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Original investigations

High risk of developing toxoplasmic encephalitis in AIDS patients seropositive to *Toxoplasma gondii*

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Abstract. We studied 41 AIDS patients in the Austrian Tyrol with respect to toxoplasma antibody titers and the presence of CNS toxoplasmosis. In no patient had primary *Pneumocystis carinii* pneumonia (PcP) prophylaxis with either trimethoprim/sulfamethoxazole or pyrimethamine/sulfadoxine been applied; the degree to which CNS toxoplasmosis is influenced by this kind of PcP chemoprophylaxis, widely used elsewhere, is still unclear. In this study 47.4% of toxoplasma-seropositive patients developed CNS toxoplasmosis, compared to the previously estimated risk of 12%–28% for developing CNS involvement in such patients. In view of the high risk of toxoplasma-seropositive patients with AIDS, increased efforts in developing a well-tolerated chemoprophylaxis to combat CNS toxoplasmosis are required.

Introduction

Central nervous system (CNS) toxoplasmosis is a common infectious complication of AIDS [5, 13, 14, 19, 25]; when left untreated it is a rapidly progressive and fatal [10, 15]. On the basis of serological studies, most cases of toxoplasmic encephalitis are considered to be due to reactivation of chronic toxoplasmosis rather than to recent infection [16, 17]. The prevalence of antibodies to *Toxoplasma gondii* in the general population of the Austrian Tyrol was the subject of an earlier investigation [6]. Here we report on the rate of occurrence of CNS toxoplasmosis in patients with AIDS. At the University Hospital in Innsbruck pentamidine inhalation for primary and secondary *Pneumocystis carinii* pneumonia PcP prophylaxis was introduced at the beginning of 1988. However, in this study no primary PcP prophylaxis with either trimethoprim/sulfamethoxazole or pyrimethamine/sulfadoxine had been given to the patients. The degree to which CNS toxoplasmosis is influenced by this kind of PcP chemoprophylaxis, widely used elsewhere, is still unclear. We suggest that the high risk that toxoplasma-seropositive patients with AIDS will develop CNS toxoplasmosis urgently calls for studies on the use of prophylactic treatment.

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Material and methods

Study population

In the Austrian Tyrol, with a population of about 600,000, the University Hospital for Dermatology and Venereal Diseases in Innsbruck is the center to which patients with AIDS are referred. Between August 1st 1985 and July 31th 1990, AIDS was diagnosed in 46 patients. Of these patients 41 were observed from the time of diagnosis of AIDS until death or up to the end of the study period by serological methods, CT scan or autopsy.

Investigations aimed at assessing the percentage of the total population of Tyrol carrying antibodies to toxoplasma were carried out in 1989; the results have been published elsewhere [6].

Diagnostic criteria

The definition of AIDS was based on the CDC (Centers for Disease Control) criteria for reporting AIDS, formulated in 1985 and revised in 1987 [2]. CNS toxoplasmosis was defined as being present when both of the following criteria are fulfilled: (1) a ring-enhancing lesion or multiple lesions seen on head computed tomography (CT) scans; (2) neurological- and CT-documented improvement in response to therapy with pyrimethamine and sulfadiazine or pyrimethamine and clindamycin [9]. It has to be stated that we did not make a definitive diagnosis of toxoplasmic encephalitis, since none of our patients were biopsy proven. Autopsy was performed on 18 out of 22 patients, including 5 patients with CNS toxoplasmosis.

Serology

An indirect immunofluorescent antibody technique (IFA) was used for the detection and titration of toxoplasma antibody [7]. The antigen substrate consisted of formalin-fixed *T. gondii* strain RH (Microbiological Research Corp., Bountiful, Utah). Fluorescein-labelled goat immunoglobulin directed either against human IgG or human IgM (bio Mérieux, Marcy l'Etoile, France) were used as second antibodies. IgG antibodies were determined by immunofluorescence in serum dilutions of 1:16 and 1:256. Sera that were also positive in the latter dilution were titrated in fourfold titer steps. Sera found to be negative on the basis of immunofluorescence were retested at a reference laboratory (Toxoplasma laboratory, Department of pediatrics, University of Vienna, Austria) using the Sabin-Feldman dye test. IgM was tested by immunofluorescence with serum starting at a 1:2 dilution and further diluted in twofold titer steps.

Results

Toxoplasma serology

Toxoplasmosa serology was carried out on 41 patients with AIDS (Table 1). Nineteen patients were seropositive for *T. gondii* (46.3%). The mean age of toxoplasma seropositives was 34.3 years, of seronegatives 30.3 years (at time of AIDS diagnosis). Further data characterizing these patients are summarized in Table 2.

