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Is sudden deafness in non-diabetic patients affected by their glycosylated hemoglobin levels?

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Abstract. – OBJECTIVE: Though the incidence of sudden sensorineural hearing loss (SSNHL) is relatively low, the disorder has a major impact on the quality of life of patients. Identifying biological markers for the disease will be useful, especially in resource-scarce areas. Our study aims to evaluate the correlation between the degree of hearing impairment and glycosylated hemoglobin (HbA1c) in patients with SSNHL.

PATIENTS AND METHODS: One hundred and thirty-eight patients with SSNHL and no history of diabetes were included in this study. The intravenous HbA1c content before treatment was correlated with the pure tone audiogram (PTA) average as per the criteria for SSNHL. Spearman correlation and the Receiver Operating Characteristic (ROC) curve were used to determine the HbA1c levels of the study participants. The critical value of HbA1c and its diagnostic implications for assessing the degree of hearing impairment in patients with SSNHL were noted.

RESULTS: There was a significant positive correlation between HbA1c and PTA in patients with SSNHL ($p<0.05$). In addition, the best HbA1c cutoff value for screening and referring an individual for a detailed audiometric evaluation of hearing impairment was 5.550%, as indicated by the ROC curve.

CONCLUSIONS: The level of HbA1c in the circulation may affect the onset, duration, and progression of SSNHL. The same parameter may be used as a diagnostic and prognostic indicator for this condition.

Key Words:
Glycosylated hemoglobin, Sudden deafness, ROC curve.

Abbreviations

Sudden sensorineural hearing loss: SSNHL; glycosylated hemoglobin: HbA1c; pure tone audiogram: PTA; Receiver Operating Characteristic: ROC; sudden hearing loss: SHL; diabetes mellitus: DM; conductive hearing loss: CHL; complete blood count: CBC; hemoglobin: HB; mean platelet volume: MPV; high-density lipoprotein cholesterol: HDL-C; low-density lipoprotein cholesterol: LDL-C; area under the curve: AUC; nicotinamide adenine dinucleotide phosphate: NADPH; nitric oxide: N.

Introduction

Sudden sensorineural hearing loss (SSNHL) is a subset of sudden hearing loss (SHL). By definition, it occurs within a 72-hour window and includes hearing loss of at least 30 dB at three consecutive frequencies in the pure-tone audiogram (PTA)[1]. The incidence of SSNHL is about 66,000 new cases per year, and it affects 27 per 100,000 people in the United States on average[2,3]. The data may be underestimated, as many affected individuals do recover spontaneously and may not seek medical care. It is also important to remember that such estimates do not take into account the fact that many affected patients might not be evaluated on the basis of an audiogram, especially in rural and primary care settings.

The etiology and pathological mechanism of SSNHL are not very clear. The current highly recognized theory is that cochlear microcirculation disorder is the main cause of sensorineural hearing loss[4]. Some studies[5,6] have shown that diabetes mellitus (DM) is associated with the development of bilateral hearing loss, especially in the high frequencies, and some DM patients exhibit SSNHL as the first symptom. Glycosylated hemoglobin (HbA1c) is formed by an irreversible slow non-enzymatic reaction between hemoglobin and blood sugar. Its synthesis rate is directly proportional to the blood sugar concentration,

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but it is not affected by temporary fluctuations in the blood sugar concentration. Currently, this is often used in the diagnosis of diabetes and blood glucose monitoring and is considered an independent and progressive risk factor for cardiovascular disease[7].

At present, most studies[8-11] focused on the relationship between HbAlc and hearing impairment in diabetic patients, but there are few studies[12,13] on the correlation between HbAlc and hearing impairment in non-diabetic patients. Our study intends to explore the correlation between the two, and to evaluate blood biochemical indicators for the degree of hearing loss in such patients. The study would also serve as a reference for detailed audiometric evaluation and follow-up research, especially in resource-starved regions where the services of an otolaryngologist or audiometrician are not available.

