

A CASE OF CYTOMEGALIC INCLUSION DISEASE

BY

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Reported cases of cytomegalic inclusion disease in which the diagnosis was made during life are uncommon. I have been able to trace reports of only four cases in which subsequent development has been normal or near normal (Gallager, 1952; Birdsong, Smith, Mitchell, and Corey, 1956; McElfresh and Arey, 1957).

It now seems established that the characteristic cells associated with the disease and first described in 1904 by Ribbert (Seifert and Oehme, 1958) are the result of infection by the salivary gland virus, so named because of the frequency of its finding in human salivary tissue. Similar cellular changes have been noted in the salivary glands of laboratory and other animals and a possible spontaneous disseminated form of the disease has been reported in guinea-pigs (Pappenheimer and Slanetz, 1942). The viruses producing these changes seem to be strictly species specific, and it was not until 1956 that Smith and also Weller, Macauley, Craig, and Wirth isolated the virus from the organs of children dying from the disease, by transmission in tissue culture of human fibroblasts. In the same year Rowe, Hartley, Waterman, Turner, and Huebner were able to demonstrate complement fixing and neutralizing antibody against this or an almost identical virus in human sera.

For over 50 years numerous reports have appeared describing the characteristic cells in nearly every organ and tissue of the body at necropsy. Generally but not always death was attributable to some other associated disease (Goodpasture and Talbot, 1921; Medearis, 1957; Seifert and Oehme, 1958). Most reported cases have been in young infants, but there are also reports of older children (Campbell, Guy, and Grey Walter, 1952) and adults (Wyatt, Simon, Trumbull, and Evans, 1953) being affected.

In 1952, Gallager described the first case diagnosed in life on histological examination of resected lung. In the same year Fetterman and later Mercer, Luse, and Guyton (1953) reported the diagnosis made by examination of the urinary sediment.

The figures so far published suggest that in 10 to 12% of post-mortem examinations on children dying

from unrelated causes cytomegalic inclusion cells are found in the salivary glands only (Farber and Wolbach, 1932; McCordock and Smith, 1934; Bodian, 1953). The present figure at this hospital is of the order of 5% (Bodian, 1959). It may be inferred from this that the virus can lead an apparently harmless existence in salivary tissue, and disseminates only under certain circumstances yet to be defined but one of which appears to be the immature state of the foetus and newborn.

The most clear-cut clinical picture of the disease is that occurring in the newborn and characterized by some or all of the following features: prematurity, early jaundice, petechiae and other evidence of a bleeding diathesis, hepatosplenomegaly, respiratory distress, opisthotonos, fits, choroiditis, anaemia, and thrombocytopenia with a normal or raised white count. There may be radiological evidence of intracranial calcification (Margileth, 1955; McElfresh and Arey, 1957; Medearis, 1957). The diagnosis is suggested by the exclusion of Rh and ABO incompatibility and syphilis by the appropriate tests and by finding thrombocytopenia, which is uncommon in most other causes of this clinical picture. Cerebral calcification may suggest toxoplasmosis, but negative complement-fixation and dye tests and a difference in the distribution of the calcification (Silverman, 1958) favour the diagnosis of cytomegalic inclusion disease. Infection in these cases is presumed to be through the placenta following subclinical infection in the mother.

No other clear clinical picture emerges from case reports although typical inclusion-bearing cells have been detected at necropsy in the appropriate organs in cases of pneumonia, chronic gastrointestinal disorders, encephalitis, and mental defect with microcephaly or hydrocephaly. It is not always clear what part the virus has played in some of these. In certain cases of microcephaly there seems to be evidence of encephalitis occurring *in utero* (Marie, Sée, Grüner, Hébert, Gennes, and Fouquet, 1957). There is no doubt that some infants who have had the generalized form of the disease are left severely mentally retarded.

Diagnosis of the generalized or disseminated form of the disease in life rests on finding the cytomegalic inclusion cells in the urine and possibly the detection of virus antibody in serum, although no reports have appeared of diagnosis based on the latter criterion. It would be unreliable if, as seems possible, infection is widespread without being clinically manifest. Liver biopsy has been used as a diagnostic aid but carries obvious hazards in such cases (Manciaux, Rauber, Gentin, Gilgenkrantz, and Guerci, 1959).

Cortisone and gamma globulin have been advocated in the treatment of the neonatal form of the disease (Birdsong *et al.*, 1956) and the case reported recovered after such treatment. Exchange transfusion should be carried out if the serum bilirubin has reached a dangerous level or is rising rapidly towards such a level.

CASE REPORT

T. G. is the second child of young parents. Their first was born prematurely and died within 24 hours from brain damage. There was no evidence of the neonatal syndrome of cytomegalic inclusion disease.

