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Fatal infection with echovirus 11

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SUMMARY Twenty-four fatal cases of echo 11 infection in the eleven years 1968–78 are presented. All were children, and could be divided into two groups according to age at death and clinical presentation. The first group comprised 12 babies who died aged between 5 and 11 days after a short illness characterised by collapse, acidosis, and bleeding. At necropsy there was evidence of disseminated intravascular coagulation with haemorrhage into many organs including the renal medulla, suprarenal glands, gastrointestinal tract, and central nervous system. Six cases showed hepatic necrosis which was massive in three. Virus was present in many tissues. Infection was probably acquired from the mothers at delivery in 3 cases. Low maternal neutralising antibody titres and prematurity were thought to be adverse factors in the outcome. The second group consisted of 12 children aged between 9 weeks and 4 years 10 months who died suddenly. Pathological findings included upper respiratory tract infection, pneumonia, encephalitis, and gastroenteritis. Six of this group had been classified as ' cot deaths '. The role of echo 11 in the death of some of these older children is unknown. This report shows the danger of echo 11 to neonates, especially if unprotected by maternal antibody.

Echo 11 has been reported to cause a wide range of clinical syndromes. The most common outcome of infection is probably a subclinical illness followed by immunity.[1] In young children, it may lead to serious illness—such as aseptic meningitis,[2] upper respiratory tract infections,[3] severe diarrhoea,[4] neonatal hepatitis,[5] and myocarditis.[6] Infection occasionally may be associated with a rash.[7] Echo 11 has also been associated with mild paralytic disease [8] and pleurodynia.[9]

Despite the severity of some of these infections reports of death due to echo 11 are scarce. Krous *et al.*[10] described a fatal infection in a newborn infant with meningitis and disseminated intravascular coagulation. In 1978 we described an outbreak in a special care baby unit with 3 deaths.[9] Further reports quickly followed [11 12] as a consequence of the epidemic spread of infection and included an account of an intrauterine death attributed to maternal infection with echo 11.[13] The striking increase in fatal infections as a result of the 1978 epidemic provided a unique opportunity to explore the pathology of echo 11 infections in detail.

Hitherto pathological descriptions had been restricted to a few isolated cases.

Methods

Brief details were provided by the Public Health Laboratory Service, Communicable Disease Surveillance Centre, Colindale, London, of 41 patients reported during the 11-year period January 1968 to December 1978 who had died with an associated echo 11 infection.

A letter explaining the purpose of our study and requesting brief clinical details, a necropsy report, and sections or blocks if available was sent to the appropriate consultant or coroner.

Material obtained in this way forms the major part of the series, although Cases 1–3 died in Cambridge and were initially studied by us.[9]

In each instance the clinical and pathological details were critically reviewed, and where possible sections for microscopial examination were prepared and stained by standard methods.[14] Cases in which information was considered inadequate were excluded.

Results

The 11-year period of the study included the 1972–73 epidemic and most of the 1977–78 outbreak. The number of deaths each year was broadly proportional to the total number of cases reported to the Communicable Disease Surveillance Centre during the same period (Fig. 1). There were 1495 reported isolations of echo 11 in 1978 which was nearly twice the recorded figure of 895 for the previous 10 years.

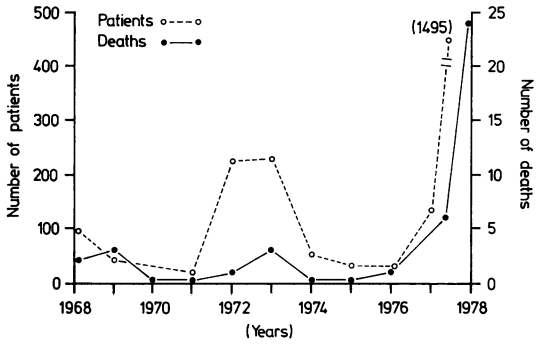

Fig. 1 *Total annual reports of echo 11 (England, Wales, and Northern Ireland, 1968 to 1978), and unselected deaths during the same period from which echo 11 was isolated. (PHLS: unpublished figures).*

During that 10-year period the majority of isolations (498/895, 56%) were from children under 5 years, many of them (219/498, 44%) under 1-year old.

Ten of the 41 fatal cases were excluded from detailed consideration because of lack of information. Seven others were excluded because infection with echo 11 was superimposed on pre-existing potentially fatal disease, and in one case because of doubt about the echovirus type. Thus 24 cases remained in which death could be attributed to echo 11. The oldest was 4 years 10 months old.

