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Cerebral aspergillosis in adult critically ill patients: a descriptive report of 10 patients from the *Asp*ICU cohort

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ABSTRACT

An unexpectedly high incidence of invasive pulmonary aspergillosis (IPA) has been reported in non-neutropenic intensive care unit (ICU) patients. After the respiratory tract, the brain is most often affected by invasive aspergillosis. However, little is known about brain involvement by *Aspergillus* in critically ill patients. In this study, demographics, risk profile, diagnosis, treatment and outcome of proven cases of invasive cerebral aspergillosis (ICA) taken from a cohort of 563 adult patients with evidenced *Aspergillus* involvement during their ICU stay were reviewed. Ten patients with central nervous system aspergillosis were identified. All had one or more host factors predisposing for invasive aspergillosis. The clinical and radiological presentation was non-specific and exclusively pulmonary-related. All but one patient had proven or probable/putative IPA. On cerebral computed tomography, lesions appeared as either solitary and hyperdense or were multiple and randomly distributed throughout the brain. One patient presented with sole meningeal infestation. *Aspergillus* infection was confirmed by brain biopsy in three subjects. Voriconazole was used as primary treatment in only one-half of the patients. Mortality was 90%. ICA is not frequently observed in adult ICU patients. Diagnosis must be considered in patients at risk presenting with proven or probable/putative IPA in association with suggestive neuroradiological findings. The brain is most likely affected through haematogenous dissemination from the lungs. Current treatment recommendations are not always applied and outcome remains dismal.

1. Introduction

Invasive pulmonary aspergillosis (IPA) is a devastating infection commonly associated with a state of immunosuppression as seen in patients with haematological cancers, haematopoietic stem cell transplant recipients and neutropenic subjects [1]. However, an unexpectedly high incidence of IPA has been reported in intensive care unit (ICU) patients without such a specific risk profile [2,3]. After the respiratory tract, the brain is most often affected by invasive aspergillosis, either as a result of direct invasion from adjacent structures (e.g. sinuses) or through haematogenous spread [4]. Little is known about brain involvement by *Aspergillus* in critically ill patients. In this study, data on demographics, risk profile, diagnosis, treatment and outcome of invasive cerebral aspergillosis (ICA) in a large cohort of ICU patients were reviewed.

2. Materials and methods

Data from the *Asp*ICU project, an international, multicentre, observational cohort study including 563 adult ICU patients from eight countries, were used. Patients were included in this study

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Table 1
Patient characteristics, underlying clinical conditions and admission diagnosis.

Patient	Age (years)	Race	Sex	Primary diagnosis	APACHE II score	Underlying condition	Corticoid pre-treatment
1	44	C	M	Liver transplant	22		Yes
2	69	C	F	Wegener's disease, renal failure	25		No
3	51	A	F	Liver failure, ARDS	29	Alcohol abuse	Yes
4	44	C	M	Pneumonia, ARDS	30		Yes
5	49	C	F	Astrocytoma, brain oedema	14	COPD	Yes
6	64	C	F	Pneumonia, ARDS	26	COPD, diabetes	Yes
7	48	C	M	Liver transplant	18	HIV+, diabetes	No
8	68	C	F	Renal transplant, pneumonia, ARDS	18	Diabetes	Yes
9	39	C	F	Endocarditis	34		No
10	73	C	M	Cerebral lymphoma, encephalopathy	20	Diabetes	No

C, Caucasian; A, Asian; M, male; F, female; ARDS, acute respiratory distress syndrome; APACHE, Acute Physiology and Chronic Health Evaluation; COPD, chronic obstructive pulmonary disease; HIV+, human immunodeficiency virus seropositive.

from November 2006 until January 2011 when *Aspergillus* involvement was evidenced by at least one positive direct test on any body site, sampled during the ICU course. In addition, patients from historical cohorts (from January 2000) were accepted if none of the required data were missing. Study methods have been described in detail elsewhere [5]. Briefly, data were collected regarding demographics, acute and underlying conditions, and clinical signs compatible with invasive fungal disease. Mycological examination encompassed culturing and galactomannan detection. Radiographic assessment included findings from chest radiography and computed tomography (CT) as well as CT imaging of the sinuses, abdomen and central nervous system (CNS).

Diagnosis of ICA required histopathological evidence of *Aspergillus* involvement of the CNS [6]. Descriptive variables are reported as number (%) or median [interquartile range (IQR)].

Local Ethics Committees or Review Boards provided approval for the study. Because of the observational nature of the study, informed consent was waived.

3. Results

3.1. Demographics and admission data

Ten patients with cerebral aspergillosis were identified. Demographic characteristics and the primary reason for ICU admission are given in Table 1. The median age was 50 years (IQR 44–68 years). Nine patients were Caucasian and one was Asian. The median Acute Physiology and Chronic Health Evaluation (APACHE) II score was 23.5 (IQR 17–29). All patients were mechanically ventilated. None of the patients had been primarily diagnosed with invasive sinusal or pulmonary aspergillosis.

3.2. Clinical signs and host risk factors

Increased core temperature was most commonly observed, presenting as refractory fever under broad-spectrum antibiotic treatment in six patients and relapsing fever in one patient. Haemoptysis occurred in one patient. Four patients were intubated on ICU arrival because of acute respiratory failure. Focal neurological abnormalities, myoclonic movements, lateralisation signs and seizures were never documented.

All patients had at least one host factor predisposing them to *Aspergillus* infection [malignancy ($n = 2$) treated with cytotoxic agents ($n = 1$); immunodeficient status or receiving immunosuppressive therapy ($n = 3$); prolonged steroid use ($n = 6$)]. Three patients were solid organ transplant recipients. None of the patients suffered from severe neutropenia (<500 cells/mm^3). Besides host factors, four patients had diabetes, two patients had chronic obstructive pulmonary disease and one patient was seropositive for human immunodeficiency virus (HIV). Chronic alcohol abuse was present in one subject (Table 1).

3.3. Mycology

Culture, galactomannan determination and microscopic results are given in Table 2. *Aspergillus fumigatus* was identified in nine patients. In all but one patient *Aspergillus* affected the lung. Five patients had positive respiratory cultures 1–5 days before ICU admission. In the remaining four patients, cultures became positive after 1–63 days of ICU stay. Respiratory cultures remained negative in one patient. According to the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) criteria [6] and a

Table 2
Mycological and radiographic findings.

Patient	Respiratory tract			Brain		Other cultures	Radiographic imaging		
	Serum/BAL galactomannan[a]	Microscopy or culture on ETA or BAL fluid	Biopsy (B) or autopsy (A)	Biopsy	Autopsy		Chest radiography	Chest CT	Brain CT
1	+/ND	–		+			NSI	NSI	ML
2	ND/ND	+			+		Cavitation	Cavitation	ML
3	–/ND	+	+ (B)	+			NSI	Cavitation	SL
4	–/ND	+		+			NSI	Nodule	SL
5	+/ND	+	+ (B)		+		NSI	NSI	ML
6	–/ND	+			+		NSI	Nodule	ML
7	+/+	+				+ (CSF and pericardial fluid)	NSI	NSI	–
8	+/ND	+			+		Nodule	Nodule	ML
9	ND/ND	+	+ (A,B)		+		NSI	NSI	ML
10	ND/ND	+			+		NSI	Air-crescent sign	ML

ND, not done; BAL, bronchoalveolar lavage; ETA, endotracheal aspirate; CSF, cerebrospinal fluid; CT, computed tomography; NSI, non-specific infiltrates; ML, multiple lesions; SL, solitary lesion.

[a] Cut-off optical density galactomannan index >0.5 was considered positive.