Aspergillosis of the Central Nervous System: Clinicopathological Analysis of 17 Patients

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The clinical, laboratory, and pathological features of aspergillosis of the central nervous system (CNS) were studied in a series of 17 autopsied patients. Two groups were defined. Group A consisted of 8 patients with diseases commonly associated with CNS aspergillosis: leukemia, lymphoma, aplastic anemia, and renal transplantation. Group B contained 9 patients with various illnesses not generally known to be associated with CNS aspergillosis. CNS aspergillosis was diagnosed and treated before death in only 1 patient. Patients in Group A received cytotoxic drugs, often had granulocytopenia, less commonly had focal neurological deficits, and seldom had seizures. Group B patients were not granulocytopenic, received no cytotoxic agents, underwent nontransplant surgery, and more frequently had focal neurological deficits. Eleven of the 17 patients (65%) had focal deficits, most of them hemiparesis. Meningeal signs were rare, but the cerebrospinal fluid was usually abnormal. The principal neuropathological process was *Aspergillus* invasion of blood vessels causing hemorrhagic infarction. Focal clinical deficits correlated neuroanatomically with *Aspergillus* lesions. In 2 patients, such lesions were detected by ^{99m}Tc-DTPA or cerebral angiography before computed tomographic scanning. The lungs were the usual portal of entry, but isolated CNS lesions occurred in 2 patients. CNS aspergillosis should be considered as a cause of new onset of focal neurological deficits in patients with illnesses that are more diverse than has generally been appreciated.

Walsh TJ, Hier DB, Caplan LR: Aspergillosis of the central nervous system: clinicopathological analysis of 17 patients. Ann Neurol 18:574–582, 1985

Cerebral aspergillosis can be considered a disease of medical progress. The incidence of cerebral and disseminated *Aspergillus* infection has increased with the advent of more aggressive medical interventions capable of impairing the host's immune response. Unlike some saprophytic, opportunistic pathogens that decimate immunocompromised patients, *Aspergillus* infection is treatable. Because most *Aspergillus* infections of the central nervous system (CNS) are not recognized before death, we reviewed a large series of patients with necropsy-proved CNS aspergillosis to identify common and important epidemiological, pathological, clinical, and laboratory features. Awareness of these features might allow earlier clinical diagnosis and treatment.

Material and Methods

The investigators examined the autopsy records of The Johns Hopkins Hospital from 1956 to 1978 and those of the Michael Reese Hospital and Medical Center from 1979 to 1985 for all patients with fungal infections of the CNS. Seventeen patients were identified with CNS infections due to *Aspergillus*, 14 due to *Cryptococcus*, 27 due to *Candida*, 2 due to *Mucor*, and 1 due to *Histoplasma*. Sixteen patients with CNS aspergillosis were from The Johns Hopkins Hospital. The primary illnesses, predisposing factors, physical findings, laboratory data, and hospital course were reviewed in all patients with *Aspergillus* infection of the CNS. All available gross and histopathological specimens from each patient were examined.

A review of the medical records at The Johns Hopkins Hospital for discharge diagnoses of aspergillosis disclosed no case of clinically diagnosed CNS aspergillosis. By contrast, the yearly incidence of clinically diagnosed cryptococcal meningitis was 1.3 per 10^4 discharges. The autopsy incidence of cryptococcal meningitis was 0.24 per 10^4 discharges.

Patient Population

We divided the 17 patients into two groups (Table 1). Group A consisted of patients with coexisting diseases already recognized as commonly associated with disseminated aspergillosis. Group A included 8 patients with acute myelogenous leukemia, acute lymphocytic leukemia, non-Hodgkin's lymphoma, aplastic anemia, and renal transplantation. A patient

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Received Dec 17, 1984, and in revised form Apr 11, 1985. Accepted for publication Apr 12, 1985.

