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Cover photo: The Australian Institute of Tropical Medicine in 1916 (photo courtesy of James Cook University)

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EDITORIAL

CHANGING OF THE EDITORIAL GUARD!

It is with great pleasure to have the opportunity to introduce and formally welcome Associate Professor John Frean (see image at left) as the new Editor-in-Chief of the Annals of the ACTM. John Frean is in the National Institute for Communicable Diseases, and Associate Professor, University of the Witwatersrand, Johannesburg, South Africa. John Frean has played a number of key roles in the College, including being a member of the ACTM College Council. In his new role, he also chairs the Publication Committee of the College, which has the Annals as its flagship publication, now in its 14th Volume.

Associate Professor John Frean takes over the reins of the Annals from Professor Derek Smith (see image at right) from the University of Newcastle, Australia. Derek Smith was appointed Editor-in-Chief of the Annals of the ACTM in 2008. Under Derek’s stewardship, two issues of the Annals were published each year in January and June/July commencing with Volume 9 (2008) through to Volume 13 (2012). Abstracts from various ACTM symposia and the Townsville Hospital Week were also included in one of the issues, particularly in more recent years. Derek Smith also produced the first special issue of the Annals and also a consolidated index in Volume 10 (Issue 1, 2009) to celebrate 15 years of the Annals (1995-2009). With Associate Professor John Frean taking over the helm as Editor-in-Chief, the College conferred the title of Editor-in-Chief Emeritus for his dedicated service to the Annals over a period of 5 years. Derek Smith continues to hold senior appointments on editorial boards of several journals, particularly in the field of occupational and environmental health and safety.

Professor Derek Smith is the second Editor-in-Chief to be conferred the title of Editor-in-Chief Emeritus. Derek succeeded Emeritus Professor John Goldsmid, who had transitioned the Annals from an irregularly published monograph series to a peer-reviewed journal. John Goldsmid also ensured that the Annals was published in full colour publication by the end of 2007, which encouraged the use of colour images. Following his retirement, Emeritus Professor John Goldsmid was confirmed as the inaugural Editor-in-Chief Emeritus in 2007, but continued to make contributions to various College publications. A College award, the John Goldsmid Award, has been dedicated to John’s contributions to the journal and is awarded to the best paper published in the Annals each year.

Professor Peter A. Leggat, AM
Executive Editor, Annals of the ACTM, and Head, School of Public Health, Tropical Medicine and Rehabilitation Sciences, James Cook University, Townsville, Queensland, Australia.

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The physical health impacts of tropical cyclones

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ABSTRACT

Tropical cyclones, also known as typhoons and hurricanes, are low-pressure weather systems characterised by extremely fast rotational winds. They disproportionately affect developing countries and have the potential to seriously disrupt basic societal functions. Like other natural disasters, cyclones also impact on health. This literature review considers the epidemiology of these events in terms of trauma, communicable disease and non-communicable disease.

Trauma is a significant cause of morbidity and mortality, although mechanisms vary between events. Both drowning and building collapse can lead to large numbers of fatalities. Minor injuries represent the primary cause of morbidity in the post-impact phase but carbon monoxide poisoning from inappropriate generator use is emerging as an important risk in both adult and paediatric patients. While communicable disease outbreaks are uncommon in developed settings, gastroenteritis, vector-borne disease and acute respiratory illness pose particular problems in developing communities. Non-communicable disease constitutes a considerable proportion of healthcare attendances following cyclones, and exacerbations as well as treatment disruptions of chronic diseases are increasingly being recognised as a cause of cyclone-related morbidity and mortality.

Although Australia has well-developed public health infrastructure, major cyclones still have the potential to cause significant human suffering. This review will assist tropical communities in planning for these severe weather events. Implicit in its findings is the importance of injury prevention strategies, communicable disease surveillance and provision for managing chronic illnesses.

Keywords: cyclones, hurricanes, typhoons, trauma, disease, communicable, non-communicable


Background

Tropical cyclones, also known as typhoons and hurricanes, are low-pressure weather systems that develop over warm ocean waters. They are characterised by extremely fast rotational winds that are generally in excess of 100 km/h.1 Approximately 119 million people are affected by an average of 80-90 individual cyclone systems each year, making them one of the most common natural disasters worldwide.4

As cyclogenesis requires warm ocean waters, cyclones typically occur between the latitudes of 30 degrees north and 30 degrees south. Regions within 500 kilometres of the equator are spared because cyclonic winds rotate in different directions in the two hemispheres. As a consequence of this distribution, cyclones predominantly affect developing communities. Of 84 nations with a history of recurrent exposure to cyclonic events, only a small minority (including Australia, New Zealand, Japan, and the United States of America) are high-income countries.2

Non-communicable disease constitutes a considerable proportion of healthcare attendances following cyclones, and exacerbations as well as treatment disruptions of chronic diseases are increasingly being recognised as a cause of cyclone-related morbidity and mortality.

Although Australia has well-developed public health infrastructure, major cyclones still have the potential to cause significant human suffering. This review will assist tropical communities in planning for these severe weather events. Implicit in its findings is the importance of injury prevention strategies, communicable disease surveillance and provision for managing chronic illnesses.

Keywords: cyclones, hurricanes, typhoons, trauma, disease, communicable, non-communicable


The human and environmental impacts of cyclone activity are the result of strong winds, heavy rainfall and storm surge, which often lead to landslides and flooding.1,3,6 In Australia, severity is rated using a five-category system based on wind velocity.7 Category four and five cyclones are expected to result in significant structural damage. Different rating systems are used internationally (such as the Saffir/Simpson Scale in North America) and vary principally according to how wind speed is measured (Figure 1).7,8

Cyclones have the potential to cause significant morbidity and mortality. They are estimated to have contributed to 1.9 million deaths in the last two centuries, and approximately 250,000 in the period 1980-2000.2,9 Their effects on health can be both direct (as a result of severe weather forces) and indirect (as a result of infrastructure damage, environmental devastation, population displacement and economic hardship). Historically, developing nations of the Asia-Pacific region have experienced the greatest absolute and proportionate mortality from tropical cyclones and other natural disasters.2

In Australia, cyclones in the last 150 years are estimated to have caused approximately 2,000 deaths, with a financial cost in excess of 6 trillion dollars.10 Over half of these deaths were caused by just five events occurring in a 50-year period from the late 1800s to the early 1900s (Figure 2). Cyclone Mahina (Cooktown, 1899) led to over 400 fatalities, representing the sixth highest death toll from any disaster in Australia since 1850.10 In more recent memory, Cyclone Tracy (Darwin, 1974) resulted in 71 deaths and approximately 650 injuries.11

Although cyclone-related morbidity and mortality in the last two decades has been relatively small,10 recent events have illustrated the ongoing potential for harm. Cyclone Yasi, a category five system, brought winds in excess of 285 km/h when it crossed the Queensland coast near Mission Beach in February 2011.12 Although Queensland escaped without a major impact on health, the cyclone still led to at least one death13 and a record number of attendances to Townsville Hospital Emergency Department (personal communication, P Aitken). The event also prompted the evacuation of both of Cairns’ hospitals (public and private), necessitating the transportation of over 350 patients to Brisbane (approximately 1700 km south).14,15

The threat posed by tropical cyclones is unlikely to abate. As a consequence of global warming and rising sea temperatures, the frequency and intensity of extreme weather events is expected to increase.16-18 Consistent with this, upward trends have been observed in the estimated lifetime-maximum wind speeds of the very strongest tropical cyclones (above the 99th percentile) over each ocean basin.19

Given the ongoing threat of tropical cyclones in northern Australia and the Asia-Pacific,12,7 it is appropriate to consider their potential impact on human health. While severe cyclone activity is known to have psychological

Cyclone Yasi crossing the Queensland coast, February 2011

Satellite image originally processed by the Bureau of Meteorology from the geostationary meteorological satellite MTSAT-2 operated by the Japan Meteorological Agency.
The consequences for mental health are beyond the scope of this paper. This literature review builds on a comprehensive analysis by Shultz et al published in 2005 and includes a specific focus on epidemiological data from recent events. It has been designed to capture the significant amount of literature produced in the wake of Hurricane Katrina (United States of America, 2005).

**Methods**

PubMed was keyword and MeSH term searched for ‘health’ with each of ‘cyclone’, ‘hurricane’ and ‘typhoon’. Results were limited to human data, English language and the last seven years (April 2005 – March 2012), as the 2005 review by Shultz et al was assumed to have included relevant peer-reviewed literature up until its publication date.

This broad search strategy identified 813 articles, most of which (62%) did not directly address the review question: 180 were only concerned with mental health, 246 were unrelated to health impacts or cyclones and 82 were editorials or opinion pieces. The abstracts of the remaining papers were reviewed and a majority were found to be qualitative in nature. Full text was obtained for the relevant articles and bibliographies of key references were scanned for applicable articles, book chapters and grey literature (Figure 3).

The 105 papers identified using this strategy were considered alongside the primary references quoted by Shultz et al (where accessible). They identified 151 relevant studies and reports, including those related to mental health.

The results of this search confirm that the volume of literature related to tropical cyclones has grown significantly since 2005. In keeping with historical experience, most of the recent papers are retrospective descriptive studies. In the discussion below, prominence has been given to more recent data. Where studies referred to the same data set, only one has been referenced. Findings are presented in the categories of trauma, communicable disease and non-communicable disease.

