Acta Neuropathol (1992) 83: 475 - 481

Acta Neuropathologica

The changing pattern of human immunodeficiency virus -associated cerebral toxoplasmosis: a study of 46 postmortem cases

C. Strittmatter, W. Lang, O. D. Wiestler, and P. Kleihues

Labor für Neuropathologie, Institut für Pathologie, Universität Zürich, CH-8091 Zürich, Switzerland

Received August 7, 1991/Accepted November 25, 1991

Summary. Frequency, pathogenesis and morphological features of toxoplasmosis were assessed in a consecutive autopsy study. Among 204 patients who died from AIDS in Zurich during 1981–1990, 46 (23 %) showed morphological evidence of cerebral toxoplasmosis. In 38 out of 46 cases (83 %), toxoplasmosis was restricted to the central nervous system (CNS) and, therefore, pathogenetically classified as reactivation of a latent infection. Acute, systemic toxoplasmosis most frequently involved heart and lungs in addition to the CNS and was observed in 7 cases (15 %). These patients probably acquired the infection during HIV-induced immunosuppression. Latent infection with intracerebral tissue cysts but no inflammatory response was present in only one case. Diffuse, necrotizing toxoplasma encephalitis with widespread, confluent areas of necrosis was mainly observed during the early period of the AIDS epidemic and restricted to 6 patients (13 %) who did not receive chemotherapy. The majority of patients (83 %) had multiple, macroscopically well-circumscribed abscesses with preferential location in the cerebral hemispheres. Of all CNS regions, the rostral basal ganglia were most frequently affected (78 % of cases). Since 1989, chronic, burnt-out lesions were observed. These were mainly composed of lipid-laden macrophages and immunocytochemistry for *Toxoplasma gondii* usually failed to detect the parasite. This changing pattern of CNS lesions probably reflects improved clinical management of patients with AIDS.

Key words: AIDS – Cerebral toxoplasmosis

Before 1980 cerebral toxoplasmosis was only occasionally observed in immunosuppressed patients [11, 15]. With the widespread distribution of HIV infection it has become the most frequent cause of brain abscesses [20].

Offprint requests to: P. Kleihues (address see above)

The pattern of opportunistic infection of the CNS associated with the acquired immune deficiency syndrome (AIDS) varies in different countries, but in all reported surveys *Toxoplasma gondii* is the most frequent non-viral opportunistic agent encountered, the frequency in AIDS patients ranging from 7 % to 48 % (Fig. 1). The present report is based on 46 cases of cerebral toxoplasmosis in a consecutive autopsy series of 204 patients who died of AIDS in Zurich, Switzerland, during the period of 1981 to 1990. Our findings indicate that the great majority of cases (approximately 85 %) results from reactivation of a latent cerebral toxoplasmosis and that improved clinical management, in particular chemotherapy, has had a profound effect on the cerebral manifestation of this parasitic infection.

Materials and methods

Patients and risk factors

Results are based on a consecutive autopsy series of 204 patients who died of AIDS in Zurich, Switzerland, during the period between April 1981 and August 1990. Of these, 171 were male and 33 female. The mean age at death was 38 years. The age distribution of patients with toxoplasmosis did not differ significantly from that of other patients with AIDS, with the exception that no case of toxoplasmosis was observed below the age of 20. Risk factors for AIDS included homosexuality or bisexuality (46 %) and intravenous drug abuse (28 %). Heterosexual transmission was assumed in 5 % of the cases. Two patients received HIV-contaminated blood transfusions. The two children in this series, aged 1 and 3 years, were from HIV-positive parents.

Morphological analysis

In 203 of the 204 cases a complete autopsy was performed. After fixation of the brain in 10 % formalin for 2 to 4 weeks, tissue samples from the frontal and parietal cortex, frontal and parietal white matter, basal ganglia, hippocampus, pons and cerebellum were investigated histologically. The spinal cord was available for investigation in 36 out of 46 patients. In these, transverse sections from the cervical, thoracic and lumbar levels were examined. In

