Cytomegalic Inclusion Disease*

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Cytomegalovirus infection causes, in contrast to other viral infections, characteristic and specific long-lasting cellular changes (Brzosko and Michalowski, 1956; Medearis, 1957; Nelson and Wyatt, 1959; Seifert and Oehme, 1957). For this reason, histopathological diagnostic investigation is of considerable value (Bardier, Bouissou, Régnier, Martinez, Bézy, and Laplanche, 1964; Fetterman, 1952; Seifert, 1961). The group of cytomegaloviruses is widely disseminated in Europe, as well as in both Americas and Asia (Brzosko, 1959; Weller and Hanshaw, 1962; Wyatt, Saxton, Lee, and Pinkerton, 1950). Fatal cases of generalized cytomegalic inclusion disease have been reported in 1-2% of routine paediatric necropsies, and localized salivary gland infection in 10-32% of unselected paediatric necropsies (Seifert and Oehme, 1957; Weller and Hanshaw, 1962; Wyatt et al., 1950). In Great Britain (Crome and France, 1959; Symmers, 1960), the condition seems to be much less common. However, the actual incidence in all countries is probably higher than that reported, since many cases, both fatal and non-fatal, remain undiagnosed. This conclusion was reached following the introduction of methods for isolation of cytomegalovirus and the development of serological procedure (Benyesh-Melnick, Dessy, and Fernbach, 1964; Carlström, 1965; Hanshaw, Betts, Gilbert, and Boynton, 1965; Stern and Elek, 1965).

It has usually been thought that this condition in infants is always congenital, but the results of the virological and serological studies of Rowe and co-workers from Washington (Rowe, Hartley, Cramblett, and Mastrota, 1958) suggest that the infection also often occurs after birth.

Over a five-year period we have observed 20 cases of generalized cytomegalic inclusion disease, which amounts to 5% of all necropsies and 6.4% of necropsies in infants under 1 year of age, and all these children died between the second and the sixth month of life. Since newborn babies are very seldom admitted to our hospital, we were not able to observe early deaths of newborns, which might have been caused by cytomegalic inclusion disease.

The following criteria for differentiating the congenital and postnatal forms of the condition in infants are suggested (Table I).

Of the 20 cases, 9 were included in the first group (Table II), and 5 in the second (Table III). 6 could not be classified with certainty because the data were incomplete. However, taking into account the available information and, particularly the histological findings, it is probable that 4 of these 6 patients were examples of neonatal infection, and that the 2 others were postnatal (Table IV).

The percentage of cytomegalic inclusion disease in our total necropsy material (5%) is rather high.

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*Paper read at the Xth Annual Meeting of the Paediatric Pathology Society in Edinburgh, 1965.

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**Table I**

<table>
<thead>
<tr>
<th>Differentiating Criteria</th>
<th>Congenital Neonatal Form</th>
<th>Post-neonatal Form</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Under 3 months</td>
<td>Over 3 months</td>
</tr>
<tr>
<td>Clinical manifestations</td>
<td>(a) Characteristic severe form including jaundice, hepatospleno megaly, and thrombocytopenic purpura, or first manifestations connected with infection observed during first 4 weeks of life</td>
<td>(a) Presence of cerebral manifestations</td>
</tr>
<tr>
<td>Necropsy findings</td>
<td>(b) Presence of cerebral manifestations</td>
<td>(b) Lack of cerebral manifestations</td>
</tr>
<tr>
<td></td>
<td>(a) Intestinal inflammation present in several viscera, cytomegalic cells, degenerating or containing intranuclear as well as cytoplasmic inclusion</td>
<td>(a) Lack of intestinal inflammation, cytomegalic cells well preserved, containing mainly intranuclear inclusions</td>
</tr>
<tr>
<td></td>
<td>(b) Salivary glands not involved or involved with same intensity as other glands</td>
<td>(b) Most intense changes in salivary glands</td>
</tr>
</tbody>
</table>

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The question immediately follows: is infection by cytomegalovirus in infants really more common in Poland than in other countries? The data from other Polish hospitals, where the percentage of diagnosed cases is much lower, raise some doubt on this question. However, a more probable explanation may be differences in necropsy procedures. In our hospital, for instance, in each case almost all viscera, and very frequently many sections of each organ, are examined microscopically.

