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The Role of Endolymphatic Hydrops in Patients with Pantonal Idiopathic Sudden Sensorineural Hearing Loss: A Cause or Secondary Reaction*

Ye-xian ZHENG[1†], Ai-guo LIU[2†], Xing-long WANG[2], Ying HU[2], Yan-fei ZHANG[2], Li-yan PENG[2#]
[1]*Department of Otorhinolaryngology, the Central Hospital of Wuhan, Tongji Medical College, Huazhong University of Science and technology, Wuhan 430014, China*
[2]*Department of Otorhinolaryngology, Tongji Hospital, Tongji Medical College, Huazhong University of Science and technology, Wuhan 430030, China*

Summary: The purpose of this study was to investigate the presence of endolymphatic hydrops (EH) in both affected and unaffected ears of patients with pantonal unilateral idiopathic sudden sensorineural hearing loss (ISSNHL) using three-dimensional fluid-attenuated inversion recovery magnetic resonance imaging (3D-FLAIR MRI) and further evaluate the significance of EH in this disorder. Twenty-seven ISSHL patients were enrolled in this study. 3D-FLAIR MRI was performed 24 h after intratympanic injection of gadolinium-diethylenetriaminepentaacetic acid (Gd-DPTA). The incidences of EH in the affected ears and contralateral unaffected ears were compared and the correlations of EH with vertigo or prognosis were analyzed using the Chi-square test. The results showed that the incidence of EH was 68.0% (17/25) in the affected ears and 34.8% (8/23) in the unaffected ears. There was a statistically significant difference between affected ears and unaffected ears in regard to the incidence of EH (P<0.05). There were no significant correlations of EH with vertigo (P=1.000) or with prognosis (P=0.359) in the affected ears. In conclusion, there is EH in the inner ear of patients with pantonal ISSNHL; EH is not related to vertigo, a concomitant symptom of ISSNHL, and the prognosis of this condition. The presence of EH may be a secondary reaction following the impairment of the inner ears with pantonal ISSNHL.
Key words: idiopathic sudden sensorineural hearing loss; endolymphatic hydrops; magnetic resonance imaging; gadolinium-diethylenetriaminepentaacetic acid

Idiopathic sudden sensorineural hearing loss (ISSNHL) is defined as a sensorineural hearing loss of 30 dB or more with at least 3 contiguous audiometric frequencies affected that develops over a 72-h period. It affects 5 to 20 per 100 000 populations with about 4000 new cases per year in the United States and 300 per 100 000 in Germany[1, 2]. The hypothesized causes include viral infection[3], circulatory disorders, allergy and immunologic reaction. In 2011, German scientists proposed five classifications of ISSNHL based on the configuration of pure tone audiograms, and speculated that each type may have different pathogenesis and etiology[2]. Among the five types of ISSNHL, pantonal hearing loss is the most common type; its treatment response was around 70% and not as good as the type with low frequency hearing loss[4–6].

Endolymphatic hydrops (EH) existed in low frequency ISSNHL patients, of which seven cases were reported by Chen *et al*[7] and 29 cases by Okazaki *et al*[8]. We believe it would be useful to know if EH also exists in pantonal ISSNHL. More pantonal ISSNHL patients included in our study in comparison to the previous researches would be helpful in detecting EH in the inner ear in this disorder. Moreover, the relationship between vertigo and EH in ISSNHL is inconclusive and worth exploring[9–12].

Intratympanic gadolinium-diethylenetriaminepentaacetic acid (Gd-DPTA) administration was first demonstrated by Nakashima *et al* in 2009 and later a three-stage standard grading scale for EH in the vestibule and cochlea was proposed to evaluate the severity of EH[13, 14]. With this imaging technique, EH can be demonstrated *in vivo*.

In this study we first investigated the existence of EH in the affected and unaffected normal ears of patients with pantonal ISSNHL using intratympanic Gd-DPTA administration and three-dimensional fluid-attenuated inversion recovery magnetic resonance

Ye-xian ZHENG, E-mail: 381154870@qq.com; Ai-guo LIU, E-mail: aiguoliu309@163.com
†Both authors contributed equally to this work.
#Corresponding author, E-mail: liyanpeng2050@163.com
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imaging (3D-FLAIR MRI) and then evaluated the relationship of EH with vertigo and the prognosis of this condition respectively.

