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Original Article

Human herpesvirus infection in drug-induced hypersensitivity syndrome, toxic epidermal necrolysis and Stevens–Johnson syndrome

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Abstract

Background: Reactivation of human herpesvirus (HHV) infection, especially HHV-6, has been observed in patients with drug-induced hypersensitivity syndrome (DIHS). In toxic epidermal necrolysis (TEN) and Stevens–Johnson syndrome (SJS), the relevance of HHV infection to the symptoms is unclear.

Methods: Patients with a diagnosis of DIHS ($n = 7$), TEN ($n = 5$) and SJS ($n = 4$) were included in the present study. These patients were evaluated for the presence of active HHV-6, HHV-7 and cytomegalovirus (CMV) infections by serological tests and polymerase chain reaction with blood.

Results: More than 3 weeks after the onset of DIHS, HHV-6 serological tests revealed a remarkable rise in IgG antibodies in six patients, including one treated without steroids. Human herpesvirus-6 DNA was detected in blood from three patients. In one patient with DIHS, reactivation of CMV was shown without reactivation of HHV-6, whereas in three patients anti-CMV IgG antibodies increased after the rise of anti-HHV-6 IgG antibodies. Anti-HHV-7 IgG antibodies did not show remarkable rises in any of these patients. As for patients with TEN and SJS, anti-HHV-6, anti-HHV-7 and anti-CMV IgG antibodies showed no significant increase, except for one patient in whom anti-HHV-6 and anti-HHV-7 IgG antibodies increased, but not more than 1 : 160, after steroid therapy. Human herpesvirus-6 DNA was not detected in the blood of those patients.

Conclusions: Human herpesvirus-6 reactivation in patients with DIHS is not due to non-specific reactivation induced by steroid therapy, but to events specific to DIHS. We hypothesize that DIHS may occur as a result of reactivation of HHV, especially HHV-6, accompanied with an allergic reaction to drugs, followed by a substantial immune response to the virus that is probably responsible for visceral involvement.

Key words: cytomegalovirus, drug-induced hypersensitivity syndrome, human herpesvirus-6, Stevens–Johnson syndrome, toxic epidermal necrolysis.

Introduction

The association between viral infection and drug eruption has been well documented in infectious mononucleosis caused by Epstein–Barr virus (EBV), in which ampicillin rash is frequently observed. In addition to EBV, human herpesvirus (HHV)-6 and cytomegalovirus (CMV; HHV-5) have also been reported as causative viruses of infectious mononucleosis-like syndrome.[1,2]

Recently, active infection of HHV-6 has been reported in drug-induced hypersensitivity syndrome (DIHS) or drug reaction with eosinophilia and systemic symptoms (DRESS).[3–6] Cytomegalovirus was also detected in a few

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patients with DIHS.[7] Drug-induced hypersensitivity syndrome is a serious adverse systemic reaction that usually occurs within 3–6 weeks from the start of treatment. It is characterized by generalized exanthematous eruption, high fever, liver dysfunction, lymphoadenopathy and marked leukocytosis accompanied by eosinophilia and atypical lymphocytosis,[8–11] occurring after administration of, particularly, anticonvulsants and salicylates. Those manifestations are also observed during infectious mononucleosis.

Toxic epidermal necrolysis (TEN) and Stevens–Johnson syndrome (SJS) also present as a serious drug-induced rash with skin excoriation, necrotic lesions on mucous membranes and visceral involvement.[12] In contrast with DIHS, TEN and SJS are not usually associated with lymphoadenopathy or with marked leukocytosis and atypical lymphocytes. Although an increase in antibodies to herpes simplex virus (HSV) is observed in some SJS patients, the active infection of HHV-6 and CMV has not been studied in TEN and SJS. Therefore, the relevance of HHV infection to these diseases has not been elucidated.

In the present study, we examined HHV infection in patients with DIHS, TEN and SJS to clarify the involvement of HHV infection in the pathogenesis of these diseases.

