PART VI

DIALYSIS: General

Chairmen: F S T Boen
           B Kuhl bäck
SERUM ANTIBODIES BEFORE AND AFTER IMMUNISATION IN HAEMODIALYSED CHILDREN

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Summary

Serum antibodies (AB) have been measured before and after vaccination in haemodialysed children. The main finding was a normal increase in AB titres following adsorbed vaccines (diphtheria, tetanus, pertussis and poliomyelitis) demonstrating a normal humoral immune ability. By contrast, a poor response to live attenuated viruses (poliomyelitis and measles) was observed. Two additional findings were an inhibitor effect of tetanus toxoid in mice by uraemic serum, and a constant negative Schick test indicative of suppressed non-specific skin reactivity.

Introduction

A number of reports have been devoted to cellular immunity in uraemia, but few to humoral immunity, and their conclusions are conflicting. The present study was undertaken with two purposes: 1) to describe the antibody (AB) response after vaccination in haemodialysed children; 2) to protect these children against infectious disease. In France, nephropathies are a contra-indication to vaccinations, and most of these children had never, or had been inadequately, immunised.

Patients and Methods

The children studied were aged 2 to 15 years. All had been treated by regular haemodialysis twice weekly for more than three months. All had a moderately restricted protein diet (1–2 g/kg/day). All received aluminium hydroxide, calcium, vitamin D and polyvitaminic supplementation (including vitamin B₆).

Blood sampling was performed before haemodialysis, at least 3 months after a blood transfusion. The post-vaccination AB measurement was made one month after the last vaccine administration.

The following AB have been measured: anti-pertussis agglutinins, anti-diphtheria AB, using the intradermal neutralisation of toxin in guinea pig, anti-tetanus
AB using the neutralisation of a lethal dose of tetanus toxoid in mice, anti-measles AB using a haemagglutination inhibition test, and anti-polio AB using the inhibition of the cytopathogenic effect of the virus in vitro. AB titres were expressed as international units for diphtheria and tetanus, and as serum dilutions for the others.

Vaccinations against pertussis, diphtheria and tetanus were performed using three inoculations of adsorbed associated vaccines (Institut Pasteur). Against poliomyelitis two vaccines were used: the oral live attenuated virus (Sabin strain) and the adsorbed inactivated vaccine (Institut Pasteur): three doses of each were given. For measles vaccine, we used a single dose of live further attenuated virus, Schwarz strain.

**Results**

Main results, expressed as sero-conversion-rates, are summarised in Table I. They are compared with the results obtained in normal infants by the Centre International de l’Enfance of Paris (CIE), which are similar to those usually reported in normal children. Sero-conversion has been defined by the development of protective AB titres in previously unimmunised children, or, in a few instances (tetanus in our series) by a post-vaccination increase greater than twofold compared with the initial titre.

**TABLE I**

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Haemodilysed Children</th>
<th>Normal Infants *†</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>sero-conversion %</td>
<td>n</td>
</tr>
<tr>
<td>Pertussis</td>
<td>18</td>
<td>100</td>
<td>109</td>
</tr>
<tr>
<td>Diphtheria</td>
<td>17</td>
<td>94</td>
<td>114</td>
</tr>
<tr>
<td>Tetanus</td>
<td>21</td>
<td>100</td>
<td>112</td>
</tr>
</tbody>
</table>

**Poliomyelitis**

1. **Inactivated**
   - Virus I: 11, 70% (100, 68%)
   - Virus II: 11, 100% (100, 83%)
   - Virus III: 11, 64% (100, 89%)

2. **Live attenuated**
   - Virus I: 19, 31% (100, 67%)
   - Virus II: 19, 64% (100, 88%)
   - Virus III: 19, 31% (100, 94%)

**Measles (live attenuated)**

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>sero-conversion %</th>
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<tbody>
<tr>
<td></td>
<td>18*</td>
<td>22</td>
</tr>
<tr>
<td></td>
<td>93</td>
<td>90</td>
</tr>
</tbody>
</table>

