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Ischemia as a potential etiologic factor in idiopathic unilateral sudden sensorineural hearing loss: Analysis of posterior circulation arteries

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Abbreviations: AICA, Anterior inferior cerebellar artery; ASCVD, Atherosclerotic cardiovascular disease; EMR, Electronic medical record; ISSNHL, Idiopathic sudden sensorineural hearing loss; MRI, Magnetic resonance imaging; PTA, Pure tone audiometry

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Abstract

The association between idiopathic sudden sensorineural hearing loss (ISSNHL) and the radiologic characteristics of the vertebrobasilar artery is unclear. We hypothesized that the degree and direction of vertebrobasilar artery curvature in the posterior circulation contribute to the occurrence of ISSNHL**.** We consecutively enrolled patients diagnosed with unilateral ISSNHL in two tertiary hospitals. Magnetic resonance images were performed in all patients to exclude specific causes of ISSNHL, such as vestibular schwannoma, chronic mastoiditis, and anterior inferior cerebellar artery infarct. We measured the following parameters of posterior circulation: vertebral and basilar artery diameter, the degree of basilar artery curvature (modified smoker criteria), and vertebral artery dominance. Pure tone audiometries were performed at admission and again 1 week and 3 months later. A total of 121 ISSNHL patients (mean age, 46.0 ±17.3 years; 48.8% male) were included in these analyses. The proportion of patients with the left side hearing loss was larger than the proportion with the right side hearing loss (left, 57.9%; right, 42.1%). The majority of patients were characterized by a left dominant vertebral artery and right-sided basilar artery curvature. The direction of the basilar artery curvature was significantly associated with hearing loss lateralization ($p=0.036$). Age and sex matched multivariable analyses revealed the absence of diabetes and right-sided basilar artery curvature as significant predictors for left sided hearing loss. There was no statistical difference between atherosclerotic cardiovascular risk score (high versus low) and hearing outcomes at 3 months. In ISSNHL, the laterality of hearing loss was inversely associated with the direction of basilar artery curvature. Our results, therefore, indicate the importance of vascular assessment when evaluating ISSNHL.

1. Introduction

Idiopathic sudden sensorineural hearing loss (ISSHL) is defined as a sensorineural hearing loss of at least 30dB in three consecutive speech frequencies occurring within the previous 3 days (Eisenman and Arts, 2000; Wei et al., 2013). The worldwide incidence of ISSHL has been reported to range from 5 to 20 per 100,000 individuals (Wei et al., 2013).

ISSHL pathogenesis remains controversial. Various causes have been proposed, including viral infection of the labyrinth of the cochlear nerve, vascular compromise, intracochlear membrane rupture, perilymphatic fistula, and autoimmune inner ear disease (Hughes et al., 1996; Eisenman and Arts, 2000; Kim et al., 2012). A number of research groups have studied the etiology of idiopathic sudden sensorineural hearing loss (ISSNHL) in the past decade; however, etiologic investigation has been limited by the impracticality of histopathologic examination. Because ISSNHL is not fatal and inner ear tissue typically is not gathered at the time of the onset, many researchers assumed ISSNHL etiology through comparative studies of several factors; nevertheless, etiologic confirmation has been lacking. Recent studies have focused on therapeutic modalities for improving the ISSNHL treatment success rate. In spite of the development of new therapies, such as the intra-tympanic steroid injection, success rates remain around 60%; by comparison, the spontaneous recovery rate of ISSNHL varies between 32% and 68% and some have suggested that the natural course of the disease was not affected by intensive therapy (Byl, 1984; Ben-David et al., 2002).

Several potential etiologies have been suggested by a number of studies. From the therapeutic point of view, almost all clinicians have accepted viral infections of the inner ear as etiologic fact because steroid treatment has been an important anti-inflammatory therapy. However, several points are not explained by viral infections as a major etiologic factor: the powerful anti-inflammatory effect of steroids does not dramatically increase hearing, laboratory tests have not confirmed viral infection, there has been little incidence of previous or concomitant viral infection, and anti-viral medications have not affected disease outcome. These results suggest that viral infections may not be the major etiologic factor in ISSNHL.

We have previously reported that hyperglycemia might be an etiologic factor of ISSNHL using that group of glucose intolerance was involved to the group of diabetes mellitus (Ryu et al., 2014). Hyperglycemia was main etiologic factor of ischemic vascular disease. We therefore focused our investigation of the etiology of ISSNHL on potential vascular origins. Some work has suggested that there may be a correlation between ISSNHL and vascular problems. For example, ISSNHL patients have an increased risk for subsequent stroke or myocardial infarction compared to those without ISSNHL (Lin et al., 2008, 2013). Additionally, atherosclerotic vascular risk factors, such as hypertension, (Duck et al., 1997) hyperglycemia (Ryu et al., 2014) and hypercholesterolemia, (Chang et al., 2014) have been associated with the development of or recovery from ISSNHL. And, some have suggested that unilateral ISSNHL may be associated with subsequent stroke in the posterior circulation (Lee et al., 2002; Martines et al., 2011). However, prospective studies of the association between cerebral ischemia and ISSNHL are lacking, and few interventional studies have demonstrated a beneficial effect in preventing or recovering from ISSNHL.

The inner ear blood supply is sourced by the internal auditory artery that usually originates from the anterior inferior cerebellar artery (AICA), which branches from the proximal part of the basilar artery. The basilar artery is the only artery that anastomoses distally in the human brain; therefore, this confluent arterial flow creates a complicated flow pattern, which is usually associated with the development of atherosclerosis (Ravensbergen et al., 1998). Actually, post-mortem studies revealed that atherosclerosis is commonly found in the vertebrobasilar junction, where the AICA usually arise from (Ravensbergen et al., 1998). The left vertebrobasilar artery is usually larger than the right one (Park et al., 2007). This asymmetric vertebral artery flow contributes to the development of basilar artery curvature in the opposite direction of vertebral artery dominancy (Tronc et al., 2000; Hong et al., 2009). Therefore, as the origin of the ipsilateral AICA is positioned more laterally, elongation or thinning of the ipsilateral AICA occurs. The cochlea is vulnerable to ischemia because it is an end organ only supplied by a few branches of the internal auditory artery and has no vascular collaterals(Perlman et al., 1959). We can thus postulate that luminal narrowing of the AICA or artery-to-artery embolism due to vertebrobasilar atherosclerosis might be associated with the development of ISSNHL.

