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της κα Ευθυμίου Χριστίνα

με θέμα:

Auditory Neuropathy: A review of the Literature.

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Επιβλέπων: Νικολόπουλος Θωμάς, Καθηγητής ΕΚΠΑ

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Πρόλογος

Ο σκοπός μου κατά τη διάρκεια της συγγραφής της βιβλιογραφικής ανασκόπησης με τίτλο «Ακουστική νευροπάθεια: Βιβλιογραφική ανασκόπηση» είναι η επισήμανση και αξιολόγηση όλων των διαθέσιμων δημοσιευμένων δεδομένων για την ακουστική νευροπάθεια, ώστε να δοθεί μια ενημέρωση για τους έως τώρα γνωστούς παθοφυσιολογικούς μηχανισμούς, τα αντίστοιχα κλινικά ευρήματα και διαγνωστικά κριτήρια αυτής της ασθένειας. Λόγω των πολλών ανεπίλυτων αντιπαραθέσεων στην βιβλιογραφία για την αντιμετώπιση της ακουστικής νευροπάθειας, ο στόχος μου είναι επιπλέον, να προσδιοριστούν οι τρέχουσες καθώς και οι μελλοντικές θεραπευτικές στρατηγικές με ορθή και όσο το δυνατόν πληρέστερη ανάλυση του θέματος. Επίσης, θα αξιολογηθούν τα οφέλη της κοχλιακής εμφύτευσης σε άτομα με ακουστική νευροπάθεια, προκειμένου να απαντηθεί ένα κλινικό ερώτημα: Ποια είναι η αποτελεσματικότητα της κοχλιακής εμφύτευσης στην ακουστική ικανότητα και στην επικοινωνία, σε ασθενείς με ακουστική νευροπάθεια;

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Χριστίνα Ευθυμίου

Αθήνα, 2019

Abstract

Auditory Neuropathy: A review of the Literature.

Introduction

Auditory neuropathy (AN) or auditory neuropathy spectrum disorder (ANSD) is a recently described form of hearing impairment where neural dys-synchrony and deterioration of temporal processing is the predominant characteristic. This condition is a clinical entity which is caused by abnormal neural encoding of sound stimuli despite preservation of sensory transduction and amplification by the outer hair cells. Auditory neuropathy can be caused by damage to the sensory inner hair cells, IHC ribbon synapses or spiral ganglion neurons.

Objective

This review of the literature aims to attain all available published evidence on auditory neuropathy in order to provide an update on recently elucidated pathophysiological mechanisms such as sensory, synaptic and neural mechanisms of this disease. The corresponding clinical findings and diagnostic criteria of AN will be identified and current rehabilitation strategies as well as future therapies will be discussed. Moreover, the role and the benefits of cochlear implantation (CI) in AN individuals will be evaluated in order to answer one clinical question: For individuals with the diagnosis of an auditory neuropathy, what is the effect of cochlear implantation on hearing and communication skills?

Methods

A review of the literature was conducted using the PUBMED, EMBASE, ERIC (Education Resources Information Center) and COCHRANE CENTRAL databases to encompass English and Greek articles from 1990 to January 2019. Terms such as “auditory neuropathy”, “auditory, neuropathy spectrum disorder”, and AN linked with key words such as “epidemiology”, “etiology”, “pathophysiology”, “diagnosis”, “management” and “cochlear implants” were used. The selection of articles followed screening for eligibility for inclusion, based on issues related to the objective of this review of the literature.

Results

A total of 299 studies that illustrate their insight on the diagnosis, pathophysiology, epidemiology, the risk factors and the etiology of auditory neuropathy were included in this literature review. 75 studies were included in the literature review, applicable to answer the posed question, regarding cochlear implants and their effects on hearing and communication skills in patients with AN. A total of 57 articles reported a significant advantage in the management of auditory neuropathy with CI, presenting improved auditory skills and language development in implanted AN patients. The remaining 17 studies demonstrated that although cochlear implantation offers the possibility of speech perception and improved hearing skills to subjects with AN, the benefit depends on the site of the lesion and confounding disorders.

Conclusion

Auditory neuropathy is not a rare disorder, especially amongst hearing-impaired children. The absence of an auditory brainstem response (ABR) and the presence of otoacoustic emissions (OAE) indicate an AN profile, but determining the exact anatomical site of the disorder, requires more in-depth audiological and electrophysiological tests combined with imaging and genetic evaluations. Timely and adequate treatment is of utmost importance, even though it still remains a challenge for the clinicians, as current hearing aid technology is not able to enhance the temporal envelope of the speech signal to compensate for temporal processing deficits associated with AN. The data gleaned in this review of the literature support the conclusion that cochlear implantation (CI) positively affects hearing and communication skills in AN individuals and even patients with mild to moderate hearing abilities with poor speech intelligibility, should be candidates for CI as they will benefit significantly in improved conversational speech discrimination post-surgically. However due to the heterogeneity of this disorder special consideration is required when undertaking hearing rehabilitation and cochlear implantation in AN patients.

Keywords: Auditory neuropathy, Auditory dys-synchrony, Hearing aids, Cochlear implants.

