Clinical Virology in Family Practice: Epidemiological and Clinical Observations of an Outbreak of Coxsackievirus B Type 1 Infection in a Kibbutz

Yair Yodfat, MD
Moshe Nishmi, PhD
Jerusalem, Israel

In the late summer and early fall of 1975, a febrile illness broke out in Kibbutz Tsorah, a communal settlement situated in the Jerusalem District, affecting 148 (33 percent) of its 446 members. Sickness was recorded in 107 (54 percent) of 198 children under 14 years of age and in 41 (17 percent) of the remaining 248 members of the kibbutz. In addition to fever, gastrointestinal and upper respiratory symptoms were predominant. Pleurodynia and myocarditis were also observed, but only in 11 (7 percent) and 5 (3 percent) patients, respectively, all adults. Coxsackievirus B type 1 was isolated from 20 (53 percent) of 38 stool specimens received. A fourfold or higher rise in titer of neutralizing antibody to one of the isolates was demonstrated in 52 (74 percent) of 70 paired sera. The epidemiologic and clinical aspects of the outbreak are discussed. The importance of correlating laboratory findings with clinical and epidemiologic observations and the importance of collaborating with the laboratory virologist in the daily practice of the family physician are stressed.

Acute infectious diseases play a major role in the work of the family practitioner.[1] These acute diseases may be caused by different infective agents, and it is impossible in most cases to identify these agents on a clinical basis only. It is well known that the same infective agent may be involved in different clinical syndromes while similar syndromes may be caused by different etiologic agents. Acute syndromes such as malaise, fever, coryza, sore throat, cough, laryngitis, bronchitis, chest and abdominal pains, myalgia, vomiting, and diarrhea may be caused by bacterial or viral agents. In most cases no bacterial agent is found and the family practitioner prescribes not only symptomatic treatment, but in order to be on the "safe" side, prefers to add antibiotics as well.

Since 1968, attempts have been made for early isolation of viral agents whenever an outbreak of a viral disease appeared likely. An example is presented of a virologic study carried out by a collaboration of a family physician and a laboratory virologist. This study describes epidemiologic, clinical, and laboratory findings in an outbreak of coxsackievirus B type 1 infection which occurred in a kibbutz during the late summer of 1975.

From the Shimshon Family Medical Center Kupat Holim Beit Shemesh and Department of Medicine A, Hadassah University Hospital, Jerusalem, Israel, and the Department of Virology, Hebrew University-Hadassah Medical School, Jerusalem, Israel. Requests for reprints should be addressed to Dr. Yair Yodfat, Shimshon Family Medical Center, Beit-Shemesh, Israel.

Material and Methods

The Kibbutz

Kibbutz Tsorah, situated 30 kilometers west of Jerusalem, is a communal agricultural settlement whose members are united by a common ideology. Property is owned in common, although each family lives in its own home together with the children. The latter spend the entire day and have their meals together in special "children's houses." Those of prekindergarten age are divided into groups of about 20. The adults have their meals separately in the common kibbutz dining room. Members under the age of 18 years constitute approximately one half of the total population of 460 on the kibbutz. The "children's house" and kibbutz school are close to each other, and there is close association among the children in their houses and with their families in the evening hours. Primary care is provided to the kibbutz by a family physician from the Shimshon Family Medical Center[2] and two nurses who are members of the kibbutz. Also, there is a nursemaid in each of the "children's houses" as well as in the school.

Recording of Cases and Collection of Specimens

Nursemaids in the "children's houses" and in the school report all diseases, irrespective of how mild or trivial the diseases may seem to be, to one of the two nurses. The latter visits the sick child on the same day, and when necessary, refers the patient to the physician. Patient's records are kept, including a detailed description of the symptoms, the date of appearance and the duration. Blood samples, throat swabs, and feces (or rectal swabs) are taken for viral and bacterial studies at the onset of the disease. Swabs for virus isolation are immediately immersed in phosphate-buffered saline (pH 7.4) containing 0.5 percent bovine albumin and antibiotics. All specimens are then placed in ice-cooled containers and transported to the laboratory in Jerusalem. Three to five hours elapse from the time the specimens are inoculated into the appropriate virologic and bacteriologic media. Two or three weeks after the onset of the illness, a second blood sample is taken.