When the fatal cases were analysed according to age at death (Table 1) it was clear that the period of greatest risk was during the first 2 weeks of life, since as many deaths occurred then as in the whole of the rest of the first year. The only 4 fatalities over age 5 years to be notified to the Communicable Disease Surveillance Centre in 1968–78 had other diseases which were sufficient to account for death. After these cases had been excluded 24 children were left, and these could be placed in one of two distinct groups according to age and clinico-pathological presentation.

Table 1 *Age at death of cases notified to CDSC (1968–78) associated with echo 11 infection*

Age at death	*Number of (unselected) cases (n=40*)*	*Number of cases studied (n=24)*	
Day			
0–7	12	8	Group 1
8–14	4	4	
15–28	0	0	
Month			
1–6	12	6	
7–12	2	1	
Year			
1–2	2	1	Group 2
2–3	1	1	
3–4	1	1	
4–5	3	2	
15	1	0	
64	1	0	
87	1	0	

*Age of one adult case not known.

Group 1. Twelve infants aged between 3 and 11 days died with an overwhelming illness characterised by a short clinical course including collapse and haemorrhage. At necropsy there was evidence of disseminated intravascular coagulation with haemorrhage in many organs, notably the renal medulla, adrenal glands, gastrointestinal tract, and central nervous system.

Group 2. Twelve children aged between 9 weeks and 4½ years died suddenly. All were presented to the pathologist as coroner's cases, often with no preceding illness.

Group 1 (Table 2)

Cases 1–3 and Case 4 have already been reported elsewhere[9 12] and these papers may be consulted for detailed clinical and epidemiological information.

Clinical history

The onset of illness in the child was preceded by maternal illness similar to that reported in proved echo 11 infection[9 13] in Cases 1, 4, and 6, and a rising titre to echo 11 was present in the mothers of 2 of these infants suggesting that infection had been acquired from them. In others, droplet spread from infected staff may have occurred.

Although 2 neonates died suddenly the clinical details of the others were very similar. The illness began several days after birth with reluctance to feed, floppiness, and pallor. The infants soon became severely ill with collapse, metabolic acidosis, and apnoeic attacks. Seven were notably jaundiced, and 4 infants had spontaneous bleeding. Hepatosplenomegaly, tender abdominal distension, ascites, oedema, and bleeding from puncture sites were variable findings. Case 4 had a macular rash and anuria, but functional renal impairment was not noted in others despite the striking findings at necropsy.

Complete coagulation studies were available only n Case 2 and showed prothrombin time 40 seconds (control 13·0), thrombin time 42 seconds (control 11·0), and fibrin degradation products 40 μg/ml (normal < 10). Other cases had similar changes and were thought to show the clinical picture of disseminated intravascular coagulation.

Although bacterial cultures in life were sterile, except in Case 11 in whom gonococci were grown from a conjunctival swab, the diagnosis was often assumed to be septicaemia and the infants treated

Table 2 *Neonates with fatal echo 11 infection (group 1)*

Case	*Sex*	*Weight (kg)*	*Age at death (days)*	*Microbiology*	*Clinical features*
1	M	2·7	5	Echo 11 from lung, liver, and spleen	Collapse and metabolic acidosis
2	M	2·0	6	Echo 11 from lung, liver, and spleen	Collapse and metabolic acidosis
3	F	2·0	9	Echo 11 from lung, liver, and spleen	Collapse and metabolic acidosis
4	M	3·0	5½	Echo 11 from CSF, liver, heart, throat, and rectum	Respiratory distress, rash, disseminated intravascular coagulation, acidosis, jaundice, shock
5	M	'Term'	7	Echo 11 from lung	Collapse
6	F	2·3	4	Echo 11 from lung and CSF. *Escherichia coli* from blood	Respiratory arrest
7	F	'Preterm'	8	Echo 11 from gut	Septicaemic illness
8	M	3	8	Echo 11 from liver	Collapse, coma, bleeding, convulsions
9	F	2·7	11	Echo 11 from CSF in life. CSF at necropsy grew *Klebsiella edwardii*	Disseminated intravascular coagulation and coma
10	M	2·8	5	Echo 11 from lung and kidney	Sudden death at home on day of discharge from hospital
11	M	1·2	7	Echo 11 from CSF, *Neisseria gonorrhoeae* from conjunctiva	Home delivery at 34 weeks' gestation. Shock and septicaemic illness
12	M	2·3	6	Echo 11 from lungs	Fits, cardiac arrest

CSF=cerebrospinal fluid.

accordingly. Despite this the condition of each continued to deteriorate and they died within 24–48 hours of the onset of the illness.

