FATAL COXSACKIE VIRUS INFECTIONS OF THE NEWBORN

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SYNOPSIS

The clinicopathological features of five cases of fatal neonatal encephalohepatomyocarditis are presented. Hemorrhagic tendency was a prominent clinical feature in four cases; histology of costochondral junction of these cases suggested subclinical scurvy. Coxsackie virus group B, type 3 was isolated in one case.

INTRODUCTION

Since the first documentation of an outbreak of neonatal disseminated Coxsackie B infection in 1955 (Montgomery, *et al*, 1955), numerous epidemics were reported in various parts of the world (Javett, *et al*, 1956; Kibrick and Benirschke, 1956; Mclean, *et al*, 1961; Rantakallio, *et al*, 1970; Rapmund, *et al*, 1959). Most of the affected infants presented with fever, rapid pulse and respiration, cyanosis and circulatory collapse; some had central nervous system involvement and features of hepatitis. Histological examination showed myocarditis, hepatitis, meningoencephalitis, and occasionally adrenal cortical necrosis and pancreatitis. From late February to early May 1974, five cases of fatal encephalohepato-myocarditis were detected in the Premature Nursery of the Kandang Kerbau Hospital. Coxsackie virus group B type 3 was isolated from the tissue in one case. The clinical picture of this outbreak was unusual in that a haemorrhagic tendency was a predominating feature. The clinicopathological studies of these cases constitute the present report.

CLINICAL FEATURES

Case 1. A 2165 gm. male Chinese infant born at 39 weeks gestation to a gravida 2 mother who had a long history of asthmatic bronchitis. The pregnancy was complicated by mild pre-eclamptic toxemia and anemia (Hb11·2gm.%). Labour was spontaneous. The baby was normal and well at birth. Subcostal retraction was noted at day 3. Chest X-ray on day 4 showed increased markings in the right lung. Treatment with Ceporax was started. Meanwhile he had slowly progressive jaundice with the serum bilirubin level reaching a maximum of 15 mg.% on day 5 when he became lethargic and stopped sucking fluid. C.S.F. showed xanthochromasia, cell count: 7/cmm., total protein 175 mg.%, glucose 82 mg.%, globulin positive, chloride 730 mg.%. Culture of C.S.F. was contaminated by *B. subtilis*. Peripheral blood showed Hb 13·4 gm.%. WBC 4,000/cmm. (poly. 72% lymph 24%). Platelet 180,000/cmm. Blood culture grew alpha hemolytic streptococci. The general condition improved slowly on continued antibiotic treatment. On day 12, he turned lethargic with depressed Moro's reflexes, poor muscular tone and a full fontenelle. He passed blood per rectum and blood stained fluid was aspirated from the stomach. The clinical course took a rapid down-turn. Hepatosplenomegaly was noted terminally. He died on day 13. Laboratory investigations showed Hb 10·4 gm.%. WBC 24,000/cmm. (early poly 47%, poly. 19%, lymph. 34%). Platelet 30,000/cmm. C.S.F.: cells 184/cmm. mainly lymphocytes, protein 110 mg.%, glucose 43 mg.% (blood glucose 95mg.%), globulin-positive, chloride 672 mg.%. Culture-sterile. Serum bilirubin—direct 2·5 mg.% indirect 10 mg.%. Alkaline phosphatase 36 units SGPT > 200 U/L (normal 9-36 U/L).

Case 2. A 2050 gm. female Chinese infant born at 39 weeks gestation to a gravida 2 mother who had a grade I rheumatic mitral incompetence and mild anemia (Hb 11 gm.%). Labour was spontaneous and the baby was well at birth. She developed a mild neonatal jaundice

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with serum bilirubin reaching 10 mg.% at day 4. On day 5, she was noted to be cyanosed, lethargic and febrile (101°F). Multiple bruises appeared over the left cheek and both lower limbs. Moro's reflex was depressed and the anterior fontenelle was full. The liver was 2 cms. below costal margin. Jaundice deepened rapidly. Laboratory investigations showed Hb 16·8 gm.%. WBC 8,700/cmm. (early poly. 10%, poly. 37%, lymph. 43%). Platelet 20,000/cmm. Activated plasma thromboplastin time 170 sec./control 49 sec. Prothrombin time (Quick's one-stage) 24 sec./control 13 sec. Serum bilirubin 23·5 mg%. Blood, stool and urine bacterial cultures were all negative. Exchange transfusion was done but the general condition did not improve and she died on day 7.