Περίληψη

Ακουστική Νευροπάθεια: Βιβλιογραφική ανασκόπηση

Εισαγωγή

Η ακουστική νευροπάθεια(AN) ή ακουστικός από-συγχρονισμός (ANSD), είναι μια διαταραχή που έχει περιγραφεί πρόσφατα και πρόκειται για παθολογική κατάσταση που αφορά την νευρική επεξεργασία των ακουστικών ερεθισμάτων. Αυτή η διαταραχή προκαλείται από μη φυσιολογική κωδικοποίηση ηχητικών ερεθισμάτων παρά τη διατήρηση της διάδοσης και ενίσχυσης των ερεθισμάτων από τα έξω τριχωτά κύτταρα. Η ακουστική νευροπάθεια μπορεί να προκληθεί από: βλάβη στα έσω τριχωτά κύτταρα, βλάβη στην συναπτική περιοχή μεταξύ έσω τριχωτών κυττάρων και δενδρίτων των νευρώνων του ελικοειδούς γαγγλίου και από βλάβη στους νευρώνες του ελικοειδούς γαγγλίου.

Σκοπός

Ο στόχος αυτής της βιβλιογραφικής ανασκόπησης είναι η επισήμανση και αξιολόγηση όλων των διαθέσιμων δημοσιευμένων δεδομένων για την ακουστική νευροπάθεια, ώστε να δοθεί μια ενημέρωση για τους έως τώρα γνωστούς παθοφυσιολογικούς μηχανισμούς αυτής της ασθένειας: στα αισθητήρια κύτταρα, στις συνάψεις και στους νευρώνες. Θα προσδιοριστούν επίσης, τα αντίστοιχα κλινικά ευρήματα και διαγνωστικά κριτήρια της AN και θα συζητηθούν οι τρέχουσες καθώς και οι μελλοντικές θεραπευτικές στρατηγικές. Επιπλέον, θα αξιολογηθούν τα οφέλη της κοχλιακής εμφύτευσης σε άτομα με AN, προκειμένου να απαντηθεί ένα κλινικό ερώτημα: Ποια είναι η αποτελεσματικότητα της κοχλιακής εμφύτευσης στην ακουστική ικανότητα και στην επικοινωνία, σε ασθενείς με AN;

Μέθοδος

Η αναζήτηση της βιβλιογραφίας πραγματοποιήθηκε με την χρήση της βάσης δεδομένων του PUBMED, EMBASE, ERIC (Education Resources Information Center) και COCHRANE CENTRAL για την ανεύρεση αγγλικών και ελληνικών άρθρων από το 1990 έως τον Ιανουάριο του 2019. Χρησιμοποιήθηκαν όροι όπως “ακουστική νευροπάθεια” και “ακουστικός απο-συγχρονισμός” και AN σε συνδυασμό με λέξεις- κλειδιά όπως “επιδημιολογία”, “αιτιολογία”, “παθοφυσιολογία”, “διάγνωση”, “διαχείριση” και “κοχλιακά εμφυτεύματα”. Εν συνεχεία, έγινε διαλογή των άρθρων και συμπεριλήφθηκαν βάση της σχετικότητας τους με τον στόχο της βιβλιογραφικής ανασκόπησης.

Αποτελέσματα

Συγκεντρώθηκαν συνολικά 299 άρθρα που παρέχουν γνώσεις σχετικά με τη διάγνωση, την παθοφυσιολογία, την επιδημιολογία, τους παράγοντες κινδύνου και την αιτιολογία της ακουστικής νευροπάθειας. Συμπεριλήφθηκαν 75 άρθρα που απαντούσαν στο ερώτημα που τέθηκε για τις επιπτώσεις των κοχλιακών εμφυτευμάτων στην ακουστική ικανότητα και την επικοινωνία σε ασθενείς με ΑΝ. Συνολικά 57 άρθρα ανέφεραν σημαντικό πλεονέκτημα στη διαχείριση της ακουστικής νευροπάθειας με κοχλιακά εμφυτεύματα, παρουσιάζοντας βελτιωμένες ακουστικές ικανότητες και ανάπτυξη ομιλίας σε ασθενείς με ΑΝ. Οι υπόλοιπες 17 μελέτες έδειξαν ότι παρόλο που η κοχλιακή εμφύτευση προσφέρει τη δυνατότητα βελτίωσης της ακουστικής ικανότητας και της ανάπτυξης της ομιλίας σε άτομα με ΑΝ, το όφελος εξαρτάται από τη θέση της βλάβης και τις συνοσηρότητες.

Συμπέρασμα

Η ακουστική νευροπάθεια δεν είναι μια σπάνια διαταραχή, κυρίως μεταξύ παιδιών με γνωστή νευροαισθητήρια βαρηκοΐα. Η ακουστική νευροπάθεια χαρακτηρίζεται από απουσία ακουστικών προκλητών δυναμικών εγκεφαλικού στελέχους (ABR) και παρουσία ωτακουστικών εκπομπών (OAE), αλλά ο προσδιορισμός της ακριβής ανατομικής θέσης της διαταραχής, απαιτεί πιο εξειδικευμένες ακουστικές και ηλεκτροφυσιολογικές εξετάσεις σε συνδυασμό με απεικονιστικό έλεγχο και γενετικές δοκιμές. Η έγκαιρη και κατάλληλη αντιμετώπιση είναι πολύ σημαντική, παρόλο που εξακολουθεί να αποτελεί πρόκληση για τους κλινικούς ιατρούς, διότι η τεχνολογία των ακουστικών βαρηκοΐας δεν είναι ακόμη ικανή να αντισταθμίσει τα ελλείμματα συγχρονισμού, αναγκαία για την αποκωδικοποίηση της ομιλίας, των ασθενών αυτών. Η πλειοψηφία των μελετών που συμπεριλήφθηκαν στην βιβλιογραφική ανασκόπηση υποστηρίζουν το συμπέρασμα ότι η κοχλιακή εμφύτευση προσφέρει σημαντικό πλεονέκτημα στην ακουστική ικανότητα και στην ανάπτυξη της ομιλίας σε άτομα με ΑΝ. Επιπλέον, ακόμη και ασθενείς με ήπια έως μέτρια ακουστική ικανότητα με φτωχή διάκριση ομιλίας θα πρέπει να είναι υποψήφιοι για κοχλιακό εμφύτευμα, καθώς θα επωφεληθούν σημαντικά στην διακριτική ικανότητα μετεγχειρητικά. Ωστόσο, λόγω της ανομοιογένειας αυτής της διαταραχής απαιτείται ιδιαίτερη προσοχή όταν γίνεται η επιλογή των ασθενών για κοχλιακή εμφύτευση έτσι ώστε να επιτευχθεί η βέλτιστη έκβαση.

