Aims

• To review the epidemiology of HHV-6 in Ireland over a 10 year period
• To determine if primary HHV-6 infection can occur in children less than 3 months of age
• To perform HHV-6 IgM and IgG testing in neonates in whom HHV-6 DNA was detected.

Introduction

• Primary HHV-6 infection occurs between 6 months and two years of age, and peaks at 6-8 months of age, following the loss of maternal antibodies.
• Acute HHV-6 infections account for 10-17% of emergency department visits with acute febrile illness in patients up to 3 years of age.
• Following primary infection, HHV-6 remains latent in the macrophage/monocyte population but can be detected in several systems of the body, including the central nervous system.
• The seroprevalence of HHV-6 in the adult population is approximately 50% in developed countries, although there may be significant differences based on geographic location, age of subjects, and sensitivity and specificity of serologic assays.
• The seroprevalence of HHV-6 in the Irish population is not known.

• HHV-6 DNA can be detected in approximately 1% of infants; however, approximately 85% of these detections are due to the presence of chromosomally integrated HHV-6 DNA (ciHHV-6).
• ciHHV-6 occurs, with viral DNA present in every nucleated cell in the body, in approximately 1% of the population; the prevalence of ciHHV-6 in Ireland is not known.
• Discriminating between acute HHV-6 infection and ciHHV-6 can be problematic: whilst HHV-6 DNA is readily detectable in many specimen types, e.g. CSF & plasma, molecular testing does not distinguish between active infection and ciHHV-6.
• Serological studies have shown that during primary HHV-6 infection, specific IgM antibodies appear during the first week and disappear after 1 month: IgG antibodies are detected later than IgM but persist indefinitely.
• Infants with ciHHV-6 can produce HHV-6 antibodies which may be in response to active replication of HHV-6 from postnatally acquired HHV-6, or from the chromosomally integrated virus.

Methods

• HHV-6 DNA results from January 2009 to March 2019 were analysed. HHV-6 DNA was detected using a real-time PCR for CSF, blood, and respiratory samples collected from patients under 3 years of age, and blood specimens from certain immunocompromised groups.
• 36 serum and plasma samples from patients under 3 months of age in which HHV-6 DNA was detected in CSF or serum, were tested for the presence of HHV-6 IgM and IgG.

Results

Table 1

<table>
<thead>
<tr>
<th>Number of samples</th>
<th>CSF HHV-6 DNA</th>
<th>SSERUM HHV-6 IgM</th>
<th>SSERUM HHV-6 IgG</th>
<th>Possible clinical interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>13</td>
<td>Detected</td>
<td>Positive</td>
<td>Negative</td>
<td>Integrated virus or acute infection with maternal antibody</td>
</tr>
<tr>
<td>11</td>
<td>Detected</td>
<td>Negative</td>
<td>Negative</td>
<td>Acute infection</td>
</tr>
<tr>
<td>1</td>
<td>Not detected</td>
<td>Negative</td>
<td>No evidence of HHV-6 infection</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>Not detected</td>
<td>Positive</td>
<td>Negative</td>
<td>No evidence of acute HHV-6 infection: Prior infection cannot be excluded</td>
</tr>
</tbody>
</table>

Discussion

HHV-6 DNA

• 87.2% of all samples tested for HHV-6 DNA were from patients 0-3 years old
• 89% of all HHV-6 DNA positive samples were from patients 0-3 years old and this is suggestive of the classical age profile of acute HHV-6 infection.
• 31% of positive samples were from patients 0-3 months old. This warrants a need for the development of an assay to differentiate between primary HHV-6 infection and ciHHV-6.
• All samples from patients greater than 3 years were from immunocompromised patients in whom detection of HHV-6 DNA suggests viral reactivation.

HHV-6 DNA & Serology in patients 0-3 months old

• In the 0-3 months old cohort, a positive HHV-6 IgG, negative HHV-6 IgM and HHV-6 DNA detected in either serum or CSF suggests the potential presence of integrated virus.
• Conversely, samples with HHV-6 DNA detected in either serum or CSF, but negative HHV-6 IgG indicates a potential acute infection.
• Of note, HHV-6 IgM was not detected in any of the children in this group.

Conclusions

• 31% of presumed primary infections occurred in children less than 3 months old, a greater proportion than previously reported.
• A relatively high number of patients in the cohort without maternal protection for HHV-6 suggests the mother was neverinfected with HHV-6.
• Therefore, this raises the possibility that the seroprevalence of HHV-6 in the Irish population may be lower than the rate of 90% reported in previous studies.

Future research

• Perform HHV-6 IgM and IgG testing in a larger 0-3 month old cohort to determine whether acute HHV-6 infection occurs sooner than the literature states and to determine where the seroprevalence of HHV-6 is lower in the Irish population.
• Perform HHV-6 testing in an antenatal cohort to ascertain the seroprevalence of HHV-6 in Ireland
• Develop an assay to investigate the occurrence of ciHHV-6 in the Irish population.

References