

High level of IgE in acute low-tone sensorineural hearing loss: A predictor for recurrence and Meniere Disease transformation

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ABSTRACT

Background: Autoimmunity may play an important role in sudden onset sensorineural hearing loss. However, little is known about the relationship between immunoglobulin E (IgE) and acute low-tone sensorineural hearing loss (ALHL).

Objectives: To investigate the relationship between IgE level and endolymphatic hydrops and outcomes of ALHL.
Methods: A total of 242 subjects with sudden onset hearing loss, including 115 with ALHL and 127 with idiopathic sudden sensorineural hearing loss (ISSHL), were included in this study. Peripheral venous blood samples of 242 subjects were collected for detection. Clinical data, IgE level, and distribution of allergens were compared between the ALHL and ISSHL groups. The ALHL group received an electrocochleogram (ECoChG) test and a follow-up in the outpatient unit or by telephone to evaluate outcomes.

Results: Compared to the values in the ISSHL group, a significantly younger onset age (42.30 ± 14.33 years old), higher female onset proportion (72/115, 62.61%), increased total IgE level (median: 66.47, interquartile range: 24.56, 180.96, IU/mL) and specific IgE level (median: 9.42, interquartile range: 1.42, 22.23 IU/mL) were noted in the ALHL group. A clear difference in allergen distribution was noted between the ALHL and ISSHL groups ($p = .001$). Total IgE and specific IgE levels were factors that contributed to the SP/AP ratio in the electrocochleogram (ECoChG) ($R^2 = 0.413$) in ALHL group. Finally, during the follow-up (17.61 ± 3.46 months) for the ALHL group, 37 subjects recurred, and 17 subjects developed Meniere Disease. In the ROC curve for ALHL recurrence, the area under the curve (AUC) of total IgE was 0.709 and that of specific IgE was 0.679. For MD transformation, the AUC of total IgE was 0.736 and that of specific IgE was 0.716.

Conclusions: High IgE levels correlated with an enhanced SP/AP ratio in ALHL. High IgE levels could be used as a predictor of ALHL recurrence and MD transformation.

1. Introduction

Sudden onset sensorineural hearing loss consists of two subtypes: idiopathic sudden sensorineural hearing loss (ISSHL) and acute low-tone sensorineural hearing loss (ALHL). ISSHL is an otologic emergency defined as the sudden onset of sensorineural hearing loss of at least 30 dB across three contiguous frequencies that occurs within 72 h or less [1]. In contrast, ALHL is defined as an acute low-tone hearing loss associated with tinnitus, a feeling of fullness in the ear, and autophonia [2]. The etiology of ISSHL and ALHL has not been completely elucidated. The inner ear is not an immune-privileged organ [3]. Sudden onset sensorineural hearing loss is closely associated with a variety of autoimmune diseases, such as systemic lupus erythematosus (SLE) [4],

multiple sclerosis [5], rheumatoid arthritis (RA) [6], Crohn's disease [7] and others. Glucocorticoid therapy is fairly effective for ISSHL and ALHL [8]. Based on the above evidence, many researchers have considered that ISSHL and ALHL might be related to autoimmunity. In previous studies [9,10], it was found that Type 1 allergic reactions played an important role in some inner ear diseases, such as Meniere Disease (MD), which consistently evolves from ALHL. However, the association between Type 1 allergic reaction and ALHL and its significance has not been revealed in other studies.

Type 1 allergic reactions are caused by re-exposure to the same allergen and the subsequent release of immunoglobulin E (IgE). In this study, levels of total IgE, which represents the total IgE level in peripheral blood; specific IgE, which is the IgE level that corresponds to a

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specific allergen; allergen distribution and their clinical significance were revealed in ISSHL and ALHL groups. The findings in this study may help us better understand the relationship among ALHL, MD, Type 1 allergic reaction and endolymphatic hydrops, providing some evidence regarding the potential pathogenesis of this disease.