METHODS

Patients

Patients with a diagnosis of DIHS (seven males), TEN (three males and two females) and SJS (two males and two females) were examined. The age range was 14–77 years in DIHS, 10–73 years in TEN and 5–54 years in SJS. The diagnosis of TEN and SJS was based on the criteria proposed by Bastuji-Garin *et al*.[13] All patients with TEN showed epidermal detachment of more than 30% of their body surface. The diagnosis of DIHS was based on the late onset (more than 2 weeks) from the start of drug therapy, the presence of widespread exanthematous eruption, high fever, liver dysfunction (alanine aminotransferase >50 IU/L) and leukocytosis (>11 000 /μL) accompanied by atypical lymphocytosis and/or eosinophilia (>600/μL).

Virological investigations were performed to examine the possibility of a viral infection. Samples of patients' sera were tested for EBV, HSV, HHV-6, HHV-7 and CMV. The sera were obtained between 2 and 11 days after the onset of the diseases for the first test and beyond day 21 for further tests. Sera were tested for anti-HHV-6 and anti-HHV-7 antibodies by fluorescent assay and by enzyme immunoassay (EIA) for anti-EBV, ant-HSV and anti-CMV antibodies. An increase of fourfold or more of titers between the samples was regarded as significant.

The polymerase chain reaction (PCR) procedure was used to detect HHV-6, HHV-7 and CMV DNA in sera and peripheral blood mononuclear cells (MNC) from five patients with DIHS and eight patients with TEN and SJS. The HHV-6 and CMV load in some of those sera and MNC was also quantified using real-time PCR.[14,15]

RESULTS

The drugs responsible and the time between the start of drug therapy and eruption are given in Table 1. In many cases, the causative drug of DIHS was an anticonvulsant (three carbamazepine and two phenytoin). Mexiletine, an anti-arrhythmic agent, and cyanamide, an alcohol-deterrent agent, also caused DIHS. As for TEN and SJS, the drug responsible was an anticonvulsant in two patients, cold medicine or acetoaminophen in three patients and omeprazole, an anti-ulcerative agent, in one patient. In two patients, the drugs responsible could not be determined because several drugs, including some antimicrobials and anti-inflammatory agents, were administered concomitantly. Six of seven patients with DIHS developed skin eruption after more than 4 weeks of therapy. All patients with TEN and SJS developed skin eruption within 3 weeks from the start of therapy.

All patients were cured after hospitalization and the treatments administered are given in Table 1. All patients with DIHS, except for one (case 2), were treated with systemic corticosteroids. Eight patients, including two DIHS patients, recovered after 500–1000 mg/day methylprednisolone pulse therapy for 3 consecutive days. A 10-year-old boy with TEN was treated with 30 mg/kg bodyweight methylprednisolone per day for 3 consecutive days and 1 mg/kg bodyweight per day cyclosporine. In patients with TEN and SJS, conservative skin dressings were used.

All patients with DIHS showed substantial leukocytosis (16 500–38 720/μL) with atypical lymphocytosis (253–3963/μL) and eosinophilia (660–12 930/μL) before corticosteroid therapy (Table 2). In contrast, leukocytosis was not observed in any patient with TEN and in only one patient with SJS before therapy. Only one patient (case 12) with TEN showed mild eosinophilia (739/μL). In one patient with TEN (case 11), mild atypical lymphocytosis (92/μL) was observed after steroid pulse therapy.

Table 1 Clinical characteristics of the patients

Diagnosis/patient no.	Age (years) /sex	Drug responsible	Delay† (days)	Steroid therapy	Cyclosporine therapy‡
Drug-induced hypersensitivity syndrome					
1	16/M	Carbamazepine	28	BMS 12 mg/day	–
2	55/M	Phenytoin	32	–	–
3	64/M	Phenytoin	28	mPSL 500 mg/day	–
4	77/M	Carbamazepine	34	PSL 60 mg/day	–
5	53/M	Mexiletine	53	PSL 10 mg/day	–
6	46/M	Cyanamide	50	BMS 8 mg/day	–
7	14/M	Carbamazepine	16	mPSL 1000 mg/day	–
Toxic epidermal necrolysis					
8	17/M	Cold medicine	2	BMS 8 mg/day	–
9	73/M	ND§	4–14	mPSL 500 mg/day	–
10	56/M	ND§	3–20	mPSL 1000 mg/day	–
11	38/M	Acetaminophen	1	mPSL 1000 mg/day	–
12	35/F	Omeprazole	9	mPSL 1000 mg/day	–
13	10/F	Cold medicine	1	mPSL 500 mg/day	1 mg/kg per day
Stevens–Johnson syndrome					
14	42/F	Carbamazepine	7	mPSL 500 mg/day	–
15	30/M	Phenobarbital	15	mPSL 1000 mg/day	–
16	26/F	Diaphenylsulfone	8	BMS 10 mg/day	–
17	5/M	Azithromycin	3	BMS 4 mg/day	–

†Time (days) between the start of drug therapy and skin eruption.