**Discussion**

**Trauma**

Trauma constitutes the majority of cyclone-related morbidity, and may occur pre-impact, at impact or post-impact. Pre-impact injury tends to be the result of preparation efforts, including reinforcing buildings, preparing generators and cleaning outdoor areas. Impact-related trauma relates to the direct impacts of destructive winds, heavy rain and storm surge, as well as the flooding and landslides that may result. Potentially harmful consequences of these forces include structural collapse, wind-blown debris, falling trees and downed power-lines. Post-impact trauma is largely a consequence of clean-up related activities as well as the loss of normal public services.
can be associated with utilities damage and the subsequent requirements for temporary measures (including stored water and power generators).\textsuperscript{1,6}

Morbidity and mortality related to each of these stages varies according to the degree of development. Deaths tend to be highest in the impact phase in developed settings, whereas developing communities tend to be affected to a greater extent in the wake of the storm front.\textsuperscript{1,6,20-22}

Data from Hurricane Katrina found that certain groups are at higher risk of trauma (and other health impacts) following cyclones. These include elderly, homeless, poor, unemployed and non-English speaking citizens as well as certain racial and ethnic groups.\textsuperscript{23-28} A recent study has identified that many of these groups are less likely to receive emergency broadcasts and evacuation orders, placing them at higher risk of trauma.\textsuperscript{29}

**Drowning**

Drowning has traditionally been the major cause of cyclone-related deaths, and typically results from storm surge and flooding in the immediate wake of the event.\textsuperscript{31} In recent times, the risk of drowning has been mitigated by the introduction of advanced warning, evacuation and shelter systems.\textsuperscript{1,15,32}

Despite these developments, drowning still constitutes a significant proportion of cyclone-related mortality. In the United States of America (US), 40% of the 971 deaths directly attributed to Hurricane Katrina (2005) were thought to result from drowning.\textsuperscript{33} An empirical relationship between the depth of flooding water and mortality has been described.\textsuperscript{30} Following Hurricane Ike (2008), drowning constituted only 7% of overall deaths but was the most frequent cause of those directly related to the storm.\textsuperscript{30} Similar rates have been seen following other US events.\textsuperscript{24}

Although limited data is available for developing settings, there are reports of drowning causing large numbers of fatalities following cyclones in Bangladesh, Mexico and the Philippines.\textsuperscript{1,30} On the contrary, however, Typhoon Rananim in China (2004) resulted in no deaths due to drowning but a significant number as a result of building collapse.\textsuperscript{36}

**Minor injuries**

Minor injuries have been observed to constitute over 70% of presentations following tropical cyclones in developed countries.\textsuperscript{1,6,21,34} Most emergency department visits occur when weather conditions have stabilised.\textsuperscript{22,32}

A 1993 review of cyclone-related injuries found significant variation in the patterns between events, as well inconsistency in the classification and coding of injuries.\textsuperscript{4} In recent events, a wide spectrum of injuries has again been observed, including puncture wounds, lacerations, abrasions, contusions, sprains and fractures.\textsuperscript{24} Following Hurricane Katrina, the commonest presentations were for lacerations, blunt trauma and puncture wounds\textsuperscript{29} and the most frequently reported mechanisms were falls and cuts.\textsuperscript{34} In other settings (eg, Cyclone Gonu in Oman, 2007) orthopaedic injuries and lacerations have predominated.\textsuperscript{39}

Although lower limb injuries were common among Hurricane Katrina evacuees in the Houston Astrodome/Reliant Park Complex site,\textsuperscript{40} this has not been the experience with other US events.\textsuperscript{34} Following Hurricane Andrew (1992), the most common body parts affected in non-fatal injuries were the upper extremities, including the fingers, hands, and arms.\textsuperscript{24,41} A recent review of all cyclone-related injuries presenting to emergency departments in Hong Kong over a six-year period supports this observation. In that study, the head (33.5%) and upper limbs (32.5%) were most often involved, with falls the commonest mechanism of injury (42.6%).\textsuperscript{21,40} Together, these data confirm that injury patterns following tropical cyclones are highly variable.

A recent study from the US has found that older citizens who were displaced from their homes had an increased fracture risk extending to 12 months following Hurricane Katrina.\textsuperscript{42} This persisted after controlling for other risk factors. Rates of accelerator-related burn injuries have also been noted to increase following hurricane seasons in the US, which is possibly related to the burning of cyclone-generated debris.\textsuperscript{43}

**Major injuries**

Life-threatening injuries may also result from tropical cyclones and tend to occur during the impact phase. For instance, following Cyclone Ike in the US, 47 (64%) of all deaths resulted from injuries, compared with 23 (31%) from illnesses. Nine percent of overall deaths were caused by falling trees.\textsuperscript{44} Following Katrina, 25% of deaths were attributed to injury and trauma, and older people were disproportionately affected.\textsuperscript{29} Motor vehicle accidents, chainsaw injuries, electrocutions and blunt trauma in the post-impact phase have also been reported.\textsuperscript{1,5,29,44}

In a developing context, collapsed buildings were the most frequent cause of death following Typhoon Rananim in China (2004). Flying debris, collapsing buildings and motor vehicle collisions together caused 46% of all significant injuries. In that event, staying outdoors and not receiving (or ignoring) the typhoon alert were found to be statistically significant risk factors for serious injury.\textsuperscript{36}

**Carbon monoxide poisoning**

Cyclone-related carbon monoxide poisoning was first described more than twenty years ago,\textsuperscript{45} but is increasingly reported as a major cause of morbidity.\textsuperscript{33,37,46-51} A majority of cases relate to the use of generators following power outages.

Following Cyclone Ike, thirteen deaths were attributed to CO poisoning and at least fifteen individuals required treatment with hyperbaric therapy.\textsuperscript{33,46} It was estimated that 82-87% of exposures were the result of improper generator use, and children were disproportionately affected.\textsuperscript{38,47} At one hospital, 54% of 37 individuals presenting with CO poisoning were under the age of 18, and 75% of these resulted from generator-powered television or video-game use.\textsuperscript{44} In Australia, the one death attributed to Cyclone Yasi (2011) was reportedly the result of asphyxiation from inappropriate generator use.\textsuperscript{13}

**Communicable diseases**

Infectious disease outbreaks are not a major cause of morbidity following tropical cyclones.\textsuperscript{1,12,54} As with other disasters, the risk of outbreaks is associated with the size, health status and living conditions of the affected population. Crowding, inadequate water and sanitation, as well as poor access to health services, increase the risk of disease transmission.\textsuperscript{52,53,55,56} For these reasons, outbreaks tend to occur in developing countries far more frequently than they do in developed environments and almost always manifest in the post-impact phase.\textsuperscript{1,55,56}

**Diarrhoeal disease**

Diarrhoeal disease is the commonest infectious consequence of cyclone activity and is frequently the only reported communicable challenge in developed countries.\textsuperscript{1,52} A variety of causative pathogens have been reported, which differ between settings based on local endemicity.\textsuperscript{56}

Outbreaks of gastroenteritis have been documented following some cyclones in the US,\textsuperscript{28,40,42} Most recently, surveillance systems detected a norovirus outbreak in a large evacuation centre in the aftermath of Hurricane Katrina.\textsuperscript{37-39} At a temporary medical facility erected at the Reliant Park Complex site, 1,173 patients were treated for gastroenteritis, representing 17% of all clinic visits and 4% of all patients who resided there for nine days.\textsuperscript{50} On the peak days, 40% of all paediatric presentations were for diarrhoea.\textsuperscript{37} While not all disease shelters experienced outbreaks, 61 sporadic cases of Salmonella spp. and toxigenic and non-toxigenic Vibrio cholerae were also reported.\textsuperscript{40}

Diarrhoeal disease outbreaks have been reported with greater frequency in developing countries.\textsuperscript{52,53,55,56} Recent examples include Cyclone Aila, in West Bengal, India (2008),\textsuperscript{56} hurricanes Gustav and Ike in Cuba (2008)\textsuperscript{63} and Cyclone Nargis in Burma (2008).\textsuperscript{50} In the latter, recently published data describes a four-fold increase in severe watery diarrhoea (suspected cholera) in the immediate wake of the event. The overall incidence of diarrhoea increased from 571 per 100,000 persons per year in 2007 to 799 in the post-Nargis months of 2008. Rates of dysentery also peaked sharply but had no impact on mortality.\textsuperscript{37} Following Aila, increases in diarrhoeal rates of
between 30 and 60% were seen in affected districts. *Vibrio cholerae* (54%) was the commonest agent, followed by *Shigella* spp. (5%). In Cuba, at least a 10% increase in gastroenteritis was seen following cyclones Gustav and Ike. More recently, reports have emerged of increased diarrhoeal disease following typhoon events in the Philippines.

**Acute respiratory infections**

As with other natural disasters and situations involving displaced persons and overcrowded shelters, cyclones carry an increased risk of acute respiratory infection. Like diarrhoeal illness, developing settings are disproportionately affected.

The most recently published data describes a peak in the incidence of acute respiratory infections (ARI) following Cyclone Nargis. A rate of 4.042 per 100,000 persons per year among children under 5 increased to 7.280 in 2008 following the event; it then fell back to 4.662 in 2009. More profound increases were seen in Nicaragua in the 30 days following Hurricane Mitch (1998), where a four-fold rise in incidence was reported. There are few reports of epidemic ARI following cyclones in developed settings. While some data suggested an increased number of adult presentations with acute respiratory infection in the wake of Hurricane Katrina, the trend was attributed to multiple cases among a single National Guard battalion. There was, however, a significant spike in the number of cases of ARI among children and adolescents, which was thought to be associated with increased environmental exposures. Firefighters exposed to floodwater reported increased rates of upper respiratory tract infection symptoms.

**Wound infections**

Despite the theoretical risk of wound infections following cyclonic activity, there is little published data to support this. This may reflect reporting bias. Following Hurricane Katrina, primary care providers noted a large number of wound infections on the lower limbs, but the severity has not been quantified. After Hurricane Ivan hit Grenada in 2004, there was an increase in the number of patients admitted to surgical facilities as a result of wound complications and diabetic foot infections.

A single Centers for Disease Control and Prevention report describes 18 cases of *Vibrio* spp.-infected wounds following Hurricane Katrina. Most patients had associated co-morbidities, and many had been wading in flood-waters. Five of these individuals subsequently died. In the wake of the same event, one hospital receiving evacuees identified a link between the presence of a wound and colonisation with multi-drug resistant organisms, but the nature of the association remains unclear.

**Sexually transmitted infections**

A small number of reports from the US suggest that the incidence of sexually transmitted infections may increase following cyclones. This has not been reported in developing regions affected by cyclones, but may reflect the integrity of surveillance systems. Following Katrina, the prevalence of gonorrhoea in high school students increased from 2.5% (8/346) to 5.1% (17/333). Although of weak statistical significance, there was an independent positive trend toward testing positive for gonorrhoea after the hurricane. The exact reason for this is not yet understood, and the results may represent sampling error.

There is also emerging data from the US about adverse impacts on human immunodeficiency virus (HIV). One study has reported a link between Katrina-associated post-traumatic stress disorder (PTSD) and viral replication. Those with PTSD were more likely than those without PTSD to have detectable plasma viral loads and CD4 cell counts <200/mm³ two years post-disaster. In addition, they were more likely to have had anti-retroviral interruptions as a consequence of the event. Robinson et al have also recently suggested that residential displacement might impact on CD4 counts. These effects are unlikely to be cyclone specific.

**Vector-borne diseases**

Cyclones have the potential to impact on the transmission of vector-borne diseases by changing vector distribution and breeding sites. As with other communicable diseases, the subsequent risk of outbreaks is compounded by crowding, loss of shelter, weakened public health systems and the interruptions of ongoing control programs. Outbreaks can only occur if the disease is endemic in the region prior to the event.

While increases in vector population following cyclones have been documented (examples include Belize post-Alma in 2008 and Mexico post-Isidore in 2002), the extent to which this has translated to disease is variable. While cases of malaria have peaked sharply in some settings, they have been seen to decline in others. Recently-published data describes an increase in malaria cases following Cyclone Nargis, but it is uncertain if this is a reflection of normal seasonal variation or a post-disaster phenomenon. Some have hypothesised that, in certain settings, the risk of arboviral infections might surpass the risk from other vector-borne diseases. This is supported by evidence of significant spikes in dengue cases following Cyclone Mitch.

