

ECHOVIRUS TYPE 11 INFECTION IN SINGAPORE

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SYNOPSIS

A clinical and virological report on a recent echovirus type 11 outbreak in Singapore is presented. Infection was most frequent and severe in infants and young children with a male predominancy. All races were affected. Unlike the echovirus type 11 outbreaks which occurred in 1978-1982 in the United Kingdom, Australia and Canada where the commonest symptom was meningitis with high mortality in neonates and infants, the most prominent symptoms observed in Singapore were respiratory. Meningitis was rare with no fatal case to date. The varied clinical manifestations and severity of echovirus type 11 infections are illustrated by case presentations. This is the first echovirus type 11 outbreak recorded in Singapore.

INTRODUCTION

Echovirus type 11 (echo 11) has been associated with occasional cases of aseptic meningitis, encephalitis, paralysis, ataxia, Guillain-Barre syndrome, respiratory infection, gastrointestinal disorder, myocarditis and exanthem. (1, 2, 3, 4) However, in recent years, attention has been drawn to the ability of echo 11 to give rise to widespread infections in the United Kingdom, including England, Wales, Scotland and Northern Ireland, in 1978 and 1982 (5, 6, 7, 8) in Australia in 1979 and 1980, (9, 10, 11) and in Canada in 1979. (12) Infants and young children were most frequently affected during these outbreaks and the commonest symptom was aseptic meningitis with high mortality in young infants. Other symptoms less frequently encountered were respiratory and gastrointestinal illnesses. There were also the odd cases of Reye's syndrome, Guillain-Barre syndrome and meningo-encephalitis.

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From January 1977 to July 1982 only 1 strain of echo 11 was isolated from 1370 clinical specimens received from hospitals, outpatient clinics in Singapore and virus isolates from the Virus Unit, Pathology Department, Singapore General Hospital, for enterovirus investigation. An increase in echo 11 infection was noted in infants and children of paediatric age during an outbreak of respiratory infection which occurred in August to December 1982. Upper and lower respiratory symptoms were the most common presentation. Other symptoms were fever, gastrointestinal disorder, carditis and hepatomegaly. Meningitis was rare. We present here the clinical and laboratory findings.

MATERIALS AND METHODS

Virus Isolation and Identification

Throat swabs, nasopharyngeal aspirates and faecal samples for enterovirus isolation were processed and inoculated into cynomolgus monkey kidney (PMK) cell cultures in triplicates. The cultures held at 37°C were observed daily for cytopathogenic effects over a period of 3 to 4 weeks. All cytopathogenic agents including isolates received from the Virus Unit, Singapore General Hospital, were identified by the conventional tube neutralisation test (1) in PMK with W.H.O. Lim, Benyesh-Melnick (LBM) enterovirus antiserum pools A to H containing antisera to poliovirus types 1 to 3, coxsackievirus types A7, A9, A16, coxsackievirus types B1, B2, B4 to B6, echovirus types 1 to 7, 9, 11 to 27, 29 to 33 and monovalent coxsackievirus type B3, echovirus type 5, 11 and 12 according to instructions given for use of these antisera.

Serology

Our department offers enterovirus serology only for coxsackievirus B myocarditis and for poliomyelitis where faecal isolation proved negative but clinical diagnosis strongly indicates poliomyelitis. Consequently, of the 14 patients in our study series from whom echo 11 was isolated, acute and convalescent sera were available from only two patients. Four of 8 patients had their first blood sample taken 12 to 72 days after onset of illness due to difficulty in recall. A second serum was taken approximately 2 weeks after the first sample from 4 of these 8 patients. Four patients abstained. The sera were tested for neutralising antibody to the echo 11 strain isolated from the respective patients by tube neutralisation test in PMK.

Thirty single sera not accompanied with specimens for virus isolation during the study period (August to December 1982) were screened for echo 11 neutralising antibody against prototype echovirus 11.

