

HIDDEN HEARING LOSS – COCHLEAR SYNAPTOPATHY

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SAŽETAK

Uvod/Cilj: Kohlearna sinaptopatija, u literaturi poznata i kao „skriveni gubitak sluha“ (engl. *hidden hearing loss*), predstavlja primarni gubitak sinapsi između unutrašnjih trepljastih ćelija i kohlearnih nervnih vlakana, dok same senzorne ćelije ostaju očuvane. Glavni etiološki faktori uključuju izloženost buci, proces starenja i upotrebu ototoksičnih lekova. Cilj ovog preglednog rada je sveobuhvatna analiza patofizioloških mehanizama kohlearne sinaptopatije i evaluacija savremenih dijagnostičkih pristupa za detekciju skrivenog gubitka sluha.

Metode: U ovom preglednom radu izvršena je analiza relevantne savremene literature i naučnih radova indeksiranih u bazama *PubMed* i *SCIndex*. Pretraga je obuhvatila radove koji se bave anatomskim i patofiziološkim mehanizmima oštećenja, kao i validacijom novih kliničkih i elektrofizioloških protokola za identifikaciju sinaptičkih disfunkcija.

Rezultati: Kliničku sliku karakteriše očuvan prag sluha na standardnoj tonalnoj liminarnoj audiometriji u tišini, ali uz izražen deficit u razumevanju govora u bučnom okruženju, praćen tinitusom i hiperakuzijom. S obzirom na to da konvencionalni testovi ne detektuju ovo oštećenje, dijagnostika se oslanja na napredne elektrofiziološke metode, prvenstveno na analizu amplitude talasa I auditivnih evociranih potencijala moždanog stabla (ABR), kao i na psihoakustičke testove govora u buci. Trenutne terapijske opcije obuhvataju upotrebu slušnih aparata sa naprednim algoritima za redukciju šuma i audiološku rehabilitaciju, dok su savremena pretklinička istraživanja usmerena ka neurotrofičkoj regeneraciji sinaptičkih veza.

Zaključak: Konvencionalni audiološki pristup nije dovoljan za detekciju kohlearne sinaptopatije, te je u kliničku praksu neophodno uvesti napredne elektrofiziološke i psihoakustičke testove. Pravovremeno razumevanje ovog entiteta ključno je za rano prepoznavanje i prevenciju trajnih auditivnih disfunkcija.

Ključne reči: skriveni gubitak sluha, kohlearna sinaptopatija, auditivni evocirani potencijali moždanog stabla, percepcija govora, tinitus

ABSTRACT

Introduction/Objective: Cochlear synaptopathy, also known in the literature as “hidden hearing loss”, represents a primary loss of synapses between inner hair cells and cochlear nerve fibers, while the sensory cells themselves remain preserved. The main etiological factors include noise exposure, aging, and ototoxic drug use. This review aims to provide a comprehensive analysis of the pathophysiological mechanisms of cochlear synaptopathy and evaluate current diagnostic approaches for detecting hidden hearing loss.

Methods: This review paper analyzes relevant literature and scientific papers indexed in the PubMed and SCIndex databases. The search included studies on the anatomical and pathophysiological mechanisms of impairment, as well as the validation of new clinical and electrophysiological protocols for identifying synaptic dysfunction.

Results: The clinical presentation is characterized by a preserved hearing threshold on standard pure-tone audiometry in quiet, but with a pronounced deficit in speech understanding in noisy environments, accompanied by tinnitus and hyperacusis. Since conventional tests do not detect this impairment, diagnosis relies on advanced electrophysiological methods, primarily the amplitude analysis of wave I of auditory brainstem responses (ABR), as well as psychoacoustic speech-in-noise tests. Current therapeutic options include hearing aids with advanced noise-reduction algorithms and audiological rehabilitation, while contemporary preclinical research focuses on neurotrophic regeneration of synaptic connections.

Conclusion: The conventional audiological approach is insufficient for detecting cochlear synaptopathy; therefore, it is essential to introduce advanced electrophysiological and psychoacoustic tests into clinical practice. Timely understanding of this entity is crucial for early identification and prevention of permanent auditory dysfunctions.

Keywords: hidden hearing loss, cochlear synaptopathy, auditory brainstem responses, speech perception, tinnitus

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Primljeno • Received: June 17, 2026; **Revidirano • Revised:** August 25, 2026;

Prihvaćeno • Accepted: September 7, 2026; **Online first:** September 25, 2026

DOI: 10.5937/smlk7-68354

UVOD

Skriveni gubitak sluha je termin koji se od nedavno koristi kako bi se opisao slušni poremećaj koji se pretpostavlja da utiče na slušno – neuralnu obradu zvučnog signala i oštrinu sluha kod osoba sa urednim nalazima tonalne liminarne audiometrije [1]. Kod klasičnog sensorineuralnog oštećenja sluha koje je uzrokovano disfunkcijom ili degenerativnim promenama na unutrašnjim i spoljašnjim redovima ćelija Kortijevog organa i/ili spiralnog gangliona dolazi do trajno povišenih pragova na audiometrijskom nalazu. Međutim, u praksi se neretko srećemo sa pacijentima koji pokazuju urednu slušnu osetljivost, ali imaju značajne perceptivne poteškoće uključujući razumevanje govora u bučnim sredinama. Takva perceptivna disfunkcija se često naziva „poremećaj obrade slušnih informacija” i smatra se da defekti u centralnim slušnim putevima igraju ključnu ulogu.

Iako se kohlearna sinaptopatija često poistovećuje sa skrivenim gubitkom sluha, ona predstavlja njegov primarni patofiziološki mehanizam, dok je skriveni gubitak sluha širi klinički entitet koji može biti uzrokovan i drugim procesima. Novija istraživanja pokazuju da do skrivenog gubitka sluha može doći i usled demijelinizacije slušnog nerva [2], degenerativnih promena slušnog nerva [3] ili neuralnog pojačanja kada mozak dobija slabije signale sa periferije pa pokušava da pojača svoju osetljivost kako bi nadoknadio gubitak [4]. Prema ovom autoru to može dovesti do pojave tinitusa i hiperakuzije.

Kohlearna sinaptopatija predstavlja rani znak gubitka sluha koji pogađa jednu od 4 osobe starije od 45 godina sa još većom prevalencom kod pacijenata sa hroničnim bolestima [5]. Predstavlja oštećenje sinapsi između unutrašnjih trepljastih ćelija i vlakana slušnog nerva tako da sinaptopatija nastaje kada se prekine veza koja prenosi zvučne signale do mozga iako su senzorne ćelije u uhu ostale neoštećene. Prema izveštaju Svetske zdravstvene organizacije od 3. marta 2026. godine predikcija je da će do 2050. godine blizu 2.5 biliona ljudi imati neki stepen oštećenja sluha, a da će preko 700 miliona zahtevati neki vid slušne rehabilitacije [6]. Na osnovu nedavnih istraživanja prevalenca skrivenog gubitka sluha, kako je opisana od strane ispitanika sa prijavljenim teškoćama u razumevanju uprkos urednom pragu sluha, procenjena je na 12% – 15% [7,8].

Veliki broj istraživanja potvrdio je da gubitak sluha i nerazumevanje govora negativno utiče na mentalno zdravlje, ponašanje i kvalitet života i da povećava rizik od socijalne izolacije, anksioznosti i depresije [9,10]. Osobe sa ovim problemom potvrđuju da nedostatak informacija u razgovorima izaziva frustraciju i anksioznost koju povezuju sa potencijalno pogrešnim tumačenjem onoga što je rečeno [11]. Autori navode i izveštaje kli-

INTRODUCTION

Hidden hearing loss is a term recently used to describe an auditory disorder presumed to affect auditory-neural processing of sound signals and hearing acuity in individuals with normal pure-tone audiometry findings [1]. In classical sensorineural hearing loss caused by dysfunction or degenerative changes affecting the inner and outer rows of hair cells of the organ of Corti and/or the spiral ganglion, permanently elevated thresholds are observed on audiometric testing. However, in clinical practice, we frequently encounter patients who have normal auditory sensitivity but significant perceptual difficulties, including difficulty understanding speech in noisy environments. Such perceptual dysfunction is often referred to as an “auditory information processing disorder,” and defects in the central auditory pathways are considered to play a key role.