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Table 1. CNS Aspergillosis: Underlying Diseases and Predisposing Factors

Patient No.	Age (yr) Sex	Underlying Disease	Cytotoxic Drugs	Cortico-steroids	Anti-biotics[a]	Surgery	Peripheral WBC (mm^{-3})
GROUP A							
1	60/M	AML	+	+	+	−	1,200
2	62/F	AML	−	+	−	−	10,200
3	65/F	Aplastic anemia	−	+	+	−	600
4	59/M	NHL	+	+	+	−	650
5	44/M	CRF	+	+	+	−	1,400
6	29/F	Renal transplant	+	+	+	+	1,900
7	53/M	Renal transplant	+	+	+	+	3,900
8	14/M	ALL	+	+	+	−	220
GROUP B							
9	72/M	Cushing's syndrome[b]	−	+	+	−	6,200
10	48/F	Mitral stenosis	−	−	+	+[c]	17,500
11	50/F	Hepatic failure[d]	−	+	+	−	19,000
12	54/M	Chronic alcoholism	−	−	−	−	5,800
13	9/M	Hepatic failure[d]	−	+	+	−	20,800
14	66/F	Hepatic failure[d]	−	+	+	−	9,000
15	64/F	Cushing's syndrome[e]	−	+	+	−	18,000
16	50/M	Acoustic neuroma	−	+	+	+[f]	13,500
17	36/M	IV drug abuse	−	−[g]	−	−[h]	11,400

[a]Multiple (3) or protracted administration (10 days).
[b]Cushing's syndrome due to ACTH-producing tumor.
[c]Prosthetic mitral valve.
[d]Acute or subacute hepatic necrosis.
[e]Cushing's syndrome due to adrenal carcinoma.
[f]Craniotomy.
[g]Dexamethasone given for cerebral edema due to previously established *Aspergillus* brain abscess.
[h]Brain biopsy performed for diagnosis of aspergillosis.

CNS = central nervous system; WBC = white blood cells; M = male; F = female; AML = acute myelogenous leukemia; NHL = non-Hodgkin's lymphoma; CRF = chronic renal failure; ALL = acute lymphocytic leukemia; IV = intravenous; ACTH = adrenocorticotropic hormone; + = factor present; − = factor absent.

with renal failure without transplantation was also included in Group A because he underwent treatment with similar cytotoxic agents. Group B included patients with coexisting diseases usually not known to be associated with aspergillosis. Group B included 9 patients with Cushing's syndrome due to adrenal carcinoma, Cushing's syndrome caused by an ectopic adrenocorticotropic hormone (ACTH)–producing tumor, hepatic failure, a prosthetic mitral valve, chronic alcoholism, intravenous drug abuse without endocarditis, and resection of an acoustic neuroma. Endogenous or exogenous elevation of systemic corticosteroids was a predisposing factor in 6 of these 9 patients, and a seventh patient (No. 17) required systemic high-dose dexamethasone for treatment of increased intracranial pressure caused by an *Aspergillus* cerebral lesion. The nature of the predisposing illness; treatment with corticosteroids, cytotoxic drugs, or antibiotics; and white blood cell counts are noted in Table 1. Group A patients with renal transplants or blood dyscrasias usually received cytotoxic drugs and often had granulocytopenia. Group B patients were not granulocytopenic, received no cytotoxic agents, and underwent nontransplant surgery. Patients in both groups often received corticosteroids and long-term or multiple antibiotic treatment.

Results

Pathology

The most common CNS necropsy lesions (in 16 of 17 patients) were solitary or multiple subcortical hemorrhagic infarcts in the cerebral hemispheres (15 patients) and/or the cerebellum (9 patients). These infarcts frequently caused pressure-induced tonsillar or transtentorial herniation (7 patients). Necrotic tissue from three of the hemorrhagic infarcts extended into the third or lateral ventricles. The brainstem was directly involved in 3 patients, none of whom had reported focal brainstem signs. A third nerve palsy in one patient (No. 6) was due to increased transtentorial herniation rather than to intrinsic midbrain disease. The meninges were affected pathologically in only 8 of 17 patients. Meningeal infection, when present, was usually focal and adjacent to regions of infection in the cerebral or cerebellar hemispheres. Grossly the meningeal lesions usually appeared as focal subarachnoid hemorrhages. Even when hemorrhages were more diffuse, the organisms microscopically remained focal.

Histological studies revealed that the cerebral infarcts consisted of varied stages of hemorrhage and coagulative necrosis, usually with no organisms yielded on cultures. Such infarcts were associated with invasion and thrombosis of intracranial vessels by *Aspergillus* hyphae. Meningeal blood vessels were involved less frequently. The angioinvasion by *Aspergillus* caused intraluminal thrombosis, necrosis of the vessel wall, and a variable polymorphonuclear infiltrate, which was reduced in the neutropenic patients of Group A.

