

# COXSACKIE VIRUS INFECTIONS PRODUCING NEUROLOGICAL LESIONS IN SINGAPORE CHILDREN

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## SYNOPSIS

Coxsackie virus as an etiological agent for children with paralysis of the limbs and aseptic meningitis has not been reported before in Singapore. This article describes three children with paralysis of the limbs where serological evidence of recent Coxsackie B virus infection was demonstrated. Coxsackie virus A9 was isolated in the fourth child who had aseptic meningitis. All the children recovered with little residual sequelae.

## INTRODUCTION

In recent years, an increasing array of immunotypes of Coxsackie and Echo viruses has been implicated in a broad spectrum of acute central nervous system disease. While poliomyelitis has been eradicated from Singapore, we still see in children sporadic cases of unilateral or bilateral paralysis, aseptic meningitis, and children with myositis of whom the etiology, hitherto, has been labelled "virus". Our laboratory findings support a Coxsackie B virus etiology in children with neurological lesions and clinical symptoms and manifestations typical of Coxsackie B virus infection. Paired sera sampled during the course of the disease showed antibody response strongly indicative of a recent infection with Coxsackie B virus, even though attempts to isolate the virus from the blood, cerebrospinal fluid and stool with few exceptions were unsuccessful. The following were children with neurological sequelae encountered during our study of Coxsackie B infections in children from 1978 to 1982.

## Clinical Case Reports

### Case 1:

T.C.S was a two-year old Chinese boy admitted with a sudden onset of weakness of the upper limb on 3.11.1980. Three days prior to this episode the mother noted tremors of the left hand and weakness of both upper limbs. The child was able to walk but was weak. On the day of admission the child had a mild fever with paralysis of the left upper limb. Immunisation history revealed that this child had received all the immunisation procedures required by the Singapore Ministry of Health, including the oral Sabin poliomyelitis vaccine and booster doses had been given six months prior to this illness. The birth and developmental histories were normal, prior to this illness. The parents were from the middle income group and this was their only child. However, as both parents were working, this child was locked after by a foster mother.

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**Physical examination** revealed a child who had a temperature of 37°C. The child weighed 16 kg., which was well above the 97th percentile using Singapore standards. The predominant feature was weakness of the left upper arm. The throat was not injected and no abnormality could be detected in the heart, lungs or abdomen. Grading of the muscle power revealed weakness predominantly of the flexor, extensors, external rotators of the shoulder and weakness of the forearm muscles mainly the supinator and pronator on the left side. The extensors of the wrist were also weak with weakness of the lumbrical muscles as well. On the right side the muscle power was better but there was a weakness of the flexors and extensors of the shoulder and weakness of the supinator and pronator muscles. The upper limb reflexes were absent on the left side. All lower limb reflexes were present and the plantar response was flexor. The clinical diagnosis was that of a viral infection affecting the lower motor neurone cells of both upper limbs, more so on the left side simulating poliomyelitis.

Laboratory investigations revealed that the haemoglobin content was 15.3 gm% with a total white cell count of 9,5000 cmm, polymorphs 26%, lymphocytes of 70%, monocytes of 3%, an eosinophil count of 1%. An electromyogram showed no evidence of denervation of the muscles. Serology for herpes simplex, mumps, measles and Japanese B encephalitis was negative. Neutralising antibody to Coxsackie B1 virus was 1 in 16 on 14.11.1980 with a four fold rise to 1:64 on 18.11.1980. The serology for Coxsackie B2, B3, B4 and B5 and B6 was negative. No virus was isolated from faecal samples inoculated into monkey kidney tissue cultures. The cerebrospinal fluid on two occasions on 3.11.1980 and on 12.11.1980 was normal in the cell count, sugar and protein contents.

While in the ward, the weakness gradually improved and ten days later he was able to lift the left arm above the shoulder. The muscle power had improved although there was a difference of ½ inch in the girth of the left upper arm and the right upper arm. Recovery of the muscles was complete three months after admission.

#### Case 2:

I.B.A. was an eight year old Malay girl, an only child adopted into the family from birth. She was referred on 4.8.1978 because of intellectual retardation. On clinical examination at that time, it was found that she was of normal physical appearance, weighing 23 kg which was at the 90th percentile Singapore standards, and measuring 126 cms (90th percentile Singapore standards). Her head circumference was 19½ inches which was at the 30th percentile using Universal standards. No abnormality could be detected in the heart, lungs and abdomen. The muscle tone and power were normal and her deep reflexes were normal and her plantar response was flexor. An intellectual assessment done on 21.8.1978 showed her intellect to be in the region of 58.

Six months later on 21.8.1978 she was admitted to the ward because of inability to walk properly for one week and this was preceded by an attack of cough, fever and coryza which resolved after a couple of days. The weakness of the left foot worried the parents because she was unable to walk.