Although cochlear synaptopathy is often equated with hidden hearing loss, it is its primary pathophysiological mechanism, whereas hidden hearing loss is a broader clinical entity that may also result from other processes. Recent studies have shown that hidden hearing loss may also result from demyelination of the auditory nerve [2], degenerative changes in the auditory nerve [3], or neural gain, whereby the brain receives weaker signals from the periphery and attempts to increase its sensitivity in order to compensate for the loss [4]. According to this author, this may lead to tinnitus and hyperacusis.

Cochlear synaptopathy represents an early sign of hearing loss that affects one in four individuals over 45 years of age, with an even higher prevalence among patients with chronic diseases [5]. Synaptopathy involves damage to the synapses between inner hair cells and auditory nerve fibers; it occurs when the connection that transmits sound signals to the brain is disrupted, even though the sensory cells in the ear remain intact. According to a World Health Organization report dated March 3, 2026, by 2050 nearly 2.5 billion people will have some degree of hearing impairment, while more than 700 million will require some form of hearing rehabilitation [6]. Based on recent studies, the prevalence of hidden hearing loss, as described by participants reporting difficulties understanding speech despite normal hearing thresholds, has been estimated at 12%–15% [7,8].

A large number of studies have confirmed that hearing loss and difficulties understanding speech negatively affect mental health, behavior, and quality of life and increase the risk of social isolation, anxiety, and depression [9,10]. Individuals with this problem report that a lack of information during conversations causes frustration and anxiety, which they associate with the

ničara da nemaju dovoljno obuke i resursa za podršku ovim pacijentima, a kao glavni nedostatak navode nedostatak jedinstvenog i standardizovanog protokola za dijagnostiku i plan lečenja osoba sa ovim problemom.

U cilju obezbeđivanja sveobuhvatnog uvida u predmetnu materiju, sproveden je strukturirani pregled literature indeksirane u bazama *PubMed* i *SCIndeks*. Strategija pretraživanja obuhvatila je selekciju naučnih članaka primenom ključnih reči u korelaciji sa kohlearnom sinaptopatijom i kliničkim entitetom skrivenog gubitka sluha (npr. *“cochlear synaptopathy”*, *“hidden hearing loss”*). Kriterijumi za uključivanje literature obuhvatili su originalne naučne radove i pregledne članke objavljene na engleskom i srpskom jeziku koji primarno istražuju etiologiju, dijagnostiku i patofiziološke mehanizme ovih stanja. Sa druge strane, kriterijumi za isključenje odnosili su se na radove u obliku sažetaka sa konferencija, prikaze slučajeva (case reports), kao i studije sa neadekvatnom ili nejasnom metodologijom procene auditivne funkcije.

Polazeći od navedenog, cilj ovog preglednog rada je da na osnovu relevantne savremene literature pruži integrativni prikaz kohlearne sinaptopatije. Rad je fokusiran na tri ključna aspekta: analizu etiologije i molekularne patogeneze poremećaja, evaluaciju njegovog uticaja na centralno procesuiranje auditivnih informacija, kao i na kritički prikaz savremenih, objektivnih dijagnostičkih metoda namenjenih detekciji skrivenog gubitka sluha.

ANATOMIJA I FIZIOLOGIJA UHA – ČULO SLUHA

Čulo sluha spada u mehanoreceptore, što znači da se mehanička draž, u ovom slučaju zvuk, u receptoru kodira akcionim potencijalima nervnih vlakana [12] i predstavlja jedno od pet osnovnih ljudskih čula koje nam omogućava da primamo i interpretiramo zvučne talase iz okoline. Osnovna uloga sluha je da sve zvukove iz okoline prikupi, sprovede, dekodira i sistematizuje te tako ovaj proces rezultira obiljem informacija koje predstavljaju osnov za razvoj komunikacijskog sistema koji izdvaja čoveka kao posebnu vrstu [13].

Čulo sluha deli se na spoljašnje, srednje i unutrašnje uvo odakle se slušnim putem informacije prenose do centara u kori velikog mozga.

Spoljašnje uvo sastoji se od ušne školjke i spoljašnjeg slušnog hodnika na čijem kraju se nalazi bubna opna. Osnovna funkcija spoljašnjeg uva odnosi se na lokalizaciju zvuka u prostoru, zatim povećava zvučni pritisak za 12dB u frekventnom opsegu od 3000Hz do 4000Hz i štiti srednje uvo od traumatskih oštećenja [14].

Srednje uvo čini sistem šupljina ispunjenih vazduhom koje su povezane Eustahijevom tubom sa gornjim spratom ždrele – epifarinksom. Srednje uvo čini bubna duplja, lanac slušnih košćica, mastoidni nastavak i

potential misinterpretation of what has been said [11]. The authors also report that clinicians lack sufficient training and resources to support these patients, identifying the absence of a unified, standardized protocol for diagnosis and treatment planning as a major deficiency.

To provide a comprehensive overview, we conducted a structured review of the literature indexed in the PubMed and SCIndeks databases. The search strategy included selecting scientific articles using keywords related to cochlear synaptopathy and the clinical entity of hidden hearing loss (e.g., *“cochlear synaptopathy”*, *“hidden hearing loss”*). The inclusion criteria comprised original research articles and review articles published in English and Serbian that primarily investigated the etiology, diagnosis, and pathophysiological mechanisms of these conditions. The exclusion criteria included conference abstracts, case reports, and studies with inadequate or unclear methodology for assessing auditory function.

Based on the above, this review aims to provide an integrative overview of cochlear synaptopathy based on relevant contemporary literature. The paper focuses on three key aspects: an analysis of the disorder's etiology and molecular pathogenesis, an evaluation of its impact on central auditory processing, and a critical review of contemporary objective diagnostic methods for detecting hidden hearing loss.

ANATOMY AND PHYSIOLOGY OF THE EAR – THE SENSE OF HEARING

The sense of hearing belongs to the mechanoreceptors, meaning that a mechanical stimulus, in this case sound, is encoded in the receptor as action potentials of nerve fibers [12]. It represents one of the five basic human senses, enabling us to receive and interpret sound waves from the environment. Hearing's fundamental role is to collect, transmit, decode, and organize environmental sounds, producing an abundance of information that forms the basis of the communication system that distinguishes humans as a unique species [13].

The sense of hearing is divided into the external, middle, and inner ear, from which auditory information is transmitted via the auditory pathway to the centers in the cerebral cortex.

The external ear consists of the auricle and the external auditory canal, at the end of which is the tympanic membrane. The external ear's primary function is to localize sound in space; it also increases sound pressure by 12 dB within the frequency range of 3000 Hz to 4000 Hz and protects the middle ear from traumatic injury [14].

The middle ear consists of a system of air-filled cavities that are connected via the Eustachian tube

Eustahijeva tuba. Bubna opna i lanac slušnih koščica vrše funkciju akustičkog transformatora koji prenosi mehaničku energiju zvučnih talasa koji se prostiru kroz vazduh u mehaničku energiju zvučnih talasa koji se prostiru kroz tečnost kohlee sa najmanjim mogućim energetskim gubicima.

Unutrašnje uvo se sastoji od koštanog labirinta i membranoznog labirinta unutar koštanog. Koštani labirint se može podeliti na tri dela. Centralna struktura se naziva vestibulum (predvorje). Na njega se sa prednje strane nastavlja kohlea dok sa zadnje strane vestibuluma polaze tri polukružna kanala. S obzirom na temu naše interesovanje se usredsređuje na kohleu, kohlearni nerv i centralne slušne puteve.

