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SPECIAL ARTICLE

Cryptococcosis in the AIDS era

Cryptococcosis is not a commonly diagnosed disease. Records of its occurrence in Britain are virtually non-existent before 1945, when the Mycological Reference Laboratory (MRL) of the Public Health Laboratory Service was first established.

Before 1984, the number of cases recognized in Britain each year seldom rose above 10. In a survey of MRL data reported by Hay *et al.* in 1980 (1) information from only 69 patients was available for analysis. Since then, the annual number of cases has increased steadily, this being a direct consequence of the AIDS epidemic. Since the disease is now being encountered in hospitals where it was previously unknown, it is the object of the present review to provide a perspective on cryptococcosis in Britain today.

The initial stage in pathogenesis of cryptococcal infection is believed to be the inhalation of minute air-borne yeast cells. All AIDS-associated cases reported in this country to date are caused by *Cryptococcus neoformans* (var. *neoformans*). Infections with *C. neoformans* var. *gatti* are rare in AIDS patients, and have not been reported in the United Kingdom. Its normal habitat is soil, enriched with pigeon droppings. Although tissue forms are characterized by budding cells 7 μm or more in diameter, surrounded by prominent capsules, the infective form is thought to be much smaller, perhaps 2–4 μm in diameter. It is not yet known if most infections arise solely by inhalation of weakly- or non-capsulated yeast cells, or if specialized sexual spores (basidiospores) may also initiate disease by the pulmonary route.

These small cells or spores of the yeast are of a size to reach and be retained in the alveoli. In most individuals, normal cellular defence mechanisms are able to prevent any significant degree of proliferation or spread of the fungus from its primary site of lodgement in the lung. The organism may nevertheless persist in the lung for months or years, even in healthy subjects. At a later date, if the host loses the capacity to contain the yeast cells, they may begin to multiply and eventually lead to active cryptococcosis.

It is likely, therefore, that most infections with *C. neoformans* arise from previously established quiescent foci. However, the agent is not uncommon in urban environments, and exposure of individuals made susceptible to opportunistic infections by loss of T-lymphocytes might conceivably result in infection directly from an exogenous source. At present, no reliable epidemiological markers have been described for *C. neoformans*. Even if these were developed it might still not prove practicable to distinguish between exogenous and what might be termed 'pseudo-endogenous' infections. The introduction of an effective system of markers could nevertheless help to provide a clearer picture of the ecology and distribution of the agent in nature, and it is hoped that these will eventually become available.

Even before the AIDS era, the diagnosis of cryptococcosis was comparatively

straightforward. In its most characteristic form (meningitis) host predisposition often provided a pointer to the aetiology. Such conditions as non-Hodgkin's lymphoma, sarcoid or leukaemia are known to be common predisposing causes in this country. Cryptococcosis in the UK almost always has a recognizable underlying disease.

Laboratory tests, including direct microscopy, culture, and serology are of considerable value in confirming presence of the disease. AIDS patients with cryptococcosis seldom present diagnostic problems, for the spinal fluid almost always contains abundant budding cells, with capsules which are readily seen on direct microscopy in India ink mounts. Experience in Britain suggests that in contrast to reports from the United States (2) weakly or non-encapsulated cells are rarely, if ever, seen in cerebrospinal fluid. The situation elsewhere in Europe is unknown. Presence of large numbers of capsulated budding cells provides solid evidence of infection: additional laboratory tests may be required only where the diagnosis remains in doubt.

The number of cases of cryptococcal meningitis in AIDS patients in the UK has increased steadily since 1984 (3). By the end of November 1988, 74 cases of AIDS-related cryptococcosis had been recorded at the MRL, 32 of these (43·2%) occurring in the current year. AIDS was the primary underlying disease in 70% of cases. The number of cases in non-AIDS patients has remained essentially unchanged. Cryptococcosis in this country develops in about 3·7% of patients with AIDS (74 of 1982), a figure rather lower than in the United States, where prevalence rates in up to 9% of AIDS patients have been reported (4). Infections are less common than those caused by CMV, *Pneumocystis carinii* or *Mycobacteria* sp., but they are being increasingly diagnosed from different parts of the country.

The latex agglutination (LA) test for cryptococcosis, introduced in 1966 (5) is one of the most reliable of all serodiagnostic tests for the mycoses. False positive results are not generally troublesome, although laboratories need to be aware of their occurrence and ensure that tests have the necessary controls. Experience built up in the 20 years following its introduction showed that titres had prognostic as well as diagnostic value. Thus, antigen titres higher than 200 correlated with high mortality. More recent experience, however, suggested that the time-honoured LA has less prognostic value in patients with AIDS.

Critical comparison of data does show some significant differences between the two groups. A constant feature of cryptococcosis in AIDS patients is its intractability. Treatment can result in its containment, but at present, cure cannot be expected from existing drug regimes. It has been suggested that cryptococcosis in AIDS patients differs in several respects from the same disease in patients without AIDS (6). These differences are reflected in patterns of antigen titres. Levels of antigen in patients with AIDS-related cryptococcosis tend to be sustained, or to increase (Table 1).

Falling antigen titres were commoner (44%) in non-AIDS sera, than in AIDS sera (16%). The most obvious differences between the two groups of patients, however, concerns the ratio of titres in sera and cerebrospinal fluid. In a larger series, 15 of 26 (57·7%) non-AIDS patients had initial CSF titres equal to (4 patients) or higher (11 patients) than serum titres. Results with AIDS patients were in striking contrast, with raised CSF: sera titre ratios in only 4 of 35 (11·4%) cases. These differences are significant and probably reflect a more widely

Table 1. *Antigen titres in CSF and sera from cryptococcal patients with and without AIDS (diagnosed in 1988)*

	CSF		Sera	
	AIDS	Non-AIDS	AIDS	Non-AIDS
Titre pattern	(n = 21)	(n = 16)	(n = 31)	(n = 16)
Rising	3	1	7	1
Falling	12	11	5	7
Constant	2	3	14	5
Variable	4	1	5	3

All patients were being treated with antifungal drugs.

disseminated population of cryptococci in subjects whose main line defence cells are diminished or lacking.

The traditional laboratory procedures remain helpful in diagnosing cryptococcal infections in AIDS patients. However, prognostic value is less obvious in these patients. Falling serum antigen titres are less common in AIDS patients, and this combined with the overall failure of chemotherapy to eradicate infection, might suggest that the sequential analysis of serum levels has only limited value in the management of patients, once the diagnosis has been established. Rising serum titres may alert the clinician to worsening of the condition, but in practical terms there may be no advantage gained by repeated latex agglutination testing. In contrast, CSF titres in AIDS patients often reveal declining numbers of cryptococci. It is noteworthy that in some patients falling CSF titres may not be accompanied by comparable reductions in serum titres (Table 1).

In a proportion of cases, treatment of cryptococcosis in non-AIDS patients may lead to cure, particularly in extraneural forms of the disease. From the point of view of management, cryptococcosis in AIDS patients is perhaps not best regarded as containable but not eradicable. The status of the disease can be assessed by periodic cultural and serological testing, but antigen testing in AIDS patients has a less contributory role in management of cryptococcosis than in non-AIDS patients.

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