COXSACKIEVIRUS B INFECTIONS IN CHILDREN WITH MYOCARDITIS

Freda M. Paul
Marguerite Yin-Murphy

SYNOPSIS

Six children presenting with fever, chest pain, abdominal pain, cardiac irregularities and malaise due to acute myocarditis were described. They were all toxaemic and ill on admission, necessitating intensive therapy care and monitoring of the hearts. Paired sera sampled during the course of disease showed significant rises highly indicative of a recent infection with Coxsackie B virus. Coxsackievirus B4 infection predominanted in the cases studied.

This paper provides supportive evidence of the role of Coxsackie B virus in the etiology of myocarditis in children. This is the first time Coxsackie B virus myocarditis in children has been reported in Singapore. Awareness of laboratory investigations to help determine the etiology of the clinical condition is necessary.

A review of the literature on Coxsackie B myocarditis in children is given.

INTRODUCTION

The Coxsackie Group B viruses are now increasingly recognised as a relatively frequent cause of myocarditis in children.

The Coxsackievirus was named by Dalldorf (1) who isolated it in 1948 from the stools of two paralysed children who lived in a small town of Coxsackie, near New York. The Coxsackieviruses are separated into Group A and Group B compromising 24 and 6 antigenic types respectively. Group A Coxsackieviruses are associated with herpangina, aseptic meningitis, exanthem, a diffuse skeletal myositis and flaccid paralysis while Group B Coxsackieviruses with patchy myocarditis, pericarditis and pleurodynia. These features may be accompanied with encephalomyelitis, hepatitis and pancreatitis. The essential difference between the two groups is the manifestation of myocardial lesions in Group B Coxsackievirus infections.

Coxsackie B myocarditis in neonatal infants was first reported from Southern Rhodesia in 1955 (2) and South Africa in 1956 (3). Similar small nursery epidemics were also reported from other parts of the world. The disease was frequently fatal. In man, as in the mouse, the newborn are susceptible to severe systemic infection by coxsackieviruses. In conditions of over-crowding and in countries where enteroviruses may be hyperendemic, most adults will be passively protected by maternal transmitted antibody. Under these conditions, primary infection with coxsackievirus and other enteroviruses are acquired relatively harmlessly during the first few months of declining passive immunity or in the next few years of early childhood when the consequences are likely to be trivial in most cases, though some will manifest such consequences as meningitis or acute myocarditis.

Department of Paediatrics
National University of Singapore
Singapore General Hospital
Outram Road
Singapore 0316

Freda M. Paul, MD, FRCPE, FRCPG, DCH
Associate Professor

Department of Microbiology
National University of Singapore

Marguerite Yin-Murphy, MA, Ph.D, Dip.Bact.
Associate Professor

With improved hygiene as seen in developing and developed countries, this accumulation of susceptible persons will allow the appearance of periodic epidemics when temporary circumstances favour the spread of an enterovirus. Since non-immuned mothers and their newborn babies are vulnerable to these viruses, it is understandable that severe cases of neonatal infection by coxsackie B viruses, sporadic or in nursery outbreaks, with myocarditis as a common feature has a usually high mortality. These first cases were reported by Montgomery in 1955 from South Africa (2) and by Jennings (4) of Coxsackievirus B fatal myocarditis with cardiomegaly.

The true incidence of Coxsackievirus carditis is difficult to determine because most reports concern positive cases and do not specify the background population of virologically negative cases with similar diseases or of infections by the same viruses without cardiac illnesses. Grist and Bell of Glasgow (5) state that Group B coxsackievirus infections can be demonstrated up to 39% of cases of otherwise unexplained acute myocarditis and pericarditis.

In 1968, Murphy and Lim (6) attempted to identify a collection of 108 virus isolated from stool samples collected from apparently healthy children in squatter areas and showed that prevailing viruses were echovirus 7 (22%), 13 (20.9%), 6 (14%), 14 (6%), 1-8 (5.5%), 26 (4%), 2 (3%), 11-19 (3%), 15 (3%), 18 (2%), 4 (1%), 9 (1%), 12 (1%) and coxsackievirus B2 (3%) respectively. In 1979, Murphy and Kay (7) gave a preliminary report of an unidentified virus from two cases of infantile myocarditis from Brunei. The virus isolated on two separate occasions in consecutive years showed characteristics of an enterovirus.

Coxsackie B virus myocarditis has not been reported in Singapore before and the purpose of this report is to make people aware of the existence of Coxsackie B virus in association with myocarditis in children. The following are the case reports of some of the children admitted to the paediatric unit of the Singapore General Hospital.

Case 1 - Myocarditis with Extrasystoles

E.S. was a 4-year old Indian girl admitted on 27.9.1976 to the paediatric unit of the Singapore General Hospital. The child was reported to have had an upper respiratory infection about two weeks prior to admission. The child was treated by a government outpatient clinic and the fever subsided but the child was noted to be a little breathless, and was taken back to the clinic by the mother. On routine examination of the heart by the doctor on duty, she discovered extrasystoles in the heart and admitted the child to the department of paediatrics. This child was the 5th member of a family of six children and the father was a labourer in the lower income group. The child was perfectly well prior to this illness.