### TABLE II

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Sex and Birth-</th>
<th>Sex</th>
<th>Age (mth.)</th>
<th>Hepatomegaly</th>
<th>Splenomegaly</th>
<th>Jaundice</th>
<th>Cerebral Signs</th>
<th>Main Clinical Manifestations</th>
<th>Site of Cytomegalic Inclusions</th>
<th>Cause of Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F 1950</td>
<td>3</td>
<td>Birth</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
<td>Sepsis, encephalopathy</td>
<td>Lungs, liver, kidneys</td>
<td>Cytomegalic inclusion disease</td>
</tr>
<tr>
<td>2</td>
<td>M ?</td>
<td>2</td>
<td>2 wk.</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td></td>
<td>Protracted pneumonia</td>
<td>Lungs, kidneys</td>
<td>Ulcerative enterocolitis with peritonitis</td>
</tr>
<tr>
<td>3</td>
<td>M 3020</td>
<td>2</td>
<td>Birth</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td></td>
<td>Encephalopathy, pneumonia</td>
<td>Lungs, liver, heart</td>
<td>Staphylococcal sepsis</td>
</tr>
<tr>
<td>4</td>
<td>M 2890</td>
<td>3</td>
<td>4 wk.</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
<td>Jaundice, abscesses of skin</td>
<td>Lungs, kidneys</td>
<td>Staphylococcal sepsis</td>
</tr>
<tr>
<td>5</td>
<td>M 2900</td>
<td>2</td>
<td>Birth</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
<td>Sepsis</td>
<td>Lungs, kidneys, brain, spleen</td>
<td>Cytomegalic inclusion disease</td>
</tr>
<tr>
<td>6</td>
<td>M 2400</td>
<td>4</td>
<td>Birth</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
<td>Sepsis, encephalopathy</td>
<td>Lungs, kidneys, lungs, heart</td>
<td>Staphylococcal sepsis</td>
</tr>
<tr>
<td>7</td>
<td>M 2000</td>
<td>2</td>
<td>1 mth.</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td></td>
<td>Acute enterocolitis, anaemia</td>
<td>Salivary glands, lungs, heart</td>
<td>Enterocolitis (E. coli B4011)</td>
</tr>
<tr>
<td>8</td>
<td>M 2150</td>
<td>2</td>
<td>1 mth.</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
<td>Sepsis, dermatitis</td>
<td>Salivary glands, lungs, liver</td>
<td>Cytomegalic inclusion disease</td>
</tr>
<tr>
<td>9</td>
<td>F 2850</td>
<td>2½</td>
<td>Birth</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
<td>Encephalopathy, chorio-retinitis</td>
<td>Lungs, liver, pancreas</td>
<td>Pneumonia with pleuritis</td>
</tr>
</tbody>
</table>

### TABLE III

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Sex and Birth-weight (g.)</th>
<th>Sex</th>
<th>Age (mth.)</th>
<th>Hepatomegaly</th>
<th>Splenomegaly</th>
<th>Jaundice</th>
<th>Cerebral Signs</th>
<th>Main Clinical Signs</th>
<th>Site of Cytomegalic Inclusions</th>
<th>Cause of Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>M 3760</td>
<td>M</td>
<td>6</td>
<td></td>
<td>-</td>
<td>-</td>
<td></td>
<td>Fibrocystic disease of pancreas</td>
<td>Salivary glands, lungs, pancreas, kidneys</td>
<td>Fibrocystic disease of pancreas, bilateral pneumonia, pneumothorax</td>
</tr>
<tr>
<td>11</td>
<td>M 2980</td>
<td>M</td>
<td>4</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td></td>
<td>Protracted pneumonia, pertussis</td>
<td>Salivary glands, lungs, pancreas</td>
<td>Staphylococcal sepsis</td>
</tr>
<tr>
<td>12</td>
<td>F ?</td>
<td>F</td>
<td>5½</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td></td>
<td>Pneumonia with abscesses and purulent pleuritis</td>
<td>Lungs</td>
<td>Congenital malformation of heart, pneumonia</td>
</tr>
<tr>
<td>13</td>
<td>F 1900</td>
<td>F</td>
<td>5½</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td></td>
<td>Congenital malformation of heart, pneumonia</td>
<td>Salivary glands, lungs, pancreas, kidneys</td>
<td>Congenital malformation of heart, pneumonia</td>
</tr>
<tr>
<td>14</td>
<td>M 2550</td>
<td>M</td>
<td>5½</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td></td>
<td>Werdnig-Hoffman disease, pneumonia</td>
<td>Salivary glands, lungs</td>
<td>Bilateral pneumonia</td>
</tr>
</tbody>
</table>

