### *3.3 Further Reading*

Krueger GRF, Koch B, Ramon A, Ablashi DV, Salahuddm SZ, Josephs SF, Streicher HZ, Gallo RC, Habermann U. Antibody prevalence to HBLV (human herpesvirus-6, HHV-6) and suggestive pathogenicity in the general population and in patients with immune

Salahuddin SZ, Kelley AS, Krueger GRF, Josephs SF, Gupta S, Ablashi DV. Human herpesvirus-6 (HHV-6) and diseases. Clin Diagn Virol 1: 81 -100, 1993

Krueger GRF, Klueppelberg U, Hoffmann A, Ablashi DV. Clinical correlates of infection with human herpesvirus-6. In Vivo 8: 457-486, 1994

## 4. SYSTEMIC REACTIONS

### *4.1 Introduction*

Systemic reactions or better "multi organ reactions" (MOR) can be observed in both primary and non-primary HHV-6 infections. Most frequently, the infection and disease of the prime target organ (e.g. the tonsils, the CNS or a transplanted organ) is accompanied by a skin rash, and liver enzymes may be slightly elevated. There are signs of "dry" oropharyngitis, cough, malaise and fatigue, fever, iridocyclitis, arthritis and some myalgia similar to other viral infections. We have seen such MOR to accompany HHV-6 associated acute febrile illnesses in babies and small children, acute tonsillitis and mononucleosis -like diseases, and in patients with bone marrow or renal transplants. Vincent Descamps has described such MOR to occur in the context of allergies, especially drug allergies, for which he coined the *terminus* DRESS (i.e. Drug Reaction with Eosinophilia and Systemic Symptoms).

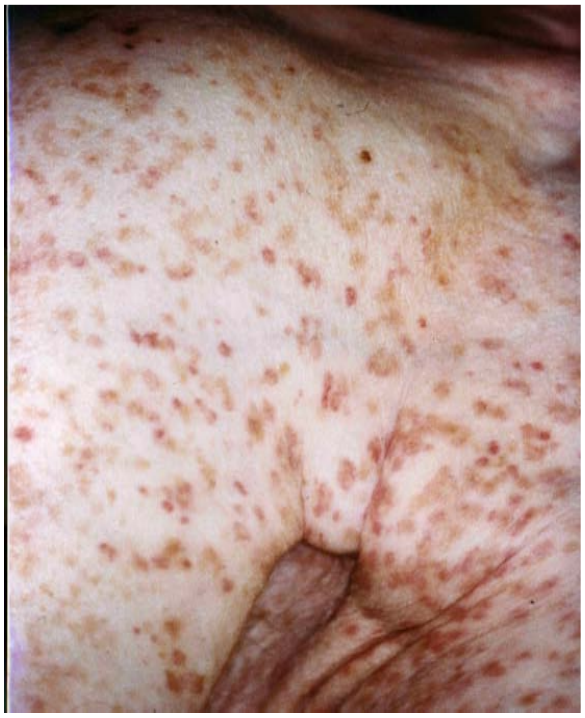
Janos Luka (personal communication) could show that EBV (Epstein-Barr virus) and HHV-6 antibody titers suggesting reactivation are more frequently observed during allergy seasons (and in allergic persons). Such reactivated lymphotropic viruses may well then further disturbe the normal immune reactivity thus contributing to the illness.

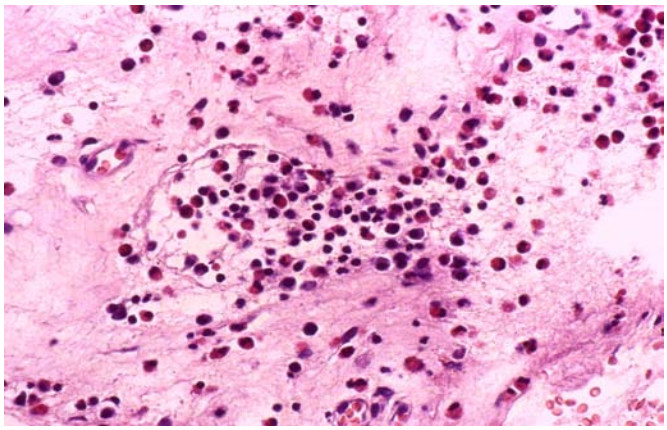
In some persons preferentially with reactivated HHV-6 and persistent viral activity (replication) a clinical syndrome may occur that has been described as postinfectious chronic fatigue syndrome (CFS) or chronic fatigue immune dysfunction syndrome (CFIDS).