Physical examination revealed a child who was thin and underweight, weighing only 19.25 kg. (25th % Singapore standards). She measured only 97 cms in height (25th % Singapore standards). She was afebrile. The heart was not enlarged clinically but on auscultation, the extrasystoles were heard every 6th beat. The blood pressure was 90/50 mm of Hg. The liver was 2 cms and the spleen was not enlarged. Laboratory investigations showed Haemoglobin of 11.2 gms%, WBC 7700 per cubic mm. Polymorphs 63%; lymphocytes 22%; monocytes 3% and eosinophils 12%. The platelet count was 315,000 cmm. The ESR was elevated being 177 mm per hour. A throat swab did not grow any pathogenic bacteria. The cardiac enzymes, serum glutamic-oxalo transaminase (SGOT) was normal being 26 units. The serum lactic dehydrogenase level was 477 units.

X-rays of the chest showed a globular heart and an electrocardiogram showed a heart rate of 150 beats/minute, with a normal mean electrical axis, there were ventricular systoles in the ratio of 1:3. Faecal samples inoculated into primary monkey cell cultures were virus negative. The patient's second serum showed a sixteen-fold neutralising antibody rise to Coxsackie B4 virus, and both the first and second sera had very high neutralising antibody to Coxsackie B2 virus as shown below.

NEUTRALISING ANTIBODY TITER IN

VIRUS	First Serum sampled on 27.09.1976.	Second Serum sampled on 12.10.1976.
Coxsackie B1	<4*	<4
Coxsackie B2	512	512
Coxsackie B3	<4	<4
Coxsackie B4	8	128
Coxsackie B5	4	4
Coxsackie B6	4	4

*4 = reciprocal of serum dilution

The high Coxsackie B2 neutralising antibody in both sera could indicate a heterotypic response to a past infection with Coxsackie B2 virus or concurrent infections with Coxsackie B2 and B4 viruses. The final diagnosis of this child was myocarditis affecting the atrioventricular node and producing ventricular extrasystoles (Figure 1(a) and Figure 1(b)). The child was in hospital for three weeks and the ESR, dropped to 10 mm from 177 mm, but the extrasystoles persisted and gradually disappeared after a period of six weeks.

Case II - Myocarditis with Extrasystoles

L.Y.S. was a 11-year old Chinese boy, who was admitted on 2.12.1980. The child had influenza-like illness about two weeks ago with fever that subsided after 4 days. The patient recovered and was active but the mother noted the child was breathless and he complained of pain over the praecordium after exertion. This child was a normal baby at birth and was normal in his development. He was the only child of parents who were both healthy.

Physical examination revealed a patient who weighed 36.4 kg. (90th % Singapore standards) and measured 1.47 meters (90th % Singapore standards). He was febrile with a temperature of 37°C. His pulse was 110 beats/minute and his respiratory rate was

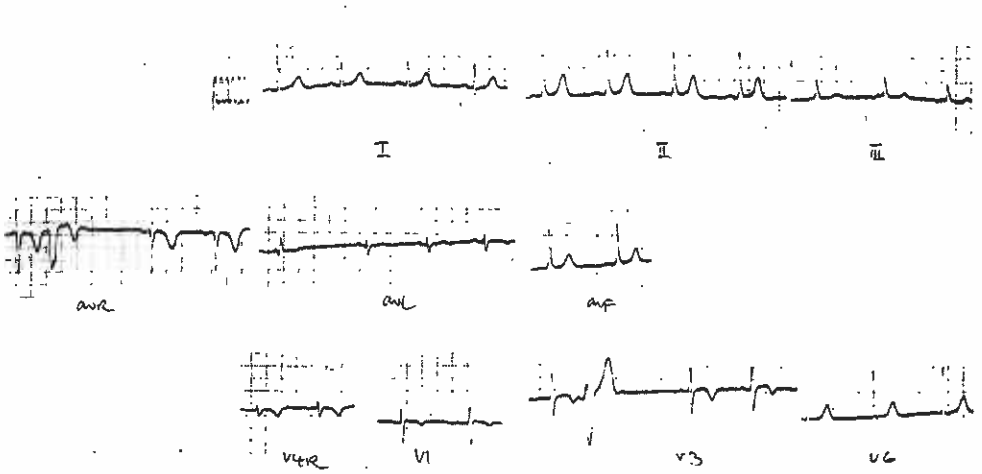

Figure 1(a) : To show low voltage and ventricular extrasystoles in V3.

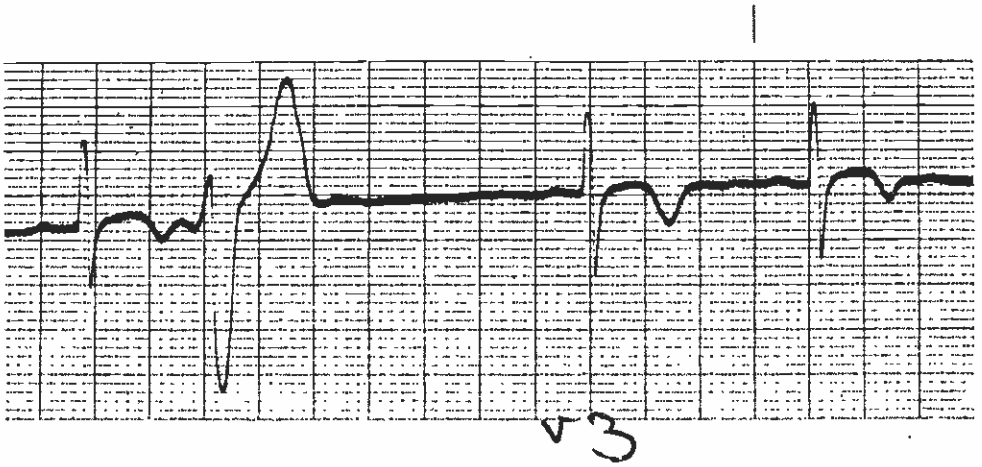

Figure 1(b) : To show close up of ventricular extrasystoles.

rapid being 30 per minute.

