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Therapy of fungal infections of the central nervous system

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Summary

Fungal infections of the central nervous system present a considerable challenge to available chemotherapy and other forms of treatment. The particular difficulties are discussed here, after an account of the fungi involved and their sensitivity to antifungal agents. Cryptococcal, coccidioidal and candidal infections are considered in more detail.

Fungal aetiology and sensitivity to antifungal agents

The fungi most associated with central nervous system (CNS) infection are listed in Table 1. Group A comprises those seen as part of a disseminated infection, and the fungi are listed in approximate descending order of difficulty of treatment, in terms of dosage and length of course for a successful outcome (Williams, 1970). Amphotericin B is effective against all these fungi, and flucytosine against sensitive strains of *Cryptococcus* and *Candida*. Miconazole also has broad-spectrum activity and may be of value, although this has been clearly demonstrated only in some cases of coccidioidomycosis and cryptococcosis of the CNS.

TABLE 1. Fungi causing central nervous system infections

A.	Disseminated infections:
	Coccidioides spp.
	Cryptococcus spp.
	Histoplasma spp.
	Blastomyces spp.
	Candida spp.
B.	Agents of cerebral phycomycosis and chromomycosis
C.	Many other opportunists

The fungi of group B are rarely identified *ante mortem*, unless they cause localized infections treated surgically. Surgery does provide the best treatment in such cases but, on the basis of successful management of subcutaneous chromomycosis, flucytosine should also be considered for the cerebral form of this disease (if the isolate is sensitive *in vitro*) and amphotericin may be administered similarly in phycomycosis.

Many other opportunist fungi may occasionally affect the CNS, either *via* the bloodstream, or by direct invasion or introduction. The choice of antimicrobial here should depend on laboratory tests.

Problems in CNS infections

Although these difficulties are not restricted to infections of the CNS they are seen very prominently in these conditions.

Delay in diagnosis

Fungal CNS infections often present insidiously and obscurely, and because of their uncommonness are often misdiagnosed, so that treatment may be initiated only at an advanced stage of the disease.

Underlying predisposition

As in many other fungal infections, those of the CNS are often seen as a complication of disease or treatment causing immunosuppression and other forms of host impairment. Even in cases where the so-called 'pathogenic' fungi occur in apparently healthy people, there must be some predisposition which selects these patients for dissemination from the mass of those exposed or locally infected (Deresinski, Galgiani and Stevens, 1977a).

Nature of the CNS lesion

Although some opportunistic infections of the CNS probably represent saprophytic growth in the CSF and very superficial meningeal inflammation, the lesions in disseminated infections are often situated deep in the brain substance (e.g. very commonly in cryptococcosis). There may be little cellular reaction (Symmers, 1968) and there is often a very large amount of fungus present (Fig. 1). Ideal conditions are provided for selection of resistant mutants, as is the case with the administration of flucytosine. The population of most yeast isolates contains pre-existing flucytosine-resistant mutants, with a frequency of approximately $1/4 \times 10^6$ cells, and the selection by the drug may occur *in vivo* as *in vitro* (Speller *et al.*, 1977). Figure 2 shows *in vitro* selection of flucytosine-resistant mutants from an isolate of *Crypt. neoformans*; similar resistant mutants colonized the patient's cerebrospinal fluid from the nineteenth day of flucytosine treatment.

