Incidence of toxoplasmosis in patients with glandular fever and in healthy blood donors

J D JOHNSON

R E HOLLIMAN

SUMMARY. The differential diagnosis of the clinical syndrome of glandular fever may include Epstein-Barr virus, cytomegalovirus and Toxoplasma gondii *infection. Some general practitioners and clinical laboratories choose to perform serological investigations for toxoplasmosis in all patients with glandular fever, who have negative Paul-Bunnell test results. The validity of this approach was assessed by a comparison of the incidence of toxoplasmosis in healthy blood donors and in a group of patients with clinically diagnosed glandular fever who had negative Paul-Bunnell tests. The results showed no significant difference in the frequency of acute or chronic toxoplasma infection between the two groups. In view of these findings, together with evidence of the lack of appropriate effective therapy for toxoplasmosis in immunocompetent individuals, and the dangers of failing to recognize concurrent severe disease of a separate aetiology, we recommend that Paul-Bunnell negative patients with clinically diagnosed glandular fever are not investigated for toxoplasmosis as a routine. However, these guidelines do not apply to patients at risk of severe sequelae from toxoplasma infection, notably pregnant women, who still require a full assessment.*

Introduction

THE obligate intracellular protozoan *Toxoplasma gondii* has a large range of intermediate hosts which includes man. Recent interest in the medical and general press has focused on the severe sequelae of this parasitic infection when acquired by an immunocompromised individual such as the fetus or a sufferer of acquired immune deficiency syndrome (AIDS). However, among immunocompetent subjects, most toxoplasma infections are asymptomatic or present with a mild, non-specific illness. A small number of individuals may suffer from a more severe clinical illness and seek medical assistance.[1] The signs and symptoms associated with acute toxoplasmosis show considerable variation but those most frequently noted include malaise, lethargy, myalgia and lymphadenopathy.[2] Patients presenting with these symptoms are often investigated for suspected glandular fever caused by Epstein-Barr virus. Cases giving a negative Paul-Bunnell reaction may represent glandular toxoplasmosis. Beverley and Beattie estimated that 7% of cases clinically diagnosed as glandular fever but giving a negative Paul-Bunnell reaction were due to toxoplasma infection,[3] while a Danish study suggested that between 3% and 7% of cases of lymphadenopathy of unknown aetiology were due to toxoplasmosis.[4]

Some medical practitioners routinely request toxoplasma serology as an initial investigation of suspected glandular fever or consider the diagnosis after Epstein-Barr virus infection has been excluded. In addition, some clinical laboratories choose to perform toxoplasma investigation in all cases where a Paul-Bunnell test has been found to be non-reactive. In this study toxoplasma serology findings have been reviewed in order to examine the validity of testing for toxoplasmosis when a negative Paul-Bunnell reaction has been recorded in a patient with a clinical diagnosis of glandular fever.

J D Johnson, CBIOL, MIBIOL, FIMLS, chief medical laboratory scientific officer and R E Holliman, MB, MSc, MRCPath, consultant medical microbiologist, St George's Hospital, London.
Submitted: 25 October 1990; accepted: 21 December 1990.

Method

Between 1988 and 1989, all patients with suspected glandular fever but a negative Paul-Bunnell test reaction who were referred by their general practitioner to one outpatient clinic were considered for the study. A serum sample from each of these patients was included in the study when the general practitioner had submitted a written request giving full details of the patient's age and sex. Control sera were obtained from healthy persons attending regular blood donation sessions in the same geographical area as the study group. The ages of persons allowed to attend blood donation sessions is restricted to those in the 20–69 years age range. This age restriction was therefore also placed on the study group.

Each serum sample included in the study was investigated in the public health laboratory for the presence of toxoplasma specific antibody using the dye test and latex agglutination test.[5] All sera with a dye test titre of 16 or more were defined as reactive and those producing a titre of less than 16 were taken to be non-reactive. A dye test titre of 16 equalled four international units. A positive latex agglutination test result was defined as a titre of 16 or more. Sera producing discordant dye test and latex agglutination reactions were further investigated using a direct agglutination test and said to be positive if a finding of four international units or more was recorded.