Necropsy findings

The main external findings are shown in Table 3. Prematurity or low birthweight was noted in half of them.

Internal examination of the 12 infants showed many similarities, and the 2 babies who died suddenly did not differ in any significant detail from the others. Haemorrhage was present in all (Table 4), and there was an accumulation of fluid in the pleural and peritoneal cavities in 6 cases. The ascites caused abdominal distension.

Kidneys. In 11 of the 12 cases the kidneys were enlarged with uniform purple medullary congestion and haemorrhage, and a pale cortex (Fig. 2). Linear fibrin thrombi were present in medullary vessels towards the tips of renal papillae in 7 of the 9 cases for whom sections were available (Fig. 3), and some showed early papillary necrosis. The cortex was essentially normal except in Case 6 in whom multiple fibrin thrombi were also present in glomeruli.

Table 3 *External findings at necropsy in 12 neonates with fatal echo 11 infection*

Findings	*Neonates (n=12)*
Jaundice	7
Bruising around puncture sites	5
Petechiae or purpura	2
Abdominal distension	3
Generalised oedema	1
<2500 g or <36 weeks' gestation	6
No external abnormality	4

Table 4 *Sites of haemorrhage found at necropsy in 12 neonates with fatal echo 11 infection*

Site	*Neonates (n=12)*
Renal medulla	11
Adrenal	11
Gastrointestinal tract	8
Central nervous system	8
Pericardium	6
Bladder mucosa	4
Intrapulmonary	2
Subpleural	1
Capsule of thymus	1
Capsule of liver	1

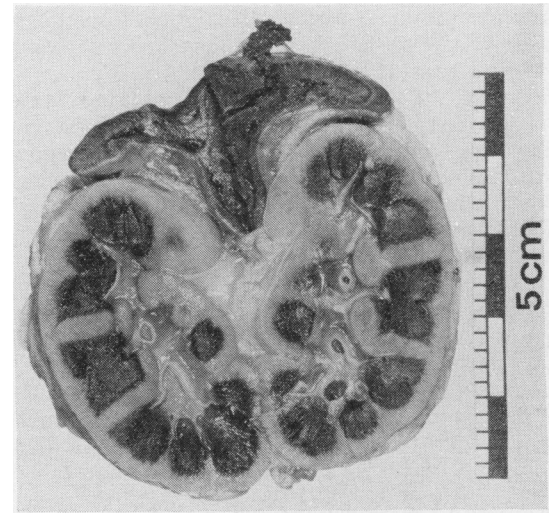

Fig. 2 *Cut surface of kidney showing characteristic congestion and haemorrhage sharply confined to the medulla. There is haemorrhage into the suprarenal gland (above).*

Adrenals. Eleven infants showed adrenal haemorrhage which was severe and bilateral in six (Fig. 2). Microscopical examination showed necrosis and haemorrhage with strands of fibrin in cortical sinusoids (Fig. 4).

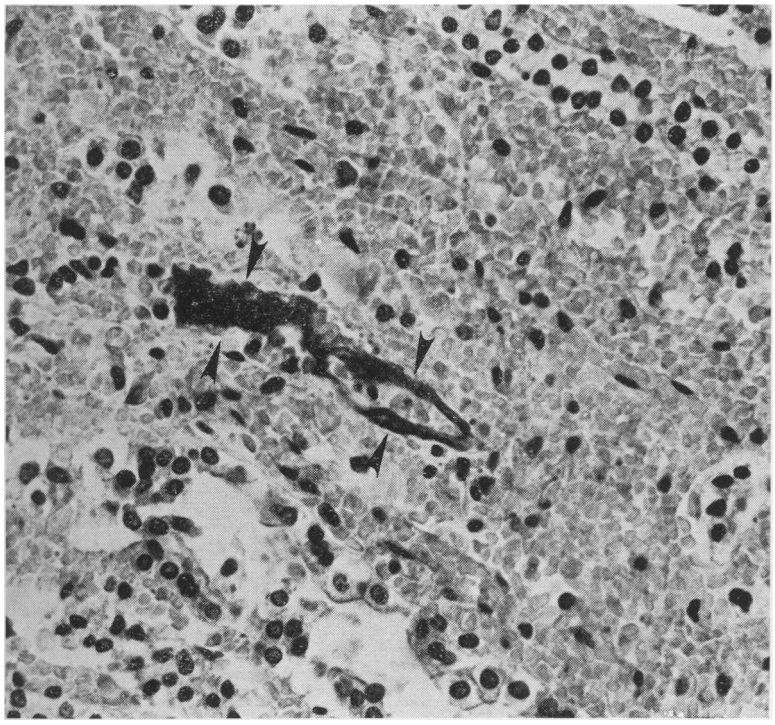

Fig. 3 *Renal medulla of an infant in group 1. There is intense interstitial congestion and haemorrhage. A fibrin thrombus is present in the centre of the field (arrows). Martius scarlet green* ×*450.*