The tongue was furred and the tonsils were enlarged. The blood pressure was 110/80 mm of Hg.

The apex beat was in the 5th left intercostal space 3 inches from the mid-sternal line. It was irregular due to extrasystoles. No abnormality could be detected in the other systems.

The following investigations were done on

3.12.1980 Haemoglobin 15.3 gm% WBC 6,200 cmm P-60% L-35% M-2% E-3% Platelets normal.

5.12.1980 The serum electrolytes were normal. SGOT was 34 I.U. (normal range was 15 to 33 I. Units). The total lactic acid dehydrogenase was 385 units. Stools was virus negative. However, the serology was strongly positive for Coxsackie B4 virus with high neutralising antibody titres registering a two-fold rise between the paired sera as shown below.

NEUTRALISING ANTIBODY TITRE IN

VIRUS	First Serum sampled on 3.12.1980.	Second Serum sampled on 17.1.1981.
Coxsackie B1	8	8
Coxsackie B2	16	16
Coxsackie B3	16	16
Coxsackie B4	64	128
Coxsackie B5 & B6	<4	<4

Radiographs of the chest did not reveal any enlargement of the heart but the electrocardiogram

showed the extrasystoles (Figure 2(a), 2(b) and 2(c)). The diagnosis was, therefore, strongly indicative of myocarditis due to Coxsackie B4 virus infection. This child's heart was monitored carefully in the intensive unit and he remained there for 72 hours. On the third day after admission, there were no extrasystoles. The child remained in hospital for 10 days and on follow-up six months later the irregularity of the heart had disappeared.

Case III – Myocarditis presenting as a pyrexia of unknown origin

L.W.C. was a 11-year old child who presented with a history of fever for 4 days with vomiting after every feed and breathlessness for 2 days. The child also complained of loss of appetite, weight and frontal headache. The child was also noted to be getting breathless after mild exertion for the last two days prior to admission. He had been treated with anti-pyretics by a general practitioner but the fever persisted.

This child was the youngest of 3 children, and both parents were healthy and other members of the family were well. Physical examination revealed a child who was ill and toxaemic with a temperature of 38°C. He complained of pain over the praecordium. He was a well covered boy weighing 35.5 kg. which was at the 97th percentile Singapore standards and he was tall measuring 153 cms, which was greater than the 97th percentile Singapore standards. The tongue was furred and the tonsils were enlarged. The apex beat was in the 5th left intercostal space three inches from the mid-sternal line, with a tachycardia of 120 beats per minute. There were no irregularities and no bruit was audible. The blood pressure was 120/80 mm of Hg. The liver was enlarged 2 cm below the right costal margin and the spleen was just palpable. The deep reflexes were increased. The clinical diagnosis was that of myocarditis. Investigations showed the haemoglobin was 15.2 gms% and the total white cell count was 11,500 cmm, with a differential count of polymorphs of 91%, lymphocytes of 6%, monocytes of 3% and a platelet count of 170,000 per cubic mm. The blood electrolytes were within normal limits. The cardiac enzymes were within normal limits. The creatininekinase was 1.8 unis and the serum glutamic-oxalo transaminase was 29 units which was normal.

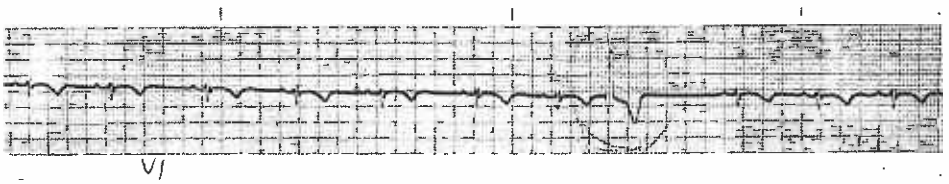

Figure 2(a) : To show low voltage and extrasystoles.

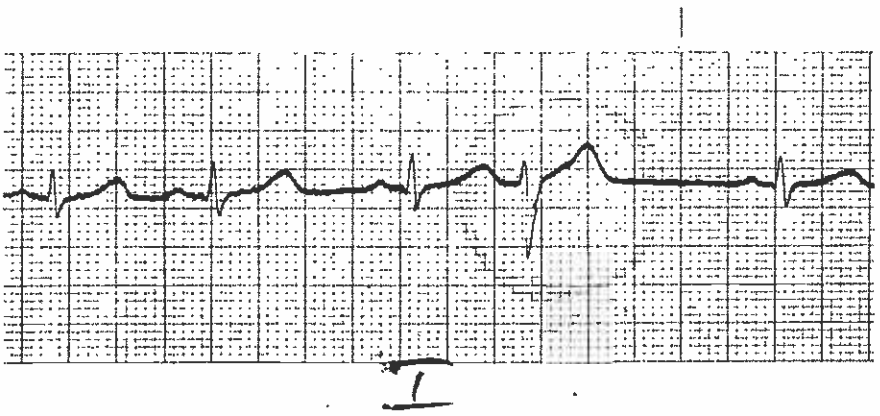

Figure 2(b) : To show extrasystoles.

