Comparisons of clinical manifestations and prognosis between giant cell arteritis patients with or without sensorineural hearing loss

A retrospective study of Chinese patients

Xiaotian Chu, MD, Dongmei Wang, MD, Yun Zhang, MD, Yue Yin, PhD, Yu Cao, MD, Xinxin Han, PhD,*

Abstract
Auditory manifestations have rarely been mentioned in studies concerning giant cell arteritis (GCA). This study explores the proportion of hearing loss (HL) in Chinese GCA patients and investigates the differences in clinical features between GCA patients with and without HL.

The study retrospectively reviewed the clinical records of 91 patients diagnosed with GCA at Peking Union Medical College Hospital (PUMCH) from November 1998 to October 2017. GCA diagnoses were reconfirmed according to the American College of Rheumatology 1990 criteria. Diagnosis of HL was made based on a patient’s symptoms combined with physical examination or ear-nose-throat (ENT) audiometry tests. Subgroup analysis was conducted according to the occurrence of HL.

Totally 23 patients (25.3%) had HL. A higher percentage of males (65.2% vs 38.2%, p = 0.025) was seen in HL group. Symptoms such as headache (91.3% vs 61.2%, p = 0.011), visual loss (56.5% vs 32.4%, p = 0.039) and CNS symptoms (39.1% vs 17.6%, p = 0.035) were more frequent in HL group. Moreover, they were more likely to have smoking history (p = 0.019), lower lymphocyte count (p = 0.049), positive ANA or APL (p = 0.047, p = 0.017) or negative biopsy results (p = 0.015). Symptom like myalgia (26.1% vs 66.2%, p = 0.001) as well as comorbid disease like coronary artery disease (p = 0.037) and hypertension (p = 0.040) was more frequent in patients without HL. Either C-reactive protein (90.91 ± 65.86 vs 76.05 ± 61.15 mg/L, p = 0.347) or erythrocyte sedimentation rate (83.04 ± 29.61 vs 93.69 ± 26.78 mm/h, p = 0.136) was high in both groups but the differences were not significant. Meanwhile, no significant differences were found in age, disease course, vascular involvement or prognosis between the two groups. Unilateral HL tended to happen at the same side with unilateral headache, visual loss, scalp tenderness or jaw claudication.

HL is probably not rare in GCA patients and is more frequently to be seen in patients presented with headache, visual loss or CNS symptoms. Differentiation of HL is necessary for specialists and GCA should be considered as a potential diagnosis especially in HL patients with high inflammatory markers. Auditory assessment should be conducted in GCA management.

Abbreviations: ENT = ear-nose-throat, GCA = giant cell arteritis, HL = hearing loss, SSHL = sensorineural hearing loss.

Keywords: giant cell arteritis, hearing loss

1. Introduction
Giant cell arteritis (GCA), also known as temporal arteritis or granulomatous arteritis, is the most common type of arteritis found in western countries. GCA usually affects females over 50 years old, and its incidence increases with age. Large or medium-sized arteries such as aorta and its primary branches, as well as cranial vessels, are frequently involved, causing typical symptoms such as temporal headache, jaw claudication, scalp tenderness, or temporal artery abnormalities (tenderness, decreased pulsation, etc). Clinical manifestations of GCA can vary in different patients. Transient or permanent visual loss caused by ischemia of vessels supplying the eyes is considered one of the most serious symptoms. Hearing loss (HL) was reported in GCA cases from time to time while previous research has seldom focused on the symptom. The mechanism underlying HL remains unclear. Previous studies have suggested that HL is caused by the involvement of vertebrobasilar or the terminal cochleovestibular vessels, and by narrowing or the occlusion of related vessels. Also, the exact incidence of HL in GCA patients still remains controversial. Haush et al have conducted a 10-year retrospective review on 271 GCA patients from Geisinger Medical Center and have found that only 4 patients had HL symptoms. Their data suggested that HL can occur at the onset of GCA or develop during the course of the disease, and it
can recover completely or partly after treatment. Moreover, Amor-Dorado et al have conducted a prospective study on 44 GCA patients and discovered that vestibular disorders were present in 39 (90%) cases; however, the exact number of patients with HL was not mentioned in the article while it demonstrated 12 (27.3%) patients had hearing improvement after treatment. The above data implied that HL is not a rare event in patients with GCA, and that it might get ignored due to poor recognition.