2. Materials and methods

2.1. Clinical data

Subjects with unilateral sudden onset sensorineural hearing loss who visited our inpatient department (Department of Otolaryngology of the Fourth Affiliated Hospital of China Medical University) from June 2018 to June 2019 were included in this study. The inclusion criteria for ISSHL were as follows [1]: (1) unilateral unfluctuating sensorineural hearing loss with sudden onset that occurs within 72 h or less; (2) hearing loss of more than 30 dB in at least three contiguous frequencies; (3) no neurologic signs except cranial nerve VIII; and (4) no identifiable cause. The inclusion criteria for ALHL were as follows [2]: (1) acute sudden onset of cochlear symptoms; (2) low-tone hearing loss, i.e., the sum of hearing levels at 0.125, 0.25 and 0.5 kHz is 70 dB or greater or the sum of hearing levels at 2, 4 and 8 kHz is 60 dB or less; (3) without vertigo; (4) no identifiable cause. The exclusion criteria for ISSHL and ALHL were as follows: (1) conductive hearing loss; (2) acoustic neuroma and intracranial space-occupying lesion; (3) acute cerebral infarction; and (4) diagnosed Meniere Disease and large vestibular aqueduct syndrome (LVAS).

Physical examinations, such as audiometric testing, high-resolution CT of temporal bone, and cranial magnetic resonance imaging, were performed on an inpatient basis to exclude a differential diagnosis. All subjects received treatment with an intratympanic steroid and outpatient or telephone follow-up during the study period. Criteria for clinical outcome for ALHL, including recurrence and Meniere Disease transformation during the follow-up period, are listed in Table 1 [11]. Detailed medical history, examination results and follow-up results were collected, including clinical data of subjects listed in Table 2.

The study protocol was approved by the Ethics Review Committee of the Fourth Affiliated Hospital of China Medical University. Each patient signed an informed consent form for participation.

2.2. Detection of total IgE, specific IgE and corresponding allergens

Three milliliters of peripheral venous blood was collected on the day of admission. Total IgE and specific IgE levels corresponding to different allergens in serum were detected by ELISA (double antibody sandwich method) after centrifugation of blood. A Total IgE ELISA testing kit (HOB® Biotech, Jiangsu, PR China) was used for the detection of total IgE levels. An Allergen and Specific IgE ELISA testing kit (HOB® Biotech,

Jiangsu, PR China) was used for detection of allergens and the level of corresponding specific IgE. The following twenty allergens were detected: house dust, alternaria, ragweed, mugwort, willow catkins, cat hair, dog hair, shrimp, crab, cod, mutton, beef, peanut, soybean, dust mite, wheat flour, cockroach, house dust mite, milk, and egg.

Specific IgE levels were graded as follows: strongly positive, >3.5 IU/mL; moderately positive, 0.7–3.5 IU/mL; weakly positive, 0.35–0.7 IU/mL; and negative, <0.35 IU/mL.

When there were two or more allergens, the highest value of specific IgE was the “peak level”. When there was only one allergen, the only value of specific IgE was the “peak level”. All experiments were performed in strict accordance with the instructions.

2.3. Electrocochleogram

Electrocochleogram (ECoCHG) was performed in the ALHL group by an experienced clinician in a sound-attenuated room. After otoscopic examination, the tested ear canal was filled with tetracaine gel and then dried. The ET wick electrode (Sanibel) was inserted into the external auditory meatus and placed on the tympanic membrane under an otomicroscope. An active electrode was placed on the ear lobe of the untested ear, and the ground electrode was placed on the lower forehead.

Impedance of the electrodes was maintained below 5 kΩ. The stimulus was a 100-μs broadband click generated by MADSEN (Otometrics®, Denmark) at an intensity of 90 dB nHL and rate of 7.1 times per second. Signals were filtered from 30 Hz to 3000 Hz. In total, 2000 repeats were performed during the total testing duration. All subjects received bilateral tests repeated each ear. Among the repeats, the largest amplitude was chosen for analysis.

The amplitudes of summing potential (SP) and action potential (AP) were measured with reference to the stimulus onset (baseline) for calculation of the SP/AP ratio.

2.4. Statistical analysis

Data were analyzed using SPSS Statistics 25.0 (SPSS Inc., Chicago, Illinois, USA). Results that exhibited a normal distribution were analyzed by independent sample *t*-test. When results did not exhibit a normal distribution, the Mann-Whitney *U* test was used for analysis. The χ^2 test was used for comparison of the abnormal rates. Multiple linear regression was performed to describe factors that contributed to the SP/AP ratio. The ROC curve was used for clinical outcome prediction. The level of statistical significance was set at $p < .05$.

