

Trial of Chinese Medicine Wu-Ling-San for Acute Low-Tone Hearing Loss

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Key Words

Acute low-tone hearing loss · Steroid · Wu-Ling-San · Diuretics

Abstract

Purpose: We used new criteria to elucidate the demographics of acute low-tone sensorineural hearing loss (ALHL) and tested the Chinese medicine Wu-Ling-San as a treatment for ALHL. **Procedures:** We reviewed the medical records of patients with ALHL seen at the outpatient clinic of the Social Insurance Central General Hospital in Tokyo from April 2006 through August 2011. Patients were treated with an oral steroid, a diuretic, or Wu-Ling-San; alone or in combination. **Results:** We identified 130 definite and 48 probable ALHL cases. The mean age and male-to-female ratio in probable cases were significantly higher than those in definite cases ($p < 0.05$). The steroid-Wu-Ling-San combination was significantly more effective (100% recovery) than the diuretic alone (59%), Wu-Ling-San alone (62%), or the steroid-diuretic combination (60%, $p < 0.05$). **Conclusions:** ALHL can develop in older patients more frequently than we expected. The steroid-Wu-Ling-San combination is a possible new treatment for ALHL.

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Introduction

Acute low-tone sensorineural hearing loss (ALHL) is a common disease encountered in daily clinical practice. ALHL patients usually visit outpatient clinics because of acute onset of tinnitus, ear fullness, or autophony with consciousness of hearing impairment. Pure-tone audiometry shows an increased hearing threshold limited to the low-frequency range. Previous reports about ALHL [1–3] have used criteria proposed in 2000 by the Acute Profound Deafness Research Committee of the Ministry of Health, Labor, and Welfare of Japan (APDRC). These criteria include normal hearing level for high tones to exclude patients with other etiologies. As a result, older patients with ALHL are potentially excluded from the studies, because high-tone thresholds tend to rise with age.

ALHL is considered to be a mild illness because it tends to resolve spontaneously [2, 4]. Indeed, most patients recover within several days; however, for some patients the hearing loss is intractable. The pathogenesis of ALHL is still unclear, but endolymphatic hydrops [5–7] and autoimmunity [8, 9] are considered to be possible causes. Thus, diuretics (such as isosorbide), steroids, or a combination of these drugs is used to treat ALHL. However, previous reports have shown conflicting results on

Table 1. Characteristics of all patients included in this study

	No steroid, diuretic, or Wu-Ling-San	Steroid alone	Diuretic alone	Wu-Ling-San alone	Steroid + diuretic	Steroid + Wu-Ling-San	Overall
Patients, n	20	30	39	29	48	12	178
Mean age, years	47.3 ± 16.8	54.0 ± 18.9	41.1 ± 14.1	49.0 ± 15.7	46.1 ± 15.2	47.0 ± 20.8	47.3 ± 16.8
Sex, male/female	6/14	10/20	15/24	9/20	12/36	4/8	56/122
Period between onset and initial visit, days	6.2 ± 3.4	3.8 ± 2.4	5.7 ± 4.0	6.5 ± 5.0	4.6 ± 3.2	5.5 ± 4.2	5.2 ± 3.7
Sum of hearing loss at 3 low frequencies, dB	97.8 ± 27.5	116.5 ± 29.1	94.2 ± 24.8	92.2 ± 23.2	117.0 ± 27.1	112.1 ± 36.2	105.7 ± 29.0

Data are given as means ± SD.

the effectiveness of diuretics and steroids [2, 3, 10], and no consensus has been reached on the best therapeutic strategy for ALHL.

Here, we investigated the epidemiology of ALHL patients visiting our outpatient clinic, including patients with probable ALHL who had elevated high-tone thresholds. We also examined the effectiveness of the Chinese medicine Wu-Ling-San, alone and in combination with a steroid, in comparison with standard treatment with isosorbide with or without steroid, or steroid alone.

Materials and Methods

Patients

We retrospectively reviewed the medical records of patients who visited the outpatient clinic of the Social Insurance Central General Hospital from April 2006 through August 2011. The local Ethics Committee approved the protocol for the study.

