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MAIN ARTICLE

Evoked response audiometry in scrub typhus: prospective, randomised, case–control study

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Abstract

Objective: To investigate the hypothesis of cochlear and retrocochlear damage in scrub typhus, using evoked response audiometry.

Study design: Prospective, randomised, case–control study.

Methods: The study included 25 patients with scrub typhus and 25 controls with other febrile illnesses not known to cause hearing loss. Controls were age- and sex-matched. All subjects underwent pure tone audiometry and evoked response audiometry before commencing treatment.

Results: Six patients presented with hearing loss, although a total of 23 patients had evidence of symmetrical high frequency loss on pure tone audiometry. Evoked response audiometry found significant prolongation of absolute latencies of wave I, III, V, and wave I–III interpeak latency. Two cases with normal hearing had increased interpeak latencies. These findings constitute level 3b evidence.

Conclusion: Findings were suggestive of retrocochlear pathology in two cases with normal hearing. In other patients, high frequency hearing loss may have led to altered evoked response results. Although scrub typhus appears to cause middle ear cochlear and retrocochlear damage, the presence of such damage could not be fully confirmed by evoked response audiometry.

Key words: Audiometry, Evoked Response; Scrub Typhus; Retrocochlear Diseases; Hearing Loss

Introduction

Scrub typhus is caused by *Rickettsia tsutsugamushi*, and is an infectious disease transmitted to humans through the bite of Trombiculid mites (also known as berry bugs; harvest mites; red bugs; scrub-itch mites) that live on mice and rats. The mite has four life cycle stages: egg, larva, nymph and adult. The larva is the only stage that can transmit the disease to humans and other vertebrates.

Scrub typhus is common in eastern and south-eastern Asia, India, northern Australia and adjacent islands, and is hence commonly known as tropical typhus.[1–3] The seasonal occurrence of scrub typhus varies in different countries according to the climate, occurring more frequently during the rainy season. Certain areas provide optimal conditions for the infected mites to thrive, such as forest clearings, river-banks and grassy regions. These small geographic regions are high-risk areas for humans, and have been termed typhus or mite 'islands'.[1] The geographical location of scrub typhus, the initial sore caused by the chigger bite, and the occurrence of blood-borne antibodies against the infectious organism are useful in establishing the diagnosis.[1–3]

The main symptoms of scrub typhus are fever, a wound at the site of the bite, a spotted rash on the trunk and swelling of the lymph glands. Scrub typhus is also associated with hearing loss, which is present in approximately one-third of cases (although few such cases of hearing loss have been reported).[1,2,4–7]

Unilateral or bilateral deafness can occur in many rickettsial diseases. The assumed mechanism for such hearing loss is cochlear and/or VIIIth nerve damage due to an immune-mediated reaction, vasculitis or demyelinating neuropathy.[4–9] The presence of cochlear and retrocochlear damage in scrub typhus has been proven histopathologically, but only in five patients.[10] No published study has investigated the audiological effects of scrub typhus within a large sample population.

Hence, we conducted a prospective, randomised, case–control study to investigate the presence of cochlear and retrocochlear damage in patients with scrub typhus, using evoked response audiometry.

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Materials and methods

This prospective, randomised, case–control study assessed 25 patients suffering from scrub typhus (the case group) together with 25 patients suffering from febrile illnesses not known to cause hearing loss (the control group). The case group patients were randomly selected (irrespective of the stage of the disease) from the department of medicine in order to avoid any biasing effect of disease severity or duration on evoked response audiometry results. The control group consisted of simple febrile cases (due to aetiology not known to cause hearing loss), in order to remove any biasing effect of increased body temperature upon evoked response audiometry.

We excluded from the study patients with a conductive or mixed hearing loss on pure tone audiometry, and any subjects with a history of smoking, hearing loss, ototoxic drug intake, noise exposure, ear disease, diabetes, hypertension, ischaemic heart disease, renal disorders, tuberculosis, or any other disease or condition known to cause hearing loss.

The study was approved by the relevant institutional review board, and informed consent was obtained from all patients included.

Subjects' ages ranged from 11 to 42 years in both groups. The case group had no sex predominance (male: female ratio = 1.08:1) and a mean presentation age of 27.36 years. The control group had a male:female ratio of 1.27:1 and a mean presentation age of 27.68 years.

The diagnosis of scrub typhus was based on clinical examination and standard laboratory tests; relevant factors included high grade fever, myalgia, headache, a characteristic rash (eschar) at the chigger bite site, thrombocytopenia, altered serum aminotransferases and positive immunological tests (i.e. Weil–Felix test and enzyme-linked immunosorbent assay). The presence of fever and a positive immunological test result were mandatory for scrub typhus diagnosis.