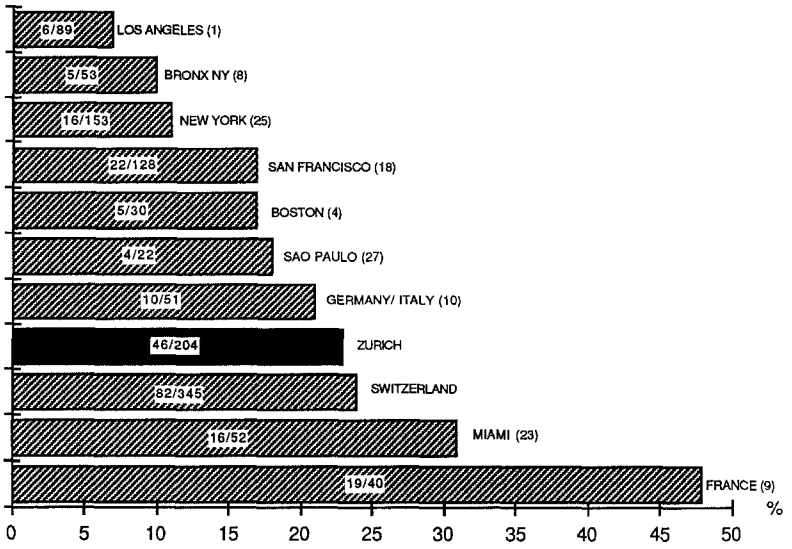

Fig. 1. Frequency of toxoplasma encephalitis in different autopsy studies. Numbers in parentheses refer to the reference list

addition, samples were taken from every macroscopically conspicuous lesion. Whole brain sections were prepared in 45 cases. Paraffin sections (4 μm) were stained with hematoxylin-eosin and Luxol-Nissl. Immunoperoxidase staining was performed with a polyclonal rabbit hyperimmune serum against *Toxoplasma gondii* (obtained from Virion, Rüschlikon, Switzerland) as described by Conley [3]. The rabbit anti-toxoplasma antiserum was used at a dilution of 1:300, followed by biotinylated swine anti-rabbit serum (1:50), and avidin-biotin complex from Dakopatts (Glostrup, Denmark).

Results

Cerebral toxoplasmosis was diagnosed in 46 of the 204 patients with HIV infection (23%). Of these, 36 were male. The mean age was 38 years, with a range from 21 to 69 years (Fig. 2). The age distribution of patients with toxoplasmosis did not differ significantly from that of other patients with AIDS, with the exception, that no case of toxoplasmosis was observed below the age of 20. CNS structures most frequently affected were the cerebral hemispheres (91%), basal ganglia (78%), cerebellum (51%), and brain stem (31%). Toxoplasma myelitis was observed in two patients (Table 1). Seven patients suffered from systemic toxoplasmosis. In addition to cerebral toxoplasmosis, these patients showed tissue cysts in the heart (3 patients), in heart and lung (2 patients) and in a lymph node (1 patient). Disseminated toxoplasmosis was only observed in a female patient from Haiti with involvement of heart, lung, liver, pancreas, esophagus, bladder, ovary and adrenal gland. On the other hand, there was no patient in the present

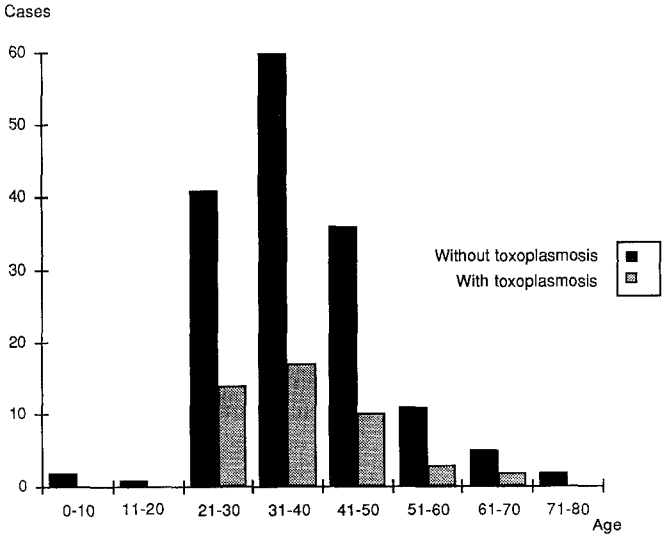

Fig. 2. Age distribution of 204 patients with AIDS. The age distribution of patients with toxoplasmosis did not differ significantly from that of other patients with AIDS