3. Results

3.1. High levels of IgE and different distributions of allergens in ALHL

In total, 242 subjects, including 115 with ALHL and 127 with ISSHL, were enrolled in this study. A comparison of clinical data between patients with ALHL and ISSHL is presented in Table 2. The onset age of ALHL (42.30 ± 14.33 years old) was significantly lower than that of ISSHL (52.72 ± 14.92 years old) ($p = .000$); the proportion of females with ALHL (72/115, 62.61%) was higher than that of ISSHL (61/127, 48.03%) ($p = .023$). An increased average hearing threshold in the impaired frequencies was noted in subjects with ISSHL (75.93 ± 24.61 dB) compared to that in subjects with ALHL (41.86 ± 8.58 dB) ($p = .000$).

Levels and positive grades of IgE are shown in Table 3. The level of total IgE in the ALHL group (median: 66.47, interquartile range: 24.56, 180.96, IU/mL) was significantly increased compared with the ISSHL group (median: 27.01, interquartile range: 6.76, 84.25, IU/mL) ($p = .000$). The peak level of specific IgE in the ALHL group (median: 9.42, interquartile range: 1.42, 22.23 IU/mL) was significantly increased compared with the ISSHL group (median: 0.68, interquartile range: 0.39, 2.68, IU/mL) ($p = .000$).

Compared to ISSHL, a higher positive grade of specific IgE ($p = .000$)

Table 1

Criteria for ALHL recurrence and Meniere Disease transformation.

ALHL recurrence
For patients diagnosed with ALHL and received treatment, in follow-up period, similar symptom, including low-tone hearing loss, ear fullness, tinnitus reappeared without vertigo.
Meniere Disease transformation
For patients diagnosed with ALHL and received treatment, in follow-up period, symptom as follows ^a appeared:
A. Two or more spontaneous episodes of vertigo, each lasting 20 min to 12 h.
B. Audiometrically documented low to medium frequency sensorineural hearing loss in one ear, deafening the affected ear on at least one occasion before, during or after one of the episodes of vertigo.
C. Fluctuating aural symptoms (hearing, tinnitus or fullness) in the affected ear.
D. Not better accounted for another vestibular diagnosis.

^a These criteria were established by Classification Committee of the Bárány Society in 2015.

Table 2

Clinical data of subjects with sudden onset sensorineural hearing loss.

Group		ALHL group		ISSHL group		p
		Number (n)	Percentage (%)	Number (n)	Percentage (%)	
n		115		127		
Age (years)		42.3±14.33		52.72±14.92		.000*
Ears	L	70	60.87%	72	56.69%	.510
	R	45	39.13%	55	43.31%	
Gender	M	43	37.39%	66	51.97%	.023*
	F	72	62.61%	61	48.03%	
Time from onset to treatment	≤7 days	73	63.48%	91	71.65%	.313
	7–14 days	31	26.96%	24	18.9%	
	≥15 days	11	9.57%	12	9.45%	
Vertigo	With	0	0%	33	25.98%	–
	Without	115	100%	94	70.02%	
Average hearing threshold in impaired frequencies (dB)		41.86±8.58		75.93±24.61		.000*
Mean follow-up time (m)		17.61±3.46		–		–
Recurrence		37	32.17%	–		–
Transformation into Meniere Disease		17	14.78%	–		–
ALHL without recurrence and MD transformation		61	53.04%	–		–

* $p < .05$.**Table 3**

Levels of total IgE and specific IgE in subjects with sudden onset sensorineural hearing loss.