Kohlea je 2,5 puta savijeni koštani kanal u obliku kućice puža po čemu i nosi ime. Sam kohlearni kanal je delimično pregrađen spiralnom laminom po sredini lumena celom dužinom kanala gde se pripajaju dve membrane– bazilarna i Rajsnerova membrana. Međuprostor između ivice spiralne lamine i lateralnog zida kohlearnog kanala premošćen je bazilarnom membranom dok ga Rajsnerova premošćuje koso naviše. Bazilarna i Rajsnerova membrana dele lumen kanala na tri skale – skalu vestibuli, skalu mediju i skalu timpani. Skala vestibuli i skala timpani su ispunjene perilimfom dok je skala medija ispunjena endolimfom. Skala vestibuli i skala timpani spojene su preko helikotrema na vrhu kohlee dok je skala medija zatvoren sistem i ne komunicira ni sa jednim drugim prostorom. U skali mediji, celom dužinom bazilarne membrane, smešten je Kortijev organ.

Senzorne ćelije Kortijevog organa su potpornim ćelijama pričvršćene za bazilarnu membranu i postavljene u jedan unutrašnji red ćelija kojih ima oko 3500 i tri reda spoljašnjih ćelija kojih ima oko 13000. Na vrhu senzornih ćelija nalaze se cilije poredane po visini koje su spojene postraničnim i vršnim vezama tako da prate pokrete jedna druge. Iznad senzornih ćelija nalazi se tektorijska membrana koja gradi krov Kortijevog organa. Pri pomeranju bazilarne membrane dolazi do smicajućih pokreta tektorijske membrane i stereocilija tj. najviše stereocilije – kinocilije ćelija spoljašnjih redova što rezultira otvaranjem kanala na vrhu stereocilija. Stereocilije unutrašnjih senzornih ćelija dopiru skoro do tektorijske membrane, ali nisu u direktnom kontaktu sa njom već se savijaju usled kretanja endolimfe koju pokreće tektorijska membrana [15].

Perilimfa je tipična ekstracelularna tečnost bogata jonima natrijuma (Na⁺) dok ima nizak sadržaj jona kalijuma (K⁺). Sa druge strane endolimfa je jedinstvena među ekstracelularnim tečnostima po tome što je njena koncentracija kalijumovih jona veća od koncentracije natrijumovih jona. Proces formiranja endolimfe i održavanje u jonskom sastavu između nje i perilimfe

to the upper part of the pharynx–the epipharynx. The middle ear comprises the tympanic cavity, the chain of auditory ossicles, the mastoid process, and the Eustachian tube. The tympanic membrane and the chain of auditory ossicles function as an acoustic transformer that transmits the mechanical energy of sound waves propagating through air into the mechanical energy of sound waves propagating through the fluid of the cochlea, with minimal energy loss.

The inner ear consists of the bony labyrinth and the membranous labyrinth located within it. The bony labyrinth can be divided into three parts. The central structure is called the vestibule. The cochlea extends from its anterior aspect, while three semicircular canals arise from its posterior aspect. Given our subject of interest, we focus on the cochlea, the cochlear nerve, and the central auditory pathways.

The cochlea is a bony canal coiled 2.5 turns in the shape of a snail shell, from which it derives its name. The cochlear canal is partially divided by the spiral lamina along the middle of the lumen throughout the entire length of the canal, where two membranes–the basilar membrane and Reissner's membrane–are attached. The space between the edge of the spiral lamina and the lateral wall of the cochlear canal is bridged by the basilar membrane, while Reissner's membrane bridges it obliquely upward. The basilar and Reissner's membranes divide the lumen of the canal into three scales–the scala vestibuli, scala media, and scala tympani. The scala vestibuli and scala tympani are filled with perilymph, whereas the scala media is filled with endolymph. The scala vestibuli and scala tympani are connected through the helicotrema at the apex of the cochlea, while the scala media is a closed system and does not communicate with any other space. The organ of Corti is located within the scala media along the entire length of the basilar membrane.

The sensory cells of the organ of Corti are attached to the basilar membrane by supporting cells and are arranged in a single inner row containing approximately 3,500 cells and three rows of outer cells containing approximately 13,000 cells. At the apical surface of the sensory cells are cilia arranged according to height and connected by lateral and tip links, allowing them to follow one another's movements. Above the sensory cells is the tectorial membrane, which forms the roof of the organ of Corti. When the basilar membrane moves, shearing movements occur between the tectorial membrane and the stereocilia, i.e., the tallest stereocilia–the kinocilia–of the outer rows of cells, resulting in the opening of channels at the tips of the stereocilia. The stereocilia of the inner sensory cells extend almost to the tectorial membrane but are not in direct contact with it; instead, they

još uvek nisu u potpunosti objašnjeni. Rajsnerova membrana formira selektivnu barijeru između dve tečnosti i dokazi ukazuju na to da se endolimfa proizvodi iz perilimfe kao rezultat selektivnog transporta jona kroz epitelne ćelije Rajsnerove membrane, a ne direktno iz krvi [16]. U mirovanju unutar senzornih ćelija potencijal je negativan: oko -45 mV kod unutrašnjih i -70 mV kod spoljašnjih senzornih ćelija dok je u endolimfi pozitivan potencijal od oko $+80$ mV. Razlika u potencijalu između endolimfe i intracelularnog prostora je 125 mV ili 150 mV što predstavlja veliku razliku u potencijalu i od velikog je značaja za hemijske procese u senzornim ćelijama [15]. Prilikom otvaranja kanala na vrhu stereocilija dolazi do ulaska pozitivnih jona kalijuma, ćelija se depolarise, luči neurotransmiter u sinaptičku pukotinu i dolazi do okidanja akcionog potencijala. Na taj način odvija se proces transdukcije – pretvaranje mehaničke energije u akcioni potencijal [17].

Kohlearni kanal je savijen oko koštanog stuba koji se naziva mediolus ili stožer. U mediolusu se nalazi sistem kanala u kojima su smeštena tela bipolarnih nervnih ćelija koje čine spiralni ganglion. To je zapravo početna tačka kohlearnog nerva. Kohlearni nerv sadrži oko 30000 vlakana, od kojih su skoro sva aferentna i skoro sva polaze sa unutrašnjih senzornih ćelija. Pored aferentnih postoji i mali broj eferentnih vlakana kohlearnog nerva što znači da oni sprovode informacije od mozga do kohlee. Njih ima samo nekoliko stotina i završavaju na senzornim ćelijama spoljašnjih redova [12]. Čak 95% aferentnih vlakana slušnog nerva povezano je sa unutrašnjim senzornim ćelijama pri čemu svaka ćelija ostvaruje 10 – 30 sinaptičkih veza zavisno od lokacije [18]. Prema ovim autorima najveći broj sinapsi nalazi se u regiji unutrašnjih senzornih ćelija najosetljivijih na zvuk (kod ljudi je to oblast srednjih frekvencija) dok ćelije koje detektuju veoma visoke i veoma niske frekvencije često imaju manji broj sinapsi od onih u sredini. Sa spoljašnjih ćelija polazi preostalih 5% aferentnih vlakana i ovde je situacija suprotna. Naime, senzorne ćelije spoljašnjih redova ostvaruju znatno manji broj sinapsi 2 – 3 i jedno nervno vlakno se grana i prikuplja informacije sa više senzornih ćelija.

Još davne 1978. godine Čarls Liberman je objavio rezultate istraživanja na slušnom nervu mačaka [19]. Ovo je pionirski rad koji je definisao tri grupe vlakana na osnovu spontanog ritma (niski, srednji i visoki) i povezao ih sa pragovima osetljivosti. Naime, vlakna visokog spontanog ritma čine 60% aferentnih vlakana koja polaze sa unutrašnjih senzornih ćelija i omogućavaju detekciju zvuka u tišini. Vlakna niskog spontanog ritma čine 15% aferentnih vlakana i ključna su za razumevanje govora u buci dok vlakna srednjeg spontanog ritma (preostalih 25%) omogućavaju mozgu da razlikuje

bend as a result of the movement of the endolymph induced by the tectorial membrane [15].