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The question immediately follows: is infection by cytomegalovirus in infants really more common in Poland than in other countries? The data from other Polish hospitals, where the percentage of diagnosed cases is much lower, raise some doubt on this question. However, a more probable explanation may be differences in necropsy procedures. In our hospital, for instance, in each case almost all viscera, and very frequently many sections of each organ, are examined microscopically.
TABLE IV
Doubtful Form of Cytomegalic Inclusion Disease (15-18 probably congenital; 19 and 20 probably postnatal)

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Sex and Birthweight (g.)</th>
<th>Age (mth.)</th>
<th>Clinical Onset (mth.)</th>
<th>Hepatosplenomegaly</th>
<th>Petechiae</th>
<th>Jaundice</th>
<th>Cerebral Signs</th>
<th>Main Clinical Signs</th>
<th>Site of Cytomegalic Inclusions</th>
<th>Cause of Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>15</td>
<td>F 2330</td>
<td>2</td>
<td>1</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Pneumonia</td>
<td>Lungs, liver, kidneys</td>
<td>Fibrocystic disease of pancreas</td>
</tr>
<tr>
<td>16</td>
<td>M 3250</td>
<td>2</td>
<td>1</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>Pneumonia, pertussis</td>
<td>Salivary glands, lungs, liver, pancreas, kidney, adrenals, intestines</td>
<td>Massive pneumonia</td>
</tr>
<tr>
<td>17</td>
<td>M 2600</td>
<td>4</td>
<td>3</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>Purulent pleuritis</td>
<td>Lungs, liver, pancreas, kidneys</td>
<td>Purulent pleuritis</td>
</tr>
<tr>
<td>18</td>
<td>M 2400</td>
<td>3</td>
<td>2</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>Interstitial pneumonia</td>
<td>Salivary glands, lung, liver</td>
<td>Pneumocystic pneumonia</td>
</tr>
<tr>
<td>19</td>
<td>M 3240</td>
<td>3</td>
<td>2</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>Bronchitis, anaemia</td>
<td>Salivary glands, lungs, pancreas, kidneys</td>
<td>Pneumocystic disease of pancreas, staphylococcal sepsis</td>
</tr>
<tr>
<td>20</td>
<td>M 4030</td>
<td>3‡</td>
<td>2</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>Enterocolitis sepsis</td>
<td>Lungs, liver, pancreas, kidneys, heart</td>
<td>Sepsis (Klebs., Esch. coli, B₄₀₁₁)</td>
</tr>
</tbody>
</table>

Large numbers of cytomegalic cells were seldom observed (Fig. 1), most often the cells were single and scattered. They were readily and most frequently found in the lungs (Fig. 2 and 3), less commonly in other viscera (Table V). In the kidneys a large number of cytomegalic cells was

![Fig. 1.—Large numbers of cytomegalic cells in the pituitary gland. (H. and E. × 320.)](http://adc.bmj.com/)

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Fig. 2.—Cytomegalic cells in alveolar space. Note slight inflammatory infiltration of alveolar septa. (H. and E. × 320.)

Fig. 3.—Cytomegalic cell in bronchial epithelium. (H. and E. × 500.)
FIG. 4.—Widespread cytomegalic transformation of renal tubular epithelium. (H. and E. × 320.)

noticed only once (Fig. 4). Usually the cells were single, often limited to vascular endothelium, and in such cases the likelihood of finding cytomegalic cells in urine seems rather small.

