Influenza-like syndrome in homosexual men: a prospective diagnostic study

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SUMMARY. In the course of a prospective study of the prevalence and incidence of infection with the human immunodeficiency virus (HIV) and risk factors for the acquired immune deficiency syndrome among 961 homosexual men, 97 initially HIV antibody seronegative men reported a febrile period lasting at least three days. In 60 of these men serological evidence for an infection was found: influenza A or B virus (17 men), HIV (14), Epstein–Barr virus (seven), parainfluenza virus type I, II or III (five), hepatitis A virus (three), cytomegalovirus (three), adenovirus (two), respiratory syncytial virus (two), hepatitis B virus (one) and Toxoplasma gondii *(one). Combined infections were found in five men. A total of 17 men seroconverted for HIV antibody. The clinical symptoms of acute HIV infection closely resembled those of influenza A or B infection. Skin rashes also occurred frequently in men with HIV infection. HIV antibody seroconversion gives rise to a number of different symptoms and primary HIV infection should be included in the differential diagnosis of prolonged febrile illness in those at risk of HIV infection.*

Introduction

PRIMARY infection with the human immunodeficiency virus (HIV), the aetiologic agent of the acquired immune deficiency syndrome (AIDS),[1-4] has been associated with an acute infectious-mononucleosis-like illness or a febrile illness.[5-11] This illness was first described in a nurse infected by a needle-stick injury,[5] but has also been seen in haemophiliacs,[7-10] intravenous drug users[9] and homosexual men.[6,8-11] The illness is of sudden onset and lasts between three and 21 days. The symptoms are fevers, sweats, malaise, lethargy, anorexia, nausea, myalgia, arthralgia, headaches, sore throat, diarrhoea, generalized lymphadenopathy and macular erythematous truncal eruptions. Acute encephalopathy,[10] lymphocytic meningitis,[9] acute neuropathy,[12] and myelopathy[13] have been seen in association with HIV antibody seroconversion.

In order to study the differential diagnosis of prolonged febrile illness in those at risk for HIV infection, 97 HIV antibody seronegative homosexual men, who suffered from pyrexia (>38 °C) for a minimum of three days were serologically tested for acute infection with cytomegalovirus, Epstein–Barr virus, influenza A and B viruses, adenovirus, respiratory syncytial virus, parainfluenza I, II and III viruses, hepatitis A and B viruses, *Mycoplasma pneumoniae, Toxoplasma gondii* and HIV.

Method

Between October 1984 and March 1986 961 asymptomatic men, living in and around Amsterdam, who had had at least two homosexual contacts in the preceding six months, were enrolled in a prospective study of the prevalence and incidence of HIV infection and risk factors for AIDS. Blood specimens and clinical and epidemiological data were collected every three months, as well as two and six weeks after HIV antibody seroconversion. Of the 961 men, 723 (75.2%) were found to be HIV antibody seronegative from the first serum sample taken. The mean age of this seronegative group was 34.9 years (standard deviation 7.7 years). Of the 723 men, 97 (13.4%) mentioned a period of fever (⩾38 °C) lasting at least three days and they were selected for the present study. Additional complaints during this febrile period, as well as the time between the last day of the period and the first seropositive sample, were recorded.

Serum samples taken before and after the febrile period were tested for the following evidence of infection:

1. The appearance of cytomegalovirus immunoglobulin (Ig)M antibodies or a fourfold rise in titre of cytomegalovirus IgG antibodies (ELISA, Department of Virology, University of Amsterdam).
2. The appearance of IgM antibodies to Epstein–Barr viral capsid antigen (ELISA, Dupont).
3. A fourfold rise in complement fixing antibody titre to influenza A and B viruses, adenovirus, respiratory syncytial virus, parainfluenza I, II and III viruses and *Mycoplasma pneumoniae* (complement fixation assay, Whittaker).
4. The appearance of IgM antibodies to hepatitis A virus (EIA, Abbott).
5. The appearance of hepatitis B virus surface antigen or antibodies to hepatitis B virus core antigen (EIA, Abbott).
6. The appearance of IgM antibodies to *Toxoplasma gondii* (EIA, Abbott).
7. The appearance of antibodies to HIV (ELISA, Vironostika Teknika, Organon; EIA, Abbott).

Results

The additional complaints suffered by the 97 men during the febrile period are given in Table 1. The most frequent complaints were coughing (50.5%), fatigue/malaise (41.2%), night sweats (33.0%) and diarrhoea (24.7%). Thirty-eight men (39.2%) mentioned other complaints, such as sore throat, myalgia and headache, which were not listed separately.

For 37 men (38.1%) there was no serological evidence of an infectious agent after the febrile period (Table 2). Fourteen men (14.4%) seroconverted for antibodies against HIV after the

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Table 1. Additional complaints suffered by the 97 homosexual men with a febrile period lasting at least three days.