Criteria for Diagnosis of ALHL

Our criteria for ALHL, modified from those proposed by the Study Group of APDRC, were as follows: (1) sensorineural hearing loss of sudden onset, with normal tympanic membrane findings; (2) symptom occurrence no more than 14 days before attendance at our department, and (3) a sum of pure-tone audiogram hearing loss at 3 low frequencies (125, 250, and 500 Hz; LT3) of 70 dB or more. We defined ALHL as 'definite' when the sum of hearing loss at 3 high frequencies (2, 4, and 8 kHz; HT3) was 60 dB or less, and as 'probable' when the sum at HT3 was more than 60 dB. We excluded 'probable' patients if the difference in HT3 between the affected and contralateral sides was greater than 10 dB, or if the difference in LT3 between the affected and contralateral side was less than or equal to 10 dB. Patients with spontaneous, positional, and positioning nystagmus were excluded from this study. Audiograms were obtained with an AA-98 audiometer (Rion, Tokyo, Japan).

Treatment

Patients were treated for 7 days with oral steroid alone (prednisolone 30 mg/day for 2 days, 20 mg/day for the next 2 days, and 10 mg/day for the next 3 days), diuretic alone (70% isosorbide 90 mg/day), Wu-Ling-San alone (7.5 g/day), a combination of the

same dosages of the steroid and the diuretic, or a combination of the same dosages of the steroid and Wu-Ling-San. At their request, some patients did not receive any of these medications. The choice of therapy was made almost randomly, although some patients refused steroids because of their adverse effects. All of the patients received vitamin B₁₂ and adenosine triphosphate disodium.

Outcomes

The outcome was evaluated within 1 week after initiation of treatment by using the criteria proposed by APDRC: 'complete recovery', hearing at LT3 recovered to within 20 dB of normal; 'partial recovery', hearing at LT3 improved by 10 dB or more compared with the initial audiogram, but not recovered to within 20 dB of normal; 'unchanged', an average loss at LT3 within 10 dB of that at the initial audiogram, and 'progression', an average loss at LT3 of more than 10 dB compared with the initial audiogram. Statistical differences were analyzed by using Student's t-test or Fisher's exact test. We considered values to be significantly different when the p value was <0.05.

Results

Patients

In the 178 patients included in this study, the overall mean age was 47.3 years and the male:female ratio was 56:122 (table 1); 130 patients had definite ALHL (table 2) and 48 had probable ALHL (table 3). Overall, there were no significant differences between treatment groups with regard to age, gender, period between onset and initial visit, or sum of LT3. However, there were significant differences between the definite and probable groups. The mean age of patients with probable ALHL was 66.6 years, significantly higher than the mean age of patients with definite ALHL (40.1 years; $p < 0.01$, Student's t test; fig. 1). The male:female ratio among probable cases was 22:26, significantly different from the ratio of definite cases, 34:96 ($p = 0.017$; Fisher's exact test). The sum of LT3 was also significantly higher in probable than in definite cases (122.2 vs. 99.7; $p < 0.01$; Student's t test).

Table 2. Characteristics of definite cases

	No steroid, diuretic, or Wu-Ling-San	Steroid alone	Diuretic alone	Wu-Ling-San alone	Steroid + diuretic	Steroid + Wu-Ling-San	Overall
Patients, n	16	16	34	21	35	8	130
Mean age, years	41.7 ± 13.9	40.3 ± 15.5	37.3 ± 10.6	43.0 ± 13.3	40.9 ± 13.8	37.8 ± 15.5	40.1 ± 13.2
Sex, male/female	4/12	2/14	13/21	4/17	9/26	2/6	34/96
Period between onset and initial visit, days	6.6 ± 3.5	4.2 ± 2.5	5.4 ± 3.9	5.6 ± 4.0	4.6 ± 3.2	5.3 ± 4.5	5.2 ± 3.6
Sum of hearing loss at 3 low frequencies, dB	93.4 ± 22.3	100.6 ± 19.4	89.7 ± 19.9	85.0 ± 17.7	119.7 ± 28.8	103.1 ± 29.3	99.7 ± 26.3

Data are given as means ± SD.