Case 3. A 2200 gm. male Chinese infant born at 33 weeks gestation to a Gravida 3 mother who had an unexplained fever of 100·4°F during labour. The infant had no spontaneous respiration at birth. After resuscitation the Apgar rating was 5 at 5 minutes. Examination at 2 hours showed moderate chest retraction, diminished air entry to right upper chest, harsh breath sound, and few crepitations. Chest X-ray showed increased markings in right upper zone. He was on oxygen and given injection Ceporax. His condition improved and remained satisfactory. Jaundice with a serum bilirubin level of 11 mg.% was noted on day 3. On day 4 he started to have cyanotic attacks and a fever of 99·1°F. Liver was felt 2 cms. below costal margin. Moro's reflex was normal and the anterior fontenelle was not full. His condition deteriorated next day and he started to have apnoeic spells. Chest X-ray showed improvement of early lesion. Laboratory investigations revealed Hb 14·0 gm. WBC 8,500/cmm. (poly. 71%, lymph. 22%). Platelet 85,000/cmm. Serum bilirubin 14·5 mg.%. Blood sugar 150 mg.%. C.S.F. moderate xanthochromasia, cells 38/cmm, total protein 170 mg.%, glucose 100 mg.%, globulin-positive, chloride 725mg.%. Petechiae were noted over dorsum of both feet on day 6 and the platelet count fell to 25,000/cmm. Apnoeic spells became more frequent. The spleen became just palpable. Bradycardia was noted terminally. Coagulation studies done on day 7 showed activated plasma thromboplastin time 350 sec./control 85 sec. Prothrombin time (Quick's one-stage) 30 sec./control 13 sec. Thrombin-Fibrinogen time 19 sec./control 12 sec. Hypofibrinogenaemia, fibrinolysin and fibrinogen degradation products were not detected. IgM 35 mg.%, IgG 740 mg.%, IgA-0 mg.%. He died on day 8.

Case 4. A 2150 gm. male Chinese infant born at 42 weeks gestation to a primigravida mother. Pregnancy, labour and delivery were uneventful. He was cyanotic since birth and a 2/6 systolic murmur was heard over the precordium. ECG and chest X-ray were normal. His condition was satisfactory until day 9 when he started to have a fever of 100·4°F. He was breathless with subcostal retraction. Repeat chest X-ray showed increased vascular markings. Laboratory investigations showed Hb—14·4 gm.%, WBC 7500/cmm. Platelet 170,000/cmm. His respiratory distress increased in severity. He started to have watery diarrhoea on day 11. He died on day 12.

Case 5. A 2145 gm. female Chinese infant born at 34 weeks gestation to a gravida 3 mother who had massive antepartum hemorrhage due to type IV placenta previa. The infant was delivered by Caesarean section. Her Apgar rating was 5 at birth. She had mild respiratory distress and transient opacity in the right lower lung field during the first 3-4 days of life. Anemia with hemoglobin level of 10·8 gm.% (PCV 40%) was noted on day 2. She also developed a mild jaundice with serum bilirubin level up to 4·6 mg.% on day 5. She was well until day 13 when she started to have irregular rapid breathing and bleeding from rectum. The spleen was enlarged 0·5 cm. and the liver 1 cm. below costal margin. The muscle tone was diminished. Her condition deteriorated rapidly. She had extensive bruising before death on day 14. Laboratory investigations showed Hb 12·4 gm.%. WBC 22,600/cmm. (early poly. 16% poly. 59%, lymph 24%). Platelet 20,000/cmm. Activated plasma thromboplastin time 5 min./control 81 sec. Prothrombin time (Quick's one-stage) 47 sec./control 13 sec. Thrombin-Fibrinogen time 33 sec./control 11 sec. TFT titer saline: 1:8, TFT titre EACA: 1:32. Serial TFT: progressively increased. Hypofibrinogenaemia with fibrinolysins were demonstrated.