All control group patients were suffering with acute upper respiratory tract infection.

The case and control groups were matched according to their age, sex, economic status, living conditions, lifestyle and occupation.

Both groups underwent clinical examination followed by audiological and clinical vestibular evaluation (i.e. positional and positioning tests) before starting any treatment. Audiometric evaluation was performed using a pure tone audiometer (AC 40 clinical audiometer, Interacoustics A/S, DK-510, Assens, Denmark) installed in a sound-proofed room within the otolaryngology department.

Evoked response audiometry was performed using EP-15 equipment (Interacoustics A/S, DK-510, Assens, Denmark) in both groups, in order to investigate the effect of scrub typhus on the auditory pathway. Patients were tested in the supine position, without sedation. Potentials were measured between active electrodes placed on the mastoid process of the side to be tested, and a reference electrode placed on the vertex. A ground electrode was placed on the forehead. The test stimulus consisted of rarefaction clicks at 80 dB SPL, delivered at a rate of 39.1 per second. The study used a low pass filter at 150 Hz and a high pass filter at 3000 Hz, with 2000 sweeps. Stimuli were delivered via head phones to the test ear.

Five waves (numbered I to V) were recorded per stimulus in each ear. The following criteria were followed for the identification of waves in brainstem evoked response audiometry. Wave I was defined as the latest of the initial peaks preceding the first major trough in the record, usually found after 1 millisecond. Wave III was defined as a major positive peak appearing between the first two negativities in the record, usually seen about 2 milliseconds before wave V. Wave V was defined as the last positive peak before the third major negativity in the record; the presence of a sharp negative deflection immediately following this wave was considered the hallmark feature of wave V. The study recorded the absolute latencies of waves I, III and V, and the interpeak latencies for waves I–III, III–V and I–V.

Statistical analysis of hearing loss was performed using Student's unpaired *t*-test. A p value of 0.05 or less was considered significant. Multiple comparisons were performed using the *t*-test with application of Bonferroni's correction; for these analyses, a p value of less than 0.004 (six latencies compared in two ears; $6 \times 2 = 12$; $0.05/12 = 0.004$) was taken as the final significance of the *t*-test.

Results

Of the 25 scrub typhus patients assessed, six patients presented with fever and hearing impairment as their initial symptoms. There was no associated vertigo or tinnitus in any of these six cases.

TABLE I
HEARING THRESHOLDS IN BOTH GROUPS, BY FREQUENCY

Group	0.5 kHz		1 kHz		2 kHz		4 kHz		8 kHz	
	R	L	R	L	R	L	R	L	R	L
Case	26.6	28.4	30.2	29.6	31.6	33.4	39.8	38.54	53.96	51.52
Control	12.8	13.2	18	16.4	22.4	20.72	25.6	24.2	27.8	27.4

Data represent mean values in dB. R = right ear; L = left ear

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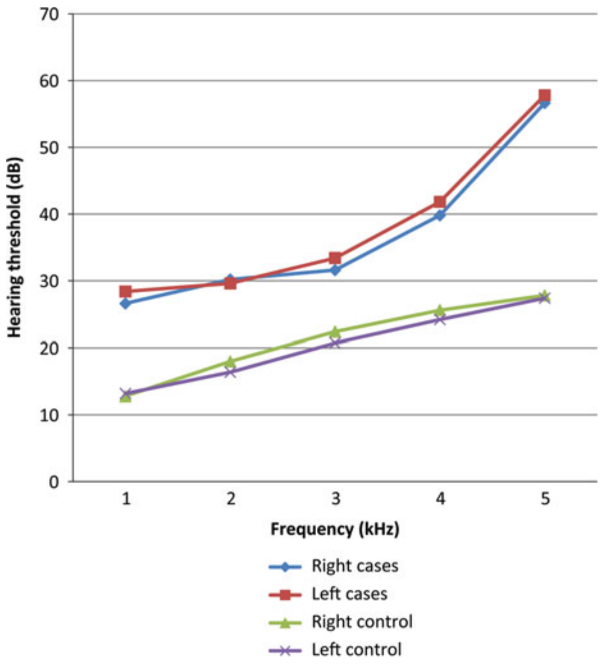

FIG. 1

Hearing loss in case and control groups, on pure tone audiometry.

Pure tone audiometry

Results for pure tone audiometry are shown in Table I and Figure 1. The control group had normal hearing levels (i.e. ≤25 dB) in both ears, except at 8 kHz. The case group had hearing loss in both ears, which increased at higher frequencies. Using the Fisher scale (i.e. the mean value of hearing thresholds at speech frequencies, i.e. 0.5, 1 and 2 kHz), 11 scrub typhus cases (44 per cent) were identified as having hearing loss, with mean hearing levels of 29.12 and 30.2 dB in the right and left ears, respectively. The other 14 cases had normal hearing levels, using the Fisher scale; however, of these 14 only two had normal hearing at all tested frequencies. There was a statistically significant difference in hearing threshold (in all tested frequencies) in case group as compared to control group ($p < 0.05$).