The aim of this research was to investigate the occurrence of HL and the clinical manifestations of GCA in patients with and without HL.

2. Materials and methods

2.1. Patients

One hundred seventeen patients diagnosed with GCA at Peking Union Medical College Hospital, Beijing, China (PUMCH) between November 1998 and October 2017 were enrolled. Patients’ clinical data, including medical records, and follow up, were retrospectively reviewed. After excluding 26 cases due to obviously incomplete data, 91 patients were included in the study. GCA diagnoses were reconfirmed according to The American College of Rheumatology 1990 classification criteria:

1. 50 years of age;
2. localized headache of new onset or new type;
3. tenderness or decreased pulsation of the temporal artery;
4. elevated erythrocyte sedimentation rate (ESR) ≥50 mm/h;
5. histologic changes of arteritis: either granulomatous lesions, usually with multinucleated giant cells, or diffuse mononuclear cell infiltration.

The presence of 3 or more criteria were enough to make a diagnosis of GCA (sensitivity 93.5%, specificity 91.2%). Temporal artery biopsy is still the gold standard for the diagnosis of GCA.

2.2. Methods

We reviewed and summarized the medical history of patients, including symptoms and signs, physical examinations, comorbid diseases, previous medical history, laboratory results and imaging results, histological results as well as follow-up data. Ninety-one patients were divided into 2 groups, that is, those with HL and those without. HL was diagnosed by ear–nose–throat (ENT) specialists based on obvious hearing impairment complained by the patients or ENT audiometry tests such as pure tone audiometry test. Stabilization was defined as relief after treatment with no relapsing symptoms after reduction of glucocorticoid; recurrence was defined as relief after treatment while symptoms relapsed or treatment-related complications such as infection occurred during the reduction of glucocorticoid.

This study has been approved by the Ethics Board of PUMCH.

2.3. Statistical analysis

Data analysis was performed using SPSS 19.0 software (IBM SPSS Statistics 19). General information was analyzed by descriptive statistics. Mean value and standard deviation were calculated for continuous variables. Categorical variables were analyzed using frequency and percentage. Independent-sample t test was applied for analyzing continuous variables. Chi-square test was applied for categorical variables where frequencies of either group are no less than 5 and total frequencies are no less than 40, otherwise, Fisher exact test will be conducted. All tests were two-sided, and P < .05 was considered statistically significant.

3. Results

3.1. Sociodemographic data and clinical manifestation

One hundred seventeen GCA patients were reviewed and 91 met the inclusion criteria. There were 23 patients (25.3%) with HL; among these, 4 patients had HL at the onset of disease. Sixty-eight patients experienced no HL during the disease course. In addition, 8 patients were diagnosed with GCA comorbid with HL during the last 5 years; among them, only 2 of them underwent pure tone audiometry test and the results both revealed sensorineural hearing loss (SSHL), 4 patients had mastoiditis features in magnetic resonance imaging, and 3 patients had unilateral HL at the same side with unilateral headache, visual loss, scalp tenderness or jaw claudication or consistent with the more severe side of those symptoms. The reason why many patients did not undergo pure tone audiometry test was that most physicians did not realize the HL symptom may be related to GCA, and they usually advised patients to go to ENT clinic after being discharged from hospital; nonetheless, many patients did not follow the physician’s advice due to various reasons.