PATHOLOGICAL FINDINGS

The main findings were seen in the heart, liver, brain, adrenal glands and lungs. These are summarised in Table I.

The myocarditis consisted of focal cardiomyolysis with acute and chronic inflammatory cell infiltrations (Fig. 1). The lesions were distributed more in the subendocardial region

TABLE I

SUMMARY OF PATHOLOGICAL FINDINGS

Case Numbers	1	2	3	4	5
Myocarditis	+	+	+	+	++
Hepatitis/Hepatic necrosis	++	+++	++	+	++
Meningoencephalitis	+	+	+	+	+
Adrenal cortical necrosis	+++	+++	+++	++	+++
Pneumonitis	+	—	+	—	+

— absent, + mild, ++ moderate, +++ severe.

of the interventricular septum and in the left ventricular wall. Myocarditis was present in all cases but was most severe in case 5.

Macroscopically all the 5 livers appeared congested without the usual features of liver necrosis such as a greenish, soft liver. Microscopically, haemorrhagic necrosis was a feature striking in 4 out of 5 cases. In Case 2, the entire liver was necrotic leaving only incomplete rims of viable hepatocytes around the portal tracts (Fig. 2). The right lobe of the liver was more severely involved than the left. In the milder cases, haemorrhagic necrosis was found mainly in the midzonal region with viable hepatocytes around the portal tracts and central veins (Fig. 3). In Case 4, there was only sinusoidal congestion with necrosis of individual hepatocytes.

Focal neuronal necrosis with acute inflammatory cell infiltration and glial reactions were seen in the inferior olivary nuclei in 4 out of the 5 cases (Fig. 4). In Cases 4 and 5, similar foci were noted in the lateral horn of the cervical and thoracic spinal cord. The meningeal lesions were irregularly distributed, and consisted of aggregations of predominantly mononuclear cells. Occasional mononuclear cell cuffings were present in the Robin-Virchow's space in the cerebral tissue.

The adrenal necrosis was massive, involving the entire fetal cortex in 4 cases (Fig. 5). In Case 4, only focal necrosis was present. Numerous purplish bodies were seen in the necrotic areas. These bodies did not react with Von Kossa or Perl's stainings.

Pneumonitis, consisting of diffuse septal edema and mild lymphocytic and polymorphonuclear cellular infiltration, was present in 3 cases. Case 4 showed focal bronchopneumonia.

Fibrin clots were present in the small pulmonary arteries and in the capillary tufts of renal

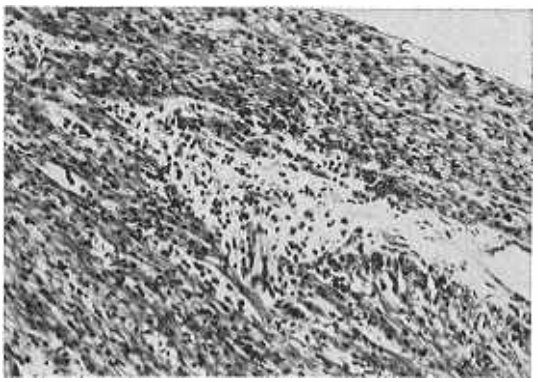

Fig. 1. Heart. Infiltration of myocardium by polymorphonuclear cells and lymphocytes. (H. & E. × 150)