Λέξεις-κλειδιά: Ακουστική νευροπάθεια, Ακουστικός από-συγχρονισμός, Ακουστικά βαρηκοΐας, Κοχλιακά εμφυτεύματα.

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LIST OF ABBREVIATIONS AND TERMINOLOGY

ABBREVIATIONS	ENGLISH TERMINOLOGY	GREEK TERMINOLOGY
AAA:	American Academy of Audiology	Αμερικάνικη Ακαδημία Ακοολογίας
AN:	Auditory neuropathy	Ακουστική νευροπάθεια
ABR:	Auditory brainstem response	Ακουστικών προκλητών δυναμικών εγκεφαλικού στελέχους
ANSD:	Auditory neuropathy spectrum disorder	Φάσμα διαταραχών της ακουστικής νευροπάθειας
ASSR:	Auditory steady-state responses	Ακουστικών δυναμικών σταθερού ερεθίσματος
AUNA1:	Auditory neuropathy, dominant 1	Ακουστική νευροπάθεια, επικρατές γονίδιο
AUNA2:	Auditory neuropathy, dominant 2	Ακουστική νευροπάθεια, επικρατές γονίδιο 2
ASHA:	American Speech- Language-Hearing Association	Αμερικάνικος όμιλος ακοής-ομιλίας- γλώσσας
CAP:	Compound action potential	Σύνθετο δυναμικό ενέργειας
CENTRAL:	Cochrane Central Register of Controlled Trials	Κεντρική καταχώρηση ελεγχόμενων δοκιμών Cochrane
CM:	Cochlear microphonic potentials	Κοχλιακό μικροφωνικό
CMT:	Charcot–Marie–Tooth disease	Νόσος Charcot–Marie–Tooth
CNS	Central nervous system	Κεντρικό νευρικό σύστημα
CT:	Computed tomography	Αξονική τομογραφία
DIAPH3:	Diaphanous-3	Ομόλογο γονιδίου Diahanous-3
DPOAE:	Distortion products otoacoustic emmissions	Ωτοακουστικές εκπομπές προϊόντων ακουστικής παραμόρφωσης

LIST OF ABBREVIATIONS AND TERMINOLOGY (CONTINUED)

ABBREVIATIONS	ENGLISH TERMINOLOGY	GREEK TERMINOLOGY
ECAP:	Electric compound action potential	Ηλεκτρικό σύνθετο δυναμικό ενέργειας
ECochG:	Electrocochleography	Ηλεκτροκοχλιογραφία
EABR	Electric auditory brainstem responses	Ηλεκτρικών ακουστικών προκλητών δυναμικών εγκεφαλικού στελέχους
ERIC:	Education Resources Information Center	Κέντρο πληροφόρησης για εκπαιδευτικά μέσα
FM:	Frequency modulated	Διαμόρφωση συχνότητας
GJB2:	Gap junction protein beta 2	Πρωτεΐνη χασματοσύνδεσμου βήτα 2
HA:	Hearing aids	Ακουστικά βαρηκοΐας
IHCs:	Inner hair cells	Έσω τριχωτά κύτταρα
IT-MAIS	Infant-Toddler Meaningful Auditory Integration Scale	Ουσιαστική κλίμακα ακουστικής ολοκλήρωσης νηπίων-παιδιών
MRI:	Magnetic resonance imaging	Μαγνητική τομογραφία
MAIS	Meaningful Auditory Integration Scale	Ουσιαστική κλίμακα ακουστικής ολοκλήρωσης
NSRAN:	Non-syndromic recessive auditory neuropathy	Μη-συνδρομική υπολειπόμενου αυτοσωματικού χαρακτήρα ακουστική νευροπάθεια
NSE:	Neuron-specific enolase	Ειδική νευρωνική ενολάση
OAE:	Otoacoustic emissions	Ωτοακουστικές εκπομπές
OHCs:	Outer hair cells	Έξω τριχωτά κύτταρα

LIST OF ABBREVIATIONS AND TERMINOLOGY (CONTINUED)

ABBREVIATIONS	ENGLISH TERMINOLOGY	GREEK TERMINOLOGY
OPA1:	Optic atrophy 1	Γονίδιο ατροφίας οπτικού νεύρου 1
OTOF:	Otoferlin	Γονίδιου της πρωτεΐνης Otoferlin
PJVK:	Pejvakin	Γονίδιου της πρωτεΐνης Pejvakin
SADL:	Satisfaction with Amplification in Daily Life	Ικανοποίηση με την ακουστική ενίσχυση στην καθημερινή ζωή
SGNs:	Spiral ganglion neurons	Νευρώνες του ελικοειδούς γαγγλίου
SNHL:	Sensorineural hearing loss	Νευροαισθητήρια βαρηκοΐα
SP:	Summating potential	Αθροιστικό δυναμικό
TEOAEs:	Transient evoked otoacoustic emissions	**Παροδικές προκλητές ωτοακουστικές εκπομπές**

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1. Introduction

Auditory neuropathy (AN) also known as Auditory Neuropathy Spectrum Disorder (ANSD) is a recently described form of hearing impairment where neural dys-synchrony and deterioration of temporal processing is the predominant characteristic (1, 2, 3). This hearing disorder is characterized by impaired neural encoding of sound stimuli despite the preservation of sensory transduction and amplification by outer hair cells and the intact frequency selectivity (4).

