Malaria in the Australian refugee population

BACKGROUND

Malaria is a serious health problem in many of the countries from which refugees come to Australia. Anopheles mosquitoes capable of transmitting malaria are present in the far north of Australia and in these areas, the detection and appropriate treatment of malaria is vital, not only for the health of the individuals and their families, but as a significant public health issue.

OBJECTIVE

This article outlines screening, assessment and management of malaria in the refugee population.

DISCUSSION

Most malaria does not follow the classic pattern of periodic fever with paroxysms of cold, hot and sweating stages. There should be a high index of suspicion for anyone from an endemic area presenting with fever, vomiting, diarrhoea, headache and/or muscle pain, even if they have been tested or treated for malaria. What is most likely to be a nonspecific viral illness in someone who has never left Australia might be an urgent life threatening illness in a recently arrived refugee. Therefore all refugees from endemic areas, whether symptomatic or not, should be screened as soon as possible after arrival. Appropriate treatment is expensive and should be monitored by a hospital, but can be done as an outpatient in some individuals. Follow up with thick and thin films as a 'test of cure' should be done at 28 days.

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Case study

Miriam, 2 years of age, came to Australia with her 17 year old Sudanese mother from a Ugandan refugee camp. Five days before leaving Africa she was screened for malaria with a rapid diagnostic test (RDT). This was reported as negative and so she was not given antimalarials before departure.

Three days after arrival, Miriam's mother went to a nearby pharmacy to buy some paracetamol as Miriam was febrile with vomiting and diarrhoea. The pharmacist called an ambulance as the child appeared flat and toxic. She was admitted to an intensive care unit where she had the following blood tests:

- haemoglobin 52 gm/L (101–131)
- platelets 62 x 10^9/L (150–450)
- C-reactive protein (CRP) 214 mg/L (<6)
- potassium 2.1 mmol/L (3.2–4.5)
- bilirubin 47 µmol/L (<20), and
- positive thick and thin films for malaria.

Films showed a parasite density of 24% (ie. 24% of all her red blood cells contained parasites) and a mixed *Plasmodium falciparum* and *P. vivax* infection. A G6PD screening test was normal.

Miriam was treated with a blood transfusion as well as intravenous quinine and oral clindamycin for 1 week, followed by a 2 week course of oral primaquine. On follow up 1 month later her: haemoglobin was 120, platelets 254, potassium 4.6, bilirubin 9, and no malaria parasites were detected on thick or thin film.

Malaria was eradicated from Australia in 1981,[1] although there has since been rare locally acquired cases in North Queensland.[2] The disease remains an important cause of death and illness in children and adults in tropical countries. Forty percent of the world's population is at risk of malaria and there are 300–500 million clinical cases throughout the world per year.[3] The worldwide annual death rate of almost 3 million people has risen in recent years, probably due to the increasing resistance to medication, and 89% of these deaths occur in Africa.[3–5] Of the approximately 13 000 refugees who arrive in Australia each year, about 70% come from areas where malaria is a major health problem. For example, in Sudan and Uganda, the countries of origin or transit of the majority of recently arrived refugees, malaria is responsible for about 30% of all outpatient attendances and about 15% of all deaths.[3,6] Malaria also occurs in southeast Asia and Pakistan, the source countries for many of the non-African refugees who come to Australia.

There are four species of Plasmodium that cause human malaria. *P. falciparum* is the cause of nearly all malaria deaths and behaves differently in many other respects to *P. vivax, P. malariae* and *P. ovale*.

