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Epidemiology of respiratory coronaviruses (HCoV) in a Dutch university hospital

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Aim: The epidemiologic characteristics of HCoV-NL63, HCoV-HKU1 and HCoV-OC43 and HCoV-229e in adult and paediatric patients were investigated. Furthermore, the genetic variability of HCoV-NL63 and HCoV-OC43 strains was investigated.

Methods: Studies were performed on respiratory samples submitted to the Virology Laboratory of the Erasmus MC for routine respiratory virus detection between June 2004 and June 2005. Samples were analysed for the presence of human coronaviruses using real-time nucleic acid amplification. Patient records were reviewed for patients tested positive.

Results: 1376 Samples were submitted. 70 Coronavirus positive samples (5.1%) were detected from 54 patients: for HCoV-OC43 40 samples from 31 patients, for HCoV-229E 1 sample from 1 patient, for HCoV-NL63 27 samples from 23 patients and for HCoV-HKU1 2 samples from 2 patients. Three patients were positive for more than one coronavirus. Other respiratory viruses were found in seven HCoV-NL63 and 9 HCoV-OC43 positive patients, respectively 30% and 29%. Peak incidences appeared during winter and springtime. For HCoV-OC43 a left skewed age distribution was found with a peak detection rate in patients 0-9 years old: median age 2.5 years. HCoV-NL63 detection rates equalled for patients 0-9 years old and 50-59 years: median age 34.8 years. 40 Patients (74%) and 29%. Peak incidences appeared during winter and springtime.

Conclusion: HCoV-OC43 and HCoV-NL63 were detected in a significant number of paediatric and adult patients, in contrast to HCoV-229E and HCoV-HKU1. Screening for these viruses is warranted.

Trent HCV study: mortality rates and ethnic differences in outcome

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Background: The Trent HCV cohort study was established in 1991 with the aim of characterising the natural history of chronic HCV (CHC) infection; over 2500 patients are enrolled, with a mean length of follow-up of >5 years.

Methods: CHC patients attending one of 7 sentinel clinics are invited to enlist with informed consent. Patient-derived data are stored in a centralised, anonymised database.

Mortality study: patients within the cohort are registered with the National Health Service Central Register. Death certificates and cancer registrations from Trent study patients are forwarded to the study group.

Ethnicity study: relevant data from all CHC patients within the cohort of Caucasian (n = 1700) and Indian sub-continent (n = 79) ethnic backgrounds were downloaded from the central database and compared.

Results: Of 228 cohort deaths, 87 were "liver related", 51 were related to injecting drug use, and 73 were "unrelated medical". Factors associated with all cause and liver-related mortality were increased age and male gender. Standardised mortality ratios were 6.4 (95%CI 4.6-10.3) and 2.1 (1.5-3.5) for males and females respectively. Compared with CHC in Caucasians, CHC in patients of Indian ethnicity was more likely to occur in females, in individuals with no clear history of risk factors, and presented at an older age with more severe liver disease.

Discussion: 5 year survival in our cohort is less than that reported in the literature; Mortality in HCV-infected patients is markedly increased compared to an age-matched population; CHC in different ethnic groups may have very different characteristics from that in Caucasian patients.

Early evolution of hepatitis C virus (HCV) quasispecies after liver transplantation

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Background and Aims: Liver cirrhosis related to chronic infection by HCV is a main indication for liver transplantation (LT). Allografts are systematically re-infected with HCV yet prognosis of infection differs from patient to patient. A high rate of nucleotide mutations during HCV replication, a differential adaptation of viral strains to the liver graft and a variable efficiency of the immune response could explain HCV recurrence. In infected patients, HCV circulates as a mixture of closely related but distinct genotypes called quasispecies. Little information is available on changes in HCV quasispecies early following transplantation.

Methods: Seventeen patients liver transplanted for HCV-related disease were included. HCV quasispecies were analyzed in plasma by cloning and sequencing the Hypervariable region 1 of E2 envelope gene before transplantation, after 7 days and one month later. NS3 was sequenced by studying three internal fragments with overlapping ends.

Results: HCV quasispecies tend to be more homogeneous at D7 than before transplantation (decrease in genetic complexity and diversity). Complexity and diversity at the amino-acid level were both diminished at day 7 after transplantation (4.7 and 6.9 respectively) compared to the time before transplantation (5.7 and 13.3 respectively). Mutations in NS3 could be observed in most patients: for one patient up to 11 non synonymous mutations were observed 3 and 6 months post-transplantation compared to HCV before transplantation.