Basilar artery curvature has been associated with the laterality of posterior circulation infarct and vestibular neuropathy (Hong et al., 2009; Chuang et al., 2011). However, only a few anecdotally reported case series have found any association between the arterial systems of the posterior brain and the clinical characteristics of ISSNHL. Therefore, we aimed to investigate whether laterality of ISSNHL is associated with characteristics of the vertebrobasilar arteries. Specifically, we hypothesized that basilar artery curvature is associated with ISSNHL laterality. Additionally, we investigated which characteristics likely contribute to the development of and the audiologic prognosis of ISSNHL. If the origin of ISSNHL is vascular, ISSNHL therapies might be modified to include precautionary treatment of ischemic vascular disease.

2. Patients and methods

2.1 Participants

From January 2008 to December 2011, we retrospectively enrolled subjects who were diagnosed with sudden sensorineural hearing loss in two tertiary teaching hospitals. Patients eligible for this study were individuals aged 20 years or more who were admitted by the Department of Otorhinolaryngology to two hospitals, and were evaluated with an initial and follow-up pure tone audiometry (PTA), magnetic resonance imaging (MRI), and MR angiography. We defined ISSNHL as a sensorineural hearing loss of at least 30 dB in three consecutive speech frequencies that occurred within the previous 3 days (Hughes et al., 1996; Eisenman and Arts, 2000). Patients with bilateral ISSNHL, with no clinical data on electronic medical record (EMR) database, with a prior history of hearing loss or chronic otitis media, and with a diagnosis of vestibular schwannoma on an MRI were excluded from the final study cohort. All patients had been treated with oral prednisolone at a dose of 60mg for 5 days with dose reductions of 20mg every 2 days and an intratympanic steroid (DEXA) injection once daily for 6 days. This study was approved by the Institutional Review Board at each participating hospital.

2. 2 Data collection and definitions

We collected demographic and clinical data through the review of the EMR system. All ISSNHL patients included in the study were evaluated with an initial and follow-up PTA. Hearing recovery was determined by comparing the PTA at the initial exam with that at the follow-up exam. Hearing gain was represented by the absolute value of changes in the averaged hearing levels at 500, 1000, 2000, and 3000 Hz, as recommended by the Committee on Hearing and Equilibrium (Committee on Hearing and Equilibrium guidelines for the evaluation of results of treatment of conductive hearing loss, 1995) Hearing outcomes were categorized into two groups: recovery (more than 15 dB of hearing gain 3 months after prognosis) and no recovery (less than 15 dB of hearing gain 3 months after prognosis). During admission, blood pressure was obtained, blood tests for diabetes mellitus and cholesterol were performed, and an electrocardiography was also performed. Hypertension was defined when patients were taking antihypertensive medications, if their systolic blood pressure was 140 mmHg or more, or if their resting diastolic blood pressure was 90 mmHg or more. Subjects were considered diabetic if they were taking medical treatments for diabetes, if they had a fasting serum glucose level of 126 mg/dL or more, if they had a non-fasting random serum glucose level of 200 mg/dL or more, or if they had a whole blood glycated hemoglobin level of 6.5% or more. Subjects were considered to have hyperlipidemia if they had a fasting total cholesterol level of 240 mg/dL or more or if they were being treated with a lipid-lowering agent. A current smoker was defined as a person smoking one or more cigarettes per day within the last 6 months.

2.3 Definitions of the radiologic parameters

MRI scans were performed with a 1.5-T scanner (Intera; Philips Medical Systems, Amsterdam, the Netherlands). T1 weighted pre- and post-gadolinium axial images [TR/TE = 450/12, field of view (FoV) = 184 x 230, matrix = 256 x 256] and T2 weighted axial images (TR/TE = 4000/100, FoV = 184 x 230, matrix = 256 x 256) were obtained, with a 5mm thickness. Additionally, T2 weighted axial internal auditory canal sequences (TR/TE = 1500/250, FoV = 180 x 180, matrix = 352 x 352) were obtained with a 2mm thickness.

Morphologic characteristics of the vertebrobasilar artery were reviewed from the contrast enhanced (CE) MR angiography. Real-time angiography was obtained by administrating a dynamic gadolinium injection at a rate of 4ml/sec. Vertebral and basilar artery diameters were measured on proximal 2 cm segments of the vertebrobasilar junction and the mid-pontine level from the CE MRA. Especially, reformatted coronal images perpendicular to the course of the basilar artery was selected for the measurement. Two independent observers who had no ISSNHL clinical information for the ISSNHL were measured diameters of the vertebral artery and the basilar artery, and discrepant results were determined with 2 observers' agreement. Vertebral artery dominancy was classified as left, right, or symmetric (Fig 1A, B, C). Lateral positioning of the basilar artery was classified into three categories (0: midline throughout; 1: medial to lateral margin of clivus or dorsum sellae; 2: lateral to lateral margin of clivus or dorsum sellae) according to the modified version of the Smoker criteria (Smoker et al., 1986; Giang et al., 1988) (Fig 1D, E, F). The direction of basilar artery curvature was classified as left, right, or straight (Fig 1G, H, I).

