Leading article

Toxoplasmosis and human immunodeficiency virus (HIV) disease

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One of the commonest opportunistic infections in patients with the acquired immunodeficiency syndrome (AIDS), is that caused by the protozoan parasite, Toxoplasma gondii. Central nervous system involvement producing encephalitis is the commonest presentation, but the eye, lung, heart, skin, liver or gastrointestinal tract may also be affected, Luft & Remington (1992). Although primary infection with T. gondii may occur in immunosuppressed individuals often leading to disseminated disease (Murray, 1991), more than 95% of toxoplasmic encephalitis (TE) is due to recrudescence of latent infection as a result of progressive loss of cellular immune surveillance and most often occurs when the CD4 lymphocyte count is less than 0·1 x 10⁹/L (Dannemann et al., 1992). Cerebral toxoplasmosis is uncommon when the CD4 lymphocyte count exceeds 0·2 x 10⁹/L (Renold et al., 1992). The central nervous system appears to be most susceptible to toxoplasma cyst reactivation compared with other tissues where cysts are found. Between 30 and 50% of HIV positive patients infected latently with T. gondii will subsequently develop toxoplasmic encephalitis (Luft & Remington, 1992), which is universally fatal in the absence of specific therapy. Such therapy is usually aimed at the tachyzoite or proliferative form of the organism. The cyst form of the parasite, the source of the infective tachyzoites, is much more difficult to eradicate.

Numerous agents have potential activity against T. gondii. Drugs interfering with folate metabolism in the tachyzoites include sulphonamides (hydropteroate synthetase or HPS inhibitors) and the dihydrofolate reductase or DHFR inhibitors, trimethoprim and pyrimethamine. The latter has the greater effect on protozoan DHFR such as malaria (Garrod, Lambert & O'Grady, 1981). Other antifolate drugs include trimetrexate, a potent inhibitor of T. gondii DHFR, piritrexin and dapsone, an HPS inhibitor.

Several inhibitors of bacterial protein synthesis also possess anti-toxoplasma activity, probably through this same mechanism of action. These include clindamycin, spiramycin and newer macrolide drugs such as roxithromycin, clarithromycin and azithromycin. The latter has the additional advantage of activity against the cyst form of T. gondii, (Huskinson-Mark, Araujo & Remington, 1991). Chlortetracycline, doxycycline and minocycline all show activity against T. gondii in animal models (Eyles & Coleman, 1954; Tabbara, Sakuragi & O'Connor, 1982; Chang, Comte & Pechère, 1990).

Interference with the parasite's ability to synthesize nucleic acids provides a third mechanism of attack. Atovaquone (566C80), an antimalarial agent, is active against both the proliferative and cyst form of T. gondii (Araujo, Huskinson & Remington, 1991). Another experimental drug in this group is arprinocid.

Immunotherapy is currently the subject of much investigation. Administration of CD8 lymphocytes, interleukin 2, interferon-gamma and -beta have shown a protective effect in experimental models (McCabe, Luft & Remington, 1984; Sharma, Hofflin & Remington, 1985; Schmitz et al., 1989; Hakim et al., 1991).

In order to prevent TE in seropositive patients with low CD4 lymphocyte counts, a number of primary prophylactic regimens have been evaluated (Clotet et al., 1991; Koeppe et al., 1991; Jacobson et al., 1992; Ruf, Schürmann & Pohle, 1992). Unfortunately due to a lack of large, prospective, randomized, controlled trials, they have given conflicting results. Some have shown protective capability against TE, even if there have been problems with eventual failures of prophylaxis or drug toxicity. In general, single agents have not been found to be satisfactory.