Table 1. Distribution of lesions in CNS toxoplasmosis

	All cases		Systemic	Reactivated
	Cases	%	%	%
Cerebral hemispheres	42/46	91	100	90
Basal ganglia	36/46	78	86	77
Cerebellum	23/45	51	57	50
Brain stem	14/45	31	43	29
Spinal cord	2/36	6	14	3

Table 2. Pathogenetic and histopathological variants of cerebral toxoplasmosis

Reactivated cerebral toxoplasmosis		38
Multiple abscesses		
recent	23	
old	3	
recent and old abscesses	5	
Necrotizing toxoplasma encephalitis	6	
Microglial nodules	1	
Systemic toxoplasmosis with CNS involvement		7
Multiple abscesses	5	
Microglial nodules	1	
Microabscesses	1	
Latent toxoplasma infection with clusters of tissue cysts		1

series without cerebral manifestation of the toxoplasma infection. Pathogenetically, cerebral toxoplasmosis was divided into three groups (Table 2).

Reactivated cerebral toxoplasmosis without extracerebral manifestations

We observed the following histopathological patterns (Fig. 3): in most patients, multiple abscesses were present which were preferentially located in the cerebral hemispheres, particularly in or adjacent to the rostral basal ganglia (Fig. 4C–F). A combination of necrotizing toxoplasma encephalitis and multiple abscesses was present in one patient treated by chemotherapy. Since the beginning of 1989, we have seen three cases with old abscesses which were macroscopically well circumscribed and exhibited a yellowish border. These patients had received intense chemotherapy with sulfadiazine and pyrimethamine. Histologically, such lesions con-