§Many drugs were possibly responsible.

‡Maximum doses of steroids administered are shown.

BMS, betamethasone; PSL, prednisolone; mPSL, methylprednisolone; ND, not determined.

Table 2 Laboratory data of the patients

Diagnosis/patient no.	Leukocytosis†	Eosinophilia‡	Atypical lymphocyte§	Liver involvement*
Drug-induced hypersensitivity syndrome				
1	+	+	++	+++
2	+	++	+++	+++
3	+++	+++	+	++
4	+	+	+	++
5	++	+++	+	++
6	+++	+++	++	++
7	+++	+++	+++	++
Toxic epidermal necrolysis				
8	–	–	–	–
9	–	–	–	++
10	–	–	–	–
11	–	–	+	++
12	–	+	–	++
13	–	–	–	–
Stevens–Johnson syndrome				
14	–	–	–	+
15	–	–	–	+
16	+	–	–	–
17	–	–	–	–

†White blood cell count ($\times 10^4/\mu L$): –, <1.1; +, between 1.1 and <2; ++, between 2 and <3; +++, ≥ 3.

‡Eosinophils ($/\mu L$): –, < 600; + between 600 and <1000; ++, between 1000 and <3000; +++, ≥ 3000.

§Atypical lymphocytes ($/\mu L$): –, <90; +, between 90 and <500; ++, between 500 and <2000; +++, ≥ 2000.

*Alanine aminotransferase (IU/L): –, <50; +, between 50 and <100; ++, between 100 and <300; +++, ≥ 300.

In patient 11, atypical lymphocytosis was observed after steroid pulse therapy.

Table 3 Reactivation of human herpesvirus (HHV)-6, HHV-7 and cytomegalovirus (CMV) in patients with drug-induced hypersensitivity syndrome showing increase of specific antibodies to HHV-6, HHV-7 and CMV

Patient	Days of the assay	HHV-6		HHV-7		CMV	
		IgG	IgM	IgG	IgM	IgG	IgM
1	12	<1 : 10	1 : 40	<1 : 10	1 : 80	0.52	32.9
	27	1 : 80	1 : 5120	<1 : 10	1 : 160	0.8	29.9
	41	1 : 20	1 : 1280	ND	ND	3.72	536
	59	<1 : 10	1 : 1280	<1 : 10	1 : 160	2.04	128
2	8	<1 : 10	1 : 80	ND	ND	ND	ND
	23	ND	1 : 1280	ND	ND	ND	ND
	42	ND	1 : 5120	ND	ND	ND	ND
3	15	<1 : 10	1 : 40	<1 : 10	1 : 160	0.1	15.6
	49	<1 : 10	1 : 80	<1 : 10	1 : 80	1.14	120
4	19	<1 : 10	1: 40	ND	ND	0.26	40.1
	36	<1 : 10	1 : 5120	ND	ND	0.53	42.8
	74	<1 : 10	1 : 320	ND	ND	0.31	539
5	47	<1 : 10	1 : 5120	ND	ND	ND	ND
6	6	<1 : 10	1 : 10	<1 : 10	1 : 20	ND	7.4
	27	ND	1 : 2560	<1 : 10	1 : 80	0.8	10.4
	65	ND	ND	ND	ND	ND	67.7
	132	ND	1 : 1280	ND	1 : 80	ND	ND
7	10	<1 : 10	1 : 10	<1 : 10	1 : 80	0.38	< 2.0
	19	<1 : 10	1 : 5120	<1 : 10	1 : 160	ND	ND
	58	<1 : 10	1 : 10 240	<1 : 10	1 : 160	0.21	< 2.0

Onset of the disease is day 1. ND, not done; –, not increased.