2.4 Comparing between cardiovascular risk calculation and audiologic hearing results

The vascular burden of each ISSNHL patient was represented and calculated as the atherosclerotic cardiovascular disease (ASCVD) risk score, as defined by the

2013 ACC/AHA Guideline on the Assessment of Cardiovascular Risk. The median and interquartile range of the ASCVD risk score of all the participants was 2.0 and 0.2-6.1, respectively. Therefore, we stratified all the participants by the ASCVD risk (high and low).

Hearing recovery after 3 months was analyzed in each ASCVD risk group (high versus low-risk), by comparing pure tone audiometry results. Pure tone audiometry was performed at the first visit, 1 week later (immediate recovering condition), and 3 months later, when complete hearing recovery was assumed. Hearing gain was represented by the absolute value of changes in the averaged hearing levels at 500, 1000, 2000, and 3000 Hz, as recommended by the Committee on Hearing and Equilibrium (Committee on hearing and equilibrium, 1995). Hearing improvement was believed to be a credible parameter for hearing recovery after ISSNHL. The hearing outcome of the two ASCVD risk groups was first categorized into the recovery group and no recovery group, as defined above. The hearing outcome was then categorized as complete recovery, partial recovery, slight recovery, or no recovery, according to Siegel's criteria (Siegel, 1975).

2.5 Statistical analysis

Variables including baseline clinical measures were presented as the mean (± standard deviation) or frequency (percent). Descriptive comparisons of radiologic characteristics of the vertebrobasilar artery (vertebral artery dominancy, and the degree and direction of basilar artery curvature) between the left and the right ISSNHL groups were performed using a χ^2 test. The linear by linear association test was used to assess the relationship between laterality of hearing loss and the radiologic characteristics of the vertebrobasilar artery. Bivariate analysis for the predictors of left sided hearing loss was performed using the multiple logistic regression analysis. Covariates were age, sex, vascular risk factors (hypertension, diabetes, hyperlipidemia, and smoking), and vertebrobasilar artery dominancy, degree of curvature according to modified Smoker criteria, and the side of basilar artery curvature. Variables with $p<0.10$ in univariate analyses were then assessed in a multivariate analysis. Forced entry with right and left ISSNHL groups was used in multivariable analysis. A two-sided $p<0.05$ was considered significant. Statistical comparisons between ASCVD risk groups and hearing improvement were based on chi-squared test. All statistical analyses were performed using SPSS version 21 (SPSS IBM, New York, USA).

3. Results

3.1 Patient characteristics

The mean age (± SD) and proportion of men in the study was 46.0± 17.3 years and 48.8% (59 of 121), respectively. The baseline characteristics of study participants are listed in Table 1. The proportion of patients with left side ISSNHL was larger than those with right-sided ISSNHL (left: 57.9%, right: 42.1%). The left dominant vertebral artery was also the majority. In contrast, right-sided basilar artery curvature was the most common basilar artery curvature, followed by left sided curvature and straight basilar artery.

3.2 Radiologic characteristics of the vertebral artery and ISSNHL laterality

Table 2 and Fig 2 illustrates the association between ISSNHL laterality and the radiologic characteristics of the vertebrobasilar artery. Patients with left side hearing loss more often also have a left dominant vertebral artery compared to patients with right side hearing loss, and those with right side hearing loss more often have a right dominant vertebral artery compared to those with left side hearing loss. However, the trend between vertebral artery dominancy and ISSNHL laterality was significant (p=0.333). Additionally, ISSNHL laterality was not associated with the degree of basilar artery curvature (p=0.477), although the association with the direction of the basilar artery curvature was significant. Patients with left-curved basilar arteries usually suffered from right side hearing loss. As the direction of the basilar artery curvature changed from left to right, the proportion of patients with left side hearing loss significantly increased (p=0.036)

Univariate analyses of predictors for left side hearing loss revealed that patients with the left side hearing loss were more often male (p=0.032), and had a higher proportion of right side basilar artery curvature (p=0.028). Diabetes was more frequently observed in patients with the right side hearing loss (p=0.004). Other factors, such as hypertension, hyperlipidemia, smoking, vertebral artery dominance, and the degree of basilar artery curvature were not significantly associated with ISSNHL laterality (Table 3). Age- and sex matched multivariate analyses identified the absence of diabetes and right side basilar artery curvature as significant predictors for left side hearing loss (Table 4).

3.3 Correlation between ASCVD risk and hearing outcome

Among the 121 ISSNHL patients, 60 belonged to the high-risk ASCVD group, and 61 belonged to the low-risk ASCVD group (Table 5). The hearing outcomes of the low-risk ASCVD group were not significantly better than those of the high-risk ASCVD group (p=0.681). Immediate hearing was tested at post-sudden hearing loss 1 week, and the hearing outcomes by response category were based on a 15dB recovery cutoff. During the follow-up period, 30 patients did not visit our clinics. Therefore, 91 patients were included in the late hearing recovery analysis. Comparing the ASCVD groups, we observed no significant differences in the late hearing response to steroid therapy (p=0.232; see Table 5). Unexpectedly, patients with high-risk for ASCVD had better late hearing recovery results than the low-risk ASCVD risk group, although the difference was not significant. We further analyzed the hearing recovery between ASCVD groups according to Siegel's criteria (Table 6). The recovery rate of the two groups did not significantly differ (p=0.697).

4. Discussion

Despite the great advances in otology over the past decades, the ISSHL etiology remains unclear. More than 100 possible causes have been implicated over the years, but most cases remain idiopathic (Hughes et al., 1996). There were many possible etiologies suggested by plenty of studies. However, many clinicians and researchers might have accepted viral infections of the inner ear environment as etiologic fact from the therapeutic point of view.