Transmission

Malaria is usually transmitted by the Anopheline mosquito but can also be transferred directly by blood transfusion, transplacentally or by accidental inoculation. Anopheles mosquitoes are still present above latitude 17–19° S in the far north of Australia. In these malaria receptive areas, the detection and appropriate treatment of malaria is of the utmost importance, not only for the health of the individuals and their families, but as a significant public health issue.[1] Patients with malaria in these areas should be treated in screened or air conditioned accommodation or preferably admitted to hospital.[4] There were 47 notifications of malaria in the Northern Territory in 2005 and 66 in 2006, and the Territory's treatment protocols reflect the additional need to be aware of the presence of gametocytes.[7] Gametocytes are the 'sexual' phase of the parasite that can persist in the circulation for several weeks and which are infective to the mosquito, and hence cause further infection to other humans.[8] Malaria is a notifiable disease in all Australian states and territories.[9]

Testing for malaria

Malaria rapid diagnostic tests (RDT), sometimes called 'dipsticks', detect specific antigens produced by the malaria parasites present in the blood. Some RDT detect only *P. falciparum*, while others also detect nonfalciparum malaria (*P. vivax, P. malariae, P. ovale*).[10] They are generally highly sensitive and specific for *P. falciparum* but unreliable for other species and should not be used for nonfalciparum species. These tests can be done quickly by most laboratories in Australia using an EDTA sample (full blood count [FBC] collection tube) or finger prick sample.[11] If the RDT is positive, it should be followed up by a thick and thin blood film (also done from an EDTA sample), which is still the 'gold standard'. A thick film to detect small numbers of parasites and a thin film to identify the species should be done regardless of other tests performed. An RDT should not be used for follow up as antigen may still be present for several weeks after the parasites have died. Follow up should always be done with thick and thin films. Some laboratories may do a polymerase chain reaction (PCR) to detect Plasmodium DNA, although this is neither validated nor commercially available at present.

Pre-arrival assessment of refugees

The majority of refugees who arrive in Australia from Africa have a 'fitness to fly' assessment that includes a RDT.[10] If the test is positive, patients are treated with a 3 day course of artemether/lumefantrine before they leave the country. However, the sensitivity of the test is only 95–98%[10] and so will miss 2–5% of those with malaria, those with early infection, a low parasite count, or those who contract infection between having the health assessment and leaving the country (sometimes up to a week). The 3 day treatment is not supervised and often not actually taken. This is consistent with figures from refugee health services around Australia confirming an incidence of malaria of 8% in Western Australia,[12] 5% in South Australia,[13] 10% in Hobart,[4] and 16% in Newcastle.[14] These figures were collected before the introduction of predeparture screening and treatment for malaria. Since this policy change, the incidence is less, but a significant number of cases still occur and we should not be lulled into a false sense of security by the existence of the predeparture screening.

Clinical presentations

Most infections are not as dramatic as Miriam's and are asymptomatic or have minimal symptoms.[15] Older patients have usually developed partial immunity to malaria and may not be symptomatic on arrival. However, as their immunity wanes, they can potentially become ill, sometimes up to several years after arrival in Australia, if the parasite is not screened for and treated appropriately.[16] Children are the most vulnerable for sudden and severe infection as they have not built up immunity. Other high risk groups include pregnant women and splenectomised adults.

Most malaria seen in refugees to Australia does not follow the traditional pattern of periodic fever with paroxysms of cold, hot and sweating stages. General practitioners should have a high index of suspicion of anyone from an endemic area with fever, vomiting, diarrhoea, headache and/or muscle pain. What is most likely to be a nonspecific viral illness in someone who has never left Australia might be an urgent life threatening illness in a recently arrived refugee. Clinical examination might reveal other signs of malaria such as splenomegaly, confusion, drowsiness, hypotension, oliguria or jaundice. Children and pregnant women in particular are at risk of becoming very unwell within a very short space of time. Altered consciousness in those with malaria might be caused by cerebral malaria, hypoglycaemia, acidosis or seizures.

Treatment

Response to treatment can be dramatic, particularly with the artemesinin derivatives. Treatment options will be influenced by:

- symptoms
- species of infection
- pregnancy status
- age of patient, and
- finances.

Detailed instructions should be given with an interpreter present about dosage regimens, side effects, follow up arrangements and the symptoms and signs of treatment failure.