Evidence of vector-borne disease in developed settings is slim. While there were concerns about a potential outbreak of West Nile virus following Hurricane Katrina, this did not occur to a significant extent. One group has reported that no mosquitoes collected from the Gulf Coast in the six weeks following that event had evidence of arbovirus infection. There is, however, data to support an increase in the incidence of animal bites and stings among exposed persons.

**Leptospirosis**

Leptospirosis is a zoonotic disease that has potential to cause significant morbidity, primarily as a result of acute renal failure. It has been commonly described following cyclones in developing settings. For example, one study reports that 19.2% of tested individuals in four flooded villages had serological evidence of active leptospirosis following a cyclone in Orissa, India (1999). A significant outbreak was seen in Taiwan following Typhoon Nali (2001) and, more recently, speculative evidence has emerged of an epidemic following consecutive events in the Philippines in 2009. There are no reports of leptospirosis outbreaks in developed settings.

**Other infections**

The review by Shultz et al revealed that a variety of other communicable disease outbreaks have been documented, including balantidiasis and typhoid. These have not been reported in more recent literature.

Of note, some infections associated with other natural disasters have not been demonstrated to follow tropical cyclones. These include tetanus, hepatitis A and hepatitis E, which have been reported in the wake of tsunamis and inland flooding. Their absence in the cyclone literature may represent publication bias. There are no recent reports on the impact on tuberculosis, except from one post-Katrina study which demonstrated no adverse consequences despite a short period of treatment program closure.

Although there is a theoretical risk of mould-associated infections following water inundation, there is little data to suggest that this risk has ever been realised to a significant degree. Presentations of chromoblastomycosis were noted following Hurricane Ike and mould was included amongst a list of environmental exposures thought to be associated with increased ARI post-Katrina. This link has been questioned, however.

In another study following Hurricane Katrina, homes with greater flood damage demonstrated higher levels of mould growth compared with homes with little or no flooding; however, no increase in the occurrence of adverse health outcomes was observed. In one paediatric sample, there was an overall decrease in mould exposure and respiratory symptoms following the event.

Following Typhoon Morakot in southern Taiwan (2009), Hsu et al found increased *Aspergillus* spp. in both indoor and outdoor environments in the immediate wake of the cyclone.

**Non-communicable disease**

More is being published about the impact of tropical cyclones on non-communicable disease (NCD) in terms of chronic illness, acute exacerbations.
and new diagnoses. This is in keeping with a trend towards increased emphasis on NCD in the broader disaster and public health literature.

The significant, overall impact of tropical cyclones on NCD has recently been illustrated by a retrospective study that sought to quantify the number of direct and indirect deaths resulting from hurricanes Charley, Frances, Ivan and Jeanne in Florida, 2004. There was an elevated mortality for up to two months following each hurricane, resulting in a total of 624 direct and indirect deaths. In contrast, the official count was 31 direct and 113 indirect deaths resulting from the four hurricanes combined. Indirect mortality accounted for most deaths, and was primarily due to heart disease (34%) and cancer (19%). Diabetes (5%) and accident-related deaths (9%) accounted for a smaller but not insignificant percentage of the elevated mortality. The elevated mortality were deaths that would not have otherwise occurred within that hurricane season.

Pre-existing illness

In developed settings, pre-existing illness accounts for a significant proportion of health care visits in the aftermath of events; following hurricanes Andrew and Katrina, greater than 33% of presentations were for chronic disease. In the case of the latter, the majority of visits were for endocrine, cardiovascular, and psychiatric disorders. Evacuees were noted to have a high burden of disease and most medications dispensed to displaced persons were for chronic conditions.

Cyclones have the potential to directly precipitate exacerbations of pre-existing illness as well as disrupt treatment regimes. A preliminary report of mortality associated with Hurricane Charley suggested that at least six of the atraumatic deaths were the direct result of exacerbated cardiac or respiratory conditions. Surveys conducted following Hurricane Katrina found that 20.6% of survivors with chronic disease cut back or terminated their treatment because of the event. Disruptions in treatment were significantly more common among the non-elderly, uninsured, socially isolated, those with housing needs and for conditions remaining relatively asymptomatic but still dangerous if untreated. Disruptions were frequently the result of problems accessing doctors and medications. This data is congruent with the profound disruption to primary and secondary health services that followed Katrina, which included the closure of 94 dialysis facilities along the Gulf Coast and the interruption of specialist HIV/AIDS clinics.

There is emerging evidence regarding the impact of treatment disruptions following cyclones. For instance, Katrina led to an increase in HbA1c for subsections of the cyclone-affected community with diabetes and negatively impacted on the provision of chronic pain management. Among patients requiring haemodialysis, 44% of patients reported missing at least one session and almost 17% reported missing three or more. The adjusted odds ratio of hospitalisation among the latter group compared to those who did not miss any dialysis sessions was 2.16.

Until recently, there has been limited data in support of a direct link between mortality and cyclone-related disruptions to public health services. While deaths due to exacerbations of chronic disease have previously been attributed to cyclone events, there has been a lack of clarity about the causative factors. The significant number of deaths among hospitalised and chronically ill patients following Hurricane Katrina has helped quantify the impact of health system disruption.

Peri-natal issues

A 2009 literature review found that, following Katrina, obstetric, prenatal, and neonatal care were compromised, but increases in adverse birth outcomes (such as preterm delivery, low birth-weight and maternal complications) were mostly limited to women seriously impacted by the cyclone. They concluded that, with a few specific exceptions, post-disaster concerns and health outcomes for pregnant and postpartum women were similar to those of other people exposed to the event.

Other studies have also failed to identify a persisting negative impact on infant and child mortality from Hurricane Katrina, despite speculation to the contrary. Routine screening of newborns was, however, temporarily interrupted by the event. One small study has identified an increase in congenital cleft palate pathology. Goenjian et al report a statistically significant increase in the cases beginning 9 months after the cyclone. An environmental cause has been hypothesised.

Hurricane Katrina may have impacted on birth rates. The total number of births in selected hurricane-affected counties decreased 19 percent in the 12 months after Hurricane Katrina compared with the 12 months before. The decrease was not consistent across all areas however, which may reflect population shifts.

Ischaemic heart disease

Although increased rates of ischaemic heart disease have been associated with other natural disasters, only recently has data emerged specifically linking acute myocardial infarction (AMI) and tropical cyclones. A single-centre retrospective cohort study following Hurricane Katrina found a three-fold increased incidence in AMI after the event. In the two years post-cyclone, there were 246 admissions for AMI (2.18% of all presentations) compared with 150 admissions (0.71%) prior to the event. The authors suggest that changes in caseload, patient demographics and health service availability only partly account for this significant discrepancy. It has been hypothesised that AMI may be a manifestation of chronic stress but increased tobacco use and medical non-compliance may also contribute. At a different institution, there was no impact on cardiothoracic operative mortality despite a significant increase in demand.

Cancer

Recent analysis has confirmed that a significant number of patients recently diagnosed with cancer were potentially displaced following Hurricane Katrina. Decreased access to care led to delayed presentations and treatment of patients with head and neck malignancies, but the clinical significance of this finding is unknown.

Other conditions

A significant increase in alcohol use and binge drinking was observed following Hurricane Katrina. This correlated with the number of exposures to hurricane-related traumatic events. In a cohort of evacuees, females and younger persons were found to be at increased risk of excess alcohol and tobacco use. In the wake of Hurricane Rita, alcohol use was seen to increase among a small group of adolescents displaying symptoms of post-traumatic stress.

Preliminary data from New Orleans also suggests that hurricanes Katrina and Rita may have altered the redistribution of certain environmental contaminants (including lead), potentially leading to an exposure risk for children in highly-contaminated areas.

Conclusion

Cyclones are severe weather events that occur relatively frequently in tropical regions. They disproportionately affect developing countries and have the potential to cause serious disruption to basic societal functions. Given the ongoing threat of tropical cyclones in northern Australia and the Asia-Pacific region, there is value in identifying their potential impacts on health.

This review was designed to expand on previous analyses by focussing on more recent literature, most of which has been generated in the US following Hurricane Katrina. The expanded volume of literature has provided a much more detailed picture of the health impact of tropical cyclones, particularly in relation to developed countries. It has also confirmed that there is a large degree of variability in the causes of morbidity and mortality between events and settings.

Trauma remains a significant cause of both, although mechanisms vary between events. Both drowning and building collapse can lead to large numbers of fatalities. Minor injuries represent the primary cause of morbidity in the post-impact phase but carbon monoxide poisoning from inappropriate generator use is emerging as an important risk in both adult and paediatric patients. While communicable disease outbreaks are uncommon in developed settings, gastroenteritis, vector-borne disease and ARI pose
particular problems in developing communities. Non-communicable disease constitutes a considerable proportion of healthcare attendees following cyclones, and exacerbations as well as treatment disruptions of chronic diseases are increasingly being recognised as a cause of cyclone-related morbidity and mortality.

Although Australia has well-developed public health infrastructure, any cyclone event that features destructive winds and rain, population displacement and interruption of basic societal functions has the potential to impact on human health. Data from the US following Hurricane Katrina has demonstrated that developed settings are not immune. The results of this review will assist tropical communities in preparing for the threats to health posed by tropical cyclones. Implicit in its findings is the importance of injury prevention strategies, communicable disease surveillance and provision for managing chronic illnesses.

References


Vitamin A, Zinc, Iron and Iodine Interventions in Children Under Five Years of Age

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ABSTRACT

Background: micronutrient deficiency accounts for approximately 10% of all deaths and disability adjusted life years in children under the age of five. Vitamin A, iron, zinc and iodine are considered the most important of the micronutrients and have massive global health implications for this demographic.

Methods: major strategies for vitamin A, zinc and iron interventions including education and dietary diversification, supplementation, fortification and integrated approaches, were reviewed.

Conclusion: vitamin A and zinc supplementation programs remain the most cost effective of all health interventions as judged by the Copenhagen consensus panel. Salt iodisation is the best example of micronutrient fortification to date, and is an excellent example of how political will, effective mar- keting and sound science can dramatically improve the health of a targeted population. There are still areas for improvement though with regards to micronutrient interventions, and it is important that new strategies are utilised appropriately. Further research is needed with regards to iron supplementation in malaria hyper-endemic regions.

Keywords: micronutrients, vitamin A, iron, zinc, iodine, deficiencies, children, supplementation, fortification


Background

Malnutrition is estimated to account for 11% of the global burden of disease.1 Malnutrition can be divided into two major categories: protein-energy malnutrition and micronutrient deficiencies.2 These two areas of nutrition deficiencies are interconnected and very often simultaneously exist. They are both complexly intertwined with geographical, socio-economic and political influences. The scope of this literature review will focus on four major micronutrient deficiencies with major global health implications for children – vitamin A, zinc, iodine and iron.