Evoked response audiometry

Evoked response audiometry results (i.e. the absolute latency of waves I, III and V, and the interpeak latency of waves I–III, III–V and I–V) were statistically analysed as shown in Table II. The case group had a statistically significant prolongation of waves I, III and V, compared with the control group ($p <$ 0.05). The case group also had significant prolongation of the wave I–III interpeak latency ($p < 0.05$) but not of the wave I–V and III–V interpeak latencies ($p >$ 0.05), compared with the control group. However, after Bonferroni correction the prolongation of wave I–III interpeak latency was shown to be statistically insignificant, compared with the control group.

Although wave I–III and I–V interpeak latencies do not normally alter in cases of hearing loss, in our study the wave I–III interpeak latency increased in six ears of scrub typhus cases with hearing loss (at speech frequencies), and in two ears of normal-hearing scrub typhus cases (Table III). An increased wave I–V interpeak latency was found in 11 ears of cases with hearing loss and in 14 ears of normal-hearing cases.

We compared the evoked response audiometry results of two normal-hearing scrub typhus cases with those of controls (Table IV). In these two cases, we observed a decrease in the wave I absolute latency and the wave III–V interpeak latency in the left ear, but an increase in all other absolute and interpeak latencies; furthermore, the latencies of wave III in the left ear and wave V in both ears, and the wave I–III and I–V interpeak latencies in the left ear, were increased more than the mean plus two standard deviations of the control group.

Although our study protocol did not include patient follow up, five patients (20 per cent) had follow-up visits three weeks after initial presentation. Of these patients, we found normal hearing thresholds in two and hearing improvement in three, at Fisher scale speech frequencies. However, all these cases had residual high frequency hearing loss. Evoked response audiometry was not repeated in these cases.

TABLE II

STATISTICAL ANALYSIS OF WAVE LATENCIES IN BOTH GROUPS

Wave latency	Ear	Latency mean (msec)		Latency SD (msec)		p
		Control	Case	Control	Case	
I absolute	R	1.36	1.48	0.09	0.32	0.09
	L	1.34	1.46	0.11	0.23	0.03
III absolute	R	3.28	3.54	0.11	0.42	0.05
	L	3.28	3.54	0.1	0.28	0.00
V absolute	R	5.19	5.45	0.08	0.47	0.01
	L	5.16	5.43	0.09	0.50	0.01
I–III interpeak	R	1.92	2.05	0.15	0.24	0.02
	L	1.93	2.08	0.15	0.28	0.02
III–V interpeak	R	1.96	1.91	0.11	0.3	0.42
	L	1.99	1.89	0.1	0.47	0.3
I–V interpeak	R	3.79	3.95	0.2	0.56	0.17
	L	3.81	3.98	0.15	0.43	0.08

SD = standard deviation; R = right; L = left

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TABLE III
PRESENCE OF INCREASED WAVE I–III AND I–V INTERPEAK LATENCIES* IN CASES WITH NORMAL AND IMPAIRED HEARING†

↑ interpeak latency*	Normal hearing (*n*)			Impaired hearing (*n*)		
	R	L	Bilat	R	L	Bilat
Wave I–III	–	2	0	4	2	2
Wave I–V	5	9	4	6	5	5

Data represent patient numbers. *Greater than mean + 2 standard deviations of control group. †At speech frequencies. R = right ear; L = left ear; bilat = abnormal values bilaterally

Discussion

This prospective, randomised, case–control study was performed at I G Medical College in northern India. To the best of our knowledge, this is the first prospective, case–control study to investigate cochlear and retrocochlear damage in patients with scrub typhus, using evoked response audiometry.

Friedmann *et al.* have reported their findings for histopathological examination of the temporal bones of scrub typhus patients.[10] They found mononuclear cellular infiltration of the macula, organ of Corti, vestibular nerve and Scarpa's ganglion. The endolymphatic duct was blocked with ossified fibrotic tissue. The VIIth and VIIIth cranial nerves had interstitial neuritis and patchy demyelination. Scarpa's ganglion and the vestibular nerve were more affected than the cochlear nerve. There was also evidence of inflammatory changes in the middle-ear cleft.

Based on these histopathological findings, scrub typhus should cause vertigo and mixed hearing loss. However, in the present study we did not find vertigo in any of our patients. Since we excluded patients with conductive and mixed hearing loss prior to study commencement, middle-ear effects could not be investigated in this study.