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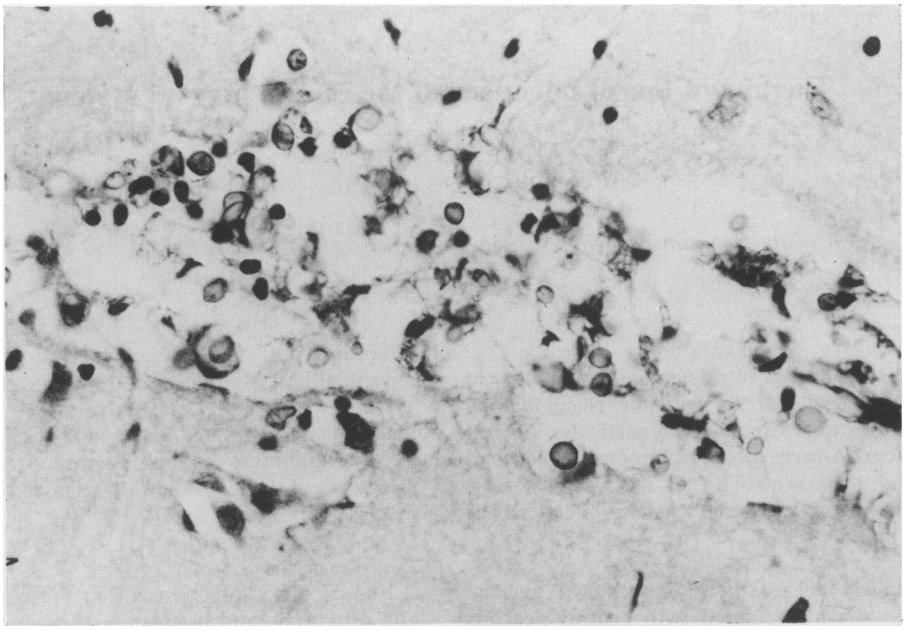

FIG. 1. Cryptococcal lesion in brain, showing capsulated yeasts with scanty cellular response (PAS, × approx. 500).

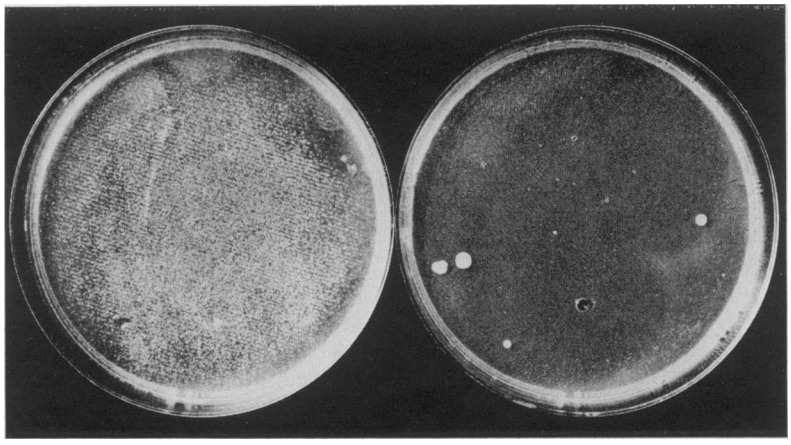

FIG. 2. Velvet pad replica plating of plate culture of cryptococcal isolate on yeast morphology agar with (right), and without (left) 100 mg/l flucytosine. Pre-existing resistant mutants have been selected on the drug-containing plate (Speller *et al.*, 1977).

Penetration barrier to antifungals

Antifungal agents are variably able to penetrate the blood/brain and the blood/CSF barrier. The latter may not be the more relevant, particularly in the case of a lipophilic drug such as amphotericin, although it is the more readily determined. Flucytosine by the oral route rapidly achieves concentrations in the CSF approaching the serum concentration (33–100% of serum concentration, with a mean of 74% in the study by Block and Bennett,

1972). In contrast, amphotericin is usually undetectable in the CSF after intravenous administration, although occasional low values are recorded (Bindschadler and Bennett, 1969); and miconazole i.v. has given CSF concentrations of < 0·1–0·77 mg/l (Deresinski *et al.*, 1977b). Fisher *et al.* (1978), in describing some therapeutic failures with miconazole, draw attention to low concentrations in the CSF and at other sites and to the need for more information about the distribution of miconazole in human subjects.

For these reasons, direct instillation of amphotericin or miconazole into the subarachnoid space has been used, by the lumbar, cervical or cisternal routes. Amphotericin B must be given with great caution, with small, accurate doses and considerable dilution with CSF, as local and general toxic effects are common. The use of a subcutaneous Ommaya reservoir attached *via* a burr hole to a catheter in the lateral ventricle allows good dilution and distribution of the drug, and ease of administration for patient and operator, although some workers have met considerable difficulties and complications in patients with fungal infections (Diamond and Bennett, 1973). Details of the intrathecal route for amphotericin are given by Williams (1970). Miconazole has been given intrathecally by all routes in doses of 5–20 mg (occasionally 30 mg) once or twice daily; side effects in 18 patients were few and transient and useful CSF concentrations were generally obtained (Deresinski *et al.*, 1977b; Sung, Grendahl and Levine, 1977; data on file with Janssen Pharmaceutical Ltd).