It is estimated that micronutrient deficiencies affect at least 2 billion people worldwide. In children less than five years of age, micronutrient deficiencies account for approximately 10% of deaths and disability-adjusted life years.3 Much of this burden stems from deficiencies in vitamin A and zinc.4 Deficiencies in vitamin A, zinc, iodine and iron are undoubtedly massive global health concerns that predominately affect developing countries. Adequate provision of these important micronutrients is vital to ensure appropriate physical, mental and cognitive development, and long-term health.4

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Finally, there is limited documentation of the impact of education and information alone. An advantage of educational programs is that they are sustainable, and if delivered effectively, promote long-lasting behaviour change in a population. There is evidence that these programs that specifically target education can work in relatively advantaged populations. However, there are several drawbacks to education programs alone. It is important to realise that changes in behaviour and practices will be confined to the socio-economic and geographical capabilities of the targeted population. The take-home message of many nutritional reviews is that education and dietary diversification is important in all nutritional interventions. However, it should not be used as a stand-alone technique, but in combination with other proven techniques that will be mentioned.

**Supplementation**

Micronutrient supplementation of targeted populations of young children has been proven to be very cost-effective, particularly for vitamin A and zinc. Supplementation is usually delivered through primary healthcare systems, and commonly coupled with immunisation programs. Supplementation programs are only effective if the supplements reach a high percentage of people in the vulnerable population, and if the delivery system has built-in quality control.

**Vitamin A supplementation**

Vitamin A (VA) supplementation is undoubtedly one of the most effective child survival interventions. Systematic review of RCTs showed that one dose of VA reduced the mortality risk of children aged between 6 months and 5 years by 12%, with two doses reducing the risk by 22%. Studies in Asia showed that neonatal supplementation reduced mortality of children between the age of 2 days and 6 months by 21%. VA was also shown to reduce the burden of multiple diseases, including persistent diarrhoea with a rate ratio of 0.45. It was estimated that nearly two-thirds of children in developing countries under the age of five received two high-dose VA supplements. What is even more impressive is that 82% of children under the age of five in the least developed countries of the world received coverage, highlighting what happens when political will and international resources are available. VA supplementation has also been shown in studies to improve the efficacy of iron supplementation by increasing haemoglobin levels. This believed to be done stimulating erythroid precursors and improving the availability of iron to the bone marrow.

**Zinc supplementation**

In 2004, a joint statement was made by UNICEF and WHO recommending zinc supplementation (ZS) in the management of diarrhoea. Despite these recommendations, as of 2010, only 46 countries utilised a zinc policy in their child health delivery. Four systematic reviews have shown that preventive ZS in children greater than 6 months was shown to reduce the overall mortality risk by 9%, and reduce the odds of stunting by 15%. A meta-analysis revealed that ZS reduces the duration of diarrhoea by 15-24%, and the frequency of lower respiratory infections by 15-24%

**Iron supplementation**

Studies have shown that iron supplementation (IoS) resulted in a haemoglobin concentration increase of 7.4 g/L. IoS alone reduced the occurrence of anaemia in regions not endemic for malaria from 6-32%. However, it is important to note that potentially there is an increased risk of childhood mortality in hyper-endemic malarial regions. This recommendation was brought about by a trial in Tanzania which showed there was an increase in mortality in children receiving IoS, and hence the trial was stopped prematurely. Several other studies have also showed a correlation between IoS and communicable diseases, although further research is needed to make this conclusive.

**Iodine supplementation**

Iodine supplementation is generally reserved for pregnant women. Iodine fortification is the leading intervention for targeting children populations which are iodine deficient.
Fortification

Food fortification with micronutrients is a constantly evolving public health intervention. Fortification can be broken down into two general approaches – central and peripheral fortification. Central fortification involves adding micronutrients to foods in a centralised manner prior to distribution or marketing. Peripheral fortification involves adding micronutrients to food in the household. The great advantage of central fortification done in a safe manner is that minimal behavioural change or motivation is necessary in the population to instigate health benefits. This approach does require sound scientific evidence, political will and leadership and effective implementation. Also, ensuring equal coverage is paramount, with rural populations often neglected in such interventions. Peripheral fortification can be utilised to target certain vulnerable sub-groups such as young children. This approach requires active participation form household leaders.

Vitamin A fortification

There have been interventions of VA fortification to foods such as cooking oils, monosodium glutamate (MSG) and sugar. Evidence for the effectiveness of fortification of these foods with VA is difficult to find, however a study showed a 30% mortality reduction in children aged 6 months – 5 years in a population in Indonesia given commercially fortified MSG.

Zinc fortification

WHO recommends zinc as a curative measure only for childhood illnesses and diarrhoea, and there is minimal data to support central zinc fortification. As a result, there is limited data on zinc fortification strategies. A study in Senegal showed food containing zinc-fortification did not increase plasma zinc concentration, unlike ZS for 15 days which did. A study in northern India where children were given fortified milk with multiple nutrients, including zinc and iron, had an 18% lower incidence of diarrhoea and a 26% lower incidence of pneumonia.

Iron fortification

There has been much debate about the efficacy of iron fortification. Similar to IrS, there is unclear data about whether this intervention is safe for children in malaria hyper-endemic regions. Iron fortification has been shown to reduce the rate of anaemia by more than two-thirds in school children in Chile. It has been estimated that iron fortification of staple foods could potentially prevent 8% of DALYs of children – a massive 123,000 DALYs. A study in India where food was fortified with iron and riboflavin showed a reduction in the prevalence of anaemia by more than half. More research, however, needs to be done in hyper-endemic malarial regions before widespread interventions can be made with sound scientific backing.

Iodine fortification

Undoubtedly the greatest success in food fortification has been with the iodisation of salt. This is a fantastic global health example of how good governance and market opportunity can improve the health of a population. Salt iodisation is estimated to reduce DALYs from iodine deficiency by 41% in children. Less than one in five developing world households were using iodised salt in 1990. In 2010, this number increased to 70%, with more than 30 developing countries reaching the universal iodised salt goal. Having said this, 24 countries in 2010 showed no growth and even decline in iodised salt coverage. In half of these countries, one in five is consuming adequate iodised salt levels. Iodised water has been shown to reduce infant mortality by more than a half in studied areas, and neonatal mortality by nearly two thirds.

Integrated approaches

Integrated approaches include child nutrition programs, the Essential Nutrition Actions approach and conditional cash transfers.

Child nutrition through child health programs

Child health weeks (CHWs) are an excellent example of delivering a range of services for child health through an existing health system. This requires a sound and effective public health structure with appropriate evaluation and monitoring. Let us take a look at Zambia, which in 2000 with the assistance of UNICEF, has been implementing half-annual CHWs. Here, alongside routine vaccinations, deworming, malaria prevention strategies and growth monitoring, vitamin A supplements are given. Evaluation performed in 2003 showed that through these CHWs, 77% of children received VA. This was shown to halve the level of VA deficiency, with anaemia being reduced by 12%.

The Essential Nutrition Actions (ENA) approach

The ENA approach evolved from the Lancet Child Survival series which reported a set of nutritional interventions that were shown to reduce childhood mortality. It was developed by WHO, UNICEF and the US Agency for International Development and includes a focus on the first two years of childhood. Vitamin A, zinc supplementation and exclusive breastfeeding in the first 6 months of life are strategies in the ENA framework. This integrated approach has been shown to be effective in numerous developing countries, with an example being Madagascar.

Conditional cash transfers (CCTs)

CCTs have become widespread in Latin America, and are based on financial payments to poor and vulnerable populations in exchange for completing certain conditions. These conditions include a certain school attendance rate for children, use of primary healthcare services and nutrition programs.

Perhaps the most successful of the CCT programs has been in Mexico, which includes food fortification and micronutrient supplementation of children aged between 6 months and 2 years. The effect on anaemia prevalence and infant growth has been markedly positive since the commencement of this program.

What needs to be done

National governments and development partners need to increase long-term investment to yield greater and further returns. More affordable, feasible and evidence-based programs are emerging, and should be utilised to expand the potential benefits of addressing these major micronutrient deficiencies. Monitoring and surveillance of nutritional programs is paramount for the success of current and future interventions. This includes population monitoring assessing change in dietary behaviours which will guide alterations of programs, allowing them to be more efficient and effective. Resources need to be mobilised in national budgets so that each country can sustain appropriate nutritional interventions on a long term basis. The media, including social media, should be utilised for awareness, motivation and mobilisation of the masses, and should be incorporated into national health systems and schools.

The 2009 Global Report on micronutrient deficiencies sets the coverage target of those receiving twice-yearly VA supplementation on a repeated basis as greater than 80%. The other ‘difficult-to-reach’ 20% who are missed in regular programs will need to be targeted with special, context-specific programs such as integrated outreach programs. Mandatory legislation of salt iodisation, with appropriate enforcement capabilities, should be made. Incentives should be made to salt processors in developing countries to ensure they iodise their salt, with a transition from a donor-dependent to a market-supported supply important for sustainability. Zinc supplementation needs to be implemented into each nation’s policy for the management of diarrhoea in children. This will involve ensuring an adequate zinc supply, with appropriate delivery strategies. Safe strategies to improve iron intake need to be made clear for policy makers and program designers. Further directed research needs to be done with regards to iron supplementation in hyper-endemic malaria regions.

Conclusion

Micronutrient deficiencies, especially that of vitamin A, zinc, iron and iodine, result in an enormous health burden on children under the age of five. Over the last few decades, there have been a large number of programs designed to target this issue. Some of these programs have been touted as being some of the most cost-effective health programs that exist today. Supplementation programs with zinc and vitamin A have produced staggering results in terms of the reduction of childhood mortality and morbidity. How-
ever, these programs need to be scaled up to ensure coverage is expanded and performed on a recurrent basis. Coverage needs to include targeting the neglected groups of a population that have been missed with other routine programs. Nutritional intervention is an evolving field, with food fortification strategies emerging as an area of great potential. Further research and data is needed however with food fortification strategies, and governments need to ensure they maintain the political will to ensure up-to-date legislative changes that promote better nutritional health.

References

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REVIEW ARTICLE
Hearing Loss in Malaria
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ABSTRACT
Background: Malaria is a preventable and treatable infectious disease; however, malaria is extremely common in many parts of the world. Hearing loss can be devastating and adversely affect individuals and populations. Malaria and antimalarial regimens may affect hearing, thus causing significant functional, social, and developmental issues. This article explores the link between hearing loss and malaria, and ototoxicity from antimalarial chemotherapy. Aim: The aim of this study was to perform a systematic literature review on hearing loss in malaria.

Design: A systematic search of the literature and a discussion of the results.

Method: A search was performed in MEDLINE via OvidSP, Scopus, and PubMed databases.

Results: Of 13 papers analysed, one was a systematic review on the direct effect of malaria on hearing loss, which suggested that malaria may directly cause hearing loss through biological processes not well understood. No prospective studies on this issue have been done to date. Collectively, reports have shown minimal evidence that antimalarial medications cause ototoxicity, except for quinine, which is well recognised as an ototoxic agent.