1 SUBJECTS AND METHODS

1.1 Patient Selection

The present study was approved by the Institutional Review Board of the Ethics Committee of Tongji Medical College, Huazhong University of Science and Technology (HUST). Informed consent was obtained from the participants. Twenty-seven patients were enrolled in this study from the outpatient department of Tongji Hospital from July 2017 to June 2018.

All the ISSNHL patients met the following inclusion criteria: (1) they had experienced a sudden-onset sensorineural hearing loss for the first time; (2) the cause of hearing loss was unknown; (3) the level of hearing loss was at least 30 dB HL in at least three contiguous frequencies with no air-bone gap; (4) there was a history of vertiginous episodes near the onset of hearing loss; (5) the interval between the onset of vertigo and the start of the MRI examination was ≤30 days; (6) no other neurological signs existed; (7) the hearing level at all frequencies (0.25, 0.5, 1, 2, 4 and 8 kHz) in the audiogram decreased to the approximate degree between 35 dB to 120 dB. The difference between the two adjacent frequency averages was less than 15 dB HL. The exclusion criteria included: (1) vertigo caused by benign paroxysmal positional vertigo, Meniere's disease or other disease; (2) fluctuating hearing loss; (3) inflammation of external or middle ear ; (4) allergy to gadolinium; (5) a history of ear surgery.

All the patients were divided into vertigo or non-vertigo group. The concomitant symptom of vertigo was defined as episodic rotational vertigo which occurred 1 day before/after the hearing loss and lasted from several hours to several days. The onset was not related to head position and the vertigo attack did not recur after recovery. The hearing level of the patients was classified into mild, moderate, severe and profound hearing loss according to standards established by the WHO in 1997. Contralateral ear with normal hearing served as the normal control.

1.2 Intratympanic Gadolinium Injection and MRI Scan

The injection procedure was as follows: (1) patients were kept in the supine position and their heads rotated to the normal side; (2) external auditory canal was disinfected with 75% alcohol, thereafter the tympanum membrane was anaesthetized using1% dicaine; (3) Gd-DTPA-dimeglumine (Magnevist; Schering AG, China) diluted eightfold in saline (0.4 mL) was injected into the tympanic cavity with a 25-gauge needle syringe at a point in the posterior inferior quadrant of the tympanic membrane; (4) the patient remained in this position for 30 min without any swallowing action; 5) the control ear underwent the same procedure.

MRI was performed 24 h after intratympanic Gd injection with a 3-T system (Siemens, Germany) using a 32-channel receive-only phased array coil. 3D-FLAIR was performed with the following parameters: repetition time (TR)=6000 ms; echo time (TE)=128 ms; inversion time=1650 ms; echo train length=23; flip angle 90°; contiguous 1 mm slice thickness; field of vision=16 cm/image; matrix=400×400. The scan time was 30 min. The images were reconstructed independently by two radiologists in an independent, double-blind manner.

1.3 Grading of EH

We applied the grading criteria which were previously described by Nakashima *et al* in 2009[14]: In the vestibule, a level of "significant" indicates a substantial enlargement of the endolymphatic space that occupied more than half of the vestibule. A level of "mild" indicates a moderate enlargement of endolymphatic space that occupied between 33.3% and 50% area of the vestibule. A level of "none" indicates no or very mild enlargement of endolymphatic space that occupied <33.3% of the vestibule. We did not score the cochlear EH. Two radiologists with experience in this field who were blinded to the patients' diagnosis evaluated the images following MRI.

1.4 Treatment

All patients received identical treatment. The regimen included intravenous Ginaton (Dr. Willmar Schwabe GmbH & Co. KG, Germany), fibrinolysin (Taiho Pharmaceutical Co., Ltd, Japan), dextran and a tapered dexamethasone (Pfizer Pharmaceuticals Ltd, America) dosing scheme. Hyperbaric oxygenation (2ATA) was also used as an auxiliary therapy. The mean duration of therapy was 14±2.76 days.

1.5 Outcomes Assessment

The air-conduction pure-tone hearing thresholds at 5 frequencies at the beginning and the end of therapy were recorded and compared. Pure Tone Audiometry (dB Hearing level, dB HL) within 10 dB HL of initial HL or within 10 dB HL of the normal HL of the unaffected ear was considered as complete recovery; pure-tone average (PTA, dB HL) within 50% of initial HL or ≥10 dB HL improvement of the HL meant partial recovery; <10 dB HL improvement in HL relative to the initial HL was considered no recovery.