Falciparum malaria

Falciparum malaria is resistant to chloroquine and requires more complex treatment than nonfalciparum malaria. The newer artemesinin based agents are recommended as combination therapy for uncomplicated falciparum malaria as they:

- have no significant drug resistance
- are rapidly effective, and
- are active against the gametocytes not killed by other antimalarials.[11,17]

The only artemesin based combination therapy currently available in Australia is artemether/lumefantrine (Riamet). The dosing schedule can be simplified to a twice daily dosing schedule for 3 days (total six doses). It is important that the medication be taken with fatty food (although a biscuit or a glass of milk may be enough).

Atovaquone/proguanil (Malarone) and mefloquine (Larium) have shorter treatment schedules, however there is occasional resistance to these drugs. Furthermore, mefloquine cannot be given to those with a history of psychiatric illness or epilepsy, and can cause vomiting in 5–10%. For this reason mefloquine should not be used in recently arrived refugees because of a high incidence of psychological morbidity such as post-traumatic stress disorder. Other medications such as quinine sulphate and doxycycline are rarely used because of increased side effects and longer dosing periods.[11]

Current recommendations for Australia suggest that all patients with falciparum malaria be admitted to hospital.[11] However, most regions in Australia have local guidelines based on outpatient treatment for refugees who meet the following criteria:

- asymptomatic or minimally symptomatic infection (not vomiting)
- not pregnant
- weighing >10 kg, and/or >12 months of age, and
- parasitaemia of <1%.[7,15]

The treatment of choice for these patients is artemether/lumefantrine, which is expensive (~$80 per course for a 70 kg adult) and should be provided by a hospital pharmacy or funded community health centre. The cost of atovaquone/proguanil is ~$56 and mefloquine is ~$21 per course.[15] Outpatient treatment of falciparum malaria should be done in close association with a hospital, not only for cost reasons, but so that expertise and facilities are available if urgently required.

Children weighing <10 kg or <12 months of age, pregnant women, those with a parasitaemia >1%, and symptomatic patients should be urgently admitted to hospital and managed as inpatients, preferably by an infectious diseases physician or paediatrician. Severely ill patients or those unable to tolerate oral medications will be treated with intravenous artesunate. Drugs considered safe in pregnant women and children include quinine sulphate, chloroquine, proguanil and clindamycin. The combination of quinine and clindamycin is generally used for pregnant women or for children weighing <10–20 kg. Artemether/lumefantrine only has marketing approval in Australia for those over 12 years of age. However, it is safe to use for children with a weight down to 20 kg (off label). Dosing is given in the latest edition of *Therapeutic Guidelines: antibiotic*.[18]

Nonfalciparum malaria

Patients with nonfalciparum malaria are usually treated as outpatients with 3 days of oral chloroquine; although chloroquine resistance has developed in parts of Indonesia, New Guinea and East Timor.[11] For patients with mixed infections of falciparum and nonfalciparum malaria, any of the treatments used for *P. falciparum* will also kill the active (asexual) phase of *P. vivax, P. ovale* and *P. malariae*.

In patients with P. vivax and *P. ovale*, hypnozoites (a dormant phase of the parasite in the liver) can cause relapses by reactivating for at least 5 years if only chloroquine is given.[8] Primaquine needs to be given for 14 days to eradicate the hypnozoites (it also kills the gametocytes of all species, although this effect is only important in malaria receptive areas).[11] The eradication of hypnozoites to prevent future relapses is sometimes called a 'radical cure'. Acute haemolysis can occur in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency if given primaquine, therefore this should be ruled out before using primaquine. Primaquine is also expensive ($60 for a 14 day course) and is best accessed through a hospital pharmacy.

Follow up

If a patient has symptoms suspicious of malaria but negative blood tests, the tests should be repeated. Patients treated on an outpatient basis should be reviewed daily for 3 days to ensure adherence and detect deterioration. If they are well and have taken all medications, they do not need repeat blood tests until 28 days. If there was a decreased FBC initially or any deterioration, then the FBC and malaria films should be repeated at 7 days. All patients treated should have a 'test of cure' with thick and thin films 28 days after commencing therapy as recrudescence (parasite numbers decreased but not completely eradicated) or relapse may occur. If treatment has been successful there should be no detectable parasites on a day 28 blood film. Rapid diagnostic tests may remain positive for a month after treatment and are not useful for follow up. Treatment failure is rare and may be due to drug resistance, the patient not completing the course of treatment, or poor gastrointestinal absorption, especially with atovaquone/proguanil or artemether/lumefantrine.