Human herpesvirus-6 and HHV-7 IgG values are fluorescent antibody titers. Cytomegalovirus antibody values correspond to enzyme immunoassay units (U/mL).

Table 4 Reactivation of human herpesvirus (HHV)-6, HHV-7 and cytomegalovirus in patients with drug-induced hypersensitivity syndrome showing viral DNA in blood mononuclear cells and in serum

Patient	Day of the assay	Viral DNA in MNC (copies/10^6 cells)			Viral DNA in serum (copies/10^6 cells)		
		HHV-6	HHV-7	CMV	HHV-6	HHV-7	CMV
1	12	< 20	–	–	–	–	–
	20	ND	ND	ND	+	–	–
	27	73	–	–	–	–	–
	41	49	–	–	–	–	+
	59	< 20	2.5×10^2	ND	ND	ND	–
3	15	ND	ND	ND	ND	ND	ND
	29	ND	ND	ND	ND	ND	9.7×10^3 copies/mL
4	19	ND	ND	ND	–	–	–
	36	ND	ND	ND	–	–	+
	74	ND	ND	ND	–	–	–
6	21	9×10^2	–	–	ND	ND	ND
7	10	3.5×10^5	–	–	ND	ND	ND

CMV, cytomegalovirus; MNC, mononuclear cell; ND, not done; –, not detected; +, detected by polymerase chain reaction.

Liver involvement was recognized in all DIHS patients (alanine aminotransferase 202–596 IU/L) and in five of 10 patients with TEN and SJS (51–175 IU/L).

In the first serum samples from patients with DIHS, IgM antibodies to HHV-6, HHV-7 and CMV were not detected. In those samples, anti-HHV-6 and HHV-7 IgG antibodies were 1 : 80 or less. However, more than 3 weeks after the onset of the disease, HHV-6 serological tests revealed a marked rise (1 : 1280–1 : 10 240) of IgG antibodies in six of seven patients with DIHS

Table 5 Reactivation of human herpesvirus (HHV)-6, HHV-7 and cytomegalovirus in patients with toxic epidermal necrolysis and Stevens–Johnson syndrome

Diagnosis	Patient no.	Increase of antibodies (IgG and IgM)			Viral DNA in blood MNC (copies/10^6 cells)		
		HHV-6	HHV-7	CMV	HHV-6	HHV-7	CMV
TEN	8*	+	+	–	ND	ND	ND
	9	–	–	–	–	–	–
	10	–	–	–	–	–	–
	11	–	–	–	–	Day 12, 1.5×10^2	–
	12	–	–	–	–	–	–
	13	–	–	–	–	–	–
SJS	14	–	–	–	ND	ND	ND
	15	–	–	–	–	–	–
	16	–	–	–	–	–	–
	17	–	–	–	–	–	–

TEN, toxic epidermal necrolysis; SJS, Stevens–Johnson syndrome; MNC, mononuclear cells; ND, not done.

*Anti-HHV-6 IgG antibody 1 : 20 (day 20), 1 : 80 (day 69); anti-HHV-7 IgG antibody 1 : < 10 (day 20), 1 : 160 (day 69).

(Table 3). Anti-HHV-6 IgM antibodies were detected in only one of the six patients after an increase in anti-HHV-6 IgG antibodies. In the remaining patient with DIHS (case 3),[7] a serological test for CMV showed increases in IgM and IgG antibodies 7 weeks after the onset of the disease without an increase in anti-HHV-6 IgG antibodies. In three patients (cases 1, 4 and 6), anti-CMV IgG antibodies also increased after the increase in anti-HHV-6 IgG antibodies. Anti-HHV-7 IgG antibodies did not show any significant increases in any of the patients with DIHS.

Human herpesvirus-6 DNA was detected in the MNC of three patients (cases 1, 6 and 7) 3 weeks after the onset of the disease (Table 4). In case 7,[16] quantitative analysis of HHV-6 load showed as high as 3.5×10^5 copies per 10^6 cells. In case 1, HHV-6 DNA was detected in the serum, followed by the appearance of CMV DNA in serum obtained 2 weeks later. In this patient, HHV-7 DNA was also detected in MNC after HHV-6 DNA was detected. In cases 1, 3 and 4, CMV DNA was detected in sera.