The geometric mean titer of immunofluorescence IgG antibodies to *T. gondii* was 1:752 for toxoplasma-seropositive AIDS patients with CNS toxoplasmosis and 1:169 for toxoplasma-seropositive AIDS patients without CNS toxoplasmosis (Table 3).

Table 1. Summarized data on 41 patients with AIDS

Patient no.	Age (years)/ sex	Transmission groups	CNS toxoplasmosis	Toxoplasma IgG titer (maximum)	Dead (before 07/31/90)	Time of observation (months) (AIDS until death or until 07/31/90)
1	21/M	H		neg.	+	4
2	44/M	G		neg.	+	12
3	45/M	G		neg.	+	18
4	25/M	D		neg.	+	11
5	25/M	D		neg.	+	8
6	29/M	HET		neg.	+	1
7	26/F	H		neg.	+	5
8	26/M	D		neg.	+	18
9	31/M	G		neg.	+	8
10	35/M	D		neg.	+	21
11	32/M	D		neg.	+	22
12	34/M	G		neg.		4
13	36/M	D		neg.		7
14	31/M	G		neg.		4
15	26/M	D		neg.		7
16	31/M	G		neg.		22
17	29/M	D		neg.		20
18	31/M	D		neg.		17
19	34/M	D		neg.		33
20	28/F	HET	+	neg.		3
21	15/M	H		neg.		16
22	33/M	D		neg.		29
23	34/M	G		1:16	+	6
24	38/M	G		1:16	+	6
25	40/M	G	+	1:4096	+	17
26	37/M	G	+	1:256	+	10
27	31/M	D	+	1:16384	+	22
28	55/M	G	+	1:16	+	7
29	31/M	D	+	1:1024	+	22
30	31/M	D		1:16	+	2
31	32/M	D		1:1024	+	23
32	26/M	D		1:256	+	1
33	39/M	G	+	1:16	+	8
34	29/F	D	+	1:4096		19
35	29/F	D		1:16		19
36	24/F	D		1:1024		12
37	21/M	H		1:1024		10
38	63/M	G		1:4096		8
39	26/M	D	+	1:256		6
40	37/M	HET		1:256		4
41	29/F	D	+	1:16384		4

M: male; F: female; H: coagulation disorder; G: homosexual/bisexual men; D: i.v. drug abusers; HET: heterosexuals

Table 2. Data on AIDS patients listed in relation to the occurrence of antibodies to *Toxoplasma gondii*

	Toxoplasma-seropositive AIDS patients	Toxoplasma-seronegative AIDS patients
Sex (male/female)	15/4	19/3
Age (mean and range in years)	34.3 15–63	30.3 21–45
Risk group:		
intravenous drug user	10	11
homosexuals	7	6
others	2	5
Alive on July 31th 1990	8	11
Time of observation (months; mean; AIDS until death or until 07/31/90)	10.8	13.2
Intracerebral mass lesions on CT scans	10	4
CNS toxoplasmosis	9[a] (47.7%)	1 (4.5%)

[a] One patient had CNS toxoplasmosis and primary CNS lymphoma concomitantly

Table 3. Data on toxoplasma-seropositive AIDS patients listed in relation to the occurrence of CNS toxoplasmosis

	AIDS patients with CNS toxoplasmosis ($n=9$)	AIDS patients without CNS toxoplasmosis ($n=10$)
Sex (male/female)	7/2	8/2
Age (mean and range in years)	35.2 26–55	33.5 15–63
Risk group:		
intravenous drug user	5	5
homosexuals	4	3
others	0	2
Alive on July 31th 1990	3	5
Time of observation (months; mean; AIDS until death or until 07/31/90)	11.8	12.2

Table 1 shows the IgG antibody titers to *T. gondii* of patients with AIDS with and without CNS toxoplasmosis. IgM antibodies to *T. gondii* were present in only one patient, a 31-year-old male with CNS toxoplasmosis (titer 1:16). All sera that were negative by IFA were also negative in the Sabin Feldman Dye test, including the specimen from a female patient with CNS toxoplasmosis.