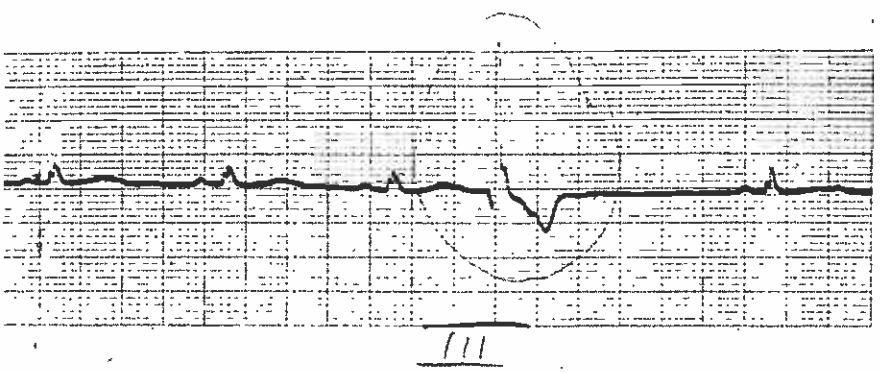

Figure 2(c): To show extrasystoles in lead III.

The serum lactic dehydrogenase level was 419 units per litre. The serum was Widal negative and no pathogenic bacteria was grown from his blood culture. The blood tests for dengue haemorrhagic fever were also negative. However, an E.C.G. done showed low voltage in leads 1, AVL and V6, characteristic of changes seen in myocarditis (Figure 3). The child was in the intensive therapy cubicle for three days and required initially intravenous fluids. He was given intravenous antibiotics, ampicillin and cloxacillin because of the high swinging temperature and enlarged tonsils. The results of serology for coxsackievirus infection is shown below.

NEUTRALISING ANTIBODY TITRE IN

VIRUS	First Serum sampled on 17.5.1980.	Second Serum sampled on 1.6.1980.
Coxsackie B1	8	8
Coxsackie B2	8	8
Coxsackie B3	16	8
Coxsackie B4	⩾128	⩾128
Coxsackie B5	4	4
Coxsackie B6	4	4

The serology for Coxsackie B virus showed a persistently high neutralising antibody titre indicative of current or recent infection by Coxsackie B4 virus.

The temperature took about five days to revert to normal and he was discharged one week after admission to hospital after the electrocardiogram was normal.

Case IV - Myocarditis with Paroxysmal Tachycardia

S.B.A.B. was a 11-year old Malay boy admitted on 17.5.1979, because of palpitations of the heart off and on for one day. The mother felt the child's heart and felt it was beating very fast and took the child to the school health doctor. Prior to this illness, he had fever, cough and cold for one day about one week before this illness, and he was treated by a general practitioner. The school health doctor recorded a heart rate of 220 beats per minute and on carotid massage, she reduced the rate to 170 beats per minute. However, the tachycardia recurred and the boy was admitted with a heart rate of 220 beats per minute.

This child had been perfectly well before and was the youngest of three children.

Physical examination revealed a child who was relatively comfortable, weighing 24.5 kg. (30th percentile Singapore standards). The temperature was 37°C. The pulse rate was 170 per minute. The pharynx was injected. Examination of the heart revealed the apex beat to be in the 5th left intercostal space with a heart rate of 170 per minute. There were no murmurs. The blood pressure was 100/60 mm of Hg. The chest was clinically clear. Examination of the abdomen revealed a liver of 1 cm. The central nervous system was normal. The clinical diagnosis was that of paroxysmal tachycardia probably due to myocarditis which was precipitating the pace maker to beat faster. A long strip electrocardiogram (Figure 4) confirmed this with a heart rate of 170 beats per minute with a good QRS complex and inverted T waves in all the limbs. The haemoglobin was 12.3 gms%, the total white cell count was 10,900 cmm with a platelet count