Conclusion: This study highlights evidence that malaria may cause hearing impairment. Although there is limited definitive evidence, the impact malaria may have on altering hearing thresholds is increasingly recognised. Most antimalarial medications are safe for the ear. Quinine produces a predictable, but reversible, hearing loss. More research should aim to identify whether a direct link exists between malaria and hearing loss because malaria is a global burden, the impact of hearing loss can be substantial, and studies evaluating drug toxicity may be confounded by deafness due to malaria itself.

Keywords: malaria, hearing loss, ototoxicity, antimalarials, chemotherapy


Introduction
Impact of malaria
Malaria is a disease of poverty that affects hundreds of millions of people worldwide, with many more at risk of exposure.1 Malaria can cause neurocognitive disorders, and it is well recognised that Plasmodium falciparum causes language disorders in children, although the mechanism is unclear.2 Hearing is a component of language and is known to be affected by some antimalarial agents.3 Although ototoxicity studies have been done to evaluate these drugs, most studies assume that the affected individual has normal hearing, since audiometric testing is usually done during and after treatment.
for acute malaria. Therefore, malaria and antimalarial agents may alter hearing thresholds causing deafness and ultimately impairing language. The impact of deafness on the individual and the population includes functional, social, and economic aspects, both in the child and adult, so exploring this proposed association may help identify new avenues for preventing hearing loss. This review of the current literature was undertaken to investigate whether malaria and antimalarial treatment regimens cause hearing problems, as the use of these drugs for febrile illness is widespread.

Malaria disease

Malaria is a parasitic infection that affected 216 million people in 2010 with 3.3 billion people at risk. Young children are at increased risk of malaria because immunity to malaria has not yet developed, and as a result young children living in endemic areas of malaria are a particular population at risk. Given that childhood development is sensitive to environmental insults, malaria can adversely affect normal growth. Deficiencies in areas such as language can occur due to restricted brain development. This can restrict learning, social interaction, and functional capacity to work, which has serious effects not only for the affected individual but at the social and economic level. These impairments are associated with a significant burden, especially in those affected in sub-Saharan Africa, which has high levels of malaria transmission.

Chemotherapy agents used for malaria treatment may also be involved in damaging the brain and, in particular, hearing function. These agents can be toxic enough to be harmful to sensitive organs such as the inner ear. For example, arteether-lumefantrine is an effective antimalarial for uncomplicated Plasmodium falciparum. Dose-response relationships have been established for artemisinin derivatives and toxicity on brain areas involved in hearing in animal studies. In stable malaria transmission situations, quinine is commonly used as a first-line agent in children with a febrile illness for presumed malaria, and can exert neurotoxic effects, as demonstrated in the laboratory. Mefloquine is mainly a chemoprophylactic agent, but its side effect profile includes neuropsychiatric disorders that have been linked to toxicity in the brain. The evidence that these agents may be involved in ototoxicity and significant hearing loss in humans will be reviewed.

Hearing loss

Hearing loss is a well-recognised global issue that affects around 278 million people in the world. In developing countries, 50% of hearing loss has been estimated to be preventable. Many cases in the developing world may have no explanation as to the cause of deafness. Although there are numerous aetiologies for hearing loss, malaria or its treatment regimens may help explain cases of unknown origin, and clarifying its role in hearing impairment may allow public health strategies to be put into practice to avoid a potentially preventable cause of deafness. Cerebral malaria, which is a complication of severe malaria, may cause persisting neurological issues, including deafness. However, many individuals do not experience cerebral malaria and yet unexplained deafness is common in malaria-endemic areas. Malaria may explain this large proportion of preventable cases of deafness.

The effect of deafness on paediatric populations has been studied and evidence suggests that deafness in children may result in poor attention span, leading to limited class participation and hindering the learning experience, restricting their potential. An association between malaria parasite density and level of concentration of schoolchildren, showing a dose-response relationship, has been suggested in a number of studies. The cause of this cognitive decline is unclear and is likely due to anaemia and brain hypoxia, but hearing loss has been suggested to be a plausible explanation. This can have serious consequences, as the effects of hearing loss can result in functional, social, and developmental issues in the developing child and these problems may continue into adulthood. The deaf adult may have poor language abilities, and consequently, limited social interaction and occupational capacity. This translates into public health and economic issues to allocate resources towards screening, rehabilitation, and hearing aid programs, for an issue which may be preventable.

Methods

Two systematic literature searches were undertaken. A systematic literature search was performed on MEDLINE via OvidSP, Scopus, and PubMed databases. The keyword ‘malaria’ was used with ‘hearing loss or ototoxicity’. A second systematic search was completed using the keywords ‘neurological or neurocognitive deficits’ and ‘malaria’ and these articles were selected based on available internal data on hearing loss. Articles were limited to English. Evidence for safety profiles of chemotherapeutic agents was limited to clinical studies.

Results

Thirteen articles were selected after analysis as meeting the inclusion criteria for this review. There were three studies looking at the direct effect of malaria on hearing, which include a systematic review, a clinical trial, and one laboratory report. Results for studies on safety of antimalarials included four clinical trials, two case control trials, one retrospective and two prospective studies, and a case report. The findings are summarised in Tables 1 and 2 and will be discussed next.

Discussion

Direct effect of malaria on hearing

There are a limited number of studies that directly investigate the association between malaria and hearing loss (Table 1). The most recent review published by Zhao and Mackenzie in 2011 analysed 14 studies and suggested an association of deafness due to the neurological deficits secondary to cerebral malaria, but could not show a strong causal relationship between uncomplicated malaria and deafness. Their study found a small but significant proportion of hearing loss was associated with a non-specific fever or febrile illness in countries where the most common cause of fever is malaria. Recall and measurement bias in these studies, however, makes it unknown as to whether causation exists. They conclude that clinically-significant hearing impairment occurs only in severe disease, and that less-noticeable hearing deficits, which may not be recognised, may be present in uncomplicated malaria.

Zhao and Mackenzie suggest that during a malarial infection prior to treatment, the level of hearing is reduced, and thus hearing may appear to be affected during the treatment period. Since baseline hearing function has been assumed to be normal in other studies, the actual amount of hearing loss is unknown and there could be potential loss due to the infection prior to treatment. These authors suggest that if this occurs, treatment may further damage hearing, and although hearing improves at follow-up compared to testing at pre-treatment, this might not represent the true hearing threshold as no baseline of hearing was recorded prior to parasitic infection in the studies they reviewed. These theories are supported by work in Ghana which showed that hearing thresholds differed significantly (p<0.001) between children with an acute illness of uncomplicated P. falciparum and healthy controls. After 9 months follow-up the study measured hearing thresholds again, and found thresholds were not significantly different among the two groups. This suggests if P. falciparum affects hearing, the deafness may be transient and reversible. This study has implications for research in drug therapy for ototoxicity, since evaluating ototoxicity during the period of acute illness may be confounded by the presumed ototoxic effect of malaria.

Although clinical studies have not been performed sufficiently to establish an association, a laboratory study by Schmutzhard et al demonstrated significant hearing loss in mice following cerebral malaria. They concluded that malaria significantly causes hearing impairment in mice by studying auditory evoked brainstem responses (ABRs), which measures hearing thresholds, before and after infection. In addition, they demonstrated that higher hearing thresholds occurred in mice with cerebral malaria compared to uncomplicated malaria, which suggests the severity of malaria has a more significant effect on hearing. There are no human studies demonstrating similar findings, probably because the mouse model of cerebral malaria is not directly comparable to human cerebral malaria.
Proposed mechanisms for hearing loss in malaria

Zhao and Mackenzie suggest that multiple mechanisms ultimately lead to damage of three core areas involved in hearing. These include the cochlea, the cochlear nerve, and the brainstem and its associated structures that participate in hearing. Indirectly, malaria may increase risk of acquiring other auditory damaging infections which can lead to hearing loss. Local microvascular changes of cochlear end arteries has been suggested to be the prime mechanism of contributing directly towards hearing loss and this pathological alteration may be implicated in lowering resistance to other infections.

The lack of causation between uncomplicated malaria and hearing loss may be because any deafness suffered from uncomplicated malaria is not recognised or is underreported. This might be compounded by the fact that the issue has not been studied in detail, according to the lack of research in the literature. The reviewed clinical studies support the need for further research in the area due to the considerable absence of evidence, especially in humans. Prospective studies should be performed to help establish whether causation exists.

Antimalarial agents and ototoxicity

Artemisinins have been thoroughly studied due to concerns regarding neurotoxicity based on animal studies. Amodiaquine-artsunate and artemether-lumefantrine were randomised in an efficacy and safety trial in Ghana, powered by 227 children aged six months to 14 years with uncomplicated malaria. No significant differences in hearing were reported during the one year study, which included a monthly follow-up period. A matched case-control that involved 68 adults on artemether-lumefantrine compared with 68 matched-controls similarly did not show evidence that artemether-lumefantrine causes hearing impairment. Hearing loss was common in the study in both groups, but statistical analysis showed that only age was a significant predictor. Hearing loss was common in the acute setting malaria may cause elevated hearing thresholds. A randomised trial as simplifying and differences of noise exposure between the two groups, making this pathological alteration may be implicated in lowering resistance to other infections.

In the same study, it was found that quinine was associated with a hearing loss of 30 dB, although this was transient. A significant number of patients (9 out of 30) on day 7 of quinine therapy complained of hearing issues, but all but one complaint about deafness disappeared by the day 28 visit, and no hearing problems were reported by day 90. Quinine is well recognised to cause toxicity to the outer hair cells of the ear, but its effect is reversible and the patients in this study did not complain of hearing issues by day 90. Historically, quinoline derivatives have a well-recognised ototoxic profile, as cinchonism, a syndrome that occurs from quinine toxicity, results in headache, deafness, and anaphylactic shock. In Tanzania, a large number of children were suspected of having profound sensorineural deafness. A subsequent pilot study found 36% of deaf children had received intramuscular quinine and/or gentamicin for ‘fever’ on admission. This highlights the potential for ototoxicity due to the improper use and monitoring of these two drugs, as they both have ototoxic properties. A study by Flanagan et al evaluating the role of measuring routine quinine levels found that hearing loss due to quinine occurs regardless of oral or parenteral route but is likely to be completely reversible. Quinine plasma levels do not appear to correlate well with hearing loss, and individual risk may be better assessed by hearing tests rather than measuring quinine levels. This is supported by an older study that produced similar results, with reversal of hearing loss within one week, according to audiograms. Evidence suggests that although quinine may produce deafness, it is a transient event that may completely return to normal, and that audiometric testing rather than blood tests may be done for those patients on quinine to reliably monitor its ototoxic effects.

