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Heart disease caused by Coxsackie virus B infection

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A study of 55 patients with heart disease suspected of being viral in origin was carried out at Medical College Hospital, Nagpur, over a period of 2 years. Virus studies as well as other routine tests were carried out on all patients.

In 19 patients a virus aetiology of the heart disease was proved by isolation of one of the subtypes of Coxsackie B virus and/or on the basis of fourfold rise in neutralizing antibody titre in paired sera. Of these patients, 5 had acute myocarditis and 5 had acute myopericarditis; 3 had acute pericarditis; 3 had congestive cardiac failure of obscure aetiology; 2 had pleuropericarditis, and the remaining 1 developed post-partum heart failure with cardiogenic shock. All had electrocardiographic abnormalities. Thirteen had cardiomegaly; 1 had a right-sided pleural effusion and 2 had pericardial effusion. Virus could not be isolated from pericardial fluid or pleural fluid in these 3 patients.

Follow-up studies up to 10 weeks from discharge revealed that 8 patients were clinically normal but 4 of these 8 had persisting ST-T wave changes, and in 4 the electrocardiogram had returned to normal. Of the remaining 11 patients, 3 had persistent chronic heart failure, 3 had vague symptoms of praecordial pain but no abnormal signs, and 5 patients were lost to follow-up.

Coxsackie viruses are common causes of upper respiratory tract infection, gastroenteritis, and other clinical syndromes. The Coxsackie group B viruses are now increasingly recognized as a cause of myocarditis with or without pericarditis. Coxsackie myocarditis in neonates was first described from Southern Rhodesia (Montgomery *et al.*, 1955). Similar small nursery epidemics were later reported elsewhere, including Amsterdam (van Creveld and De Jager, 1956). Fletcher and Brennan (1957) in Northern Ireland first reported the case of a man with pericarditis due to Coxsackie B_4 virus, and numerous adult cases have since been reported (Gordon, Lennette, and Sandrock, 1959; Null and Castle, 1959; Smith, 1966, 1970; Sainani, Krompotic, and Slodki, 1968; Bell and Grist, 1968).

In the present study, we investigated all cases of pericarditis and/or myocarditis and cases of congestive cardiac failure of obscure aetiology to determine how frequently a viral aetiology could be established.

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Subjects and Methods

The present study was carried out in the Medical College Hospital, Nagpur, over a 2-year period. All patients with symptoms suggestive of viral infection, viz. malaise, headache, pharyngitis, nausea, chest pain with signs of acute pleurodynia, or acute myocarditis, acute pericarditis, or acute pleuropericarditis, were included in this study. Patients with non-specific congestive cardiac failure and those with viral infection and proved arrhythmias were also included. The study of each patient included a full clinical history, physical examination, and investigations: haemogram, erythrocyte sedimentation rate, urine examination, serial electrocardiograms, chest *x*-ray, enzyme studies, and viral studies. Patients were followed up for 6 to 10 weeks after discharge, when detailed clinical examination, electrocardiogram, and chest *x*-ray were done.

Viral studies

Throat swabs Material was obtained by rubbing the posterior pharynx, the tonsils, and faucial pillars vigorously with two sterile cotton swabs.

Rectal swabs A moist sterile swab was inserted into the rectum and was rubbed until faecal material adhered to it.

Serum A minimum of two blood samples was required for antibody tests. The first serum sample was collected within 48 hours of admission; a second sample