RESULTS

Clinical Findings

Case reports were obtained from medical consultants in charge. Ten (71.4%) of the 14 patients in our study series were hospitalised and the remaining 4 (28.6%) were outpatients. Table 1 shows the ratio of males to females affected was 10:4. Seven (50%) of the patients were below 1 year old, six (49.9%) between 13 months to 11 years and one (7.1%) 34 years old. Thirteen (92.9%) of these patients had respiratory symptoms ranging from cold, cough, tonsillitis, pharyngitis, bronchitis, bron-

Table 1 Clinical Findings

CASE	DATE	SEX	AGE	PROVISIONAL DIAGNOSIS	RESPIRATORY	GASTRO- INTESTINAL	CARDITIS	CENTRAL NERVOUS SYSTEM	FEVER	HOSPITALISED IN	OUTPATIENTS OF
1	13.08.82	M	5 yrs	tonsillitis & vomiting	+	+			+	SGH	
2	23.08.82	M	3 wks	myocarditis & Wolff Pakinson White Syndrome			+		+	TTSH	
3	17.09.82	M	2 mths	bronchitis & tracheomalacia	+	+				TTSH	
4	21.09.82	M	4 mths	bronchitis & viral pneumonia	+				+	AH	
5	23.09.82	M	7 mths	bronchitis & pneumonia	+				+	SGH	
6	05.10.82	F	34 yrs	? influenza	+				+		AMKP
7	14.10.82	F	6 mths	viral fever & pharyngitis	+				+	SGH	
8	15.10.82	M	7 yrs	DHF & meningitis	+		+	+	+	Mt EH	
9	19.10.82	M	2 yrs	PUO & URTI	+				+	AH	
10	26.10.82	F	5 mths	bronchitis	+					SGH	
11	02.11.82	M	7 yrs	? influenza	+				+		AMKP
12	17.11.82	M	3 yrs	URTI	+				+		COC
13	22.11.82	F	10 dys	intussusception & bronchopneumonia	+	+				AH	
14	01.12.82	M	11 yrs	URTI	+				+		COC

DHF = Dengue Haemorrhagic Fever
 PUO = Pyrexia of Unknown Disease
 URTI = Upper Respiratory Tract Infection

SGH = Singapore General Hospital
 TTSH = Tan Tock Seng Hospital
 AH = Alexandra Hospital

Mt EH = Mount Elizabeth Hospital
 AMPK = Ang Mo Kio Polyclinic
 COC = Clementi Outpatient Clinic

chopneumonia and pneumonia. Dyspnoea and subcostal retardation were observed in severe cases. Two (14.3%) had accompanying carditis. Only one (7.1%) presented meningitis and petechial haemorrhages were seen around the mouth of this patient. Fever was registered in 11 (78.6%) patients. These illnesses of varying severity lasted from approximately 1 to 4 weeks.

We present below five case reports to illustrate the varied clinical manifestations observed.

Case 1. Reported by Dr W.K. Lee of Ward 50, Tan Tock Seng Hospital.

Q.Z.H. was an eleven months old infant hospitalised on 18.8.82 with a history of poor feeding and excessive crying for one day.

Physical examination revealed him to be dyspnoeic with heart rate of 150 per minute and no murmurs. The lungs were clear. The liver was enlarged to 5 cm below the subcostal margin and the spleen was just palpable. There was no neurological deficit.

Soon after admission, the infant became sweaty and cyanosed. The electrocardiogram (ECG) showed raised S.T. segments. Blood gas analysis showed metabolic acidosis. A diagnosis of myocarditis with cardiac failure was made. The infant had to be intubated and was started on digoxin and lasix.

On 19.8.82, the infant developed paroxysmal atrial tachycardia at a rate of 200 per minute. This was converted to sinus rhythm with intravenous verapamil. Subsequently, his condition stabilised and was extubated.

Laboratory investigations revealed a total white cell count of 15,100 per cmm, polymorphs 55%, lymphocytes 41%, monocytes 2% and eosinophils 2%. Cardiac enzymes were raised. Echo 11 was isolated from the stool. The neutralising antibody titre to echovirus type 11 was 1/5 and 1/320 in serum sampled on 23.8.82 and 6.9.82 respectively.

On discharge (4.9.82) twenty-three days after admission, the ECG showed Wolff Parkinson White syndrome. He was maintained on verapamil and digoxin. He was well on outpatient follow-up.

Case 2. Reported by K.Y. Chan, Consultant, Paediatric Physician and Neurologist, Mount Elizabeth Hospital.

