Case Report

Reversible hearing impairment: delayed complication of murine typhus or adverse reaction to azithromycin?

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Delayed and reversible hearing loss occurred in a 55-year-old male patient with murine typhus infection. The patient had the initial symptoms of headache, fever and chills, followed by the occurrence of bilateral hearing loss on day 9 from fever onset. Murine typhus was diagnosed with a high IgM titre by indirect immunofluorescence assay. After treatment with azithromycin and prednisolone, the fever and other symptoms subsided gradually and bilateral hearing loss improved 3 weeks later. Though an adverse reaction to azithromycin could not be ruled out, delayed onset of hearing loss was more likely a complication of murine typhus, mainly because the hearing loss did not occur during the azithromycin usage period. Although hearing loss due to murine typhus is rare, clinicians should be alert to the existence of such a delayed complication.

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Introduction

Murine typhus, caused by *Rickettsia typhi*, has various clinical manifestations. Fever and headache are the most common clinical presentations. Other symptoms and signs include rash, arthralgia, hepatomegaly, abdominal pain, cough, diarrhoea and confusion (Bernabeu-Wittel *et al.*, 1999; Dumler *et al.*, 1991; Fergie *et al.*, 2000; Gikas *et al.*, 2002; Hernandez Cabrera *et al.*, 2004; Silpapojakul *et al.*, 1993; Whiteford *et al.*, 2001). Among the rare neurological complications, central nervous system abnormality is the most commonly described presentation (Masalha *et al.*, 1998; Silpapojakul *et al.*, 1991; Vallejo-Maroto *et al.*, 2002). Peripheral nerve involvement has only been reported in a limited number of case reports (Tsiachris *et al.*, 2008; Vander *et al.*, 2003). Here we present a case of reversible bilateral hearing loss associated with murine typhus.

Case report

A healthy 55-year-old male presented to our emergency department on 20 December 2005 with a 4-day history of headache, fever and chills. He did not complain of any

obvious upper airway symptoms such as cough, rhinorrhoea or sore throat. He was alert and his neck was not rigid. There was no skin rash. The remaining physical examination was unremarkable. The chest radiography revealed infiltration over the left low lobe. Laboratory tests revealed a white blood cell count of $5600 \mu\text{l}^{-1}$ (normal range, $4000\text{--}10\,000 \mu\text{l}^{-1}$), an elevated C-reactive protein level of $78.3 \mu\text{g ml}^{-1}$ (normal $<5 \mu\text{g ml}^{-1}$), an elevated aspartate aminotransferase (AST) level of 103 U l^{-1} (normal range, $10\text{--}35 \text{ U l}^{-1}$) and an elevated alanine aminotransferase (ALT) level of 76 U l^{-1} (normal range, $10\text{--}40 \text{ U l}^{-1}$). He received oral medications including cephadrine (250 mg q.i.d. per os), acetaminophen (500 mg t.i.d. per os) and azithromycin (500 mg q.d. per os) for 3 days, then he was discharged.

Five days later, this patient visited our emergency department again due to sudden bilateral hearing loss. His body temperature was 38.1°C . No obvious ear/nose/throat abnormality was noted after detailed examination by a specialist. Brain computed tomography revealed no space-occupying lesion. Laboratory tests revealed a mildly elevated white blood count ($9950 \mu\text{l}^{-1}$), elevated C-reactive

protein level ($82.7 \mu\text{g ml}^{-1}$) and elevated aminotransferases (AST, 150 U l^{-1} ; and ALT, 208 U l^{-1}).

He was admitted to the neurological intensive care unit with suspected meningitis with acoustic nerve involvement. Cerebrospinal fluid studies revealed that the cell count was $2 \text{ cells } \mu\text{l}^{-1}$ (lymphocyte/monocyte: 0/2), glucose was 44 mg dl^{-1} (normal range $40\text{--}80 \text{ mg dl}^{-1}$) and protein was 77 mg dl^{-1} (normal range $15\text{--}45 \text{ mg dl}^{-1}$). Aerobic and anaerobic cultures of the cerebrospinal fluid yielded no pathogen. Both India ink and cryptococcus antigen results were negative. The results of Venereal Disease Research Laboratory (VDRL) testing for syphilis, virus isolation and varicella-zoster virus IgM were all negative.