A recent review of primary prophylaxis against toxoplasmosis in HIV disease proposed that only daily sulphamethoxazole/trimethoprim (800 mg/160 mg) or dapsone (50 mg/day)/pyrimethamine (50 mg/week) should be considered for clinical use.
amides may also produce a number of nephro-
acute therapy. In addition, zidovudine may
concurrently to counteract the toxic effect of
(Israelski, Tom & Remington, 1989). Sulphon-
viral drugs which should be avoided during
pyrimethamine on the bone marrow.
acid (leucovorin), at a dose of at least
should not be stopped prematurely. Folinic
et al., 1991), and these drugs
incidence of opportunistic toxoplasmosis as
comparative with pyrimethamine/
sulphonamides, although side effects due to
cladamycin and requiring discontinuation of
therapy, were seen in 30% of patients; these
included skin rash, neutropenia and gastro-
intestinal disturbance, especially diarrhoea.
Pseudomembranous colitis may occur rarely.
Alternative drug combinations which may
be of use in the management of acute toxo-
plasmosis include sulphamethoxazole and trimeth-
oprime/sulphamethoxazole (160 mg/
mg) or tablet twice daily twice a week is
that it combines protection against both TE
and Pneumocystis carinii pneumonia (PCP)
(Carr et al., 1992). This is likely to enhance
acceptability and increase patient compliance.
A recently published open, randomized,
controlled trial involving 362 patients in
France demonstrated that a dapsone-
pyrimethamine (50 mg once daily/50 mg once
a week) combination drastically reduced the
incidence of opportunistic toxoplasmosis as
well as PCP (Girard et al., 1993). Dapsone has
a longer half-life and fewer side-effects
compared with sulphonamides. Unfortunately
both combinations were associated with side-
effects necessitating dose reduction or cessa-
tion of therapy; a lower dose combination
(dapsone 100 mg/pyrimethamine 25 mg
weekly) was ineffective (Malloias et al., 1993).
Standard first line therapy for acute toxo-
plasmosis is a combination of pyrimethamine
50–75 mg/day and sulphadiazine 4–6 g/day
orally, starting with a loading dose of
100–200 mg pyrimethamine to rapidly estab-
lish high blood levels, and continued for 6
weeks. These drugs act synergically against the
parasite, but a high rate of side-effects leads to
discontinuation of therapy in up to 45% of
patients (Haverkos, 1987); rash and fever are
the most frequent side-effects. Patients with
AIDS who suffer from sulphonamide induced
rashes may be successfully desensitized
(Tenant-Flowers et al., 1991), and these drugs
should not be stopped prematurely. Folinic
acid (leucovorin), at a dose of at least
10 mg/day orally should be administered
concurrently to counteract the toxic effect of
pyrimethamine on the bone marrow.
Haematotoxicity is potentiated by antiretro-

viral drugs which should be avoided during
acute therapy. In addition, zidovudine may
have an antagonistic effect on pyrimethamine
(Israelski, Tom & Remington, 1989). Sulphon-
amides may also produce a number of nephro-
toxic side-effects such as crystalluria,
haematuria, and renal failure. These are
managed by rehydration, urinary alkaliniz-
ation and dose reduction (Simon, Brosius &
Patients who are intolerant of sulphon-
amides may be treated with a combination of
pyrimethamine and clindamycin
(1200–4800 mg/day) orally or intravenously.
Two prospective, controlled studies (Katlama
et al., 1991 (preliminary findings); Dannemann et al.,
1992), have shown this combination to be
comparable with pyrimethamine/
sulphonamides, although side effects due to
cladamycin and requiring discontinuation of
therapy, were seen in 30% of patients; these
included skin rash, neutropenia and gastro-
inestinal disturbance, especially diarrhoea.
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that it combines protection against both TE
and Pneumocystis carinii pneumonia (PCP)
(Carr et al., 1992), pyrimethamine and azithromycin (Saba
et al., 1992), pyrimethamine and doxycycline
(Hagberg, Palmertz & Lindberg, 1993), clinda-
mycin and 5-fluoro-uracil (Dhiver et al., 1993),
and atovaquone monotherapy (Kovacs et al.,
1992). No large scale clinical study has vali-
dated any of these regimens so far.
Following treatment of acute toxoplasmosis,
patients will almost always relapse unless they
are given life-long maintenance therapy (Cohn
et al., 1989) because of the inability of most of
these drugs to destroy the cyst form of the
parasite. Maintenance therapy consists of
25–50 mg pyrimethamine and 2–4 g sulphadia-
zine daily (Leport et al., 1988). Patients unable
to tolerate higher doses of sulphonamides
during the acute treatment phase may still be
successfully managed on this regimen which
also has the advantage of preventing PCP. If
sulphonamides are contraindicated pyrimetha-
mine (25 mg/day) and clindamycin (at least
1200 mg/day) may be given (Remington &
Vildé, 1991; Uberti Foppa et al., 1991). It
appears that intermittent (twice weekly)
therapy with pyrimethamine and sulphadia-
zine (Pedrol et al., 1990), or high dose pyri-
methamine (50 mg/day) alone (de Gans et al.,
1992), may also be effective as chronic suppres-
sive therapy. Other alternatives include pyri-
methamine plus dapsone and atovaquone
monotherapy.
There is no doubt that as the number of
patients with AIDS increases worldwide, acute
toxoplasmosis and its primary prevention,
treatment and secondary prevention will
become more important. At present, the choice
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of therapy for each situation is made difficult by the lack of large, properly controlled trials demonstrating efficacy. Most of the available drugs are beset with problems of side-effects and patients may eventually refuse treatment altogether (Pedrol et al., 1990). There is a need for new, well tolerated antitoxoplasmic agents and especially those with anti-cyst activity, whereby it may be possible to eradicate the organism completely, thus removing the need for suppressive therapy.

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