Serum monoclonal immunoglobulins in childhood

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Serum monoclonal immunoglobulins in childhood. Of 18 children with monoclonal immunoglobulins in their sera, 13 had a primary or secondary immunodeficiency. The monoclonal immunoglobulin belonged to each of the three main Ig classes, and in 3 children multiple monoclonal components were detected. The level of the monoclonal component exceeded 0·5 g/100 ml in 7 cases. The monoclonal immunoglobulin disappeared spontaneously in 9 children. The significance of this homogeneous component and the importance of the underlying immunodeficiency are outlined.

Material and methods

Seventy-three serum samples from 18 children were studied by electrophoresis and immunoelectrophoresis. Most of the children were being followed in our clinic on account of haematological or immunological diseases, and were submitted to a systematic Ig survey. In a few a sudden increase in the erythrocytic sedimentation rate sometimes provided stimulus to perform immunoelectrophoretic analysis.

Electrophoresis was performed in 1% agar gel, the proteins being stained with amido black, and in cellulose acetate, the level of the homogeneous components being estimated as a percentage of the total uptake of ponceau red. Immunoelectrophoretic analysis was carried out in barbitone buffer pH 8·2, ionic strength 0·05, with a variety of rabbit antisera prepared in our laboratory and conveniently absorbed, including antisera specific for $\gamma$, $\mu$, $\alpha$, $\delta$, $\kappa$, and $\lambda$ chains.

Quantitation of the immunoglobulin classes not including the monoclonal components was performed by radial diffusion in agar with specific antisera incorporated into the gel (Mancini, Carbonara, and Hermans, 1965). Antinuclear antibodies were sought by the indirect immunofluorescence technique on liver sections. Antibodies to human and rabbit $\gamma$-globulin were detected by the latex F II and Waaler Rose reactions.

Our criteria for defining a population of Ig molecules as 'monoclonal' were (1) an abnormal bow reacting with antisera corresponding to only one type of heavy and light chain on immunoelectrophoresis; (2) a discrete homogeneous peak with sharp borders migrating by electrophoresis in the same region as the immunoelectrophoretic bow. Both criteria were fulfilled in 14 of 18 cases. In the other cases, the monoclonal Ig level was not sufficient to induce a sharp peak but the light chain typing, either by immunoelectrophoresis of the whole serum or after sucrose density gradient ultracentrifugation for IgM components confirmed its antigenic homogeneity.

We have excluded from this study two kinds of abnormalities. Firstly, we do not report here the cases with a monoclonal protein characteristic of the $\alpha$-chain disease (Seligmann et al., 1968) which occurs in young adults and children (Seligmann, Mihaesco, and Frangione, 1971). Secondly, we do not consider as monoclonal the IgG showing only a restricted cathodal electrophoretic mobility, which are often encountered in the sera of young children (Golebiowska and Rowe, 1967). In our own experience these IgG molecules with restricted electrophoretic heterogeneity always shared both $\kappa$- and $\lambda$-chains and could not therefore be considered as antigenically homogeneous.

The criterion for the disappearance of the monoclonal Ig was the failure to detect on subsequent sera homogeneous protein previously detectable by electrophoresis and/or immunoelectrophoresis (Danon and Seligmann, 1972).

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at least IgG being found while in
in summarized ml
Danon 208

Two of them showed excretion of CSF tests.

Antinuclear factors were found in 5 of 16 cases with titres as high as 1 g/100 ml in 2 cases. No DNA antibodies were detected by complement fixation or precipitin tests. Rheumatoid factor was found in 3 sera. Two of these had both antinuclear and anti-γ-globulin antibodies.

The proteinuria was investigated in 6 patients. Two of them showed excretion of a very small amount of Bence-Jones protein, detectable only after urine concentration (Cases 5 and 10). The CSF was investigated in 2 patients (Cases 5 and 13), monoclonal IgG being found in both.

**Clinical findings.** The clinical diagnoses are summarized in the Table. It is noteworthy that at least 5 children suffered from a primary immunodeficiency. At the time of examination they had never received γ-globulin injections (nor thymus or marrow grafts). 6 children had leukaemia or lymphosarcoma, all receiving chemotherapy, and 4 being in complete remission. In 5 cases the monoclonal Ig was known not to be present at the time of diagnosis and appeared at a later stage, as shown by successive electrophoretic patterns. As a rule, these serial studies were performed at intervals of several weeks or months so that the precise time of monoclonal Ig appearance could not be ascertained except in the following case.