In the present study, we found hearing loss in 11 cases (44 per cent) at speech frequencies, while 23 cases (92 per cent) had hearing loss at frequencies of 2 kHz or greater. This hearing loss was symmetrical and sensorineural in character, and was likely to be due to cochlear pathology.[11] These findings are consistent with previously reported histopathological identification of cochlear damage in scrub typhus cases.[10] Our evoked response audiometry results were suggestive of auditory neural damage up to the lateral lemniscus in scrub typhus patients: we observed statistically significant ($p < 0.05$) prolongation of wave I, III and V latencies and the wave I–III interpeak latency.

It is well established that wave I and V latencies are prolonged in high frequency cochlear and retrocochlear loss, and that the wave V latency increases with increased hearing loss at 4 kHz.[12–15] Jerger and Johnson reported that wave V latency is stable up to 60 dBHL (hearing threshold) and then increases in a linear fashion for a maximum of approximately 0.4 milliseconds through 90 dBHL.[15] In patients with high frequency loss, wave V latency increases, requiring a greater intensity level before this wave can be identified.[13,16] At low intensity levels, the latency is greatly delayed because only the apical region (1–2 kHz) contributes to the response. Higher intensity levels involve the basal cochlear region, responsible for hearing at 4 kHz and higher, which is activated within a short interval, leading to decreased wave latency. Furthermore, in cases of cochlear pathology, the latency at 80 dBnHL can be near-normal due to the recruitment phenomenon. Sometimes, the wave I–V interpeak latency interval decreases because wave I is prolonged more than wave V.[12] The wave I–V interval has been reported to decrease progressively with increased cochlear hearing loss at higher frequencies.[17] However, in our study we also observed retrocochlear pathology in two scrub typhus cases with normal hearing. This indicates that scrub typhus can affect both the cochlear and retrocochlear regions, in agreement with previously reported histopathological findings.[10]

TABLE IV
WAVE LATENCIES OF CONTROLS AND TWO NORMAL-HEARING CASES*

Wave latency	Ear	Control		NH case mean
		Mean	SD	
I absolute	R	1.36	0.09	1.45
	L	1.34	0.11	1.17
III absolute	R	3.28	0.11	3.27
	L	3.28	0.1	3.52
V absolute	R	5.19	0.08	5.34
	L	5.16	0.09	5.35
I–III interpeak	R	1.92	0.15	2.05
	L	1.93	0.15	2.35
III–V interpeak	R	1.96	0.11	2.07
	L	1.99	0.1	1.83
I–V interpeak	R	3.79	0.2	4.14
	L	3.81	0.15	4.19

Data represent milliseconds unless otherwise specified. *At all tested frequencies on pure tone audiometry. NH = normal-hearing; SD = standard deviation; R = right; L = left

- **This case–control study used pure tone and evoked response audiometry to evaluate hearing in 25 scrub typhus cases and 25 age- and sex-matched controls (with febrile illnesses not associated with hearing loss)**
- **Of the 25 cases, 11 had symptomatic hearing loss, 23 had high frequency hearing loss and two had normal hearing**
- **Previously reported cases of scrub typhus had histopathological evidence of middle-ear, cochlear and retrocochlear damage**
- **This study found evidence of cochlear and retrocochlear hearing loss, but none of middle-ear, vestibular or facial nerve damage**

In this study, five scrub typhus patients showed hearing improvement in the speech frequencies but residual high frequency hearing loss. It may be the case that the disease prompts an inflammatory response which resolves with medication, leading to hearing improvement especially in the lower frequencies; however, this hypothesis is based on only five cases. Twenty-three of our scrub typhus cases had high frequency hearing loss, with altered evoked responses as discussed above.

Our study's evoked response audiometry results are in agreement with previously reported histopathological evidence for cochlear and retrocochlear damage in cases of scrub typhus. However, only limited inferences can be drawn from this data, as only two of our scrub typhus patients had normal hearing, and other cases had high frequency hearing loss which may have affected evoked response results. The middle-ear effects of scrub typhus were not evaluated, as patients with conductive and/or mixed hearing loss were excluded from the study. The study was also limited by the lack of evoked response audiometry in the follow-up period. Further research is therefore needed to investigate more fully the audiological effects of scrub typhus, using evoked response audiometry.

Conclusion

This study proved cochlear and retrocochlear damage in scrub typhus but further similar research is needed to investigate all the otological effects of scrub typhus. Although, histopathological evidence is the gold standard and has higher validity but needs temporal bone excision, therefore audiology plays a major role in clinical research. ERA is a highly sensitive and specific investigation, and appeared beneficial in understanding the pathogenesis of hearing damage in scrub typhus.

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