Cytomegalovirus Infection in Early Infancy

Five Atypical Cases

G. McENERY and H. STERN

From the Department of Child Health, Hammersmith Hospital, and the Department of Virology, St. George's Hospital Medical School, London


Cytomegalovirus infection in early infancy. Five cases of neonatal cytomegalovirus infection are described. None of them had the classical picture of neonatal cytomegalic inclusion disease. Two were cases of rhesus isoimmunization and two others were regarded initially as possible cases of ABO incompatibility. They were given intrauterine or postnatal exchange transfusions. Two of these cases were fatal, and one of them was remarkable in that cytomegalic cells were found at necropsy only in the salivary glands.

One infant was born apparently well, apart from certain skeletal and corneal developmental anomalies, and probably acquired his cytomegalovirus infection naturally at about the time of birth.

The possibility of introduction of cytomegalovirus infection by exchange blood transfusion is discussed, along with some of the resulting diagnostic problems.

Infection with cytomegalovirus during pregnancy is a cause of abortion (Diosi et al., 1967) and of severe illness of the newborn. It has gradually become apparent, however, with the wider use of virological techniques, that congenital infection is more frequent than previously realized, and that some of the affected infants have a relatively mild illness (Stern, 1968).

The present report describes 5 cases of cytomegalovirus infection presenting in a wide variety of ways, which occurred during a 2-year period in one neonatal ward.

Case Reports

Case 1. A female infant, the third child of healthy British parents, was born after induction of labour at 37 weeks. The mother was rhesus negative and her previous infant had required exchange transfusion for isoimmunization. The present infant's birthweight was 2460 g. and her head circumference 31 cm. She was jaundiced, and the liver and spleen were palpated 2 cm. and 1 cm., respectively, below the costal margin. Her cord blood showed group O rhesus positive, haemoglobin 10·2 g./100 ml., total serum bilirubin 5 mg./100 ml., and Coombs test strongly positive. An exchange transfusion of 485 ml. blood was given within a few hours of birth. Serum bilirubin increased to a maximum of 18 mg./100 ml. (indirect bilirubin 12·0 mg./100 ml.) by the third day, and then began to fall. However, some jaundice persisted and at 2 weeks of age serum bilirubin was still 11 mg./100 ml., with only 4 mg. as indirect-reacting component, suggesting an obstructive element to the jaundice. Serum lactic dehydrogenase was 370 I.U. (normal range 50-176 I.U.), but serum 5-nucleotidase values of 11 and 13 I.U. were within normal limits. By 3 weeks of age, the serum bilirubin had fallen to 3·5 mg./100 ml., all indirect-reacting. Serum immunoglobulin levels, before the exchange transfusion, were IgG 750 mg./100 ml., IgA 10 mg./100 ml., IgM < 10 mg./100 ml.

Cytomegalovirus was isolated from the infant's throat and urine at 18 days of age; her cytomegalovirus complement-fixing antibody titre was 1:32. Virus was also isolated from the mother's urine, collected at the same time; her antibody titre was 1:128. Serum and urine specimens were obtained from the blood donor 3 months after the transfusion; his cytomegalovirus complement-fixing antibody was < 1:8, and virus could not be isolated from the urine. The infant continued to excrete virus in the urine for at least 6 months. A second urine specimen collected from the mother 3 months after the first failed to yield virus.

The infant's head circumference of 31 cm. at birth was on the 25th centile. At 16 months of age it was 44 cm. which was below the 3rd centile. However, motor and mental development have been within normal limits.

Case 2. This first child of Chinese parents was born at 34½ weeks' gestation after an otherwise normal pregnancy. He weighed 1740 g. and the head circum-
ference was 29.5 cm. (on the 25th centile for this period of gestation). The infant became jaundiced within 24 hours of birth, the serum bilirubin increasing to 18.5 mg./100 ml. (indirect bilirubin 16.5 mg./100 ml.) at 2½ days of age. His blood group was A rhesus positive. The mother's blood was O rhesus positive but contained no immune anti-A antibodies. G6PD content of the red blood cells was normal, Coombs test was negative and there was no reducing substance in the urine. Blood film showed occasional nucleated red cells but no spherocytes, and the red cell fragility curve and haemoglobin electrophoresis pattern were normal. Serum immunoglobulins on the second day of life were IgG 510 mg./100 ml., IgA < 2 mg./100 ml., IgM 10 mg./100 ml.