Clinical investigators began to describe groups of patients with normal or slightly elevated audiogram pure tone thresholds and absent or severely abnormal auditory brainstem responses (ABRs) as early as the 1970's, but with the advent of the otoacoustic emissions (OAEs) in the 1980's, these patients were found to have normal cochlear function. This unique division of hearing dysfunctions known as ANs was identified as clinically significant in 1996 by Starr and his colleagues (4). Since then, researchers have sought to elucidate the pathophysiology, the risk factors, the diagnostic tests and the clinical outcomes of this disorder. Over time the literature illustrated that AN was manifest in different ways and degrees, and as the result of numerous etiologies, thus leading to the adoption of the term ANSD. Further advances in the AN field, though, made this term redundant.

Patients with this disorder report that they "can hear but cannot understand", thus auditory neuropathy is a term that was initially coined for a specific type of hearing disorder affecting speech comprehension beyond alterations in audibility (5). Understanding of speech is almost always severely degraded especially when these signals are embedded in background noise (6). A high degree of precision is required in order to discern and accurately represent complex and continually varying acoustic signals, such as speech. Hence, even subtle alterations, affecting any point in the peripheral or central auditory mechanisms, can have a remarkable impact on perception (6). Patients with AN are able to respond to sounds appropriately, but their ability to decode speech and language is hindered as this hearing impairment affects processing of acoustic temporal cues, essential for: (a) speech discrimination; (b) sound localization; and (c) distinguishing signals from background noise (1, 7, 8). The ability to combine signals from both ears to maximize perception may also be affected due to the temporal-processing deficit that these patients present with (6).

The pathophysiology of the disease is abstruse and equivocal. Its ambiguity lies in that AN is not a single disease but a constellation of pathologies affecting the auditory pathway. It is well established that the sequence of sound processing along the auditory system commences with the outer hair cells (OHCs) which amplify and sharpen the resonance of cochlear

structures in response to sound pressure waves and the next stage is transduction by inner hair cells (IHCs). Speech intelligibility and binaural performance rely greatly on the afferent ribbon synapses at the base of the IHCs which trigger sustained, temporally accurate activity in auditory neurons (9). A wide range of disease mechanisms have recently been elucidated, due to human genetic studies and analysis of animal models of auditory neuropathy, which include loss of IHCs or IHC synapses, impaired synaptic transmission to spiral ganglion neurons (SGNs), and compromised propagation of auditory information along the auditory nerve. Thus, it is lucid that in AN, the hearing impairment is initiated downstream from mechanoelectrical transduction and cochlear amplification of OHCs. The desynchrony of neural discharges, which successively leads to severe impairment in the individuals' temporal processing abilities, without compromising the amplification function of the inner ear is the prevalent pathophysiological mechanism of AN.

There are multiple etiologies of AN phenotype. However, the etiologic factors have not been identified in approximately 50% of patients (10). An elegant description, by Rance and colleagues, demonstrates the various locations of lesions that can cause AN and outlines a few etiologies at each lesion site (11). The disease mechanisms causing AN entail selective loss of IHCs with preserved OHC function; otoferlin (OTOF) gene mutations, encoding the protein otoferlin, have been associated with deficits in neurotransmitters; dendritic anomalies due to auditory trauma or genetic mutations (optic atrophy 1, OPA1); damage to auditory ganglion cells secondary to hyperbilirubinemia; congenital aplasia or hypoplasia of auditory nerve; myelin disorders such as Charcot–Marie tooth disease (4, 12); and lesions causing irregularities to the auditory nerve such as a cerebello-pontine angle lesion or multiple sclerosis (11). Other neurological disorders associated with auditory neuropathy are Leber's Hereditary Optic Neuropathy and Deafness-Dystonia-Optic Neuronopathy syndrome (Mohr-Tranebjaerg syndrome) (4) and Refsum's Disease (13) among others. Furthermore, mitochondrial disorders such as Friedreich's ataxia (14, 15, 16), autoimmune disorders (e.g., Guillain–Barre´ syndrome) and nutritional disorders (17) as well as degenerative changes accompanying aging (18) may give rise to a progressive form of AN. A dys-synchrony in the central auditory processing pathway is thus provoked by these lesions, leading to a number of complications.

The risk factors for the development of AN include both congenital and perinatal insults. The literature has frequently portrayed that neonatal insults such as prematurity, hyperbilirubinemia, hypoxia, central nervous system (CNS) immaturity, low-birth weight and mechanical ventilation are strongly associated with the presentation of AN (19, 20, 21, 22). Infections such as bacterial meningitis, encephalitis and post-viral infections such as measles

and mumps, and the administration of ototoxic drugs such as antibiotics and diuretics, in the neonatal intensive care units, have also been implicated as significant risk factors for the development of AN (19, 23, 24, 25, 26).

Auditory neuropathy is a disorder in which behavioral threshold measures do not match with other measures of auditory function such as ABR data (Figure 1) and speech understanding scores (27).