In the present study, ISSNHL laterality was significantly associated with diabetes and the direction of the basilar artery curvature. More than half of the patients in this study had a left dominant vertebral artery with a right angulated basilar artery. Patients with diabetes had increased odds of having right side ISSNHL, and those with right basilar artery curvature more often had left side ISSNHL. Two major proposed etiologies for ISSNHL development are vascular (vertebrovascular ischemia) and inflammatory theories (Stokroos and Albers, 1996; Haberkamp and Tanyeri, 1999). Hinojosa and Kohut showed temporal bone histopathology in

ISSNHL, with a loss of sensory epithelium of the cochlear and the vestibular labyrinth, which the authors suggested to be an involvement of the inner ear infarction (Hinojosa and Kohut, 1990). Since the early 2000s, evidence of vascular involvement (specifically, AICA infarction) has been repeatedly suggested; however, any form of therapy in the ISSNHL, including gingko biloba, (Desloovere et al., 1988) hyperbaric oxygen therapy, (Pezzoli et al., 2015) and hemodilution (Klemm et al., 2007) were not associated with a consistent benefit. Therefore, many clinicians abandoned the anti-ischemic therapies and focused on anti-inflammatory treatments.

Nevertheless, there remains a significant level of interest in the association between vertebrobasilar ischemia and ISSNHL. Lin et al. reported a causal relationship between stroke and ISSNHL diagnosis; specifically, ISSNHL patients had a 1.65-fold increase in stroke risk compared to patients without ISSNHL (Ryu et al., 2014). In addition, isolated hearing loss after artery-to-artery embolism or AICA infarction had previously been shown to play a role in ISSNHL development (Watanabe et al., 1994; Lee et al., 2002 and 2004; Lee and Baloh, 2005). Hemorheological alterations, such as elevated plasma fibrinogen and increased plasma viscosity, which favor arterial thromboembolic vascular events, have also been associated with the occurrence of ISSNHL (Ohinata et al., 1994; Suckfull and Hearing Loss Study Group, 2002). Our results could additionally support the vascular hypothesis, as some risk factors such as diabetes and some hemodynamic characteristics such as vertebrobasilar curvature, might contribute to the ISSNHL etiology.

In general, atherosclerosis tends to preferentially develop in focal regions where the artery is diverged, converged or bent (Ravensbergen et al., 1998; Resnick et al., 2003; Cunningham and Gotlieb, 2005). In post-mortem studies, atherosclerosis is preferentially localized on the outer wall of bifurcations, where the wall shear stress is oscillatory or low (Zarins et al., 1983). The basilar artery is the only artery converging distally in the human brain (Ravensbergen et al., 1998). Usually, the left vertebral artery is larger than the right vertebral artery, and the resulting asymmetric flow pattern contributes to the development of a basilar artery curvature in the opposite direction of the dominant vertebral artery. At the vertebrobasilar junction, wall shear stress is decreased at the inner wall, opposite to the basilar artery curvature (Hademenos and Massoud, 1997). In our study, patients with left dominant vertebral artery frequently also had rightcurved basilar arteries and left side ISSNHL. This hypothesis was reported previously and illustrated in Fig. 3 (Kim et al., 2012). Most basilar arteries are straight type in early life; however, the asymmetric confluent flow pattern resulting from asymmetric vertebral arteries eventually causes vascular remodeling of the basilar artery. As a result, stretching and thinning of the AICA in the opposite direction of basilar artery curvature may be observed concurrently with shear stress-induced atherosclerosis in the inner wall of the basilar artery. These morphological changes may contribute to the development of ISSNHL on the same side as the vertebral artery dominancy.

Reiss et al. studied lateralization of sudden deafness in 489 patients that were characterized predominantly by left side hearing loss, especially the female patients (Reiss and Reiss, 2014). In our patients, left side hearing loss was also predominant, but was more evident in male patients. Therefore, we suggest that vertebral artery dominance, rather than gender, is a pragmatic explanation for the laterality of the hearing loss.

Oral or tropical steroid use is a widely used treatment for ISSNHL (Stobbs et al., 2014). However, little evidence support its efficacy in ISSNHL (Wei et al., 2013).

Steroid treatment could be beneficial in some patients with an inflammatory etiology, but it might be harmful in patients with vascular etiologies. Systemic steroids have a glucocorticoid effect and are associated with enhanced von Willebrand factor and plasminogen activator inhibitor-1 synthesis, which in turn induces a prothrombotic state (Huang et al., 1995; Morange et al., 1999). It is therefore important to differentiate between vascular and inflammatory etiology to maximize the efficacy of steroid treatment in ISSNHL. Therefore, some morphologic patterns, such as vertebral artery dominancy and the direction of the vertebrobasilar curvature might be helpful in the inference of vascular etiologies in ISSNHL.

Our data have some limitations that apply to all patients with hearing loss. First, the retrospective nature of the data may introduce selection bias. Second, we only included patients with unilateral hearing loss. However, bilateral hearing loss is more frequently associated with specific causes, such as infection, inherited disorders, and noise or drug exposures. Therefore, it is quite reasonable to only include patients with unilateral hearing loss in studying clinic-radiologic characteristics of ISSNHL. Though with these limitations, our data has some of strength in through radiological evaluation.

In the current study, vertebrobasilar curvature was associated with the laterality of sudden sensorineural hearing loss. Our results therefore underscore the need for vascular assessment when evaluating ISSNHL. Additionally, ISSNHL patients with other vascular risk factors might benefit from preventive treatments for cerebral or cardiac vascular attacks. In future prospective trials, radiologic evaluations of vertebrobasilar artery characteristics should be thoroughly performed to enable the differentiation between vascular and other causes of ISSNHL.

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References

Ben-David, J., Luntz, M., Podoshin, L., Podoshin, L., Sabo, E., Fradis, M., 2002. Vertigo as a prognostic sign in sudden sensorineural hearing loss. Int. Tinnitus. J. 8, 127-128.

Byl, FM. Jr., 1984. Sudden hearing loss:eight years' experience and suggested prognosis table. Laryngoscope. 94, 647-661.