Patients and Methods

Study Participants

The medical records of all patients diagnosed with SSNHL between Jan 2018 and Dec 2020 in the Division of Otorhinolaryngology at Peking University Shenzhen Hospital were examined in this study. Taking all complete data into consideration, 138 patients with SSNHL were included. There were 73 men (52.9%) and 65 women (47.1%), ranging in age from 20 to 83 years with a mean age of 44.41±14.86 years. Three patients (2.2%) had bilateral involvement, only the right side was affected in 57 patients (41.3%), and only the left side was affected in 78 patients (56.5%), as shown in Table I.

The inclusion criteria were: (1) diagnosis of SSNHL based on PTA (GSI 61, Grason Stadler, Eden Prairie, MN, USA); (2) SSNHL was defined as sensorineural hearing impairment of ≥ 30 dB over at least three consecutive frequencies on PTA, which developed within a period of 72 h[14]; (3) Informed consent was obtained from all study participants.

The exclusion criteria were: (1) conductive hearing loss (CHL); (2) History of type I or type II diabetes; (3) history of recurrent vertigo, fluctuating hearing loss and acoustic trauma; (4) known retro-cochlear lesions; and (5) cases where the patients failed to appear for audiometric tests.

Table I. Characteristics of SSNHL patients.

	Value
Gender	
Female	65 (47.1)
Male	73 (52.9)
Age (years)	44.41 ± 14.86
SSNHL site	
Left	78 (56.5)
Right	57 (41.3)
Both	3 (2.2)

Methods

Audiometric Tests

The air and bone conduction pure-tone averages were obtained by averaging the air- and bone-conduction thresholds at 0.5, 1, 2, and 4 kHz. The severity of the hearing loss was classified as mild (26-40 dB HL), moderate (41-60 dB HL), severe (61-80 dB HL), and profound (≥ 80 dB HL).

Laboratory Tests

Laboratory data collected from the participants during hospitalization included the following: complete blood count (CBC), hemoglobin (HB) level (g/L), mean platelet volume (MPV), HbA1c level (%), total cholesterol level (mg/dL), high-density lipoprotein cholesterol (HDL-C) level (mg/dL), low-density lipoprotein cholesterol (LDL-C) level (mg/dL), and triglyceride level (mg/dL). HbA1c levels were measured using capillary electrophoresis (Capillarys 3), and biochemical assays were conducted with the Beckman AU5800 (Brea, CA, USA).

Statistical Analysis

Spearman correlation analysis was used to analyze the measurement data that did not conform to a normal distribution, and the Receiver Operating Characteristic (ROC) curve was used to determine the diagnostic cut-off point and evaluate the index. $p < 0.05$ was chosen as the cutoff for statistical significance. Data analysis was performed using SPSS Statistics 22 (IBM, Armonk, NY, USA).

Results

The association between laboratory tests and audiometric tests in SSNHL patients was determined using Spearman correlation analysis, which revealed that HbA1c was positively cor-

Table II. Association between laboratory tests and audiometric tests.

Characteristics	$\bar{x} \pm s$	PTA	
		rs	*p*-value
Age (years)			0.536
TG (mmol/L)	1.36 ± 2.13	0.006	0.951
TC (mmol/L)	5.04 ± 0.98	-0.049	0.596
HDL (mg/L)	1.35 ± 0.27	-0.071	0.436
LDL (mg/L)	3.33 ± 0.79	-0.057	0.533
HbA1c (%)	5.71 ± 0.74	0.456	< 0.001
WBC ($*10^9$/L)	8.60 ± 2.84	0.033	0.704
RBC ($*10^{12}$/L)	4.72 ± 0.52	-0.036	0.674
Hb (g/L)	138.75 ± 14.07	0.027	0.753
PLT ($*10^{12}$/L)	252.53 ± 62.42	-0.129	0.132
MPV	10.50 ± 0.92	0.133	0.119

TG, triglycerides; TC, total cholesterol; HDL, high-density lipoprotein; LDL, low-density lipoprotein; HbA1c, glycosylated hemoglobin; WBC, white blood cells; RBC, red blood cells; Hb, hemoglobin; PLT, platelets; MPV, mean platelet volume.

related with the degree of hearing loss, with r = 0.456 and $p < 0.001$. Other laboratory parameters showed no obvious differences ($p > 0.05$), as shown in Table II.