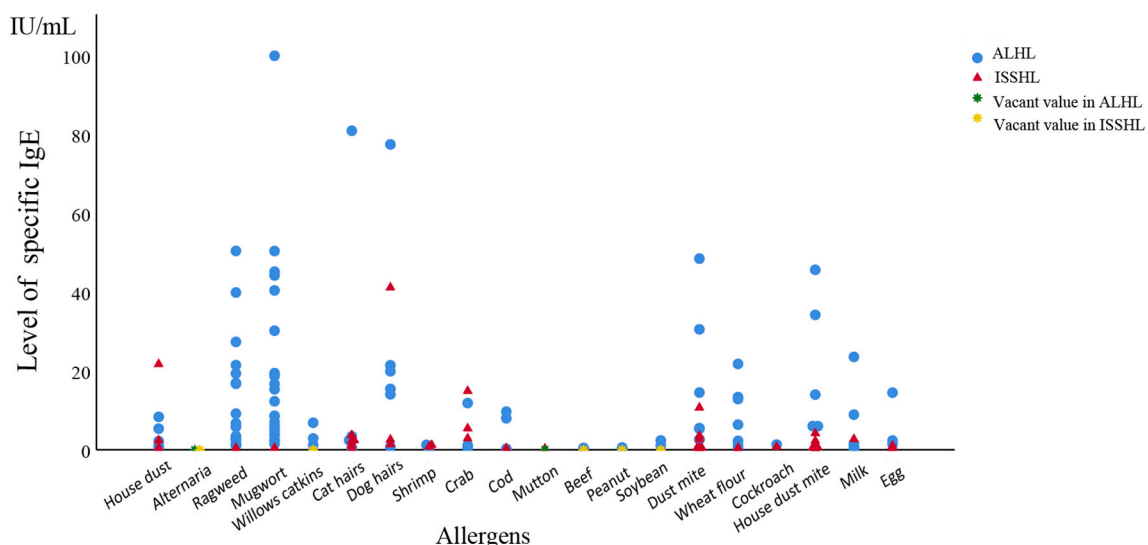
Group		ALHL group		ISSHL group		p
		Number (n)	Percentage (%)	Number (n)	Percentage (%)	
Level of total IgE (IU/mL)		66.47 (24.56, 180.96) ^a		27.01 (6.76, 84.25) ^a		.000*
Peak level of specific IgE (IU/mL)		9.42 (1.42, 22.23) ^a		0.68 (0.39, 2.68) ^a		.000*
Positive grade of specific IgE (n)	Negative	61	53.04%	94	74.02%	.000*
	Weak positive	9	7.82%	17	13.39%	
	Moderate positive	12	10.43%	12	9.50%	
	Strongly positive	33	28.70%	4	3.15%	
Number of positive specific IgE results (for each)	0	61	53.04%	94	74.02%	.003*
	1–2	42	36.52%	27	21.26%	
	≥3	12	10.43%	6	4.72%	

* $p < .05$.^a Median, interquartile range.

and more positive specific IgE results for each subject were noted in the ALHL group ($p = .003$) (Table 3).

A clear difference in allergen distribution was noted between the two groups (Fig. 1). In this study, 105 and 55 positive specific IgE results and their corresponding allergens were detected in the ALHL group and that the ISSHL group, respectively. In the ALHL group, mugwort was the

most common allergen (22/105, 20.95%) followed by ragweed (17/105, 16.19%). The allergens dust mite, house dust mite, wheat flour, and milk were also common (7/105, 6.67% for each). Other allergens were also positively detected as follows: dog hair (6/105, 5.71%); cat hair and house dust (5/105, 4.76% for each); willow catkins, shrimp, crab, cod, and egg (3/105, 2.86% for each); beef, peanut, and soybean (2/105,

**Fig. 1.** Allergens distribution and specific IgE level (weak positive or higher grades) of ALHL and ISSHL.

1.91% for each); and cockroach (1/105, 0.95%). Mutton and Alternaria were negative. In the ISSHL group, house dust was the most common allergen (11/55, 20.00%) followed by dust mite (9/55, 16.36%). The following allergens were also positively detected: cat hairs (6/55, 10.91%); egg (5/55, 9.09%); house dust (4/55, 7.27%); dog hair, crab, and wheat flour (3/55, 5.45% for each); mugwort, ragweed, shrimp and mutton (2/55, 3.64% for each); and cod, milk and cockroach (1/55, 1.82% for each). Alternaria, willow catkins, beef, peanut, and soybean were negative. The allergen distribution was compared between the two groups, and the results were statistically significant ($p=.001$).

3.2. Total and specific IgE levels positively contributed to the SP/AP ratio

The regression relationship was revealed in Fig. 2. In this multiple regression model, the R^2 is 0.413, whereas Durbin Watson Value was 2.024. The B value for the peak level of specific IgE was 0.004 ($p=.001$), whereas that of total IgE was 0.001 ($p=.000$). The VIF value for this model was 1.822.

3.3. Total and specific IgE levels were predictors for ALHL recurrence and MD transformation

In total, 115 subjects with ALHL received outpatient or telephone follow-up (mean follow-up time: 17.61 ± 3.46 month). During this period, 37 (32.17%) subjects recurred, and 17 (14.78%) subjects developed Meniere Disease.