Other common lesions were microabscesses consisting of hyphae, and an intense focal polymorphonuclear and mononuclear reaction, seen especially in Group B patients. Microabscesses in the more severely granulocytopenic patients of Group A contained scant polymorphonuclear leukocytes and some mononuclear cells with unchecked proliferation of organisms. The angular dichotomously branching septate hyphae infiltrated brain tissue in a centrifugal pattern, with necrotic tissue remaining in the abscess center and with hyphal structure and polymorphonuclear leukocytes at the advancing border of larger abscesses. Organisms at times extended from cortical and subcortical abscesses to involve the meninges focally and invade meningeal blood vessels. An unusual form of clinically occult meningeal involvement occurred along the spinal cord and spinal nerve roots of a young woman (No. 6) who received high-dose corticosteroids and azathioprine for renal transplantation. There was, however, no invasion of the spinal cord, nerve roots, or adjacent blood vessels. Inflammation was scant as a result of peripheral granulocytopenia.

A fatal and unusual lesion, occurring in a 64-year-old woman with adrenal carcinoma, was a 2-cm *Aspergillus* mycotic aneurysm of the left posterior cerebral artery. Rupture of the aneurysm resulted in extensive subarachnoid hemorrhage and left occipitoparietal lobe infarction. *Aspergillus* infected only the arterial wall. No other foci of infection were found in the brain or elsewhere; however, the paranasal sinuses, which were not inspected at autopsy, may have served as an occult source of initial fungemia.

The most common portal of entry in patients with CNS aspergillosis was the lower respiratory tract in 15 of 17 patients. The source in 1 patient was a prosthetic mitral valve, and the source in another could not be identified. *Aspergillus* pneumonia was characterized by hyphal infiltration, angioinvasion, and a necrotizing polymorphonuclear infiltrate in non-neutropenic patients. All but 1 patient with lower respiratory tract aspergillosis had *Aspergillus* pneumonia. That patient was an intravenous "T's and blues" (pentazocine and tripelennamine) abuser who had widespread pulmonary angiomatoid vascular malformations containing polarizable material identical to that found at the sites of his injections. Such vascular channels may have allowed *Aspergillus* spores injected with contaminated powder to bypass the pulmonary capillary bed and gain direct access to the cerebral arterial circulation.

Disseminated aspergillosis—defined as infection of the CNS, lungs, and at least one other organ—occurred in 11 patients. Infection restricted to the CNS and lungs developed in 4 patients, and isolated CNS aspergillosis was present in 2 patients. Extracranial and extrapulmonary lesions differed between Groups A and B, again with respect to the paucity of inflammatory cells in the former and relative intensity of polymorphonuclear leukocytes in the latter. All patients with pulmonary aspergillosis had a wider distribution of organisms in the lungs at autopsy than was indicated by the distribution of pulmonary infiltrates on chest radiographs. Radiographically inconspicuous pulmonary aspergillosis occurred in more foci in Group A patients, probably because of a granulocytopenia-associated decrease in polymorphonuclear leukocyte infiltration in the lung parenchyma. Pulmonary infiltrates were those of a bronchopneumonia and were clinically misdiagnosed as a bacterial pneumonitis in all but 1 patient.

Clinical Neurological Features

Meningismus or signs of meningeal irritation were noted in only 1 patient who had a subarachnoid hemorrhage caused by rupture of a mycotic *Aspergillus* aneurysm. Focal neurological deficits were noted in 10 patients (Table 2). The most common focal deficit was a hemiparesis, which invariably was caused by hemorrhagic infarction in the contralateral subcortical white matter. Ipsilateral intention tremor developed in a 9-year-old boy with a cerebellar hemorrhagic infarct. Focal or generalized seizures occurred in 3 patients. Group B patients had more focal neurological deficits (7 of 9) than Group A patients (3 of 8). Headache was a rare feature of CNS aspergillosis. Only Patient 15, who presented with subarachnoid hemorrhage caused by mycotic aneurysm, was noted to have headache. Focal deficits were abrupt in onset, were not associated with hypotension, and did not remit. Focal neurological deficits and focal seizures generally occurred either as an initial presenting problem in 4 patients or as a new neurological event after an extended hospitalization in 6 patients (Table 3). Only one patient (No. 17) with a focal neurological deficit developed subsequent new multifocal neurological defects. He presented with focal motor seizures of the right limbs followed sequentially by dysarthria, global aphasia, right hemiplegia, and left-sided focal seizures. Development of a focal neurological deficit was generally followed by confusion and a gradual loss of consciousness over 1 to several days.