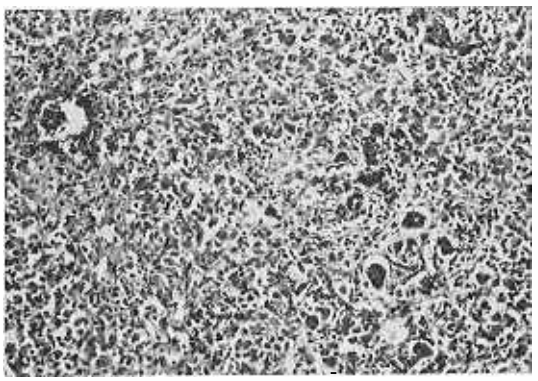

Fig. 2. Liver. Massive coagulative necrosis involving entire lobule with no surviving hepatocytes. (H. & E. × 150)

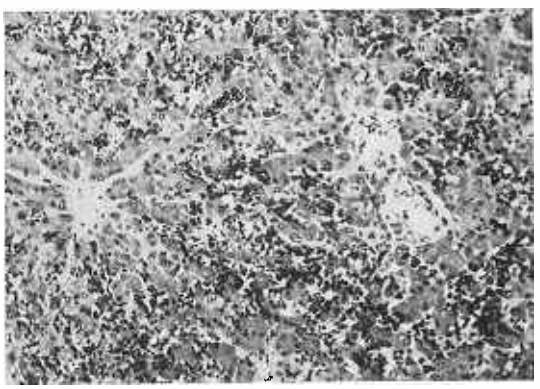

Fig. 3. Liver. Congestion, focal necrosis and lymphocytic infiltration in midzonal region of a lobule. (H. & E. × 150)

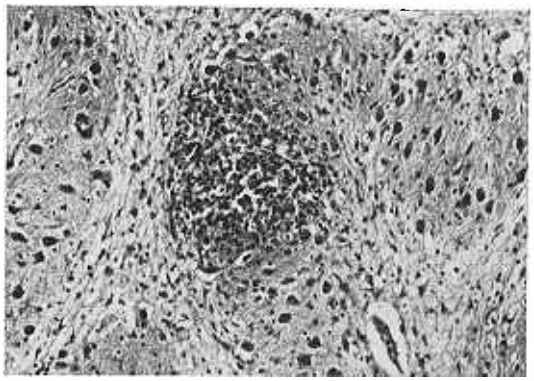

Fig. 4. Olivary nucleus. Focal neuronal necrosis with glial proliferation and acute and chronic inflammatory cell infiltrations. (H. & E. × 150)

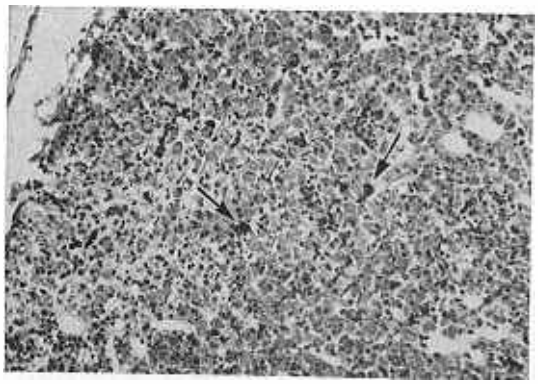

Fig. 5. Adrenal cortex. Massive coagulative necrosis with few purplish stippled bodies (arrows) (H. & E. × 150)

glomeruli of Case 5. Focal haemorrhages in skin, esophagus, small intestine, epicardium, lungs, brain and thymus were noted in all cases. execept Case 4. Histological features of kidneys, lungs and cerebellum were consistent with the respective gestational ages.

There were no necrotic or inflammatory lesions in the pancreas, kidneys and adipose tissue in the neck and omentum in any of the cases. No significant changes were noted in the thymus, spleen, vermiform appendix, Peyer's patches, and mesenteric lymph nodes.

Histological sections of ribs (right 7th or 8th were sectioned routinely) showed features suggestive of Vitamin C deficiency (Table II) in 4 out of 5 cases (Figs. 6, 7, 8).

Heart and fecal specimens from Case 5 were inoculated into monkey kidney tissue culture and into suckling mice. Coxsackie virus group B type 3 was isolated in both specimens.