Conclusion

Screening and appropriate treatment of all refugees who have come from countries where malaria is endemic is essential as soon as possible after arrival in Australia. Those with falciparum malaria, even if asymptomatic, can progress rapidly to become severely ill or have persistent parasitaemia which can cause anaemia or other symptoms many years later.[15] The public health fear of the reintroduction of malaria into Australia is another reason to be vigilant.[1]

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References

1. Bryan J, Foley D, and Sutherst R, Malaria transmission and climate change in Australia. Med J Aust 1996;164:345–7.
2. Brookes DL, Ritchie SA, van den Hurk AF, Fielding JR, Loewenthal MR. Plasmodium vivax malaria acquired in far north Queensland. Med J Aust 1997;166:82–3.
3. World Health Organisation. World Malaria Report 2005. Available at http://rbm.who.int/wmr2005/ [Accessed May 2007].
4. Zweck N, et al. Guidelines for screening and management of infectious diseases in refugees from sub–Saharan Africa based on a single initial blood sample after arrival in the Northern Territory. The Northern Territory Disease Control Bulletin 2004;11:13–7.
5. Breman J, Alilio M, Mills A. Conquering the intolerable burden of malaria: what's new, what's needed: a summary. Am J Trop Med Hyg 2004;71(Suppl 2):1–15.
6. Website of Kevin Andrews MP Minister for Immigration and Citizenship. Media Centre: Minister Commends Work with African Refugees. 2005. Available at www.minister.immi.gov.au/cam/media/media-releases/2005/jc05056.htm [Accessed May 2007].
7. Centre for Disease Control Northern Territory. The Northern Territory Disease Control Bulletin, 2007. Available at www.nt.gov.au/health/docs/cdc_bulletin_mar_2007.pdf [Accessed May 2007].
8. Gill G, Beeching N. Lecture notes on tropical medicine. 5th edn. USA: Blackwell Publishing, 2004.
9. Charles DM, Hart J, Davix WA, Sullivan E, Dowse GK, Davis TM. Notifications of imported malaria in Western Australia, 1990–2001: incidence, associated factors and chemoprophylaxis. Med J Aust 2005;182:164–7.
10. World Health Organisation. Making rapid diagnosis work. 2005. Available at www.wpro.who.int/sites/rdt/home.htm [Accessed May 2007].
11. Therapeutic Guidelines. Therapeutic guidelines: antibiotic. Ver. 12. Melbourne, Victoria: Therapeutic Guidelines Limited, 2003.
12. Martin J, Mak D. Changing faces: a review of infectious disease screening of refugees by the Migrant Health Unit, Western Australia in 2003 and 2004. Med J Aust 2006;185:607–10.
13. Johnson D. Rates of infectious diseases and nutritional deficiencies in newly arrived African refugees presenting to the Migrant Health Service, South Australia in 2005. Adelaide: Central Northern Adelaide Health Service, 2007.
14. Davis J, Webber M. A prospective audit of infectious diseases in 222 newly arrived African refugees (poster). RACP Congress, Cairns 2006.
15. Chih D, Heath C, Murray R. Outpatient treatment of malaria in recently arrived African migrants. Med J Aust 2006;185:598–601.
16. Howden BP, Vaddadi G, Manitta J, Grayson ML. Chronic falciparum malaria causing massive splenomegaly 9 years after leaving an endemic area. Med J Aust 2005;182:186–8.
17. World Health Organisation. Guidelines for the treatment of malaria. 2006 Available at www.who.int/malaria/docs/TreatmentGuidelines2006.pdf [Accessed May 2007].
18. Therapeutic Guidelines. Therapeutic guidelines: antibiotic. Ver. 13. Melbourne, Victoria: Therapeutic Guidelines Limited, 2006; p. 145.

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