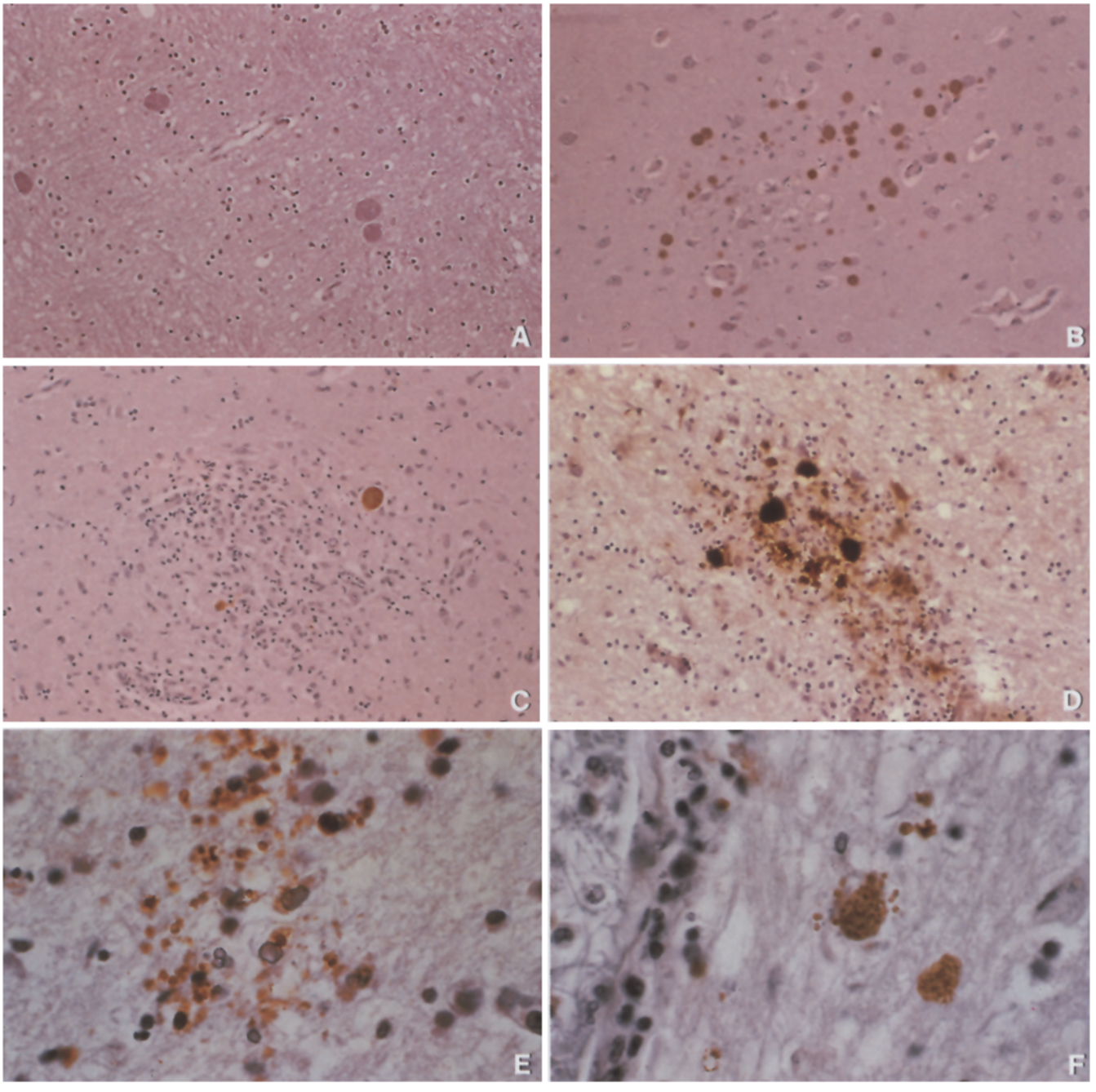

Fig. 3A–F. Toxoplasma encephalitis. **A** Latent infection with intact cysts without necrosis or inflammatory response. **B** Disseminated small foci with numerous tissue cysts but little or no tissue response (systemic toxoplasmosis). **C** Nodular toxoplasma encephalitis. **D** Necrotizing toxoplasma encephalitis with multiple tissue cysts and intracellular tachyzoites at the periphery of necrosis. **E** Clusters of free tachyzoites in brain tissue adjacent to areas of necrosis. **F** Rupture of a tissue cyst with release of free tachyzoites. **B–F** immunocytochemistry for *Toxoplasma gondii*