TABLE I *Summary of data in 19 cases of Coxsackie myopericarditis*

Case No.	*Age and sex*	*Clinical diagnosis*	*Chest x-ray*			*Electrocardiogram*	
			Admission	*Discharge*	*Follow-up*	*Admission*	*Discharge*
1	7 F	Myocarditis	Normal	Normal	Normal	ST depression	Normal
2	35 F	Cardiogenic shock (post partum)	Cardiomegaly, pulmonary congestion	Same	Cardiomegaly	LV hypertrophy and ST depression	LV hypertrophy
3	3 F	Myopericarditis	Cardiomegaly	Same	Normal	ST elevation and sinus bradycardia	Normal
4	24 F	Myopericarditis	Cardiomegaly	Normal	Normal	ST depression, atrial fibrillation	ST depression
5	28 F	Myopericarditis	Cardiomegaly	Normal	Normal	ST elevation	ST elevation
6	16 M	Myopericarditis	Normal	Normal	Normal	ST depression and sinus bradycardia	Normal
7	25 F	Congestive cardiac failure	Cardiomegaly, pulmonary congestion	Cardiomegaly	Cardiomegaly	ST elevation	ST elevation
8	38 F	Myocarditis	Cardiomegaly, pulmonary congestion	Normal	Normal	ST depression and sinus bradycardia	Normal
9	33 F	Congestive cardiac failure	Cardiomegaly, pulmonary congestion	Normal	Normal	ST depression	Normal
10	15 M	Pericarditis	Cardiomegaly	Normal	Normal	ST elevation	ST depression
11	22 M	Myocarditis	Cardiomegaly	Normal	Normal	Complete heart block	Normal
12	25 M	Myopericarditis	Cardiomegaly	Normal	Normal	ST depression	ST depression
13	22 M	Cardiomegaly, pulmonary congestion	Normal	Normal	ST depression	ST depression	ST depression
14	26 M	Myocarditis	Normal	Normal	Normal	ST depression	Normal
15	33 F	Myocarditis	Normal	Normal	Normal	ST depression	ST depression
16	35 M	Pericarditis	Pericardial effusion	Same	Normal	ST depression, low voltage	ST depression
17	21 M	Pleuropericarditis	Cardiomegaly, pleuritis	Cardiomegaly	Normal	ST elevation	Normal
18	32 M	Pleuropericarditis	Pericardial effusion, and pleural effusion	Same	Normal	ST elevation	Normal
19	38 M	Pericarditis	Cardiomegaly	Normal	Normal	ST elevation	Normal

was examined after two weeks and, if possible, a third after three weeks.

All samples were immediately sent to the Central Public Health Engineering Research Institute. For isolation of virus from throat and rectal swabs, primary rhesus monkey cell culture tubes were used. Final results were recorded after passing the sample three times in monkey kidney tissue culture tubes and noting the cytopathic effect. The positive samples (viral isolates) were neutralized with the pooled (Coxsackie B_1 to B_6) antisera to determine the virus type. At the same time, paired sera were tested for rising neutralizing antibody titre against the Coxsackie B group viruses in serial dilution. In the case of pleural effusion and pericardial effusion, the serous fluid was also examined for isolation of virus using monkey kidney tissue culture cells.

Observations

Over a 2-year period, viral studies were performed in 55

	ESR		*Peak level of serum enzymes*		*Antibody titre*		*Type of virus*	*Virus isolation source*
Follow-up	*Admission*	*Discharge*	*GOT*	*GPT*	*Initial*	*Second*		
Normal	32	10	23	8	1:8	1:128	B_2	Stools
LV hypertrophy	24	10	60	55	1:8	1:64	B_4	—
Normal	28	13	13	10	1:16	1:128	B_4	—
ST depression	14	9	28	24	1:8	1:64	B_3	—
Normal	26	10	50	30	1:16	1:128	B_5	Stools
Normal	26	20	55	50	1:16	1:128	B_4	—
ST elevation	15	8	60	25	1:8	1:64	B_3	Stools
Normal	38	20	25	20	1:16	1:128	B_5	Stools
Normal	56	40	60	46	1:8	1:128	B_4	—
Normal	23	14	90	60	1:16	1:64	B_5	—
Normal	34	20	65	30	1:8	1:64	B_4	—
Normal	24	10	52	60	1:16	1:128	B_2	Stools
ST depression	35	15	55	40	1:16	1:128	B_5	Stools
Normal	15	5	10	10	1:16	1:64	B_4	Stools
ST depression	12	2	65	50	1:8	1:64	B_3	—
ST depression	60	10	60	75	1:16	1:128	B_4	—
Normal	45	22	24	15	1:32	1:64	B_3	Throat
Normal	12	10	15	25	1:8	1:64	B_5	—
Normal	10	8	40	60	1:32	1:128	B_4	Stools

patients; only 19 patients satisfied the accepted criteria of Coxsackie viral infection. Observations on these 19 patients are given in the accompanying Tables.

Discussion

Of 55 patients in the present series who were suspected of suffering from viral heart disease, 19 were positive for Coxsackie B virus infection; all were under 40 years of age and presented clinically with acute myocarditis and acute myopericarditis (5 each); acute pericarditis and congestive cardiac failure (3 each); pleuropericarditis (2); and postpartum heart failure with cardiogenic shock (1) (Table 1).

