Invasive aspergillosis in a patient with MELAS syndrome

D H McKee, P N Cooper, D W Denning

Abstract
Invasive infection with the opportunistic fungus *Aspergillus fumigatus* predominantly affects people with impaired cell mediated immunity. The case of a 31 year old woman with no identified cause for immunosuppression who presented with severe refractory aspergillosis of the paranasal sinuses is reported. She subsequently developed clinical and molecular evidence of mitochondrial encephalomyopathy with lactic acidosis and stroke-like events (MELAS) syndrome. It is proposed that MELASS syndrome may represent an unusual risk factor for the development of invasive aspergillosis and mechanisms are supported by which mitochondrial dysfunction may predispose to this. (J Neurol Neurosurg Psychiatry 2000; 68: 765–767)

Keywords: Aspergillus infection; MELAS syndrome

*Aspergillus fumigatus* is an opportunistic infection which usually affects the lungs, sinuses, or the tracheobronchial tree. Risk factors for the development of invasive aspergillosis include severe inherited abnormalities of granulocyte function such as chronic granulomatous disease and severe combined immunodeficiency syndrome, cytotoxic chemotherapy for malignancies such as leukaemia and lymphoma, AIDS, and iatrogenic immunosuppression in transplant recipients. The risk of developing invasive aspergillosis in the normal healthy and fully immunocompetent host is negligible, although a few such cases have been described.1 2

The syndrome known as mitochondrial encephalomyopathy with lactic acidosis and stroke-like events (MELAS) is one of a group of disorders known to be caused by mutations in mitochondrial DNA. The cardinal features of the disorder are stroke-like episodes before the age of 40, encephalopathy characterised by seizures, dementia, or both, and lactic acidosis or ragged red fibres on muscle biopsy.

In addition to the cardinal features of the disease, many other manifestations have been described including sensorineural deafness, diabetes mellitus, cardiac conduction abnormalities, and intestinal pseudo-obstruction.4 No previous association between MELAS syndrome and opportunistic infection has been reported.

Case report
A previously fit and well 34 year old woman presented in 1991 complaining of blockage of the right nostril associated with bloody discharge. On examination there was gross deviation of the nasal septum and some crusting around the right nostril. Cranial CT showed extensive mucosal change with a soft tissue mass in the right nasal cavity and maxillary antrum, extending into the right ethmoid and sphenoid sinuses and with associated bony destruction of the medial wall of the right orbit. A submucosal resection was performed and disclosed large amounts of thickened green necrotic material. A biopsy subsequently grew *Aspergillus fumigatus*. Despite two extensive internal debridements the disease progressed. External ethmoidectomy was performed and further histology confirmed continuing invasion of the mucosa by hyphae, with no evidence of a host reaction to the infection.

Further treatment with itraconazole failed despite high doses, and treatment with amphotericin B, both deoxycholate and lipid associated (Amphocil), resulted in a partial response which was attributed to the drug. In 1992, in view of persisting infection she was treated with the now withdrawn azole drug saperconazole. This resulted in an impressive resolution in symptoms and radiological signs and the patient remained well for 3 years after discontinuation of saperconazole.5

In 1995, four years after the initial diagnosis of invasive aspergillosis, she developed diabetes mellitus, which required insulin for glycaemic control. At the same time it was noticed that she had ECG evidence of Wolff-Parkinson-White syndrome, which was asymptomatic. Later that year she underwent a subtotal colectomy with ileorectal anastomosis because of severe slow transit constipation causing functional intestinal obstruction. The colon was found to be histologically normal.

In 1996 the patient had a recurrence of the invasive sinus aspergillosis, which was treated with sinus washouts and intravenous liposomal amphotericin (Ambisome), along with granulocyte colony stimulating factor to good effect.

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Aspergillus is crucial part of the defence against fungi such as bacterial and fungal infections, particularly chronic granulomatous disease, which characteristically result in impaired immunity to bacterial and fungal infections, particularly Aspergillus. An unusual feature of neutrophilic killing of Aspergillus is that, unlike other microorganisms, the fungus is not ingested but rather killed extracellularly.

It is well known that acidic, lactate based peritoneal dialysate solutions have a detrimental effect on neutrophil function, and that the longer the exposure to one of these solutions the worse is the ability of neutrophils to form superoxide anions which are necessary for the effective killing of many microorganisms including Aspergillus. Perhaps the most important potential mechanism of neutrophil dysfunction in the patient described is the likelihood of longstanding lactic acidosis, which in MELAS syndrome is often accompanied by episodes of more severe acidosis coinciding with intercurrent infection.

It is interesting to note that despite these potential causes for impaired neutrophil function in MELAS syndrome, the patient underwent full immunological investigation at the beginning of her disease and no abnormalities were discovered. This may be because standard neutrophil function testing involves measurement of phagocytosis of Candida; however, this is a relatively crude assay and only major defects would be elicited by these tests. Furthermore, no measure of extracellular killing is obtained. It is thus possible to have immune defects which result in significant reduction in defence against Aspergillus with normal laboratory testing of Candida phagocytosis and killing. In addition, in vitro testing under buffered conditions may not elucidate problems related to in vivo lactic acidosis, which is likely to be a significant factor in the patient described.
A further possible discrepancy could arise because of the phenomenon of heteroplasmia which is found in mitochondrial disorders. In genetic disorders affecting the nuclear DNA, the mutations are expected to be equally distributed in cells throughout the body. In mitochondrial DNA mutations, heteroplasmia ensures random distribution of the abnormal mitochondria and the numbers of mitochondria affected may vary dramatically in different cells and tissues. It is possible that by chance the neutrophils assayed in vitro had a low proportion of mutant mitochondrial DNA, and if outnumbered in vivo by cells with a high mutant load this could cause a significant degree of immunosuppression by the mechanisms postulated above.

This is the first reported case of invasive aspergillosis in a patient with a mitochondrial disorder. Although the mechanism is unknown, mitochondrial disorders may represent an unusual risk factor for the development of this infection, and further studies are needed to assess the effects of mitochondrial dysfunction on the immune system. MELAS syndrome and other mitochondrial defects should be excluded in patients with invasive aspergillosis not apparently immunocompromised.

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