Perilymph is a typical extracellular fluid rich in sodium ions (Na^+), while it has a low concentration of potassium ions (K^+). In contrast, endolymph is unique among extracellular fluids because its potassium ion concentration is higher than its sodium ion concentration. The process of endolymph formation and maintenance of its ionic composition relative to perilymph has not yet been fully elucidated. Reissner's membrane forms a selective barrier between the two fluids, and evidence indicates that endolymph is produced from perilymph as a result of selective ion transport through the epithelial cells of Reissner's membrane, rather than directly from the blood [16]. At rest, the potential within the sensory cells is negative: approximately -45 mV in inner sensory cells and -70 mV in outer sensory cells, whereas the endolymph potential is positive, at approximately $+80$ mV. The potential difference between the endolymph and the intracellular space is 125 mV or 150 mV, a large difference that is important for the chemical processes occurring in sensory cells [15]. When channels at the tips of the stereocilia open, positively charged potassium ions enter the cell, causing depolarization, the release of neurotransmitters into the synaptic cleft, and the generation of an action potential. This is the process of transduction—the conversion of mechanical energy into an action potential [17].

The cochlear canal coils around a bony core called the modiolus, or central pillar. The modiolus contains a system of canals in which the cell bodies of bipolar nerve cells forming the spiral ganglion are located. This is essentially the starting point of the cochlear nerve. The cochlear nerve contains approximately $30,000$ fibers, almost all of which are afferent and originate from the inner sensory cells. In addition to afferent fibers, there is also a small number of efferent fibers in the cochlear nerve, meaning that they transmit information from the brain to the cochlea. There are only several hundred of them, and they terminate on the sensory cells of the outer rows [12]. As many as 95% of the afferent fibers of the auditory nerve are connected to inner sensory cells, with each cell forming 10 – 30 synaptic connections depending on its location [18]. According to these authors, the greatest number of synapses is found in the region of the inner sensory cells most sensitive to sound (in humans, this is the middle-frequency region), whereas cells detecting very high and very low frequencies often have fewer synapses than those in the middle. The remaining 5% of afferent fibers originate from the outer cells, where the situation is reversed. Namely, the sensory cells of the outer rows form significantly fewer synapses (2 – 3),

nijanse između umereno tihih i umereno glasnih zvukova. Bez njih prelaz sa tihih na glasne zvukove bio bi nagao i neprecizan.

U godinama koje su usledile Liberman je sa saradnicima vršio istraživanja različitih uticaja na senzorne ćelije i ćelije spiralnog gangliona došavši do zaključka da izloženost buci, prirodan proces starenja i ototoksični lekovi dovode do trajnih oštećenja prvenstveno sinapsi između unutrašnjih senzornih ćelija i vlakana niskog spontanog ritma, a zatim i srednjeg spontanog ritma [20–22]. Iz tog razloga vlakna visokog spontanog ritma detektuju tihe zvuke, a oštećenje sinapsi ostaje sakriveno iza urednih vrednosti na audiometrijskom nalazu. Tako su 2009. godine Kujawa i Liberman dokazali da buka koja izaziva privremeni gubitak sluha zapravo trajno uništava sinapse. Termin koji su koristili je primarna neuralna degeneracija dok je sam termin kohlearna sinaptopatija tek 2013. godine upotrebljen kako bi se preciznije definisao skriveni gubitak sluha [23]. Od tada ovaj termin je opšte prihvaćen i postaje standard u literaturi.

DIJAGNOSTIČKE METODE

U Srbiji je zvanično u upotrebi MKB-10 (Međunarodna klasifikacija bolesti 10. revizije) kao važeći sistem šifriranja u zdravstvenom sistemu. Najnovija verzija MKB-11, usvojena je na 72. Svetskoj zdravstvenoj skupštini 2019. godine i stupila je na snagu 1. januara 2022. godine [24]. Iako je ova revizija zvanično stupila na snagu, države članice se nalaze u različitim fazama implementacije jer prelazak zahteva korenite izmene u informacionim sistemima i obuku osoblja. U 11. reviziji Svetska zdravstvena organizacija je uvela znatno preciznije kategorije pa tako MKB-11 sadrži zvaničnu šifru AB57: auditivna sinaptopatija ili neuropatija (Auditory synaptopathy or neuropathy). Kako se navodi u klasifikaciji ova šifra se odnosi na nedostatak sinhronizacije neuralnog prenosa slušnih informacija zbog oštećenja unutrašnjih senzornih ćelija i njihovih sinapsi ili ćelija spiralnog gangliona i kohleranog živca uz očuvanu funkciju spoljašnjih redova senzornih ćelija.

U svetu još uvek ne postoji jedinstveni dijagnostički zlatni standard za definitivnu potvrdu kohlearne sinaptopatije kod ljudi, zbog čega se dijagnoza postavlja indirektno, kombinacijom različitih elektrofizioloških i bihevioralnih testova. Tokom inicijalnog pregleda izvodi se tonalna liminarna audiometrija koja uglavnom pokazuje urednu slušnu osetljivost bez povišenih pragova na audiometrijskom nalazu. S obzirom da se pacijenti najčešće žale na nerazumevanje govora u bučnim sredinama veliki broj istraživanja kao ključni funkcionalni test navode govornu audiometriju u buci, zatim evocirane potencijale moždanog stabla, elektrokohleografi-

and a single nerve fiber branches and collects information from multiple sensory cells.

As early as 1978, Charles Liberman published the results of research on the auditory nerve of cats [19]. This pioneering study defined three fiber groups based on spontaneous firing rate (low, medium, and high) and associated them with sensitivity thresholds. Specifically, high-spontaneous-rate fibers account for 60% of afferent fibers originating from inner sensory cells and enable sound detection in silence. Low-spontaneous-rate fibers account for 15% of afferent fibers and are essential for understanding speech in noise, whereas medium-spontaneous-rate fibers (the remaining 25%) enable the brain to distinguish nuances between moderately quiet and moderately loud sounds. Without them, the transition from quiet to loud sounds would be abrupt and imprecise.

In the years that followed, Liberman and his colleagues investigated various effects on sensory cells and spiral ganglion cells and concluded that exposure to noise, the natural aging process, and ototoxic drugs cause permanent damage, primarily to the synapses between inner sensory cells and low-spontaneous-rate fibers, followed by damage to medium-spontaneous-rate fibers [20–22]. For this reason, high-spontaneous-rate fibers detect quiet sounds, while synaptic damage remains hidden behind normal values on audiometric testing. Thus, in 2009, Kujawa and Liberman demonstrated that noise exposure causing temporary hearing loss actually permanently destroys synapses. They used the term primary neural degeneration, whereas cochlear synaptopathy was not used until 2013, when it was introduced to more precisely define hidden hearing loss [23]. Since then, this term has been widely accepted and has become standard in the literature.

DIAGNOSTIC METHODS

In Serbia, the ICD-10 (International Classification of Diseases, 10th Revision) is officially in use as the valid coding system in the healthcare system. The latest version, ICD-11, was adopted at the 72nd World Health Assembly in 2019 and came into effect on January 1, 2022 [24]. Although this revision officially came into effect, Member States are at different stages of implementation because the transition requires fundamental changes to information systems and staff training. In the 11th revision, the World Health Organization introduced considerably more precise categories; thus, ICD-11 contains the official code AB57: auditory synaptopathy or neuropathy (Auditory synaptopathy or neuropathy). As stated in the classification, this code refers to a lack of synchronization of the neural transmission of auditory information due to damage to the

ju i u poslednje vreme koristi se testiranje amplitude i praga akustičkog refleksa mišića srednjeg uva [25,26].

