ORIGINAL ARTICLE

Could the thick of retinal nerve fiber layer be a potential measure of axonal loss in hearing loss?

¿Podría el espesor de la capa de fibras nerviosas de la retina ser una potencial medida de la pérdida axonal en la pérdida auditiva?

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Abstract

Objective: *The objective of the study is to compare the optic coherence tomography (OCT) parameters of the healthy and affected sides of patients with idiopathic sudden sensorineural hearing loss (ISSNHL) and to investigate the relationships between these and the improvement in hearing levels.* **Methods:** *A bilateral eye evaluation of patients diagnosed with ISSNHL was performed with OCT. The ganglion cell complex (GCC) and retina nerve fiber layer (RNFL) thickness values were recorded and the differences between the two eyes were examined.* **Results:** *An evaluation was made of 39 patients with a mean age of 44.82 ± 14.90 years. The RNFL thickness of the eyes was determined to be mean 89.87 ± 3.65 µm on the affected side and 103.87 ± 3.98 µm on the healthy control side (p = 0.0001). The mean GCC was determined to be mean 90.46 ± 3.49 µm on the affected side and 103.77 ± 3.96 µm on the healthy control side (p = 0.0001).* **Conclusions:** *A statistically significant difference was observed between the healthy and affected eyes of patients with ISSNHL with respect to mean GCC and mean RNFL thickness. OCT could be a useful technique for measuring this neural degeneration.*

Keywords: *Ganglion cell complex. Retinal nerve fiber layer. Optic Coherence Tomography. Sudden hearing loss.*

Resumen

Objetivo: *Comparar e investigar los parámetros de la tomografía de coherencia óptica (OCT) de los lados sanos y afectados de pacientes con pérdida auditiva neurosensorial súbita idiopática (PANSI).* **Método:** *La evaluación ocular bilateral de los pacientes diagnosticados con PANSI se realizó con OCT. Se registraron los valores de espesor del complejo de células ganglionares (CCG) y de la capa de fibras nerviosas de la retina (CFNR), y se examinaron las diferencias entre los dos ojos.* **Resultados:** *Se evaluaron 39 pacientes, con una edad media de 44.82 ± 14.90 años. Se determinó que el grosor de la CFNR de los ojos era una media de 89.87 ± 3.65 µm en el lado afectado y 103.87 ± 3.98 µm en el lado de control sano (p = 0.0001). Se determinó que el CCG medio era 90.46 ± 3.49 µm en el lado afectado y 103.77 ± 3.96 µm en el lado de control sano (p = 0.0001).* **Conclusiones:** *Se encontró una diferencia estadísticamente significativa entre los ojos sanos y afectados de pacientes con PANSI con respecto al CCG medio y al espesor medio de la CFNR. La OCT podría ser una técnica útil para medir esta degeneración neuronal.*

***Palabras clave*:** *Complejo de células ganglionares. Capa de fibras nerviosas de la retina. Tomografía de coherencia óptica. Pérdida auditiva repentina.*

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Introduction

Idiopathic sudden sensorineural hearing loss (ISSNHL) is an emergency ear, nose, and throat (ENT) condition characterized by hearing loss of more than mean 30 dB in at least 3 consecutive frequencies within 72 h[1]. ISSNHL is seen at a frequency of 5-20/100,000/year, and studies have reported an increasing incidence[2]. When the etiological factors are examined, a cause cannot be determined in < 5% of cases[3]. Potential causes include viral infections, vascular disorders, metabolic disorders, trauma, autotoxicity, autoimmune diseases, developmental anomalies, and psychogenic disorders[3]. The most commonly accepted etiologies are immune system-mediated mechanisms, vascular disorders, and viral infections[4,5]. Secondary sensorineural hearing loss can occur due to causes such as neoplasm, stroke, or irradiation[5]. Despite high rates of spontaneous recovery, such as 40-65%, reported in the literature, the etiology and pathogenesis have not yet been fully clarified[4]. The point most focused on in studies of etiology and pathogenesis is vascular disorders. When it is taken into consideration that the cochlear microvascular system cannot be measured *in vivo*, recent studies have concluded that indirect evaluation of the cochlear microvascular system using retinal imaging may present an alternative[6]. In such circumstances, the findings obtained with optic coherence tomography (OCT) may be explanatory for the etiology of sudden hearing loss.