There are other systemic diseases such as vasculitis and collagen-vascular diseases which may be accompanied by reactivated HHV-6 infection the implication of which still needs investigation.

### *4.2 Figures*

Characteristic features of systemic reactions are also shown in the paragraphs of respective organ systems (e.g. skin, oropharynx, tonsils, liver).





Adult patient with HHV-6 reactivation and DRESS: allergic skin eruption (left), allergic (polypoid) rhinitis and eosinophilia (above).

Table 3: CELL CULTURE AND INFECTION STUDIES WITH PBL FROM PATIENTS WITH CVD

| PATIENT I-NR | AGE/SEX | DIAGNOSIS | PRIMARY CULTURE %HHV-6+ [1] (days) | SUPERINFECTION OF HSB2 %HHV-6+ [1] (days) | ISH | VIRUS LINE |
|---|---|---|---|---|---|---|
| 2235/89 | 58F | APL | IgG 80% (20)<br>IgM 5% (20)<br>IgA Ø | 80% (4)<br>10% (4)- 20% (18)<br>10% (4)- 15% (18) | + | HHV-6Co1 |
| 2189/89 | 48F | UCVD | IgG 5% (35)<br>IgM Ø<br>IgA Ø | 90% (5)<br>5% (22)<br>5% (7)- 80% (19) | + | HHV-6Co2 |
| 2224/89 | 29F | SLE | IgG 50% (22)<br>IgM Ø<br>IgA Ø | 50% (2)- 80% (5)<br>5% (2)- 10% (9)<br>10% (3)- 50% (14) | + | HHV-6Co3 |
| 2231/89 | 49F | RA | IgG 5% (24)<br>IgM 5% (24)<br>IgA 10% (24) | 5% (14)- 40% (16)<br>Ø<br>5% (14) | + | HHV-6Co4 |
| 2300/89 | 64M | UCVD | IgG Ø<br>IgM Ø<br>IgA Ø | 10% (1)- 70% (7)<br>Ø<br>5% (6) | + | HHV-6Co5 |
| 2278/89 | 36F | SLE | IgG Ø<br>IgM Ø<br>IgA Ø | 5% (1)- 10% (16)<br>Ø<br>5% (1) | + | HHV-6Co6 |

1) IFA with standardized IgG-, IgM-, IgA-positive patientsera

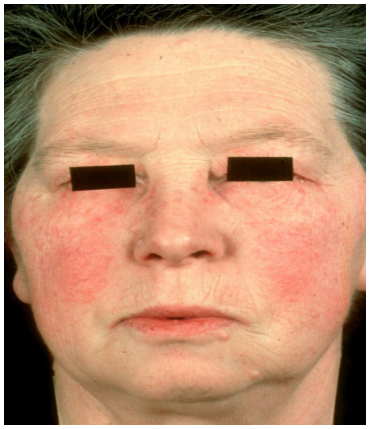
Abbreviations: CVD: collagen-vascular diseases; APL: atypical polyclonal lymphoproliferation; ISH: in situ hybridization for viral DNA; UCVD: unclassified collagen vascular disease; SLE: systemic lupus erythematosus; RA: rheumatoid arthritis; IFA: immunofluorescence assay with known HHV-6 IgG positive patients' sera

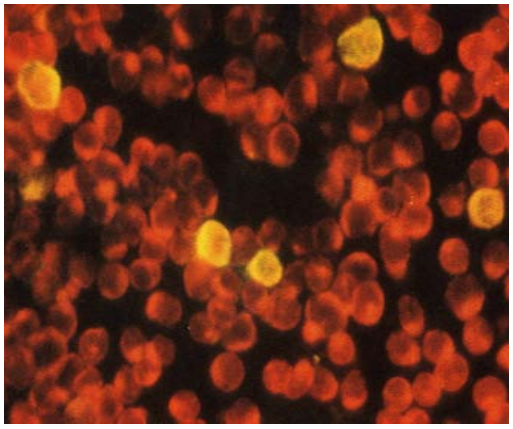
Table II. *Herpesvirus serology indicative of active infection.*

| Disease | NR of cases | HHV-6 | EBV | CMV |
|---|---|---|---|---|
| SLE & UCVD | 56 | 55.3% | 17.7% | 1.8% (one case) |
| RA | 92 | 6.5% | 28.8% | |
| SHARP | 1 | + | Ø | Ø |
| APL& RA | 1 | Ø | Ø | Ø |
| Ab prevalence | | 90% | 98% | 63% |