Chang, S.L., Hsieh, C.C., Tseng, K.S., Weng, S.F., Lin, Y.S., 2014. Hypercholesterolemia is correlated with an increased risk of idiopathic sudden sensorineural hearing loss: a historical prospective cohort study. Ear. Hear. 35, 256-261.

Chuang, Y.M., Chern, C.M., Liao, W.H., Hsu, L.C., Lien, C.F., Lirng, J.F., Shiao, A.S., Ko, J.S., 2011. Contribution of intracranial vertebral artery asymmetry to vestibular neuropathy. J. Neurol. Neurosurg. Psychiatry. 82, 823-825.

Committee on hearing and equilibrium, 1995. Committee on hearing and equilibrium guidelines for the evaluation of results of treatment of conductive hearing loss. Otolaryngol. Head. Neck. Surg. 113, 186-187.

Committee on Hearing and Equilibrium guidelines for the evaluation of results of treatment of conductive hearing loss, 1995. American Academy of Otolaryngology-Head and Neck Surgery Foundation, Inc. Otolaryngol. Head. Neck. Surg. 113, 186-187.

Cunningham, K.S., Gotlieb, A.I., 2005. The role of shear stress in the pathogenesis of atherosclerosis. Lab. Invest. 85, 9-23.

Desloovere, C., Meyer-Breiting, E., von Ilberg, C., 1988. [Randomized double-blind study of therapy of sudden deafness: initial results]. Hno. 36, 417-422.

Duck, S.W., Prazma, J., Bennett, P.S., Pillsbury, H.C., 1997. Interaction between hypertension and diabetes mellitus in the pathogenesis of sensorineural hearing loss. Laryngoscope. 107, 1596-1605.

Eisenman, D., Arts, H.A., 2000. Effectiveness of treatment for sudden sensorineural hearing loss. Arch. Otolaryngol. Head. Neck. Surg. 126, 1161-1164.

Giang, D.W., Perlin, S.J., Monajati, A., Kido, D.J., Hollander, J., 1988. Vertebrobasilar dolichoectasia: assessment using MR. Neuroradiology. 30, 518-523.

Haberkamp, T.J., Tanyeri, H.M., 1999. Management of idiopathic sudden sensorineural hearing loss. Am. J. Otol. 20, 587-592; discussion 593-585.

Hademenos, G.J., Massoud, T.F., 1997. Biophysical mechanisms of stroke. Stroke. 28, 2067-2077.

Hinojosa, R., Kohut, R.I., 1990. Clinical diagnosis of anterior inferior cerebellar artery thrombosis. Autopsy and temporal bone histopathologic study. Ann. Otol. Rhinol. Laryngol. 99, 261-272.

Hong, J.M., Chung, C.S., Bang, O.Y., Yong, S.W., Joo, I.S., Huh, K., 2009. Vertebral artery dominance contributes to basilar artery curvature and peri-vertebrobasilar junctional infarcts. J. Neurol. Neurosurg. Psychiatry. 80, 1087-1092.

Huang, L.Q., Whitworth, J.A., Chesterman, C.N., 1995. Effects of cyclosporin A and dexamethasone on haemostatic and vasoactive functions of vascular endothelial cells. Blood. Coagul. Fibrinolysis. 6, 438-445.

Hughes, G.B., Freedman, M.A., Haberkamp, T.J., Guay, M.E., 1996. Sudden sensorineural hearing loss. Otolaryngol. Clin. North. Am. 29, 393-405.

Kim, C., Sohn, J.H., Choi, H.C., 2012. Vertebrobasilar angulation and its association with sudden sensorineural hearing loss. Med. Hypotheses. 79, 202-203.

Klemm, E., Bepperling, F., Burschka, M.A., Mosges, R., Study, G., 2007. Hemodilution therapy with hydroxyethyl starch solution (130/0.4) in unilateral idiopathic sudden sensorineural hearing loss: a dose-finding, double-blind, placebo-controlled, international multicenter trial with 210 patients. Otol. Neurotol. 28, 157-170.

Lee, H., Sohn, S.I., Jung, D.K., Cho, Y. W., Lim, J.G., Yi, S.D., Lee, S.R., Sohn, C.H., Baloh, R.W., 2002. Sudden deafness and anterior inferior cerebellar artery infarction. Stroke. 33, 2807-2812.

Lin, C., Lin, S.W., Lin, Y.S., Weng, S.F., Lee, T.M., 2013. Sudden sensorineural hearing loss is correlated with an increased risk of acute myocardial infarction: a population-based cohort study. Laryngoscope. 123, 2254-2258.

Lin, H.C., Chao, P.Z., Lee, H.C., 2008. Sudden sensorineural hearing loss increases the risk of stroke: a 5-year follow-up study. Stroke. 39, 2744-2748.

Lee, H., Ahn, B.H., Baloh, R.W., 2004. Sudden deafness with vertigo as a sole manifestation of anterior inferior cerebellar artery infarction. J. Neurol. Sci. 222, 105-107.

Lee, H., Baloh, R.W., 2005. Sudden deafness in vertebrobasilar ischemia: clinical features, vascular topographical patterns and long-term outcome. J. Neurol. Sci. 228, 99-104.

Martines, F., Dispenza, F., Gagliardo, C., Martines, E., Bentivegna, D., 2011. Sudden sensorineural hearing loss as prodromal symptom of anterior inferior cerebellar artery infarction. ORL. J. Otorhinolaryngol. Relat. Spec. 73, 137-140.

Morange, P.E., Aubert, J., Peiretti, F., Lijnen, H.R., Vague, P., Verdier, M., Négrel, R., Juhan-Vague, I., Alessi, M.C., 1999. Glucocorticoids and insulin promote plasminogen activator inhibitor 1 production by human adipose tissue. Diabetes. 48, 890-895.