Sero-conversion one month after the last vaccine administration

*† Studies performed by the CIE. These percentages are indicative, as they do not deal with true control children, but with younger children

* Six had a second injection without increase in AB titre
Pertussis

Of the 18 children studied, 13 had no agglutinins, 5 had low titres (40–160). After vaccination, a marked increase in AB titres was observed in all, reaching 320–2500 in 10 of the previously unimmunised children, 1280 to 10240 in the others: such an increase was apparently higher than is usually observed in normal children, but controls were not available for valid comparison.

Diphtheria

Of the 28 children investigated, 27 had no detectable AB prior to vaccination. Seventeen were immunised and all but one developed AB, a sero-conversion rate similar to that observed in normal children.

Despite the absence of circulating AB, the Schick test using intradermal diphtheria toxoid was negative in 28/29 patients, including 16 children who had no previous history of immunisation. The same diphtheria toxoid used in 10 unimmunised normal infants gave positive reactions. A second test was done in three children after a successful kidney transplantation and was positive.

Tetanus

Circulating tetanus AB were detected in 39 of the 46 children investigated, of whom 21 had no previous vaccination. Although there is no spontaneous immunity against tetanus, 14 of these 21 children had tetanus AB titres considered to be protective (0.1 to 0.15 U/ml). The results were confirmed in 5 patients using blind measurement in another laboratory (Institut Pasteur) whereas no detectable AB were found in 8 normal control infants. The 21 previously unimmunised children received three inoculations of tetanus toxoid. In all a significant increase in AB was observed (0.1 to 5 U/ml). The rise in AB was similar to that observed in the 8 control infants, and to that which is usually obtained in normal children.

Measles

Measles AB were measured in 52 children. All children with a previous history of the disease had protective AB titres, as usually observed in a normal population. Eighteen children without detectable AB received one dose of live attenuated virus. Fourteen failed to achieve sero-conversion. Six patients received a second inoculation, again with no result. The sero-conversion rate in normal children is above 95%, and the inefficiency of the measles vaccine was unusual.

Poliomyelitis

Thirty children had undetectable AB against at least one of the poliomyelitis viruses. Nineteen received 3 doses of live oral vaccine. The sero-conversion rate was low: 31%, 64% and 31% respectively for viruses I, II and III. This percentage was significantly lower than that reported in normal infants, and significantly lower than that obtained in the 11 haemodialysed patients who received
inactivated vaccine. In the latter, sero-conversion rate was 70%, 100% and 64%, and was similar to that reported in normal infants.

Discussion

Many reports have given evidence of deficient immunity in uraemia\(^2,3\). Most studies have dealt with cellular immunity. Their results, although sometimes conflicting, have demonstrated a defective cellular immune response. The main findings have been the prolonged survival of grafts\(^4\), the decreased graft versus host reaction when the transplanted cells have been taken from uraemic animals\(^5\), a lymphopenia with reduced circulating T cells\(^6\), a poor lymphoblastic transformation in the presence of non specific\(^6,7,8\) or specific\(^6,8,9\) stimulation or in mixed lymphocyte cultures\(^10\). One of the more frequently described abnormalities has been the absence of the skin hypersensitivity reaction\(^6,10,11\).

The purpose of the present study was not to provide data regarding cellular immunity. However, an unexpected finding in uraemic children was the almost constant negative Schick test, that is the absence of skin reaction to intradermal diphtheria toxoid. The effect of toxoid is purely toxic and by no means immunologically mediated, and the reaction disappears only when the toxoid is neutralised by circulating AB. As most of the patients studied had no detectable AB and no antecedent vaccination, a suppressed non-specific skin reactivity is likely.

A similar absence of skin reaction to non-specific toxins has been reported by Malaviya et al\(^11\) who used dinitrochlorobenzene and croton oil. In view of these data, the value of skin tests for assessing cellular immunity may be questioned.

