Antibodies to the EB Virus in Renal Transplant Recipients

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In order to prevent graft rejection, renal transplant recipients are given agents such as steroids and cytotoxic agents which suppress the immunological defences of the body. It is therefore probable that the incidence of at least some viral diseases will be increased.

During the past five years, we in Aarhus have studied the occurrence and clinical manifestations of infection caused by members of the herpes group of viruses in immunosuppressed graft recipients. In previous papers, (Andersen & Spencer, 1969; Spencer & Andersen, 1970) we have documented the fact that the varicella-zoster virus and the cytomegalovirus are responsible for a greater amount of illness in these patients than is the case among normal subjects. A study of the situation regarding the herpes simplex virus is in progress.

The present report concerns a fourth member of the herpes family of viruses, the so-called Epstein-Barr, or EB virus. This virus was originally discovered by Epstein and Barr in tissue cultures of cells from a Burkitt’s lymphoma, a lymphoma predominantly found in Central African children. A great deal of evidence has since been presented indicting the EB virus as the agent involved in infectious mononucleosis. (McCollum, 1970) Aetiologic studies have, however, been hampered by the inability to isolate and culture the virus. Evidence of infection can only be obtained indirectly by demonstration of antibody using lymphocytes from infected patients as antigen.

To study the incidence of EB virus infection in renal graft recipients, sera from 30 randomly selected patients from the Aarhus transplantation series were examined. Employing an indirect, two-layered immunofluorescent technique (Spencer & Andersen, 1971), antibody levels were determined in serum taken at the time of transplantation and at approximately one, two, three and six months post-transplant. Significant, that is four-fold, rises
in antibody titre and thereby evidence of infection were found in three patients, a man of 31, and two girls aged 11 and 18 (Table I). These antibody changes are considered specific as studies have demonstrated the lack of cross-reactivity between the EB virus and other herpes virus antigens. (Andersen et al, 1971)

Table I. Data concerning three patients with rise in antibody to Epstein-Barr virus after renal allotransplantation

<table>
<thead>
<tr>
<th>Patient No</th>
<th>Age</th>
<th>Sex</th>
<th>Pre-Transplant</th>
<th>Day of significant rise in antibody titre</th>
<th>Highest level</th>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>31</td>
<td>M</td>
<td>40</td>
<td>138</td>
<td>320</td>
<td>Fever, Sore Throat, Cervical Lymphadenopathy</td>
</tr>
<tr>
<td>61</td>
<td>11</td>
<td>F</td>
<td>20</td>
<td>90</td>
<td>320</td>
<td>None</td>
</tr>
<tr>
<td>63</td>
<td>18</td>
<td>F</td>
<td>40</td>
<td>45</td>
<td>320</td>
<td>Fever</td>
</tr>
</tbody>
</table>

After identification of the three patients with rises in EBV antibody, an attempt was made to determine what, if any, factors differentiated these patients from those not evidencing antibody rises (Table II).

Table II. Comparison of various factors between patients with and those without rise in EBV antibody

<table>
<thead>
<tr>
<th>Factor</th>
<th>Patients with antibody rise</th>
<th>Patients without antibody rise</th>
<th>Significance (p)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (average)</td>
<td>20 years</td>
<td>33 years</td>
<td>ns</td>
</tr>
<tr>
<td>Cytomegalovirus disease</td>
<td>3 of 3</td>
<td>6 of 27</td>
<td>0.02</td>
</tr>
<tr>
<td>Glomerulonephritis as primary renal disease</td>
<td>3 of 3</td>
<td>10 of 27</td>
<td>0.05</td>
</tr>
<tr>
<td>Transplanted during summer months</td>
<td>2 of 3</td>
<td>3 of 27</td>
<td>0.05</td>
</tr>
<tr>
<td>Good post-transplant renal function</td>
<td>3 of 3</td>
<td>18 of 27</td>
<td>ns</td>
</tr>
<tr>
<td>Splenectomy</td>
<td>1 of 3</td>
<td>4 of 27</td>
<td>ns</td>
</tr>
<tr>
<td>Septicaemia or other severe bacterial infection</td>
<td>1 of 3</td>
<td>7 of 27</td>
<td>ns</td>
</tr>
<tr>
<td>Wide-spread candida infection</td>
<td>1 of 3</td>
<td>3 of 27</td>
<td>ns</td>
</tr>
<tr>
<td>Units of blood given at transplantation (average)</td>
<td>2.0</td>
<td>2.5</td>
<td>ns</td>
</tr>
</tbody>
</table>