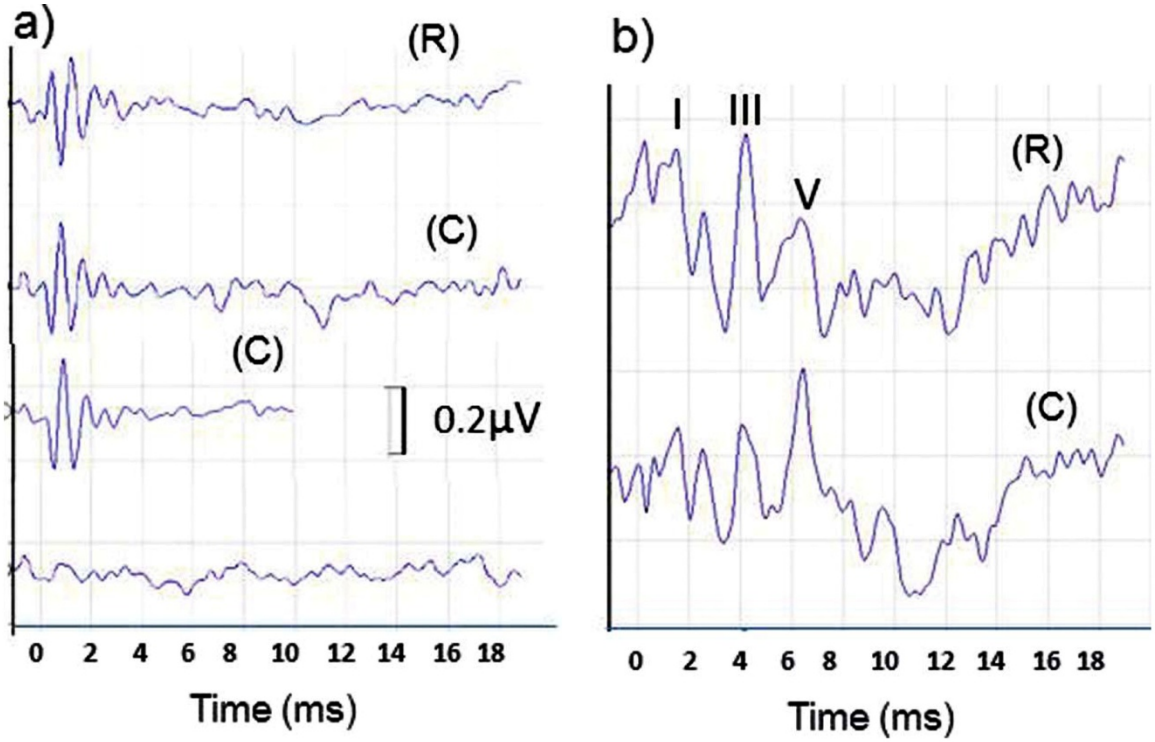

Figure 1. Auditory brainstem response (ABR) traces showing the cochlear microphonic with no neural response recorded from a 1-month-old infant (Panel a): Note that the waveforms recorded using rarefaction (R) and condensation (C) clicks (37.7 clicks/s) appear to be mirror images (two upper traces). A fast click rate of 83.3 clicks/s results in no adaptation (third trace). The disappearance of the response in the clamped tube condition, bottom trace, confirms the response is not stimulus artifact. In contrast, the ABR traces in Panel b show an ABR recorded from a 2-month-old infant with normal hearing. Waves I, III, and V are present, and there is no significant latency shifts between the rarefaction and condensation waveforms. (Adapted from Auditory neuropathy spectrum disorder: a review. 2014. LW Norrix, DS Velenovsky. J Speech Lang Hear Res. 57(4):1564-76. Copyright © 2014 American Speech-Language-Hearing Association.)

Due to the tonotopic layout of the cochlea, frequency cues to sound are encoded in the cochlea and so is the intensity of sound. Therefore, patients with AN are frequently able to show notably good pure tone audiograms (PTAs) relative to their speech perception (Figure 2). These patients have severely impacted speech comprehension because the temporal qualities of sound are encoded and processed in the neurons of the auditory pathway, and it is the temporal qualities that are essential for physiological speech comprehension (28).