Table 3. Characteristics of patients with probable ALHL

	No steroid, diuretic, or Wu-Ling-San	Steroid alone	Diuretic alone	Wu-Ling-San alone	Steroid + diuretic	Steroid + Wu-Ling-San	Overall
Patients, n	4	14	5	8	13	4	48
Mean age, years	72.5 ± 6.1	69.7 ± 4.6	66.6 ± 4.0	64.8 ± 9.8	60.2 ± 8.7	65.5 ± 18.7	66.6 ± 8.4
Sex, male/female	2/2	8/6	2/3	5/3	3/10	2/2	22/26
Period between onset and initial visit, days	4.5 ± 2.1	3.4 ± 2.2	7.4 ± 5.0	8.9 ± 6.7	4.8 ± 3.1	6.0 ± 4.1	5.3 ± 4.2
Sum of hearing loss at 3 low frequencies, dB	115.0 ± 42.2	134.6 ± 28.2	125.0 ± 34.8	111.3 ± 26.4	109.6 ± 21.2	130.0 ± 46.5	122.2 ± 30.1

Data are given as means ± SD.

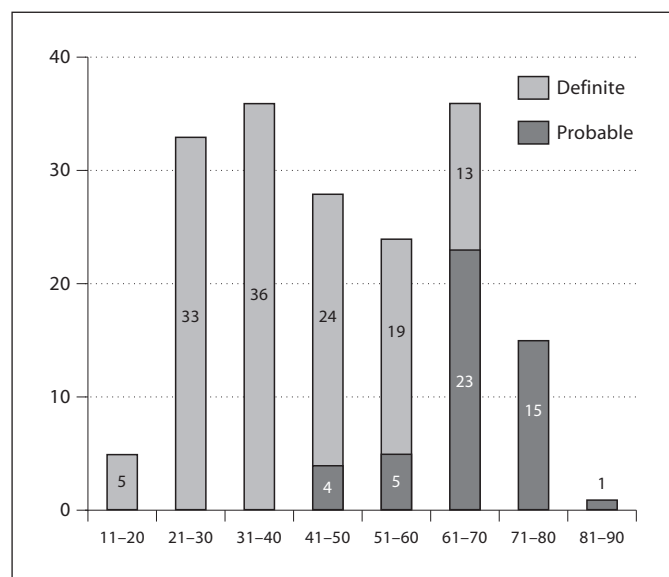


Fig. 1. Age distribution of ALHL patients in this study. Numbers in bars are the numbers of patients in each age group. In total, there were 130 patients with definite ALHL and 48 with probable ALHL.

Treatment Outcome

When all patients were considered together, the overall recovery rate (complete and partial recovery) was 67%. The overall recovery rates were 80% in the group that did not receive steroid, diuretics, or Wu-Ling-San; 73% in the steroid-only group; 59% in the diuretics-only group; 62% in the Wu-Ling-San-only group; 60% in the steroid-diuretic combination group, and 100% in the steroid-Wu-Ling-San combination group (fig. 2). The steroid-Wu-Ling-San combination provided significantly more improvement than the diuretic alone ($p = 0.01$; Fisher's exact test), the Wu-Ling-San alone ($p = 0.02$; Fisher's exact test), and the steroid-diuretic combination ($p = 0.01$; Fisher's exact test). Similar tendencies were seen when definite cases (fig. 3) and probable cases (fig. 4) were analyzed separately, but no statistically significant differences in the recovery rates were observed between groups ($p > 0.05$; Fisher's exact test). In addition, the recovery rates did not differ significantly when each treatment group was compared between the definite and probable cases ($p > 0.05$; Fisher's exact test).

Fig. 2. Treatment outcomes for all ALHL patients in this study. The total recovery rate (complete and partial recovery) was significantly higher in the steroid-Wu-Ling-San combination group than in the groups receiving a diuretic alone, Wu-Ling-San alone or a steroid-diuretic combination ($p < 0.05$, Fisher's exact test).