W.P.J. was a seven years old boy hospitalised on 5.10.82 because of frontal headache and vomiting for one day.

Physical examination revealed that the child was afebrile, crying in pain with pale nasal mucosa, swollen on the right side more than the left. The throat was slightly injected. Chest examination showed the percussion note unimpaired, vesicular breath sounds and respiratory rate of 24 breaths per minute and regular. The heart rate was 120 beats per minute with soft systolic murmur (grade 1) at the apex. Blood pressure was 112 per minute. The abdomen was slightly distended, liver just palpable. There was neck rigidity, Kernig's sign was negative, deep tendon reflexes was normal and plantar response bilaterally flexor. Petechial haemorrhages were seen around the mouth. A provisional diagnosis of meningitis and dengue haemorrhagic fever was made.

Laboratory investigations showed C.S.F. pressure was normal and clear, cells nil, glucose 78 mg/dl, chloride 125 mmol/l, protein 20 mg/dl, globulin negative and

no organism seen. Culture of C.S.F. yielded no bacteria. The white cell count was 11600 cmm, polymorphs 92%, lymphocytes 7%, monocytes 1%, eosinophil nil, platelets 170,000 cmm and mESR was 10 mm/hr. Biochemical examination for enzymes on 14.10.82 revealed S.G.O.T. of 25 u/l and 30 u/l a week later (21.10.82). The CPK-MB tested at the same time was 49.7 IU/l and 7.7 IU/l. Electrocardiogram showed sinus tachycardia rate of 187 beats/minute. Echo 11 was isolated from the stool sample and neutralising antibody titres of 1/160 and 1/320 were detected in serum taken on 15.10.82 and 1.11.82 respectively.

Case 3. Reported by Dr B. Ang of Ward 28, Paediatric West, Singapore General Hospital.

N.A. was a five months old girl hospitalised on 20.10.82 because of difficulty in breathing for 4 days. She had a slight cough but no preceding fever or upper respiratory tract infection. Physical examination revealed respiratory rate of 60 breaths/minute with subcostal retraction. Coarse crepitations were heard on both sides of the lungs but there was no rhonchi.

Laboratory investigations showed white cell count of 14,600 cmm, polymorphs 28% and lymphocytes 70%. Blood gas analysis showed PO₂ 74, PCO₂ 36, and pH 7.34. Echovirus 11 was isolated from her stool and the neutralising antibody to this virus in serum taken on 11.11.82 was 1/80.

She became very dyspnoeic the day following admission (21.10.82) and was monitored in ICU for 2 days. She improved with MBE and hood oxygen and was subsequently discharged on 27.10.82.

She was re-examined on 12.10.82 and was found to be well with only occasional cough. There was no dyspnoea and the lungs were clear.

Case 4. Reported by Dr S.C. Goh of the Department of Paediatrics, Alexandra Hospital, Singapore.

D/O A.K.L. was a ten day old child hospitalised on 14.11.82 because of loose yellow stools mixed with blood and mucous following every feed for two days and vomiting yellow fluid on the first day after burping. She was a full term normal vaginal delivery. She weighed 8 lb 5 oz at birth. There was no history of abdominal distension or fever.

On physical examination she was found to be ill and afebrile. Twitching of the right upper limb was noticed and the neck was hyperextended. These symptoms stopped spontaneously. The heart beat was regular, lungs clear, abdomen distended and mildly tense. A mass was felt in the right hypochondrium. The perineum was red.

Laboratory investigations revealed the haemoglobin to be 16.6, the white cell count 15,900 cmm, blood urea 49, Na 112, K 5.8, Cl 88 and blood sugar 151 mg. Serum sodium 112 mmol/l, potassium 5.8 mmol/l and chloride 88 mmol/l. X-ray of the chest showed upper zone pneumonia in the right lobe. Abdominal x-ray showed fluid level in small bowel. Cerebral spinal fluid showed xanthochromic cells of 1, glucose 106 mg/dl and chloride 655 mmol/l. Echo 11 was isolated from nasal aspirate. No serum was submitted for serology.