Neurological deficits or focal seizures could be explained by the location of abscesses or hemorrhage.

Table 2. Physical Findings and CSF Analysis

Patient No.	Meningeal Signs	Focal Deficits	Seizures	Opening CSF Pressure (mm H_2O)	Glucose (mg/dl)	Total Protein (mg/dl)	WBC (mm^{-3})	PMN (%)	MN (%)	RBC (mm^{-3})
GROUP A										
1	–	–	–	...	...	...	...	...	...	...
2	–	–	–	...	...	...	...	...	...	...
3	–	–	–	...	...	...	...	...	...	...
4	–	R hemiparesis	–	200	40	...	52	0	100	10
5	–	–	–	...	...	...	...	...	...	...
6	–	Third nerve palsy	–	190	56	109	1,200	32	68	180
7	–	–	Focal	310	160	85	77	83	17	0
8	–	Central facial weakness	–	140	60	30	1	0	100	220
GROUP B										
9	–	–	–	130	65	75	...	...	...	...
10	–	L hemiparesis	–	...	...	...	...	...	...	...
11	–	–	–	...	...	...	...	...	...	...
12	–	R hemiparesis	General-ized	...	...	...	...	...	...	...
13	–	R ataxia	–	...	...	...	...	...	...	...
14	–	L hemiparesis	–	...	...	...	...	...	...	...
15	+[a]	R hemiparesis	–	...	90	145	15	0	100	Only xan-thocro-mia
16	–	R hemiparesis	–	...	19	141	9	89	11	921
17	–	R hemiparesis	Focal	160	73	90	133	43	57	0

[a]Subarachnoid hemorrhage (mycotic aneurysm).

CSF = cerebrospinal fluid; WBC = white blood cells; PMN = polymorphonuclear leukocytes; MN = mononuclear cells; RBC = red blood cells; R = right; L = left; – = absent; + = present; ... = data not available.

Table 3. Clinical Course of Patients with Focal Deficits or Seizures

Patient No.	Onset of Focal Deficit or Seizure (hospital day)	Course of Level of Consciousness after Onset of Deficit or Seizure	Death (hospital day)
GROUP A			
4	22	Sudden LOC 1 day later	23
6	38	Gradual but progressive lethargy and LOC over 8 days	46
7	62	Sudden LOC with fixed and dilated pupils 4 days later	66
8	35	Gradual LOC over 2 days	37
GROUP B			
10	71	Stable until cardiac arrest 4 days later	75
12	1	Sudden cardiorespiratory arrest 17 days later	17
13	24	Gradual LOC over 9 days	33
14	43	Gradual but progressive LOC over 2 weeks	68
15	1	Initial lethargy, then improvement on dexamethasone 2 days later followed by progressive deterioration	9
16	1	Progressive LOC over 12 days	12
17	1 (R-sided jacksonian seizure) 8 (dysarthria followed by aphasia) 15 (right hemiplegia)	Alert until day 15 when right hemiplegia and stupor abruptly developed	20

LOC = loss of consciousness; R = right.

All neurological deficits and focal seizures were explained by cerebral and cerebellar hemispheral lesions. A third-nerve palsy was due to increased intracranial pressure; no lesions were found in the third nerve or Edinger-Westphal nuclei. A central facial weakness was due to a contralateral cerebral *Aspergillus* abscess. Although abscesses and hemorrhagic infarcts were present in the brainstem of several patients, no correlative clinical deficits were noted during the hospital course. Seven of the 9 patients with focal deficits or seizures had more brain lesions than were predicted by the neurological examination. While all focal neurological findings had correlative neuroanatomical lesions accounting for the clinical findings, other lesions in the same patients were clinically occult (Table 4).

Table 4. Neuropathological Correlation between Neurologic Findings and Aspergillus *Lesions*

Patient No.	Location(s) of Lesions	Focal Neurological Deficit or Seizure
GROUP A		
1	R basal ganglia, L occipital lobe, R cerebellar hemisphere	None
2	Multiple	None
3	L basal ganglia	None
4	Multiple	R hemiparesis
5	Cerebellum	None
6	Multiple	Third nerve palsy
7	R parietal lobe	L focal seizures
8	Multiple	Central facial weakness
GROUP B		
9	Multiple	None
10	R basal ganglia, L parietal lobe	L hemiparesis
11	L parietal lobe	None
12	Multiple (including L frontal and L parietal lobes)	R hemiparesis
13	Multiple (including cerebellum)	R ataxia
14	R temporal and R parietal lobes	L hemiparesis
15	L posterior cerebral mycotic aneurysm with infarct of L temporal lobe and L internal capsule	R hemiparesis
16	Multiple (including L cerebral hemisphere and cerebellum)	R hemiparesis
17	Multiple (including L parietal lobe, L temporal lobe, and L frontal lobe)	R focal seizures R hemiparesis Dysarthria aphasia

L = left; R = right.