OCT is an imaging technique with good patient compliance that can be easily applied and provides information in depth and high resolution about the internal structure of the retina using the optic reflective characteristics of the tissues with the aid of an 830 nm diode laser light close to infrared[7,8]. The axial resolution of OCT is extremely high at 8-10 microns, and as slices can be obtained similar to a microscopic image, it is defined as a non-invasive tissue biopsy[7]. Therefore, with the measurement of the morphology of the retina nerve fiber layer (RNFL), evidence is provided of neurodegeneration with the visualization of myelin loss in the retina[9].

OCT is used in the diagnosis and follow-up of many diseases that have accompanying degeneration. These include anterior ischemic optic neuropathies (ON), other toxic and inflammatory ON, multiple sclerosis (MS), neuromyelitis optica, pseudotumor cerebri, migraine, optic nerve head drusen, and Alzheimer's disease. To the best of our knowledge, there is no study in the literature showing whether or not there is neurodegeneration using optic imaging in ISSNHL patients.

The aim of this study was to use OCT to determine whether or not there was neurodegeneration in ISSNHL patients and, if so, how early-determined neurodegeneration changed with treatment.

Materials and methods

This prospective, monocentric study was conducted in the ENT clinic of a training and research hospital. Approval for the study was granted by the Local Ethics Committee (100/05: December 14, 2020). Informed consent was provided by all the study participants. The study included patients who presented at our clinic with the complaint of sudden hearing loss and were diagnosed with ISSNHL as a result of an audiometric examination. Before treatment, both eyes of each patient were evaluated separately with OCT by an ophthalmologist.

The patients included in the study were those with symptom duration of < 30 days, who started treatment because of ISSNHL, and completed the treatment protocols appropriately. Before and after treatment, all the patients underwent an audiogram, a full ENT examination, and temporal contrast magnetic resonance imaging (MRI). Patients were excluded from the study if symptoms had been ongoing for longer than 30 days, if they had Meniere's disease, acoustic trauma, chronic middle ear inflammation, cerebellopontine angle pathologies, SNHL associated with autotoxic drug use, a history of autological surgery, bilateral ISSNHL, newly diagnosed vestibular Schwannoma, glaucoma, macula degeneration, uveitis, retinal or choroidal vascular disease, a history of retinal surgery, ocular trauma or optic neuropathy, optic nerve head or retinal anomaly, or who were referred to our clinic after having started treatment.

The patients included in the study were started on treatment with 1 mg/kg/day oral methylprednisolone, and this was reduced by 16 mg every 3 days. Audiological tests were performed before and after treatment. Speech discrimination scores (SDS) were recorded, and pure tone average (PTA) values were calculated at 0.5, 1, 2, and 4 kHz. The change in PTA values after treatment was analyzed according to the Furuhashi criteria (Table 1)[10].

OCT

OCT scanning was performed on the same day as the ophthalmological examination by experienced

Table 1. Furuhashi criteria for the assessment of audiological hearing outcomes

	Criteria
Complete recovery	PTA < 20 dB or identical to contralateral non-affected ear
Marked improvement	PTA improvement > 30 dB
Slight improvement	PTA improvement between 10 and 30 dB
No recovery	PTA improvement < 10 dB

PTA: pure tone threshold average (500, 1000, 2000, and 4000 Hz).
Source: Furuhashi, A., et al., Sudden deafness: long-term follow-up and recurrence. Clin Otolaryngol Allied Sci, 2002. 27(6): p. 458-63.

operators using the RTVue SD-OCT system (RTVue-XR 100 Avanti software v.6.1, Optovue, Inc., Fremont, CA, USA). OCT was performed in a dark room on both eyes after dilatation of the pupils. The macula and optic nerve head were evaluated, while the RNFL and ganglion cell complex (GCC) thicknesses were measured separately. Measurements were repeated three times for each eye to reduce measurement errors. The RNFL 3.45 protocol was used for peripapillary RNFL analysis, with the thickness measured at a diameter of 3.45 mm around the center of the optic disc. The total number of A-scans with a circumference was 2225. The results were displayed on a color map with customized software, with normative data adjusted for age and optic disc size (Fig. 1). A peripapillary RNFL thickness map was expressed as a numerical value. GCC thickness was measured using the GCC protocol, composed of 15 vertically oriented B scans 7.0 mm in length (800 A scans each), separated by 0.50 mm, together with a single horizontally oriented B scan 7.0 mm in length (12,934 A-scans), all centered on the macula by the operator. The center of the GCC scan was shifted 1.0 mm temporally to be able to better sample the temporal peripheral macula with the nasal visual field.