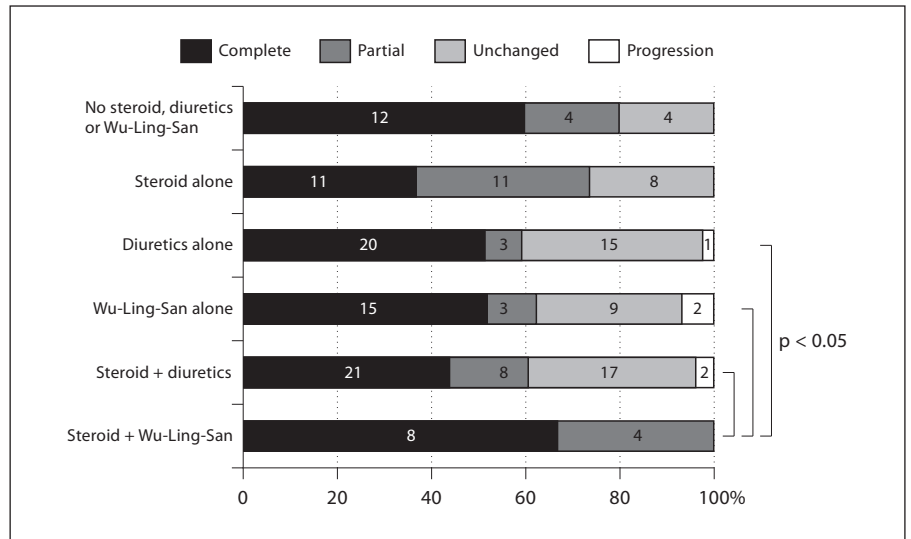


Fig. 3. Treatment outcomes in patients with definite ALHL.

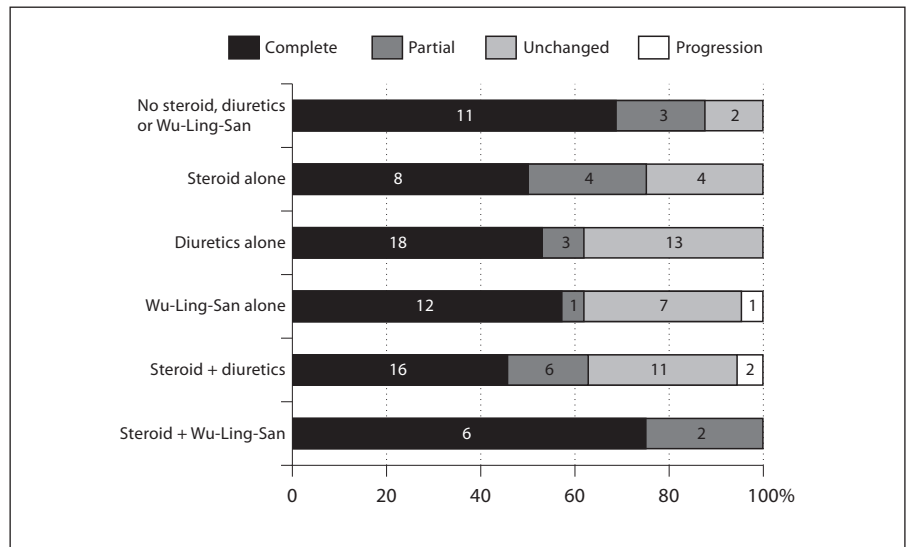
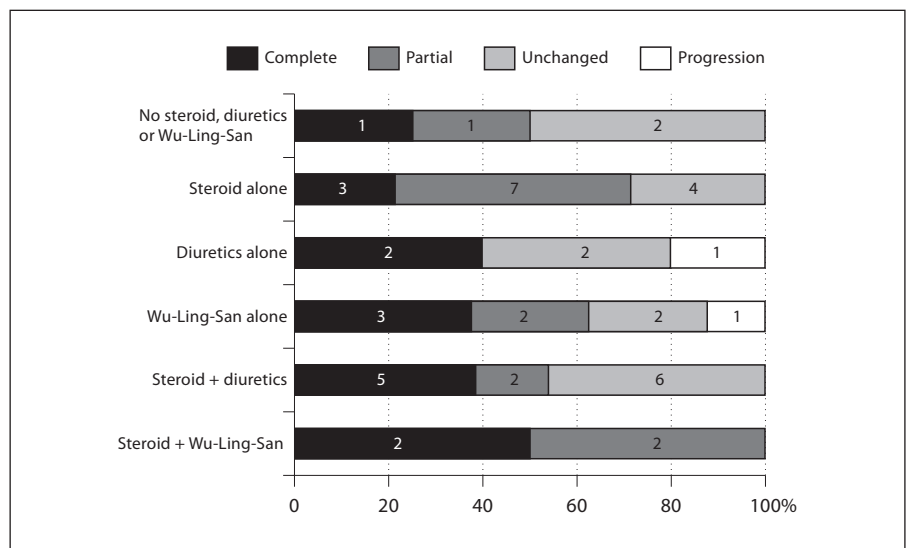