Laboratory Investigations

Cerebrospinal fluid (CSF) was obtained in only 8 of the 17 patients (Table 2); white blood cell counts ranged from 1 to 1,200/mm^3 (average, 212/mm^3). If the single patient with a white blood cell count of 1,200/mm^3 is excluded, the other 6 patients averaged 46/mm^3. Mononuclear cells predominated; 4 of 7 patients had some polymorphonuclear cells in the CSF. An important clue to aspergillosis was the presence of red blood cells in 4 of 7 patients. CSF protein levels were usually slightly elevated (average, 96 mg/dl). Only 1 patient had a strikingly low CSF glucose value. Three of 6 patients had normal CSF pressure. Serological tests for *Aspergillus* infection were not performed in any of the 17 patients. Vertebral angiography in Patient 15 demonstrated a ruptured aneurysm of the left posterior cerebral artery, but this lesion was not attributed to infection by the patient's physicians. In general, the few other neuroradiographic studies performed did not reveal important abnormalities. Computed tomography (CT) was performed in only 4 patients (Table 5). Technetium-99m–diethylenetriaminepentaacetatic acid (^{99m}Tc-DTPA) radionuclide brain scanning demonstrated striking left cerebral uptake corresponding to an area of *Aspergillus* infection, while CT images in the same patient revealed only slight local edema. Pulmonary infiltrates were present on chest radiographs in those patients who had pulmonary and CNS aspergillosis. Only 3 patients had positive fungal cultures during life. The specimens were sputa and a brain biopsy. All other patients had only positive autopsy cultures for *Aspergillus*. The most frequently isolated species was *A. fumigatus*.

Electroencephalography was performed in 3 patients and revealed localizing voltage depression in 2 patients, corresponding to their deficits. The third patient with diffuse slowing had multiple cerebral abscesses and hemorrhages.

A diagnosis of CNS aspergillosis was established ante mortem in only 1 patient (No. 17) who underwent open brain biopsy and culture. While an opportunistic fungal infection was frequently considered in Group A patients because of the nature of the underlying disease, a diagnosis of CNS aspergillosis was *not* established in any patient in this group. Neurological findings in Group B patients were ascribed to metabolic encephalopathy (Patients 11 to 14), intracerebral hemorrhage caused by impaired coagulation function (Patients 11 to 14), local effects of surgery (Patient 16), or bacterial endocarditis (Patient 10). Only 2 patients received systemic antifungal therapy. Patient 17

Table 5. Electroencephalographic and Neuroradiographic Studies in Patients with CNS Aspergillosis

Patient No.	Electroencephalogram	Radionuclide Brain Scan	CT Scan	Cerebral Angiography
GROUP A				
6	R occipital focus of decreased activity suggesting space-occupying lesion	Normal	NP	Normal
7	NP	Normal	NP	NP
GROUP B				
9	NP	NP	Sphenoidal, maxillary, and ethmoidal sinusitis	NP
14	Diffuse slowing	NP	NP	NP
15	L-sided voltage depression	NP	Normal	Occlusion of L posterior cerebral and superior cerebellar arteries
16[a]	NP	NP	Intracerebral hematoma of L cerebellar hemisphere; hydrocephalus	NP
17	NP	Increased uptake on L parietal lobe	Edema of L parietal lobe	NP

[a]Patient previously underwent posterior fossa surgery.

CNS = central nervous system; CT = computed tomography; R = right; L = left; NP = not performed.

received intravenous amphotericin B and 5-fluorocytosine for recognized CNS aspergillosis, and Patient 9 received intravenous amphotericin B for pulmonary aspergillosis.

Discussion

Group A patients with renal transplants or blood dyscrasias usually received cytotoxic drugs, often had granulocytopenia, less commonly had focal neurological deficits, and seldom had seizures. Group B patients were not granulocytopenic, received no cytotoxic agents, underwent nontransplant surgery, and had a greater frequency of focal neurological deficits. Patients in both groups had excess endogenous or exogenous corticosteroids and were treated with long-term or multiple antibiotics.