Govorna audiometrija predstavlja metodu ispitivanja sluha, odnosno sposobnost razumevanja reči van konteksta neke rečenice, tj. izolovano izgovorenih reči. Razumevanje govora podrazumeva percepciju zvučnog stimulusa, kao i prepoznavanje i razumevanje govorne poruke. Da bi se postiglo razumevanje govorne poruke potrebna je očuvanost svih struktura koje učestvuju u prijemu, prenosu i razumevanju sagovornika, a to su očuvanost čula sluha, auditivnog puta, primarnih i sekundarnih kortikalnih centara, tercijarnih asocijativnih kortikalnih oblasti, kao i kognitivnih sposobnosti. Ukoliko postoje lezije na nekim od ovih struktura doći će do teškoća u razumevanju govorne poruke [27].

Tokom izvođenja govorne audiometrije u buci ključan je odnos jačine stimulusa (govora) i pozadinskog šuma – SNR (signal/noise ratio). Matematički to je jednostavna razlika između jačine govora i jačine buke i izračunava se po formuli: $SNR = \text{jačina govora (dB)} - \text{jačina buke (dB)}$. Nulti SNR (0 dB) predstavlja odnos gde su govor i buka iste jačine. Kod testiranja kohlearne sinaptopatije ključno je koristiti niske ili negativne SNR uslove npr. (0 dB ili -5 dB). Osobe sa sinaptopatijom prikazaće drastičan pad u razumevanju reči čim se SNR smanji, iako im je prag sluha urednih vrednosti [28].

Za kompletnu kliničku evaluaciju kohlearne sinaptopatije od izuzetnog značaja je primena i drugih specifičnih metoda. U tom kontekstu, bihevioralni testovi vremenske rezolucije, poput *Gaps-in-Noise (GIN)* testa, omogućavaju preciznu procenu sposobnosti procesiranja vremenskog aspekta zvuka koji je često narušen kod skrivenog gubitka sluha. Sa druge strane, psihoa-kustičko ispitivanje u vidu proširene visokofrekventne audiometrije (iznad 8 kHz) predstavlja izuzetno senzitivnu metodu za detekciju ranih faza oštećenja sinapsi pre nego što se jave promene na standardnim audiometrijskim frekvencijama.

Auditivni evocirani potencijali. Postoji veći broj termina koji se odnose na ispitivanje auditivnih odgovora moždanog stabla, a svi oni proističu iz različitih skraćenica na engleskom jeziku [14]. Tako se u literaturi mogu sresti različite skraćenice: ABR – Auditory Brainstem Response (auditivni odgovor moždanog stabla), BERA – Brainstem Evoked Response Audiometry (audiometrija evociranih odovora moždanog stabla), BAEP – Brainstem Auditory Evoked Potentials (auditivni evocirani potencijali moždanog stabla) koje, u stvari, znače isto, a predstavljaju objektivnu metodu za ispitivanje sluha koja beleži nervnu aktivnost od kohlee duž slušnog puta do vrha moždanog stabla [12].

Test podrazumeva postavljanje elektroda na čelo i mastoidni nastavak kako bi se zabeležila električna ak-

inner sensory cells and their synapses or to the cells of the spiral ganglion and cochlear nerve, with preserved function of the outer rows of sensory cells.

No single diagnostic gold standard exists worldwide for definitive confirmation of cochlear synaptopathy in humans; therefore, clinicians establish the diagnosis indirectly through a combination of electrophysiological and behavioral tests. During the initial examination, pure-tone audiometry is performed, which generally shows normal auditory sensitivity without elevated thresholds on the audiometric findings. Given that patients most commonly complain of difficulty understanding speech in noisy environments, a large number of studies identify speech audiometry in noise as a key functional test, followed by auditory brainstem responses, electrocochleography, and, more recently, assessment of the amplitude and threshold of the acoustic reflex of the middle-ear muscles [25,26].

Speech audiometry is a method of hearing assessment, i.e., the ability to understand words outside the context of a sentence, namely, individually spoken words. Speech understanding involves perceiving an auditory stimulus and recognizing and comprehending a spoken message. In order to achieve comprehension of a spoken message, the integrity of all structures involved in the reception, transmission, and comprehension of the speaker must be preserved. These include the sense of hearing, the auditory pathway, the primary and secondary cortical centers, the tertiary associative cortical areas, and cognitive abilities. If lesions are present in any of these structures, difficulties in understanding a spoken message will occur [27].

During speech audiometry in noise, the key parameter is the relationship between stimulus (speech) intensity and background noise–SNR (signal-to-noise ratio). Mathematically, this is the simple difference between speech intensity and noise intensity and is calculated using the formula: $SNR = \text{speech intensity (dB)} - \text{noise intensity (dB)}$. A zero SNR (0 dB) represents a ratio in which speech and noise are of equal intensity. When testing for cochlear synaptopathy, it is essential to use low or negative SNR conditions, e.g., 0 dB or -5 dB. Individuals with synaptopathy will show a drastic decline in word recognition as SNR decreases, even though their hearing thresholds are within normal limits [28].

For a complete clinical evaluation of cochlear synaptopathy, the application of other specific methods is also of great importance. In this context, behavioral tests of temporal resolution, such as the *Gaps-in-Noise (GIN)* test, enable precise assessment of the ability to process the temporal aspects of sound, which is often impaired in hidden hearing loss. On the other hand, psychoacoustic testing in the form of extended high-frequency audiom-

tivnost mozga kao odgovor na slušne stimuluse, često predstavljene kao klikovi ili tonovi. Ovaj snimljeni neuronski odgovor se pažljivo analizira kako bi se identifikovali različiti talasi koji odgovaraju različitim fazama slušne obrade u moždanom stablu. Ispitivanjem latencija i amplituda ovih talasa, lekari mogu da utvrde prisustvo i lokaciju abnormalnosti, bacajući svetlo na prirodu i obim oštećenja sluha, nervne disfunkcije, pa čak i suptilne lezije moždanog stabla [29].

Istraživanja su pokazala da se na ovaj način kod urednog sluha u prvih 10ms dobija sedam karakterističnih talasa koji se obeležavaju rimskim brojevima. Posebno stabilni i zato klinički značajni su prvih pet talasa i među njima se izdvajaju prvi – I, treći – III i peti – V talas [12]. Prvi talas je odraz aktivnosti u kohlearnom živcu u nivou kohlee i latenca – vremenski interval od klika do vrha talasa je oko 2 ms. S obzirom na temu naše istraživanje se usredsređuje na amplitudu i latencu samo prvog talasa.

Talas I predstavlja elektro-fiziološki korelat sumiranog akcionog potencijala distalnog segmenta slušnog nerva [30]. Formiranje ovog talasa inicirano je mehanoreceptorskom aktivacijom unutrašnjih trepljastih ćelija, koje usled akustičke stimulacije oslobađaju neurotransmitter – glutamat u sinaptičku pukotinu. Vezivanjem neurotransmitera za postsinaptičke receptore aferentnih vlakana spiralnog gangliona dolazi do sinhrona depolarizacije neurona i okidanja akcionog potencijala na slušnom nervu [31]. Tokom testa koristi se klik stimulus koji je kratak i nagao što tera veliki broj neurona na istovremenu reakciju. Pri niskim intenzitetima zvuka talas I je jedva uočljiv jer reaguju samo vlakna visokog spontanog ritma [19]. Kako se zvuk pojačava (preko 70–80 dB HL) aktiviraju se i vlakna niskog spontanog ritma. Tek kada se aktiviraju oba tipa vlakana zajedno dobijamo maksimalnu amplitudu talasa I [23,32].

Pokazatelj kohlearne sinaptopatije na ABR testu jeste pad amplitude talasa I pri visokim intenzitetima stimulacije, dok latenca ovog talasa ostaje nepromenjena [22]. Autori navode da vlakna visokog spontanog ritma ostaju neoštećena te i dalje uredno provode impuls tako da informacija stiže do elektrode tačno na vreme. Brzina provođenja impulsa kroz preostala vlakna nije usporena pa samim tim nema ni produženja latence.