At 74 hours of life an exchange transfusion of 360 ml. was carried out after which the serum bilirubin level continued to fall. Cytomegalovirus was isolated from urine collected 24 hours after the exchange transfusion. The complement-fixing antibody titre in the serum was 1:256. Urine and serum specimens were obtained from both the blood donor and the infant's mother one month subsequently. Cytomegalovirus was isolated from the mother's urine, and her antibody titre was 1:128. Virus could not be isolated from the donor, and his antibody titre was < 1:8. Virus was again isolated from the infant's urine at 6 weeks of age.

At 7 months his progress is normal. The head circumference has remained between the 25th and 50th centiles.

**Case 3.** This infant, who was the sixth child of Nigerian parents, was born by normal delivery at 38 weeks' gestation, and weighed 3440 g. During the 32nd week the mother had developed an illness diagnosed clinically as chicken-pox. The infant was apparently well at birth except for stunting of the toes, and bilateral central corneal opacities, associated with anterior chamber cleavage syndrome. X-rays showed that each toe of the right foot had an absent distal phalanx, and each toe of the left foot had two absent phalanges.

Serum immunoglobulins levels at 5 days of age were IgG 1100 mg./100 ml and IgM 160 mg./100 ml. The mother's varicella-zoster complement-fixing antibody titre in the serum was 1:20, and the infant's was 1:80. The toxoplasma dye test was positive to a titre of 1:16 in both mother and infant, and the herpes simplex complement-fixing antibody titre was 1:60 in both. Nose, throat, and conjunctival swabs, and urine were cultured specifically for rubella virus without success. Urine was first obtained for cytomegalovirus culture from the infant at 7 weeks of age; this proved to be positive. At this time the cytomegalovirus complement-fixing antibody titre was < 1:8 in both infant and mother. At 3 months of age cytomegalovirus was again isolated from the infant's urine, but never from the mother's. The cytomegalovirus antibody titre in both mother and child was then 1:128. At 5 months of age the serum immunoglobulins were IgG 390 mg./100 ml., IgA 18 mg./100 ml., and IgM 38 mg./100 ml.

Gross generalized aminoaciduria was detected at 3 months of age, but subsequent development has been normal. At 2½ years of age there is no evidence of mental retardation, though the skull circumference is between the 3rd and 10th centiles. The eyes show no abnormality and there is no aminoaciduria.

**Case 4.** This was the seventh child of English parents. He was born with gross hydrops fetalis due to rhesus isoimmunization. The previous infant was unaffected by rhesus incompatibility but the fifth child had died with hydrops fetalis. The husband was heterozygous with respect to D rhesus antigen. In this pregnancy the titre of rhesus antibodies was 1:128 and the peak optical density difference of the amniotic fluid was 0.3 at 27½ weeks' gestation. Two intrauterine intraperitoneal blood transfusions were given at 28 and 30 weeks. The mother was delivered by cesarean section after spontaneous onset of labour at 33 weeks' gestation. The infant was grossly hydropic, weighing 2230 g. The liver was palpated 3 cm. and the spleen 2 cm. below the costal margin. Cord blood showed group B rhesus positive, Hb 8.6 g./100 ml and a strongly positive Coombs test.

Abdominal paracentesis was performed in the left ilioc fossa and 100 ml. blood-stained ascitic fluid removed; 0.02 mg. lanatoside C was given intravenously, and 0.02 ml. mersalyl intramuscularly. An exchange transfusion was started at 45 minutes of age, using 120 ml. of partially packed blood. At 8 hours of age positive pressure ventilation was started on account of increasing periods of apnoea and an arterial Po2 of 20 mm. Hg. Refractory hypoglycaemia persisted for 24 hours and was treated with intravenous glucose and intramuscular hydrocortisone 5 mg. given 4 times daily for 2 days. A large diuresis occurred after the administration of 0.017 mg. ethacrynic acid intravenously. At 20 hours of age a second exchange transfusion of 370 ml. blood was given. A left pneumothorax developed on the second day of life and was treated by an intercostal drain, but chest x-rays suggested continuing lung infection; they showed diffuse mottling and consolidation with a honeycomb appearance in some areas. It was never possible to wean him off the respirator, and he died at 7 weeks of age of respiratory insufficiency. His head circumference at birth was 30 cm. which is on the 50th centile, but after relief of oedema, it remained just over the 10th centile. None of the blood donors was examined for evidence of cytomegalovirus infection.