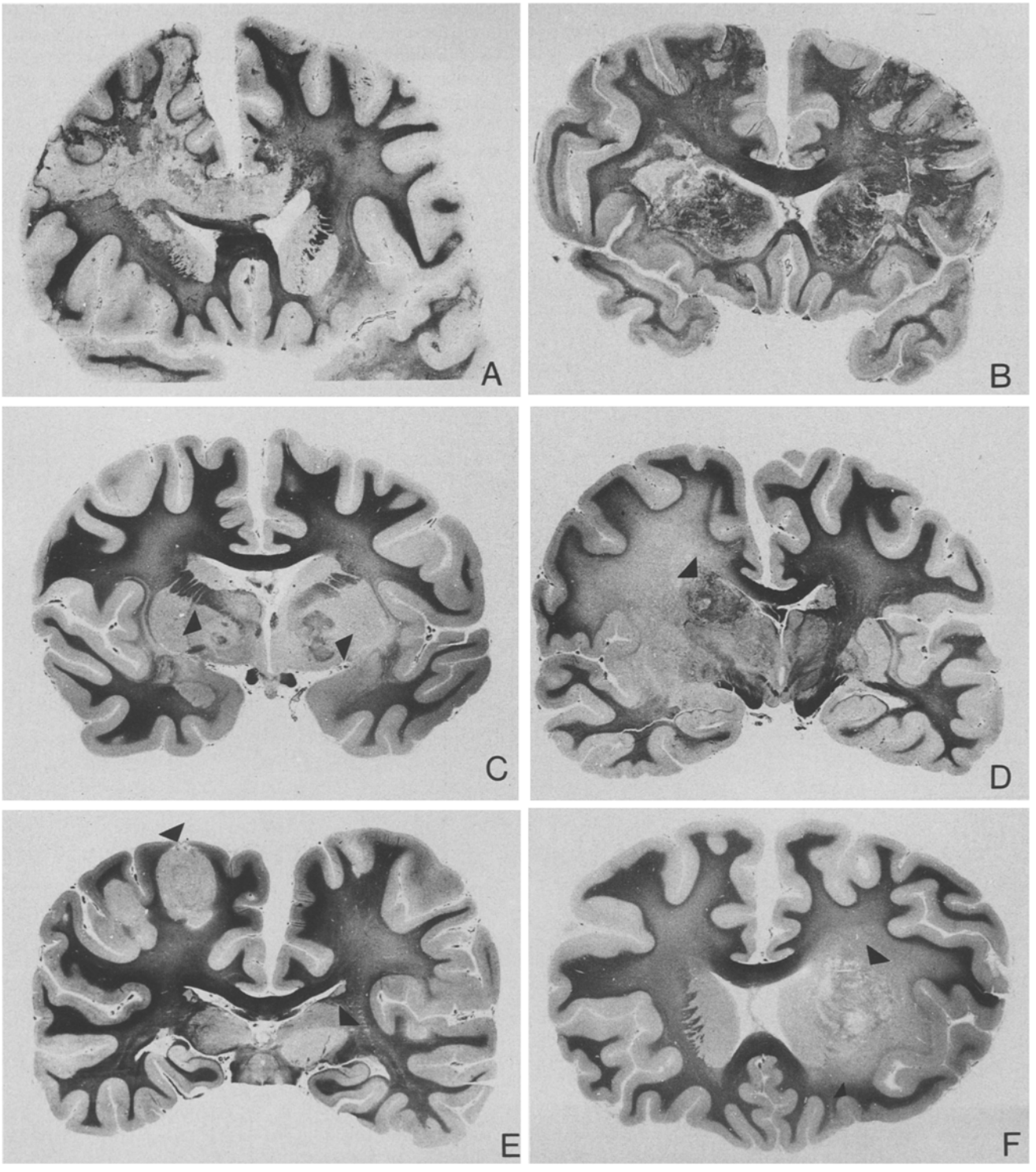

Fig. 4A–F. Whole brain sections from six cases with toxoplasma encephalitis. **A, B** Widespread, confluent areas of necrosis in both cerebral hemispheres and the basal ganglia (necrotizing toxoplasma encephalitis). **C, E** Multiple abscesses, and **D, F** solitary abscesses in with preferential location in the basal ganglia (reactivated toxoplasmosis)

sisted of lipid-laden macrophages with a surrounding area of gliosis but showed only a scarce residual inflammatory response. Occasional tissue cysts were identified immunocytochemically in the adjacent brain tissue in two of these patients. Five patients displayed both recent and old abscesses. In six patients, widespread, poorly demarcated confluent areas of necrosis were detectable (Fig. 4A, B). Thrombosis of vessels was frequently encountered. The inflammatory response with multiple tissue cysts at the periphery of the necrosis was generally weak in these cases (Fig. 3D, E). We termed this manifestation necrotizing toxoplasma encephalitis [16, 17].

All but one of these patients died during the early period of the AIDS epidemic (1984–1986) and none of them had received chemotherapy. One patient showed a nodular toxoplasma encephalitis restricted to the pons (Fig. 3C).

Systemic toxoplasmosis with CNS involvement

Three morphological patterns in patients with systemic toxoplasmosis were observed. In most patients, multiple abscesses were present, which were macroscopically well circumscribed. Histologically, these lesions showed a center of necrosis, surrounded by a rim of macrophages, lymphocytes and occasional granulocytes. Vascular proliferation was also present at the periphery of the tissue necrosis. Immunohistochemical staining for *Toxoplasma gondii* showed a variable number of tachyzoites and encysted bradyzoites. In one patient, the brain was macroscopically inconspicuous but, upon histological analysis, showed multiple microglial nodules containing occasional encysted bradyzoites. We termed this lesion nodular toxoplasma encephalitis. Another patient with a macroscopically inconspicuous brain showed small foci of necroses with inflammatory reaction in the basal ganglia (micro-abscesses; Fig. 3B).

Latent infection

Intact cysts without necrosis or inflammatory response are characteristic of inactive or latent infection [33]. In our series, we observed one case with intact tissue cysts in the parietal white matter as the only histopathologically identifiable lesion (Fig. 3A).

Several patients presented with neuropathological lesions in addition to those caused by *Toxoplasma gondii*. In ten cases cerebral toxoplasmosis was associated with HIV leukoencephalopathy with white matter pallor, gliosis and scattered multinucleated giant cells but little or no inflammatory reaction [14]. In two patients we diagnosed an HIV encephalitis [2]. Additional CNS lesions included cytomegalovirus infection (two patients), aspergillus abscesses (one patient), metastatic non-Hodgkin lymphoma (one patient) and vacuolar myelopathy (three patients).