2 RESULTS

The clinical characteristics of the 27 patients are listed and summarized in table 1. The mean age was 41.85±16.92 years and the ratio of female to male was 13∶14. Eleven left ears and 16 right ears made up the affected ears. The mean values and standard deviations of the pre-PTA and post-PTA were 86.94±24.20 dB

and 59.47±29.75 dB respectively in the affected ears (fig. 1). The median and interquartile range of deafness duration was 10 (range: 5–20) days. An axial view of the visible EH image is shown in fig. 2.

Gd-DTPA demonstration rate was 92.59% (25/27) in the affected ears and 85.19% (23/27) in the normal ears. The incidence of EH was 68.00% (17/25) in the affected ears and 34.78% (8/23) in normal ears. Comparisons between affected and normal ears are listed in table 2 and the corresponding MRI images are displayed in fig. 3 and 4.

Of the affected 27 ears, perilymphatic spaces of the vestibule were clearly visible in 22 ears; 5 ears had barely visible gadolinium in the vestibule. Among

Table 1 Summary of patient characteristics

Variables	Total
All patients (*n*)	27
Patient sex (*n*)	
Female	13
Male	14
Age (year, mean±SD)	41.85±16.92
Ear affected (*n*)	
Left	11
right	16
Onset time (day)	10 (range: 5–20)
Vertigo	12
Pretreatment PTA (mean±SD)	86.94±24.20 dB
Postreatment PTA (mean±SD)	59.47±29.75 dB
PTA gain (*n*)	
No recovery	8
Partial recovery	15
Complete recovery	4

n means number.

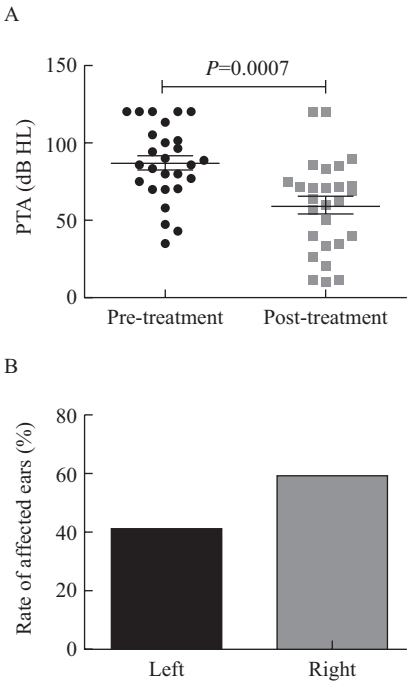

Fig. 1 A: PTA results before and after treatment; B: the rate of the affected ears on each side; PTA: pure-tone average

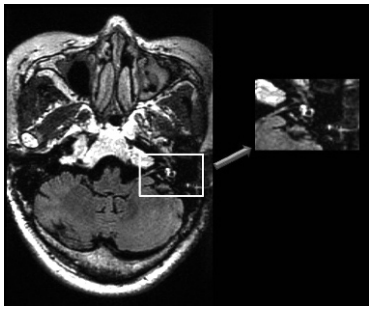

Fig. 2 3D-FLAIR magnetic resonance image of the left ear of a 63-year-old woman with ISSNHL in the axial plane
The image was taken 24 h after intratympanic injection of Gd. The white rectangle demonstrates our region of interest. Gd is clearly demonstrated in the vestibule and semicircular canals in this image.

Table 2 Comparison of the incidences of EH between the affected and unaffected ears in pantonal ISSNHL patients

EH degree	Affected ear *n* (%)	Unaffected ear *n* (%)	*P**
None	8 (32)	15 (65.2)	
Mild	11 (44)	4 (17.4)	0.021
Significant	6 (24)	4 (17.4)	

*The comparison was between "None" group and "Mild+Significant" group.