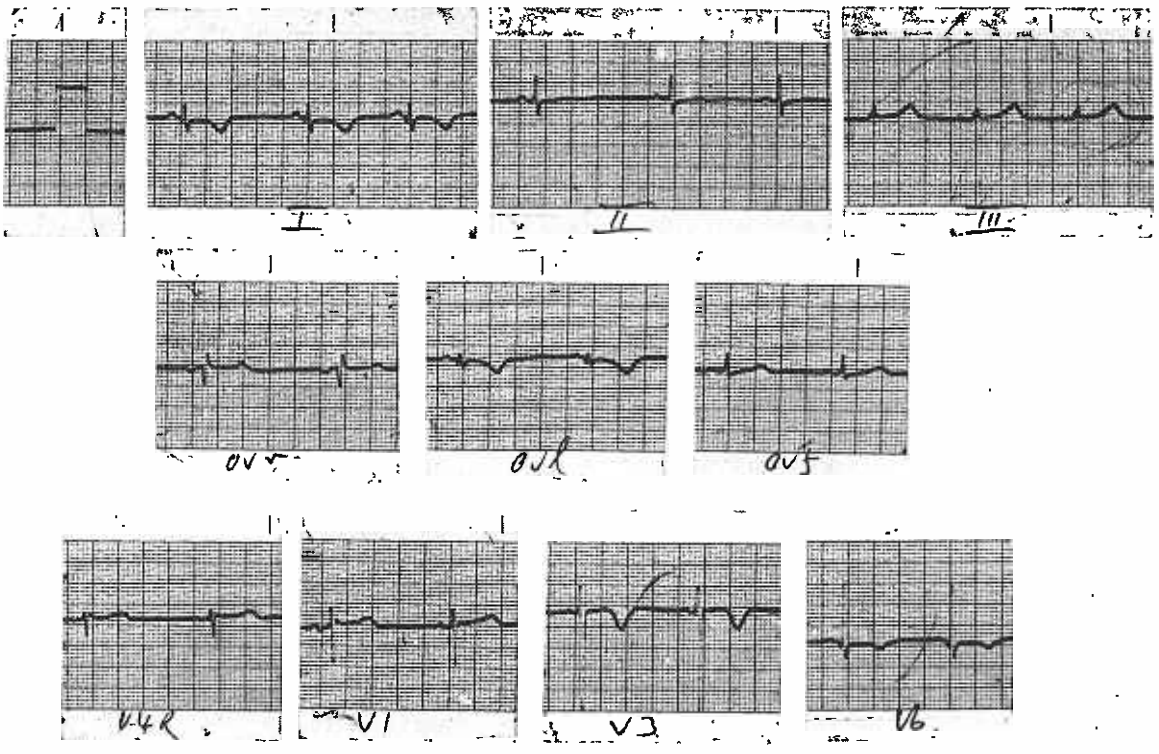

Fig. 3 : To show low voltage in leads I, II, III and V6.

of 170,000 cmm. The ESR was 50 mm per hour. The electrolytes were quite normal.

The serum glutamic-oxalo transaminase level was 29 units which was not raised and the lacto dehydrogenase level was 455 units. Radiographs of the heart revealed the heart to be enlarged. Serology for influenza, parainfluenza, and mycoplasma infection was negative. No respiratory virus was isolated from the nasal aspirate and no virus was isolated from the stools. However, neutralising antibody titre to Coxsackie B4 virus was 1/40 for the first sample and two weeks later the titre was 1/80. Neutralising antibody to the remaining coxsackie-viruses was 1/20. The child's electrocardiogram reverted to normal after a week's stay with hospital bed rest.

Case V - Viral Myocarditis

L.P.W. was a 3-year old Chinese girl who had fever which occurred rather suddenly associated with chills without rigors. She was seen by a general practitioner who gave her antipyretic which reduced the fever but the temperature recurred again. With the second onset of fever, the child was taken to another general practitioner who gave her another antipyretic with no avail. The child then complained of severe epigastric pain and her appetite was poor. She looked very pale and was rushed into hospital. This child had been very healthy before with no episodes of heart trouble.

The child was the elder of 2 children, and the family was well.

Physical examination revealed a child weighing 12.3 kg. (50th percentile Singapore standards). She was of average height but the main feature was a temperature of 39°C with a toxic appearance of the face. The respiratory rate was 30 per minute and the pulse rate was 140 per minute. The skin was warm and dry with no visible petechiae. The throat was mildly injected. Examination of the heart showed the apex beat to be in the 5th left intercostal space just outside the mid-clavicular line with a tachycardia and loud first and second heart sounds. No murmurs were audible on admission. The blood pressure was 90/60 mm of Hg. The central nervous system was normal. The liver was enlarged 3 cms and the spleen was enlarged to 2 cms. The clinical diagnosis was that of a pyrexia of unknown origin and the possibilities of subacute bacterial endocarditis, malaria, typhoid and haemorrhagic fever were entertained. However, all blood tests for the above were negative. The throat swab culture and the blood culture were normal.

The haemoglobin was 12.8 gm% and the total white cell was 7100 cmm, with polymorphs of 50%, and a lymphocyte count of 35% and monocytes of 2%. The platelet count was normal. The ESR was 50 mm on admission and one week later dropped to 30 mm per hour and later to 17 mm per hour.

Radiographs of the heart showed the configuration to be widened with congested lung fields. An electro-cardiogram showed inverted T-waves in leads 4, 5 and 6. It is after the radiographs and electrocardiograms were done that the possibility of myocarditis was entertained (Figures 4, 5(a) and 5(b)).

The serum glutamic-oxalo transaminase was 31 units, which is the top limit of normal and the serum lactic dehydrogenase was very elevated being 602 I.U., the normal range being 180 to 280 I.U. The temperature settled and the pulse rate was 100 beats/minute on the third day after admission. However, a systolic bruit was audible to the left of the sternum with a widely split second sound. This child was followed up as an outpatient for six months and on the last follow up date her heart clinically was not enlarged and a faint systolic bruit was audible. The heart size was not enlarged radiologically.

The patient's sera showed neutralising antibody response indicative of current coxsackievirus B3 infection as shown below.