Mefloquine might potentially affect hearing, since the side effect profile of mefloquine includes neuropsychiatric disturbances, likely due to its neurotoxic properties. However, an open-label phase IV study of African children with uncomplicated malaria treated with three-day artemesin and mefloquine failed to demonstrate convincing evidence of hearing loss (95% CI: 0.0 to 1.73 % of patients), although this was not the direct end-point of their study. A prospective study of 93 patients with uncomplicated malaria on three-day mefloquine-artsunate in Thailand also could not suggest clinical evidence via audiometric and ABR testing. This study tested ABr on day 0 and day 7, and did not find evidence to suggest artsunate or mefloquine are toxic to the auditory system. One Canadian case report concerned a 67-year-old woman who had mefloquine chemophrophylaxis and developed unilateral sudden profound sensorineural hearing loss and tinnitus, which resolved spontaneously at day 93 of her illness, but no causal interpretation could be made.

Artemether-lumefantrine does not appear to cause hearing loss and this evidence supports its safety in this context. These clinical studies confirm

<table>
<thead>
<tr>
<th>STUDY TYPE, SAMPLE SIZE</th>
<th>METHOD OF MEASUREMENT</th>
<th>FINDINGS</th>
<th>AUTHOR &amp; REFERENCE</th>
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<tr>
<td>Systematic literature review</td>
<td>Review of 14 studies</td>
<td>Falciparum infection may potentially lead to hearing loss</td>
<td>Zhao and Mackenzie20</td>
</tr>
<tr>
<td>Clinical trial artemesinumefloquine (n=37), artemetherlumefantrine (n=35), or amodiaquine (n=8) in children</td>
<td>Audiometric thresholds compared to controls</td>
<td>In the acute setting malaria may cause elevated hearing thresholds</td>
<td>Adjei et al21</td>
</tr>
<tr>
<td>Mice murine cerebral malaria (n=20)</td>
<td>Auditory brainstem response testing</td>
<td>Significant hearing impairment</td>
<td>Schmutzhard et al22</td>
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Table 1 Summary of evidence suggesting the direct effects of malaria on hearing

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<th>STUDY TYPE AND TOTAL SIZE</th>
<th>STUDY FACTOR, SAMPLE SIZE, AND METHODOLOGY</th>
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<th>AUTHOR &amp; REFERENCE</th>
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<tr>
<td>Randomised efficacy and safety trial (n=227)</td>
<td>Random treatment of uncomplicated malaria in children 6 months to 14 years to amodiaquine-artesunate (n=116) or artemether-lumefantrine (n=111), follow-up in 28 days for reports of adverse events</td>
<td>Rare instances of side effects and no reports of hearing impairment nor abnormal neurological signs</td>
<td>Adjei et al²⁴</td>
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<td>Case-control (n=136)</td>
<td>Group treated with artemether-lumefantrine within 5 years (n=68) vs matched controls (n=68) compared for audiometric differences</td>
<td>No audiometric difference between cases and controls</td>
<td>Hutagalung et al²⁵</td>
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<td>Randomised, prospective open-label three-arm study (n=265)</td>
<td>Random assignment to artemether-lumefantrine (n=159), atovaquone-proguanil (n=53), or artesunate-mefloquine (n=53) and auditory brain response (ABR) comparison</td>
<td>No difference in ABR; 2-4 dB pure-tone threshold improvement</td>
<td>Carrasquilla et al²⁶</td>
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<td>Matched case-control trial (n=300)</td>
<td>Artemether-lumefantrine (n=150) to treat uncomplicated malaria vs age-, gender-, weight- and race-matched controls (n=150) who did not suffer malaria and did not have antimalarial therapy with comparison of audiometric findings</td>
<td>Subjects in the artemether-lumefantrine group had significant hearing loss compared to controls</td>
<td>Toovey and Jamieson²⁷</td>
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<td>Randomised double-blinded controlled trial (n=77)</td>
<td>Random assignment to receive artemether/lumefantrine (n=23) or quinine (n=26) or atovaquone/proguanil (n=28) and comparison of peripheral and brainstem auditory pathway assessment</td>
<td>No impact of standard oral dosing of artemether-lumefantrine on either peripheral or brainstem auditory pathways; transient hearing loss on day 7 with quinine therapy</td>
<td>Gurkov et al²⁸</td>
</tr>
<tr>
<td>Retrospective audit (n=82)</td>
<td>Quinine plasma level results and correlation with toxicity effects</td>
<td>Hearing loss occurs almost invariably but may not occur in a dose-response relationship</td>
<td>Flanagan et al³⁰</td>
</tr>
<tr>
<td>Experimental study (n=22)</td>
<td>Audiometric testing before and after doses of quinine administered in 12 healthy subjects and 10 patients with falciparum malaria</td>
<td>High frequency loss reversible within one week</td>
<td>Tange et al³¹</td>
</tr>
<tr>
<td>Experimental phase IV open label study (n=213)</td>
<td>Treatment of African children with uncomplicated P. falciparum treated over three days with artesunate-mefloquine combination with follow-up to report adverse events</td>
<td>No reports of hearing loss</td>
<td>Frey et al³²</td>
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<td>Prospective study (n=93)</td>
<td>3-day oral artesunate-mefloquine in patients with uncomplicated falciparum and auditory testing before the first dose and seven days after the first dose was started</td>
<td>No threshold changes of significance (changes did not exceed 10 dB)</td>
<td>Carrara et al³³</td>
</tr>
<tr>
<td>Case report</td>
<td>Case analysis of a woman on chemoprophylactic weekly mefloquine</td>
<td>Sudden right ear severe sensorineural hearing loss and tinnitus with spontaneous resolution after day 93 of hearing loss</td>
<td>Wise and Toovey³⁶</td>
</tr>
</tbody>
</table>
existing knowledge of quinine as an ototoxic drug that is used in malaria treatment. Limited available evidence does not currently support the hypothesis that mefloquine is ototoxic. There were no other clinical reports of ototoxicity of other antimalarial drugs, including atovaquone-proguanil, sulfadoxine-pyrimethamine, or halofantrine.

Conclusions

This review of the literature found a small number of studies that support an association between malaria and hearing loss. This suggests that further research should be done to better clarify this association and its impact on the individual. In particular, studies should concentrate on the long-term consequences, if any, of this phenomenon. Most antimalarial agents appear not to cause ototoxic reactions, with the exception of quinine, which has a predictable response. The evidence for deafness due to mefloquine is poor. The lack of strong evidence of a direct correlation between malaria and hearing loss may be because any deafness suffered from malaria is not appreciated or is underreported. This might be compounded by the fact that the issue has not been well recognised, suggested by the limited studies within the literature. In addition, there are few studies which record a baseline auditory threshold before becoming infected with malaria. Both clinical and non-clinical studies support further clinical research to identify an association and clarify mechanisms that cause deafness during a malarial episode, as this may provide a strategy to prevent potentially avoidable cases of hearing loss.

References


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CASE REPORT

TB or not TB: The clinical and diagnostic challenge of suspected pericardial tuberculosis

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Royal Melbourne Hospital, Grattan St, Parkville VIC

ABSTRACT

A 61-year-old Vietnamese-born male presented to an inner-city tertiary hospital after urgent medivac retrieval from Vietnam. He had a presumed diagnosis of severe cardiogenic failure, and on admission rapidly deteriorated with a large pericardial effusion and cardiac tamponade seen on echocardiogram. He was admitted to the intensive care unit, and underwent investigation and treatment for suspected tuberculosis (TB) pericarditis. All diagnostic measures available, however, were negative for TB. This case highlights the clinical and diagnostic challenge of pericardial TB, and that further research is needed to aid clinicians.

Keywords: tuberculosis, pericarditis, diagnosis, interferon-gamma, PCR


Introduction

Tuberculous pericarditis is an uncommon complication of TB, and rarely seen in the developed world due to low overall prevalence. However, worldwide, TB is still a major cause of morbidity and mortality, with progress substantially undermined by the HIV epidemic and emerging drug resistance. It remains a disease of poverty, linked to overcrowding and undernutrition. The increasing prevalence of co-infection with HIV in developing countries has led to a marked increase in rates of TB pericarditis, and in endemic areas, aetiology of pericarditis is most commonly attributed to TB.

Case report

A 61-year-old Vietnamese-born male, having lived in Australia for the past six years, presented to a large inner-city tertiary hospital after urgent medivac retrieval from Vietnam. He had a background history notable for atrial fibrillation (on warfarin), with pacemaker for tachy-brady syndrome, hypertension, dyslipidemia and non-alcoholic steatohepatitis. He was previously independent, a practising Buddhist, and lived alone with a supportive family close by. He often holidayed in Vietnam to visit friends and family.

Whilst in Vietnam he was admitted to hospital two months prior to his transfer with severe biventricular heart failure. His admission was complicated by an extended-spectrum beta-lactamase E. coli catheter-related sepsis, requiring transfer to the intensive care unit (ICU). Despite a prolonged course of meropenem and amikacin, he had persistent hypotension and anasarca unresponsive to aggressive diuresis. Echocardiography performed in Vietnam was reported as asymmetric hypertrophic cardiomyopathy with no evidence of flow obstruction and moderate pulmonary hypertension.

On admission to hospital in Australia, the patient appeared to be in cardiogenic shock, with a systolic blood pressure of 85 mmHg. He was jaundiced, with tender hepatomegaly and severe peripheral oedema. Chest x-ray (Fig. 1) showed a large globular heart and bilateral pleural effusions. The patient was afebrile, with normal white cell count and C-reactive protein of 20 mg/L. Liver function tests revealed mixed picture deranged liver enzymes, hyperbilirubinemia and hypoalbuminemia. The working diagnosis was one of ongoing cardiogenic failure, complicated by altered conscious state and congestive hepatopathy due to severe right heart failure.

A few hours after admission the patient required emergency attention for hypotension, with systolic blood pressure recorded as 75 mmHg. An urgent bedside transthoracic echocardiogram (TTE) demonstrated a large pericardial effusion (4 cm), preserved left ventricular function with mild left ventricular hypertrophy, and evidence of early signs of cardiac tamponade. There was no evidence of hypertrophic cardiomyopathy. Pericardiocentesis was performed, with 1.2 litres of blood-stained pericardial fluid drained. Results of the pericardial fluid analysis, showing an exudate, are detailed in Table 1.

The patient was reviewed by the Infectious Disease team, who thought that a diagnosis of pericardial TB was unlikely, due to the absence of prodromal symptoms and no known contacts with TB, with the only risk factor being country of birth. They suggested investigation for TB, a liver cirrhosis work-up including abdominal ultrasound, and to continue meropenem to cover for ongoing possible sepsis.

On day three of admission, the patient was again hypotensive and febrile. Vancomycin was added to meropenem to cover for nosocomially-acquired infection. Repeat TTE showed small pericardial effusion and normal pericardial thickness. The patient was transferred to the ICU for haemodynamic monitoring and support.

All cultures as part of the septic screen were negative, as were sputum samples for acid-fast bacilli and a Quantiferon-TB Gold test. Abdominal ultrasound revealed small volume ascites and the liver cirrhosis screen was normal. Further investigations were done: rheumatological screen, serology for schistosomiasis and strongyloides, cytomegalovirus, Epstein-Barr virus and HIV serology; all were negative.