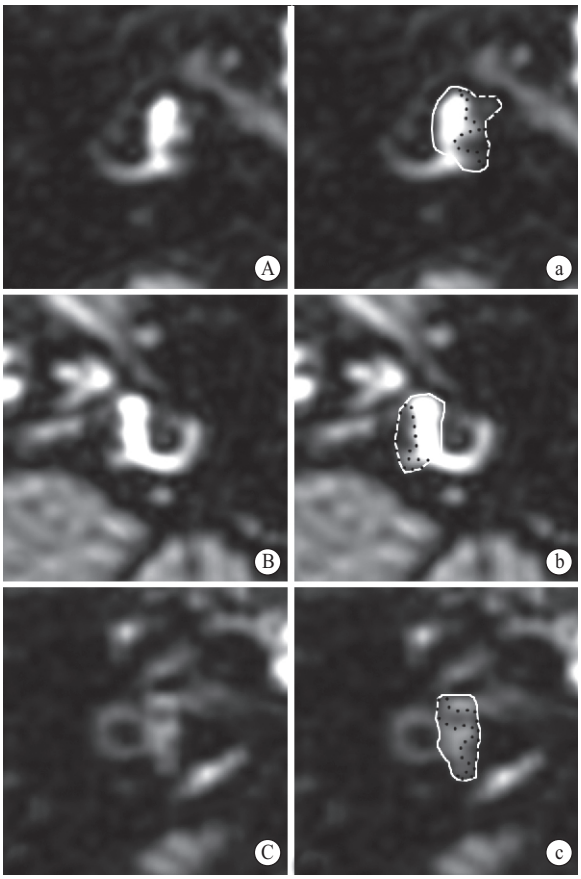

Fig. 3 A–C: EH in the affected ears of the patients with ISSNHL; a–c: the line drawings of A, B, C, respectively
A: no EH; B: mild EH; C: significant EH; a–c: The solid line indicates the fluid space in the vestibule and the dotted line indicates the endolymphatic space. Area rates of the endolymphatic space to the vestibular fluid space are 33.3%, 50.0% and 74.7% in A, B and C, respectively.

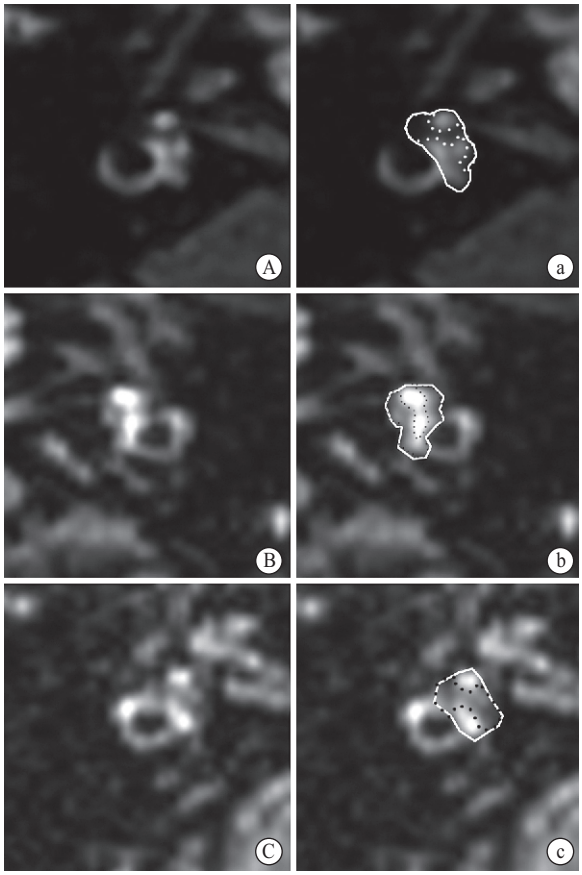

Fig. 4 A–C: EH in the normal ears of the patients with ISSNHL; a–c: the line drawings of A, B, C, respectively
A: no EH; B: mild EH; C: significant EH; a–c: The solid line indicates the fluid space in the vestibule and the dotted line indicates the endolymphatic space. Area rates of the endolymphatic space to the vestibular fluid space are 30.0%, 49.1% and 53.7% in A, B and C, respectively.

these five ears, gadolinium could be observed in the cochlea and the semicircular canals in 3 ears. We classified those 3 ears as significant EH because we considered that the vestibule was invisible due to the compression of the extremely enlarged endolymphatic space which inhibited the passage of gadolinium from the scala tympani of the cochlea to the vestibule (fig. 5). There were statistically significant differences between the affected ears and the normal ears in regard to the incidence of EH (P=0.021) (table 2).