As for patients with TEN and SJS, anti-HHV-6, HHV-7 and CMV IgM antibodies were all negative and the IgG antibodies for those viruses showed low values (anti-HHV-6 IgG 1 : ≤ 80, anti-HHV-7 IgG 1 : ≤ 160, anti-CMV IgG < 2.0) during the course of the disease (Table 5). In case 8, anti-HHV-6 IgG and anti-HHV-7 IgG antibodies showed increases within this range on day 69 (day 20 anti-HHV-6 IgG antibody 1 : 20, anti-HHV-7 IgG antibody 1 : ≤ 10; day 69 anti-HHV-6 IgG antibody 1 : 20, anti-HHV-7 antibody IgG 1 : 160). Human herpesvirus-6 DNA was not detected in patients examined except for one patient with TEN, in whom HHV-7 DNA was detected in the MNC with atypical lymphocytosis.

Serological tests for EBV and HSV showed no IgM and stable IgG titers in any patient with DIHS, TEN and SJS. Hepatitis B virus in the sera and serological tests for hepatitis C virus were negative in all patients.

Discussion

The role of HHV-6 in the pathogenesis of DIHS has been debated in recent years and it has not been clarified whether active HHV-6 infection is specific to DIHS. It was reported that patients who developed macropapular exanthema due to drugs were not positive for HHV-6 DNA by PCR and by immunohistochemical analysis in any exanthematous skin and peripheral blood lymphocytes.[17] However, there have been no reports in which HHV infection has been investigated in patients with TEN and SJS.

Human herpesvirus-6 infection occurs in children before 2 years of age. It is usually asymptomatic and symptomatic primary infection induces exanthema subitum. However, severe primary infection may cause mononucleosis-like syndrome, hepatitis, meningoencephalitis and interstitial pneumonitis, mostly in immunosuppressed patients, such as bone marrow transplant recipients.

In sex of our seven DIHS patients, active HHV-6 infection was evidenced by a marked rise in anti-HHV-6 IgG antibodies and, in one of patient, low titers of anti-HHV-6 IgM antibodies were detected, which could have been due to either primary infection or reactivation. In all three

patients in whom we investigated HHV-6 DNA in MNC by PCR, the HHV-6 genome was detected. However, the meaning of HHV-6 DNA in MNC is controversial when the number of DNA copies is not high, because it can be detected in more than 30% of healthy persons.[18] In two of the three patients with a positive result by PCR analysis, the number of DNA copies in MNC was as high as 9×10^2 copies per 10^6 and 3.5×10^5 copies per 10^6 cells. As for the other patient with a rather low value of HHV-6 DNA copies in MNC, HHV-6 DNA was also detected in the serum. This indicated active replication of HHV-6, because HHV-6 DNA is never detected in the serum of healthy subjects.[18] Therefore, these data seem to indicate reactivation of HHV-6 in those patients.

Infection with other human β-herpesvirus, namely HHV-7 and CMV, for which primary infection occurs, as with HHV-6, in early childhood, was also investigated in those DIHS patients. None of the patients examined showed an increase of antibodies against HHV-7. However, HHV-7 DNA was detected in MNC on day 59 following HHV-6 DNA detection in one patient. This may indicate that HHV-6 may have induced HHV-7 reactivation in the patient, because both HHV-6 and HHV-7 are known to infect and reside in circulating $CD4^+$ lymphocytes[19] and HHV-7 reactivation has been reported to trigger reactivation of HHV-6.[20] In four patients with DIHS, reactivation of CMV was recognized. Three showed an increase of anti-CMV IgG antibodies and positive PCR results for CMV in the serum after reactivation of HHV-6. The remaining patient was positive for the CMV genome in the serum without HHV-6 active infection, although HHV-6 genome in blood was not examined. These findings indicate that CMV infection may contribute to the aggravation of symptoms of DIHS in at least some patients. Otherwise, steroid therapy may induce reactivation of CMV without any contribution to the symptoms, although the role of CMV reactivation after HHV-6 reactivation is not clear in DIHS.