Statistical analysis

The Statistical Package for the Social Sciences software (SPSS, version 22.0 for Windows; SPSS Inc., Chicago, Illinois, USA) was used to perform all analyses. Kolmogorov–Smirnov and P-P plot tests were used to verify the normality of the distribution of continuous variables. The results were reported as means standard deviations, or in situations in which the distributions were skewed, as the median (minimum-maximum). Categorical variables were presented as percent. The comparison of categorical variables between the groups was done using Pearson's chi-square and Fischer's exact test, whereas continuous variables were compared using an independent sample t-test and the Mann–Whitney U test according to homogenity. SDS values before and after treatment were evaluated with the Wilcoxon signed-rank test. A $p < 0.05$ was considered statistically significant.

Results

The study started with a total of 62 patients. Of these, 23 were excluded; 4 did not complete follow-up, 17 were newly diagnosed with comorbidity, and 2 had hearing loss in the ear that was thought to be healthy. Thus, the evaluations were completed with 39 patients, comprising 16 (41%) females and 23 (59%) males with a mean age of 44.82 ± 14.90 years. The patients were diagnosed, treated, and followed up for ISSNHL on the left side in 15 cases and on the right side in 24.

The PTA values of the patients were mean 61.25 before treatment and 30.00 after treatment. The SDS was 68% before treatment and 88% after treatment. When the patients were evaluated according to the Furuhashi criteria, full recovery was seen in 15 (38.4%) patients. Full recovery and significant improvement were accepted as treatment successes, and 23 patients were determined to have benefited from the treatment. The treatment was not successful for 16 patients. A slight improvement was seen in 6 of these patients and no improvement in 10 (Table 2).

The RNFL thickness of the eyes was determined to be mean 89.87 ± 3.65 μm on the affected side and 103.87 ± 3.98 μm on the healthy control side ($p = 0.0001$). The mean GCC was determined to be mean 90.46 ± 3.49 μm on the affected side and 103.77 ± 3.96 μm on the healthy control side ($p = 0.0001$).

The patients were separated into two groups according to their response to treatment: those with full recovery-significant improvement, and those with slight or no improvement. The mean RNFL thickness was found to be 89.72 ± 3.59 μm in the successful group and 90.05 ± 3.66 μm in the group with an unsuccessful response to treatment, with no statistically significant difference observed ($p = 0.991$). The GCC values were mean 90.38 ± 3.47 μm in the successful treatment group and 90.07 ± 3.55 μm in the unsuccessful group ($p = 0.991$).

When the affected eyes of only the patients showing full recovery (n: 15) were compared with those of the