Ohinata, Y., Makimoto, K., Kawakami, M., Haginomori, S., Arak,i M., Takahashi, H., Blood viscosity and plasma viscosity in patients with sudden deafness. 1994. Acta. Otolaryngol. 114, 601-607.

Park, J.H., Kim, J.M., Roh, J.K., 2007. Hypoplastic vertebral artery: frequency and associations with ischaemic stroke territory. J. Neurol. Neurosurg. Psychiatry. 78, 954-958.

Perlman, H.B., Kimura, R., Fernandez, C., 1959. Experiments on temporary obstruction of the internal auditory artery. Laryngoscope. 69, 591-613.

Pezzoli, M., Magnano, M., Maffi, L., Pezzoli, L., Marcato, P., Orione, M., Cupi, D., Bongioannini, G., 2015. Hyperbaric oxygen therapy as salvage treatment for sudden sensorineural hearing loss: a prospective controlled study. Eur. Arch. Otorhinolaryngol. 272, 1659-1666.

Ravensbergen, J., Ravensbergen, J.W., Krijger, J.K., Hillen, B., Hoogstraten, H.W., 1998. Localizing role of hemodynamics in atherosclerosis in several human vertebrobasilar junction geometries. Arterioscler. Thromb. Vasc. Biol. 18, 708-716.

Resnick N, Yahav H, Shay-Salit A, Shushy, M., Schubert, S., Zilberman, L.C., Wofovitz, E., 2003. Fluid shear stress and the vascular endothelium: for better and for worse. Prog. Biophys. Mol. Biol. 81, 177-199.

Ryu, O.H., Choi, M.G., Park, C.H., Kim, D.K., Lee, J.S., Lee, J.H., 2014.

Hyperglycemia as a potential prognostic factor of idiopathic sudden sensorineural hearing loss. Otolaryngol. Head. Neck. Surg. 150, 853-858.

Siegel, L.G., 1975. The treatment of idiopathic sudden sensorineural hearing loss. Otolaryngol. Clin. North. Am. 8, 467-473.

Smoker, W.R., Corbett, J.J., Gentry, L.R., Keyes, W.D., Price, M.J., McKusker, S., 1986. High-resolution computed tomography of the basilar artery: 2. Vertebrobasilar dolichoectasia: clinical-pathologic correlation and review. Am. J. Neuroradiol. 7, 61-72.

Stobbs, N., Goswamy, J., Ramamurthy, L., 2014. How are we managing sudden sensorineural hearing loss in the United Kingdom?: Our Experience. Clin. Otolaryngol. 39, 385-388.

Stokroos, R.J., Albers, F.W., 1996. Therapy of idiopathic sudden sensorineural hearing loss. A review of the literature. Acta. Otorhinolaryngol. Belg. 50, 77-84.

Suckfull, M., Hearing Loss Study G., 2002. Fibrinogen and LDL apheresis in treatment of sudden hearing loss: a randomised multicentre trial. Lancet. 360, 1811-1817.

Tronc, F., Mallat, Z., Lehoux, S., Wassef, M., Esposito, B., Tedgui, A., 2000. Role of matrix metalloproteinases in blood flow-induced arterial enlargement: interaction with NO. Arterioscler. Thromb. Vasc. Biol. 20, E120-126.

Watanabe, Y., Ohi, H., Shojaku, H., Mizukoshi, K., 1994. Sudden deafness from vertebrobasilar artery disorder. Am. J. Otol. 15, 423-426.

Wei, B.P., Stathopoulos, D., O'Leary, S., 2013. Steroids for idiopathic sudden sensorineural hearing loss. Cochrane. Database. Syst. Rev. 7, CD003998.

Zarins, C.K., Giddens, D.P., Bharadvaj, B.K., Sottiurai, V.S., Mabon, R.F., Glagov, S.,

1983. Carotid bifurcation atherosclerosis. Quantitative correlation of plaque localization with flow velocity profiles and wall shear stress. Circ. Res. 53, 502-514.

Reiss, M., Reiss, G., 2014. Laterality of sudden sensorineural hearing loss. Ear. Nose. Throat. J. 93, 318-320.

Table 1

Patient Demographics.

Characteristic	Number of patients (%)*
Age, years (±SD)	46.0 (±17.3)
Male, %	59 (48.8%)
Onset of admission, days	6.3 (±9.8)
Hypertension, %	24 (20.0%)
Diabetes, %	17 (14.2%)
Hyperlipidemia, %	14 (11.8%)
Smoking, %	15 (12.5%)
Side of hearing loss	
Left	70 (57.9%)
Right	51 (42.1%)
Vertebral artery dominancy	
Left	70 (57.9%)
Right	33 (27.3%)
Symmetric	18 (14.9%)

Lateral positioning of the basilar artery	
0 (midline throughout)	26 (21.5%)
1 (medial to lateral margin of clivus or dorsum sellae)	83 (68.6%)
2 (lateral to lateral margin of clivus or dorsum sellae)	12 (9.9%)
Direction of curvature of the basilar artery	
Left	28 (23.1%)
Straight	26 (21.5%)
Right	67 (55.4%)
Pre tone audiometry	
initial, dB	67.5 (±28.1)
follow up, dB	61.3 (±31.8)

*continuous variables are presented as mean ± standard deviation

Table 2

Associations between laterality of hearing loss and radiologic parameters.

		Hearing loss side		
		Left (N=70)	Right (N=51)	*P* value*
Vertebral artery dominancy	Left	41 (59.4)	16 (23.2)	0.333
	Symmetric	12 (17.4)	6 (11.5)	
	Right	16 (23.2)	17 (32.7)	
Degree of curvature	0	16 (23.2)	10 (19.2)	0.477
	1	48 (69.6)	35 (67.3)	

	2	5 (7.2)	7 (13.5)	
Direction of BA curvature	Left	11 (15.7)	17 (33.3)	0.036
	Straight	16 (22.9)	10 (19.6)	
	Right	43 (61.4)	24 (47.1)	

*p-values are presented for the results of the linear by linear association analyses.