U osnovi kohlearne sinaptopatije leži glutamatergična eksitotoksičnost; usled nemogućnosti brzog uklanjanja viška glutamata pri glasnim zvucima (preko 80–90 dB HL), dolazi do patološkog priliva jona u postsinaptičke terminale. Sinaptopatija selektivno uništava sinapse na vlaknima niskog spontanog ritma koja imaju visok prag aktivacije i reaguju tek na glasne zvuke. Zbog toga izostaje njihov doprinos pa je ukupni sumirani akcioni potencijal, odnosno amplituda talasa I znatno manja nego kod zdravog uva [23].

etry (above 8 kHz) represents a highly sensitive method for detecting early stages of synaptic damage before changes occur at standard audiometric frequencies.

Auditory evoked potentials. Several terms refer to the assessment of auditory brainstem responses, each derived from different English abbreviations [14]. Thus, various abbreviations can be found in the literature: ABR – Auditory Brainstem Response, BERA – Brainstem Evoked Response Audiometry, BAEP – Brainstem Auditory Evoked Potentials, etc., which, in fact, mean the same thing and represent an objective method for hearing assessment that records neural activity from the cochlea along the auditory pathway to the upper part of the brainstem [12].

The test involves placing electrodes on the forehead and mastoid process to record the brain's electrical activity in response to auditory stimuli, often presented as clicks or tones. This recorded neural response is carefully analyzed in order to identify different waves corresponding to different stages of auditory processing in the brainstem. By examining the latencies and amplitudes of these waves, physicians can determine the presence and location of abnormalities, shedding light on the nature and extent of hearing impairment, neural dysfunction, and even subtle brainstem lesions [29].

Studies have shown that, in individuals with normal hearing, seven characteristic waves are obtained within the first 10 ms, designated by Roman numerals. The first five waves are particularly stable and therefore clinically significant, among which waves I, III, and V are distinguished [12]. Wave I reflects activity in the cochlear nerve at the level of the cochlea, and its latency—the time interval from the click to the peak of the wave—is approximately 2 ms. Given the focus of our study, we focus only on the amplitude and latency of wave I.

Wave I represents the electrophysiological correlate of the summed action potential of the distal segment of the auditory nerve [30]. The formation of this wave is initiated by mechanoreceptor activation of the inner hair cells, which, in response to acoustic stimulation, release the neurotransmitter glutamate into the synaptic cleft. Binding of the neurotransmitter to postsynaptic receptors of the afferent fibers of the spiral ganglion leads to synchronous depolarization of the neurons and the generation of an action potential in the auditory nerve [31]. During the test, a brief, abrupt click stimulus causes many neurons to respond simultaneously. At low sound intensities, wave I is barely detectable because only high-spontaneous-rate fibers respond [19]. As the sound intensity increases (above 70–80 dB HL), low-spontaneous-rate fibers are also activated. Only when both fiber types are activated together is the maximum amplitude of wave I obtained [23,32].

Karakteristike talasa I, prvenstveno njegova amplituda pri visokim intenzitetima stimulacije, direktno odražavaju gustinu i funkcionalni integritet ovih bazičnih sinaptičkih spojeva, čineći ga primarnim biomarkerom u istraživanju kohlearne sinaptopatije [33].

Elektrokohleografija (ECoG) predstavlja objektivnu elektrofiziološku metodu koja registruje najranije električne potencijale kohlee i inicijalnog segmenta slušnog živca, što direktno odgovara talasu I auditivnih potencijala moždanog stabla [22]. Ključna prednost ove metode u kontekstu istraživanja kohlearne sinaptopatije, odnosno skrivenog gubitka sluha, ogleda se u njenoj sposobnosti da izoluje funkcionalni status unutrašnjih senzornih ćelija i njihovih pripadajućih sinaptičkih veza sa aferentnim vlaknima slušnog živca [33]. ECoG signal se sastoji od tri komponente: kohlearnog mikrofonizma (CM), sumacionog potencijala (SP) i akcionog potencijala (AP). Dok su generatori CM i SP locirani u receptorima – unutrašnjim i spoljašnjim senzornim ćelijama, AP direktno odražava sinhronu depolarizaciju vlakana slušnog nerva. Kod kohlearne sinaptopatije uočava se specifičan patofiziološki profil: pošto su same unutrašnje senzorne ćelije očuvane, amplituda sumacionog potencijala ostaje u granicama normale. Međutim, usled selektivnog propadanja sinapsi i gubitka vlakana niskog spontanog ritma, dolazi do drastičnog smanjenja amplitude akcionog potencijala pri visokim intenzitetima stimulacije [23]. Posledično, ovaj selektivni pad amplitude dovodi dospecifičnog rasta matematičkog odnosa SP/AP [34]. Klinički i istraživački značaj ECoG-a leži upravo u prepoznavanju ovog specifičnog šablona – normalan SP uz redukovani AP – što u praksi omogućava diferenciranje sinaptopatije od Menijerove bolesti kod kojeg povišen SP/AP odnos nastaje primarno zbog patološkog rasta same SP komponente [35].

Stapedijalni refleksi je nevoljna kontrakcija mišića srednjeg uva m. stapedijusa (*m. stapedius*) koja se javlja kao zaštitni mehanizam pri izlaganju glasnim zvucima. Zvuk jačine 70-80 dB refleksno ukružuje lanac slušnih košćica prigušujući prenos zvučnih talasa ka unutrašnjem uvu [36].

Stapedijalni refleks se prvenstveno aktivira preko vlakana niskog spontanog ritma koja imaju visok prag aktivacije i reaguju tek na glasne zvuke. Upravo ova vlakna, kako je već naglašeno, su najosetljivija na oštećenja izazvana bukom ili starenjem i prva stradaju u procesu sinaptopatije. Kod osoba sa ovim stanjem, pragovi za izazivanje stapedijalnog refleksa mogu biti povišeni, dok amplituda i rast snage refleksa slabe [37].

Iako je u eksperimentalnim studijama na životinjama dokazano da je refleks mišića srednjeg uva visoko osetljiv marker za rano prepoznavanje oštećenja sinapsi slušnog živca [38] njegova primena kod ljudi još uvek je u fazi istraživanja.

An indicator of cochlear synaptopathy on the ABR test is a decrease in the amplitude of wave I at high stimulus intensities, while its latency remains unchanged [22]. The authors state that high-spontaneous-rate fibers remain undamaged and therefore continue to conduct impulses normally, so that the information reaches the electrode at the expected time. The conduction velocity of impulses through the remaining fibers is not reduced and, consequently, there is no prolongation of latency.

The underlying mechanism of cochlear synaptopathy is glutamatergic excitotoxicity; because the cochlea cannot rapidly remove excess glutamate during exposure to loud sounds (above 80–90 dB HL), ions pathologically influx into the postsynaptic terminals. Synaptopathy selectively destroys synapses on low-spontaneous-rate fibers, which have a high activation threshold and respond only to loud sounds. Consequently, their contribution is absent, and the total summed action potential, i.e., the amplitude of wave I, is significantly lower than in a healthy ear [23].

The characteristics of wave I, particularly its amplitude at high stimulus intensities, directly reflect the density and functional integrity of these fundamental synaptic connections, making it a primary biomarker for investigating cochlear synaptopathy [33].

