Rare disease

PCR negative cerebral malaria in a traveller returning from Mumbai

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Summary

The incidence of imported malaria to the UK is significant. The authors report a case of a healthy young man diagnosed with PCR negative cerebral malaria, a week after returning from Mumbai. The patient presented with acute confusion and vomiting. His condition deteriorated quickly warranting intubation, ventilation and transfer to intensive therapy unit. Extensive investigation did not find an underlying cause. Antimalarial treatment was initiated based on clinical suspicion despite a negative malarial screen. A rapid response to treatment followed such that the patient was extubated within 24 h. This case highlights the need for the UK Health Protection Agency to review its risk classification of malaria for travellers to Mumbai. Additionally, clinicians should promptly initiate antimalarial treatment in an unwell traveller returning from an endemic area when there is a high clinical suspicion even in the absence of a positive initial malaria screen.

BACKGROUND

Increasing travel to endemic areas by returning migrants and holidaymakers means that the incidence of imported malaria to the UK remains high. The Health Protection Agency (HPA) reports that over the past 20 years there have been between 1370 and 2500 reported cases of imported malaria in the UK each year.¹ Indeed, a recent capture-recapture study by Cathcart and coworkers² shows that these figures are likely to be an under-representation. Worryingly, the proportion of cases attributed to the most fatal *falciparum* species is increasing and has accounted for over 75% of imported malaria in the last 5 years. The relative lack of experience in dealing with malaria and its sequelae in the UK can make treatment difficult. Consequently, prevention in the form of chemoprophylaxis is better than cure.

This case is important for a number of reasons. First, it emphasises the rapidly progressive nature of cerebral malaria, the presentation of which can be vague. Second, it demonstrates that Mumbai is a city in which travellers are at significant risk of malaria, despite the UK HPA describing the risk as extremely low.³ Lastly, it sets a precedent for the management of this disease, in the context of a negative malarial screen.

CASE PRESENTATION

We report a case of a previously well 21-year-old man who presented to the emergency department with acute confusion and vomiting, 1 week after returning from Mumbai, India, where he had been partially compliant with an anti-malarial regimen of chloroquine and proguanil. A collateral history taken from the patient's next of kin did not reveal any previous medical, family or social history of note. On examination, the patient was afebrile and haemodynamically stable, with marked agitation and Glasgow coma scale 9/15. There were no focal neurological signs. Multiple bite

marks were noted on the lower limbs, consistent with mosquito bites.

INVESTIGATIONS

CT of the head was unremarkable and lumbar puncture demonstrated a normal opening cerebrospinal fluid pressure, normal biochemistry and negative bacterial culture. Initial blood tests showed leucocytosis ($18.4 \times 10^9/l$), hyponatraemia (126 mmol/l) and mild hyperbilirubinaemia (20 μ mol/l). Initial malarial antigen and blood films were negative. Blood cultures were negative. Malarial PCR was later reported as negative.

DIFFERENTIAL DIAGNOSIS

After initial assessment, the differential diagnoses included meningitis, encephalitis and cerebral malaria.

TREATMENT

The patient was treated empirically for bacterial meningitis and viral encephalitis with ceftriaxone and acyclovir. Urgent elective intubation and ventilation were conducted and the patient was nursed in an intensive therapy unit setting. On day 3, without showing any signs of recovery, intravenous quinine was commenced to cover for cerebral malaria even though three consecutive thick and thin blood films and malarial antigen had been negative. There was a prompt response such that the patient was extubated on day 4 and stepped down to the general ward on day 5. An oral antimalarial regimen of quinine and doxycycline was then continued for 7 days.

OUTCOME AND FOLLOW-UP

Having completed his course of antimalarial medication, the patient was discharged from hospital on day 12 and resumed all of his premorbid activities within 2 weeks.

Eighteen months on, the patient remains fit and well, with no physical or psychological complications of his illness.

DISCUSSION

There are no cases in the literature describing cerebral malaria as the most likely diagnosis in an unwell returning traveller with negative blood films, serology and PCR.

Did the patient actually have cerebral malaria? There are a number of arguments which would support this diagnosis despite negative blood films, serology and PCR. False negative malarial tests can occur if the patient has taken partially effective prophylaxis.⁴ Clinical features including rigors and unexplained hyponatraemia⁵ are consistent with *falciparum* malaria. Significantly, the patient made a rapid recovery following intravenous quinine treatment. Finally, the consultant microbiologist, based on many years of experience working in endemic malarial areas, felt that the presentation was in keeping with that of cerebral malaria.

Mumbai, in the state of Maharashtra, is an increasingly popular holiday destination among British travellers. The National Travel Health Network and Centre describes the risk of malaria in Mumbai as being 'very low' and suggests that chemoprophylaxis is not required.³ This advice is supported by the HPA Advisory Committee on Malaria Prevention (ACMP) and is given to travellers. However, there is a growing incidence of malaria in Maharashtra with 200 000 positive cases between 2009 and 2010, resulting in over 320 deaths.⁶ Media reports suggest that the majority of these cases are occurring in Mumbai.⁷ Limited figures from the Municipal Cooperation for Greater Mumbai showed that there were 20 000 confirmed malaria cases and 40 deaths in Mumbai between January and August 2010 alone,⁸ confirming its endemic nature. Given that local incidence correlates with the risk for travellers,⁹ these figures clearly suggest increased risk for those returning from this city.

Cerebral malaria is potentially fatal and is rapidly progressive. Current malaria guidelines¹⁰ advise that in the absence of a positive diagnosis, malarial treatment should not be initiated unless expert guidance has recommended it. This case has shown that it is possible to have cerebral malaria with false negative blood films and serology, especially in the context of partial prophylaxis. Although, nested PCR is highly sensitive, a recent report shows that up to two in every hundred cases are not detected by this method.¹¹ Therefore, it may be

advisable to treat those cases with a high clinical suspicion immediately, without waiting for a positive malarial screen, especially when the most sensitive tests such as malarial PCR can take several days to obtain from a reference laboratory.

Learning points

- ▶ Contrary to advice from the UK HPA, chemoprophylaxis against malaria should strongly be considered for travellers to Mumbai.
- ▶ Effective chemoprophylaxis depends on complete compliance with an efficacious antimalarial regimen.
- ▶ Cerebral malaria, a neurological manifestation of the disease, progresses rapidly and may be fatal without prompt treatment.

Competing interests None.

Patient consent Obtained.

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