In nine patients with TEN and SJS, either IgG or IgM antibodies for HHV-6, HHV-7 and CMV increased during the course of the disease. In one patient with SJS, IgG antibodies for HHV-6 and HHV-7 increased after steroid therapy, but those values were not high. Human herpesvirus-6 DNA was not detected in any of the eight patients examined. Only one patient was positive for HHV-7 DNA after steroid pulse therapy. Therefore, HHV infection does not seem to play an important role in the pathogenesis of TEN and SJS.

Regarding the relationship between HHV-6 reactivation and steroid therapy in patients with an adverse drug reaction, this should be discussed because reactivation of HHV has been reported in immunosuppressed patients after transplantation.[21] One of our patients with DIHS showed HHV-6 reactivation despite the fact that he had not received steroids or other immunosuppressive therapy. In another patient, just 10 mg prednisolone had been administered prior to the increase in anti-HHV-6 IgG antibodies. In addition, despite massive administration of corticosteroids, all patients with TEN and SJS showed negative results for HHV-6 reactivation. Taken together, these data indicate that HHV-6 reactivation in patients with DIHS was not due to non-specific polyclonal reactivation induced by steroid therapy, but to events specific to DIHS.

It has not been elucidated how HHV-6 infection contributes to the pathogenesis of DIHS. Although viral infection may be responsible for the development of the symptoms, the trigger of HHV-6 reactivation remains to be clarified. Hypogammaglobulinemia was recognized in some patients at the onset of DIHS.[6,14,22] This may indicate a disturbance of the immune system in those patients, although it is known that some patients who are administered anticonvulsants show hypogammaglobulinemia even without DIHS.[23,24] Furthermore, it has been reported that in patients with DIHS, metabolites of the drugs generated through abnormal, detoxification pathways are cytotoxic or capable of disturbing the immune system.[25,26] The induction of antibodies to cytochrome P450 components could be related to virus infection in DIHS.[6,27] In addition, many factors, such as positive patch testing and the drug-induced lymphocyte stimulation test, suggest an allergic mechanism in DIHS.[26,28]

Thus, we hypothesize that DIHS may occur as a result of reactivation of HHV, especially HHV-6, accompanied by an allergic reaction to drugs in patients whose immune system has been affected by drugs. This may be followed by a substantial immune response to the virus, which is probably responsible for the visceral involvement, such as liver dysfunction.

REFERENCES

1 Akashi K, Eizu Y, Sumiyoshi Y *et al*. Severe infectious mononucleosis-like syndrome and primary human herpesvirus 6 infection and in an adult. *N. Engl. J. Med.* 1993; **329**: 168–71.

2 Kano Y, Shiohara T. Current understanding of cytomegalovirus infection in immunocompetent individuals. *J. Dermatol. Sci.* 2000; **22**: 196–204.

3 Descamps V, Bouscarat F, Laglenne S *et al*. Human herpesvirus 6 infection associated with anticonvulsant hypersensitivity syndrome and reactive haemophagocytic syndrome. *Br. J. Dermatol*. 1997; **137**: 605–8.

4 Suzuki Y, Inagi R, Aono T *et al*. Human herpesvirus 6 infection as a risk factor for the development of severe drug-induced hypersensitivity syndrome. *Arch. Dermatol.* 1998; **134**: 1108–12.

5 Tohyama M, Yahata Y, Yasukawa M *et al*. Severe hypersensitivity syndrome due to sulfasalazine associated with reactivation of human herpesvirus 6. *Arch. Dermatol.* 1998; **134**: 1113–17.

6 Descamps V, Valance A, Edlinger C *et al*. Association of human herpesvirus 6 infection with drug reaction with eosinophilia and systemic symptoms. *Arch. Dermatol.* 2001; **137**: 301–4.

7 Aihara M, Sugita Y, Takahashi S *et al*. Anticonvulsant hypersensitivity syndrome associated with reactivation of cytomegalovirus. *Br. J. Dermatol*. 2001; **144**: 1231–4.

8 Silverman AK, Fairlei J, Wong RC. Cutaneous and immunologic reaction to phenytoin. *J. Am. Acad. Dermatol.* 1988; **18**: 721–41.

9 Handfield-Jones SE, Jenkins RE, Whittaker SL *et al*. The anticonvulsant hypersensitivity syndrome. *Br. J. Dermatol.* 1993; **129**: 175–7.