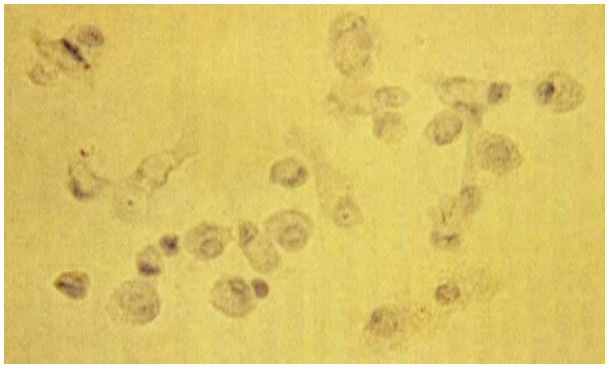
(for antibody titers see text)

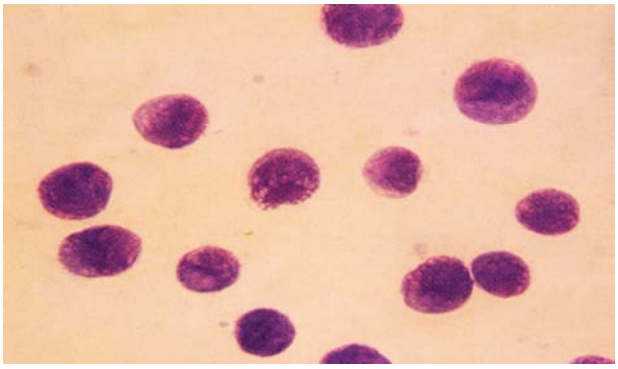
Abbreviations:
EBV: Epstein-Barr virus
CMV: cytomegalovirus
SLE: systemic lupus erythematosus
UCVD: unclassified collagen vascular disease
RA: rheumatoid arthritis
SHARP: Sharp syndrome
APL: atypical polyclonal lymphoproliferation



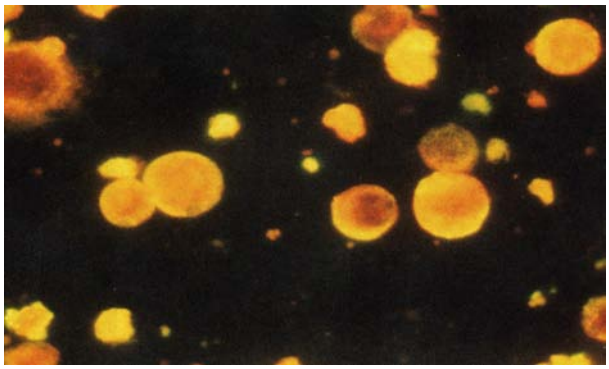


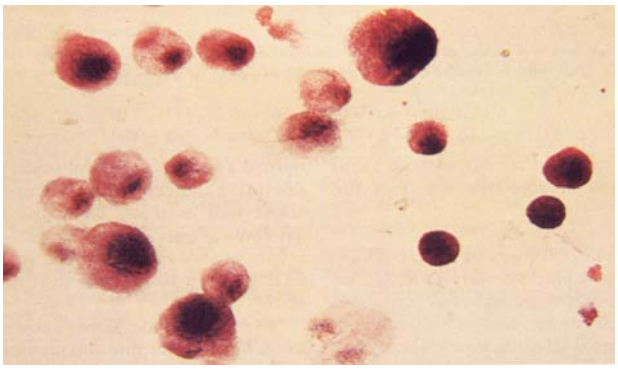
SLE patient (left) with HHV-6 IgG IFA positive peripheral blood smears (right)



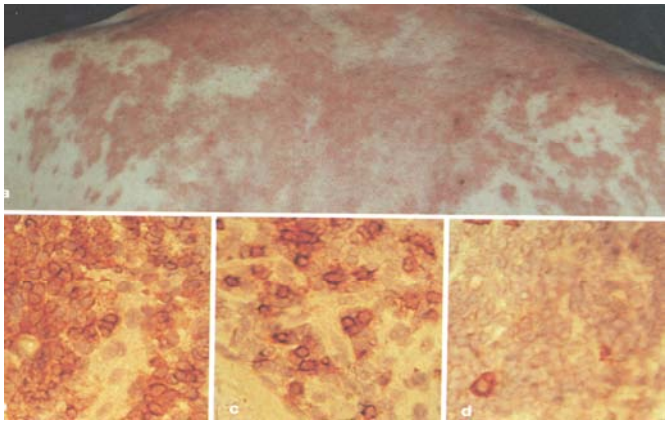


Primary culture of PBL from HHV-6 positive SLE patient (left) and superinfected HSB2 cells (right)