The most common symptoms were dyspnoea, pain in the chest, malaise, fatigue, and fever (Fig. 1). An apical systolic murmur (grade 2/6) was audible

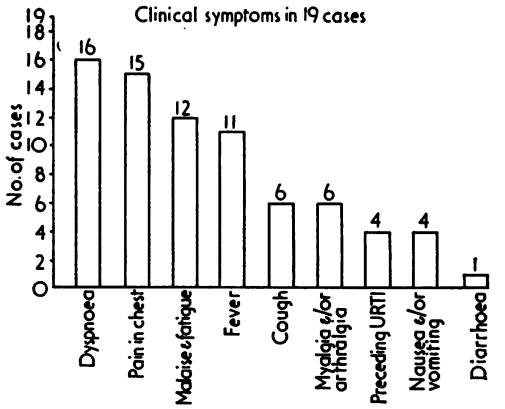

FIG. 1 *Important clinical symptoms in 19 proved cases of Coxsackie heart disease.*

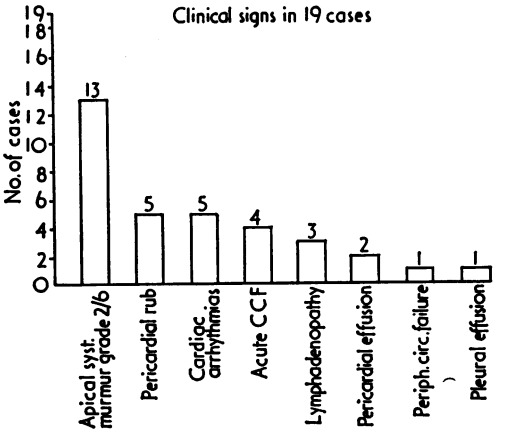

FIG. 2 *Important clinical signs in 19 proved cases of Coxsackie heart disease.*

in 13 and pericardial friction was heard in 5 patients. The murmur subsequently disappeared in all. Five patients presented with arrhythmias and 4 were admitted with acute congestive cardiac failure (Fig. 2).

Fourteen patients had leucocytosis with predominance of neutrophils; in 13 the erythrocyte sedimentation rate was raised and in 12 serum enzymes were raised. Chest *x*-rays revealed cardiomegaly in 12, normal heart size in 5, and pericardial effusion in 2 patients. Pulmonary congestion was noted in 4 patients and right-sided pleural effusion was seen in one. All the 19 patients had electrocardiographic abnormalities (Table 1).

Current criteria for a diagnosis of Coxsackie B virus infection were met in all the 19 patients (Table 1). Of 42 patients with acute myopericarditis studied by Bell and Grist (1968), 12 showed evidence of Coxsackie infection. Smith (1966) studied 10 patients with suspected viral heart disease, in whom he proved virus aetiology in 6. Sainani *et al.* (1968) in their study of 57 patients with heart disease found evidence of Coxsackie virus infection in 22 patients.

Myocardial tissue at necropsy was obtained in 2 of 3 patients with myocarditis who died. The tissue was examined for virus isolation with negative results. In both, viral studies during life were also negative. Pericardial fluid from 2 and pleural fluid from 1 was examined for Coxsackie B virus with negative results.

Post-partum cardiomyopathy is poorly understood. There were 3 patients with post-partum heart failure with cardiogenic shock in this study but viral studies were positive in only 1 patient (Case 2,

TABLE 2 *Follow-up of 19 cases of Coxsackie B infection*

Final state	*No. of cases*	*Electrocardiographic changes*	*Chest x-ray*
1) Deaths	Nil	—	—
2) Chronic heart failure	3	LV hypertrophy and ST depression in 1; normal in 2	Cardiomegaly in 2; normal in 1
3) Praecordial pain, but no abnormal physical signs	3	Normal in 2; ST depression with low voltage in 1	Normal
4) No symptoms, no signs	8	Slight ST depression in 3; ST elevation in 1; normal in 4	Normal Normal
5) Lost to follow-up	5	—	—

Table 1). Sainani *et al.* (1968) found cases of so-called post-partum heart diseases caused by Coxsackie virus infection.

A 6 to 10 week follow-up of proved cases in the present study was carried out. Of 19 patients, 8 were asymptomatic without abnormal physical findings. Of these, 4 had normal electrocardiograms, 3 had persisting ST depression, and 1 had persistent ST elevation. Three patients had praecordial pain but no abnormal physical signs. Three patients had persistent chronic heart failure. The remaining 5 patients were lost to follow-up (Table 2). Sainani *et al.* (1968) in their 2-year follow-up study found that Coxsackie B virus infection may result in permanent heart damage. Of 22 patients, 5 had persistent symptoms, and signs of chronic heart failure. Hastreiter and Miller (1964) stressed that myocarditis and endocardial fibroelastosis may be stages of the same disease, often coexisting clinically and histologically. Sainani (1973) considers that so-called 'idiopathic cardiomyopathy' may occasionally be a late effect of Coxsackie virus infection.

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