A provisional diagnosis of intussusception with intestinal obstruction, electrolyte imbalance resulting in fits and bronchopneumonia was made. The patient was managed symptomatically with ampicillin (IV 62.5 mg 6H), gentamycin

(IM 7 mg 8H), Phenobarbitone (IM 10 mg stat and 5 mg 8H) and intravenous replacement of electrolytes. The patient developed apnoea 3 hours after admission and was put on respirator.

Laparotomy revealed hyperemic transverse colon, redundant sigmoid colon, no volvulus, high caecum and enlarged intestinal lymph nodes. The small intestine, stomach, liver, spleen and appendix were normal. The intussusception reduced spontaneously. The patient was discharged on 12.12.82.

Case 5. Reported by Dr K.L. Chan of Ang Mo Kio Out patient Department, Singapore.

Y.K.H. was a seven year old boy examined on 1.11.82. He had a history of cough, sore throat and fever for 3 days.

Physical examination revealed a mild injected throat with enlarged tonsils. Heart beat was regular, lungs clear, liver and spleen not palpable. The provisional diagnosis was "Influenza" and he was treated symptomatically and discharged.

A throat swab sample yielded echovirus 11 and neutralising antibody titre of 1/40 was detected in a single serum sample on 22.12.82.

Virological Findings

Of a total of 18 enterovirus strains isolated from 45 specimens during August to December 1982, 14 isolates were echo 11. The echo 11 strains were isolated from 4 faecal samples, 4 throat swabs and 6 nasopharyngeal aspirates.

Neutralising antibody to echo 11 was negative ($<1/5$) in two sera sampled at the acute stage of infection, but titres ranging from 1/40 to 1/1280 were registered in eight first serum sampled within 12 to 77 days of onset of illness. A second serum taken a fortnight later from 4 of these 8 patients showed that the antibody titres were maintained at a level equal to the first sample in two cases, a two-fold rise was registered in one, and a four-fold drop in the remaining case.

Neutralising antibody to echo 11 was detected in 5 of 30 patients who did not send specimens for virus isolation. Two of these patients who were provisionally diagnosed as viral hepatitis cases had titres of 1/80 and 1/320 respectively. One case diagnosed as viral pneumonitis had a titre of 1/40, a case of Query coxsackievirus B infection had a titre of 1/40 and another case of diabetes mellitus a titre of 1/80.

DISCUSSION

Although the United Kingdom, Australia and Canada were affected by widespread echo 11 outbreaks during 1978 to 1982 no such report was cited from Southeast Asian countries. Instead, during this period, countries in Southeast Asia including Singapore were involved in big epidemics of acute haemorrhagic conjunctivitis caused by Enterovirus type 70 and Coxsackievirus A24 variant. One may wonder as to whether the prevailing picornaviruses of epidemic conjunctivitis at that time had not prevented echo 11 from establishing, and from initiating an outbreak in Singapore, a popular stopover for travellers around the globe all year round.

Our record of enterovirus study from January 1977 to July 1982 showed that only one strain of echo 11 was

identified from 145 strains of enterovirus isolated from 1370 specimens received from hospitals and outpatient clinics in Singapore. The echo 11 strain was isolated from a nasal aspirate collected from a 7 year old girl with respiratory infection and asthma in 1979. An increase in isolation rate of echo 11 was first evident in August 1982 during an outbreak of respiratory infection which lasted to December of the same year. Fourteen (77.7%) of 18 enteroviruses isolated from 45 specimens during this period were echo 11. Serological response of patients investigated confirmed an echo 11 etiology. Five of 30 patients ranging from 18 to 64 years old whose sera were received for enterovirus investigations during this period has neutralising antibody titres 1/40 to 1/320 to echo 11. No specimen was sampled from these 30 patients for virus isolation.

Infection was most frequent and severe in infants under 1 year old with a male predominancy as observed during the echo 11 outbreaks of 1978-1982 in European countries. However, unlike cases observed in United Kingdom, Australia and Canada, the most common symptom was not meningitis in our study series but respiratory. The respiratory symptoms ranged from pharyngitis, tonsillitis, bronchitis, bronchopneumonia and pneumonia. Dyspnoea and sub-costal retraction were seen in severe cases. Carditis not cited by the European counterpart was seen in 11.3% of patients examined. In one instance, the infant was cyanosed with symptoms of myocarditis and cardiac failure. Fever was present in the majority and a few patients had accompanying gastrointestinal disorder. Meningitis was present only in one patient who had also petechial haemorrhages around the mouth and was provisionally diagnosed as dengue haemorrhagic fever and meningitis. One may speculate as to whether the successful poliomyelitis immunisation campaign adopted in Singapore has not in some manner altered the disease pattern of echo 11 from the severe involvement of the central nervous system and the consequent high infantile mortality observed in European countries.