**Necropsy.** There was bilateral pulmonary consolida-tion, hepatosplenomegaly, mild ascites, and periportal adhesions. The brain weighed 315 g., which was 91 g. below the mean for its gestation (Schulz, Giordano, and Schulz, 1962).

Both kidneys contained microcysts. Histological examination showed numerous typical cytomegalic cells in the lungs, as well as in the pancreas and kidneys.

**Case 5.** This second child of Jamaican parents was born severely hydropic after 37½ weeks' gestation. During the pregnancy the mother, whose blood group
was O rhesus positive, was anaemic, and hydramnios had developed. The placenta was very oedematous. The infant was asphyxiated at birth, giving occasional gasps only and had a heart rate of 48 a minute with generalized cyanosis and flaccidity. An endotracheal tube was passed, and oxygen given by intermittent positive pressure, before regular respirations were established. The liver edge was 3 cm. below the costal margin and the abdomen was tense with ascites. Cord blood examination showed group B rhesus positive, Hb 12.2 g./100 ml and direct Coombs test negative. Haemoglobin electrophoresis showed 61% HbF, but HbA was present and there was a trace of Hb Barts. He was given mersalyl 0.2 ml., digoxin 0.03 mg., and 10 ml. of 3.6% THAM via an umbilical venous catheter. Transfusion was started at 60 minutes of age, exchanging 120 ml. of infant's blood with 110 ml. of 4-day-old citrated blood. He died at 130 minutes of age.

Necropsy. Histological examination of the submandibular glands revealed the presence of many cytomegalic cells with intranuclear and cytoplasmic inclusions (Fig.). There was patchy cytomegaly in the adrenal glands but the cells did not have inclusion bodies. The heart showed areas of myocardial necrosis and fibrosis, with diffuse inflammatory cell infiltration and fibroelastic thickening of the endocardium. There were bilateral tentorial tears with a subdural haematoma, but the brain (Dr. J. M. Anderson, Maudsley Hospital) showed no abnormality though its appearance suggested a gestational age of 34–35 weeks.

Discussion

With wider use of virological techniques it has become apparent that neonatal cytomegalovirus infection is much more widespread than previously thought, and also that infected infants may have milder clinical features than those traditionally associated with cytomegalic inclusion disease (Starr and Gold, 1968; Stern, 1968; Hanshaw, Steinfield, and White, 1968). Failure to thrive, transient purpura, jaundice, or hepatosplenomegaly may be the only features. Indeed infection may be unassociated with any clinical abnormality. While it seems probable that the milder forms of congenital disease are the result of infection comparatively late in intrauterine life, this is not yet certain (Sever and White, 1968).

Four infants of the present series (Cases 1, 2, 4, and 5) were born with either jaundice or hydropic disease, which, in the absence of virological and histological studies, might easily have been attributed entirely to blood group incompatibility. Case 1 undoubtedly suffered from rhesus incompatibility. The persistence of the jaundice with an obstructive element and the abnormal liver function tests were, however, unusual and could have been due to the superimposed cytomegalovirus infection. Urine was not examined for virus until the 17th day after
birth, but excretion of virus by the mother and the absence of evidence of infection in the blood donor strongly suggest that the infant's infection was congenital and not acquired from the donor blood used at exchange transfusion. Rhesus incompatibility was also present in Case 4, and the necropsy confirmed that this was complicated by generalized cytomegalic inclusion disease. Unfortunately, the latter diagnosis was made only after death at the 7th week, and there is no evidence for deciding between true congenital infection and infection acquired from the blood transfusions, either intrauterine or postnatal. The steroids used in treatment might have helped to convert an otherwise mild acquired infection into generalized disease. Whether the cytomegalic inclusion disease, particularly the extensive pulmonary involvement, contributed to the clinical picture and fatal result is uncertain. A chronic pneumonitis, unresponsive to antibiotics and associated with increasing hypoxia, together with the transient pneumothorax and gradual radiological opacification of the lung fields are common problems in babies on long-term pressure ventilation with oxygen.