Duration of dialysis pre-transplant        | 2 months                    | 3 months                       |

ns = not significant
An obvious difference was the younger age of the former group, the average of the other patients being 33 years. This is perhaps not surprising as infectious mononucleosis is a disease of younger persons. The three patients with EBV antibody rises were further characterised by the following: in all three histologic examination revealed signs of chronic glomerulonephritis and all had had cytomegalovirus disease; two had been transplanted during the summer months (the third during the late spring), and post-transplant renal function had been good in all three.

They had received an average of two units of blood at transplantation and been treated with intermittent dialysis for an average of 2 months pre-transplant, and one each had undergone splenectomy, had a wide-spread candida infection or suffered from severe bacterial infection. Using Fisher's 'exact' test (onesided) the incidence of these factors was compared with that seen in the 27 other patients and a p-value of 2% was found for cytomegalovirus infection and just over 5% for summer transplantation and glomerulonephritis. There was no correlation with the other factors.

Thus, apart from the somewhat younger ages of patients with rises in EBV antibody and the fact that all had had cytomegalovirus disease, they appeared to differ in no way from the other members of the study group.

In all three patients a rise in heterophile antibodies by the Paul-Bunnell test was also found, but only in patient 10 was this rise to a significant level.

As this was a retrospective study, clinical records had to be relied upon for possible symptoms in association with antibody rises. Patient 10 had a transient febrile illness with sore throat and enlarged cervical lymph nodes approximately two months before increased antibody levels could be demonstrated. Studies have shown that high titres are often seen several weeks to a few months after clinical episodes of infectious mononucleosis (Hirshaut et al, 1969). In patient 63 two short bouts of fever of unexplained aetiology were seen shortly before titre increase. No symptoms were recorded in the chart of patient 61. The laboratory records of these patients do not mention the presence of abnormal mononuclear cells in the peripheral blood.

Thus, at least by hindsight, this study presented a probable explanation for two febrile episodes in two kidney transplant patients. This, together with previous experience, leads us to the general conclusion that infection with herpes viruses is responsible for a not insignificant number of post-transplant fevers.

REFERENCES

Spencer, E. S. and Andersen, H. K. (1971) Acta Medica Scandinavica,
in press

OPEN DISCUSSION

R SELLS (Liverpool): Did you have the opportunity to find out whether the
donors in these three cases had suffered from any virus diseases of this
nature?

SPENCER: No. That would, of course, be of interest; two of the patients
had received cadaver kidneys, and the other was a related live donor transplant done approximately three years before our study took place. These studies were done on sera which we had collected over a period of several years. We made no attempt to trace the possible source of infection.

D N S KERR (Newcastle): Did you go back and review the blood films of
these patients through their febrile illnesses and see whether they showed
glandular fever cells when they were immunosuppressed?

SPENCER: No, again such slides are not stored, and it was not possible to
do this. Anybody looking at slides of peripheral blood from transplanted
patients is aware that abnormal lymphocytes are extremely common.
Whether this is a function of the immunosuppressive therapy, or whether it
is due to viral infection is hard to say. In the clinical record of these
patients no mention was made of abnormal lymphocytes being present, and
if such cells had been present in large numbers some note would probably
have been made – it usually is.

P MICHELESEN (Louvain, Chairman): Have you any observations on other
patients treated with immunosuppressive drugs?

SPENCER: No, only on renal transplant recipients.