Rickettsial disease was suspected due to impaired liver function tests and fever episodes. Indirect immunofluorescence assays for scrub typhus and Q fever were negative. An indirect immunofluorescence assay (*R. typhi* IFA slide kit; PanBio) performed at the Taiwan Center for Disease Control laboratory revealed positive IgM and IgG (both $>1:640$) against *R. typhi* on the 14th day after his fever onset. Positivity of murine typhus infection is determined by a fourfold increase of IgG in paired serum samples or any IgM more than 1:80.

Empiric antimicrobial agents acyclovir (750 mg q.8 h), ceftriaxone (1 g q.12 h) and vancomycin (1 g q.12 h) were prescribed at admission. Prednisolone $30 \text{ mg per os b.i.d.}$ was also prescribed for the hearing impairment. The dose of prednisolone was tapered over 10 days. The fever subsided 2 days later and he expressed subjectively slight improvement of bilateral hearing ability.

Magnetic resonance imaging examination of the brain on day 3 of admission revealed no intracranial lesions. The result of his pure tone audiometric test was bilateral hearing impairment of total frequency. This patient was discharged on 5 January 2006. His hearing ability recovered with residual bilateral high-frequency hearing loss, which was measured by a pure tone audiometric test 11 days after discharge (Fig. 1) and at a 1-year follow-up visit.

Discussion

Neurological complications of rickettsial diseases occur in 2–5 % of patients (Marrie & Raoult, 1992). Nervous system complications may develop in the early phase of the disease or as a delayed complication (Archibald & Sexton, 1995; Masalha *et al.*, 1998; Vallejo-Maroto *et al.*, 2002). Among the rare peripheral nerve complications of rickettsial diseases, facial paralysis in murine typhus infection and Guillain-Barré syndrome associated with scrub typhus have been reported (Lee *et al.*, 2007, 2009; Vander *et al.*, 2003). Hearing impairments can manifest as unilateral or bilateral hearing loss in many rickettsial diseases (Table 1). Hearing impairment in Rocky Mountain spotted fever has been known for decades to be a long-term sequela (>1 year) (Archibald & Sexton, 1995; Steinfeld *et al.*, 1988) or a transient deficit (Dolan *et al.*, 1986). However, hearing

Fig. 1. Results of pure tone audiometric tests on 26 December 2005 (a) and 16 January 2006 (b).

impairment as a manifestation of murine typhus was only reported in 2008, where a murine typhus patient had sudden bilateral hearing loss 3 weeks after the onset of his symptoms (Tsiachris *et al.*, 2008). Here we report a murine typhus patient who developed sudden hearing loss 9 days after fever onset. Both hearing impairment events presented as a delayed complication.

Tetracycline-based antibiotics, including doxycycline, are the first choice for treatment for rickettsial diseases. A study from Thailand reported that a 3-day course of azithromycin (500 mg q.d.) was as effective as a 7-day course of doxycycline (100 mg q.12 h) for rickettsial diseases (Phimda *et al.*, 2007). The fact that our patient became afebrile with azithromycin also reveals its effectiveness. Hearing loss has been noted as an adverse effect of azithromycin since 1994 (Wallace *et al.*, 1994). When the adverse effect of azithromycin is associated with prolonged treatment duration for *Mycobacterium* lung diseases or people living with human immunodeficiency virus, it is usually reversible (Lo *et al.*, 1999; Tseng *et al.*, 1997; Wallace *et al.*, 1994). In other instances, hearing impairment related to a short course of azithromycin usage was mostly irreversible in healthy patients (Mick & Westerberg, 2007; Ress & Gross, 2000), with the exception of one case (Mamikoglu & Mamikoglu, 2001). Although our patient had received a short course of azithromycin treatment, we assume that this hearing impairment event was related to

Table 1. Clinical characteristics of cases of rickettsial disease-related hearing loss reported in the English literature

A case with deafness, urinary incontinence and peripheral neuropathy was reported without detailed description of the related duration and management of deafness (Archibald & Sexton, 1995).