ROC curves for these two outcomes are shown in Fig. 3A, B. Regarding ALHL recurrence, the area under the curve (AUC) of total IgE was 0.709 ($p=.000$) and that of specific IgE was 0.679 ($p=.002$). The cutoff value for total IgE was 177.42 IU/mL (maximal Youden's index: 0.373, sensitivity: 0.514, specificity: 0.859) and that of specific IgE was 3.03 IU/mL (maximal Youden's index: 0.401, sensitivity: 0.568, specificity: 0.833).

Regarding MD transformation, the area under the curve (AUC) of total IgE was 0.736 ($p=.002$) and that of specific IgE was 0.716 ($p=.005$). The cutoff value for total IgE was 177.42 IU/mL (maximal Youden's index: 0.453, sensitivity: 0.647, specificity: 0.806), and that of specific IgE was 3.53 IU/mL (maximal Youden's index: 0.423, sensitivity: 0.647, specificity: 0.776).

4. Discussion

The cause of sudden onset sensorineural hearing loss in most patients was never identified. However, indicators of significant differences were noted between ALHL and ISSHL regardless of the pathogenesis or clinical features [2]. The possible cause of ALHL may be endolymphatic hydrops, which is similar to the etiology of Meniere Disease (MD). Previous studies reported some abnormal test results in patients with ALHL, such as positive findings on a glycerol test, an enhanced summing potential versus the action potential (SP/AP) ratio on an electrocochleogram (ECoChG) and endolymphatic hydrops manifestation in gadolinium-enhanced magnetic resonance imaging of the inner ear [12,13], and these results are similar to those noted in Meniere Disease. At the same time, cohort studies reported that approximately 30% of ALHL patients develop MD [12].

The cause of endolymphatic hydrops in MD or ALHL remains unclear. In previous studies, high level of total and specific IgE were widely reported in the peripheral blood of patients with MD compared to controls, and these levels were equivalent to those noted for a stronger Type 1 allergic reaction [14]. However, the relationship between Type 1 allergic reaction and ALHL was not revealed in previous studies.

In this study, levels of total IgE, specific IgE and 20 corresponding allergens in the peripheral blood of patients with ALHL and ISSHL were detected. A significant predominance of total IgE levels and specific IgE levels was noted in ALHL compared to ISSHL. A clear difference in the distribution of allergens was noted between ALHL and ISSHL. In the ALHL group, the most common allergens were mugwort and ragweed, whereas those of ISSHL were dust mites and house dust mites.

The inner ear is not completely isolated from air tract. This information may be helpful to understand inner ear sensitization. Inhalant allergens, such as mugwort and ragweed, act on middle ear mucosa via the eustachian tube. Subsequently, sensorineural hearing loss may be caused by IgE produced locally in the middle ear mucosa after allergen exposure. This inner ear damage was indicated in some patients with eosinophilic otitis media (EOM), but its mechanism remains unclear [15]. The round window membrane may play an important role in this process. Given its excellent permeability, IgE and inflammatory cytokines were allowed into the inner ear, causing increasing bone conduction hearing loss. However, a case report of a patient who suffered from EOM and MD simultaneously has not been published to date. This may be caused by distinct locations and pathways of IgE-