Conclusion: Here we describe HCV genetic evolution during the early phase after LT, the best time to make an antiviral treatment optimal. Possible links between NS3 mutations and prognosis of recurrent hepatitis deserve to be analysed.

Impact of targeted vaccination on HBV genotypes in Amsterdam

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Background and Aim: The Netherlands have adopted a policy of hepatitis B virus (HBV) vaccination targeted towards high-risk groups, rather than universal vaccination. In 1996, a pilot program started in Amsterdam. We performed a retrospective molecular epidemiological cross-sectional survey covering 12 years (1992–2003).

Methods: Mandatory reported HBV cases were classified according to probable mode of transmission. Retrospective DNA sequencing was performed on 85 sera of patients with acute hepatitis B infections. We amplified the S-gene (nt 112–778) for phylogeny.

Results: The number of reported cases of acute HBV in Amsterdam declined from 214 before to 128 after the start of vaccination in 1998. An estimated 39–65% of those who should be vaccinated are presently still susceptible for HBV. Before 1998, phylogenetic analysis showed 3 main clusters: (I) men having sex with men (MSM, genotype A), (II) people from Morocco (genotype D), and (III) intravenous drug users (IDU) and heterosexual partners (genotype D). After 1998, the cluster with IDU and their heterosexual partners had disappeared. In the total 12-year study period the same HBV strain circulated among MSM in Amsterdam. Although the number of susceptible MSM in Amsterdam declined, the number of acute hepatitis B cases among MSM did not.

Conclusions: The decline of acute hepatitis B infections in Amsterdam was ascribed to a lack of reported HBV cases among IDU, probably due to a decline in injecting behavior. Increased sexual risk
behavior in the last decade among MSM in Amsterdam may have balanced the positive effects of the targeted vaccination program.

**O13** Neurological disease associated with seasonal B19 virus infection in the United Kingdom

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**Background:** Erythrovirus B19 (formerly parvovirus B19), is the cause of the common childhood illness erythema infectiosum (EI). B19V is rarely considered as a cause of neurological illness although there have been isolated case reports describing neurological symptoms in patients during or following EI. A recent retrospective study suggests that the virus is present in the CSF of almost 5% of undiagnosed paediatric encephalitis/encephalitis cases in the United Kingdom. We tested cerebrospinal fluid (CSF) samples from paediatric and adult patients, collected during periods of high and low B19V incidence.

**Patients Details and Methods:** A total of 227 CSF samples were sent to Manchester Royal Infirmary Clinical Virology Laboratory for testing for suspected viral meningoencephalitis were tested. Of these 138 were collected in the high incidence and 89 in the low incidence period. All CSF samples were tested using B19V-specific nested DNA PCR and all positive CSF samples were tested for the presence of anti-B19V antibodies using immunoblot test.

**Results:** Ten of 227 CSF samples were positive for B19V DNA (4.4%). In the high B19V incidence cohort, 9/138 samples (6.5%) were positive. In the low incidence cohort 1/89 cases (1.1%) were positive. Anti-B19V antibody (iGg) was detected in four out of ten B19V positive CSF samples suggesting that a functioning immune response against the virus was occurring.

**Conclusions:** B19V is associated with neurological illness in both children and adults. The finding of a higher incidence of B19V DNA positive CSF during community outbreaks suggests the virus may be an unrecognised cause of meningoencephalitis.

**O14** HHV-6 DNA in CSF and diagnosis of encephalitis

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**Background and Aims:** The prevalence and concentration of HHV-6 DNA in the cerebrospinal fluid (CSF) of the immunocompetent in primary infection was compared with that in viral chromosomal integration.

**Methods:** Samples from 510 immunocompetent individuals with suspected encephalitis were tested. HHV-6 DNA concentration (log10 copies/ml) was measured in CSF, serum and blood using PCR. Primary infection was defined by antibody seroconversion and/or low concentration HHV-6 DNA in a seronegative serum. Chromosomal integration was defined by high concentration viral DNA in serum or blood.

**Results:** The prevalences of CSF HHV-6 DNA in primary infection and chromosomal integration were 2.5% and 2.0% respectively in young children (<2 years) and 0% and 1.3% respectively in the older children/adults. The mean concentration of CSF HHV-6 DNA in children with primary infection was significantly lower than that in patients with viral chromosomal integration. Only HHV-6B DNA was found in primary infection whereas in viral integration both HHV-6A and B were detected.