ROC Curve Analysis

To further determine the best cut-off value for HbA1c in the diagnosis of hearing loss in non-diabetic patients with sudden hearing loss, we performed ROC curve analysis. PTA is the gold standard for determining the degree of hearing loss in SSNHL patients. We selected two levels wherein a value ≥ 61 dB HL was considered severe (extremely severe) while a value ≤ 60 dB HL was considered mild to moderate. The ROC curve for HbA1c and the degree of hearing loss in SSNHL patients are plotted in Figure 1 (area under the curve (AUC) = 0.737, SE = 0.044, p = 0.000), which shows that HbA1c has a certain diagnostic value. The best cut-off value was 5.550%, which was selected as the optimum value for the diagnostic index, with a corresponding sensitivity of 66.7% and specificity of 67.3%, as shown in Table III.

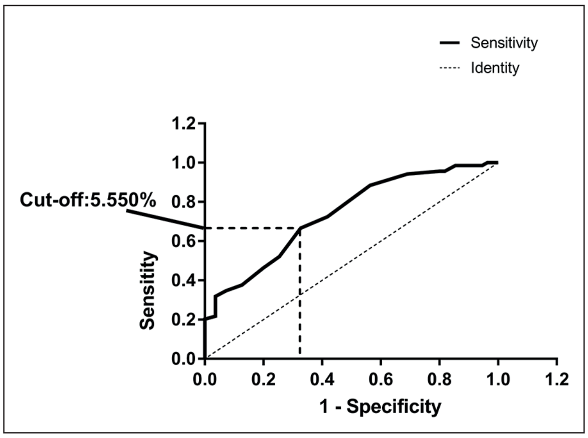

Figure 1. HbA1c ROC curve.

Discussion

The pathophysiology of SSNHL remains controversial, and inner ear microcirculation, viral infections, immune response, neuropathy, and other theories abound. Most studies[15,16] proposed inner ear microcirculation disorders as the main cause. Yamagishi et al[17] observed that microcirculatory problems in the inner ear are reflected on histopathology as capillary stenosis and epineural vascular sclerosis, both of which cause ischemia of the cochlear nerve and subsequent dysfunction. Bainbridge et al[18] found that more than 54% of diabetic patients had different degrees of hearing loss and 79% of these patients had high-frequency hearing loss. Several mechanisms underlie the microcirculatory disturbances in SSNHL seen in diabetics. These include the elevation of blood sugar, which causes the activation of polyol pathways and consumes a large amount of nicotinamide adenine dinucleotide phosphate [NADPH- a coenzyme of nitric oxide (NO)]. It thus reduces NO synthesis, affecting vasodilation, and causes a significant increase in blood viscosity and predilection for thrombosis and blockage of blood vessels. It triggers inflammation and oxidation mediated by hyperglycemia, directly causing

Table III. ROC results.

Factors	AUC	SE	*p*-value	95% CI	cut-off value	Sensitivity	Specificity
HbA1c	0.737	0.044	0.000	0.650-0.823	5.550	0.667	0.673

vascular endothelial cell damage. Furthermore, it aggravates the susceptibility of diabetic patients to lipid metabolism disorders, which can further worsen microvascular diseases.

HbA1c is an advanced glycation end product that reflects the state of glucose metabolism 2-3 months before venous blood sampling. The value is thus less affected by emergency states such as acute hyperglycemia. Therefore, it can be used as a stable and accurate marker of circulating blood glucose.

Many previous studies[8-11] focused on the relationship between HbA1c and hearing impairment in diabetic patients. Okhovat et al[8] reported that HbA1c level was positively correlated with the hearing threshold in patients with type I diabetes. Srinivas et al[9] found that patients with type II diabetes had a history of more than 10 years and a blood HbA1c > 8%, and the prevalence of sensorineural hearing loss was more than 85%. Weng et al[10] and similar studies reached the same conclusion that higher HbA1c levels in patients with type II diabetes were correlated with more severe hearing loss in SSNHL. Nagahama et al[11] suggested that the increased HbA1c not only complicates the difficulty of treatment, but also has an adverse effect on the prognosis.

At present, most studies[10,19] on the relationship between HbA1c and SSNHL are mainly focused on diabetic patients, but hearing may be affected by a variety of disorders of glucose and lipid metabolism. We excluded patients with a known history of diabetes so as to lend more vigor to our study.

