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A SEROEPIDEMIOLOGIC STUDY OF CYTOMEGALOVIRUS INFECTION: Limited Communicability in a Recruit Training Population

by

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A SEROEPIDEMIOLOGIC STUDY OF CYTOMEGALOVIRUS INFECTION:
Limited Communicability in a Recruit Training Population

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SUMMARY PAGE

THE PROBLEM

A retrospective serological study was made using pre- and post-training sera obtained from Marine recruits to determine the contribution, if any, made by cytomegalovirus (CMV) to illness among Marine Corps trainees. Additional sera from hospitalized Marines were included in the study.

FINDINGS

Sixty-nine percent of incoming recruits had no detectable complement fixing antibody to CMV. One percent seroconverted during the 14-week training period. CMV antibody rises were not observed in 45 patients with etiologically undiagnosed respiratory illness. One man hospitalized with a 20-day history of marked general malaise and nocturnal diaphoresis showed a significant antibody to CMV, suggesting an etiological relationship.

APPLICATION

The serological data suggest that rarely does CMV contribute to the hospitalization of Marine Corps trainees. The data further suggest that CMV has limited communicability among young adults, and that very intimate contact is necessary for CMV transmission from one man to another.

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Lynn G. Maddry, Ph.D., M.S.P.H., Director of the Laboratory Division of the North Carolina State Board of Health, confirmed all CMV antibody rises and performed the serologic tests for influenza antibodies.

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ABSTRACT

A seroepidemiologic study for cytomegalovirus (CMV) infections was performed on a military base. Four hundred ten (69.7%) of 588 incoming recruits had no detectable (<1:2) CMV complement fixation (CF) antibody. Six recruits (1.0%) seroconverted during the 14-week training period. CMV antibody rises were not observed in 45 patients with etiologically undiagnosed acute respiratory disease. Similarly, no CMV antibody rises were observed in 93 patients with Australia antigen negative viral hepatitis or in 35 patients with an infectious mononucleosis syndrome (three were monospot negative). One man was hospitalized with a 20-day history of marked generalized malaise and nocturnal diaphoresis and showed a significant CF antibody rise to CMV during hospitalization. All who showed a fourfold rise of CMV antibody titers had no initially detectable antibody. These data suggest very intimate contact and limited communicability as characteristics of natural transmission in our adult population. Low levels of CMV CF antibody may offer protection in the uncompromised host.

INTRODUCTION

The cytomegaloviruses (CMV), members of the herpesvirus family, were discovered in 1956,[1] and have been recognized as important pathogens causing congenital defects. The clinical spectrum of congenital infection includes microcephaly, cerebral calcifications, optic atrophy, chorioretinitis, thrombocytopenic purpura, hemolytic anemia, jaundice and hepatosplenomegaly.[2] Microscopically, typically large nuclear inclusions are seen which measure 20 to 40 microns in size. In adults these viruses are primarily opportunistic pathogens, causing illness in patients with altered immune defenses or in patients receiving a large number of transfusions. Up to 75% of patients with leukemia or lymphoma or recipients of renal allographs develop clinically significant CMV disease, often with a fatal pneumonitis.[3,4] Between 5 and 10% of patients undergoing cardiopulmonary bypass develop a self-limited, heterophil-negative infectious mononucleosis syndrome as a result of CMV infection.[5-7] Despite these uncommon events, 20 to 70% of people have complement fixing (CF) antibodies to CMV by age 20, and 40 to 80% have CF antibodies by age 50,[8,9] Such data would imply that most infections are asymptomatic or go unrecognized. As a result, little is known about the spectrum of primary infections in normal individuals, and more has to be learned about the portal of entry, host response and infectious potential of these DNA viruses.

Our location on a military base offers us an unusual opportunity to perform seroepidemiologic studies of a population of young adults. By design, recruits eat, sleep, wash, and train closely together. Since we collect an initial serum specimen on all entering recruits, we can easily measure the prevalence of preexisting antibody. By collecting sera on these same men at the completion of training, we have measured the incidence of CMV infection during the training period, attempting to gain some insight into the infectious potential of this group of viruses. The results of our study are herein reported.