TABLE V
Site of Cytomegalic Inclusions

<table>
<thead>
<tr>
<th>Site</th>
<th>Number of Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lungs</td>
<td>20</td>
</tr>
<tr>
<td>Kidneys</td>
<td>12</td>
</tr>
<tr>
<td>Liver</td>
<td>11</td>
</tr>
<tr>
<td>Salivary gland</td>
<td>10</td>
</tr>
<tr>
<td>Pancreas</td>
<td>8</td>
</tr>
<tr>
<td>Brain</td>
<td>6</td>
</tr>
<tr>
<td>Heart</td>
<td>4</td>
</tr>
<tr>
<td>Intestine</td>
<td>3</td>
</tr>
<tr>
<td>Adrenals</td>
<td>2</td>
</tr>
<tr>
<td>Spleen</td>
<td>1</td>
</tr>
<tr>
<td>Hypophysis</td>
<td>1</td>
</tr>
</tbody>
</table>

The question may arise whether or not cytomegalic inclusion disease was the primary cause of death in these cases. In only 3 cases considered to be neonatal were no changes found other than those of cytomegaly. In the other 17 instances there were 4 of fibrocystic disease of the pancreas with bacterial pneumonia, 4 of staphylococcal sepsis, 3 of acute enterocolitis caused by *Esch. coli* B40111, 1 of pneumocystic pneumonia, and 5 of massive pneumonia, 2 with exudative pleurisy (Table VI).

In view of the rather high frequency with which the cytomegalovirus can be isolated from the urine in apparently healthy children, it is possible that during a symptomless 'localized' salivary gland infection, single cytomegalic cells may be formed in other organs. The presence of these cells may be associated with persistent viruria and viraemia. In such an event, the great effort involved in the search for cytomegalic cells in various organs does not seem to have any clinical significance. One can expect, however, that in infants under 6 months of age, combined virological and histopathological investigations of a series of cases may furnish some information of considerable clinical and diagnostic value.

TABLE VI
Cause of Death

<table>
<thead>
<tr>
<th>Condition</th>
<th>Number of Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytomegalovirus infection only</td>
<td>3</td>
</tr>
<tr>
<td>Cytomegalovirus + fibrocystic disease of pancreas</td>
<td>4</td>
</tr>
<tr>
<td>and bacterial pneumonia</td>
<td></td>
</tr>
<tr>
<td>Cytomegalovirus + staphylococcal sepsis</td>
<td>4</td>
</tr>
<tr>
<td>Cytomegalovirus + acute enterocolitis caused by <em>Esch. coli</em> B40111</td>
<td>3</td>
</tr>
<tr>
<td>Cytomegalovirus + pneumocystic pneumonia</td>
<td>1</td>
</tr>
<tr>
<td>Cytomegalovirus + massive pneumonia</td>
<td>5</td>
</tr>
</tbody>
</table>
Cytomegalic Inclusion Disease

Summary

Reported and discussed are 20 cases of generalized cytomegalic inclusion disease in infants 2-6 months of age.

Criteria for differentiating the neonatal and postnatal form of the condition are suggested on the basis of clinical manifestations and necropsy findings.

Generalized cytomegalic inclusion disease was found in 5% of unselected necropsies from the laboratory of morbid anatomy of a Warsaw Children’s Hospital. This apparently high figure is probably related to the rather detailed microscopical examination undertaken, since the cytomegalic cells in the investigated organs were most frequently single. Moreover, in 17 of the 20 cases other changes were found, which might have been the cause of death.

The problem is discussed, whether during a symptomless, so-called localized, salivary gland infection, single cytomegalic cells may perhaps be formed in other organs, and be associated with persistent viruria.

I wish to thank Dr. Adam Michalowski for his interest and for his help. I also wish to thank my colleagues—the clinicians, for the clinical data.

References


Cytomegalic inclusion disease.

K. Gajl-Peczalska

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