**Case 7.** This child was first seen in 1967 for an acute lymphoblastic leukaemia. A complete remission was induced. During the following three years he was under maintenance therapy with mercaptopurine and amethopterine, with reinductions at regular intervals with prednisone, vincristine, and rubidomycin. He was admitted to hospital in October 1970 for an unexplained fever (relapse of the leukaemia was excluded). The sedimentation rate was 25 mm in the first hour and the serum electrophoresis pattern was normal (Fig. 1). 12 days later the sedimentation rate had risen to 160 mm and the serum protein electrophoresis revealed a discrete γ-peak (Fig. 2). Immunoelectrophoresis showed a diffuse increase of IgM and IgG with a monoclonal κ IgG. Virological and serological investigations led to the diagnosis of cytomegalovirus infection. Cytomegalovirus antibodies reached a titre of 1/1600 and decreased thereafter.

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Diagnosis</th>
<th>Immuno-suppressive therapy*</th>
<th>Age</th>
<th>Monoclonal Ig type (g/100 ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.5</td>
</tr>
<tr>
<td>1</td>
<td>Severe combined immunodeficiency</td>
<td>6 mth</td>
<td>Gκ + Gλ</td>
<td>+</td>
</tr>
<tr>
<td>2</td>
<td>Severe combined immunodeficiency</td>
<td>13 mth</td>
<td>Gλ</td>
<td>+</td>
</tr>
<tr>
<td>3</td>
<td>Wiskott-Aldrich syndrome</td>
<td>5 mth</td>
<td>Gλ</td>
<td>+</td>
</tr>
<tr>
<td>4</td>
<td>Wiskott-Aldrich syndrome</td>
<td>10 yr</td>
<td>Gλ + Aλ</td>
<td>+</td>
</tr>
<tr>
<td>5</td>
<td>Primary immunodeficiency</td>
<td>6 mth</td>
<td>Gκ</td>
<td>+</td>
</tr>
<tr>
<td>6</td>
<td>Possible immunodeficiency</td>
<td>14 mth</td>
<td>Gκ</td>
<td>+</td>
</tr>
<tr>
<td>7</td>
<td>Lymphoblastic leukaemia</td>
<td>5 yr</td>
<td>Gκ</td>
<td>+</td>
</tr>
<tr>
<td>8</td>
<td>Lymphoblastic leukaemia</td>
<td>15 yr</td>
<td>Gλ</td>
<td>+</td>
</tr>
<tr>
<td>9</td>
<td>Acute myeloblastic leukaemia</td>
<td>14 yr</td>
<td>G</td>
<td>+</td>
</tr>
<tr>
<td>10</td>
<td>Myelomonocytic leukaemia</td>
<td>3 yr</td>
<td>Gκ</td>
<td>+</td>
</tr>
<tr>
<td>11</td>
<td>Subacute myeloblastic leukaemia</td>
<td>5 yr</td>
<td>Mκ</td>
<td>+</td>
</tr>
<tr>
<td>12</td>
<td>Lymphoblastosarcoma</td>
<td>5 yr</td>
<td>Gκ</td>
<td>+</td>
</tr>
<tr>
<td>13§</td>
<td>Subacute sclerosing panencephalitis</td>
<td>6 yr</td>
<td>Gλ + Gλ</td>
<td>+</td>
</tr>
<tr>
<td>14</td>
<td>Familial lymphohistiocytosis</td>
<td>8 yr</td>
<td>G</td>
<td>+</td>
</tr>
<tr>
<td>15</td>
<td>Chromosomal abnormality</td>
<td>3 wk</td>
<td>M</td>
<td>+</td>
</tr>
<tr>
<td>16</td>
<td>Chromosomal abnormality</td>
<td>2 yr</td>
<td>Aλ</td>
<td>+</td>
</tr>
<tr>
<td>17</td>
<td>Schönlein-Henoch purpura and nephropathy</td>
<td>20 mth</td>
<td>Gκ</td>
<td>+</td>
</tr>
<tr>
<td>18</td>
<td>Thrombotic thrombocytopenic purpura</td>
<td>14 yr</td>
<td>Gλ</td>
<td>+</td>
</tr>
</tbody>
</table>

*Before discovery of monoclonal Ig; †Interval between finding of monoclonal Ig and first electrophoresis or immunoelectrophoresis showing no monoclonal Ig.*