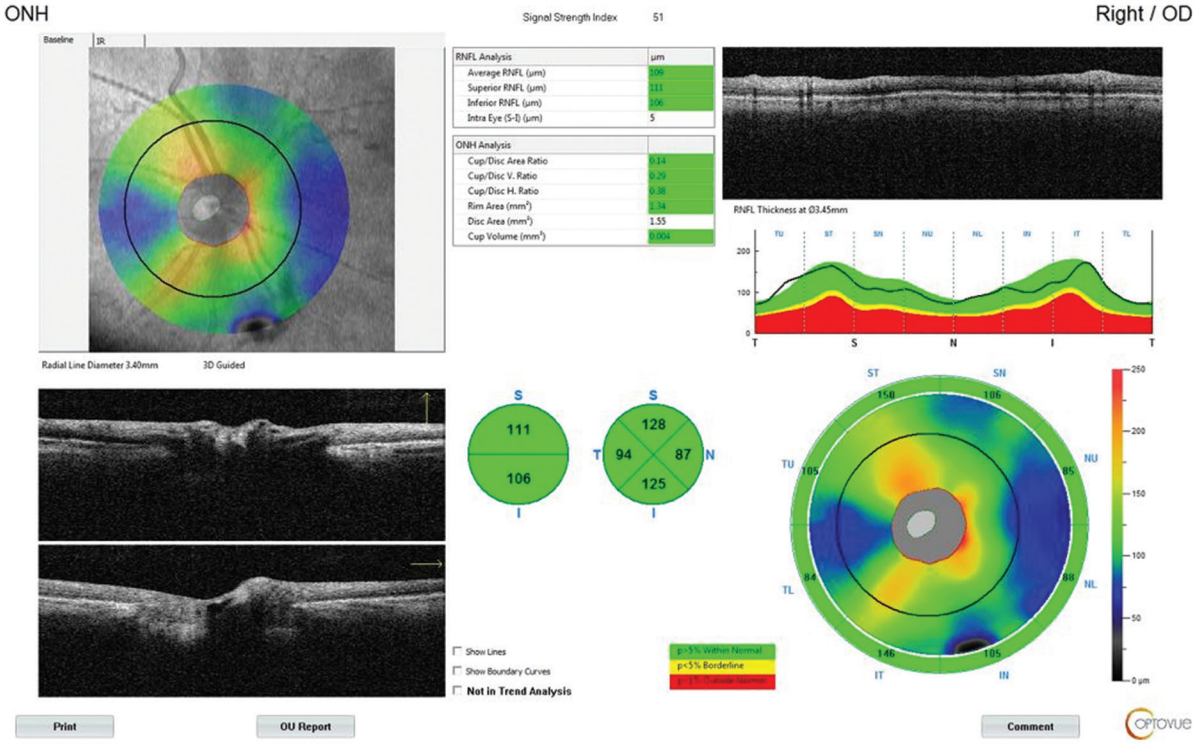

Figure 1. *Optic coherence tomography sample of a patient.*

Table 2. Post-treatment categorization according to the Furuhashi criteria

	Number of patients (%)
Complete recovery (1)	15 (38.4)
Marked improvement (2)	8 (20.7)
Slight improvement (3)	6 (15.3)
No recovery (4)	10 (25.6)

Table 3. The OCT findings according to the responses to treatment

	GCC	RFNL	p-value
Complete recovery (n: 15)	90.01 ± 3.49	89.61 ± 3.64	0.989
Marked improvement (n: 8)	89.21 ± 3.51	89.01 ± 3.71	
Slight improvement (n: 6)	90.52 ± 3.39	89.98 ± 3.60	
No recovery (n: 10)	88.89 ± 3.41	89.71 ± 3.59	
Successful (n: 23)	90.38 ± 3.47	89.72 ± 3.59	0.991
Not successful (n: 16)	90.07 ± 3.55	90.05 ± 3.66	
Full recovery (n: 15)	90.51 ± 3.41	89.66 ± 3.52	0.993
No full recovery (n: 24)	90.23 ± 3.51	90.1 ± 3.55	

other patients (n: 24), the mean RNFL thickness values were 89.66 ± 3.52 µm and 90.1 ± 3.55 µm, respectively, with no statistically significant difference determined (p = 0.993) (Table 3).

Discussion

The results of this study showed that the RNFL thickness measured with OCT in patients with ISSNHL was statistically significantly thinner in the eye on the affected side, as if accompanied by neurodegeneration, compared to the healthy side (affected side: 89.87 ± 3.65 µm, healthy side: 103.87 ± 3.98 µm, p = 0.0001). The GCC thickness was also statistically significantly thinner in the eye of the affected side compared to the healthy side (affected side: 90.46 ± 3.49 µm, healthy side: 103.77 ± 3.96 µm, p = 0.0001). A significant improvement was determined in these patients in the PTA values (from 61.25 to 30) and the SDS (from 68 to 88%). The etiology of neurodegeneration, which progresses with the loss of nerve cells, causing dysfunction of the nerve or organ associated with this loss, has not been fully determined. The results of this study

showed a statistically significant level of neurodegeneration in the eye on the affected side in patients with ISSNHL.

In a study that examined the cardiovascular risk factors of patients with sudden hearing loss, it was stated that ISSHNL could be associated with vascular endothelial dysfunction[11]. In studies by Fusconi et al. to determine the prevalence of thrombophilic risk factors in stroke associated with sudden hearing loss, central retinal vein occlusion, and small vessel disease, and to investigate the vascular hypothesis in the pathogenesis of sudden hearing loss, it was concluded that hyperhomocysteine, which is a common cause of thrombophilia, was associated with sudden hearing loss. That study also suggested that it was necessary to confirm the hypothesis that the small peripheral vessels of the ears, eyes, and brain provided by all the supra-aortic branches are affected by the same thrombotic factors. Ophthalmic symptoms may be the only finding in Susac syndrome, which is an uncommon cause of recurrent retinal artery occlusion and emerges with sensorineural hearing loss[12]. In the current study, vascular endothelial dysfunction, which can be a cause of ISSNHL, may have caused neurodegeneration. The RNFL was statistically significantly thinner in the eye on the affected side, as if accompanied by neurodegeneration, compared to the healthy side (affected side: 89.87 ± 3.65 μm, healthy side: 103.87 ± 3.98 μm, p = 0.0001).

A study of an elderly population in southern Italy investigated the relationship between macular vascular density and age-related peripheral sensorineural hearing loss (presbycusis) and determined an association between retinal vascularity and central hearing processing pathology[13]. There are also studies that have concluded that when it is taken into consideration that the cochlear microvascular system cannot be measured *in vivo*, indirect evaluation of the cochlear microvascular system using retinal imaging may present an alternative[6]. In such conditions, the findings obtained with OCT may be explanatory for the etiology of sudden hearing loss.