We found that HbA1c was positively correlated with the PTA ($p < 0.001$), which is consistent with the results of previous studies[12,13]. The results of this study indicate that in non-diabetic SSNHL patients, the level of HbA1c may be related to the hearing loss in the affected ear. Zhou et al[12] suggested that HbA1c binds to vascular endothelial cell receptors and promotes the release of a large amount of vascular endothelin, thus affecting vasodilation in the cochlea. HbA1c can reduce the release of prostacyclin and NO in endothelial cells, leading to weakened anti-platelet aggregation and a predisposition to thrombus formation. HbA1c may activate the renin angiotensin aldosterone system, which not only promotes vasospasm in the cochlea but can also easily lead to thrombus formation. Kang et al[13] believe that HbA1c is continuously elevated in hitherto non-diabetic patients, leading to a vascular oxidative stress reaction in the cochlea, with cochlear microvascular lesions and hearing loss. In addition, we believe that cochlear hair cells have a poor tolerance to hypoxia, and HbA1c has a high affinity for oxygen. The increase of HbA1c affects the release of O_2, causing hair cell hypoxia and hearing impairment. In addition, local tissue hypoxia may cause a transient increase in red blood cells. This, coupled with an increase in the HbA1c content and the combined action of the two, causes changes in the microcirculation hemodynamics.

Based on the positive correlation between HbA1c and hearing loss in non-diabetic patients with SSNHL, it is possible to further quantify the corresponding relationship between HbA1c and hearing loss. According to the PTA level in the affected ear, the degree of hearing impairment was divided into two categories in our study: mild-moderate and severe (extremely severe), and statistical analysis with the ROC curve was performed on the basis of HbA1c. The results showed that the optimal cut-off value for HbA1c in the probability of either mild to moderate, or severe hearing loss, is 5.550%, with a sensitivity of 0.667 and a specificity of 0.673. This means that when the HbA1c is greater than 5.550% in non-diabetic patients with SSNHL, the hearing impairment may be more severe. With this inference, this cutoff value could be used as a means to select patients for a further and detailed evaluation and/or more aggressive treatment options, especially in resource starved regions. It could also serve as a marker for prognosis, especially in family and general practice.

We hope that the study will have wider implications for the future. First, if the patient has hearing loss but no conditional hearing test has been performed general physicians and family practitioners may be able to predict the severity of the impairment using the HbA1c level. Second, the baseline HbA1c level may be used as a prognostic indicator for the recovery of hearing.

Third, HbA1c may be used as an indicator of sudden deafness. Fourth, the prospect of controlling the level of HbA1c through drugs and other measures should be explored in future research to promote the recovery of hearing.

Limitations

The limitations in our study are as follows: our research is a retrospective and cross-sectional analysis and, therefore, does not reflect dynamic changes in the HbA1c before and after treatment; our sample size is small and may not accurately reflect the correlation; and our subgroup analysis is not robust enough to compare unilateral and bilateral disease. Centers, where the services of an otolaryngologist and/or audiometrician are available, might even find our study a little farfetched. The authors would like to specify that though this is a limitation, it might have its usefulness in primary care settings as a quick and easy marker for the detailed evaluation and/or further referral of these patients to higher centers.

Conclusions

In summary, the HbA1c level of non-diabetic patients with sudden deafness is well correlated with the degree of hearing loss. By expanding the sample size and increasing the collection of HbA1c data longitudinally to observe dynamic changes, both diagnosis and prognosis in sudden deafness could be vastly enhanced.

Conflict of Interest

The Authors declare that they have no conflict of interests.

Availability of Data and Materials

The datasets generated and analyzed during the present study are available from the corresponding author on reasonable request.

Ethics Approval

This study was approved by the Scientific Ethics Committee of Peking University Shenzhen Hospital Reference. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Consent to Participate

Informed consent was obtained from all study participants.

Authors' Contribution

Guo-Hui Zeng and Hong-Yu Liu designed/performed most of the investigation, data analysis and wrote the manuscript; Yong-Jin Su provided pathological assistance; Dong-Hui Lu contributed to interpretation of the data and analyses. All of the authors have read and approved the manuscript.

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