Tendency to relapse

CNS infections, expecially coccidioidomycosis and cryptococcosis are notorious for late relapse after treatment, and careful follow-up with full examination, CSF examination and serology (antigen and antibody examination as indicated) is mandatory.

General problems

The general supportive care for any patient undergoing a long, debilitating illness, often with disturbance of consciousness, must not be forgotten.

Treatment of individual conditions

Coccidioidal meningitis

This is one of the most difficult CNS infections to treat, despite the resistance of most of the human population to dissemination of this disease, and the generally superficial situation of the lesions. Amphotericin has been the mainstay of treatment, with full intravenous regimens and a total dose in the region of 3–4 g. Intrathecal amphotericin should be instituted routinely and continued until the CSF returns towards normal and there is no serological evidence of active disease (Winn, 1962).

Nevertheless a proportion of patients remains unresponsive or relapses and it is in this group that miconazole has been most successfully tried in the United States, with intravenous infusions of 1800–3600 mg daily, and intrathecal treatment as described above. Considering the selection of patients as previous treatment failures, the results have been encouraging; a disappointing number of relapses may reflect the relatively short courses administered (Deresinski *et al.*, 1977a, b; Sung *et al.*, 1977).

Ambruticin, an antibiotic derived from a myxobacterium, is at present showing promise in animal experiments, with fungicidal effectiveness and good tolerance (Levine, Ringel and Cobb, 1978), but no human use has yet been reported, and there are considerable differences between the acute murine infection and human coccidioidomycosis.

Cryptococcal meningitis

The classical treatment for cryptococcal meningitis is amphotericin B, and this is frequently effective by the intravenous route, in total doses in the region of 2·5–3·0 g. Failure or relapse with repeated isolation of cryptococci may necessitate intrathecal administration.

Flucytosine alone has been shown to have a similar success rate, but relapse is frequent and the emergence of high level resistance, as described above, is a problem, especially in patients with more severe underlying disease. The use of a combination of flucytosine and amphotericin has been tried, on the basis that resistance to flucytosine may be prevented and that a reduced dose of the relatively toxic amphotericin may be used. Experiments *in vitro* and in animals show synergistic activity between the drugs (Medoff, Comfort and Kobayashi, 1971; Block and Bennett, 1973); on the other hand, toxic effects may be increased (Medoff and Kobayashi, 1975). An extended series reported the safety and efficacy of the combination (Utz *et al.*, 1975) and the results of a controlled trial that has shown the superiority of the combination over either drug alone are expected shortly. The combination of amphotericin and flucytosine is thus the definitive treatment for this condition at the present time.

Miconazole has been tried in a number of cases where the use of the other drugs was unsuccessful or contra-indicated. It is a reasonable alternative with at least some clinical response in over 50% of cases treated (data on file with Janssen Pharmaceutical Ltd). Further evaluation is necessary.

Candidal infection

This is becoming the commonest cerebral mycosis to be found at post-mortem, as disseminated lesions

in the brain substance (Parker, McCloskey and Lee, 1978), but less commonly presents as a meningoencephalitis that can be diagnosed and treated. Most reported cases have been treated with amphotericin, in shorter courses than those used for cryptococcosis and coccidioidomycosis, and with variable results; flucytosine has also been successful in almost all reported cases in which it has been tried.

Conclusion

All the major antifungal agents for systemic disease have a role in the treatment of CNS infection. The chronic, fluctuating and relapsing course of these infections, and the small number of patients treated at any medical centre, make assessment of the various agents extremely difficult (Krick and Remington, 1975) but amphotericin B is an established treatment, flucytosine has achieved a definite limited role, and miconazole is a most promising addition to therapeutics.

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Notes