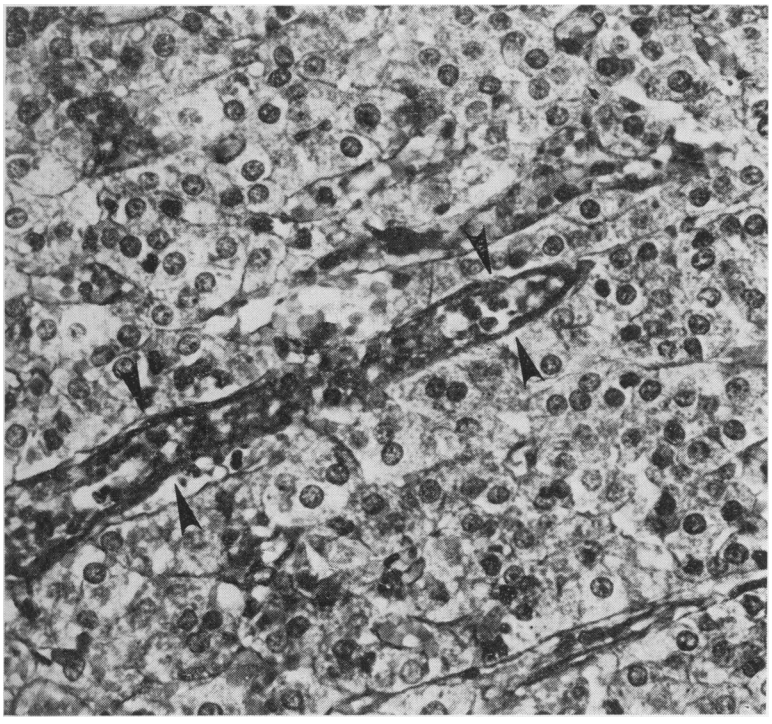

Fig. 4 *Linear deposits of fibrin in an adrenal cortical sinusoid (arrows). Martius scarlet green* ×*450.*

Liver. Abnormalities were found in 9 cases, the liver being enlarged, congested, and mottled. Sections were available from 10 cases and showed extensive centrilobular necrosis with fibrin deposition in sinusoids in 3, and massive hepatic necrosis in two. A further case in which sections were not submitted also had almost total necrosis of the hepatic parenchyma.

Gastrointestinal tract. The intestines were intensely congested, often with subserosal petechial haemorrhages. Submucosal haemorrhages were found at all levels of the gastrointestinal tract with bloodstaining of its contents.

Lymphoreticular system. Sections of spleen from 9 cases showed congestion of the red pulp, which in many contained pyknotic nuclei, fibrin, and nuclear debris. There were many macrophages filled with red cell fragments, the latter also occasionally being seen free in the sinusoids. The white pulp lacked properly formed germinal centres, but mitoses were common. Marginal and medullary sinusoids in mesenteric lymph nodes were filled with blood.

Other necropsy findings were less specific. A single case showed interstitial pneumonia, and another a lymphocytic meningitis. Eight of the 12 infants had haemorrhages into the central nervous system, and there was massive cerebellar haemorrhage in 2 cases. Formal neuropathological examination of fixed brain in 5 cases showed no evidence of encephalitis. No inflammatory infiltration was seen in the myocardium to suggest myocarditis, although Case 2 had necrosis of subendocardial muscle fibres similar to that described in circulatory collapse. Pericardial petechial haemorrhages were found in 6 cases.

Group 2 (Table 5)

Clinical history

Clinical details were incomplete, as only Cases 21 and 24 had been seen by a doctor before death. Case 19 was said to have had an 'acute infection' and Case 18 was described as being ' chesty ' for several days before death.

Case 21 died after a 2-week illness with an upper respiratory tract infection and febrile convulsions. Case 24 had a 2-day history of gastroenteritis and died very shortly after admission to hospital.