Samples producing a dye test result of 31 international units or more were tested for the presence of toxoplasma specific immunoglobulin-M using a double sandwich enzyme linked immunosorbent assay (DS-ELISA) and an immunosorbent agglutination assay (ISAGA),[6] which would indicate recent infection.

The results were analysed using the chi square test and the annual seroconversion rate calculated by dividing the percentage of seropositive patients by the mean age. The study was carried out over a one year period and the calculation assumes a linear conversion rate.

Results

Sera from 2235 patients with a clinical diagnosis of glandular fever were investigated during the course of the study. In 1097 cases the age of the patient was not recorded; for 388 patients there was no record of their sex; 129 individuals were below the age of 20 years and 12 were older than 69 years. These patients were therefore excluded from the study. The remaining 609 patients comprised the study group. In this group 226 were male and 383 female. The mean age was 31 years. Of 183 individuals in the control group, 95 were male and 88 female; the mean age was 43 years.

Toxoplasma serology findings for each group of patients, analysed by sex and age, are presented in Table 1. Correcting for age and sex there was no significant difference in the

prevalence of toxoplasma antibody between the study and control groups. The incidence of recent infection, as indicated by the detection of toxoplasma specific immunoglobulin-M was similar in both groups. The annual seroconversion rate was calculated to be 0.4% for the study group of patients and 0.6% for the control population. In the control group 30 sera had a result of 31 international units or more and in the study group 52 sera had 31 units or more. These sera were therefore tested for IgM by DS-ELISA and ISAGA. Specific immunoglobulin-M was detected in two members of the study group by DS-ELISA and ISAGA and in three patients by ISAGA only, reflecting the differences in sensitivity of the two assays. The corresponding figures for the control population were one and five, respectively.

Table 1. Toxoplasma serology results for study and control patients.

Age (years)	Sex	Percentage of patients positive to dye test for seroconversion (total number of patients)			
		Study group		Control group	
20–29	M	*9.2*	(130)	*4.5*	(22)
	F	*9.8*	(225)	*21.1*	(19)
30–39	M	*15.2*	(66)	*30.0*	(20)
	F	*15.2*	(105)	*10.5*	(19)
40–49	M	*31.6*	(19)	*35.0*	(20)
	F	*6.7*	(30)	*19.0*	(21)
50–59	M	*0.0*	(6)	*35.0*	(20)
	F	*21.1*	(19)	*21.1*	(19)
60–69	M	*0.0*	(5)	*38.5*	(13)
	F	*0.0*	(4)	*30.0*	(10)

Discussion

Toxoplasmosis, although a relatively common infection, is usually asymptomatic in the individual. In the United Kingdom 0.5–1.0% of the population seroconvert each year.[7] Consequently, when studying this disease it is important to include a control group of individuals. The individuals included in the control group were limited to an age range of 20–69 years; this resulted in the study group being restricted to this age range. However, the results are of importance. Correcting for sex and age distribution between the case and control groups permits a valid comparison of the incidence of toxoplasmosis in the two sets of patients. The seroprevalence of toxoplasmosis shows a consistent rise with increasing age but the mean age of patients diagnosed as showing associated lymphadenopathy is in the third decade of life.[2] Below 15 years of age toxoplasma lymphadenopathy is recognized more frequently in males but the reverse is found in adults aged 25 years or older. The preponderance of cases among male children is said to reflect greater contact with oocysts in soil and more solicitous care of baby girls. Adult females may have greater exposure to *T gondii* from preparing vegetables and raw meat and caring for domestic cats. It is claimed women are more likely to detect cervical lymphadenopathy than men owing to cosmetic habits.[8]

Diagnosis of toxoplasma infection is based on serological investigation. Sub-optimal sensitivity and specificity has been noted for several methods but the use of multiple tests, including the established reference assay, the dye test, minimizes misdiagnosis.[9] The detection of recent toxoplasma infection involves the measurement of specific immunoglobulin-M. It has been shown that each technique used in the present study is highly specific for toxoplasma infection and that the ISAGA is more sensitive than DS-ELISA.[6]