Discussion

Frequency of toxoplasma encephalitis

Immune-competent patients with recently acquired toxoplasmosis typically present with regional lymphadenopathy and/or uveitis with chorioretinitis. Connatal toxoplasmosis often affects the brain in addition to the visual system [22]. Neurological manifestations occur in less than 1 % of adult immune competent patients [32] but are somewhat more common in patients with immune suppression, e.g., advanced stages of lymphoproliferative disease, and organ transplant recipients [7, 24, 31]. AIDS patients develop cerebral toxoplasmosis more frequently than any other opportunistic infection. In our series, encephalitis due to *Toxoplasma gondii* occurred in 46 out of 204 patients (23 %). This corroborates other studies showing that cerebral toxoplasmosis is the most frequent cause of focal brain lesions in patients with HIV infection [21, 29]. In the present study, the incidence is lower than that observed in reports from Miami [23] and France [7], but higher than in most other autopsy studies [1, 4, 10, 13, 18, 25, 27]. The variation in the frequency of toxoplasma encephalitis, which is evident from Fig. 1, may partly be due to the fact that some autopsy series are based on referred cases rather than consecutive sampling. Furthermore, the prevalence of a serological reaction to *Toxoplasma gondii* in the adult population shows considerable geographic variation with generally lower figures in cold regions and at high altitude when compared to hot and humid areas [6, 19]. The high incidence in the Miami study was attributed to the large proportion of patients of Haitian origin. In Switzerland, a prevalence of 40 %–50 % has been reported [12]. During childhood and adolescence, there is a continuous increase in seroprevalence, ranging from 2.3 % in the 1st year of life to 46 % at the age of 20. In the present series, only three patients were below the age of 20. None of these showed evidence of latent or reactivated cerebral toxoplasmosis.

Pathogenesis and morphological patterns

The mechanisms of resistance to *Toxoplasma gondii* are still poorly understood but there is evidence that lymphokines may play a key role. Suzuki et al. [30] observed that infected mice treated with a monoclonal antibody to interferon-gamma developed fatal systemic toxoplasmosis, whereas untreated animals developed chronic toxoplasmosis. It is assumed that interferon activates macrophages which in turn eliminate the parasite. There is also experimental evidence that the reduction of T4 lymphocytes which is a hallmark of AIDS has a profound effect on the course of toxoplasma infection [34]. Selective reduction of T4 cells in infected mice caused severe systemic disease with predominant affection of lungs and liver but few or no CNS lesions. In contrast, monoclonal antibody-induced T4 reduction in mice with chronic infection produced a reactivation of the infection with preferential CNS involvement. These observations correlate well with the autopsy findings in AIDS patients. In our series, a total of 7 out of 46 patients (15 %) presented with generalized systemic toxoplasmosis which always included CNS involvement. We assume that these patients acquired the infection during the period of HIV-induced immunosuppression [21, 24]. Although only a minority of patients suffered from systemic toxoplasmosis, this was invariably the cause of death. It is, therefore, recommendable to advise HIV-positive individuals to avoid potential sources of toxoplasma infection, notably cats and raw meat. On the other hand, our data indicate that in most

AIDS patients (85%), cerebral toxoplasmosis was due to reactivation of a latent cerebral toxoplasma infection. It is well established that during chronic infection in the immune-component host, the CNS preferentially harbors the parasite in the form of tissue cysts, rendering itself prone to toxoplasma encephalitis upon reactivation during periods of reduced immune surveillance [7, 26, 28, 36].

The location of toxoplasmosis within the CNS (Table 1) could suggest that tissue cysts persist most frequently in the cerebral hemispheres, particularly in the basal ganglia which were affected in 36 out of 46 patients (78%). However, our data also show that the location of *Toxoplasma gondii*-induced brain lesions is similar in patients with acute systemic and reactivated latent infection. This suggests that the predilection for the cerebral hemispheres and basal ganglia reflects the primary distribution of the parasite in the CNS rather than a selective persistence of tissue cysts in certain brain regions.

Multiple CNS infections are common in AIDS patients. Additional CNS lesions should always be considered in patients with signs of cerebral toxoplasmosis. HIV encephalopathy was observed in 20% of the cases, i.e., at an incidence similar to that in patients without toxoplasma encephalitis [16, 17]. Cytomegalovirus encephalitis, aspergillus encephalitis and metastatic non-Hodgkin lymphoma were also encountered in patients with cerebral toxoplasmosis. It remains to be established whether and to what extent infectious agents, including opportunistic viruses, cooperate to enhance their adverse effects on the CNS of AIDS patients [35].