Electrococleography (ECoG) is an objective electrophysiological method that records the earliest electrical potentials of the cochlea and the initial segment of the auditory nerve, which directly corresponds to wave I of the auditory brainstem potentials [22]. The key advantage of this method for investigating cochlear synaptopathy, i.e., hidden hearing loss, is its ability to isolate the functional status of the inner sensory cells and their associated synaptic connections with the afferent fibers of the auditory nerve [33]. The ECoG signal consists of three components: the cochlear microphonic (CM), the summing potential (SP), and the action potential (AP). While the generators of CM and SP are located in the receptors – the inner and outer sensory cells – the AP directly reflects the synchronous depolarization of auditory nerve fibers. In cochlear synaptopathy, a specific pathophysiological profile is observed: because the inner sensory cells themselves are preserved, the amplitude of the summing potential remains within the normal range. However, because synapses selectively degenerate and low-spontaneous-rate fibers are lost, the action-potential amplitude drops drastically at high stimulus intensities [23]. Consequently, this selective amplitude decrease leads to a specific increase in the mathematical SP/AP ratio [34]. The clinical and research significance of ECoG lies precisely in the identification of this specific pattern – normal SP with reduced AP –

Tabela 1. Usporedni prikaz očekivanih dijagnostičkih nalaza kod zdravog uva i uva sa kohlearnom sinaptopatijom

Dijagnostička metoda	Nalaz kod zdravog uva	Nalaz kod uva sa kohlearnom sinaptopatijom
Tonalna liminarna audiometrija (ADG)	Uredan prag sluha (0–20 dB) na svim standardnim frekvencijama	Uredan prag sluha (0–20 dB) na svim standardnim frekvencijama
Proširena visokofrekventna audiometrija	Očuvani pragovi čujnosti na visokim frekvencijama	Povišenje pragova čujnosti iznad 8kHz
Govorna audiometrija u buci	Visok procenat razumevanja reči; stabilan i uredan SNR prag	Drastičan pad u razumevanju reči sa smanjenjem ili negativnim vrednostima SNR-a
Auditivni evocirani potencijali (ABR)	Uredne amplitude i latencije svih talasa (I–V) pri visokim intenzitetima (80–90 dB HL)	Selektivno smanjenje amplitude talasa I pri visokim intenzitetima stimulusa uz očuvane latencije
Elektrokohleografija (EcochG)	Uredan odnos amplituda sumacionog i akcionog potencijala (SP/AP)	Značajno povišen odnos amplituda SP/AP usled redukcije amplitude akcionog potencijala
Akustički (stapedijalni) refleksi	Uredan prag izazivanja refleksa na standardnim intenzitetima	Povišeni pragovi ili potpuno odsustvo refleksa, praćeno bržim zamorom (<i>decay</i>) refleksa
Testovi vremenske rezolucije (GIN test)	Uredan (nizak) prag detekcije pauze u šumu	Povišen prag detekcije pauze

Table 1. Comparison of expected diagnostic findings in a healthy ear and an ear with cochlear synaptopathy

Diagnostic method	Findings in a healthy ear	Findings in an ear with cochlear synaptopathy
Pure-tone audiometry (ADG)	Normal hearing thresholds (0–20 dB) at all standard frequencies	Normal hearing thresholds (0–20 dB) at all standard frequencies
Extended high-frequency audiometry	Preserved hearing thresholds at high frequencies	Elevated hearing thresholds above 8 kHz
Speech audiometry in noise	High percentage of word recognition; stable and normal SNR threshold	Drastic decline in word recognition with decreasing or negative SNR values
Auditory evoked potentials (ABR)	Normal amplitudes and latencies of all waves (I–V) at high intensities (80–90 dB HL)	Selective reduction in the amplitude of wave I at high stimulus intensities with preserved latencies
Electrocochleography (ECoG)	Normal amplitude ratio of the summing potential to the action potential (SP/AP)	Significantly elevated SP/AP amplitude ratio due to a reduction in action potential amplitude
Acoustic (stapedial) reflex	Normal reflex elicitation threshold at standard intensities	Elevated thresholds or complete absence of the reflex, accompanied by more rapid reflex decay
Temporal resolution tests (GIN test)	Normal (low) gap-detection threshold in noise	Elevated gap-detection threshold

SAVREMENI TERAPIJSKI PRISTUPI

Tehnološka i amplifikaciona rešenja

S obzirom da u trenutnoj kliničkoj praksi ne postoje odobreni farmakološki protokoli za kauzalno lečenje, odnosno za direktnu strukturnu obnovu oštećenih sinapsi, savremeni tretman kohlearne sinaptopatije primarno je usmeren na ublažavanje pratećih simptoma. Kako je audiogram kod ovih pacijenata po pravilu uredan, terapijska paradigma se ne fokusira na pojačavanje pragova čujnosti, već na poboljšanje funkcionalnog sluha u nepovoljnim akustičkim uslovima.

Primarni problem pacijenata sa sinaptopatijom nije nemogućnost detekcije zvuka, već nemogućnost izdvajanja korisnog signala (govora) iz pozadinske buke. U ovakvim situacijama od velike pomoći mogu biti slušni aparati sa uskopojasnim direkcionim mikrofona i digitalnom redukcijom šuma. Pored slušnih aparata mogu se koristiti i bežični FM sistemi. Ovi uređaji detektuju glas govornika putem mikrofona koji je

which in practice enables differentiation of synaptopathy from Ménière's disease, in which an elevated SP/AP ratio occurs primarily due to a pathological increase in the SP component itself [35].

The stapedius reflex is an involuntary contraction of the middle-ear muscle *m. stapedius* that occurs as a protective mechanism during exposure to loud sounds. A sound intensity of 70–80 dB reflexively stiffens the chain of auditory ossicles, attenuating the transmission of sound waves to the inner ear [36].

The stapedius reflex is primarily activated through low-spontaneous-rate fibers, which have a high activation threshold and respond only to loud sounds. As noted, these fibers are most susceptible to damage from noise or aging and are the first to be affected in synaptopathy. In individuals with this condition, the thresholds for eliciting the stapedius reflex may be elevated, while the amplitude and growth of reflex strength are reduced [37].

postavljen u blizini ili pričvršćen na govorniku i prenosi signal direktno u uvo pacijenta putem zvučnika ili preko bežične veze sa slušnim aparatom [39].

Klinička primarna prevencija i otoprotekcija

U kontekstu prevencije trajnih auditivnih disfunkcija, važnu ulogu za lekare praktičare ima primarna prevencija neposredno pre ili nakon akustičke traume. Kliničke studije ukazuju na to da primena farmakološke antioksidativne zaštite – prvenstveno visokih doza vitamina A, C i E, kao i N-acetilcisteina (NAC) – može ublažiti oksidativni stres i eksitotoksičnost u unutrašnjem uhu. Ovi antioksidativni protokoli pokazali su potencijal u očuvanju integriteta trakastih (*ribbon*) sinapsi ukoliko se primene unutar ranog terapijskog prozora nakon izloženosti buci [40].

Eksperimentalni farmakološki pristupi (Klinička ispitivanja)

Trenutno se u svetu dve farmaceutske kompanije nalaze u različitim fazama razvoja potencijalnih terapijskih rešenja koja ciljaju direktnu obnovu oštećenih sinapsi između unutrašnjih senzornih ćelija i vlakana slušnog nerva. Međutim, važno je naglasiti da su ovi farmakološki pristupi još uvek u eksperimentalnoj fazi i da njihova klinička efikasnost kod ljudi tek treba da bude potvrđena kroz dalja detaljna istraživanja.

Nemačka farmaceutska kompanija AudioCure vrši testiranje leka pod nazivom AC 102 i trenutno se čeka objava rezultata završene Faze 2. U ovoj fazi vršena je ocena efikasnosti, bezbednosti i podnošljivosti pojedinačne intratimpanične doze leka u poređenju sa oralnim kortikosteroidima – sadašnjim standardom lečenja iznenadnog idiopatskog sensorineuralnog gubitka sluha [41].

U pretkliničkim studijama na životinjama, molekul AC102 je pokazao izuzetne rezultate. Istraživanje je sprovedeno na mongolskim gerbilima (pustinjskim miševima) i potvrdilo je da je jedna doza leka ubrizgana u srednje uvo dovela do regeneracije trakastih (*ribbon*) sinapsi. Nakon 5 nedelja od primene leka, ponašanje koje ukazuje na prisustvo tinitusa je kod testiranih subjekata skoro u potpunosti nestalo. Registrovano je ponašanje povezano sa tinitusom samo kod jednog od ukupno petnaest testiranih subjekata za razliku od kontrolne grupe kod koje je ovo ponašanje registrovano kod jedanaest od trinaest subjekata [42].