Stools and paired blood samples

were received from 12 kibbutz members. Stools only were available for virus isolation from 26 other members. Paired blood specimens for serologic studies were drawn from 58 more patients.

Primary rhesus monkey kidney cultures were used for the isolation of viruses and for passaging the isolates. Identification was carried out with the help of pools of type specific hyperimmune sera.[3,4]

Paired sera were examined for the presence of an antibody capable of neutralizing one of the coxsackievirus B type 1 isolates by techniques previously described.[5]

Results

During August and September 1975, sickness was recorded in 148 (33 percent) of the 446 members of the kibbutz.

Epidemiologic findings

Table 1 summarizes the morbidity rates in different age groups. Sickness was most prevalent in the one-to-four-year-old age group, affecting 50 (91 percent) of 55 children in this group. Illness was also widespread, though not to the same extent, among younger children, affecting 9 (64 percent) of 14 six-to-11-month-old infants, and 4 (36 percent) of 11 infants less than 6 months old. A considerable attack rate was also evident in 5-to-14-year-old children, with 44 (37 percent) of 118 exhibiting various disease symptoms. The 15-to-24-year-old group was affected least, sickness being recorded in only 5 (10 percent) of 52 kibbutz members composing this group. Higher morbidity rates of 17 percent and 19 percent were noted in the two oldest age groups. These rates were, however, well below the overall attack rate of 33 percent for the entire community.

Clinical findings

The symptoms observed in the course of the outbreak are given in Table 2. Fever was recorded in 125 (84 percent) of the 148 patients. Pharyngitis and abdominal pain were also common, occurring in 49 percent and 46 percent of the patients respectively. Less common were symptoms of cough, vomiting, diarrhea, and otitis media, observed in five to ten percent of the sick. The occurrence of pleurodynia and myocarditis in 11 and 5 adult patients, respectively, was particularly noteworthy. Figure 1 shows the electrocardiogram (ECG) of a patient presenting with pleurodynia. Inversion of the T waves in V_3, V_4, and V_5 are noted, together with depression of the ST segment in II and AVF, indicative of myocarditis. The ECG recorded two weeks later is shown in Figure 2 and has reverted to normal.

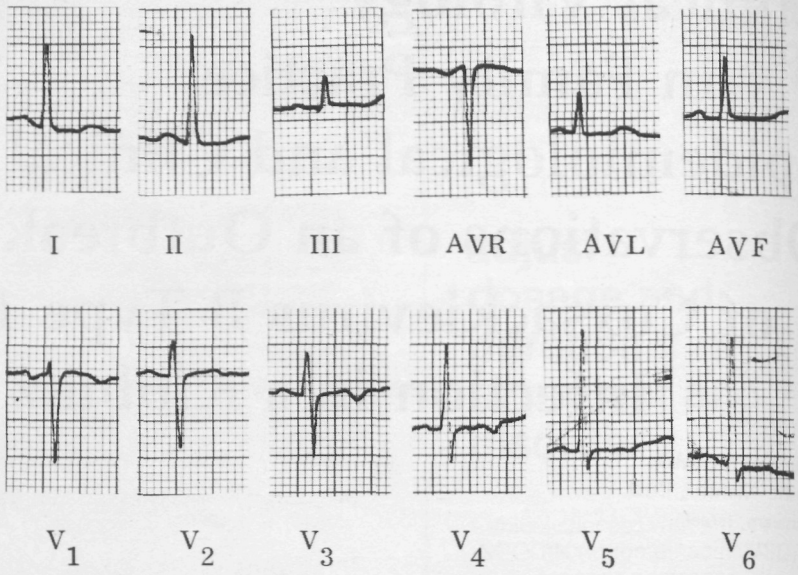

Figure 1. ECG showing myocarditis.