Pathological changes observed in our cases are similar to those reported in a previous study [5, 24]. Widespread, confluent necrotizing lesions were mainly observed in patients who did not receive adequate chemotherapy during the early period of the AIDS epidemic (5 out of 11 cases with toxoplasmosis diagnosed in Zurich between 1984 and 1986). Patients treated with sulfadiazine and/or pyrimethamine tended to show abscess formation. Since the beginning of 1989, we have increasingly observed old, burnt-out lesions mainly composed of lipid-laden macrophages. These occurred in patients who were successfully treated with chemotherapy. The 5 patients showing both old and recent abscesses may have been treated ineffectively.

Intact toxoplasma cysts without significant tissue reaction were found in only one case (Fig. 3A). A similar observation was recently made by Vinters and Anders [33]. Since it is known that immune deficiency facilitates the rupture of tissue cysts [7]; Fig. 3F), these cases may represent the initial stage of reactivation of a latent infection or an intermediate stage of immunosuppression with multiplication of cysts but still partially functioning defence mechanisms. In a case with systemic toxoplasmosis we observed disseminated foci with numerous tissue cysts but little or no inflammatory response (Fig. 3B). This observation supports the view that multiplication of tissue cysts constitutes a typical event in early stages of toxoplasma encephalitis.

References

1. Anders KH, Guerra WF, Tomiyasu U, Verity MA, Vinters HV (1986) The neuropathology of AIDS: UCLA experience and review. Am J Pathol 124:537–558
2. Budka H, Wiley CA, Kleihues P, Artigas J, Asbury AK, et al (1991) HIV-associted disease of the nervous system: review of nomenclature and proposal for neuropathology-based terminology. Brain Pathol 1:143–152
3. Conley FK, Jenkins KA, Remington JS (1981) *Toxoplasma gondii* infection of the central nervous system: use of the peroxidase-antiperoxidase method to demonstrate toxoplasma in formalin fixed, paraffin-embedded tissue sections. Hum Pathol 12:690–698
4. de la Monte SM, Ho DD, Schooley RT, Hirsch MS, Richardson EP (1987) Subacute encephalitis of AIDS and its relation to HTLV-III infection. Neurology 37:562–569
5. Farkash AE, Maccabee PJ, Sher JH, Landesman SH, Hotson G (1986) CNS toxoplasmosis in the acquired immune deficiency syndrome: a clinical-pathological-radiological review of 12 cases. J Neurol Neurosurg Psychiatry 49:744–748
6. Feldmann HA (1968) Toxoplasmosis. N Engl J Med 279:1431–1437
7. Frenkel JK, Nelson BM, Arias-Stella J (1975) Immunosuppression and toxoplasmic encephalitis. Clinical and experimental aspects. Hum Pathol 6:97–111
8. Ghatak NR, Poon TP, Zimmermann HM (1970) Toxoplasmosis of the central nervous system in the adult. A light and electron microscopic study of three cases. Arch Pathol 89:337–348
9. Gray F, Gherardi R, Keohane C, Favolini M, Sobel A, Poirier J (1988) Pathology of the central nervous system in 40 cases of acquired immune deficiency syndrome. Neuropathol Appl Neurobiol 14:365–380
10. Gullotta F, Kuchelmeister K, Masini T, Ghidoni P, Cappricci E (1989) Zur Morphologie der HIV-Encephalopathie. Zentralbl Allg Pathol 135:5–13
11. Hooper DC, Pruitt AA, Rubin RH (1982) Central nervous system infection in the chronically immunosuppressed. Medicine 64:166–188
12. Hurwitz E (1965) Die Toxoplasmose in der Schweiz. Schweiz Med Wochenschr 95:77–83
13. Kato T, Hirano A, Llena JF, Dembitzer HM (1987) Neuropathology of acquired immune deficiency syndrome (AIDS) in 53 autopsy cases with particular emphasis on microglial nodules and multinucleated giant cells. Acta Neuropathol (Berl) 73:287–294
14. Kleihues P, Lang W, Burger PC, Budka H, Vogt M, Maurer R, Lüthy R, Siegenthaler W (1985) Progressive diffuse leukoencephalopathy in patients with acquired immune defiency syndrome (AIDS). Acta Neuropathol (Berl) 68:333–339
15. Krick JA, Remington JS (1978) Toxoplasmosis in the adult: an overview. N EngL J Med 298:550–553
16. Lang W, Miklossy J, Deruaz JP, Pizzolato GP, Schaffner T, Gessaga E, Kleihues P (1989) Neuropathology of the acquired immune deficiency syndrome (AIDS): a report of 135 consecutive autopsy cases from Switzerland. Acta Neuropathol 77:379–390
17. Lang W, Miklossy J, Deruaz JP, Pizzolato GP, Schaffner T, Gessaga E, Kleihues P (1990) Definition and incidence of AIDS-associated CNS lesions. In: Rotterdam H, Racz P, Alba Greco M, Cockerell CJ (eds) Progress in AIDS pathology, vol 2. Field and Wood, Philadelphia, pp 89–101
18. 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
19. Luft BJ, Remington JS (1983) Toxoplasmosis. In: Hoeprich PD (ed) Infectious diseases, 3rd edn. Harper and Row, Philadelphia, pp 1133–1145