Fig. 4. Treatment outcomes in patients with probable ALHL.



Discussion

We examined the demographics and immediate treatment outcomes of patients with ALHL attending our outpatient clinic. When definite and probable cases were combined, the peak age of onset was in the mid-40s, and the male:female ratio was about 1:2. The combination of an oral steroid and Wu-Ling-San was more effective than the oral steroid or diuretic alone, neither of which significantly improved ALHL.

Since Abe [11] argued that ALHL is a separate disease from idiopathic sudden hearing loss, many studies have presented the epidemiological characteristics of, and therapeutic options for, ALHL. The criteria used to diagnose ALHL have varied in previous reports and continue to be a topic of discussion. Yamasoba et al. [5] diagnosed hearing loss as ALHL when the sum of LT3 was 100 dB or more and the sum of HT3 was 60 dB or less. Nozawa et al. [7] reported their criteria as an average hearing loss at LT3 of 30 dB or more and an average hearing loss at HT3 of 20 dB or less. APDRC proposed in 2000 that the diagnostic criteria should be an LT3 sum of 70 dB or more and an HT3 sum of 60 dB or less, and many studies follow these criteria. All of these standards include normal hearing levels at high tones and have, therefore, potentially excluded elderly ALHL patients, because the threshold for hearing high tones tends to be elevated in the aged population. The incidence and peak age of onset have therefore likely been underestimated. We included probable cases when HT3 was symmetrically impaired, in accordance with the 2006 recommendation of APDRC. This resulted in about one quarter of our cases being probable cases. Previously, the peak age of ALHL onset was reported to be in the late 40s to 50s [1, 2, 4, 7]. In our study, the mean age at onset was 47.3 years; however, the mean age of patients with definite ALHL was 40.1 years and that of patients with probable ALHL was 66.6 years. In addition, the ratio of males:females has been reported as 1:2 to 1:3 [2, 3, 7]; among our definite cases the ratio was similar (32:89, or 1:2.8), but the ratio among our probable cases was almost 1:1. This shift from female predominance to equal frequency in both sexes suggests an age-related change in the pathogenesis of ALHL. The sum of LT3 was also higher in probable cases than in definite cases, probably because hearing of low tones is also affected by aging.

ALHL is considered to be a mild disease because it tends to resolve spontaneously. Often the symptoms are so mild that some patients choose to leave it untreated. However, we also sometimes encounter intractable cases. The pathogenesis of ALHL is still unclear, but Ménière's dis-