Physical examination revealed a child who looked well except for a left equinovirus deformity of the foot. There was no wasting of the muscles but the muscle power of the left ankle was affected. There were no sensory changes. The muscle power in the upper limbs and upper part of the lower limbs was normal. The deep reflexes were increased.

A week later, in the ward, she developed a similar defor-

mity of the right foot, making her totally unable to walk. She was put on active physiotherapy and referred to the orthopaedic surgeon for special boots and a walker and with these aids over a period of three or four months she was able to walk.

The haemoglobin was 13.8 gms% with a total white of 14,700 cmm, polymorphs being 78%, lymphocytes 13%, monocytes 3% and eosinophils 16%. The ESR was 10mm per hour. The cerebrospinal fluid was normal, the cell count being zero, glucose 50mgm% and the total protein was 40 mgm%.

The serum creatinekinase was 16 units, indicating there was no muscle disease. Neutralising antibody to Coxsackie B4 virus was 1:40. Three weeks later during the course of the disease there was a four-fold rise in titre of 1:160, indicating a recent infection with Coxsackie B4 infection. However, the stool and the cerebrospinal fluid were virus negative. For the whole of 1979 and 1980 she walked to school in special boots aided with calipers. The muscle weakness of the ankles gradually improved and 3 months later in March 1981 she had residual weakness of the left foot but managed to walk without boots and calipers. At present the power and deformity of both feet have returned to normal and she attends the special school for educationally subnormal children.

#### Case 3:

T.S.T. was a two-year old boy hospitalised because of inability to walk due to weakness of the legs noted after a fall. Prior to this the child was ill with fever for two days attributed to "influenza". The fall was not a serious one and occurred as the child was walking.

The child was reported to be a normal baby at birth, and developed normally being able to sit up at 5 to 6 months, and walked at 9 months, he was able to run quite well before the episode of fever and weakness of the legs. The child was toilet-trained by 1½ years and bladder and bowel functions were not affected by the present illness. The children was said to be an intelligent child.

Family studies did not reveal anything abnormal. The child was an only child and the parents were both working and belonged to the middle income group. The grandmother looked after the child.

Physical examination revealed a child with a temperature of 37°C. He weighed 11.5 kg which was average for a Singapore baby and measured 86 cms. which was of average height for a Singapore baby. The throat was injected and the tonsils were both enlarged. No abnormality could be detected in the heart and lungs. Neurologically, there was no spinal abnormality nor external injury. The child was able to walk when supported under the arms. There was weakness of both lower limbs but no wasting of the muscles. Sensation to pain was intact. All deep reflexes were increased and the plantar response was flexor. The clinical diagnosis was a myelitis due to a viral infection.

Laboratory investigations showed the haemoglobin to be 12.3 gms%, white cell count of 7100 cmm, polymorphs 60%, lymphocytes 29%, monocytes 4% and eosinophils were 1%. The platelet count was normal. The cerebrospinal fluid was normal. The throat swab did not grow any pathogenic bacteria. Radiographs of the spine were normal. Serology for neurotropic virus, i.e. mumps, measles, Japanese B virus, herpes simplex and poliomyelitis was negative. The following were the results of the Coxsackie B virus neutralising antibody titre.

A four-fold neutralising antibody rise from 1/32 to 1/128 to the Coxsackie B4 virus was demonstrated. Coxsackie B2 neutralising antibody titre of 1/32 was present also in all three sera. Serological response could be due to a recent Coxsackie B4 virus infection, with a past infection with

## Coxsackie Virus Serology

	3.5.81 First Serum	31.5.81 Second Serum	2.8.82 Third Serum
Coxsackie B1	1/8	1/4	1/4
Coxsackie B2	1/32	1/32	1/32
Coxsackie B3	1/16	1/16	1/16
Coxsackie B4	1/32	1/64	1/128
Coxsackie B5	1/4	1/4	1/4
Coxsackie B6	1/4	1/4	1/4

Coxsackie B2 virus or concurrent infection with both viruses.

On the 5th day after admission the child was much better and was able to walk well. The deep reflexes, however, were increased. This child was followed up six months later and was found to have fully recovered with no residual sequelae.

## Case 4:

LM.K. was a four-month old baby admitted because of diarrhoea of two weeks duration, and fever for one day. The baby was a full term normal baby at birth and weighted 7 lbs. 11 ozs. and was never breast fed. He thrived on powdered milk. The baby at 4 months was able to hold up his head.

Physical examination revealed a child who had a temperature of 38°C. His weight was 6.5 kg (50th percentile Singapore standards) and measured 65 cms (50th percentile Singapore standards). The anterior fontanelle was tense and full. The pharynx was injected. No abnormality could be detected in the heart, lungs and abdomen. The liver was palpable to the extent of 2 cm. Examination of the fundus did not reveal any papilloedema. There was no facial palsy. The tone was increased in both lower limbs with increased knee and ankle jerks. The plantar response was flexor.