There was no statistically significant difference in prognosis between EH group and no EH group (P=0.359) (table 3).

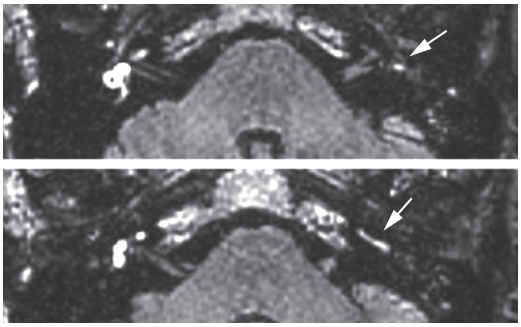

Fig. 5 Significant EH (as indicated by white arrows) in the basal turn of the cochlea (top panel) and the semicircular canal (bottom panel)

Table 3 Analysis of the relationship between prognosis and EH in the affected ears of pantonal ISSHL patients

EH Degree	Prognosis		
	Effective *n* (%)	Invalidation *n* (%)	P^*
None	4 (23.5)	4 (50.0)	
Mild	8 (47.1)	3 (37.5)	0.359
Significant	5 (29.4)	1 (12.5)	

The comparison was between "None" group and "Mild+Significant" group. There was also no difference when comparing "None+Mild" group and "Significant" group. *: P value was derived from Fisher's Exact test.

Pearson Chi-square test and Fisher's Exact test showed there was no significant difference in EH incidence between "vertigo group" and "non-vertigo group" in the affected ear group and unaffected ear group (P=1.000) (table 4).

3 DISCUSSION

Our research confirmed that EH occurred in the pantonal type of ISSNHL using MR imaging. The rate of EH was slightly higher (68%) in the vestibule in comparison to 57.1% reported by Chen *et al* and 44% by Okazaki *et al*[7, 8], but lower to 88% published by shimono *et al*[15]; EH also existed in 34.8% of the unaffected normal hearing ears, which was comparable to 38% in Okazaki's study[8]. In the German clinical practice guidelines of 2011, ISSNHL was classified into five types with regard to audiometric pattern, and the possible pathological mechanisms were discussed[2]: 1. The high frequency hearing loss may be caused by inner hair cell damages (at least 60

Table 4 Analysis of the relationship between vertigo and EH in affected ears of pantonal ISSHL patients

EH Degree	Vertigo group			Non-vertigo group		
	Affected ear *n* (%)	Unaffected ear *n* (%)	P^*	Affected ear *n* (%)	Unaffected ear *n* (%)	P^*
None	2 (25)	5 (62)		4 (28.6)	9 (64.3)	
Mild	4 (50)	1 (12)	0.315	6 (42.8)	3 (21.4)	0.058
Significant	2 (25)	2 (25)		4 (28.6)	2 (14.3)	

*: P value was derived from Pearson Chi-square test.

dB of hearing loss) or outer hair cell damage (up to approximately 50 dB of hearing loss); 2. The low frequency range of hearing loss is probably due to an EH or a local circulatory disturbance of the lamina spiralis; 3. A pathogenic substrate of pantonal hearing loss is, above all, a functional impairment of the stria vascularis and/or of the supplying vessels; 4. Deafness or bordering on numbness may be due to occlusion (thrombotic/embolic) of the common cochlear artery or the spiralis modioli artery; 5. The pathogenetic basis of the rare tub-shaped sinking in the middle frequency range is local bleeding disorders in the area of the lamina spiralis ossea with hypoxic damage to the organ of Corti as well as gene defects. Our findings vividly depict the existence of EH in pantonal hearing loss in contrast to the above classification which proposes that low-frequency ISSNHL occurs because of EH. Our observations could, perhaps, be incorporated into this existing classification and act as a framework not only for formulating newer and more adequate guidelines but also provide a new avenue for further research.

Until now it is unclear about the role of EH in ISSNHL patients. Two questions may help us to understand the EH in this kind of ISSNHL: (1) Is EH an etiology of the pantonal ISSNHL? and (2) Is EH a kind of pathological change of the pan tonal ISSNHL?