It is hoped that this report will serve to alert laboratories in neighbouring countries to keep a look out for an echo 11 etiology in future outbreaks of respiratory illnesses aside from outbreaks of aseptic meningitis. Also to encourage collaborative study between our laboratory and investigators in neighbouring countries on the multiple manifestations of echo 11 infection which is gaining prominence.

ACKNOWLEDGEMENT

We are grateful to Associate Professor F.M. Paul and Dr B. Ang of Department of Paediatrics, Singapore General Hospital; to Dr K.Y. Chan, Consultant, Paediatric Physician and Neurologist of Mount Elizabeth Hospital; to Dr S.C. Goh of Department of Paediatrics, Alexandra Hospital; to Dr W.K. Lee and Dr L. Ho of Department of Paediatrics, Tan Tock Seng Hospital and Dr K.L. Chan and Dr K.H. Yap of Ang Mo Kio Outpatient Department and their staff, for providing us with the clinical specimens and case reports.

REFERENCES

1. Melnick J L, Wenner H A and Phillips C A: Enterovirus in Lennette E H and Schmidt N J. Diagnostic Procedure for Viral, Rickettsial and Chlamydial Infections. 5th Edition, 1979; 471-534. (American Public Health Association Inc., Washington).

2. Drew J H: Echo 11 virus outbreak in a nursery associated with myocarditis. Australian Paediatric Journal 1973; 9:90-5.
3. Tagaya I Moritsugu Y: Epidemic of Echovirus 11 infections in Japan in 1971. Japan Journal of Medical Science and Biology 1973; 26:149-54.
4. Modlin J F: Fatal Echovirus 11 Disease in Premature Neonates. Paediatrics 1980; 66:775-80.
5. World Health Organisation Weekly Epidemiology Record: Enterovirus Surveillance. Echovirus Type 11, 1978; 47:338.
6. Nagington J, Wreghitt T G, Gandy G et al: Fatal echovirus 11 in outbreaks in special care baby unit. Lancet 1978; 2:725.
7. Davies D P, Hughes-C A, MacVicar J et al: Echovirus 11 infection in special care baby unit. Lancet 1979; 1:96.
8. World Health Organisation Weekly Epidemiology Record: Enterovirus Surveillance. Echovirus Type 11, 1982; 44:340.
9. World Health Organisation Weekly Epidemiology Record: Enterovirus Surveillance. Echovirus Type 11, 1980; 15:109.
10. World Health Organisation Weekly Epidemiology Record: Enterovirus Surveillance. Echovirus Type 11, 1980; 55:217.
11. Kennett M L, Donaldson A, Marshall, J A and Williamson H G: Echovirus type 11 infection in Melbourne — 1953-1980. Journal of Hygiene (Cambridge), 1981; 87:305-312.

Table 2 Neutralising Antibody to Echovirus Type 11

CASE	ONSET OF ILLNESS	SERUM SAMPLED ON	NEUTRALISING ANTIBODY TITRE TO ECHOVIRUS TYPE 11
1	13.08.82	1a* 30.10.82	320 [•]
2	23.08.82	2a 23.08.82 2b+ 07.09.82	<5 320
3	17.09.82	3a 26.10.82 3b 10.11.82	640 640
5	23.09.82	5a 23.09.82 5b 05.10.82	<5 1280
6	05.10.82	6a 09.11.82 6b 24.11.82	1280 1280
8	14.10.82	8a 15.10.82 8b 01.11.82	160 320
9	19.10.82	9a 09.11.82	320
11	02.11.82	11a 22.12.82	40
12	17.11.82	12a 29.11.82 12b 13.12.82	320 80
14	01.12.82	14a 19.01.83	640

a* = first serum sample

b+ = second serum sample.

• = reciprocal of serum dilution.

serology was not carried out on four patients.