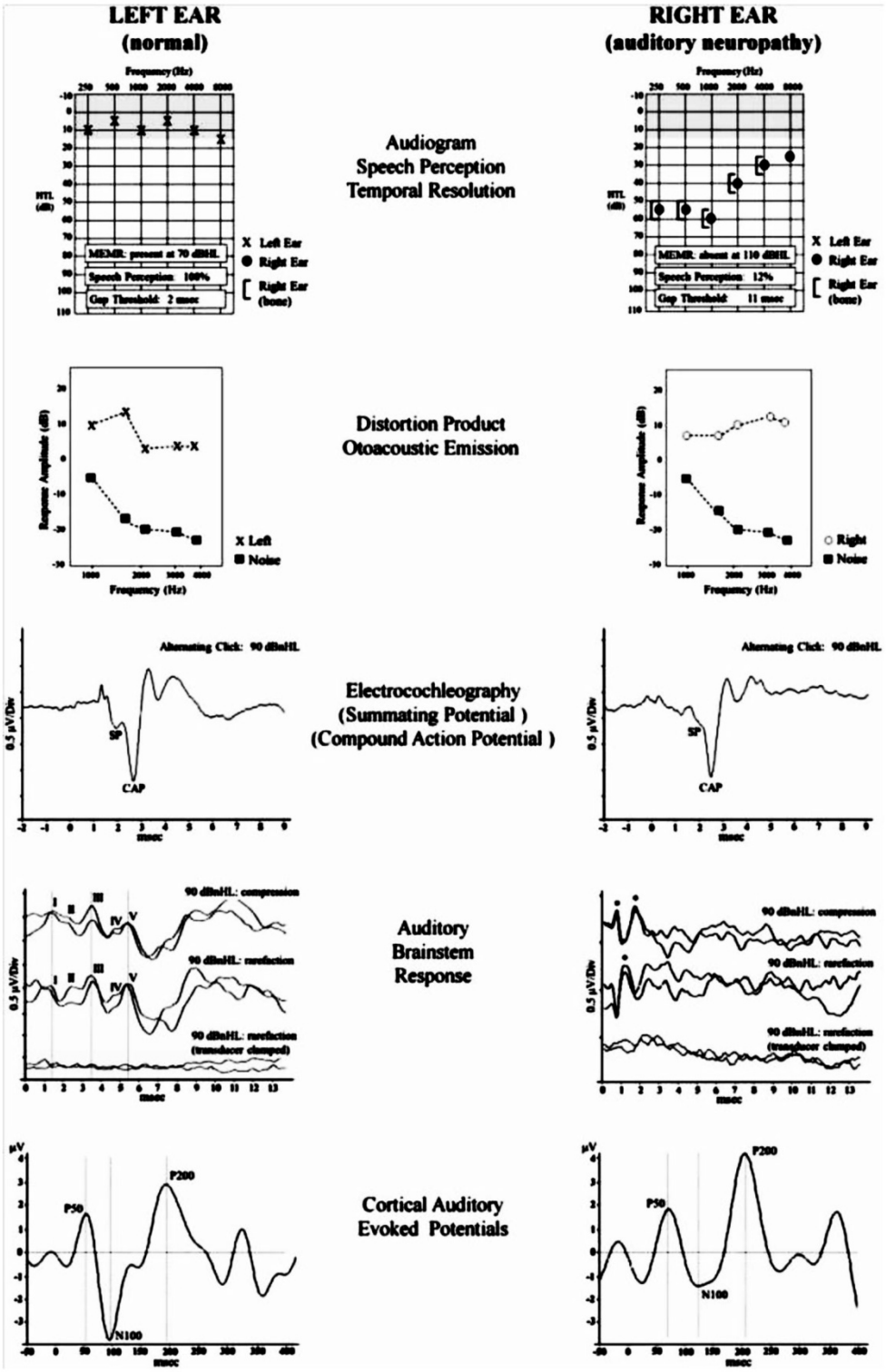

Figure 2. Audiological and electrophysiological results for an individual with unilateral auditory neuropathy. Panels on the left were obtained for stimuli presented to left (normal) ear. Panels on the right represent results for right (auditory neuropathy) ear. The 'audiogram' is the pattern of behavioural sound detection thresholds displayed as a function of stimulus frequency. The shaded area represents the normal sensitivity range. Electrocochleography and ABR testing used acoustic clicks at maximum presentation levels [90 dBnHL (decibels normal hearing level)]. For the right side the ABR is absent but the cochlear microphonic (asterisks) is present. The microphonic shows a phase reversal with change in stimulus polarity (compression/rarefaction) confirming that the potential is of pre-neural origin. The sinusoidal waveform disappears when the stimulus tube is clamped indicating that the potential is not stimulus artefact. (Adapted from Pathophysiological mechanisms and functional hearing consequences of auditory neuropathy. G Rance, A Starr. 2015. Brain.138(Pt 11):3141-58.Copyright 2015 by Oxford University Press on behalf of the Guarantors of Brain.)

AN is a hearing disorder characterized by the presence of OAE and cochlear microphonic potentials (CM) due to the integrity of OHC activity (Figure 2), absent or grossly abnormal brainstem evoked auditory potential, auditory thresholds incompatible with speech thresholds and altered acoustic reflexes (29). Starr and colleagues, having studied temporal bones from subjects dying with AN concluded that the abnormalities of both ABRs and hearing could be attributed to the loss of auditory nerve fibers and altered neural transmission (30).

Auditory neuropathy is a relatively new clinical entity, thus there is still little evidence on its incidence, prevalence and natural history (31). AN seems to be a common cause of hearing impairment, as approximately 1 in 7000 neonates is identified as having abnormal auditory nerve function through 'new-born hearing screening' evaluation (32). The prevalence of AN ranges between 0.23 and 2% in infants ''at risk'' for hearing impairment and it reaches up to 10% in children with permanent hearing loss, moreover, there is a subset of patients that have a unilateral form of the disorder accounting for approximately 7% of children with AN (33). The literature has also demonstrated progressive forms of AN which may occur with a wide range of conditions, as mentioned previously (10, 11, 14, 24). AN has been categorized into two distinct groups regarding the age of symptom onset; an early-onset form, typically associated with a neonatal presentation, and a delayed-onset form, which is commonly accompanied by generalized neuropathy. It is of interest to note that only 25% of AN cases are older than 10 years when the symptoms of the disease primarily occur (24) whereas 80% of patients with symptom onset commencing after the age of 15 present with generalized neuropathic disorders (34). Due to the different cochlear and auditory nerve pathologies and the many pathophysiological mechanisms that have been identified, it is coherent that there is a vast inter and intra-subject variability which defines its patient population, thus making it difficult to discern accurate prevalence.