10 Callot V, Roujeau J-C, Bagot M *et al*. Drug-induced pseudolymphoma and hypersensitivity syndrome: Two different clinical entities. *Arch. Dermatol.* 1996; **132**: 1315–21.

11 Chopra S, Levell NJ, Cowley G *et al*. Systemic corticosteroids in the phenytoin hypersensitivity syndrome. *Br. J. Dermatol.* 1996; **134**: 1109–12.

12 Roujeau JC, Stern RS. Severe adverse cutaneous reactions to drugs. *N. Engl. J. Med.* 1994; **331**: 1272–85.

13 Bastuji-Garin S, Rzany B, Stern RS *et al*. Clinical classification of cases of toxic epidermal necrolysis, Stevens–Johnson syndrome, and erythema multiforme. *Arch. Dermatol.* 1993; **129**: 92–6.

14 Tanaka N, Kimura H, Iida K *et al*. Quantitative analysis of cytomegalovirus load using a real-time PCR assay. *J. Med. Virol.* 2000; **60**: 455–62.

15 Tanaka N, Kimura H, Hoshino Y *et al*. Monitoring four herpesviruses in unrelated cord blood transplantation. *Bone Marrow Transplant.* 2000; **26**: 1193–7.

16 Aihara Y, Ito S, Kobayashi Y *et al*. Carbamazepine-induced hypersensitivity syndrome associated with transient hypogammaglobulinemia and reactivation of human herpesvirus 6 infection demonstrated by real-time quantitative PCR. *Br. J. Dermatol.* 2003; **149**: 27–33.

17 Le Cleach L, Fillet AN, Agut H *et al*. Human herpesviruses 6 and 7. *Arch. Dermatol.* 1998; **34**: 1155–7.

18 Waranabe T, Kawamura T, Jacob SE *et al*. Pityriasis rosea is associated with systemic active infection with both human herpesvirus-7 and human herpesvirus-6. *J. Invest. Dermatol.* 2002; **119**: 793–979.

19 Lusso P, Secchiero P, Crowley RW *et al*. CD4 is a critical component of the receptor for human herpesvirus 7: Interference with human immunodeficiency virus. *Proc. Natl Acad. Sci. USA* 1994; **91**: 3872–6.

20 Tanaka-Taya K, Kondo T, Nakagawa N *et al*. Reactivation of human herpesvirus 6 by infection of human herpesvirus 7. *J. Med. Virol.* 2000; **60**: 284–9.

21 Yoshikawa T, Suga S, Asano Y *et al*. Human herpesvirus-6 infection in bone marrow transplantation. *Blood* 1991; **78**: 1381–4.

22 van Ginneken EEM, van der Meer JWM, Netten PM. A man with a mysterious hypogammaglobulinemia and skin rash. *Neth. J. Med.* 1999; **54**: 158–62.

23 Dosch HM, Jason J, Gelfand EW. Transient antibody deficiency and abnormal T suppressor cells induce by phenytoin. *N .Engl. J. Med.* 1982; **7**: 406–9.

24 Ishizaka A, Nakanishi M, Kasahara E *et al*. Phenytoin-induced IgG2 and IgG4 deficiencies in a patient with epilepsy. *Acta Paediatr.* 1992; **81**: 646–8.

25 Mauri-Hellweg D, Bettens F, Mauri D *et al*. Activation of drug-specific $CD4^+$ and $CD8^+$ T cells in individuals allergic to sulfonamides, phenytoin, and carbamazepine. *J. Immunol.* 1995; **155**: 462–72.

26 Shear NH, Spielberg SP. Anticonvulsant hypersensitivity syndrome. *In vitro* assessment of risk. *J. Clin. Invest.* 1988; **82**: 1826–32.

27 Leeder JS, Gaedigk A, Lu X *et al*. Epitope mapping studies with human anti-cytochrome P450 3A3A antibodies. *Mol. Pharmacol.* 1996; **49**: 234–43.

28 Galindo Bonilla PA, Romero Aguilera G, Feo Brito F *et al*. Phenytoin hypersensitivity syndrome with positive patch test. A possible cross-reactivity with amitriptyline. *Invest. Allergol. Clin. Immunol.* 1998; **8**: 186–90.