Table 3

Univariate and multivariate analyses for predictors of left side hearing loss.

	Univariable analysis		Multivariable analysis	
	OR (95% CI)	*P*	*aOR (95% CI)	*P*
Age, year	0.98 (0.96-1.00)	0.052	0.99 (0.97-1.02)	0.522
Male	2.25 (1.07-4.70)	0.032	2.61 (1.13-6.02)	0.025
Risk factor (%)				
Hypertension	0.74 (0.31-1.79)	0.507		
Diabetes	0.18 (0.05-0.58)	0.004	0.15 (0.04-0.58)	0.006
Hyperlipidemia	0.43 (0.14-1.29)	0.131		
Smoking	1.25 (0.42-3.69)	0.686		
Vertebral artery dominance				
Right	1.0 (referent)	-		
Symmetric	2.13 (0.64-7.02)	0.216		
Left	1.59 (0.69-3.67)	0.273		
Degree of curvature				

0 (midline)	1.0 (referent)	-		
1 (mild)	0.90 (0.37-2.22)	0.821		
2 (moderate)	0.45 (0.11-1.80)	0.257		
Direction of curvature				
Left	1.0 (referent)	-	1.0 (referent)	-
Straight	2.47 (0.83-7.39)	0.105	2.36 (0.73-7.61)	0.151
Right	2.77 (1.12-6.86)	0.028	3.80 (1.38-10.52)	0.010

Table 4

Factors associated with the left sided ISSNHL in 121 patients as determined by multivariate analysis of predictors for left side hearing loss.

Predictors	aOR (95% CI)	*P* value
Diabetes	0.15 (0.04-0.58)	0.006
Direction of curvature		
Left	1.0 (referent)	-
Straight	2.36 (0.73-7.61)	0.151
Right	3.80 (1.38-10.52)	0.010

Age and sex adjusted.

Table 5

Comparison of hearing recovery rates between ASCVD high-risk and low-risk groups.

ASCVD risk group	Patient number	recovery	No recovery	*P* value
High, immediate hearing	60	11(18.3%)	49(81.7%)	
Low, immediate hearing	61	13(21.3%)	48(78.7%)	0.681
High, late hearing	44	26(59.1%)	18(40.9%)	
low, late hearing	47	22(46.8%)	24(53.2%)	0.232

Immediate hearing was tested at post-sudden hearing loss 1 week. Late hearing was tested at post-sudden hearing loss 3 month. Hearing outcomes by response category was based on a 15 dB recovery cutoff.

Table 6

Comparison of hearing recovery rates using Siegel's criteria.

ASCVD risk group	Patient number	CR	PR	SR	NR	*P* value
High, late hearing	44	17(38,6%)	9(20.5%)	7(15.9%)	11(25.0%)	
low, late hearing	47	20(42.6%)	6(12.8%)	6(12.8%)	15(31.9%)	0.697