Technologies available to improve audibility and clarity for individuals with AN are hearing aids (HAs), cochlear implants, and frequency modulated (FM) systems. Typically the initial remediation of choice for mild to severe degrees of hearing loss and generally the only management option for children under the age of 1 year regardless of degree of hearing loss are HAs and/or FM systems. The development of auditory and communication skills in children with prelingual onset of AN is the principle treatment goal. However, management and rehabilitation is an important practical challenge due to this disorder's heterogeneity. Furthermore, predictions as to the outcome of each therapeutic intervention are guarded as a significant number of the pediatric population with AN may have conditions or co-morbidities that negatively impact outcomes irrespective of the treatment strategy (35); therefore, the management of patients with this disorder should be individualized and

modified accordingly, taking into account each patient's needs and progress (36). Conventional amplification may be the initial intervention that can be attempted in order to maximize audibility and clarity, but providing HAs to patients (particularly children) with AN is currently a controversial issue. Firstly, there is skepticism regarding the safety of HA use for AN, due to the damage to cochleae with OHC function and secondly, providing conventional amplification to AN subjects with inherent auditory pathway limitations will increase the likelihood that it will simply produce a louder but equally distorted signal to these individuals (3, 15, 34, 36, 37). HAs can cause significant noise exposure resulting in both temporary and permanent hearing threshold shifts. Thus, the possibility of acoustic trauma through over-amplification is potentially greater in ears with ''normal'' endocochlear function, especially since suppression and acoustic reflex mechanisms that are thought to protect the cochlea from excessively loud sounds may be inactive in AN subjects (15, 38). Currently, positive evidence of improvement of aural acuity with conventional HAs remains anecdotal, as the majority of reports describe poor acceptance of amplification due to insufficient benefit or interference with communication. On the other hand, the use of FM systems in AN subjects' environment settings might offer a low-risk option, as there are minimal risks to surviving OHCs due to minimal amplification levels, yet benefit of improving the signal- to noise ratio may be gained (39). Hence, it seems that AN individuals may benefit from FM systems, either because lucid speech may be enhanced, or for utilization during the evaluation period before CI.

The recognition of greater numbers of AN cases with severe to profound hearing loss, the frequently poor speech perception performance of affected subjects, and limited success with conventional amplification has led many clinicians and patients to consider the cochlear implant management option, despite the specific risks the procedure may entail. Indeed, the ultimate option towards rehabilitation of the compromised processing of auditory information in AN children is CI. The decision to implant AN individuals is strongly supported by a continuously growing body of evidence, suggesting significant advantages in improvement of auditory and language skills in these patients (35, 40). The ability of the CI to partially supersede the functions of the auditory sensory cells and directly stimulate the auditory nerve, benefiting neural synchrony and thus contributing to the development of hearing skills is the basis of this management option for these individuals. Theoretically, the electric signals provided by the CI may improve the auditory pathway's synchronization (41), consequently mitigating temporal processing in AN subjects. The first criterion that needs to be met, for the selection of candidates for cochlear implantation, is the preservation of a normal sized auditory nerve, as shown by MRI. Secondly, children older than one year of age are

implanted as there is a possibility of spontaneous recovery due to the preservation of OHCs, thus making CI a controversial issue in younger children (20, 42). Currently, the literature has demonstrated that most subjects with CIs show normal ABRs to electric stimulation and significant improvement in hearing and speech development, thus CI provide a viable means of improving functional hearing in most individuals with AN (43, 44).

In light of the heterogeneous nature of AN, the high degree of interest among audiologists (American Speech- Language-Hearing Association [ASHA], 2008) and the many unresolved controversies surrounding its pathophysiology and management recommendations, a systematic review was undertaken to examine the current state of the published evidence. This literature review imparts an update on recently elucidated knowledge on AN and aims to convey recently illustrated pathophysiological mechanisms such as sensory, synaptic and neural mechanisms of AN and their corresponding clinical findings. Furthermore, due to the lack of diagnostic tests that accurately diagnose the site of dysfunction and the boundless array of functional outcomes, AN can be difficult to diagnose. Thus, another purpose of this review is to synthesize and analyze existing evidence pertaining to the diagnostic criteria and the battery of tests used to diagnose AN. Moreover, this literature review identifies treatment options, discusses current rehabilitation strategies as well as future therapies and explores the benefits of CIs in enhancing auditory signal processing for the affected individuals. The findings in this review will also highlight areas where further research is needed. Finally, one clinical question will be addressed concerning CI: For children with the diagnosis of an auditory neuropathy, what is the effect of cochlear implantation on hearing and communication skills?

2. Method

A qualitative systematic review of Greek and English literature was carried out to assess the current knowledge on AN, its pathophysiological mechanisms, its clinical presentation and its management recommendations. The review of the literature was conducted using the PUBMED, EMBASE, ERIC (Education Resources Information Center) and COCHRANE CENTRAL databases to encompass English and Greek articles from January 1990 to January 2019. Randomized control trials (RCTs) of AN were also sought by applying a search strategy to the Cochrane Central Register of Controlled Trials (CENTRAL). Terms pertaining to “auditory neuropathy”, “auditory, neuropathy spectrum disorder”, “auditory dyssynchrony”, and AN linked with key words such as “epidemiology”, “etiology”, “pathophysiology”, “diagnosis”, “therapy”, “management” and “cochlear implants” were used. The search strategy furthermore, combined AN with CI and “speech perception” and

"speech intelligibility". The above-mentioned key words provided a large number of scientific studies, which were then screened and analyzed for relevance. The search results were last updated on the 16th of January 2019. Furthermore, related articles were also found after a thorough hand search of all the references of the previously included articles. Following this search strategy titles and abstracts were read and reviewed and, when appropriate, included for further study.