NEUTRALISING ANTIBODY TITRE IN

VIRUS	First Serum sampled on 30.11.1979.	Second Serum sampled on 7.12.1979.
Coxsackie B1	<4	<4
Coxsackie B2	<4	4
Coxsackie B3	16	64
Coxsackie B4	16	16
Coxsackie B5	<4	<4
Coxsackie B6	<4	<4

Case VI - Coxsackie B4 Myocarditis Presenting with Epigastric Pain and Heart Block

B.S. was a 11-year old Sikh boy admitted on 28.11.1979 with a history of epigastric pain on and off for about

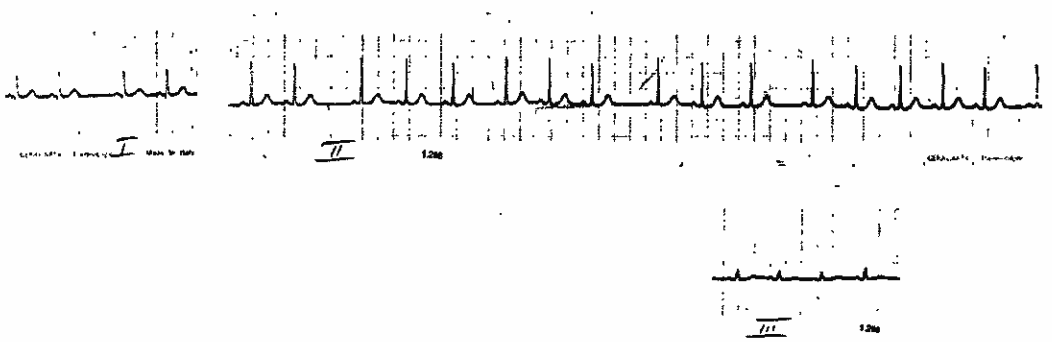

Fig. 4 : To show tachycardia and low voltage in lead 3.

one month. The epigastric pain was not related to meals and was associated with malaena or diarrhoea. The patient was the seventh of nine children and had been perfectly healthy before this, except for an appendicitis two years ago, which required an appendicectomy.

Physical examination revealed a child weighing 36.5 kg. (70th % Singapore standards) and with a temperature of 37°C. The pharynx was not injected and examination of the heart revealed the apex beat to be in the fourth left intercostal space with dual rhythm. No bruit was audible. The blood pressure was 100/70 mm Hg. The chest was clinically clear. Examination of the abdomen showed that the liver

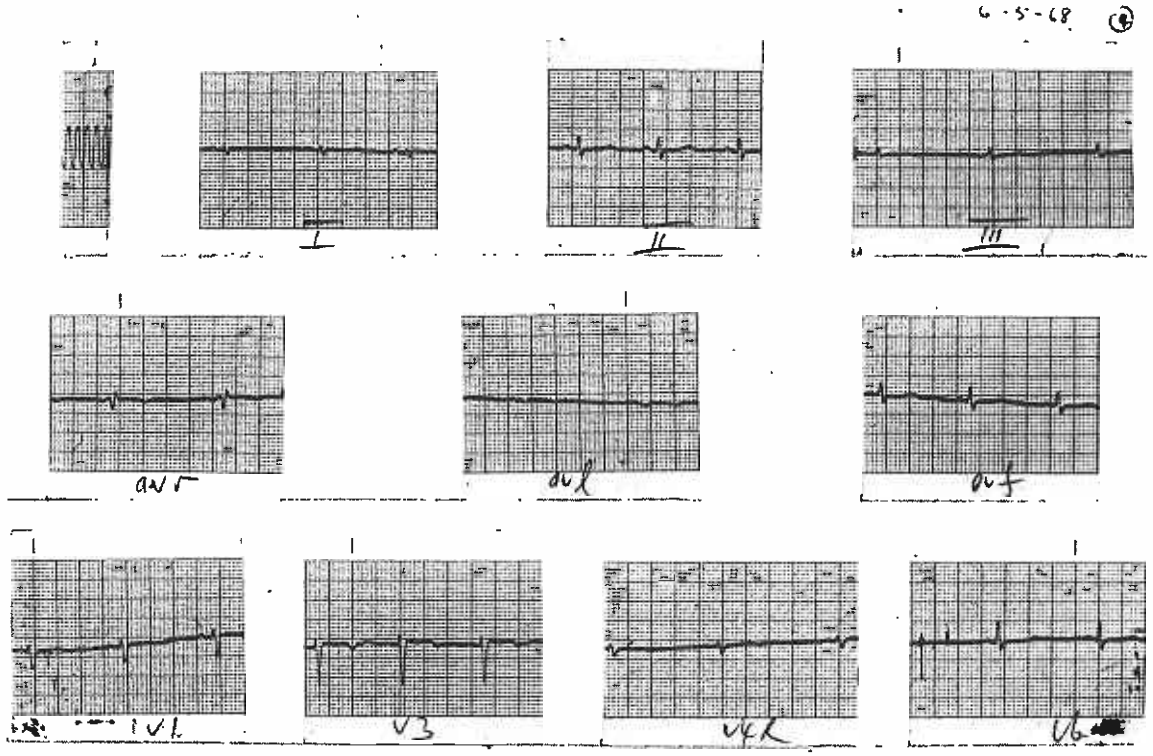

Fig. 5(a) : To show low voltage and inverted T waves in leads I, II and V6.