Necropsy findings

The abnormalities described at necropsy were mainly confined to the respiratory tract and were non-specific. Six cases showed subserosal petechial haemorrhages. Other abnormalities were hyperaemia of the trachea and major bronchi (6 cases), frothy fluid in the trachea (5 cases), areas of pulmonary collapse (4 cases), and basal bronchopneumonia (2 cases). No abnormality was seen macroscopically in 2 infants.

The predominant abnormalities shown in microscopical examination were mild to moderate tracheobronchitis (3 cases), acute bronchiolitis (1 case), a perivascular and interstitial lymphocytic infiltrate (1 case), and sparse foci of lymphocytes and neutrophils in the lung parenchyma. Other children showed pulmonary oedema and congestion only.

Sections of other organs were examined if available.

Table 5 *Deaths associated with echo 11 infection in older children (group 2)*

Case	*Sex*	*Age*	*Microbiology*	*Circumstances of death*	*Findings at necropsy*
13	M	9 weeks	Echo 11 from lung	Cot death	Respiratory infection
14	M	10 weeks	Echo 11 from myocardium. Abnormal child with pericentric inversion of chromosome I	Cot death	—
15	M	10 weeks	Echo 11 from faeces. Cytomegalovirus from lung	Cot death	Respiratory infection
16	F	11 weeks	Echo 11 from nose but not lung	Cot death	Respiratory infection
17	M	4 months	Echo 11 from lung and nose. Haemophilus from bronchial swab	Cot death	Respiratory infection
18	M	5½ months	Echo 11 from spleen and faeces, *Escherichia coli* from CSF at necropsy	Sudden death 'chesty'	Pneumonia
19	F	6 months	Echo 11 from faeces but not from lung or spleen	Sudden death 'acute infection'	Early pneumonia
20	M	17 months	Echo 11 from trachea	Sudden death	Acute tracheobronchitis
21	F	2 years	Echo 11 from lung, trachea, and brain. Mumps virus* and *Haemophilus influenzae* grown from throat	Unexpected death after 2 weeks' febrile convulsions	Respiratory infection. Encephalitis
22	M	3 years	Echo 11 from throat and urine	Sudden death	Respiratory infection
23	M	4½ years	Echo 11 from trachea	Sudden death	Acute bronchopneumonia
24	F	4 years 10 months	Echo 11 from faeces	2 days of gastroenteritis. Died shortly after admission	Acute infection. Gastroenteritis

*Mumps virus isolated from throat swab 2 weeks before death.

Fibrin thrombi and haemorrhage were not a feature of this group. Early perivascular cuffing was seen in sections of brain from Case 21. Although echo 11 was found in a sample of heart from Case 14 there was no microscopical evidence of myocarditis. Case 24 showed dehydration, congestion of the mucosa of the gastrointestinal tract, and pronounced lymphocytic infiltration of portal tracts in the liver.

Discussion

This retrospective study is thought to provide a reasonably complete picture of fatal echo 11 infection in England, Wales, and Northern Ireland during the period 1968–78. A similar epidemic pattern was reported in the USA.[15]

The sample was probably biased towards those cases in which pathologists were likely to submit samples for virus culture at necropsy. Thus although no deaths among adults were shown to be due to echo 11 we cannot be sure that it never produces a fatal infection in them. Deaths are almost certainly more common among children than the figures presented here would suggest. The clinical diagnosis in neonates was often septicaemia, and it is likely that the true diagnosis was sometimes missed because a virus was not sought.

Because of the difficulty in obtaining data retrospectively, and the dangers inherent in studying histological material and reports often made for quite another purpose, a deliberate attempt was made not to over-interpret the findings. This was particularly true in group 2 where the necropsy report was sometimes in the form of a brief coroner's report, and sections of lung restricted to one or two random samples of uninflated parenchyma.

Despite these difficulties group 1 presents a clearly defined syndrome which can be attributed with confidence to infection with echo 11. All the deaths occurred between the 4th and 11th day of life, and infection was probably acquired by droplet spread or direct contact.[9] Since 3 of the mothers had been ill just before the birth of an infected infant the possibility of transplacental infection cannot be excluded. We studied one stillborn infant of a mother with a severe echo 11 infection, and found no evidence of infection in the child.[13] Paterson and Smith[16] described maternal infection with echo 8 leading to premature delivery of an apparently unaffected baby who died of hyaline membrane disease shortly after birth. Transplacental spread has been described in echovirus types 14, 19, and 22.[17–19] Infection may occur readily at the time of birth since nasopharyngeal and faecal excretion is common.