ease also impairs hearing of low tones, and ALHL patients often show positive results on glycerol tests and electrocochleography [5, 7]. Therefore, the same etiology – endolymphatic hydrops – is suspected as a potential cause of ALHL, and ALHL is treated with the diuretic isosorbide, which reduces endolymphatic hydrops. On the other hand, immunological studies [8, 9] have suggested that autoimmunity is involved in the development of ALHL, so immunosuppressive drugs such as steroids are often given for ALHL via the oral [1, 10], intravenous [1], or intratympanic [12] route. Adenosine triphosphate and vitamin B₁₂ are also used to improve circulation and metabolism in the inner ear [4]. The effectiveness of steroids, diuretics, adenosine triphosphate, and vitamin B₁₂ differs among reports. Suzuki et al. [10] reported that oral steroids are effective and diuretics are not. Morita et al. [3] showed the merit of steroid-diuretic combinations and the ineffectiveness of administration of a steroid or diuretic alone. Kitajiri et al. [2] reported that steroids had no effect on ALHL. These conflicting results have inhibited the establishment of a standard therapy for ALHL. Our treatment outcomes were similar to those previously reported: 70% of patients recovered within 1 week [1, 10]. We found no significant differences in recovery between those receiving a steroid, a diuretic, a steroid-diuretic combination, or no steroid or diuretic. This implies that ALHL has varied etiologies in addition to endolymphatic hydrops and autoimmunity.

Wu-Ling-San is a Chinese medicine made from five kinds of Chinese herbal powders: Poria, Rhizoma Alismatis, Polyporus, Cortex Cinnamomi, and Rhizoma Atractylodis Macrocephalae. This drug promotes urinary output and is therefore used as a mild diuretic in cases of edema. In Japan and China, Chinese medicines made from herbs have been used therapeutically for more than 2,000 years. The Japanese Ministry of Health, Labor, and Welfare has approved 236 empirically selected Chinese medicines, including Wu-Ling-San. Although minor adverse effects of stomach irritation and skin eruption are sometimes experienced, few major adverse effects of Wu-Ling-San have been reported, according to information from pharmaceutical companies. However, the precise pharmacological effects of Chinese medicines are still under investigation. Ye [13] and Hirata [14] reported the effectiveness of Wu-Ling-San treatment for Ménière's disease. Therefore, we speculated that Wu-Ling-San would improve endolymphatic hydrops and tried it as a treatment for ALHL instead of isosorbide. We found that, as with isosorbide, treatment with Wu-Ling-San as a single agent failed to improve ALHL. Suzuki et al. [10] reported that isosorbide was not effective against ALHL in the short

term, because diuretics require a long time to improve endolymphatic hydrops. We expect that Wu-Ling-San would work on a similar time course. In contrast, Wu-Ling-San in combination with an oral steroid was more effective than the diuretic alone, Wu-Ling-San alone, or the steroid-diuretic combination. Because ALHL is considered to be pluricausal, a combination therapy would be expected to provide more improvement than a single therapy; the steroid would be effective against autoimmunity, and Wu-Ling-San would be effective against endolymphatic hydrops. However, the steroid-diuretic combination did not improve ALHL more than other treatments, whereas the steroid-Wu-Ling-San combination did so effectively, perhaps because Wu-Ling-San, which is composed of 5 ingredients, may have pharmacological effects other than diuresis. This result implies that Wu-Ling-San combined with a steroid has a synergistic effect on the cochlea. Wu-Ling-San also has an advantage over isosorbide in its taste. Isosorbide is a very bitter-tasting liquid medicine, and many patients stop using it. Wu-Ling-San also tastes bitter, but it is easier to ingest than isosorbide, as it is administered in powder form. Indeed, 5 patients could take isosorbide only once and dropped out from our study, all patients treated with Wu-Ling-San in this study completed the full treatment course. The steroid-Wu-Ling-San combination could thus be a new therapeutic option for treating ALHL. However, the pharmacological effects of Wu-Ling-San on the cochlea are currently unclear, and animal studies are needed to reveal the precise mechanism of action. As only a limited number of patients were included in this study, a randomized controlled study should also follow.

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Conclusion

We analyzed the epidemiology and short-term treatment outcomes of ALHL in patients with definite or probable disease. The mean age and the male:female ratio differed between patients with definite and probable ALHL, likely because of an age-related change in pathogenesis. Oral steroids, diuretics, and steroid-diuretic combination therapy did not improve ALHL, but a combination of the Chinese medicine Wu-Ling-San and an oral steroid was significantly more effective than the diuretic alone, Wu-Lin-San alone, or the steroid-diuretic combination. However, little information is currently available about the pharmacological effects of Wu-Ling-San on the cochlea, and animal studies should be performed to elucidate the mechanism of action.

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