Aspergillus infections of the CNS have been described in patients with disseminated aspergillosis complicating an underlying malignancy [41, 76]. Eighty-four percent of the 191 patients with disseminated aspergillosis described in the two largest series [41, 76] had a malignancy, usually leukemia or lymphoma (Group A diseases). Recognition that primary diseases, such as those noted in Group B, may also be a clinical setting for CNS aspergillosis is the key to the early clinical diagnosis of this infection. This study of 17 autopsy-proved cases of CNS aspergillosis from two university hospitals with diverse medical and surgical patient populations contained only 7 of 17 patients (41%) with neoplastic disease, only 3 (18%) with leukemia or lymphoma, and only 4 (24%) with granulocytopenia. That nongranulocytopenic patients and those without leukemia, lymphoma, or renal transplantation constitute an important population at risk for CNS aspergillosis is evidenced by single case reports or small case series that include traumatic quadriplegia [45], chronic alcoholism [44], intravenous drug abuse [8, 10, 12, 26, 35, 43, 62], open heart surgery with ensuing fungal endocarditis [3, 18, 69], dissecting aortic aneurysm [9], diabetes [49], direct inoculation through neurosurgery [20, 23], trauma [27], pulmonary tuberculosis [33, 60], systemic lupus erythematosus [39, 55], cardiac transplantation [6, 31], allergic bronchopulmonary aspergillosis [61], pulmonary sarcoidosis [51], subacute hepatic necrosis [4, 66, 67], and no apparent underlying disease [14, 15, 35, 48, 52, 54, 58, 59, 65].

The importance of systemic corticosteroids as a predisposing factor in aspergillosis is well known [2, 29, 41, 63, 76], but the role of corticosteroids in certain patient populations in this study bears noting. Cushing's syndrome in Patients 9 and 15 was caused by endogenous hypercortisolism from an ectopic ACTH-producing tumor and an adrenal carcinoma, respectively. While *Cryptococcus* meningitis is a known complication of endogenous hypercortisolism [7, 21], *Aspergillus* infection of the CNS as a complication of endogenous Cushing's syndrome has only recently

been described [70]. Effective management of the infection requires both systemic antifungal therapy and correction of the hypercortisolemic state.

Hepatic failure has not been generally recognized previously as a predisposing factor of CNS aspergillosis [4, 66, 67]. The neurological findings in Patients 11, 13, and 14 with subacute hepatic necrosis were clinically attributed to hepatic encephalopathy or to intracranial hemorrhage caused by coagulopathy. Infarcts caused by *Aspergillus* tended to be especially hemorrhagic in these patients, perhaps reflecting their coagulation defects. The development of focal neurological deficits in patients with liver failure treated with corticosteroids should arouse suspicion of CNS aspergillosis.

Cardiovascular surgery, especially prosthetic valve implantation, is yet another clinical setting in which CNS aspergillosis may develop [3, 18]. A series of patients with *Aspergillus* endocarditis contained 23 (56%) of 41 patients with clinical evidence of cerebral emboli to the brain and 16 (57%) of 28 evaluable autopsies with CNS emboli [34]. Fever and clinically overt emboli to the CNS were also the most common presenting manifestations of *Aspergillus* endocarditis in children [3]; the brain was involved in 9 of 10 of these autopsied patients. Blood cultures are usually negative, and echocardiographic studies only rarely delineate vegetations because of interfering echoes from the prosthesis. Nonprosthetic mural *Aspergillus* endocarditis, which may also serve as a nidus for embolization to the brain [68], may not be detected by echocardiography.

CNS aspergillosis characteristically causes focal neurological signs. The most common focal deficit in this study was hemiparesis, usually secondary to one or more hemorrhagic infarcts in the contralateral subcortical white matter. An ipsilateral intention tremor and dysmetria developed in a 9-year-old boy as the result of a cerebellar *Aspergillus* hemorrhagic infarct. This relatively high frequency (65%) of focal neurological deficits was also noted in 10 of 13 patients in one series [41], in 9 of 12 patients in another series [54], and in individual case reports [30, 37, 42].