**Conclusions and Discussion:** Apart from primary infection, chromosomal integration is the most likely cause of HHV-6 DNA in the CSF of the immunocompetent. In such cases, viral chromosomal integration should be excluded before diagnosing encephalitis.

[Abstracts: Oral Presentations #11]

**O15** Identification of new pathogens involved in infectious uveitis

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**Background:** Uveitis is an inflammation of the uvea, including the iris, the ciliary body, the choroid and the retina. In approximately 20% of cases uveitis is caused by a systemic disease, whereas in 30% the inflammation is the result of an intraocular infection, with Toxoplasma gondii, Herpes simplex virus, Varicella zoster virus and Cytomegalovirus being the most common causes. In the remaining 50% of cases, rapid discrimination between infectious and non-infectious uveitis is of major importance for patient management, since these two conditions have entirely different treatment regimens and visual prognoses. The purpose of this study was to identify other pathogens involved in uveitis.

**Methods:** Ocular fluid samples from 78 patients with an undiagnosed uveitis were investigated by real-time PCR for the presence of Adenovirus, Human herpes virus 6, Epstein–Barr virus, Coronavirus, Influenzaviruses, Parainfluenzaviruses, Enteroviruses, Parechoviruses, Respiratory syncytial virus, Human metapneumovirus and Rubella virus. In addition, aqueous humor of 32 patients with Fuchs heterochromic iridocyclitis (FHI), a chronic intraocular inflammation, were examined for intraocular antibody production against Rubella virus.

**Results:** Of 78 patients, one patient with posterior uveitis was positive for Rubella virus and four patients with anterior uveitis were positive for Parechovirus. Analysis of the clinical data of the latter suggested that Parechovirus is involved in keratouveitis. Moreover, 30 of 32 (94%) patients with FHI, but none of the control subjects, had intraocular antibody production against Rubella virus.

**Conclusions:** Parechovirus appears to play an important role in keratouveitis. Furthermore, these studies confirm that Rubella virus is associated with FHI.

**O16** Human cytomegalovirus-specific CD4+ and CD8+ T-cells in organ transplant recipients

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**Objective:** To evaluate human cytomegalovirus (HCMV)-specific CD4+ and CD8+ T-cell kinetics in solid organ transplant recipients and the potential impact of monitoring HCMV-specific immune response on management of HCMV infection.

**Methods:** Absolute and HCMV-specific CD4+ and CD8+ T-cell counts were monitored in 38 solid organ (20 heart, 9 lung, and 9 kidney) transplant recipients during first year after transplantation by a novel assay based on T-cell stimulation with HCMV-infected autologous dendritic cells. Patients were enrolled in a pre-emptive therapy protocol based on administration of antiviral therapy upon reaching either antigenemia or DNAemia cutoff values.

**Results:** Of 78 patients, one patient with posterior uveitis was positive for Rubella virus and four patients with anterior uveitis were positive for Parechovirus. Analysis of the clinical data of the latter suggested that Parechovirus is involved in keratouveitis. Moreover, 30 of 32 (94%) patients with FHI, but none of the control subjects, had intraocular antibody production against Rubella virus.

**Conclusions:** Parechovirus appears to play an important role in keratouveitis. Furthermore, these studies confirm that Rubella virus is associated with FHI.

**Background:** Among the various pathogens involved in infectious uveitis, infections due to Toxoplasma gondii and Varicella zoster virus are the most common. In addition, a recent study has suggested that Parechovirus is involved in keratouveitis. Moreover, these studies confirm that Rubella virus is associated with FHI.

**Methods:** Ocular fluid samples from 78 patients with an undiagnosed uveitis were investigated by real-time PCR for the presence of Adenovirus, Human herpes virus 6, Epstein–Barr virus, Coronavirus, Influenzaviruses, Parainfluenzaviruses, Enteroviruses, Parechoviruses, Respiratory syncytial virus, Human metapneumovirus and Rubella virus. In addition, aqueous humor of 32 patients with Fuchs heterochromic iridocyclitis (FHI), a chronic intraocular inflammation, were examined for intraocular antibody production against Rubella virus.

**Results:** Of 78 patients, one patient with posterior uveitis was positive for Rubella virus and four patients with anterior uveitis were positive for Parechovirus. Analysis of the clinical data of the latter suggested that Parechovirus is involved in keratouveitis. Moreover, 30 of 32 (94%) patients with FHI, but none of the control subjects, had intraocular antibody production against Rubella virus.

**Conclusions:** Parechovirus appears to play an important role in keratouveitis. Furthermore, these studies confirm that Rubella virus is associated with FHI.