In this study the prevalence of toxoplasmosis and of recent infection was found to be similar in the group of patients clinically diagnosed as having glandular fever and in the control population. The clinical syndrome of glandular fever includes lymphadenopathy, malaise, lethargy and pyrexia. However, only 20% of patients with histologically confirmed toxoplasma lymphadenopathy have associated systemic symptoms and the frequency of mononucleosis syndrome owing to *T gondii* infection is low.[2] A recent study found that only one of a group of 41 patients with persistent Paul-Bunnell negative glandular fever fatigue syndrome had evidence of active toxoplasmosis.[10] When acute toxoplasmosis is diagnosed in the immunocompetent individual, specific therapy is rarely indicated. There is no convincing evidence that treatment reduces the duration or severity of associated illness, and the anti-parasitic agents available, notably sulphonamides, pyrimethamine and clindamycin, are potentially toxic. Concurrent toxoplasmosis and lymphoma or other severe disease has been reported.[2,11] Consequently there is a danger that the signs and symptoms of a life threatening disease could be thought to be due to coexistent toxoplasma infection, and that there will thus be a delay in correct management.

In view of the lack of appropriate effective therapy, the danger of missing a diagnosis of severe concurrent disease, and the low incidence findings of the present study, we recommend that Paul-Bunnell negative patients with a clinical diagnosis of glandular fever are not routinely investigated for toxoplasmosis. This recommendation only applies to the immunocompetent individual; patients at risk of severe sequelae from toxoplasmosis, particularly pregnant women, require complete investigation.

References

1. Barker CC, Farthing CP, Ratnesar P. Toxoplasma, an innocuous disease? *J Infect* 1984; **8:** 67-69.
2. McCabe RE, Brooks RG, Dorfman RF, Remington JS. Clinical spectrum of 107 cases of toxoplasmic lymphadenopathy. *Rev Infect Dis* 1987; **9:** 754-774.
3. Beverley JK, Beattie CP. Glandular toxoplasmosis: a survey of 30 cases. *Lancet* 1958; **2:** 379-384.
4. Remington JS, Barnet LG, Meikel M, Lunde MN. Toxoplasmosis and infectious mononucleosis. *Arch Int Med* 1962; **110:** 744-753.
5. Johnson J, Duffy K, New L, *et al.* Direct agglutination test and other assays for measuring antibodies to *Toxoplasma gondii*. *J Clin Pathol* 1989; **42:** 536-541.
6. Duffy KT, Wharton PJ, Johnson JD *et al.* Assessment of an immunoglobulin-M immunosorbent agglutination assay (ISAGA) for the detection of toxoplasma specific IgM. *J Clin Pathol* 1989; **42:** 1291-1295.
7. Fleck DG, Kwantes W. *The laboratory diagnosis of toxoplasmosis. PHLS monograph 13.* London: HMSO, 1980.
8. Beverley JK, Fleck DG, Kwantes W, Ludlam GB. Age–sex distribution of various diseases with particular reference to toxoplasmic lymphadenopathy. *J Hyg Camb* 1976; **76:** 215-228.
9. Holliman RE, Johnson J, Duffy K, New L. Discrepant toxoplasma latex agglutination test results. *J Clin Pathol* 1989; **42:** 200-203.
10. Read R, Larson E, Harvey J, *et al.* Clinical and laboratory findings in Paul-Bunnell negative glandular fever-fatigue syndrome. *J Infect* 1990; **21:** 157-165.
11. Wilcox MH, Powell RJ, Pugh SF, Balfour AH. Toxoplasmosis and systemic lupus erythematosis. *Ann Rheum Dis* 1990; **49:** 254-257.

Acknowledgements

We are most grateful to Mrs D Lyndon for the preparation of this manuscript and her assistance with analysis of the data.

Address for correspondence

Mrs J D Johnson, Public Health Laboratory, St George's Hospital, Blackshaw Road, London SW17 0QJ.