that maximum concentrations of ciclosporin A in plasma were substantially lower in African Americans than in white people. Moreover, a significantly higher P-glycoprotein-mediated rhodamine efflux from lymphoid cells has been shown in individuals with the C/C genotype. Thus, the C/C genotype could be a factor restricting access of HIV-1 protease inhibitors to their major cellular target, the CD4-T-lymphocytes, which are known to express P-glycoprotein. Further studies are needed to clarify the mechanism by which the C3435T polymorphism leads to decreased P-glycoprotein expression and to define its role as a susceptibility factor for infectious diseases and drug treatment with P-glycoprotein substrates.

We thank Andrea Zwicker for technical assistance. This study was supported by the Bundesministerium für Bildung und Forschung grant 01GG9846 and the Robert Bosch Foundation, Stuttgart, Germany


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Prediction of severe disseminated adenovirus infection by serum PCR

Marcela Echavarria, Michael Forman, Maarten J D van Tol, Jaak M Vossen, Patricia Charache, Aloys C M Kroes

Adenoviruses are increasingly recognised as viral pathogens that can cause fatal infections in immunocompromised patients, particularly recipients of haematopoietic stem-cell grafts. Adenovirus infections are not easily diagnosed and the development of a severe infection cannot be predicted by standard culture techniques. In a pilot study, we investigated the value of adenovirus DNA detection in serum as a marker of disseminated disease in 14 patients with defined patterns of adenovirus infections. The results show that the appearance of adenoviral DNA in serum preceded the development of a severe or fatal adenovirus infection. Because proper management is dependent on early diagnosis and differentiation from other conditions, this test may be a valuable tool in the management of adenovirus infection.

Lancet 2001; 358: 384–85

Adenoviruses are a common cause of self-limiting infections of the respiratory or gastrointestinal tract. Adenoviruses are frequently found in individuals with immunocompromised patients, and these viruses may persist in a latent form after infection. In these cases, the reactivated virus may be shed asymptomatically or may cause disease—eg, pharyngitis, conjunctivitis, pneumonia, haemorrhagic cystitis, colitis, hepatitis, or encephalitis. These infections may cause fatal disease—particularly in young patients—by widespread dissemination, which can be difficult to recognise. An increasing incidence of adenovirus infections has been observed in recipients of stem-cell transplantation, with mortality rates as high as 25%. Early detection of dissemination would permit accurate diagnosis and the prompt initiation of appropriate clinical management. Localised disease cannot be distinguished from disseminated disease by viral cultures.

The presumed pathogenesis of viral reactivation originating from the respiratory or gastrointestinal tract would imply that the appearance of adenovirus in serum is associated with an early stage of viral dissemination. In this pilot study, and with a PCR method described in 1998, we investigated the value of adenovirus DNA detection in serum as a marker of disseminated disease in stem-cell-transplantation recipients.

The incidence and outcome of adenovirus infection were retrospectively studied in 328 consecutive paediatric recipients of an allogeneic stem-cell grafts transplanted during 1985–99 at the Leiden University Medical Center, Leiden, Netherlands. Urine, throat, and stool samples were cultured at least once every 2 weeks during the initial 6 months after transplantation and subsequently as clinically indicated. Adenovirus was recovered from 38 (12%) of recipients. 17 (45%) of these patients had symptoms of adenovirus disease, and the infection was fatal in seven (18%) of them. No clustering of distinct serotypes or a typically seasonal distribution of the first occurrence of positive cultures was evident within this population. 14 patients were selected for investigation of the presence of adenovirus DNA in blood and divided into four clinical categories: A=control cases (with no evidence of adenovirus infection and with negative culture results); B=symptom-free patients, with adenovirus culture-positive samples; C=patients with localised adenovirus-disease—ie, enteritis or haemorrhagic cystitis; and D=patients with a clinical diagnosis of fatal disseminated adenovirus-disease, supported by cultures or necropsy findings. Clinical data and viral serotypes are given in the table.

48 serum samples from these 14 patients were tested in a blinded manner at Johns Hopkins Medical Institutions, Baltimore, USA, for the presence of adenovirus DNA by PCR, using methods described previously for urine, and subsequently optimised for serum (sensitivity of adenovirus detection: 0-1 plaque-forming units/mL). A positive result was defined as the presence of a 139 base-pair band in the agarose gel with corresponding signal after Southern blot hybridisation and autoradiography.