Virologic findings

A summary of the laboratory findings is presented in Table 3. A total of 38 stool specimens and 70 paired blood samples were received from 96 patients. Twenty of the 38 fecal samples yielded coxsackievirus B type 1, an isolation rate of 53 percent. A fourfold or higher increase in titer of neutralizing antibody to 100 $TCID_{50}$ of one of the isolates was demonstrated in 52 (74 percent) of the 70 paired sera examined. Laboratory confirmation of infection was based on virus isolation in 12 cases, on a significant increase in titer of neutralizing antibody in 44 cases, and on both virus recovery and serologic findings in 8 more cases.

Discussion

Since discovery in 1948,[6] coxsackieviruses, which are enteroviruses, have been associated with a wide variety of clinical syndromes, generally mild to moderate, but occasionally severe and even fatal in outcome.[7-9] Of 900 coxsackievirus B type 5 infections reported by the British Public Health Service in 1965, meningoencephalitis was associated with 31 percent of the infections, myalgia with 23 percent, Bornholm disease, a respiratory disorder, with 15 percent of the infections, gastroenteritis with 9 percent, and cardiomyopathy with 5 percent of the infections. Death was recorded in six cases following neurologic, respiratory, or cardiac symptoms.[10] Since transplacental spread of coxsackieviruses from mother to fetus has been demonstrated,[11,12] the viruses apparently play a role in spontaneous abortions and congenital heart disease.[13,14] Their etiologic association has been well established, with severe, often fatal, infections of neonates characterized by myocarditis, hepatitis, and meningoencephalitis.[8]

The present study demonstrates variations in the reactions of different individuals to infection with the same virus type. The symptoms in a 35-year-old kibbutz member and his

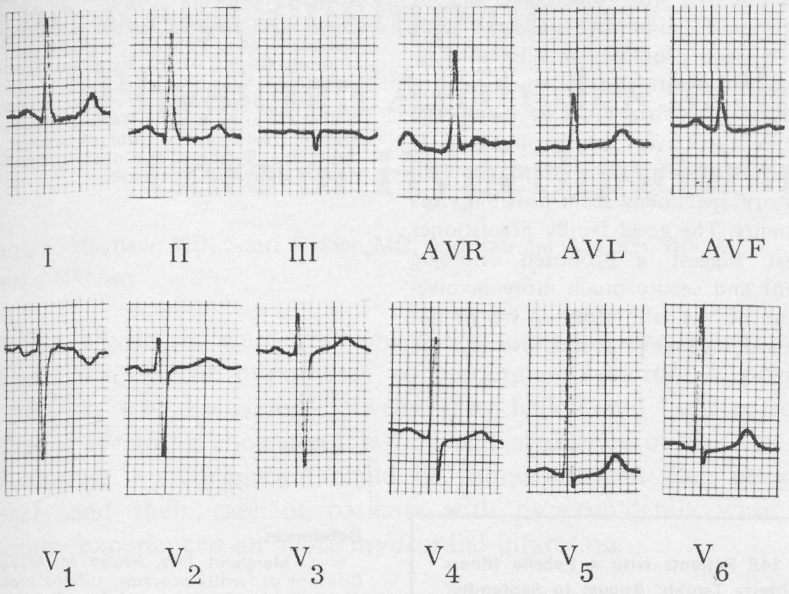

Figure 2. Reversion to normal, two weeks later.

two-year-old daughter will illustrate this point. On the night of September 6th, the father experienced intense pain extending from the left hypochondrium, across the thorax, to the left shoulder. Breathing accentuated the pain. In the morning he awoke with malaise accompanied by fever (temperature 38 C, 100.4 F) and pharyngitis. The acute thoracic pain persisted for 24 hours, gradually abating over a period of three days. The patient's ECGs in disease and on regaining health are shown in Figures 1 and 2, respectively. The daughter presented at the same time with symptoms of restlessness, high fever (temperature 39 C, 102.2 F) lasting for five days, and diarrhea persisting for a week. Coxsackievirus B type 1 was isolated from stool specimens, and a significant rise in neutralizing antibody was demonstrated in paired blood samples in both cases.

