3.3 Further Reading

Krueger GRF, Koch B, Ramon A, Ablashi DV, Salahuddin 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 disorders.


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, 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 lymphotrophic viruses may well then further disturb 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>
<thead>
<tr>
<th>PATIENT</th>
<th>AGE/SEX</th>
<th>DIAGNOSIS</th>
<th>PRIMARY CULTURE (\text{HHV-6}^{+1}) (days)</th>
<th>SUPERINFECTION OF (\text{HHV-6}^{+1}) (days)</th>
<th>ISH</th>
<th>VIRUS LINE</th>
</tr>
</thead>
<tbody>
<tr>
<td>2235/89</td>
<td>58F</td>
<td>APL</td>
<td>IgG 80% (20)</td>
<td>80% (6)</td>
<td>+</td>
<td>HHV-6Co1</td>
</tr>
<tr>
<td>2189/89</td>
<td>48F</td>
<td>UCVD</td>
<td>IgG 5% (35)</td>
<td>90% (5)</td>
<td>+</td>
<td>HHV-6Co2</td>
</tr>
<tr>
<td>2224/89</td>
<td>29F</td>
<td>SLE</td>
<td>IgG 50% (22)</td>
<td>50% (7) - 80% (15)</td>
<td>+</td>
<td>HHV-6Co3</td>
</tr>
<tr>
<td>2231/89</td>
<td>49F</td>
<td>RA</td>
<td>IgG 5% (24)</td>
<td>5% (14) - 40% (16)</td>
<td>+</td>
<td>HHV-6Co4</td>
</tr>
<tr>
<td>2300/89</td>
<td>54M</td>
<td>UCVD</td>
<td>IgG 10% (24)</td>
<td>10% (1) - 70% (7)</td>
<td>+</td>
<td>HHV-6Co5</td>
</tr>
<tr>
<td>2278/89</td>
<td>36F</td>
<td>SLE</td>
<td>IgA 5% (1)</td>
<td>5% (1)</td>
<td>+</td>
<td>HHV-6Co6</td>
</tr>
</tbody>
</table>

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.

<table>
<thead>
<tr>
<th>Disease</th>
<th>NR of cases</th>
<th>HHV-6</th>
<th>EBV</th>
<th>CMV</th>
</tr>
</thead>
<tbody>
<tr>
<td>SLE &amp; UCVD</td>
<td>56</td>
<td>55.3%</td>
<td>17.7%</td>
<td>1.8% (one case)</td>
</tr>
<tr>
<td>RA</td>
<td>92</td>
<td>6.5%</td>
<td>28.8%</td>
<td></td>
</tr>
<tr>
<td>SHARP</td>
<td>1</td>
<td>+</td>
<td>Ø</td>
<td>Ø</td>
</tr>
<tr>
<td>APL &amp; RA</td>
<td>1</td>
<td>Ø</td>
<td>Ø</td>
<td>Ø</td>
</tr>
</tbody>
</table>

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

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

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)
4.3 Further Reading


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.