephalitis with a typical clinical picture, including a characteristic EEG-pattern and/or a lesion of the temporal lobe detectable by computed tomography. Two further patients had an aseptic meningitis and a myelitis, respectively. The diagnoses were confirmed during the acute phase of the disease with demonstration of intrathecal production of HSV IgG. In three patients HSV was detected by isolation and/or IF on brain biopsy specimens. Samples for specific IgG subclass analysis were obtained 4 to 18 days after the onset of neurological symptoms. Additional samples from patients no 26 and 31 were taken during follow up 3 months and 1 year after the encephalitis, respectively. All patients with encephalitis were treated with acyclovir. Five HSVE patients and the patient with meningitis had a good outcome with no or minor sequelae. There were no deaths but five HSVE patients had remaining moderate-severe focal symptoms. The patient with myelitis remained quadraplegic.

Group III (neurologically normal patients)
Serum and CSF from 14 patients, eight females, mean age 57, were chosen as controls. All were VZV and HSV seropositive. The patients were neurologically normal and the samples were collected in connection with spinal anaesthesia for orthopaedic surgery.

Antibody assays
The IgG subclass ELISAs for HSV, VZV and cytomegalovirus (CMV) IgG have been described previously.[11] Briefly, microplates (Nunc Immunoplates I, Nunc, Aarhus, Denmark) were coated with CMV, HSV or VZV antigen. One hundred microlitres of the samples, diluted 10-fold in ELISA buffer starting at 10^{-1} for CSF and at 10^{-2} for serum, was added to the plates. After washing, monoclonal mouse antihuman IgG1–4 antibodies were added. The anti-IgG2 clone HP 6014 (Center of Disease Control, Atlanta, Ga.) was used in a dilution of 1:50.000. The other ascitic antibodies, from Seward Laboratories (London, UK), were used in the following dilutions: for IgG1 (clone NL16) 1:2000, for IgG3 (ZG4) 1:2000 and for IgG4 (RJ4) 1:800. The second antibody, horseradish-peroxidase (HRPO)-labelled rabbit antimouse Ig (Dako, Copenhagen, Denmark) developed a colour reaction with orthophenylenediamine (OPD, Dako). The optical density (OD) at A490 nm was read in a Dynatech MR600 (Arlington, VA.). The highest interassay coefficient of variation for any subclass was 0·15. All samples from any one patient were tested simultaneously. A μ-capture ELISA with rabbit antihuman μ-chain immunoglobulin (Dako) and peroxidase labelled VZV antigen (National Bacteriological Laboratory, Stockholm, Sweden) was used to detect VZV IgM. For HSV IgM detection, samples were treated with RF-absorbance (Behringwerke, Marburg, West Germany) and assayed in an ELISA with HSV nucleocapsid antigen prepared from Vero cells and peroxidase labelled rabbit antihuman μ-chain Ig (Dako).

For detection of intrathecal IgG synthesis the blood brain barrier was evaluated both by analysis of a reference antiviral IgG, CMV and/or measles,[12] and by comparisons between the antiviral IgG subclasses where CMV again served as a reference IgG, as described previously.[9] Briefly, serum samples were compared with corresponding CSF samples diluted 100-fold less. An identical or higher OD value for a specific antibody was taken to show intrathecal synthesis of that antibody provided the brain blood barrier was intact.

Results

Group I (VZV associated neurological disease)
VZV IgG1 was detected in serum and CSF of all 22 patients; 12 patients had VZV IgG2, 19 had VZV IgG3 and 13 had VZV IgG4 in serum and CSF (table). Intrathecal anti VZV IgG synthesis of at least two IgG subclasses was detected in all immunocompetent patients studied between days 7 and 21 after onset of neurological symptoms (table). Intrathecal VZV IgG1 synthesis was detected in 19 patients, IgG2 in eight, IgG3 in 12 and IgG4 in six. Of the 10 patients not showing VZV IgG3 synthesis in CSF, seven had an interval of <1 week and two an interval of $\geqslant 4$ weeks from the onset of neurological signs to the sampling. Intrathecal VZV IgG synthesis of any subclass was undetectable in two patients (nos 15 and 22). These samples were obtained 2 days after onset of neurological symptoms. The same was true for patient no 17, only producing intrathecal VZV IgG1. In patients no 1, 3 and 4, whose samples were obtained 1 to 6 months after the onset of neurological symptoms, an intrathecal production of three or four anti VZV IgG subclasses was detected. A comparison of intrathecally synthesised anti VZV IgG subclasses was made between patients with zoster and meningoencephalitis who developed degenerative cerebellar signs or radiculopathy or presented with such symptoms and those who did not develop such complications. VZV IgG2 was more common in the former group ($p < 0{\cdot}05$ Fischer's exact test) than in the other. Significant differences were not found for anti VZV IgG1, 3 or 4.