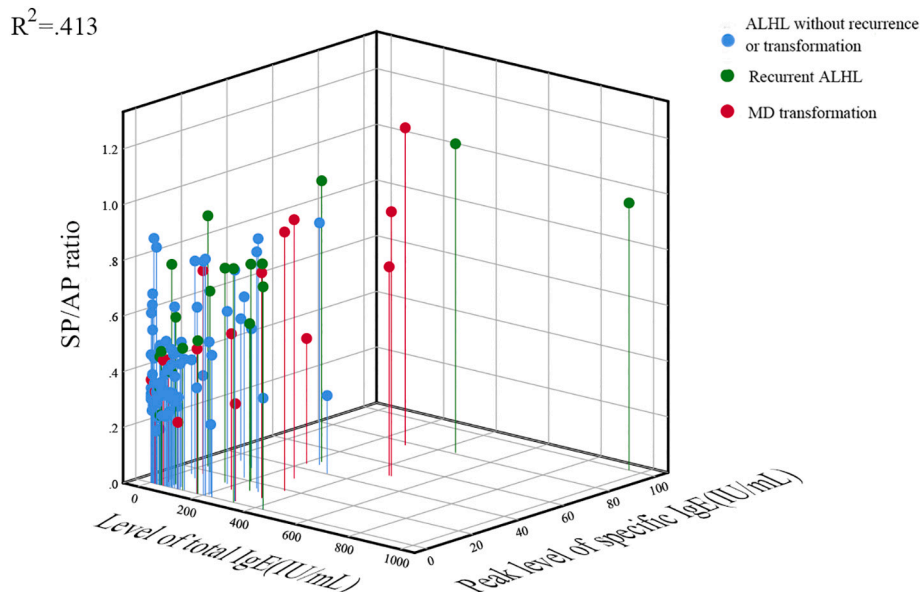


Fig. 2. Scatter diagram including total IgE levels, peak specific IgE levels and SP/AP ratio of 115 subjects with ALHL.

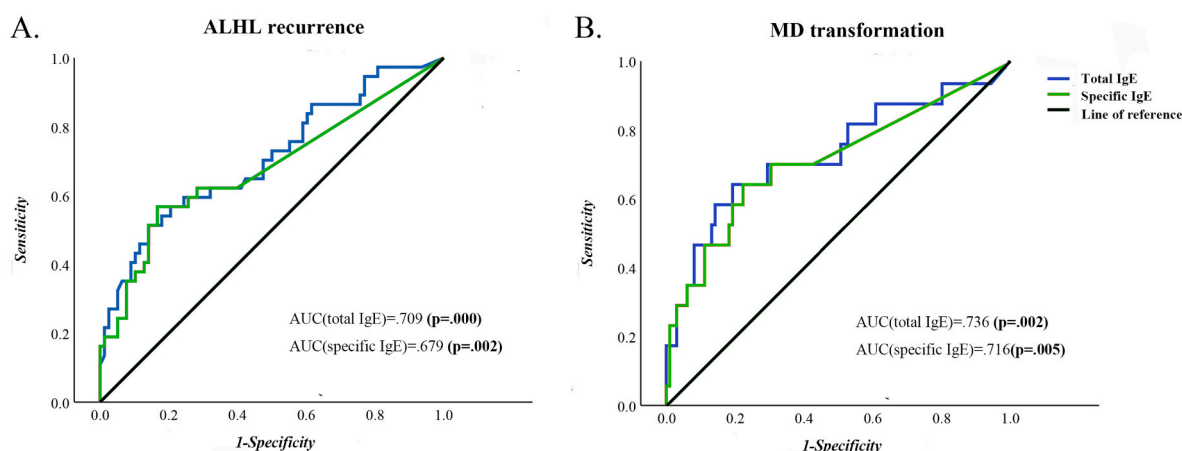


Fig. 3. A. ROC curve of total IgE and specific IgE for ALHL recurrence. B. ROC curve of total IgE and specific IgE for MD transformation.

immunopositive cell activation. For EOM, eosinophils are activated by the IgE-FcεRI pathway in the middle ear mucosa. For ALHL, mast cells and basophils [16] are likely activated in the inner ear by IgE passed through the round window membrane.

IgE in the circulation may be another cause of inner ear sensitization, and this mechanism is also applicable to food allergens [16]. In pre-sensitized individuals, the peak IgE level in serum occurs 4–6 weeks after allergen exposure [17]. IgE circulating in the small vessels around the endolymphatic sac activates mast cells and basophils, and the reabsorption capacity of the endolymphatic sac is subsequently affected. In this process, endolymphatic hydrops may form and constitute the pathological basis of ALHL. Endolymphatic hydrops cause a bias in the basilar membrane and affects the operating point of the cochlear microphonic (CM), producing a direct current (DC) offset. This phenomenon elevates the SP/AP ratio [18], potentially explaining why total and specific IgE levels are factors that contribute to the SP/AP ratio in the ALHL group in our study.