The absence of maternal antibody in Cases 1–3 with lack of passive immunity in the infant may explain the severity of the infection in these children as has been observed in other neonatal virus infections—for example varicella.[20] The protective action of maternal antibody is suggested by the antenatal antibody status of the mothers in the Cambridge outbreak. Neutralising antibody was sought in antenatal sera stored after rubella tests. There were 18 babies at risk and there was no antibody to echo 11 in the 5 mothers for whom serum was available and whose babies developed symptoms, including the 3 fatal cases. Conversely antibody was present in 2 of 3 mothers whose babies were infected but had no symptoms, and in one of 2 mothers whose babies were not infected.[9] It is suggested that maternal antibody protects from symptomatic infection, but not from asymptomatic colonisation.

A panel of blood donors with neutralising antibody was bled for serum. This was provided for inoculation of the babies in 2 small special care baby unit outbreaks, and no further cases occurred. In one special care baby unit 6 babies whose mothers had no neutralising antibody did not develop infection. However, the numbers are too few for firm conclusions to be drawn.

Enterovirus infections are generally believed to be more severe in neonates, although the reasons are not clear. The marked susceptibility of suckling mice to coxsackieviruses has been attributed to greater availability of virus receptors[21] and to the inability to produce interferon.[22]

The major pathological processes in these infants appear to be overwhelming virus infection and disseminated intravascular coagulation. Echo 11 was isolated from many sites, probably reflecting viraemia, so that it was difficult to separate direct cytopathic effects from damage secondary to circulatory failure and disseminated intravascular coagulation.

The evidence for disseminated intravascular coagulation was clinical, haematological, and histological. Thrombi in the kidney and adrenal gland occurred *pari passu* with evidence of parenchymal damage, while in at least one case it preceded microscopical evidence of liver damage. Many mechanisms might act together to produce disseminated intravascular coagulation—such as viraemia, endothelial damage, shock, and acidosis.

The gross and microscopical pathological features were not specific, but constituted a recognisable syndrome. The renal changes were particularly striking and were similar in appearance to those described by Krous *et al.*[10] in fatal echo 6 infection, and by Philip and Larson[18] in a neonate dying of echo 19 infection. Thomas found a similar appearance in the kidneys of 6 of 1000 consecutive necropsies on stillborn and newborn infants after prolonged

labour without evidence of virus infection, although thrombi were not present in the medulla.[23] The changes we observed were probably a variant of haemorrhagic renal medullary necrosis of infancy.[24]

Adrenal haemorrhage, which was almost invariably present in these neonates, was attributed to multiple factors including a coagulation defect, infection, and hypoxia.[25]

Hepatic necrosis, which was complete in 3 of the cases described here, has also been seen in echo 9,[26] echo 14,[17] and echo 19 infection.[18]

Lymphocytic meningitis and pneumonia were expected findings from clinical reports, although histological evidence was present in only one case of each. Mycocarditis was not seen in this series although one infant showed pronounced focal myocardial necrosis probably secondary to circulatory collapse.[27] However, it may be that the necrosis we saw represented foci of myocarditis in view of the almost complete lack of inflammatory response seen elsewhere. Echo 11 was isolated from the myocardium of 2 of 4 cases of myocarditis cited by Drew,[6] but no details are given of the patients' ages or histological findings.

Erythrophagocytosis in the spleen was interpreted as possible evidence of red cell damage, the red cell fragments being derived from erythrocytes damaged in the circulation either by virus or disseminated intravascular coagulation. This feature is also seen in some of the viral haemorrhagic fevers of adults associated with other viruses.[28]

The older children described in group 2 were quite different from the babies in group 1. The pathological findings in many were minor, and generally confined to the respiratory tract. In nearly all the presentation was that of a 'cot death' or sudden infant death syndrome and the pathological findings, particularly those in the lungs, were similar to previous descriptions.[29] Many other echo types have been isolated from cases of sudden infant death syndrome[30–32] although their significance, like that of other viruses in this syndrome, is unknown.

Only 5 of the children in group 2 could be said with any certainty to have died of echo 11 infection—that is of gastroenteritis, respiratory infection, and possibly encephalitis—and these may not differ significantly from cases successfully treated.[33] In the others echo 11 may have contributed to death—for example by predisposing to bacterial infection, or acting as a 'trigger' in sudden infant death syndrome.

Echo 11 is a rare cause of death, but clinicians should be aware of the danger of this virus to very young babies, especially in epidemics.

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