VZV IgM was found in serum and/or CSF from 16 patients. Three of the six patients not showing VZV IgM suffered from postherpes zoster myelopathy and/or polyneuropathies (nos 1, 3 and 4). Their samples

were collected late in the course of neurological disease (after 1–6 months). In the remaining three patients (nos 15, 16 and 19) samples were obtained 6, 2 and 9 days after the vesicular eruption.

Nine of 17 HSV seropositive patients had intrathecally synthesised HSV IgG of low titre. This was not linked with other signs of HSV disease, an anti-HSV IgG titre rise or anti-HSV IgM. The intrathecal synthesis of HSV IgG was restricted to IgG1 in eight of nine patients. Patient no 3 with polyneuropathy also had HSV IgG2 and IgG3 synthesis.

Group II (HSV associated neurological disease)
Ten out of 12 patients had intrathecal VZV IgG synthesis restricted to IgG1. HSV IgG1 were found in all 12 patients, IgG2 in four and IgG4 in nine. HSV IgG1 was intrathecally synthesised in 12 patients, IgG2 in four, IgG3 in 11 and IgG4 in eight. The HSV IgG1–4 absorbance levels in both serum and CSF were significantly higher ($p < 0.05$ Mann Whitney) than the absorbance values for HSV antibodies in group I and in the controls. Patients no 26 and 31 showed an unchanged pattern of intrathecal HSV IgG1, 2, 3 and 4 synthesis at follow-up after 3 months and 1 year, respectively.

Control patients
VZV IgG1 was found in all 14 sera and in nine CSF samples. VZV IgG2 or 3 were not detected in any CSF samples; one control patient had VZV IgG4 in the CSF. HSV IgG1 was found in all serum and CSF samples. HSV IgG2 was not found in serum or CSF. Twelve patients had HSV IgG3 and eight had IgG4 in the CSF. Neither specific intrathecal VZV, HSV antibody synthesis nor specific IgM was found in the controls.

Subclass IgG and IgM differences between patient groups
Simultaneous anti-HSV IgG1 and anti-VZV IgG1 synthesis was common in both group I and II, although the IgG1 antibody directed against the respective pathogenic virus usually showed higher OD values than the non-specific IgG1. Quantitative analysis of intrathecally synthesised anti-VZV and anti-HSV IgG would have allowed a correct diagnosis only in 12/36 patients from groups I and II. In particular, the detection of intrathecally synthesised VZV IgG1 was similar in groups I and II ($p > 0.9$, Fisher's exact test). A differentiation between the groups was, however, possible by analysis of anti-VZV and HSV IgG subclasses. Intrathecal synthesis of two or more VZV or HSV IgG subclasses correlated with the respective pathogen ($p < 0.01$, Fisher's exact test). A combination of the two analyses (first total IgG followed, if necessary, by IgG subclasses) allowed a diagnosis in 33/36 of the patients. Of the remaining patients, only early samples were available from two and late samples from one. Further, VZV IgM in CSF correlated with intrathecal synthesis of VZV IgG1 and 3 ($p < 0.05$, Fisher's exact test), while HSV IgM in serum correlated with intrathecal synthesis of HSV IgG1, 3 and 4 in the patients with neurological symptoms. Eight out of 22 patients with VZV disease had both VZV IgM and intrathecally produced VZV IgG3.