Previous outbreaks of disease in the kibbutz associated with echoviruses types 4[3] and 9[15,16] were confined to children. In another outbreak associated with coxsackievirus B type 4[16] and the present type 1, disease symptoms were exhibited by adults as well as children. There may be various reasons for the variation in the reaction of a stable, well-defined, rural community to strains of different enterovirus groups. Echoviruses may be more prevalent in the area, so that immunity to them may be acquired at a younger age. Moreoever, differences in the epidemiologic features of coxsackievirus and echovirus infections may account for an increased likelihood of adult involvement in coxsackievirus disease outbreaks. Thus, coxsackieviruses tend to be excreted in stools for a longer time (up to 70 days). Although the fecal-oral route predominates in the spread of enteroviral infections in general, respiratory contagion, more likely to affect adults, is more common with coxsackieviruses.[9,17] Another important point to be considered is the higher infectivity rate of the coxsackieviruses to contacts. In a continuing surveillance of viral infections in metropolitan New York families, it has been found that, whereas 76 percent of susceptibles and 25 percent of immunes may be infected with coxsackieviruses, only 43 percent of susceptibles and practically no immunes are prone to infection with echoviruses.[17]

Table 1. Attack Rates in Various Age Groups in an Outbreak of a Febrile Illness Associated with Coxsackievirus B Type 1 Among 446 Members of Kibbutz Tsorah, August to September 1975

Age Group (years)	No. of Members	No. Sick	% Sick
1/12-5/12	11	4	36
6/12-11/12	14	9	64
1-4	55	50	91
5-14	118	44	37
15-24	52	5	10
25-59	184	34	19
60+	12	2	17
Total	446	148	33

Cardiomyopathy resulting from coxsackievirus infections may follow one of several courses.[9] Most often, as in the five cases recorded in the present outbreak in the kibbutz, symptoms subside following an acute infectious phase, and recovery is complete with no sequelae. Occasionally in adults, but more often in neonates and infants, acute myocarditis may terminate in early death.[8,9] Chronic heart disease of short or long duration has also been recorded in follow-up studies.[18,19]

Evidently, the wide spectrum of symptoms caused by the same virus often pose problems in clinical diagnosis and treatment. However, identification of a virus must be within the capability of every family physician. It is not sufficient to send to the laboratory specimens from possible virus patients. The good family practitioner must suggest a proposed etiologic agent and secure much more involvement of the laboratory in his or her attempts to isolate and identify the virus.

Table 2. Frequency of Various Symptoms in 148 Patients with a Febrile Illness Associated with Coxsackievirus B Type 1 in Kibbutz Tsorah, August to September 1975

Symptom	No. of Patients Affected	%
Fever	125	84
Pharyngitis	73	49
Abdominal pain	68	46
Otitis media	15	10
Pleurodynia[a]	11	7
Diarrhea	10	7
Vomiting	8	5
Cough	7	5
Myocarditis[a]	5	3

a = In adults only

Table 3. Summary of Virologic Findings in an Outbreak of a Febrile Illness Associated with Coxsackievirus B Type 1 in Kibbutz Tsorah, August to September 1975

Type of Specimen	No. Received	No. Positive	% Positive
Stools	38	20[a]	53
Paired Sera	70	52[b]	74
Total	108	72	67

[a]Virus isolated in rhesus monkey kidney cultures

[b]A fourfold or higher rise in titer of neutralizing antibody to 100 $TCID_{50}$ of one of the isolates

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