OCT entered ophthalmology practice in the 1990s and now has a wide range of uses in the diagnosis and follow-up of glaucoma, diabetic retinopathy, and especially in many different retinal diseases affecting the macula. OCT imaging can reveal axonal loss with RNFL thickness measurements and neuronal damage with GCC measurements[14]. In recent years, there has been great interest in the use of OCT in neurodegenerative diseases. Clinical studies have shown that these diseases lead to a decrease in RNFL thickness, which is mainly formed from retinal ganglion cells and the axons of these cells[15]. The RNFL shows a similarity to gray matter in the brain, and changes in thickness are only due to axon damage. When examined in this respect, the retina is accepted as a part of the brain that can be easily observed. Changes in retinal vascular density have the potential to be an ocular biomarker for neurodegenerative conditions.

A series of studies conducted on Alzheimer's disease, which is the most common form of neurodegeneration, have shown that the disease is not limited to the brain, but the retina is also greatly affected[16,17]. The thickness of the RNFL and GCC has been shown to be reduced in Alzheimer's patients compared to healthy individuals[18]. The current study results showed that the RNFL and GCC thickness values were 89.87 ± 3.65 μm and 90.46 ± 3.49 μm, respectively, on the affected side and were determined to be statistically significantly thinner than the healthy side.

The RNFL thickness measured with OCT was compared with MRI findings in a study of MS patients, and it was determined that this test could indirectly show brain atrophy[19]. When compared with a control group, the RNFL thickness was found to be significantly thinner in the MS patients[20]. Hearing loss can also be seen in this disease, for which early diagnosis is important, and some patients may present with hearing loss as the first complaint[21]. Just as the determination of OCT findings in this disease could contribute to the etiology, they could also make a difference in the early identification of patients. However, it is difficult to draw clear conclusions from the available data, and there is a need for further studies of specific groups diagnosed with sudden hearing loss.

To be able to observe a change in RNFL values, there has to be at least 50% cell damage in the GCC[22]. This development in idiopathic optic neuritis cases is a process. The pattern and degree of loss in GCC number and RNFL thickness can be useful in differentiating the underlying etiology[23]. The determination of a significant difference in RNFL thickness within a short time of presenting with sudden hearing loss makes it possible to be able to interpret the emergence of the disease with different pathophysiologies, or the severity of the disease, or it suggests the possibility of experiencing an asymptomatic process that will reveal this effect.

PTA is a value that is calculated by taking the mean values of 500, 1000, 2000, and 4000 Hz frequencies in the audiogram. These frequencies are the frequencies at which people perceive speech. In the current study group with full recovery and significant recovery according to the Furuhashi criteria (59%), GCC of 90.38 ± 3.47 and RFNL of 89.72 ± 3.59 were determined, and in the unsuccessful group with slight or no improvement, GCC was 90.07 ± 3.55 and RFNL was 90.05 ± 3.66 (p = 0.991). Although not statistically significant, this change was observed to be positive and was considered to be promising with respect to the possibility that neurodegeneration can be improved with treatment.

The primary limitation of this study was the low number of patients. The main reason for this was that the prevalence of ISSNHL patients in the general population is 5-20/100,000, and with advancing age, these patients have comorbidities that could affect the vascular base. Another limitation was that there were no post-treatment and long-term serial OCT data. However, this study can be considered valuable as the first study in the literature to have presented the OCT results of patients diagnosed with ISSNHL, and it could be a foundation for further studies.

Conclusion

There have been many previous studies of ISSNHL, which is an ENT emergency requiring early diagnosis and treatment. In respect of etiology, diagnosis, and referral for treatment, neurodegeneration and perhaps the degree of this degeneration can be diagnosed earlier, and more rapid interventions can be made with the use of OCT to take RNFL and GCC measurements.

Author contributions

Kaya Celik E: conceptualization, methodology, software. Doluoglu S: Data curation, Writing-Original draft preparation, Writing-Reviewing and Editing Acar M, Keseroglu K: visualization, investigation. Bayir O: software, validation. Mutlu M, Saylam G.: supervision.

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Conflicts of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Ethical disclosures

Protection of human and animal subjects. The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

Use of artificial intelligence for generating text. The authors declare that they have not used any type of generative artificial intelligence for the writing of this manuscript nor for the creation of images, graphics, tables, or their corresponding captions.

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