TABLE II

HISTOLOGICAL CHANGES IN RIBS

Case Numbers	1	2	3	4	5
"Cupping" of costo-chondral junction	++	++	++	—	+
Diminished osteoid formation	++	++	++	—	+
Microfractures	+	—	—	—	+
Subperiosteal hemorrhage	—	++	—	—	—

— absent, + mild, ++ moderate.

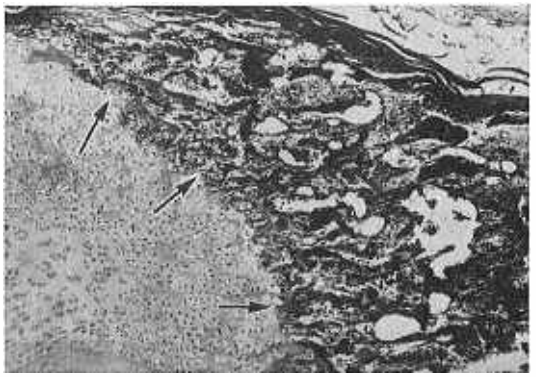

Fig. 6. Costochondral junction. Moderately severe "cupping" (arrows) (H. & E. × 45)

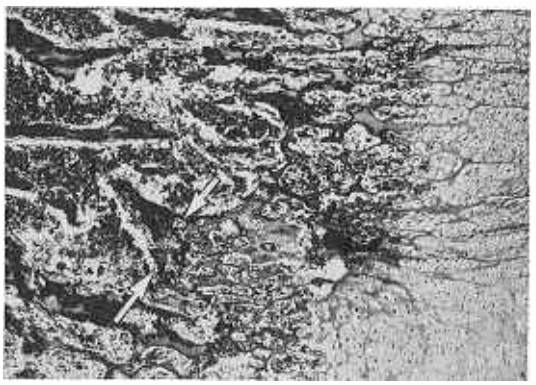

Fig. 7. Costochondral junction. Diminished osteoid deposition around calcified cartilage columns and microfracture (arrows) (H. & E. × 45)

DISCUSSION

The close similarity of the pathological lesions in the five cases suggests a common etiological agent. The combination of myocarditis, hepatitis, or hepatic necrosis, encephalomyelitis and adrenal cortical necrosis in the newborn has been reported only in Coxsackie virus infections. Coxsackie virus group B type 3 was isolated in the heart and faeces of

Fig. 8. Rib. Subperiosteal haemorrhage (arrows) (H. & E. × 150)

Case 5. During the period of the present outbreak in Singapore, Coxsackie virus B3 was isolated in one case of fatal myocarditis in an adult and in 8 cases of Bornholm's disease (Lee, 1974).

The clinical course of neonatal Coxsackie B virus infections may show a biphasic pattern. The first phase is relatively mild, consisting of fever, anorexia, coryza or bouts of loose stools. This is followed by apparent recovery for 1-8 days, and then a more severe second phase characterised by fever and fulminating circulatory collapse. In the present series the first phase of illness appeared to be present in Cases 1, 3 and 5 and consisted of respiratory distress with transient pulmonary consolidation. A bleeding diasthesis was the predominant features of the second phase. This is quite unusual. In a review of 25 cases, Kibrick and Benirschke (1956) could find only one case with bleeding tendency.

Disseminated intravascular coagulopathy was present in Case 5 as shown by the presence of fibrinolysins in the blood and multiple small fibrin thrombi in the lungs and kidneys. The bleeding tendency in Cases 1, 2 and 3 cannot be explained on the basis of disseminated coagulopathy. In these cases massive liver necrosis may have resulted in the depletion of clotting factors. However, the liver necrosis in these cases appeared recent and in all cases except Case 2, there remained a significant amount of viable liver tissue. Other factors predisposing to bleeding tendency may have to be considered. It is interesting to note that all the five cases had low birth weight due to prematurity in Cases 3 and 5, and to retarded intrauterine growth or fetal malnutrituion in Cases 1, 2 and 4. Histological sections of costochondral junctions showed features suggestive of early scurvy in four cases. It is possible that subclinical scurvy may have contributed to the bleeding tendency in these cases.

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