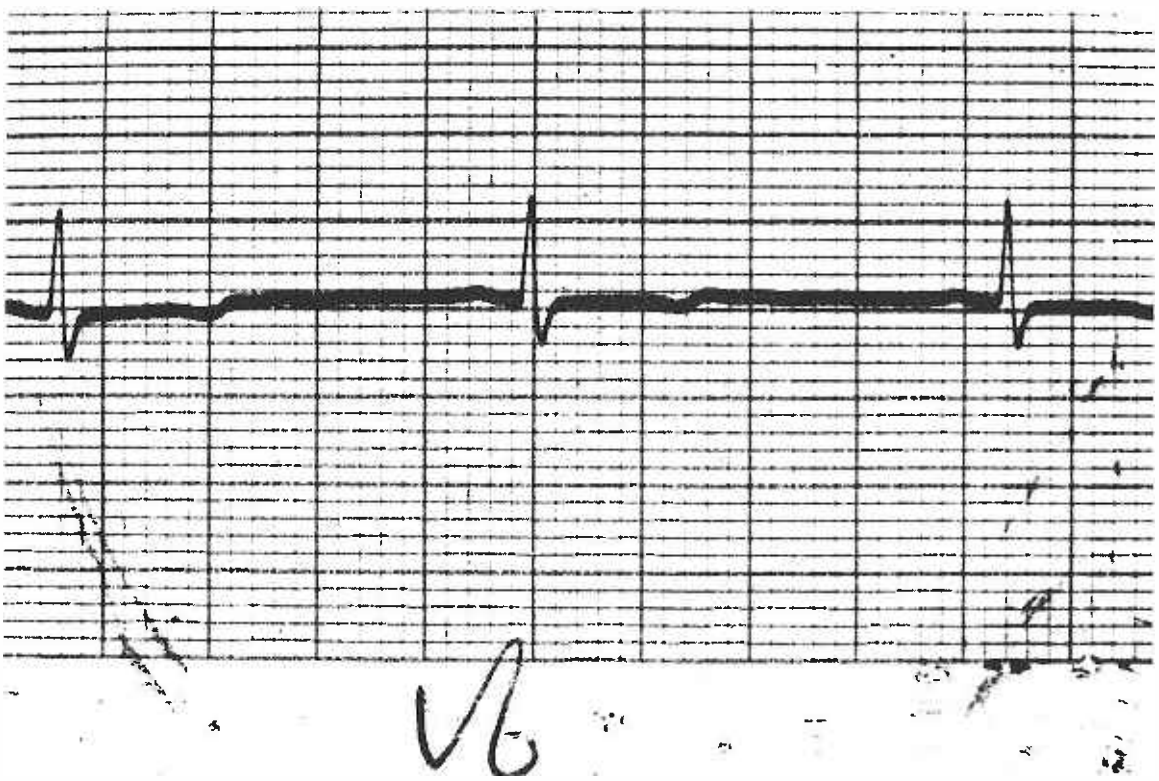

Fig. 5(b) : To show inverted T waves in lead 6.

and spleen were not palpable and the central nervous system was normal. The next day after admission, the patient complained of pain for four continuous days, retrosternal in nature. Initially, the diagnosis was that of reflux oesophagitis or a peptic ulcer and radiographs of the abdomen showed faecal shadows. However, an irregular rhythm was audible over the heart and this was confirmed by an electrocardiogram which showed a RSR heart block. The blood pressure was normal, being 110/70 mm of Hg.

Investigations showed the haemoglobin was 19.7 gm% and the total white cell count was 6,500 cmm, with a polymorpho nuclear count of 75%, lymphocytes of 22%, monocyte of 2% and eosinophils of 1%. The platelet count was 250,000 per cubic mm. The urinary diastase was 4 units (normal). The glucose tolerance test was normal and examination of the stools did not reveal any ova. A barium meal was done and this showed no abnormality of the oesophagus, stomach or duodenum. Coxsackie B4 virus antibody titre was 1/64 for the first serum and four weeks later this rose to 1/128. Neutralising antibody titres of 1/4 and 1/128 to B1 were present in the first and second sera as shown below. This could indicate concurrent infection with coxsackieviruses B1 and B4. However, a heterotypic antibody rise to B1 or B4 following infection with either cannot be ruled out.

NEUTRALISING ANTIBODY TITRE IN

VIRUS	First Serum sampled on 28.11.1979.	Second Serum sampled on 10.12.1979.
Coxsackie B1	<4	128
Coxsackie B2	<4	<4
Coxsackie B3	32	32
Coxsackie B4	64	128
Coxsackie B5	<4	<4
Coxsackie B6	<4	<4

This patient was followed up as an outpatient one month after admission and he still complained of restrosternal pain. The heart clinically was normal and the electrocardiogram was normal. The child was followed up regularly for six months and no retrosternal pain was present. The heart was normal. This child's diagnosis was myocarditis presenting with abdominal pain due to Coxsackie B4 virus.

DISCUSSION

In 1966, Kleevens and Lee (8) showed in an urban area of Singapore that stools of Chinese children, aged 0 to 6 years of age from families in the lower income group living under two different environmental conditions (modern flats and squatter dwellings) showed the overall prevalence of enterovirus to be 21.7%, consisting of 2.1% of poliovirus, 5.2% coxsackievirus, 10.8% echovirus and 3.5% untyped virus. Coxsackievirus B4 and echovirus 6, 7 and 13 were particularly prominent. Later, Yin-Murphy and Lim (6) showed in a total of 109 (75%) out of 146 isolates which were previously not identified that echovirus types 1(8), 2, 4 to 9, 11(19), 14, 15, 17, 18 and Coxsackievirus A9 were associated with cases previously diagnosed as poliomyelitis, aspetic meningitis and viral encephalitis. Echoviruses 1(8), 2, 4, 6-9, 11(19), 12-15, 18, 26 and coxsackieviruses B2 and B5 were found in normal children.