Scientists had put forward that some types of sudden deafness can be caused by EH, known as "endolymphatic deafness"[16]. The impairments of the endolymph secretory structures such as the stria vascularis, spiral ligament and supporting cells lead to sensorineural hearing loss. These structures are responsible for the secretion of endolymph, a fluid characterized by a high potassium concentration, a low sodium concentration and a positive potential. But so far, no further evidence has been found to support "endolymphatic deafness" theory. Although EH was observed in MR imaging of ISSNHL patients, this finding alone is not sufficient to explain that EH is the cause of ISSNHL.

Furthermore, our study showed that the concomitant symptom of vertigo was not related to EH incidence in the vestibule of both affected ears (P=0.856) and unaffected ear (P=0.933), which differs from previous reports. Chen *et al*[7], in a study involving seven patients, reported that there may be a relationship between EH and ISSNHL in the presence of vertigo. However, in a light microscopic study of the temporal bone, no clear-cut pathologies such as membrane ruptures or endolymphatic hydrops were identified in the vertiginous and nonvertiginous ears, ultimately demonstrating that there was no morphologic correlation of vertigo associated with ISSHL[17]. Combining with our results, we deduced that EH might not be a key cause of the symptoms of vertigo in pan tonal ISSNHL. A possible reason for the vertigo in ISSNHL could be functional impairment of the supplying vessels such as the vestibular artery or the vestibule cochlear artery, which could influence the vestibular function of affected ears. The relationship between vertigo and EH in ISSNHL is worthy of future exploration. Additionally, our research showed the post-treatment PTA values had no significant relationship with the EH degree (P=0.359), which meant that EH might not be a prognostic factor in ISSNHL. Similar results have been shown by other authors[10–12].

We infer that the presence of EH in the affected ears with ISSNHL could be considered as secondary EH[18, 19] from our results. Here our secondary EH refers to a result of ISSNHL, not a cause. Reasons are as follows: 1. The concomitant symptom of vertigo was not related to EH in the vestibule of the affected ears; 2. EH was not a prognostic factor in pan tonal ISSNHL; 3. EH was observed even in the unaffected ears, which could neither be explained in a cause-effect manner nor vice versa, and helped cement our belief. This secondary EH speculation could also explain the phenomenon that unaffected ears with ISSNHL show EH. If a pantonal ISSNHL patient showed EH in both affected and unaffected ears at the same time, the possible reason could be that the disordered blood flow of the affected ear increased the permeability of the endolymphatic blood–labyrinth barrier (BLB)[20–22] or caused free radical release which led to increased vascular permeability followed by damage of the endolymphatic secretory structures such as the stria vascularis, spiral ligament and supporting cells, and finally caused the EH in the affected ear; the unaffected ear probably showed EH because of systemic response of either inflammatory, allergic or autoimmune cause. For example, after the damage of the affected ear, the inflammotory factors, such as intercellular adhesion molecule-1[23], or nuclear factor-κB[24], were over-expressed; increased expression of ICAM-1 resulted in extravasate of leukocytes into the unaffected ear cochlea which caused increased inflammatory response and possibly disrupted the normal fluid balance in the inner ear. If a patient showed EH in the unaffected ear but not in the affected ear, it could be that profound EH led to extreme compression of the perilymphatic space of the vestibule, thus preventing the entry of Gd. Consequently EH could not be detected in the affected ear. In such a situation even though EH was present, it was unlikely to be localized on contrast enhanced MRI. In the unaffected ear, secondary EH might be triggered by the ISSNHL of the contralateral ear.

Reasons for the low concentration of Gd in the inner ears could be due to: 1. Gd ran out through the eustachian tube owing to the swallowing action after Gd injection in the tympanic cavity; 2. the lower permeability of the round window membrane in some patients; 3. extreme compression of the perilymphatic

space because of the profound EH.

Nevertheless, our measurements have two limitations. Firstly, we did not take into account the interval between the onset of ISSNHL and the time of imaging, which may affect the results of MRI. Secondly, we were unable to score EH in the cochlea because of the low resolution of images.

In conclusion, there is EH in the inner ear of patients with pan tonal ISSNHL, which is not related to their concomitant symptom of vertigo and prognosis of ISSNHL. The presence of EH may be a secondary reaction following the impairment of the inner ears with pan tonal ISSNHL.

Conflict of Interest Statement

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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