Case 2 experienced a transient haemolytic jaundice after birth for which there was no obvious cause. The mother's blood group was O, and the infant's was A, but anti-A antibodies were absent from the mother's serum. Haemolytic anaemia is one of the most constant features of neonatal cytomegalic inclusion disease (Emanuel and Kenny, 1966). There is no doubt that this infection was congenital. This is also the case in the last infant (Case 5) who died shortly after birth. The remarkable feature of the latter was the localization of cytomegalic cells to the salivary glands. Such localized salivary gland disease is characteristic of the acquired infections of early childhood, but is rarely observed under 2 months of age, and does not appear to have been reported previously in a newborn baby (Weller and Hanshaw, 1962). Generalized disease, however, cannot be excluded since cytomegalic cells may be scanty and difficult to find even in heavily infected organs (Stern, Lambert, and Shakespeare, 1963). The relation of cytomegalic inclusion disease to the presence of myocarditis in this case is uncertain.

Case 3 is probably an example of symptomless infection with cytomegalovirus. The late development of cytomegalovirus complement-fixing antibodies in both the infant and mother indicate that infection occurred probably just after or possibly even just before birth. The illness which the mother had late in pregnancy probably was chicken-pox in view of the high titres of varicella antibody. However, the infant seems to have been unaffected and subclinical chicken-pox in the neonate has never been described. The raised IgM is therefore more likely to be due to the cytomegalovirus infection. Certainly both infections occurred too late in pregnancy to have been responsible for the skeletal and ophthalmic anomalies. The only developmental anomalies which can be linked with cytomegalovirus infection in anything but a chance relation are micropolygyria and porencephaly (Crome, 1961).

The complication of rhesus and other blood group incompatibilities in the newborn baby by cytomegalovirus infection has been reported recently by a number of authors (Emanuel and Kenny, 1966; Alford et al., 1967; Jack et al., 1967; King-Lewis and Gardner, 1969). It seems unlikely that this association is due to chance. Kääriäinen, Klemola, and Paloheimo (1966a) and Kääriäinen et al. (1966b) have demonstrated the possibility of transmission of cytomegalovirus infection by blood transfusion; this occurred in as many as one-third of patients undergoing open-heart surgery, who require large amounts of blood from multiple donors. Intrauterine and neonatal exchange transfusions often also require several donors, and indeed this method of transmission has been confirmed in at least one case recently (King-Lewis and Gardner, 1969). Obviously this can produce problems in diagnosis, as in the present series, particularly as rhesus incompatibility and cytomegalovirus can both cause similar illnesses. During the past 18 months we have been screening all donors giving blood for exchange transfusions. 52 donors were used in 41 cases. 60% of them were sero-negative for cytomegalovirus antibodies at the time of transfusion, but of 28 who were followed subsequently, only 1 was found to be excreting cytomegalovirus in the urine. However, the baby who received his blood made excellent progress, and showed no evidence of having contracted cytomegalovirus infection.

It is not yet certain whether the relatively late infection contracted from intrauterine or early postnatal exchange transfusion is clinically significant. Observations on mental development are particularly important, for congenital cytomegalovirus infection can still cause mental retardation and microcephaly even when the infant is apparently well at birth (Weller and Hanshaw, 1962; Stern, 1968). Cases 1 and 3 have small heads but mental development is not obviously abnormal after 7 and 16 months, respectively.

The serum immunoglobulins were measured shortly after birth in 3 of our infants (Cases 1, 2, and
3) Viral infections in utero commonly cause obvious increases in the IgM fraction, and sometimes also in the IgA component of the baby's serum, and this has also been described in congenital cytomegalovirus infection (Alford et al., 1967; Sever and White, 1968; McCracken and Shinefield, 1965). Only Case 3 showed a significant increase in the IgM level. However, normal levels of serum immunoglobulins at birth do not exclude the presence of congenital cytomegalovirus infection, as has been pointed out by Sever and White (1968). It may be that the effect on the serum immunoglobulins depends at least partly on the stage of gestation at which infection occurs.

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Correspondence to Dr. G. McEnery, Department of Child Health, Hammersmith Hospital, London W.12.
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G. McEnery and H. Stern

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