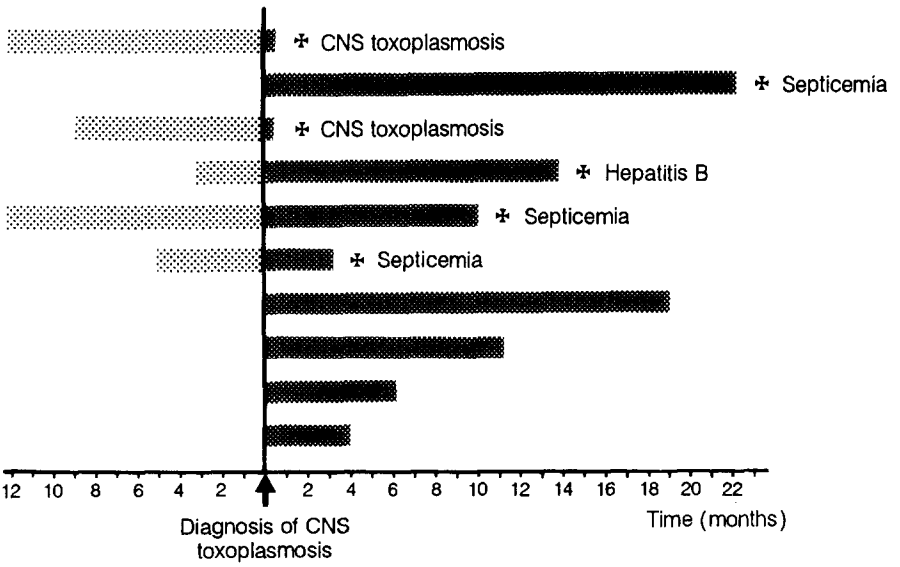

Fig. 1. Time ob observation of ten patients with CNS toxoplasmosis; from diagnosis of AIDS until death or until 07/31/90. Final causes of death are listed

Prevalence of CNS toxoplasmosis

Intracerebral mass lesions were found in the CT scans in 14 (10 seropositive for *T. gondii,* 4 seronegative) of the 41 AIDS patients.

CNS toxoplasmosis was diagnosed in 9 out of the 19 (47.4%) patients with positive toxoplasma serology and in 1 out of the 22 (4.5%) patients with negative toxoplasma serology. Other causes of intracerebral mass lesions were tuberculoma (1×), progressive multifocal leucoencephalopathy (2×), hemorrhage (1×); one patient developed primary CNS lymphoma at the time when the multiple lesions of CNS toxoplasmosis had receded.

The single case of CNS toxoplasmosis without detectable antibodies to *T. gondii* was a 29-year-old female. Apart from a history of seizures, she was quite well; on CT scans multiple contrast-enhancing lesions were found and after empirical therapy with pyrimethamine and sulfadiazine, the lesions diminished continuously and resolved completely after 6 weeks.

CNS toxoplasmosis was the index diagnosis of AIDS (i.e., first clinical manifestation) in 5 of the 41 (12.2%) patients, including the above-mentioned woman with negative toxoplasma-serology (Fig. 1).

Toxoplasmic chorioretinitis occurred concomitantly with CNS toxoplasmosis in 2 out of the 10 patients with CNS toxoplasmosis. Both of these cases were seropositive for *T. gondii.*

Discussion

In most cases CNS toxoplasmosis in AIDS results from reactivation of a latent infection in patients with preexisting antibodies to *T. gondii.* Serological evidence

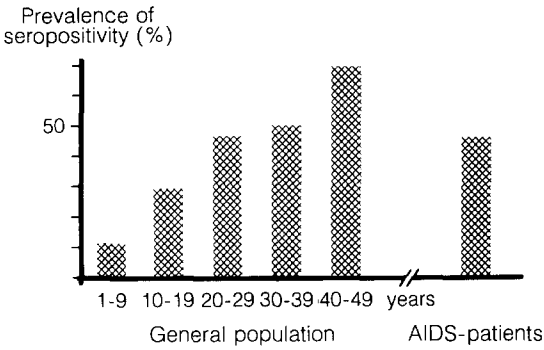

Fig. 2. Comparison of patients with AIDS (mean age: 32.2 years) and the general population in the Tyrol with respect to the percentage of toxoplasma-seropositive individuals

of prior infection with *T. gondii* was present in 46.3% of the AIDS patients analyzed in this study, a rate of seropositivity correlating with that of the general population in the same age group (Fig. 2).

The overall probability of developing CNS toxoplasmosis was distinctly higher in toxoplasma-seropositive individuals of this study compared with other studies where the risk for developing CNS toxoplasmosis in such patients was estimated to be 12%–28% [9, 11, 25]. In the Tyrol, 47.4% of toxoplasma-seropositive patients with AIDS developed CNS toxoplasmosis. The finding of this high rate of CNS toxoplasmosis may be explained by two facts: (1) the follow-up of the patients in Tyrol was uninterrupted from the time of diagnosis of AIDS until death or until the end of this study; (2) although pentamidine inhalation for primary and secondary PcP prophylaxis was introduced at the University Clinic in Innsbruck at the beginning of 1988, no patient in this study had received primary PcP prophylaxis with either trimethoprim/sulfamethoxazole or pyrimethamine/sulfadoxine. Only one of the patients admitted before 1988 received trimethoprim/sulfamethoxazole as a secondary PcP-prophylaxis (he died within three months after this episode due to lymphoma without developing CNS toxoplasmosis). The degree to which CNS toxoplasmosis is influenced by this kind of PcP chemoprophylaxis is still unclear, although the efficacy of sulfonamides in combatting *T. gondii* has long been known [21, 22].