Francusko – američka biotehnološka kompanija Cilcare trenutno radi na razvoju eksperimentalnog neurotrofnog leka pod nazivom CIL001. Aktivni molekul u leku CIL001, paliroden, prvobitno je razvila velika farmaceutska kuća Sanofi Aventis za neurodegenerativne bolesti. Cilcare je 2020.godine otkupio licencu od

Although experimental studies in animals have shown that the middle-ear muscle reflex is a highly sensitive marker for early detection of damage to auditory nerve synapses [38], its application in humans remains in the research phase.

CONTEMPORARY THERAPEUTIC APPROACHES Technological and Amplification Solutions

Given that there are currently no approved pharmacological protocols for the causal treatment of cochlear synaptopathy, i.e., for the direct structural restoration of damaged synapses, contemporary treatment of cochlear synaptopathy is primarily aimed at alleviating associated symptoms. Because the audiogram in these patients is generally within normal limits, the therapeutic paradigm focuses not on amplifying hearing thresholds, but on improving functional hearing under unfavorable acoustic conditions.

The primary problem in patients with synaptopathy is not the inability to detect sound, but the inability to extract the useful signal (speech) from background noise. In such situations, hearing aids with narrowband directional microphones and digital noise reduction can be highly beneficial. In addition to hearing aids, wireless FM systems can also be used. These devices detect the speaker's voice through a nearby microphone or one attached to the speaker and transmit the signal directly to the patient's ear via a loudspeaker or through a wireless connection with the hearing aid [39].

Clinical Primary Prevention and Otoprotection

To prevent permanent auditory dysfunction, primary prevention immediately before or after acoustic trauma plays an important role for practicing physicians. Clinical studies indicate that the use of pharmacological antioxidant protection – primarily high doses of vitamins A, C, and E, as well as N-acetylcysteine (NAC) – may attenuate oxidative stress and excitotoxicity in the inner ear. These antioxidant protocols have shown potential to preserve the integrity of ribbon synapses when administered within the early therapeutic window after noise exposure [40].

Experimental Pharmacological Approaches (Clinical Trials)

Currently, two pharmaceutical companies worldwide are at different stages of developing potential therapeutic solutions aimed at directly restoring damaged synapses between inner sensory cells and auditory nerve fibers. However, it is important to emphasize that these pharmacological approaches are still in the experimental phase and that their clinical efficacy in

kompanije Sanofi kako bi ovaj molekul preusmerio isključivo na lečenje unutrašnjeg uva i sinaptopatije. S obzirom da je lek još uvek u fazi kliničkih ispitivanja (faza 1b/2a) podaci o njegovoj uspešnosti se još uvek prikupljaju i nisu dostupni javnosti. Sama kompanija je izuzetno optimistična i promovise ovo jedinjenje kao mogući lek za sinaptopatiju i tinitus. Na dodeli nagrada Hearing Technology Innovator Awards 2024. godine ovo jedinjenje je proglašeno pobednikom u kategoriji terapija [43].

ZAKLJUČAK

Uvođenje prvih farmakoloških rešenja za regeneraciju kohlearnih sinapsi, praćeno formalnom implementacijom specifične šifre unutar Međunarodne klasifikacije bolesti, označice istorijsku promenu u audiologiji. Međutim, uspeh ove terapijske revolucije neće zavisiti samo od efikasnosti samog leka, već od spremnosti zdravstvenog sistema da prepozna i adekvatno selektuje pacijente. Kako bismo spremni dočekali trenutak kada ovi lekovi pređu iz kliničkih studija u apoteke neophodno je paralelno sprovesti pripreme u dva ključna pravca:

- **standardizacija dijagnostičkih protokola** - trenutni skrining sluha i dalje se primarno oslanja na tonalnu liminarnu audiometriju koja je slepa za kohlearnu sinaptopatiju. Zdravstveni sistemi moraju u redovnu praksu uvrstiti govornu audiometriju u buci kao i napredne elektrofiziološke testove. Bez ove dijagnostičke tranzicije, pacijenti sa skrivenim gubitkom sluha ostaće neprepoznati i uskraćeni za pravo na novu terapiju.
- **stratifikacija pacijenata i dugoročno praćenje podataka.** Klinička implementacija šifre bolesti u MKB omogućice precizno epidemiološko praćenje. Ovaj fond podataka postaje temelj za izgradnju oštih indikacionih kriterijuma i stratifikaciju pacijenata na osnovu stepena i reverzibilnosti oštećenja.

Kohlearna sinaptopatija više nije teorijski koncept sa životinjskih modela, već klinička realnost na pragu farmakološkog rešenja. Pravovremena priprema dijagnostičkog aparata, zakonodavstva u zdravstvu (kroz MKB) i edukacija stručne javnosti predstavljaju imperativ. Samo tako se može osigurati da, u trenutku kada regenerativni lekovi postanu komercijalno dostupni, tranzicija od „skrivenog gubitka sluha” do efektivnog terapijskog odgovora i neuroregenerativne restauracije slušnog puta bude brza, bezbedna i klinički efikasna.

Sukob interesa: Nije prijavljen.

humans has yet to be confirmed through further detailed research.

The German pharmaceutical company AudioCure is testing a drug known as AC102, and the results of the completed Phase 2 trial are currently awaiting publication. In this phase, researchers evaluated the efficacy, safety, and tolerability of a single intratympanic dose of the drug compared with oral corticosteroids—the current standard treatment for sudden idiopathic sensorineural hearing loss [41].

In preclinical animal studies, the AC102 molecule demonstrated remarkable results. The study was conducted in Mongolian gerbils (desert mice) and confirmed that a single dose of the drug administered into the middle ear resulted in regeneration of ribbon synapses. Five weeks after drug administration, tinnitus-related behavior had almost completely disappeared in the tested subjects. Tinnitus-related behavior was recorded in only one of the fifteen tested subjects, compared with the control group, in which this behavior was recorded in eleven of thirteen subjects [42].

The French-American biotechnology company Cilcare is currently developing an experimental neurotrophic drug known as CIL001. The active molecule in CIL001, paliroden was originally developed by the major pharmaceutical company Sanofi Aventis for neurodegenerative diseases. In 2020, Cilcare acquired a license from Sanofi to redirect the molecule exclusively toward treating the inner ear and synaptopathy. Because the drug is still in the clinical trial phase (Phase 1b/2a), efficacy data are still being collected and are not publicly available. The company itself is highly optimistic and promotes this compound as a potential treatment for synaptopathy and tinnitus. At the 2024 Hearing Technology Innovator Awards, this compound won the therapeutics category [43].

CONCLUSION

The introduction of the first pharmacological solutions for regenerating cochlear synapses, accompanied by the formal implementation of a specific code within the International Classification of Diseases, will mark a historic change in audiology. However, the success of this therapeutic revolution will depend not only on the drug's efficacy, but also on the healthcare system's readiness to recognize and select patients appropriately. In order to be prepared for the moment when these drugs move from clinical trials to pharmacies, preparations must be undertaken simultaneously in two key directions:

- **Standardization of diagnostic protocols** – current hearing screening still primarily relies on pure-tone audiometry, which is insensitive to cochlear synaptopathy. Healthcare systems must incorporate

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speech audiometry in noise as well as advanced electrophysiological tests into routine practice. Without this diagnostic transition, patients with hidden hearing loss will remain undiagnosed and deprived of access to the new therapy.

- **Patient stratification and long-term data monitoring.** The clinical implementation of the disease code in the ICD will enable precise epidemiological monitoring. This data will form the basis for establishing precise indication criteria and stratifying patients by the severity and reversibility of the damage.

Cochlear synaptopathy is no longer merely a theoretical concept derived from animal models, but a clinical reality on the threshold of a pharmacological solution. Timely preparation of diagnostic infrastructure, healthcare legislation (through the ICD), and education of the professional community are imperative. Only then can we ensure that, once regenerative drugs become commercially available, the transition from “hidden hearing loss” to an effective therapeutic response and neuroregenerative restoration of the auditory pathway will be rapid, safe, and clinically effective.

Conflict of interest: None declared

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