Meningeal signs such as meningismus, headaches, Brudzinski's sign, and Kernig's sign were uncommon in this patient group and occurred in only Patient 15. This patient was initially seen because of a subarachnoid hemorrhage caused by rupture of an *Aspergillus* mycotic aneurysm of the left posterior cerebral artery. The predilection of *Aspergillus* for invasion of subcortical blood vessels with resulting thrombosis and hemorrhage explains the predominance of focal deficits and the paucity of meningeal signs. This tendency to invade blood vessels has been described in several cases [30, 38, 65, 70, 74] in which the primary problem was subarachnoid hemorrhage due to rupture of an *Aspergillus* mycotic aneurysm of a major extracerebral artery. Fungal intracranial aneurysms are uncommon; they arise from major cerebral arteries and are most frequently caused by *Aspergillus* [30, 65, 74]. Bacterial intracranial aneurysms arise in peripheral cerebral arterial branches, are often multiple along a single arterial distribution, and are usually smaller (1 to 2 mm in diameter) than intracranial aneurysms caused by fungi (5 to 10 mm in diameter) [17, 30, 53]. Rarely, the predominant clinicopathological process in aspergillosis of the CNS is meningitis [4, 8, 43, 55, 62].

Although CSF analysis did not contribute to a specific diagnosis, it often showed a mildly elevated protein level and a decreased to normal glucose concentration. The CSF white blood cell count was usually less than $100/mm^3$ with various distributions of polymorphonuclear and mononuclear cells. *Aspergillus* has been cultured from the CSF in only 9 reported cases [4, 8, 32, 35, 40, 46, 55, 62, 65]. The relative infrequency with which *Aspergillus* infects the meninges and the lack of diffuse meningeal involvement may account for the paucity of CSF findings.

Radionuclide brain scanning with ^{99m}Tc-DTPA in Patient 17 demonstrated well-defined areas of activity in the cerebral hemisphere that were proved pathologically to be *Aspergillus* cerebritis and infarction. CT images obtained simultaneously showed only cerebral edema in this region. Radionuclide brain scanning with ^{99m}Tc-DTPA may be more sensitive than CT for detecting diffuse intracranial infectious disease [50] and possibly early *Aspergillus* cerebritis. Electroencephalography also showed early focal changes in 2 of our patients. The findings on CT are not specific, and early lesions may be missed even when electroencephalography and neurological examinations show localizing signs. Subtle low-attenuation defects, minimal mass effect, and poor contrast enhancement without ring configuration in 5 patients with intracranial aspergillosis suggested that CT may be neither sensitive nor specific in the diagnosis of aspergillosis of the brain [26] and that the extent of *Aspergillus* involvement may be underestimated by CT [19]. A ring-enhancing abscess lesion appears to be a late or advanced change in the evolution of intracranial aspergillosis [16]. Lesions may resolve slowly even after cure [75]. However, CT provides excellent delineation of hydrocephalus caused by *Aspergillus* meningitis [35, 56] and of rhinocerebral and invasive paranasal sinus aspergillosis [13]. Radionuclide brain scanning and CT may be complementary diagnostic tools permitting early detection and anatomical delineation of CNS aspergillosis.

The CT scan was normal in Patient 15 when performed earlier in her hospitalization, while cerebral angiography demonstrated occlusion of the left posterior cerebral artery. Occlusion of cerebral arterial

branches by *Aspergillus* may be documented by arteriography [1] and correlates with hypodense areas seen on CT scans, representing necrosis secondary to infarction [64].

Serological diagnosis of aspergillosis by detection of serum antibodies is a specific but not necessarily sensitive means of diagnosing disseminated aspergillosis [57]. *Aspergillus* antigens have been demonstrated in serum and pleural fluid [72, 73] but have not been reported in CSF.

The successful outcome of treatment of CNS aspergillosis is predicated upon early recognition. Several reports have demonstrated recovery from CNS aspergillosis [5, 11, 20, 24, 25, 28, 36, 42, 47, 59]; however, response to antifungal therapy is often poor, perhaps reflecting late diagnosis. Many patients with aspergillosis have a treatable underlying illness and yet succumb to *Aspergillus* infection of the CNS [71]. *Aspergillus* infection of the CNS is no longer rare but is a frequent complication of disseminated aspergillosis that occurs in a wide range of susceptible hosts.

The authors gratefully acknowledge the helpful suggestions of Arthur C. Clarke, MD, during this study and thank Ms Nancy M. Kelly for her expert secretarial assistance.

Dr Walsh is currently a Clinical and Research Associate of the University of Maryland Cancer Center and a recipient of the Janssen Medical Mycology Fellowship Award of the National Foundation for Infectious Diseases.

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