A computed tomography of the chest, abdomen and pelvis was ordered for further assessment and to investigate the possibility of malignancy. It revealed a re-accumulated large pericardial effusion and large bilateral pleural effusions. There was no evidence of malignancy or lymphadenopathy.

The impression from the Infectious Disease team was that there was not enough evidence to diagnose and treat pericardial TB. However, as it remained the primary differential diagnosis, pericardial and pleural biopsy was recommended. This occurred uneventfully (Table 2) and the patient was commenced on standard anti-TB therapy and high-dose prednisolone on day eight of admission.

The patient remained in the ICU for a further three weeks with minimal clinical response. Ongoing issues of hypotension requiring significant inotropic support, severe right heart failure, sepsis unresponsive to broad antimicrobial treatment, and multi-organ failure ensued. The patient remained on anti-TB therapy and high-dose prednisolone. All results, including the pericardial...
biopsy, were negative for TB. Repeat CT chest however revealed new right upper lobe pulmonary nodules and sub-centimetre mediastinal lymph nodes not noted on previous imaging.

In light of this, and due to ongoing haemodynamic instability, the patient underwent a full heart study. Haemodynamic findings were consistent with constriction or restriction. Definitive diagnosis could not be made as the patient was in atrial fibrillation and respiratory variation was not able to be assessed due to the patient’s conscious state. A pericardectomy, from these results, was not recommended.

Despite maximal ICU support, the patient’s clinical state continued to deteriorate. A decision was made, in accordance with the family, to cease active management. The patient was palliated and died one day later. Unfortunately, due to religious beliefs, an autopsy was not performed.

**Discussion**

TB pericarditis typically presents with non-specific symptoms of fever, night sweats and weight loss; cough, dyspnoea and pleuritic chest pain are also common. A minority of patients, however, present with features of constrictive pericarditis, of these, most present with symptoms of cardiac failure.

Pericardial involvement by *M. tuberculosis* commonly develops through lymphatic spread from adjacent lung, tracheal, bronchial or mediastinal lymph nodes, or via haematogeneous spread from primary infection. It is often due to reactivation and the primary source of infection is not found. It is the immune response to the viable acid-fast bacilli in the pericardium that is responsible for morbidity, as a hypersensitivity reaction mediated by TH1 lymphocytes causes the resultant pericardial effusion.

Constrictive pericarditis tends to manifest in one of three syndromes: cardiac tamponade, constrictive pericarditis, or effusive-constrictive pericarditis. Effusive-constrictive pericarditis has evidence of both constriction and pericardial effusion, complicated by early signs of cardiac tamponade. It often becomes apparent after pericardiocentesis because constriction remains even after removal of pericardial fluid. Chronic granulomatous inflammation

<table>
<thead>
<tr>
<th>INVESTIGATION</th>
<th>FINDINGS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium</td>
<td>140 mmol/L</td>
</tr>
<tr>
<td>Potassium</td>
<td>3.6 mmol/L</td>
</tr>
<tr>
<td>Chloride</td>
<td>95 mmol/L</td>
</tr>
<tr>
<td>Creatinine</td>
<td>89 umol/L</td>
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<tr>
<td>Urea</td>
<td>10.9 mmol/L</td>
</tr>
<tr>
<td>Glucose</td>
<td>4.3 mmol/L</td>
</tr>
<tr>
<td>Albumin</td>
<td>23 g/L</td>
</tr>
<tr>
<td>Lactate dehydrogenase</td>
<td>957 iU/L</td>
</tr>
<tr>
<td>Microscopy &amp; culture</td>
<td>Leukocytes +</td>
</tr>
<tr>
<td>Microscopy for TB</td>
<td>Auramine-rhodamine stain: no acid-fast bacilli detected</td>
</tr>
<tr>
<td>Cytology</td>
<td>The smears contain scant mesothelial cells with foamy macrophages and inflammatory cells including eosinophils. No malignant cells are identified. Consistent with inflammation.</td>
</tr>
<tr>
<td><em>M. tuberculosis</em> complex DNA PCR</td>
<td>Negative</td>
</tr>
<tr>
<td>Mycobacterial culture</td>
<td>Negative (after four weeks)</td>
</tr>
</tbody>
</table>

**Table 2** Results of pericardial biopsy analysis

<table>
<thead>
<tr>
<th>INVESTIGATION</th>
<th>FINDINGS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Histopathology</td>
<td>Sections show fibroadipose connective tissue. The stroma contains a sparse lymphoplasmacytic chronic inflammatory cell infiltrate. No active or granulomatous inflammation is seen. No refractile foreign body material is identified. There is no evidence of malignancy. Conclusion: mild non-specific chronic inflammation.</td>
</tr>
<tr>
<td>Microscopy for TB</td>
<td>Auramine-rhodamine stain: no acid-fast bacilli detected</td>
</tr>
<tr>
<td><em>M. tuberculosis</em> complex DNA PCR</td>
<td>Negative</td>
</tr>
<tr>
<td>Mycobacterial culture</td>
<td>Negative</td>
</tr>
</tbody>
</table>
leads to thickened, fibrosed pericardium with evidence of calcification.6,7 This underlying pathology inhibits adequate diastolic filling, reducing venous return and lowering cardiac output.8 Prompt diagnosis and treatment of constrictive pericarditis due to TB is paramount to reduce mortality.7,8,9 Diagnosis relies on isolation of tubercle bacilli in pericardial fluid, which is often difficult.8 A definitive diagnosis is only made with one of positive culture, acid-fast bacilli stain in pericardial fluid or detection of tubercle bacilli, and/or typical caseating granuloma on pericardial biopsy.2,8 It is considered likely in the presence of pericardial effusion and TB isolated from sputum or other sites, with a positive clinical response to anti-TB therapy.2,9 Negative initial investigations do not rule out TB as the cause of pericarditis.8,9 Szmears with Ziehl-Neelsen (ZN) staining of pericardial fluid have poor sensitivity, with only 40-60% being positive.9 Culture is often slow, taking up to 6-8 weeks, and is also of low sensitivity.2,8 Empiric therapy is often commenced with clinicians relying heavily on clinical grounds only for diagnosis.8 However, this subjects the patient to unnecessary adverse effects and long duration of anti-TB chemotherapy.8

Initial evaluation of TB pericarditis is as demonstrated by the case. Echocardiography is useful and accurate for the detection of pericardial effusion and tamponade.2,8 The suggestion of tamponade is an absolute indication for pericardiocentesis. Resultant pericardial fluid analysis due to TB is classically an exudate, with high protein level and lymphcytic counts.2

Unfortunately, due to resource limitation, pericardial fluid in our case was not analysed for adenosine deaminase concentration (ADA). Its measurement has been found to be useful, with levels ranging from 30-60 U/L indicative of the presence of TB pericarditis.9 An observational study by Reuter et al8 on 233 patients in South Africa found that an ADA level of >40 U/L had an 87% sensitivity and 89% specificity for TB. Another study in Korea used both ADA and carcinoembryonic antigen to investigate the aetiology of pericardial fluid. They found no significant difference in ADA level between the group of patients with definite TB and those with suspected TB. Their study found a sensitivity and specificity of 93% and 97% respectively for a cut-off level of >40 U/L.10 Higher levels of ADA have also been found to be a prognostic indicator for the development of constrictive pericarditis and subsequent pericardectomy.2,11

The advent of testing for pericardial interferon-gamma, using the T.SPOT TB assay, and its diagnostic potential for TB pericarditis has been described in numerous studies.8,9,12,13 The T.SPOT TB assay is an enzyme-linked immunospot (ELISPOT) assay that measures the gamma interferon response of lymphocytes to the tuberculosis antigens ESAT-6 and CFP-10.14,15 The result is reported as number of IFN-gamma-producing T cells (spot-forming cells).14 If the spot counts in the TB antigen wells exceed a specific threshold relative to the control wells, an individual is considered positive for M. tuberculosis infection.14 The test should also be performed concurrently on peripheral blood; a significantly positive ratio between pericardial and peripheral blood suggests compartmentalisation and adds further evidence to the presence of tuberculous pericarditis.9,12

The TB.SPORT TB assay differs from the QuantiferON-TB Gold In-Tube (QFT-GIT) assay used in Australia, an ELISA-based test that uses three TB antigens (ESAT-6, CFP-10, TBB7.7).14 Both have FDA approval. QFT-GIT is a quantification of the IFN-gamma response to TB antigens, and is considered positive for M. tuberculosis infection if the response is above a test cut-off.14 The sensitivity of T-SPOT TB has been reported as 90%, superior to that of QFT-GIT, with a sensitivity of 80%. Both have specificity greater than 95%.14 Neither is accurate in the differentiation between latent and active tuberculosis infection.14 There is no available literature on the use of QFT-GIT as a diagnostic aid for pericardial TB.

Pericardial tissue can be sent for microscopy and culture, and examined histologically for granulomatous inflammation and caseous necrosis.1 Biopsy of the pericardium is usually reserved for when clinical suspicion is still high, duration of illness more than 3 weeks, and the aforementioned investigations have not yielded a positive result.14 However, it is usually only performed on patients from non-endemic areas, as it may add further morbidity without diagnostic value.1,4,12

PCR for M. tuberculosis is available, as was performed in this case. Cegielski et al compared the use of PCR, culture and histopathology for diagnosis of TB on either pericardial fluid or tissue biopsy.15 The sensitivity of PCR was higher with tissue specimens (12 of 15; 80%) than with fluid specimens (2 of 13; 15%; P = 0.002).15 In their study, including both specimen types, TB infection was correctly identified by culture in 30 out of 43 patients (70%) compared with 14 out of 28 patients (50%) by PCR.15 There was one false positive PCR result of a patient with Staphylococcus aureus pericarditis.15

The standard four drug anti-tuberculous therapy remains the cornerstone of treatment of TB pericarditis, with reduction in mortality from 80-90% to 8-17% in HIV-negative patients, and the development of constrictive pericarditis reduced from 88% to 10-20%.1

The exact role of adjuvant corticosteroids remains unclear.1,4,7,16,17 Only small studies have been conducted, with two of them before the HIV era. Limited data suggests that the use of corticosteroids can shorten the time of clinical symptoms and prevent fluid reaccumulation.17 Their use does not appear to affect the likelihood of progression to constriction.1 Guidelines from the American Thoracic Society, Centers for Disease Control, and Infectious Diseases Society of America issued in 2003 support the use of prednisolone 60 mg/day for 4 weeks with a tapering dose over the next 7 weeks.1 Further research is needed, with much anticipated results from the Investigation of the Management of Pericarditis (IMP) trial, a large multicentre randomised controlled trial currently underway.9

Pericardectomy is indicated in patients with persistent constrictive pericarditis. The timing and appropriate candidacy for surgical intervention is controversial. Some recommend a trial of medical therapy, with pericardectomy for patients who do not clinically respond after 4 to 8 weeks.1,14 Others suggest all patients with constrictive pericarditis should undergo pericardectomy once medical therapy has commenced.1

Conclusion

There is still much to know about tuberculosis pericarditis. There is scope for further research in diagnosis and clinical management, including the use of corticosteroids. TB pericarditis remains an uncommon but important clinical manifestation of extra-pulmonary TB, requiring a high index of suspicion on the clinician’s behalf. Worldwide, ongoing measures to reduce the incidence of infection with M. tuberculosis must be continued with vigilance.