Among 91 GCA cases, 50 (54.9%) were female (male: female ratio 1:1.22). However, more males were observed in the HL group (65.2% males vs 38.2% females, P = .025). In addition, no age differences were found between the 2 groups. Considering clinical manifestations, out of 91 GCA patients, 74 and 64 presented with fever and headache, respectively, which were also the most frequent symptoms. Patients with HL experienced more headache, visual loss and central nervous system (CNS) symptoms (P = .011, P = .039, P = .035), reported a lower ratio of myalgia (P = .001) and were also more likely to have smoking history (P = .019) compared to patients without HL. With respect to comorbid diseases, patients with HL had lower percentage of hypertension (P = .040), coronary heart disease (CHD) (P = .037), diabetes mellitus, cerebrovascular disease, malignancy, and dyslipidemia history, while the differences were not significant in diabetes mellitus, cerebrovascular disease, malignancy, and dyslipidemia history (Table 1).

3.2. Laboratory results

Comparisons of blood cell counts between the 2 groups illustrated that patients with HL had lower lymphocyte counts than patients without HL (P = .049). Eight out of 23 and 5 out of 13 GCA patients with HL showed positive antinuclear antibody (ANA) and antiphospholipid antibody (APL) (lupus anticoagulant, anticardiolipin antibody, anti-β2 glycoprotein 1 antibody). Ten out of 65 and 7 out of 61 GCA patients without HL had positive ANA and APL, respectively. The percentage of positive ANA and APL were significantly higher in HL group (P = .047, P = .017, respectively). Meanwhile, the level of C-reactive protein and ESR in both groups were higher than normal range, but there was no significant difference between the 2 groups (Table 2).

3.3. Artery involvement and biopsy results

No remarkable differences of artery distributions were found between the 2 groups when evaluating their imaging results. The number of patients receiving temporal artery biopsy was 11 out
of 23 and 36 out of 68, respectively. Five patients (45.5%) in HL group and 9 patients without HL were lost during follow-up. No statistically significant difference was found between the 2 groups regarding the percentage of patients who were stable, unstable, developed a malignancy or died (Table 4).

### 4. Discussion

GCA is the most common systemic arteritis in European and American populations, with the approximate prevalence of 17/100,000 among people from North America and North Europe who are over 50 years of age.[11] Previously, it has been thought that GCA is uncommon in Asian populations, and according to the research published by Kobayashi in 2003, occurrence of GCA in Japan was only 1.47/100,000.[8,11,12] The incidence of GCA in China is still unknown, and limited research has been published. From January 1998 to December 2017, only 117 patients were comorbid with atherosclerotic plaque and high risk of thrombosis were prescribed aspirin as an antiplatelet treatment. In the 4 patients who experienced HL at the onset of disease, no specific treatment was applied to deal with HL. Moreover, the conditions of HL after application of those treatment were described in only a small number of GCA patients when they were discharged from the hospital. Most of the patients did not deal with or pay attention to HL after they got out of the hospital, and this was mostly because that the doctors neglected to emphasize the importance of examination and follow-up of hearing.

#### 3.5. Follow-up information

The average follow-up time was 86.04 (3–218) months. Five patients in the HL group and 9 patients without HL were lost during follow-up. No statistically significant difference was found between the 2 groups regarding the percentage of patients who were stable, unstable, developed a malignancy or died (Table 4).