MATERIAL AND METHODS

Subjects

Recruits entering the Marine Corps Recruit Depot, Parris Island, S.C. trained for eight weeks in platoons numbering approximately 80. Without intervening leave (a 10-day leave period was instituted in April 1971), men were transferred to Infantry Training Regiment (ITR), Camp Lejeune, NC Here they formed companies numbering approximately 250 and trained for an additional five to eight weeks depending on their specialty. Serum specimens were collected on arrival at Parris Island, on arrival at ITR, and at departure from ITR. Additional serum specimens were collected from trainees and seasoned troops at Camp Lejeune as part of an ongoing surveillance of acute respiratory disease (ARD), infectious mononucleosis, and viral hepatitis.

Study Design

All Marines were studied in the calendar years 1970 and 1971. Parris Island arrival sera from 588 men were tested for CMV antibody levels to determine the prevalence of antibodies in incoming recruits. Of these, sera from 431 men arriving successively between

20 June and 31 August 1971 were sampled and were further tested for CMV CF antibody on arrival and at departure from PIR; these men formed the "prospective group." The remaining 157 were arrival sera of men hospitalized in 1970 with ARD. Paired sera of the ARD patients and infectious mononucleosis or viral hepatitis patients were tested to determine if CMV infection was illness-related. An admission and two-week specimen from each patient were tested.

The ARD patients included 45 trainees in whom no etiologic agent was identified in 1970 by virus or *Mycoplasma pneumoniae* isolations or serologic studies. The remaining 112 had positive isolations and/or CF antibody rises to adenovirus, *M pneumoniae*, or parainfluenza virus types 1 or 3. Ninety three successive Australia antigen negative (Hyland Laboratories counterelectrophoresis kit) viral hepatitis patients hospitalized in 1970 and 1971 comprised the hepatitis group. The infectious mononucleosis group included successive patients, 32 with a positive monospot test (Wampole Laboratories kit) and three with a negative test on both an admission and a two-week specimen.

Serology

Routine CMV CF tests were performed. The antigen was prepared commercially from the AD-169 strain.* Tests were carried out in disposable microtiter plates,[10] using 4 to 8 units of antigen with overnight fixation at 4°C.

RESULTS

Of the sera tested from 588 men arriving at Parris Island boot camp, 410 (69.7%) had no detectable CF antibody (<1:2) to CMV (Table 1). Four of 431 (0.9%) men followed prospectively for approximately 14 weeks showed serologic evidence of CMV infection during the 14-week period (Table 2). An additional two men hospitalized with the clinical diagnosis of acute respiratory disease had seroconverted before hospitalization, suggesting an overall 1.0% seroconversion rate during the training period. One man with a viral syndrome (*vide infra*, originally thought to have viral hepatitis) showed serologic evidence of CMV infection. None of the 157 ARD patients, none of the 93 viral hepatitis patients, and none of the 35 infectious mononucleosis patients developed a fourfold rise in CMV antibody during their acute illness. All seven who showed a fourfold CF antibody rise had no detectable CMV antibody (titer <1:2) in their initial serum.

TABLE 1

Distribution of CMV Antibody Titers in Men Arriving at Parris Island Boot Camp*

Reciprocal CF Titer	No. Men with Indicated Titer	Percent
<2	410	69.7
2	26	4.4
4	47	8.0
8	64	10.9
16	29	4.9
32	11	1.9
64	1	0.2
	588	100.0

*Average age was 19 years.

*Microbiological Associates, Rockville, Md.