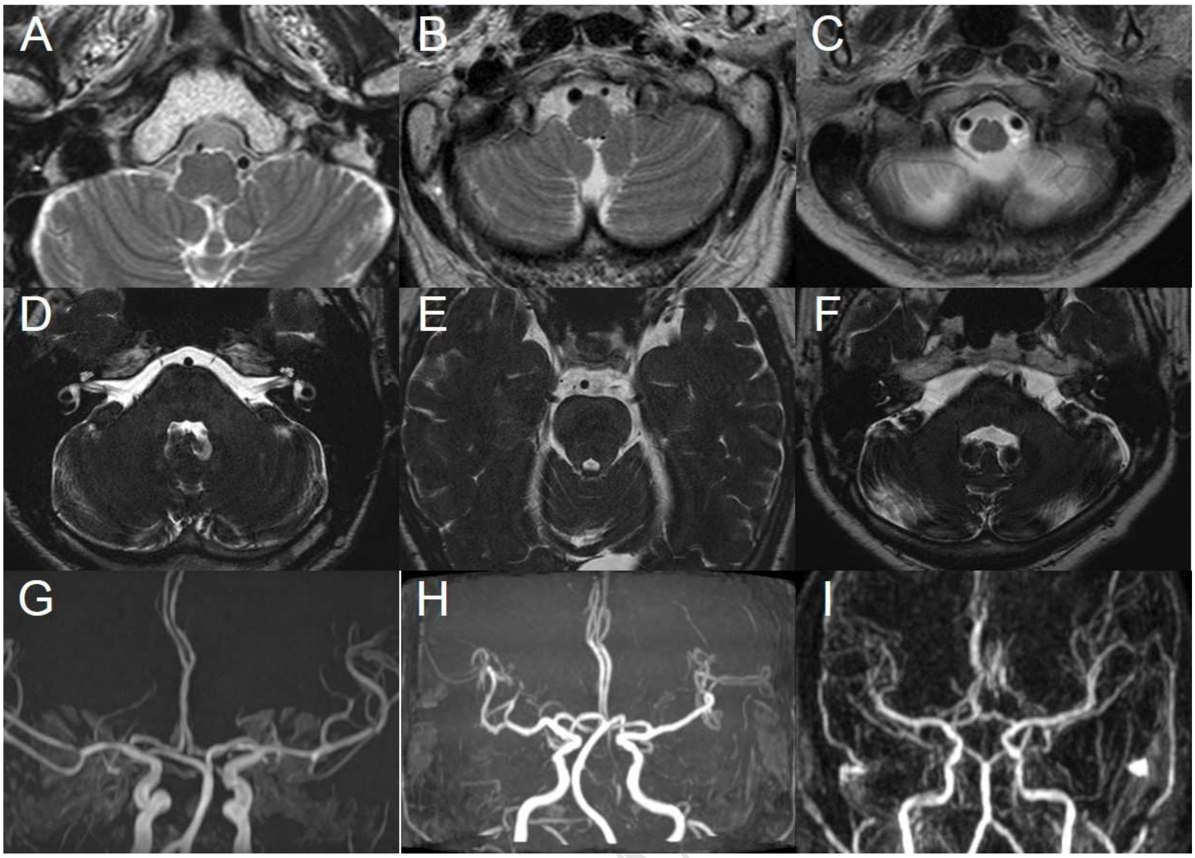
Figure Legends

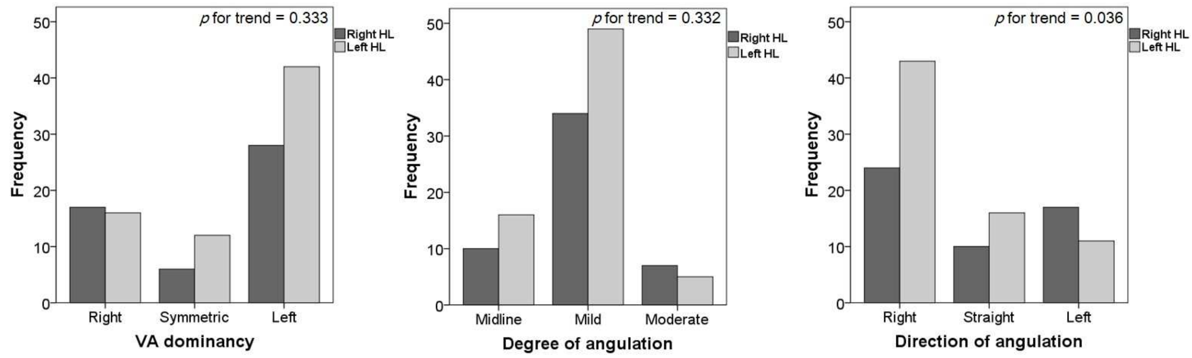
Fig. 1. Upper columns: Classification of vertebral artery dominancy. A: The left vertebral artery was dominant over the right one. B: The right vertebral artery was dominant over left one. C: The sizes of both vertebral arteries were symmetric. Middle columns: The classification of basilar artery position. D: midline throughout, E: medial to lateral margin of

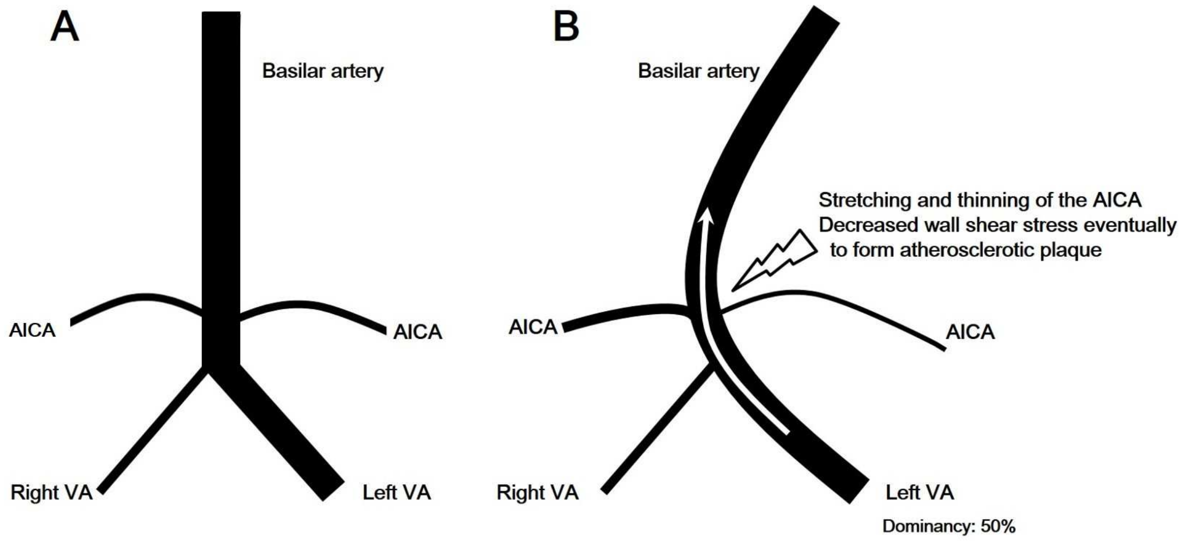
clivus or dorsum sellae. F: lateral to lateral margin of clivus or dorsum sellae. Lower columns: Classification of basilar artery curvature. G: The basilar artery is curved to the left side. H: The basilar artery is curved to the right side. I: The basilar artery was positioned straight.

Fig. 2. Comparison between hearing loss laterality and verterbral artery dominance (left panel), degree of basilar artery curvature (middle panel), and direction of basilar artery curvature (right panel).

Fig. 3. The suggested effects of vertebrobasilar curvature that cause sensorineural hearing loss via decreased wall shear stress at the side opposite to basilar artery curvature.


A
B
C
D
E
F
G
H
I


p for trend = 0.333
Right HL
Left HL
Frequency
50
40
30
20
10
0
Right
Symmetric
Left
VA dominancy
p for trend = 0.332
Midline
Mild
Moderate
Degree of angulation
p for trend = 0.036
Right
Straight
Left
Direction of angulation


A
Basilar artery
AICA
AICA
Right VA
Left VA
B
Basilar artery
Stretching and thinning of the AICA
Decreased wall shear stress eventually
to form atherosclerotic plaque
AICA
AICA
Right VA
Left VA
Dominancy: 50%

highlights

1. The direction of the basilar artery angulation was significantly associated with hearing loss lateralization

2. Our results underscore the need for vascular assessment when evaluating ISSNHL

3. ISSNHL patients with other vascular risk factors might benefit from preventive treatments for cerebral or cardiac vascular attacks