Complaints	No. (%) of men
Coughing	49 (*50.5*)
Fatigue/malaise	40 (*41.2*)
Headache, sore throat, myalgia	38 (*39.2*)
Night sweats	32 (*33.0*)
Diarrhoea	24 (*24.7*)
Nausea	18 (*18.6*)
Dyspnoea	16 (*16.5*)
Lymphadenopathy	14 (*14.4*)
Skin rashes	13 (*13.4*)
Vomiting	10 (*10.3*)
Weight loss (>10%)	5 (*5.2*)

febrile period while a further three (3.1%) seroconverted for HIV together with one or more other infectious agents. In 41 men (42.3%) serological evidence was found for one infection other than HIV while one man had two infections other than HIV and one man three.

The complaints suffered in relation to the evidence for acute infection are shown in Table 3. Coughing occurred most frequently in men with influenza A or B infection while skin rashes were seen most often in men with HIV infection. Headache, sore throat and myalgia, and lymphadenopathy occurred as frequently in men infected with HIV as in those infected with influenza A or B, while fatigue or malaise occurred nearly as often.

The seasonal distribution of the 67 infections found in the study period is shown in Figure 1. No infections occurred between October 1984 and December 1984 and no specific seasonal distribution was found for infections with cytomegalovirus, Epstein–Barr virus, parainfluenza III virus or hepatitis A and B viruses. Seven out of 10 cases of influenza A and all three cases of parainfluenza I and II were found in early spring, autumn and winter. All eight cases of influenza B and all three

Table 2. Serological evidence for acute infection in 97 homosexual men with a febrile period lasting at least three days.

Infectious agent	No. (%) of men sero-positive	Time between febrile period and positive serum sample (weeks)	
		Median	Range
HIV	14 (*14.4*)	4	1.5–20
Influenza A	9 (*9.3*)	3	1–6
Influenza B	8 (*8.2*)	3	1–6
Epstein–Barr virus	7 (*7.2*)	6	2–6
Parainfluenza I, II and III	5 (*5.2*)	3	3–6
Hepatitis A	3 (*3.1*)	2, 4 and 6	
Cytomegalovirus	3 (*3.1*)	3, 6 and 10	
Adenovirus	2 (*2.1*)	4 and 8	
Respiratory syncytial virus	2 (*2.1*)	1.5 and 2	
Hepatitis B	1 (*1.0*)	3	
Toxoplasma gondii	1 (*1.0*)	3	
Mycoplasma pneumoniae	0 (*0.0*)	–	
Cytomegalovirus + respiratory syncytial virus	1 (*1.0*)	5	
Epstein–Barr virus + influenza A + adenovirus	1 (*1.0*)	4	
HIV + hepatitis B	1 (*1.0*)	2	
HIV + parainfluenza III	1 (*1.0*)	3	
HIV + Epstein–Barr virus + parainfluenza III	1 (*1.0*)	8	
Total	60 (*61.9*)	4	1–20
None	37 (*38.1*)	4	1–10

Table 3. Complaints suffered in relation to the evidence for acute infection in 97 homosexual men with a febrile period lasting at least three days.

	Percentage of men with acute infection										
	Coughing (*n* = 49)	Fatigue/ malaise (*n* = 40)	Headache, sore throat, myalgia (*n* = 38)	Night sweats (*n* = 32)	Diarrhoea (*n* = 24)	Nausea (*n* = 18)	Dyspnoea (*n* = 16)	Lymph-adeno-pathy (*n* = 14)	Skin rashes (*n* = 13)	Vomiting (*n* = 10)	Weight loss (⩾10%) (*n* = 5)
HIV	*6.1*	*15.0*	*15.8*	*9.4*	*8.3*	*5.6*	–	*28.6*	*30.8*	*20.0*	–
Influenza A or B	*24.5*	*20.0*	*15.8*	*25.0*	*16.6*	*11.1*	*18.8*	*28.6*	*7.7*	–	*20.0*
Epstein–Barr virus	*4.1*	*7.5*	*2.6*	*9.4*	*8.3*	–	*18.8*	–	–	–	*20.0*
Parainfluenza I, II and III	*8.2*	*5.0*	*7.9*	*12.5*	*8.3*	–	*12.5*	–	*7.7*	–	*20.0*
Hepatitis A	*2.0*	*2.5*	*2.6*	*3.1*	*4.2*	*5.6*	–	*14.3*	–	–	*20.0*
Cytomegalovirus	*2.0*	*5.0*	*2.6*	*3.1*	–	–	*6.3*	–	–	–	*20.0*
Adenovirus	*2.0*	–	*5.3*	–	–	–	–	*7.1*	*7.7*	–	–
Respiratory syncytial virus	*4.1*	–	–	–	–	–	*6.3*	*7.1*	–	–	–
Hepatitis B	*2.0*	–	–	–	*4.2*	–	*6.3*	–	–	–	–
Toxoplasma gondii	–	–	–	*3.1*	–	*5.6*	–	–	–	*10.0*	–
Multiple infection	*6.1*	*7.5*	*5.3*	–	*4.2*	*11.1*	–	–	*7.7*	*10.0*	–
No serological evidence for infection	*38.8*	*35.0*	*42.1*	*34.4*	*45.8*	*61.1*	*31.3*	*14.3*	*38.5*	*60.0*	–

n = number of men with complaint.