These two preliminary studies made one aware of the prevailing types of echovirus and coxsackievirus in Singapore. Later in 1979, Yin-Murphy and Kay (6), reported two fatal cases of myocarditis where a hitherto unidentified virus isolated showed characteristics of an enterovirus. They stated that the significance of this virus in its association with infantile myocarditis required further investigations. We now report six children with myocarditis that occurred between the years of 1978 and 1980 in Singapore where although virus was not isolated from the stool, significant neutralising antibody rises between paired sera or unusually high titres indicative of coxsackievirus infection were registered. These children with myocarditis were either missed or unidentified in the etiology of their disease in Singapore.

Smith (9) reported ten adult patients with heart diseases believed to be due to coxsackievirus. Six had the syndrome of acute benign pericarditis and presented with chest pains suggestive of pericarditis and mimicking myocardial infarction. The remaining patients had evidence of myocarditis without associated pericarditis. In adults, one associates chest pain with myocardial infarction but in children one does not think of myocardial disease when a child complains of retrosternal pain. Fifty percent of the children in our series of study at some stage of the disease complained of pain over the praecordium.

Nearly all the children had fever characteristic of any viral infection, but this feature coupled with an irregularity of the heart or a tachycardia as noted by the parents is another significant feature. Fortunately most of our children reached us early and awareness in the diagnosis of myocarditis made the doctor put the child in the intensive care unit for monitoring the heart. Intensive care therapy is necessary as sudden deaths can occur from myocarditis. None of our children were in severe cardiac failure as deaths could also occur from the latter. Fatalities have been reported to be much higher in the neonates. Saphir and Nathan (10) reported five cases, three of whom died within the first two weeks of neonatal life. The decreasing incidence of fatal non-specific myocarditis with increasing age brings to mind a mirror image of an infantile antibody response curve. A possible explanation lies in a deficiency in protective antibody; either the lack of transplacental antibodies, defective or an immature immunological response.

From an epidemiological point of view, over-crowding is an important factor and half of the children were from crowded home conditions. We had children from the upper social strata as well. Although coxsackievirus infection exists all the time, during epidemics, coxsackieviruses contribute significantly to acute cardiac disease.

The mere isolation of a coxsackievirus from the alimentary tract cannot be considered of unequivocal

etiologic significance because subclinical infection is common and intestinal carriage can extend over several weeks. However, such isolations are more meaningful when substantiated by significant rise in specific antibody response between acute and convalescent sera. Virus isolation from cardiac disease are often difficult because by the time cardiac symptoms are detected by clinicians, the active excretion of virus has already ceased. Diagnosis must often be attempted on the basis of serological findings alone. Interpretation of serological findings are made difficult by the fact often the four-fold or greater rise in antibody response between paired sera considered as indicative of recent or current infection is not registered because by the time the first blood sample is taken from a patient with myopericarditis the antibody titre has already peaked. Under such circumstances, one would interpret the significance of unchanging antibody titres with the knowledge that residual antibodies from past infection with these viruses are widespread. In our experience, a neutralising titre of 16 is not commonly encountered in children of paediatric age in Singapore (to be published) and titres of 64 and above can be regarded as suggestive of recent infection. The difficulty in interpreting serological findings in terms of the specific virus involved in adult cases who commonly respond to infection with antibodies reacting with more than one member of the coxsackievirus B is less frequently encountered in infants and young children. Supporting epidemiological data from the community and serologic evidence from the patient with accompanied clinical findings provide the final evidence in an established etiology.

ACKNOWLEDGEMENT

We wish to acknowledge Mrs Chua Phuay Hong, technician in the Department of Microbiology, National University of Singapore for her expert technical assistance.

REFERENCES

1. Dalldorf G: The Coxsackie group of viruses. Science 1949; 100: 594.
2. Montgomery J, Gear J, Prinsloo F R, Kahn M and Kirach Z G: Myocarditis of the newborn. S Afr. Med. J. 1955; 29: 668.
3. Javett S N, Haymann S, Mundel B et al: Myocarditis in the newborn infant. A study of an outbreak associated with Coxsackie group B virus infection in a maternity home in Johannesburg. J. Paediat. 1956; 48: 1.
4. Jennings R C: Coxsackie group B fatal neonatal myocarditis associated with cardiomegaly. J. Clin. Path. 1966; 19: 325.
5. Grist N R and Bell E J: Coxsackie virus of the heart, American Heart Journal 1969; 77: 295.
6. Yin-Murphy M and Lim K A: Enteroviruses in Singapore. Singapore Medical Journal 1968; 9: 252.
7. Yin-Murphy and Kay R W W: Preliminary report on an unidentified virus from infantile myocarditis. South-East J. Trop. Med. Public Health 1979; 10: 477.
8. Kleevens I W L and Lee L H: The occurrence of enteroviruses in children from modern flats and squatter dwellings in Singapore. Singapore Medical Journal 1966; 7: 5.
9. Smith W G: Adult Heart Diseases due to Coxsackie Virus Group B. British Heart Journal 1966; 28: 204.
10. Saphir O and Nathan A C: Myocarditis in infancy. A.M.A. Archives of Pathology 1967; 64: 446.