Furthermore, animal experimental studies have shown evidence that endolymphatic sac appears to be the target of allergic activity. Histamine receptors, including H₁, H₂ and weakly immunoreactive H₃ receptors, were found in endolymphatic sac of rabbit models [3]. By these receptors, histamine released from mast cells may cause damage to signal transduction and calcium response of endolymphatic sac, contributing to endolymphatic hydrops [19]. Studies about antagonist of receptors have also revealed several facts about the relationship between endolymphatic sac and allergic reaction. In 2,4-dinitrophenylated-*Ascaris* (DNP-As) sensitized guinea pig models, endolymphatic hydrops and its development was prevented by H₁ receptor antagonist [20] and leukotriene receptor antagonist [21]. Additionally, Takeda et al. have revealed an elevated level of plasma vasopressin (p-AVP) in sensitized guinea pig models, which may constitute a possible pathway in formation of endolymphatic hydrops [21].

Given that a high level of total and specific IgE in ALHL was presented, which was similar to that noted with MD, IgE detection deserves more attention in the prediction of MD transformation or ALHL recurrence. Our study provided a cutoff value for IgE levels in ALHL for MD transformation (total IgE: 177.42 IU/mL, specific IgE 3.53 IU/mL) and its recurrence (total IgE: 177.42 IU/mL, specific IgE: 3.03 IU/mL). This value may help us evaluate whether IgE levels initiate ALHL recurrence and MD transformation. Regarding total IgE and specific IgE, total IgE exhibited a better predictive ability given the greater area under the curve (AUC) for total IgE in this study. Detection of specific IgE did not cover all allergens, but total IgE did. This difference may represent a main reason for its stability as a predictor.

The mechanism by which IgE participates in ALHL recurrence or MD transformation remains unclear. However, the mechanism of IgE production maintenance still deserves more attention. Allergen-specific IgE

memory persists over years and even decades in humans and is accompanied with continuous IgE production. During this period, upon exposure to an allergen, a rapid increase in IgE levels can be induced [22]. This increase in IgE levels could explain the long duration and fluctuation of recurrent ALHL and MD. However, this finding does not indicate that an anti-allergic treatment is effective for recurrent ALHL and MD. The reason for this notion lies in the fact that the IgE baseline exhibits considerable stability in individuals although IgE depletion from human blood only leads to a temporary decline and a subsequent rapid return [23]. Encouragingly, a recent study indicated that IgE+ memory B cells played an important role in the process of IgE production maintenance. Therapeutics targeting IgE+ memory B cells, such as eculizumab, which blocks the membrane-bound IgE B cell receptor, are effective in reducing IgE levels continuously [24]. However, further clinical trials are needed to carefully evaluate its efficacy and safety in the therapy of recurrent ALHL and MD.

Consistent with previous studies [2,25], a younger female predominance was noted in ALHL. However, the possible cause of this predominance was not revealed in previous studies. Type 1 allergic reaction may provide evidence. Diseases based on Type 1 allergic reaction mechanisms, such as asthma, allergic rhinitis and eczema [26], exhibited a similar predominance of gender and age (increased incidence in females and young age of onset), which might be attributed to hormones or genetic factors. Other features of ALHL, such as its acute onset and good response to glucocorticoid treatments, also correspond to the overall process of Type 1 allergic reaction.

In this study, we revealed that IgE level may play an important role in ALHL onset, recurrence and transformation. However, several limitations in this study should be noted. Low total and specific IgE levels were noted in some patients with ALHL, indicating that Type 1 allergic reactions might not occur in every patient. The etiological evidence for ALHL and MD is multidisciplinary, so all cases with ALHL or MD are not explained by an IgE-dependent mechanism. To overcome this limitation, further studies and clinical trials are still needed.

5. Conclusion

A high level of IgE correlated with an enhanced SP/AP ratio in ALHL. High IgE levels could be used as a predictor of ALHL recurrence and MD transformation.

Author statement

1. We guarantee that our manuscript is original, has never been published and has not been simultaneously submitted to any other journal or electronic medium.

- The manuscript has been read and approved by each author. All authors confirm that the manuscript represents our honest work and are unanimous in the financial or other relationship.
- The authors declare no potential conflicts of interest. We confirm that all authors have agreed with the submission in its present form.
- The study was reviewed and approved by the Faculty of Science Ethics Committee at the Fourth Affiliated Hospital of China Medical University.
- Each of the coauthors has seen and agrees with each of the changes made to this manuscript in the revision and to the way his or her name is listed.

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Declaration of competing interest

The authors report no conflict of interest. The authors alone are responsible for the content and writing of the paper.

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