Discussion

The present study demonstrated that neurological symptoms of VZV infection were strongly associated with intrathecal synthesis of two or more VZV IgG subclasses. The neurological complications occurred in a close temporal relationship with a clinical and serologically confirmed cutaneous VZV infection in 14/22 patients. In these patients, intrathecally produced IgG1 was usually detected already at the onset of neurological symptoms. It was followed by IgG3 and less commonly by IgG2 and IgG4. The results indicated that intrathecal VZV IgG1 synthesis was followed by production of VZV IgG3 within two weeks. A concomitant HSV IgG synthesis in these patients was restricted to IgG1. Intrathecally produced VZV IgG3 and IgM appeared simultaneously in CSF from patients with acute meningoencephalitis. This simultaneous occurrence shows that intrathecal VZV IgG3 is a marker of a recent VZV reactivation in CNS, as it is of VZV infection peripherally.[11]

We found intrathecally produced VZV IgG subclasses of more than one IgG subclass in three of four patients with VZV associated syndromes occurring 1 month to 3 months after the VZV cutaneous eruption. The fourth patient with polyneuropathy showed intrathecal synthesis also of HSV IgG subclasses. The characteristic VZV IgG subclass development was also found in samples from patients with meningoencephalitis without any known cutaneous VZV infection and in those with a retinal necrosis heralding the meningoencephalitis. Thus, the VZV IgG subclass findings in these patients did not deviate from the findings in the 14 patients with a close temporal relationship between cutaneous and neurological VZV symptoms.

The study included 22 patients with various VZV associated neurological complications. A recent VZV infection could be diagnosed on the basis of serological confirmation and/or detection of clinical cutaneous VZV infection in all 22 patients. Most patients presented with neurological symptoms in close connection with an acute VZV infection, while 8/22 were investigated because of neurological symptoms of uncertain origin. Two patients had a VZV infection during the preceding months and two had a retinal necrosis preceding the neurological disease. Two patients had meningoencephalitis as the only

symptom. Five patients either presented with or developed late neurological complications, with polyneuropathy, myelitis and/or cerebellar degeneration. Such postinfectious symptoms usually occur, as in our patients, 3 weeks to 3 months after the VZV infection.[5] Two out of six patients in this category were left with neurological deficits. The high proportion of such late complications of VZV reactivation/infection probably had to do with the selection of patients. Retinal necrosis is a known complication of cytomegalovirus (CMV) infection. Our patients with retinal necrosis (nos 3 and 14) had no evidence of ongoing or recent CMV infection serologically. The retinal necroses were diagnosed as manifestations of reactivated VZV infection. One patient (no 14) was left with a hemiplegia, the cause of which could be VZV arteritis producing contralateral hemiplegia, an uncommon complication of herpes zoster ophthalmicus.

IgG2 was more common among patients with severe postvaricella zoster syndromes than in patients with uncomplicated meningoencephalitis ($p < 0.05$ Fisher's exact test). This difference seemed to be restricted to IgG2 and did not concern IgG3 and IgG4 irrespective of the time interval from onset of neurological symptoms. This finding comes from just a few patients and further studies are necessary to establish an etiological relationship.

Patients with neurological disease caused by HSV were recently shown to have a multi-IgG subclass anti-HSV response and a concomitant production of VZV IgG restricted to IgG1, intrathecally.[9] The restriction of non-specific antibody to IgG1 was helpful for ruling out a VZV infection in the serological diagnosis of HSVE. In VZV associated disease the VZV and HSV IgG subclass patterns were reversed. We suggest that either of a simultaneous VZV or HSV IgG1 response may be due to polyclonal B-cell activation or the few cross-reacting antigens present,[13-15 19] whereas an IgG multi-subclass response reflects actual antigen stimulation from replicating virus. It was recently shown that in multiple sclerosis, an inflammatory disease with polyclonal B-cell stimulation,[17] the antiviral antibodies synthesised in the CNS are restricted to IgG1.[16 17]

The present study underlined the necessity of studying intrathecal synthesis of anti VZV IgG in the investigation of meningoencephalites, myelopathies and neuropathies. The mere detection of intrathecally synthesised anti-VZV IgG does not necessarily confer diagnostic specificity. VZV and HSV subclass analysis appears to differentiate VZV and HSV infection of the nervous system. IgG subclass analysis also against other antigens will probably aid the future diagnosis of neurological diseases. We suggest that analysis of specific antiviral IgG subclasses should be undertaken if preliminary studies on specific IgG and IgM are inconclusive. The analysis requires an additional incubation with subclass specific antibodies; this may seem costly but should be technically feasible at any diagnostic laboratory.

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