T. G. was also born prematurely after 32 weeks' gestation which was uncomplicated (maternal Wassermann reaction negative). The birth weight was 3 lb. 6 oz. No abnormality was noted until she was a month old, when she started having cyanotic attacks with progressive dyspnoea. On admission she was limp and grey and no air was entering over the left side of the chest. Radiographs showed a large air-containing cyst in the left lower chest displacing the mediastinum to the right. A left lower lobectomy was performed by Mr. H. H. Nixon after deflation of the cyst. Microscopy of the resected lobe showed considerable collapse, lobular pneumonia with some suppuration, and early interstitial fibrosis. A small number of cytomegalic inclusion cells were seen. A heavy growth of *Staphylococcus aureus* was obtained from the left pleural space.

Her condition improved dramatically after deflation of the cyst and post-operatively she was nursed in moist oxygen and treated with tetracycline. Over the next three days her pulse and respiratory rates rose and were little modified by changing the antibiotic to penicillin in view of the sensitivity of the organism *in vitro*. Oedema developed; no cardiac murmur was heard. Radiographs showed no mediastinal shift and good aeration of the remaining lung tissue.

It was noted that the liver was enlarged 2 in. below the costal margin and the spleen 1½ in. Haemoglobin fell in 10 days from 90% to 53%. Other investigations were as follows: W.B.C.s, 16,000/c.mm. with 14 normoblasts per 100 W.B.C., reticulocytes 2.6%, platelets 110,000/c.mm., plasma proteins 3.8 g.%, electrophoresis showing low albumin and reduced β globulin, blood urea 19 mg.%, E.C.G. normal, urine infected with *E. coli*.

There were several possible causes for deterioration in her condition. She may have had a staphylococcal infection of the remaining left lung although there was no clinical or radiological evidence. She had a urinary infection and also a low haemoglobin and plasma proteins. It was difficult to be sure whether or not she was also in cardiac failure. It seemed possible that cytomegalic inclusion disease had become generalized. It was not possible accurately to deduce the mechanism of the anaemia, but haemolysis probably played the main part although clinical jaundice did not appear. This view is supported by the fact that one month after all infection had been controlled the haemoglobin had again fallen by more than 1% per day in the presence of reticulocyte counts of 4% to 6%.

Cytomegalic cells were not found in the urine, but unfortunately they were searched for on only one occasion.

She was treated with digoxin, gantrisin, penicillin, and small transfusions of packed red cells. She was also given two injections of γ globulin. Cortisone was considered but rejected as severe haemolysis was not a feature, nor did there appear to be any bleeding tendency.

She gradually recovered, but the liver and spleen remained enlarged for some weeks. She was discharged home at the age of 3 months weighing 8 lb. 12 oz. At this time the liver remained palpable 1½ in. and the spleen ½ in. below the costal margins. Haemoglobin was 75%, a chest radiograph normal, and plasma proteins 6.4 g.%. Since then she has been seen on several occasions and was readmitted with another urinary infection which responded to streptomycin. An intravenous pyelogram at the time was normal.

Now, at the age of 19 months, she appears to be a normal infant both mentally and physically. The liver and spleen are no longer palpable.

DISCUSSION

This infant nearly died from the effects of staphylococcal pneumonia which caused a tension cyst in the left lower lobe. Histology of the resected lobe unexpectedly revealed cytomegalic inclusion cells. The virus infection was either acquired after birth or by placental transmission. If the latter, then the inference would be that the infection was latent and only manifested itself in the presence of a severe bacterial infection. It is postulated that post-operatively she developed generalized cytomegalic inclusion disease. It can be argued that there are other explanations of the sequence of events. However, the persistence of haemolysis and hepatosplenomegaly for weeks after recovery from bacterial infection in an otherwise thriving infant coincides with clinical reports of cases of the generalized disease in young infants.

The characteristic cells were not found in one urine specimen, but this may be a transient phenomenon. The occurrence of two urinary

infections in this infant seems to be incidental. Such infections have not been a feature of reported cases.

This case is reported for two reasons. First, because there are few reported cases of apparently complete mental and physical recovery from generalized cytomegalic inclusion disease. For the reasons outlined above, and which are open to controversy, this is believed to be such a case. It can be argued that, had histology not revealed cytomegalic inclusion cells in the resected lung, a diagnosis of the generalized disease would not have been considered when anaemia and hepatosplenomegaly supervened. This argument is the second reason for reporting the case. It is felt that frequent examination of the urine (and possibly serology) when infants present a similar problem might bring to light cases in which the diagnosis would not otherwise have been suspected.

SUMMARY

The literature on cytomegalic inclusion disease is briefly reviewed.

The case is reported of a premature infant who recovered from staphylococcal pneumonia with a tension cyst of the lung and cytomegalic inclusion disease which is believed to have been generalized.

It is suggested that a greater awareness of the disease might lead to its more frequent diagnosis in similar cases.

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