### Table 1

| Clinical features and comorbid diseases of the patients with hearing loss and without hearing loss. | GCA with HL | GCA without HL | P-value |
|---|---|---|---|
| Age, yr (diagnosis) | 63.70±7.58 | 65.87±7.67 | .244 |
| Disease course, mo | 10.72±16.00 | 8.09±17.81 | .511 |
| Sex | | | |
| Male | 15 (65.2) | 26 (38.2) | .025* |
| Female | 8 (34.8) | 42 (61.8) | |
| Headache | 21 (91.3) | 43 (63.2) | .011 |
| Fever | 19 (82.6) | 55 (80.9) | .854 |
| Scalp tenderness or pain | 6 (26.1) | 18 (26.5) | .971 |
| Tenderness and abnormal pulsation of temporal artery | 6 (26.1) | 14 (20.6) | .582 |
| Visual loss | 13 (56.5) | 22 (32.4) | .039 |
| Myalgia | 6 (26.1) | 45 (66.2) | .001* |
| CNS symptoms | 9 (39.1) | 12 (17.6) | .395 |
| Jaw claudication | 7 (30.4) | 19 (27.9) | .619 |
| Arthralgia | 8 (34.8) | 39 (57.4) | .061 |
| GI symptoms | 3 (13.0) | 9 (13.2) | .963 |
| Constitutional symptoms | 16 (69.6) | 45 (66.2) | .765 |
| Weight loss* | 16 (69.6) | 34 (50.0) | .103 |
| Atherosclerosis | 5 (21.7) | 21 (31.1) | .094 |
| Smoking | 13 (56.5) | 20 (29.4) | .199 |
| Tumor family history | 4 (17.4) | 12 (17.6) | .972 |
| Diabetes | 3 (13.0) | 11 (16.2) | .694 |
| Cerebrovascular disease | 1 (4.3) | 7 (10.3) | .309 |
| Coronary artery disease | 1 (4.3) | 12 (17.6) | .037* |
| Hypertension | 4 (17.4) | 28 (41.2) | .040* |
| Dyslipidemia* | 5 (21.7) | 26 (38.2) | .149 |

#### Table 2

| Laboratory findings of GCA patients with or without hearing loss. | GCA With HL | GCA without HL |
|---|---|---|
| | Mean±SD | n (%) | Total n | Mean±SD | n (%) | Total n | P-value |
| ESR, mm/h | 83.04±29.61 | 23 | 93.69±26.78 | 68 | .136 |
| CRP, mg/L | 90.91±65.86 | 23 | 76.05±61.15 | 68 | .347 |
| ALB, g/L | 32.26±5.11 | 23 | 32.67±4.47 | 68 | .737 |
| WBC, ×10^9/L* | 9.09±4.55 | 23 | 9.18±4.14 | 68 | .399 |
| LYM, ×10^9/L | 1.29±0.51 | 23 | 1.55±0.71 | 66 | .049* |
| HGB, g/L | 106.0±21.02 | 23 | 105.80±19.01 | 66 | .300 |
| PLT, ×10^12/L | 401.48±141.94 | 23 | 372.11±155.65 | 68 | .410 |
| ANA positive | 8 (34.8) | 23 | 10 (15.4) | 65 | .047* |
| ANCA positive | 5 (22.7) | 22 | 8 (12.9) | 62 | .274 |
| APL positive | 5 (23.8) | 13 | 7 (11.5) | 61 | .017* |

#### Table 3

| Artery involvement and biopsy results in patients with or without hearing loss. | With | Without |
|---|---|---|
| Intracranial vessels | 11 (57.9) | 19 | 23 (48.9) | 47 | .510 |
| Extracranial vessels above aorta | 17 (89.5) | 41 | 41 (87.2) | 69 | .801 |
| Extracranial vessels below aorta | 11 (57.9) | 33 | 70.2 | 36 | .336 |
| Biopsy negative | 5 (45.5) | 11 | 4 (11.5) | 36 | .015* |

HL = hearing loss. *The difference in proportion of patients who were biopsy negative are significant between two groups.
Table 4

| Follow-up information of GCA patients with or without hearing loss. | GCA with HL n (%) | Total | GCA without HL n (%) | Total | P |
|---|---|---|---|---|---|
| Stable | 8 (44.4) | 18 | 29 (40.2) | 59 | .726 |
| Unstable | 4 (22.2) | 22 (37.2) | 252 | | .252 |
| Tumor | 1 (5.6) | 1 (1.7) | 1 (1.7) | | .648 |
| Death | 5 (27.8) | 7 (11.9) | 7 (11.9) | | .103 |

HL = hearing loss.