TABLE 2

Number of Men in the Hospitalized and Prospective Recruit Populations Who Showed Serologic Evidence of CMV Infection

Group Studied	No. in Group	Seroconversions
Prospective (1971)	431	4
Acute respiratory disease (1970)*	157	0
Viral hepatitis	93	0
Infectious mononucleosis	35	0
Viral syndrome	1	1

*Two men had seroconverted to CMV prior to hospitalization at Camp Lejeune and after arriving at Parris Island.

specimens (Table 3). The following brief narrative summarizes the patient who seroconverted during hospitalization:

A 21-year-old white Lance Corporal was admitted following a 20-day period of marked generalized malaise with headache and nausea. Other symptoms during this period included one episode of coughing blood-stained sputum, darkened urine for four days, and nocturnal diaphoresis and chills. His past history revealed no serious illnesses, and a review of systems was non-contributory. A physical examination was completely normal. His initial blood count revealed a hemoglobin of 14.4 gm%, a hematocrit of 45 volumes %, white blood cell count of 5100 cells/mm^3 with 63% neutrophils, 1 band, 32 lymphocytes, 2 monocytes, and 2 eosinophils. Sedimentation rate was 10 mm/hr.

The following laboratory data were negative or within normal limits: urinalysis, serology, serum bilirubin, alkaline phosphatase, SGOT, SGPT, LDH, monospot test, chest film, intermediate PPD skin test, three malaria smears, two sputum cultures, and two urine cultures. The patient was never febrile, and he became asymptomatic on the fourth hospital day. Acute and convalescent sera did not show a CF antibody rise to adenovirus, *M. pneumoniae*, paraintluenza virus types 1, 2, and 3, and influenza virus types A and B. Hemagglutination inhibition tests showed no rise to influenza A_2 Hong Kong or B Massachusetts. A diagnosis of

TABLE 3

Complement Fixing Antibody Titers of Seven Men Who Showed Evidence of CMV Infection

	Reciprocal Titer		
Prospective Group	Arrive P.I.	Arrive ITR	Depart ITR
#1	<2	8	8
#2	<2	<2	16
#3	<2	<2	32
#4	<2	16	16
	Reciprocal Titer		
ARD Group	Arrive P.I.	Acute	Conv.
#5	<2	16	16
#6	<2	8	8
		Reciprocal Titer	
Patient with Viral Syndrome		Acute	Conv.
#7		<2	64

CMV was made serologically (Table 3), although there were no typical mononuclear blood changes and no attempt was made to isolate CMV due to the retrospective nature of the study.

DISCUSSION

Previous reports suggested that conditions of crowding predispose to CMV infection and facilitate transmission.[8,9,11] In this regard, a sociologic survey of 383 men at this Base in 1968 revealed that only 60% had finished high school, 60% had three or more siblings, and 32% had five or more siblings.[12] We have no reason to assume a dissimilar composition of recruits in 1970 and 1971. The combination of a low socioeconomic background and high prevalence of CMV susceptibles (reciprocal titer <2) would be at variance with "crowding" theories.

Future longitudinal studies may show periodic fluctuations in titers from negative to positive to negative again, and there may be some antigenic variation demonstrated with different CMV strains. However, the present finding of 1% seroconversion during a closely crowded training period would favor very intimate contact as the primary mode of transmission and very limited communicability for this virus in normal adults. The 1% seroconversion rate to CMV per 14 weeks contrasts with 13% EB virus seroconversion rate in susceptible recruits at this Base,[12] and compares with our preliminary work (unpublished) showing that *Herpes hominis* virus infections occur at a rate of one per 500 per 14 weeks. Thus, communicability for CMV appears to be in an intermediate position between the latter two related DNA viruses. We recognize also a possibility that children may be the main source of these three viral infections in adults, and rates in our "protected" population may be different from similarly crowded civilian groups.

We investigated many of our patients with ARD, infectious mononucleosis, and viral hepatitis to see if these men had CMV-associated disease. None showed serologic evidence of CMV illness, and we conclude that in our population CMV infection does not commonly manifest itself with these syndromes. A single man with a history of prolonged malaise and nocturnal diaphoresis had a fourfold rise in CMV antibodies during hospitalization, yet presented with a completely normal physical examination, and had a normal biochemical and hematologic laboratory profile. It is not surprising that similarly infected adults with nonspecific complaints will not be properly diagnosed. Finally, since no patient with a reciprocal CMV CF titer of two or greater showed further antibody rise, it may be that very low serum CF antibody levels protect against natural infection in the uncompromised host.

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