Disease	Unilateral or bilateral	Day of onset of fever	Antimicrobial agent	Steroid	Recovery, duration of hearing loss	Reference
Murine typhus	Bilateral	5	Azithromycin, 500 mg q.d. for 3 days	Prednisone 30 mg q.d. tapered over 10 days	Yes, 22 days	This case
Rocky Mountain spotted fever	Bilateral	21	Doxycycline, 200 mg q.d. for 21 days	Nil	Yes, 14 days	Tsiachris <i>et al.</i> (2008)
	Bilateral	Same day	Chloramphenicol, cefoperazone	Nil	Yes, 50 days	Steinfeld <i>et al.</i> (1988)
	Bilateral	16	Tetracycline for 10 days	40 mg per day for 10 days	Yes, 14 days	Dolan <i>et al.</i> (1986)
Mediterranean spotted fever	Unilateral	18	Doxycycline, 200 mg q.d. for 10 days	Nil	Yes, 90 days	Tsiachris <i>et al.</i> (2008)
African tick-bite fever	Unilateral	>63	Initially no anti-rickettsial treatment; doxycycline* after hearing loss developed	Prednisone 37.5 mg daily, followed by four courses of intravenous methyl prednisolone 1 g q.o.d. for 6 days.	No recovery	Jensenius <i>et al.</i> (2006)
Scrub typhus	Bilateral	17	Ceftriaxone 1 g q.12 h for 7 days, doxycycline 200 mg q.d. for 7 days	Nil	Yes, 24 days	Mahajan & Bakshi (2007)
	Bilateral	7	Doxycycline 200 mg q.d. for 7 days	Nil	Yes, 22 days	Premaratna <i>et al.</i> (2006)
	Bilateral	14	Chloramphenicol and doxycycline*	Nil	Yes, rapid recovery, 6 months, confirmed by audiometry	
	Bilateral (two cases)	10, 9	Tetracycline*	Nil	Yes, rapid recovery, objective recovery in 2 weeks–3 months	Premaratna <i>et al.</i> (2006)
	Bilateral (three cases)	11, 12, 10	Doxycycline*	Nil	Yes, rapidly improved	

*Data on the duration of antimicrobial therapy are not available.

murine typhus because: (1) the hearing loss developed 4 days after stopping azithromycin treatment, not during the period of azithromycin usage; and (2) the hearing deficit was reversible in an otherwise healthy patient after receiving a short course of azithromycin.

A study on spotted fever group rickettsiae revealed the involvement of *Rickettsia* in endothelial cells, increasing microvascular permeability (Walker, 2007) and progressing to a vasculitis which affected the vasa vasorum of the cochlea or the vasa nervosum of the cochlear nerve. The above was proposed on the occurrence of a hearing impairment (Tsiachris *et al.*, 2008). In animal model studies, cortisone was found to have no effect on the development of immunity and on the resistance to challenge with murine typhus (Downs & Whitmire, 1957). Early administration of doxycycline and corticosteroids is not beneficial for *Rickettsia rickettsii* infection because the pathogenesis includes not only an immunological reaction but also direct invasion (Breitschwerdt *et al.*, 1997; Walker & Henderson, 1978). In the only two murine typhus-related hearing impairment cases, hearing impairment was a delayed complication, occurring after the systemic inflammation symptoms developed. This suggested that the mechanism of the hearing loss may partly be an immunological process or a sequela of nerve destruction. Also, Guillain-Barré syndrome (Lee *et al.*, 2007, 2009) as a complication of rickettsial diseases suggests that the occurrence of an immunological process could cause neuropathy.

There are no definitive guidelines for managing sudden hearing loss associated with rickettsial diseases. The impact of corticosteroids on the pathogenesis of rickettsial diseases is controversial (Downs & Whitmire, 1957; Wei *et al.*, 2006). Previous reports described that the management of hearing impairment induced by rickettsial disease was either conservative or involved continuing antibiotic treatment (Table 1). The patient in the only previous murine typhus case involving hearing loss recovered without steroid therapy, but he received prolonged doxycycline treatment (Tsiachris *et al.*, 2008). Our patient recovered without prolonged antimicrobial therapy but prednisolone was used for 10 days. The limited number of cases of hearing loss related to rickettsial diseases (Table 1) makes the analysis of the benefit from steroid use and effective antibiotic therapy inconclusive.

To our knowledge, this is the first report of hearing impairment associated with murine typhus in Asia. It would be helpful for clinicians to recognize that murine typhus could manifest as fever associated with subsequent hearing impairment. Appropriate diagnosis and empirical antibiotics are necessary, whereas corticosteroid treatment is still controversial, for managing the hearing impairment complication related to murine typhus.

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