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* predominately 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 MELAS syndrome may represent unusual risk factors for the development of invasive aspergillosis and mechanisms are supported by which mitochondrial dysfunction may predispose to this.

Keywords: Aspergillus infection; MELAS syndrome

Invasive aspergillosis, 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.

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.

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 devia-

Further treatment with itraconazole failed despite high doses, and treatment with amphotericin B, both deoxycholate and lipid associated (Ambisome), resulted in a partial response but was discontinued when the patient developed bilateral 40 dB sensorineural hearing loss 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.

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.

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.
She then remained well until 1998 when she presented acutely with headache, photophobia, and confusion. She had a witnessed generalised convulsion followed by several right sided focal motor seizures. Treatment with aciclovir was started for possible herpes simplex encephalitis, and an MRI of the brain showed high signal in the left temporal lobe on T2 weighting, consistent with that diagnosis. However, analysis of the CSF was normal and polymerase chain reaction (PCR) for herpes simplex was negative. She was discharged but returned unwell and a brain biopsy was performed to look for evidence of cerebral aspergillosis or other pathology. The biopsy showed non-specific changes with inflammation and oedema only. The patient began to improve spontaneously; however, her neurological status subsequently relapsed and she began to have frequent right sided focal motor seizures, with episodes of epilipsea partialis continua. Repeat MRI showed additional right sided temporal lobe involvement. At this point she was transferred to a neurology unit for further investigation. Her CSF lactate was found to be raised at 3.17 mmol/l (normal range 0.63–2.44 mmol/l) with a venous lactate of 2.60 mmol/l (normal up to 2.44 mmol/l). Analysis of mitochondrial DNA from peripheral blood demonstrated the presence of the A3243G MELAS mutation, whereupon the diagnosis of MELAS syndrome was made. She remains disabled with increasing dementia, epilepsy, and focal weakness of the right leg, but is inappropriately euphoric.

**Discussion**

In view of the case outlined above, we suggest that MELAS syndrome may represent an unusual risk factor for the development of opportunistic infection with *Aspergillus fumigatus*. We propose several possible mechanisms by which mitochondrial dysfunction may predispose to this.

The mitochondrial mutation in MELAS syndrome results in a severe disruption of oxidative mitochondrial function, which affects multiple cells throughout the body, but tends to affect most severely those cells with a high oxygen consumption such as neurons, myocytes, and endocrine cells. The exact mechanism of cellular damage is not fully elucidated; however, there is evidence to suggest that dysfunction of the respiratory chain enzymes of the inner mitochondrial membrane results in both excess toxic free radical accumulation and insufficient energy production for the needs of the cell.

Neutrophils and other phagocytes form a crucial part of the defence against fungi such as *Aspergillus*. Effective function of neutrophils depends on a series of steps conventionally divided into stimulus detection and transduction, chemotaxis, ingestion, degranulation, and microbial killing.

After stimulus detection the neutrophil must move actively by diapedesis to the site of inflammation. The mechanism of the movement involves, as in muscle cells, the interaction of actin and myosin and the consumption of ATP as an energy source for this active process. Defects in the mitochondrial respiratory chain enzymes may render the neutrophil unable to produce the energy necessary to power effective chemotaxis. Degranulation of neutrophils similarly requires active movement of actin on myosin and is an energy dependent process indirectly relying on mitochondrial function. Neutrophilic microbial killing is effected by several mechanisms, but the most important of these is an oxygen dependent killing system termed the “respiratory burst of phagocytosis”. This comprises a rapid set of metabolic events which begin with the reduction of molecular oxygen to superoxide, a free radical anion, by the multicomponent enzyme system NADPH oxidase.

Superoxide free radicals proceed to form hydrogen peroxide and other more potent reactive oxygen species which are toxic to ingested microorganisms and effect microbial killing, along with significant damage to the neutrophils themselves. Although the NADPH oxidase enzyme system is not mitochondrial in location, the generation of NADPH and its maintenance in a reduced state requires functional respiratory chain enzymes.

Defects in the NADPH oxidase enzyme system are known to produce various forms of 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 dialysis 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 heteroplasmy 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, heteroplasmy 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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