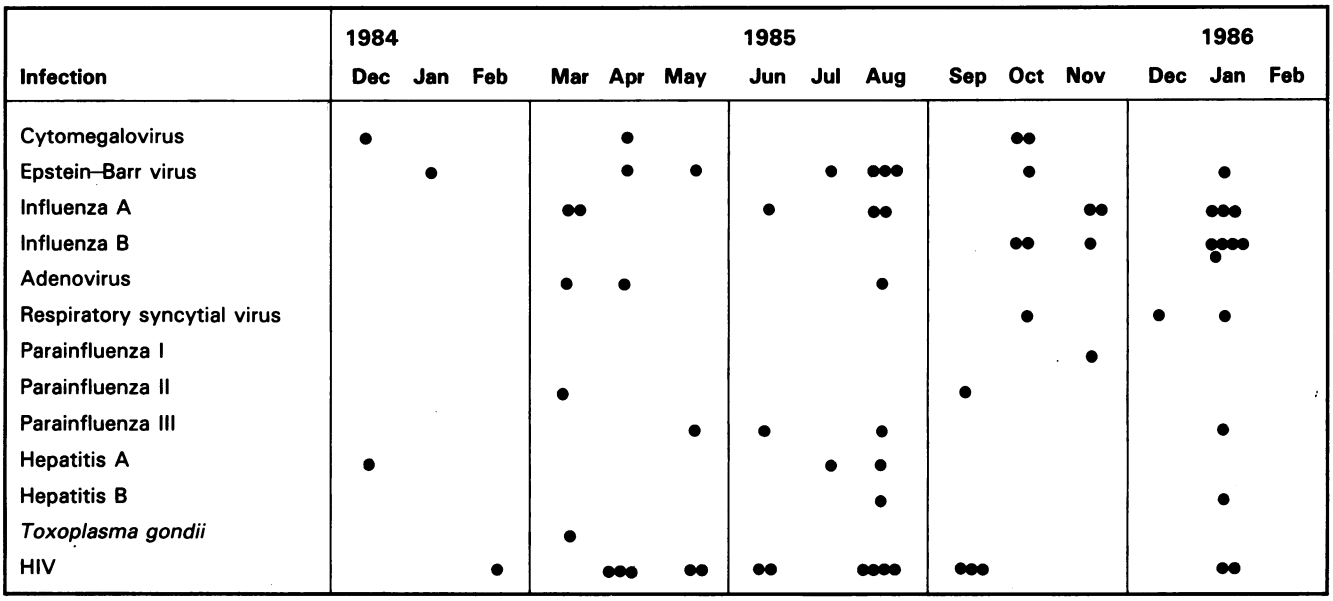

Figure 1. *Seasonal distribution of the 67 infections in 97 homosexual men at risk for HIV infection, who had a febrile period lasting at least three days over the period October 1984 to March 1986.*

respiratory syncytial virus infections occurred in autumn and winter. Adenovirus infections occurred in spring and late summer. Most HIV infections occurred in spring and summer (11 out of 17). Of the 37 men without serological evidence for infection, the febrile period occurred during spring in four men, during summer in nine, during autumn in 14 and during winter in 10.

Discussion

Of 723 initially HIV antibody seronegative homosexual men, 97 had an influenza-like illness lasting at least three days. Thirty-seven men had no antibody reactivity against the 12 infectious agents tested. Gastrointestinal and respiratory infections for which no laboratory evidence was sought may have caused their symptoms. In the remaining 60 men serological evidence for an infection was found, of which influenza A or B and HIV infections were the most common. The seasonal distribution of infections with influenza A and B viruses, parainfluenza I and II viruses, respiratory syncytial virus and adenovirus was in agreement with previous studies in the general population.[14-17] The lack of a specific seasonal distribution for infections with cytomegalovirus, Epstein–Barr virus, parainfluenza III virus and hepatitis A and B viruses was also in agreement with previous studies.[15,18-20] There have been no previous reports of the seasonal distribution of HIV infections. In the present study 11 out of 17 HIV infections occurred in spring and summer. There is no obvious explanation for this phenomenon except perhaps more frequent and hazardous sexual contacts during holidays.

The complaints mentioned in association with HIV antibody seroconversion were not as severe as those reported previously,[6] when an acute infectious mononucleosis-like illness was described. Skin rashes occurred frequently in HIV infection, while influenza-like symptoms, such as headache, sore throat and myalgia, were seen as frequently in men infected with HIV as in those infected with influenza A or B. The results of this study suggest that influenza-like syndrome is an appropriate designation of the clinical symptoms of HIV infection. HIV antibody seroconversion gives rise to a number of different symptoms, so clearly primary HIV infection should be included in the differential diagnosis of prolonged febrile illness in those at risk of HIV infection.

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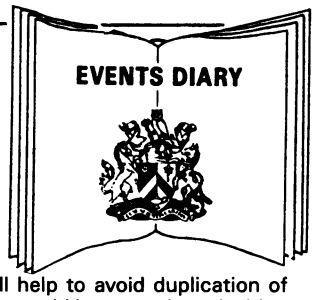

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