HHV-6 + IFA of superinfected HSB2 (left) and respective in situ hybridization (pZVH14 probe)



Dermal infiltrates in HHV-6+ SLE:
Top: exanthema on trunc.
Bottom lymphocyte typing by immunohistochemistry:
Left: CD4+ T cells, center CD8+ T cells,
Right: CD19+ B cells.

Usual HHV-6 IgG IFA titers of patient's sera 1:80 to 1:1280 (HSB2 & HHV-6A)

## Chronic Fatigue Syndrome (CFS): A Critical Evaluation of Testing for Active Human Herpesvirus-6 (HHV-6) Infection: Review of Data of 107 Cases

Mathias Wagner, MD
Gerhard R. F. Krueger, MD
Dharam V. Ablashi, DVM, MS, Dip Bact
James E. Whitman, PhD

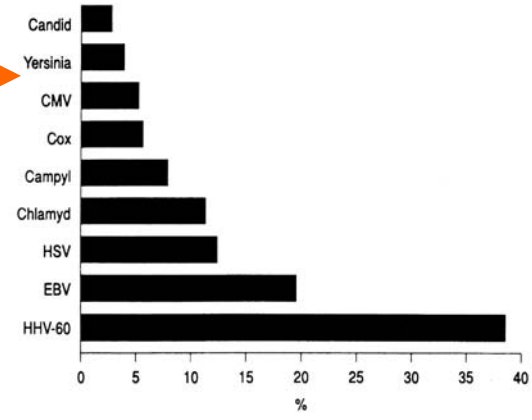
J Chron Fatigue Syndr Vol 2: 3-16, 1996

**Table 10.** Diagnostic Value of CFS Symptoms (according to Hoffmann,Kroeger & Krueger, ref. 9).

| | |
|---|---|
| *Major Criterium:* | Fatigue according to Holmes criteria (positive in 100% of the cases) |
| *Minor Criteria* | (5 of which must be present in CFS): |

1. Sore throat
2. Irritability
3. Depression
4. Other neuropsychiatric complaints
5. Lack of concentration
6. Lymphadenopathy
7. Temperature changes
8. Forgetfullness
9. Anxiety
10. Cough
11. Headache
12. Skotoma

* CFS subgroups proposed by the IIIP workgroup:
I. Primary CFS:
I. A. Post-infectious CFS (PICFS)
I. B. CFS without proven infection (NICFS)
II. Secondary CFS:
II. A. CFS post-primary psychiatric disease (PPCFS)
II. B. CFS post-defined physical disease, e.g., tumor (PDCFS)
III. Unclassified CFS (UCCFS):
Cases neither fulfilling criteria for primary nor secondary CFS



### *4.3 Further Reading*

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Wiersbitzky S, Ratzmann GW, Brims R, Wiersbitzky H. Reactivation in children of juvenile chronic arthritis and iridocyclitis associated with human herpesvirus-6. Paediatr Grenzgeb 31: 203-205, 1993

Descamps V, Valance A, Edlinger C, Fillet AM, Grossin M, Lebrun-Vignes B, Belaich S, Crickx B. Association of human herpesvirus 6 infection with drug reaction with eosinophilia and systemic symptoms. Arch Dermatol 137: 301-304, 2001

Wagner M, Krueger GRF, Ablashi DV, Whitman JE. Chronic fatigue syndrome (CFS): A critical evaluation of testing for active human herpesvirus-6 (HHV-6) infection: Review of data from 107 cases. J Chron Fatigue Syndr 2: 3-16, 1996

*Review article:*
Krueger GRF, Ablashi DV. Human herpesvirus-6: A short review of its biological behavior. Intervirology 46: 257-269, 2003

## 5. CARDIOVASCULAR SYSTEM

### *5.1 Introduction*

Cardiovascular symptoms and respective pathological changes have been reported occasionally in active HHV-6 infections. A comprehensive review was published by Max Buja (2006). HHV-6 frequently appears to reside in vascular endothelial cells, and viral DNA has also been extracted from myocardial tissue. The various cardiovascular lesions found in association with active HHV-6 infection are summarized in Table 2.