PCR results of the 14 patients are summarised in the table. All sera from control patients, those with symptom-free shedding, and those with localised disease (categories A, B, and C) were negative for adenovirus by PCR. Of four patients with disseminated adenovirus disease (category D), three had strongly positive PCR results on multiple samples. One of these patients had a positive adenovirus-PCR even before transplantation. These three patients had hepatitis and multiorgan failure with or without enteritis. The fourth patient, with pneumonia, had only a weakly positive PCR result on day 57 after transplantation. This patient had continuously positive adenovirus-culture stool samples, and died on day 97. On necropsy this patient was found to have adenovirus-positive cultures from the liver, colon, and lung.
Serum samples close to death were not available. All four patients had a positive adenovirus-PCR result several weeks before the development of disease and all subsequently died with a clinical diagnosis of disseminated adenovirus disease. They either did not receive antiviral therapy with ribavirin or were treated only in the last few days before they died, without a noticeable response.

Our study shows that although positive serum PCR specifically predicted dissemination, adenovirus detection by culture from different samples—eg, stool, urine, or throat swab—did not. There was no difference in adenovirus recovery from these sites among symptom-free patients or those with localised or disseminated adenovirus disease. In the study group, the negative predictive value of adenovirus DNA detection in serum for disseminated disease was 100%.

A positive finding of viral DNA in serum may help to differentiate adenovirus disease from other causes of pneumonia or hepatitis. Up until now, clinical observation and viral culture have not facilitated an early diagnosis of adenovirus-associated disease. Because antiviral drugs—eg, ribavirin and cidofovir—are probably effective only in the earliest stages of disease,1 the timely recognition of disseminated adenovirus infection is important. Early diagnosis could also avoid the need for additional diagnostic procedures, such as organ biopsy sampling. Our study shows that adenovirus in serum is associated with the development of disseminated disease. This association may allow a new and sensitive marker for this increasingly recognised and potentially severe infectious complication, which apparently imposes practical restrictions to the extent of immunosuppression that can be achieved, at least in children. The value of this approach should be assessed more extensively in a prospective study design.

We thank E P A de Klerk, in Leiden, and J C de Jong and G J J van Doornum at the Department of Virology, Erasmus University Medical Center, Rotterdam, for providing valuable assistance with serotyping of the virus strains.


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Incidence of childhood acute lymphoblastic leukaemia in Yorkshire, UK

Richard G Feiltbower, Anthony V Moorman, Gareth Dovey, Sally E Kinsey, Patricia A McKinney

Between 1980 and 1998, in the north-west of England, a significant rise in childhood acute lymphoblastic leukaemia was caused by an increase in the precursor B-cell form of this disease. We analysed data on children who were diagnosed with leukaemia in Yorkshire, UK, between 1974 and 1997. The incidence of acute lymphoblastic leukaemia remained stable, although a non-significant yearly increase of 2·4% was noted for the precursor B-cell form of this disease from 1980 onwards. The precursor B-cell form accounted for 80% of all acute lymphoblastic leukaemia. Our data are not consistent with increasing incidence for precursor B-cell acute lymphoblastic leukaemia, although numbers of children with acute myeloid leukaemia are rising.

Lancet 2001; 358: 385–87

The incidence of childhood leukaemia has risen in the UK.1 In a study from the north-west region of England,2 McNally and colleagues suggested that the increase in the childhood peak (ages 1–4 years) was due to a 3% rise per year of precursor

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**Table:**

<table>
<thead>
<tr>
<th>Patient Number</th>
<th>Category</th>
<th>Adenovirus associated disease</th>
<th>Adenovirus associated outcome (day after SCT)</th>
<th>Adenovirus-culture results (sites)</th>
<th>Adenovirus-PCR</th>
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<tbody>
<tr>
<td>1</td>
<td>A</td>
<td>None</td>
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<td>–</td>
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<td>B</td>
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<td>12/31</td>
<td>None</td>
<td>+ (F,T)</td>
</tr>
<tr>
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<td>1</td>
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<tr>
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<tr>
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<td>11</td>
<td>D</td>
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<td>12/31</td>
<td>Death (66)</td>
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<td>D</td>
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<td>D</td>
<td>Pneumonia</td>
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<td>Death (97)</td>
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</table>

**SCT**=stem-cell transplantation. A=adenovirus negative controls; B=symptom-free shedding of adenovirus; C=localised adenovirus disease; D=disseminated adenovirus disease; –=negative; +=positive; F=faeces; U=urine; T=throat. *Weakly positive.

**Results of adenovirus cultures and detection of viral DNA in serum by PCR in four categories of recipients of stem-cell grafts**

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