GCA effects mainly large or medium-sized arteries such as aorta and its primary branches as well as cranial vessels. Auditory dysfunction is frequently asymmetrical, and it is in keeping with the asymmetrical cranial manifestations reported in many GCA patients. The results of our research are consistent with these findings. Currently, temporal artery biopsy is still the golden standard for GCA biopsy. In HL group, GCA patients with negative biopsy accounted for nearly half of the patients (5/11, 45.5%), while in patients without HL, only 11.1% (4/36) had negative results. A previous study has revealed that small-vessel vasculitis, which is defined as aggregates of mononuclear inflammatory cells surrounding a capillary, distant from an uninflamed temporal artery, is strongly associated with symptoms of polymyalgia rheumatica (PMR) in GCA patients with or without PMR. So, the pathological features of GCA patients with HL may be different from the typically acknowledged histological findings, indicating another kind of GCA. The
difference is so impressive that physicians and pathologists should pay more attention to this phenomenon that HL in GCA is potentially associated with different biopsy result. 40% to 50% or more patients experience relapse in application of glucocorticoids or during the reduction of glucocorticoids, and long-term, large dose of glucocorticoids has been related to relapse. According to the follow-up information, the ratio of stable patients, relapse, tumor occurrence, or death revealed no remarkable difference between 2 groups, while the percentage of stable patients was less than 50% in both groups and the relapse proportion was quite considerable (22.2% vs 37.3%). These data are consistent with the previous study where almost half of the patients experienced relapse, thus suggesting that more attention should be paid to this problem. This study was conducted retrospectively, and the conditions of HL after glucocorticoid treatment were described in only a small number of GCA patients when they were discharged from the hospital due to the poor recognition of this symptom. According to our study, some GCA patients did not experience improvement in hearing, while other patients totally or partly recovered from HL after glucocorticoid treatment, which was consistent with previous research. It is not clear whether the time from the onset of HL to glucocorticoid therapy influences recovery, or it is the kind of HL that matters. Previous research has revealed that early use of glucocorticoid in patients with idiopathic sudden SSHL leads to a better prognosis. Accordingly, ENT specialists may offer glucocorticoid treatment early in patients diagnosed with idiopathic sudden SSHL after making comprehensive assessment of the patients and administering audiometric follow-up during treatment.

The challenge of GCA diagnosis is that the disease is rare in China and the clinical manifestations vary in different patients. In our study, we retrospectively reported 91 patients among which 25.3% reported HL, which illustrates that HL in GCA patients is not rare. Rheumatologists should pay more attention to this symptom and should seek ENT consultation to ensure a more comprehensive diagnosis and management of patients with GCA. Meanwhile, ENT specialists should be more alert and should consider GCA when dealing with an older patient presenting HL symptom as well as headache, visual loss, CNS symptoms or fever. Early recognition and steroid treatment may lead to a better prognosis of GCA and HL. Glucocorticoid could be offered early as an option and follow-up could be performed in patients diagnosed with idiopathic sudden SSHL.

5. Conclusions
This study demonstrated that HL was not rare in Chinese GCA patients. Rheumatologists, neurologists, ophthalmologists, and ENT clinicians should consider GCA when patients present HL as well as headache, visual loss, CNS symptoms or fever.

The results from the present study should be interpreted with caution. First, this is a retrospective study that had some missing clinical data. Second, the patients recruited in this study are all admitted to hospital due to the poor recognition of this symptom. According to our study, some GCA patients did not experience improvement in hearing, while other patients totally or partly recovered from HL after glucocorticoid treatment, which was consistent with previous research.

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Author contributions
Conceptualization: Hong Jiang.
Formal analysis: Xiaotian Chu, Dongmei Wang, Yun Zhang.
Investigation: Yue Yin, Yu Cao, Xinxin Han, Min Shen.
Methodology: Xuejun Zeng.
Validation: Xuejun Zeng.
Writing – original draft: Xiaotian Chu.
Writing – review and editing: Dongmei Wang, Yun Zhang, Xuejun Zeng.

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