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**data in the 18 cases**

<table>
<thead>
<tr>
<th>Other Ig classes</th>
<th>Antinuclear factor</th>
<th>Rheumatoid factor</th>
<th>Additional features</th>
<th>Disappearance of monoclonal Ig†</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgM</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>IgA</td>
<td>—</td>
<td>—</td>
<td>Cytomegalovirus infection</td>
<td>2 mth</td>
</tr>
<tr>
<td>IgM</td>
<td>ND</td>
<td>ND</td>
<td>Cytomegalovirus infection</td>
<td>1 yr</td>
</tr>
<tr>
<td>IgA</td>
<td>+</td>
<td>+</td>
<td>Cytomegalovirus infection</td>
<td>2 mth</td>
</tr>
<tr>
<td>IgA</td>
<td>+</td>
<td>+</td>
<td>Cytomegalovirus infection</td>
<td>15 dy</td>
</tr>
<tr>
<td>IgM</td>
<td>—</td>
<td>ND</td>
<td>Cytomegalovirus infection</td>
<td>8 mth</td>
</tr>
<tr>
<td>IgM</td>
<td>ND</td>
<td>ND</td>
<td>—</td>
<td>2 mth</td>
</tr>
<tr>
<td>IgM</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>2 mth</td>
</tr>
</tbody>
</table>

More such component; †Daloz et al. (1965); §Loirat, Danon, and Broyer (1971). ND, not done; N, normal.

The child recovered. The level of the monoclonal Ig slowly decreased and finally disappeared after 6 months.

**Discussion**

This report clearly shows that the occurrence of serum monoclonal Ig is not a very exceptional event during childhood and that such immunoglobulin abnormalities may be detected in very young infants as well as in older children. None of the 18 children reported in the present study was affected with myeloma or Waldenström's macroglobulinaemia, emphasizing that it is probably only α-chain disease which in childhood leads to a presumably malignant plasmacytic proliferation characterized by a monoclonal Ig (Trunberry et al., 1970; Stoop et al., 1971; Seligmann et al., 1971).

As far as the associated diseases are concerned, the striking finding in the present study is that 13 of the 18 children were affected with primary or secondary immunodeficiency. The common diagnosis in the primary immunodeficiency group was either severe combined immunodeficiency or the Wiskott-Aldrich syndrome. Among the other patients, 7 were under immunosuppressive therapy when the monoclonal Ig was detected, most suffering from a malignant haematological disease.

Our findings may be partly related to the fact that our department is mainly devoted to haematology and immunology. However, most of the case reports documenting monoclonal Ig in childhood also

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*Fig.—Successive agar gel electrophoresis of the sera of Case 7 (lymphoblastic leukaemia): (1) 29 October 1970, (2) 11 November 1970.*
concern patients with immunodeficiency diseases: Wiskott-Aldrich syndrome (Radl et al., 1967; Blaes et al., 1971), ataxia telangiectasia (Cawley and Schenken, 1970), and severe combined immunodeficiency (Stoop, Ballieux, and Weyers, 1962; Schaller et al., 1966; Becroft and Douglas, 1968). In these cases and in those reported here, the patients had received neither γ-globulin nor thymus or bone marrow grafts. In contrast, Harboe et al. (1966) and Radl et al. (1972) have also documented the appearance of monoclonal Ig after the grafting of lymphoid cells into infants affected with severe combined immunodeficiency.

The occurrence of monoclonal Ig associated with acute leukaemia has been reported by Stoop et al. (1968), Lindqvist, Ragab, and Osterland (1970) and Hitzig and Jako (1971). These 3 children, as well as our 5 were all treated by immunosuppressive therapy. One of our children (Case 12) was not affected with a malignant haematological disease but had been treated for 2 years by immunosuppressive therapy for a nephrotic syndrome: 3 months after withdrawal of treatment, a subacute sclerosing panencephalitis appeared and led to death 6 months later (Loirat et al., 1971).

These data strongly suggest that the appearance of monoclonal Ig is favoured by an underlying immunodeficiency whether primary or secondary. Though a precise antibody activity of the homogeneous component has not been proven, it seems probable that monoclonal Ig in childhood often represents homogeneous antibodies similar to the antibodies of restricted heterogeneity elicited in man and rabbits by immunization with carbohydrate antigens (Krause, 1970). In several cases the appearance and detection of the monoclonal Ig coincided with a viral infection. Monoclonal Ig has recently been found in several newborns affected with congenital toxoplasmosis (C. Griscelli, G. Desmont, and D. Frommel, personal communication, 1972). It is of great interest that in half of our cases the monoclonal components were transient. This transient character is similar to the findings in rabbit immunized with streptococcal carbohydrates (Osterland et al., 1966). Immunodeficiency could well be a predisposing factor for some antigenic stimuli to induce formation of uniform antibodies. This hypothesis is in accordance with previous findings in animals in which the immunological defects were induced experimentally (Humphrey, Parrot, and East, 1964; Pierce, Chubb, and Long, 1966).

REFERENCES


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