In our opinion, the change from systemic PcP chemoprophylaxis to pentamidine inhalation, which is now the commonly recommended prophylaxis against PcP [8, 12, 24], might be responsible for a general increase in the rate of CNS toxoplasmosis.

Out of 14 patients with intracerebral mass lesions on CT scan, 10 had CNS toxoplasmosis (9 patients were seropositive for *T. gondii*). This emphasizes the validity of the recommendation that in patients with antibodies to *T. gondii* and intracerebral mass lesions, an empirical therapy is warranted [4]. CNS toxoplasmosis in toxoplasma-seronegative patients seems to be a rare event [9, 20]. Negative serology does not completely rule out toxoplasmic encephalitis since approximately 3% of patients with toxoplasmic encephalitis do not have Toxoplasma antibodies in their serum [15, 17]. In our study, 1 of 10 patients with CNS toxoplasmosis was seronegative. This 28-year-old patient with no detectable antibodies to *T. gondii* also showed a diminished antibody response to HIV itself [absence of antibodies to p17 and p24 was demonstrated by westernblot (Diagnostic Biotechnology Pte Ltd, Singapore)].

The geometric mean of the titer was higher in the group with CNS toxoplasmosis than in the non-affected group; an observation also made by Grant [9]. In our study, this difference was not significant according to statistical analysis, which may be due to the relatively small number of patients (Mann-Whitney test, $Z = 1.25$, $P = 0.21$).

IgM titers, useful in diagnosing manifest infection in non-immunocompromised hosts, are rarely helpful in patients with AIDS [1, 23]. In this study only one patient had IgM antibodies (titer 1:16) to toxoplasma. The CNS toxoplasmosis in this 31-year-old male patient could be interpreted as a recently acquired toxoplasma infection.

It has to be stated that we did not make a definitive diagnosis of toxoplasmis encephalitis, since none of our patients were biopsy proven. However, in recent years, empirical anti-toxoplasma therapy has been accepted as an alternative to biopsy in selected patients with AIDS [3].

As the identification of subjects at risk for CNS toxoplasmosis minimizes delays in diagnosis and permits earlier institution of treatment, we strongly recommend routine screening of patients with HIV infection for *T. gondii* antibody. Since about 80%–90% of CNS toxoplasmosis occurs when the CD4 T cell count is below 100/mm^3 [18], thorough neurological and fundoscopic examinations are advisable in such patients. Subtle neurological or behavioral changes should be investigated promptly by head CT scans. Drug toxicity, observed in up to 60% of the patients, is currently the main problem in the systemic prophylaxis of CNS toxoplasmosis in immunodeficient patients [10]. Since toxoplasma-seropositive individuals with AIDS run such a high risk of developing CNS toxoplasmosis, the efficacy of prophylactic therapy urgently needs further investigation.

References

1. Brooks RG, McCabe RE, Remington JS (1987) Role of serology in the diagnosis of toxoplasmic lymphadenopathy. Rev Infect Dis 9:775–782
2. Centers for Disease Control (1987) Revision of the CDC surveillance case definition for acquired immunodeficiency syndrome. MMWR 36 [Suppl]:1–15
3. Chaisson RE, Volberding PA (1990) Clinical manifestations of HIV infection. In: Mandell GL, Douglas RG, Bennett JE (eds) Principles and practice of infectious diseases, 3rd edn. Churchill Livingstone, New York Edinburgh London Melbourne, pp 1059–1092
4. Cohn JA, McMeeking A, Cohen W, Jacobs J, Holzman RS (1989) Evaluation of the policy of empiric treatment of suspected toxoplasma encephalitis in patients with the acquired immunodeficiency syndrome. Am J Med 86:512–527
5. Derouin F, Beauvais B, Lariviere M (1986) Serological study of the prevalence of toxoplasmosis in 167 patients with acquired immunodeficiency syndrome (AIDS) or chronic lymphadenopathy syndrome (LAS). Biomed Pharmacother 40:231–232
6. Fille M, Allerberger F, Dierich MP (1989) Untersuchungen über den Durchseuchungsgrad an Toxoplasmose in Tirol. Mitt Österr Sanitätsverwalt (Vienna) 90:1–3
7. Fleck DG, Kwantes W (1980) The laboratory diagnosis of toxoplasmosis. PHLS Monograph 13. Her Majesty's Stationery Office, London
8. Girard PM, Landman R, Gaudebout C, Lepretre A, Lottin P, Micon C, de Truchi P, Matheron S, Camus F, Farinotti R, Marche C, Couland JP, Saimot AG (1989) Prevention of *Pneumocystis carinii* pneumonia relapse by pentamidine aerosol in Zidovudine-treated AIDS patients. Lancet I:1348–1353
9. Grant IH, Gold JWM, Rosenblum M, Niedwiecki D, Armstrong D (1990) Toxoplasma gondii serology in HIV-infected patients: the development of central nervous system toxoplasmosis in AIDS. AIDS 4:519–521