References
CASE REPORT

An unusual case of Q fever in an immunised sheep officer

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3. School of Public Health, University of the Witwatersrand, Johannesburg, South Africa

ABSTRACT

It is often thought that Q fever vaccination is 100% protective against the disease. An unusual case of Q fever and its debilitating consequences is described here in a sheep industry development officer, who had been immunised. This report highlights the need for further research into improving Q fever testing and taking appropriate preventive measures against the disease. An urgent review of the current occupational health and safety policy is recommended, with implementation of universal mandatory Q fever immunisation for all new abattoir, cattle, goat, sheep and other workers, who may be exposed to Q fever, prior to the commencement of any field work.

Keywords: Q fever, zoonosis, vaccination, agriculture, prevention


Background

Q fever is a common zoonosis, with an almost worldwide distribution, caused by Coxiella burnetii.1 Farm animals and pets are the principal reservoirs of infection and transmission to humans is usually via inhalation of contaminated aerosols. Occupational groups with close association with farm or wild animals are most at risk. Immunisation is usually protective. A case of Q fever in a previously immunised Victorian sheep industry development officer (a ‘sheep officer’) is presented. In general, the qualification requirements of a sheep officer include an undergraduate degree in the areas of science or agriculture, with optional industrial training or postgraduate education. At the time of the project, there was universal no Q fever vaccination program nor a requirement for vaccination in place for new staff such as this sheep officer. Although presumably she would have been aware of the disease, there was no formal training in prevention of Q fever required for the role.

Case report

A 24-year-old Victorian sheep officer presented to her general practitioner in June 2009 with a 3-month history of tiredness, intermittent headaches, dry cough, vomiting and diarrhoea. On presentation, all her vital signs and physical examination were unremarkable, except that she was obese with a body mass index of 35. Investigations included full blood examination, electrolytes, thyroid function test, iron, vitamin B12, folate and coeliac serology; all were within normal limits. Infectious diseases screening for toxoplasmosis and Epstein-Barr virus was negative. Cytomegalovirus IgG was positive, but IgM was negative. Subsequent Q fever serology (Pabino ELISA, Alere) revealed positive phase 2 IgG and negative phase 2 IgM, whereas the phase 1 complement fixation titre (CFT) was 16 and phase 2 CFT was 8 (Table 1). The pathologist’s interpretation was ‘Q fever serology suggestive of chronic Q fever infection. The seropositivity unlikely to be due to vaccination’.2

The patient returned for follow up a few months later in October 2009. She continued to experience intermittent headaches, fatigue, dry cough and vomiting. On further questioning, she had received Q fever vaccination on 19th March 2009, one week prior to the immunisation. She was tested by her company three weeks prior to the testing. The patient’s employer did not enquire about vaccinations. Furthermore, the patient was unaware that she needed to avoid exposure to Q fever for two weeks following the vaccination, as it takes approximately two weeks for protective immunity to develop.3

Further investigations to exclude Q fever complications were normal, including transthoracic echocardiogram, chest X-ray, and brain computed tomography scan. Repeat full blood examination revealed mild leukocytosis (11.8 x 10^9/L; reference range (rr) 4-11 x 10^9/L) and lymphocytosis (4.1 x 10^9/L; rr 1-4 x 10^9/L). Erythrocyte sedimentary rate was raised (23 mm/hr; rr, <12 mm/hr). Brucellosis and leptospirosis serology was negative. Repeat Q fever serology was identical to that performed earlier.

The patient referred to an infectious disease physician. A 4-week course of doxycycline 100 mg twice daily was prescribed. In the following month, the patient reported moderate improvement in symptoms, with less cough, fewer headaches and resolution of diarrhoea. In December 2009, the patient still complained of ongoing fatigue, dizziness, cough, headache and myalgia. In February 2010, her symptoms remained the same. Q fever serology was again repeated which revealed a reduction in the level of phase 1 CFT (from 16 to 8). Other serological parameters remained the same (see Table 1).
The patient continued to experience fatigue with minimal exertion physically and mentally. Work performance had been greatly affected and she could only work up to 5 hours/day. Her headaches and dizziness persisted over the next 12 months. Worker’s compensation was involved and the claim was accepted and substantiated. On occasions when she wanted to work longer hours such as going to field trips, she often had to spend the next day in bed, recovering from her exertion. In December 2010, she was diagnosed with post-Q fever fatigue syndrome by an infectious diseases expert. No further courses of antibiotics were prescribed. She was referred to a psychologist for ongoing support and counselling. Due to fatigue and impaired working performance, she constantly experienced frustration and low mood. In August 2011, she was diagnosed with depression and the antidepressant sertraline was trialled without much improvement. She was unable to work and had to resign from her job in June 2012. Her current treatment comprises regular vitamin D, vitamin C, zinc, and vitamin B₁₂ supplements. To date, the patient has remained debilitated from fatigue and not capable of resuming any work. This has affected her family relationships significantly.

Discussion

Q fever is a zoonosis caused by the highly infectious *C. burnetii*, an obligate Gram-negative intracellular organism. Cattle, sheep and goats are the main reservoirs for infection in humans. Humans are infected by contact with infected animals or their products. In Australia, since the introduction of the Q fever vaccine (first in the abattoirs in 1991, and later more widely in the rural community in 2001-2006 through the National Q Fever Management Program), the incidence rate has dropped substantially, from 800 cases annually prior to the program to 303 notified cases in 2009.¹

In this case, chronic Q fever infection was diagnosed on the basis of both positive phase 1 and phase 2 CFT (titres of 16, 8 respectively).² *C. burnetii* has phase 1 and phase 2 lipopolysaccharides against which the human body mounts an antibody immune response. Detecting these antibodies forms the basis of laboratory diagnosis. Phase 2 antibodies are positive in acute Q fever, whereas phase 1 antibodies remain elevated in chronic disease.³ During acute Q fever, IgM antibodies develop against phase 1 and phase 2 forms, whereas IgG antibodies develop only against the phase 2 forms. The current Q fever vaccine (Q-VAX, CSL, Australia)³ composed of a killed suspension of virulent phase 1 organisms, stimulates immune response predominantly against phase 1 antigen.

In Australia, Q-VAX can only be given to people who are tested negative on both serology and skin tests, and this patient was no exception. However, she developed dry cough, headaches and diarrhea shortly after vaccination. There are a few possible scenarios. Firstly, she could have contracted Q fever just prior to the pre-vaccination tests. As the antibodies only often develop 2 to 3 weeks after inoculation, it was possible that her pre-vaccination tests were performed prior to the development of detectable antibodies. Secondly, she could have contracted Q fever after being immunised but before the development of protective immunity, as vaccination during the incubation of Q fever does not prevent the onset of the disease. Thirdly, the vaccination might have failed to confer immunity. This would challenge the 100% protection claimed for Q fever vaccination.⁷

With respect to treatment, doxycycline 100 mg twice daily was recommended to treat acute Q fever.⁸ Although a prolonged course of treatment is suggested to treat chronic Q fever endocarditis,⁹ there is no universal consensus as to the best treatment for chronic infection. In this instance, as the initial serology was low positive and without any systemic complications, only a one month course of doxycycline was prescribed, with good response. Despite treatment, the patient continued to have symptoms ascribed to post-Q fever fatigue syndrome. Patients often present with prolonged lassitude, myalgia, arthralgia, sweats and painful lymphadenopathy.¹⁰ The dominant symptom is an incapacitating fatigue out of proportion to the degree of prior activity, as exemplified in this case. This often lasts beyond a year, up to more than 10 years.¹¹ A United Kingdom study reported that chronic fatigue was experienced in 65% of Q fever sufferers.¹² In Australia, post-Q fever fatigue syndrome is the most common chronic sequel to acute Q fever, affecting 10-15% of patients.¹³ It is believed that cytokines and other immune mediators generated by the dysregulated cell-mediated immunity in response to a persisting low level of *C. burnetii* antigens, result in the symptoms.¹⁴

This case highlights several important issues in relation to microbiology and occupational health. Firstly, more research is needed to ascertain the current vaccine’s claimed protective effectiveness. Secondly, as the current serology and skin test may not detect recent subclinical infection, there is a need to develop and employ more sensitive diagnostic tests to detect Q fever infection earlier. The use of PCR for earlier diagnosis might be a cost-effective consideration. Most importantly, with respect to occupational safety, there should be an urgent call to review the current occupational safety policy, with implementation of universal mandatory Q fever immunisation of all new abattoir, cattle, goat and sheep workers, that may be exposed to Q fever, prior to the commencement of any field work. They should be advised that it takes around two weeks before the vaccination becomes protective and that they should avoid exposure in the meantime.

Acknowledgements

We would like to acknowledge A/Prof Ross Philpot, infectious disease physician, for his assistance in the preparation of the manuscript.

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<table>
<thead>
<tr>
<th>Table 1</th>
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<tr>
<td>INVESTIGATION</td>
<td>JUNE 2009</td>
</tr>
<tr>
<td>Phase 1 CFT titre</td>
<td>16</td>
</tr>
<tr>
<td>Phase 2 CFT titre</td>
<td>8*</td>
</tr>
<tr>
<td>Phase 2 IgM</td>
<td>Negative</td>
</tr>
<tr>
<td>Phase 2 IgG</td>
<td>Positive</td>
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</tbody>
</table>

* A single CFT titre of >8 for antibodies to phase II antigen indicates past infection.²  
** A trial of doxycycline was given in Nov 2009.
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The format of the Annals of the ACTM will, in general, follow guidelines of the "Uniform requirements for manuscripts submitted to biomedical journals" and published by the International Committee of Medical Journal Editors (http://www.icmje.org/index.html).

The Annals will appear twice a year and will consider for publication, papers on a wide range of topics relating to tropical and travel medicine. All papers will be refereed prior to acceptance for publication. Papers will be included in one of the following categories:

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d) Research Reports (1,000-2,000 words)
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Figures to be included: 1/4 page size = 250 words; 1/2 page size = 500 words etc. One page with images is approximately 900 words, two pages with image is approximately 1,800 words. Manuscripts should be double spaced and a short summary should be included at the beginning of the paper after the title and author details. Title page with contributor names and addresses should be on a separate page. Each table and figure should be on a separate page together with an appropriate caption, explanatory notes etc. Any acknowledgements should be included at the end of the paper before the references. Where appropriate, authors must confirm in the paper that experimental procedures on humans and animals conformed to accepted international ethical guidelines. References should be numbered consecutively in order of first appearance in the text. For details of references, consult the “Uniform requirements for manuscripts submitted to biomedical journals” available at http://www.icmje.org/index.html.

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