The clinical diagnosis was that of an aseptc meningitis with gastroenteritis. Investigations revealed a haemoglobin of 13.6 gms% with a total white of 11,000 cmm, polymorphs 7%, lymphocytes of 24%, monocytes 3% and eosinophils of 0%. The platelet was 285,000 cmm. The CSF findings were as follows:-

## CSF Chart

Date	Colour	Cell	T.P. mgm%	Chloride mgm%	Sugar	Glob.	Poly	Lymph
17.6.80	clear	126	40	714	53	+ ve	Nil	Nil
20.6.80	clear	67	70	702	63	+ ve	Nil	Nil
28.6.80	clear	Nil	30	702	46	+ ve	Nil	Nil

Serology for measles, herpes simplex, Japanese B encephalitis and mumps encephalitis was negative. Coxsackie virus A9 was isolated. Sera was not available for determination of antibody levels.

The child continued to show good progress. On admission, the head circumference was 43 cms, which was at the 97th percentile Singapore standards and all deep reflexes were increased.

On the following day the head circumference decreased to 42 cms but the anterior fontanelle was tense and the lumbar puncture fluid showed a cell count of 67 with a total protein of 70 mgm%, chloride of 707 mgm%, sugar of 66 mgm% and globulin was negative. Four days later the head circumference decreased to 41.5 cms and eight days later it was 40 cms, which was at the 50th percentile for his age. All the deep reflexes were increased. The head circumference chart was as follows:-

## Head Circumference Chart

Date	Head Circumference	Percentage of Norm.
17.6.80	44 cms	97%
19.6.80	43 cms	97%
20.6.80	42 cms	90%
23.6.80	41.5 cms	75%
26.6.80	41.0 cms	70%
28.6.80	40 cms	50%

This child has been followed up from a developmental point of view and the child was physically and intellectually normal.

## DISCUSSION

In 1966 Kleeven and Lee (1) showed that 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% poliovirus, 5.2% coxsackie virus, 10.8% echovirus, and 3.5% untyped viruses. Coxsackie B4 and echovirus 6, 7 and 13 were particularly prominent.

Later Yin-Murphy and Lim in 1968 (2) showed Echovirus type 1, 2, 4 to 9, 11, 14, 16, 17, 18 and 19 and Coxsackie virus A9 were associated with cases clinically diagnosed as poliomyelitis, aseptic meningitis and viral encephalitis.

These two preliminary studies made one aware of the prevailing types of echovirus and Coxsackie virus in Singapore. The above three cases give evidence of paralysis of muscles in children simulating poliomyelitis where Coxsackie B virus was the etiology.

Virological studies carried out on a series of 511 patients with suspected viral central nervous system disease at the Los Angeles County General Hospital in 1968 by Lennette et al (3) showed that in 368 cases of aseptic meningitis a total of 20 different types were obtained of which Coxsackie B5 was the most frequent. Other agents associated with paralytic illness included Coxsackie virus types B2, B3, B5, echovirus and mumps virus.

Neutralising antibody response to Group B Coxsackie virus in patients with central nervous system disease was studied by Lennette, Shinomoto, Schmidt and Magoffin (4).

In these studies, homotypic neutralising antibody was almost always demonstrated in patients from which a Group B Coxsackie virus was isolated. Four-fold or greater homologous antibody rises were demonstrated in 6% of patients from whom Group B coxsackie virus infection is relatively rapid. Most of these patients with a four-fold or greater antibody rise show some elevation in titre by the end of the first week after the onset of illness. A significant antibody rise was demonstrated in 70% to 80% of the cases in which the titre of the acute phase serum was less than 1:32. The serological response of our cases agrees with our findings.

## REFERENCE

1. Kleeven JW, Lee LH: The occurrence of enterovirus in

children from modern flats and squater dwellings in Singapore. Singapore Medical Journal 1966; 7: 7-11.  
 2. Yin-Murphy M, LIM KA: Enterovirus in Singapore. Singapore Medical Journal 1968; 9: 252-6.  
 3. Lennette EH, Magoffin RL, Knauf EG: Viral Central Nervous

System Disease. J.A.M.A. 1962; 179: 687-95.  
 4. Lennette EH, Shinomoto TT, Schmidt NJ, Magoffin RL: Observations on the neutralising antibody response to Group B Coxsackie virus in patients with central nervous system disease. Journal of Immunology 1961; 86: 257-66.

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<u>Dermatosis</u>	<u>No. of Patients (Women)</u>	<u>(Average length of treatment)</u>
Contact allergic eczema	16	1-4 months
Unspecified Vulvitis	10	8-30 days
Thrush Vulvitis in the new born	6	10 days
Seborrhoea of the scalp in the newborn	2	8 days
Intertrigo — with strong macerations	6	2-6 months
Kraurosis vulvae et ani	4	4-7 months
Seborrhoea of the scalp in pregnancy	8	5 months
Total	52	



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