An important percentage of patients were without detectable AB against pertussis, diphtheria and poliomyelitis. This is probably due to the lack of antecedent immunisation in the children who had congenital or early kidney diseases, or to the lack of a booster injection in the remainder, since the presence of a nephropathy is a contra-indication to immunisation according to French Law. By contrast, almost all children apparently had protective tetanus AB titres. In 14 of these children, no antecedent vaccination could be found despite careful and repeated inquiries. The absence of immunisation cannot be certain in all cases, and it has been demonstrated that tetanus AB persist longer than pertussis and diphtheria AB when no booster injection has been given. However, absence of previous immunisation is very likely in some children who had kidney disease from infancy.

Antibody response to antigenic stimulation has been poorly studied in uraemia, and the available data have been conflicting, possibly because of the heterogeneity of the patients and methods used.

A reduced immune response was found by Wilson et al\(^12\) studying AB to typhoid somatic and flagellar antigens, by Boulton-Jones et al\(^9\) using keyhole limpet haemocyanin antigen, and by Pabico et al\(^13\) using influenza vaccine. The absence of anti-hepatitis B antibodies with persistence of circulating antigen has been well demonstrated in numerous series of haemodialysed patients.

Other authors found a normal AB response: Stoloff et al\(^14\) obtained a normal diphtheria AB increase after a booster injection. Balch\(^15\) obtained a normal response to tetanus toxoid, and Jordan et al\(^16\) using influenza vaccine found a
similar response in haemodialysed patients and in controls. It has been suggested that the AB response was normal only when a first antigenic stimulation had occurred before GFR was reduced, that is only after a booster injection. On the contrary, there was no AB increase following a first antigenic injection performed in uraemia.

The data reported herein demonstrate that a normal AB response is observed following toxoid and inactivated vaccine administration, whether a booster or a first inoculation is given. Increase in AB titres was similar to that reported in normal children. It may be concluded that humoral immune response to antigenic stimulation is unaltered in uraemia.

Contrasting with the marked AB increase following inactivated vaccines, a poor response to live attenuated vaccines (poliomyelitis and measles) has been observed, whereas in normal subjects these vaccines result in a high sero-conversion rate. Usually, live and inactivated poliomyelitis vaccines result in a similar AB increase. This finding may be compared with those of Pabico et al. and of Jordan et al. Both authors studied the response to influenza vaccine in chronic renal failure. The former found a deficient response using the live attenuated virus, and the latter found a normal response using inactivated vaccine. The reasons for the difference between the two kinds of vaccines remain to be explained. As the humoral response to antigen has been found to be normal in uraemia, other defects preceding the antigen release may be suspected. A defect of penetration or dissemination of the virus in the patients' cells, a defect of phagocytosis or a macrophagic dysfunction may be postulated but remain to be investigated.

References

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Open Discussion

GURA (Israel) It has been stated previously that there is a certain similarity between the many immunological abnormalities of uraemic and of protein malnourished patients. You stated in your presentation that your patients were moderately protein-restricted and since we know that uraemic children have a higher requirement per kilogram body weight than uraemic adults, I wonder whether you have looked or taken into consideration the nutritional status of your patients, especially when comparing those with other groups previously reported.

KLEINKNECHT I said that dietary protein was moderately restricted, but it was much higher than the minimal requirement for normal treatment. It was one to two grams per kilo. It was not consistent with protein malnutrition for normal children, and there was no evidence of protein malnutrition as far as plasma transferrin, albumin or total protein are concerned.

GURA Were these values normal?

KLEINKNECHT Yes.

BOEN (Amsterdam) Did the children develop clinical symptoms after live vaccine injection?

KLEINKNECHT No, vaccinations were well tolerated, except for three patients who had moderate fever after pertussis injections. No reaction was observed after measles, for example, but there was no antibody response either.