10. Haverkos HW (1987) Assessment of therapy for toxoplasma encephalitis. The TE Study Group. Am J Med 82:907–914
11. Hofflin JM, Conley FK, Remington JS (1987) Murine model of intracerebral toxoplasmosis. J Infect Dis 155:550–557
12. Kovacs JA, Masur H (1989) AIDS commentary: prophylaxis of *Pneumocystis carinii* pneumonia: an update. J Infect Dis 160:882–886
13. Leport C, Raffi F, Matheron S, Katlama C, Regnier B, Saimot AG, Marche C, Vedrenne C, Vilde JL (1988) Treatment of central nervous system toxoplasmosis with pyrimethamine/sulfadiazine combination in 35 patients with the acquired immunodeficiency syndrome. Am J Med 84:94–100
14. Levy RM, Bredesen DE, Rosenblum ML (1985) Neurological manifestations of the acquired immunodeficiency syndrome (AIDS): experience at UCSF and review of the literature. J Neurosurg 62:475–495
15. Luft BJ, Remington JS (1988) AIDS commentary. Toxoplasmic encephalitis. J Infect Dis 157:1–6
16. Luft BJ, Conley F, Remington JS, Laverdiere M, Wagner KF, Levine JF, Craven PC, Stranberg DA, File TM, Rice N, Meunier-Carpentier F (1983) Outbreak of central-nervous-system toxoplasmosis in Western Europe and North America. Lancet I:781–784
17. Luft BJ, Brooks RG, Conley FK, McCabe RE, Remington JS (1984) Toxoplasmic encephalitis in patients with acquired immune deficiency syndrome. JAMA 252:913–917
18. Matheron S, Dournon E, Garakhanian S, Leport C, Detruchis P, Gaudebout C (1990) Prevalence of toxoplasmosis in 356 AIDS and ARC patients before and during Zytovudine treatment. VI. Conference on AIDS, San Francisco, June 1990. Regents of the University of California, San Francisco, abstract Th.B476
19. Mills J (1986) *Pneumocystis carinii* and *Toxoplasma gondii* infections in patients with AIDS. Rev Infect Dis 8:1001–1011
20. Pedrol E, Gonzales-Clemente JM, Gatell JM, Mallolas J, Mirol JM, Craus F, Alvarez R, Mercader JM, Berenguer J, Jimenez de Anta MT, Valls ME, Soriano E (1990) Central nervous toxoplasmosis in AIDS patients: efficacy of an intermittent maintenance therapy. AIDS 4:511–517
21. Sabin AB, Warren J (1941) Therapeutic effect of the sulfonamides on infection by an intracellular protozoon (toxoplasma). J Bacteriol 41:80–86
22. Solbreux P, Sonnet J, Zech F (1990) A retrospective study about the use of cotrimoxazole as diagnostic support and treatment of suspected cerebral toxoplasmosis in AIDS. Acta Clin Belg 45:85–96
23. Suzuki Y, Israelski DM, Dannemann BR, Stepick-Biek P, Thulliez P, Remington JS (1988) Diagnosis of toxoplasmic encephalitis in patients with acquired immunodeficiency syndrome by using a new serologic method. J Clin Microbiol 26:2541–2543
24. Thomas S, O'Dohety M, Bateman N (1990) *Pneumocystis carinii* pneumonia: aerolised pentamidine gives effective prophylaxis. Br Med J 300:211–212
25. Wong B, Gold JW, Brown AE, Lange M, Fried R, Grieco M, Mildvan D, Giron J, Trapper ML, Lerner CW (1984) Central nervous system toxoplasmosis in homosexual men and parenteral drug abusers. Ann Intern Med 100:36–42