20. Luft BJ, Remington JS (1988) Toxoplasmic encephalitis. J Infect 157:1–6
21. Luft BJ, Brooks RG, Conley FK, McCabe RE, Remington JS (1984) Toxoplasmic encephalitis in patients with acquired immune deficiency syndrome (AIDS). JAMA 252:913–917
22. McCabe RE, Remington JS (1990) *Toxoplasma gondii.* In: Hoeprich PD (ed) Infectious diseases, 4th edn. Harper and Row, Philadelphia, pp 2090–2103
23. Moskowitz LB, Hensley GT, Chan JC, Gregoris J, Conley FK (1986) The neuropathology of the acquired immune deficiency syndrome. Arch Pathol Lab Med 108:867–872
24. Navia BA, Petito CK, Gold JWM, Cho E-S, Jordan BD, Price RW (1986) Cerebral toxoplasmosis complicating the acquired immune deficiency syndrome: clinical and neuropathological findings in 27 patients. Ann Neurol 19:224–238
25. Petito CK, Cho E-S, Lemann W, Navia BA, Price RW (1986) Neuropathology of acquired immunodeficiency syndrome (AIDS): an autopsy review. J Neuropathol Exp Neurol 45:635–646
26. Remington JS, Cavanaugh EN (1965) Isolation of encysted form of *Toxoplasma gondii* from human skeletal muscle and brain. N Engl J Med 273:1308–1310
27. Rosemberg S, Lopes MBS, Tsanaclis AM (1986) Neuropathology of acquired immunodeficiency syndrome (AIDS) – Analysis of 22 Brazilian cases. J Neurol Sci 76:187–198
28. Ruskin J, Remington JS (1976) Toxoplasmosis in the compromised host. Ann Intern Med 84:193–199
29. Snider WD, Simpson DM, Nielsen S, Gold JWM, Metroka CE, Posner JB (1983) Neurological complications of acquired immune deficiency syndrome: analysis of 50 patients. Ann Neurol 14:403–418
30. Suzuki Y, Orellana MA, Schreiber RD, Remington JS (1988) Interferon-gamma: the major mediator of resistance against *Toxoplasma gondii.* Science 240:516–518
31. Townsend JJ, Wolinsky JS, Baringer JR, Johnson PC (1975) Acquired toxoplasmosis. A neglected cause of treatable nervous system disease. Arch Neurol 32:335–343
32. Velimirovic B (1984) Toxoplasmosis in immunosuppression and AIDS. Infection 12:315–317
33. Vinters HV, Anders KH (1990) Neuropathology of AIDS. CRC Press, Boca Raton, pp 79–90
34. Vollmer TL, Waldor MK, Steinman L, Conley FK (1987) Depletion of T-4+ lymphocytes with monoclonal antibody reactivates toxoplasmosis in the central nervous system: a model of superinfection in AIDS. J Immunol 138:3737–3741
35. Wiley CA, Grafe M, Kennedy C, Nelson JA (1988) HIV and JC virus in AIDS patients with progressive multifocal leukoencephalopathy. Acta Neuropathol 76:338–346
36. Wong B, Gold JWM, Brown AE, Lange M, Fried R, Grieco M, Milvan D, Giron J, Tapper ML, Lerner CW, Armstrong D (1984) Central nervous system toxoplasmosis in homosexual men and parenteral drug abusers. Ann Intern Med 100:36–42