The selection of articles followed screening for eligibility for inclusion, based on issues related to the objective of this review of the literature. Full text articles were retrieved for screening where any uncertainty existed about a study's eligibility. The eligibility criteria for inclusion of the research studies in this review were as follows: all English and Greek studies published in journals from 1990 to January 2019 were included and so were studies of both adults and children of all the world's populations. Due to the plethora of knowledge concerning the pathophysiological mechanisms of AN which have been gleaned from studies based on animal models, it was imperative that animal studies also be included in this literature review. It is important to note that studies were not excluded based on type or study design, as the inclusion of all studies provides a more comprehensive look at the current body of evidence. Therefore, all epidemiological, experimental, clinical studies, case series and literature reviews were added. Moreover, no restrictions were made on outcome measures used. As for the exclusion criteria: articles that were not published in the English or Greek language were not included in the aforementioned period, neither were Letters to the editor, Case reports and pharmacological models. It is of significance to note that although case reports were not included in the literature review, case series, describing a set of patients, were. Furthermore, unpublished studies were excluded in this review. All the publications that were not excluded in the first stage were assessed and reviewed in full for the selection and inclusion in this literature review.

The relevant studies were analyzed to assess and present the current knowledge on the clinical and pathophysiological features of AN that distinguish site/s of dysfunction along the auditory pathway. This review addresses the diagnostic criteria that ascertain the sites of dysfunction, which include: (1) presynaptic disorders which have an effect on IHCs and ribbon synapses; (2) postsynaptic disorders which have an impact on unmyelinated auditory nerve dendrites; (3) postsynaptic disorders influencing auditory ganglion cells and their myelinated axons and dendrites; and (4) central neural pathway disorders affecting the auditory brainstem. Animal research and genetic testing, which is rapidly evolving worldwide, has profoundly advanced our understanding of the disease mechanisms of AN, particularly those affecting sound encoding at the hair cell ribbon synapses. The relevant

studies regarding the genetic association to AN were identified and analyzed in order to elucidate their connection to the pathophysiology of the disease. Furthermore, the genes and their mutations associated with isolated AN are presented, as well as the gene mutations causal in syndromic AN.

Data from the relevant research studies was reviewed in order to portray the knowledge on the plethora of risk factors and etiologies which are associated with this heterogeneous form of hearing loss. The studies included describe and identify the congenital etiologies culpable for AN, which severely affects the development of language, an ability that is strictly related to a period of sensitivity that declines with age. The literature was analyzed in order to demonstrate that cortical plasticity and efficient auditory input is required for the development of language skills, thus in children with congenital AN these skills are greatly hindered. The applicable data that was included presented all the genetic and congenital etiologies of AN and their clinical presentations. These included syndromic, nonsyndromic, and mitochondrial genetic factors as well as cochlear nerve deficiency occurring as a result of failure of the nerve to develop either partially (hypoplasia) or completely (aplasia or agenesis). In addition to the aforementioned, the studies analyzed also present other hereditary conditions that may be associated with AN; these include Charcot-Marie-Tooth and Friedreich's ataxia. Both of these hereditary conditions involve progressive neurological degeneration and generally are not diagnosed until after the neonatal period. The studies presented also display the etiologies and risk factors of the acquired forms of AN, when the onset of the disorder is delayed until childhood or adult life and leads to severe impairment of speech perception and progressive deterioration, due to the abnormalities of auditory input. The acquired etiologies accountable for AN detected in the literature, encompass a vast variety of risk factors which included prematurity, neonatal hyperbilirubinaemia, neonatal anoxia, neonatal mechanical ventilation, hypoxia, low birth weight, extreme prematurity, ototoxic drug exposure, autoimmune disorders (e.g., Guillain–Barre´ syndrome), infections such as meningitis, neoplasms (e.g., acoustic neuroma), nutritional disorders, and degenerative changes accompanying aging.

Relevant studies reviewed, display the diagnostic tools implemented in AN patients and describe the different combinations of test results that may arise in these individuals and how they may be classified according to the site of lesion. The diagnostic workup described and analyzed includes OAEs, CM, acoustic reflexes, ABR, behavioral PTA, speech audiometry and summating potentials measured via a transtympanic membrane electrode.

Eligible research studies were assessed to evaluate the clinical expression of AN in both child and adult populations. The data collected discloses the difficulties in determining the prevalence of AN in adult populations as the physiologic assessments used to discern the condition (ABR/CM/OAE) are not routinely undertaken unless there are specific clinical indicators for retrocochlear abnormality. On the other hand, the studies presented revealed that in the pediatric populations AN is a relatively high-incidence disorder, particularly amongst babies in the neonatal intensive care unit as is distinguished by the electrophysiologic examination and universal neonatal screening. The research was analyzed in order to reveal that this hearing disorder is indeed relatively specific for auditory percepts dependent on temporal cues which include, speech comprehension, gap detection, masking level differences, and low-frequency difference levels, whereas percepts dependent on intensity cues are normal. Furthermore, the literature examined disclosed that the likely factors contributing to the temporal processing defects in AN are loss of fibers (deafferentation) and/or altered synchrony of nerve impulses in the remaining fibers due to demyelination and incomplete remyelination. Moreover, the studies included also presented exceptions to the criteria for defining AN.

Data and principles were reviewed in order to identify treatment options useful in improving auditory signal processing for the affected patients and explore their benefits as a function of site of lesion. Treatment modalities which include FM systems, HAs, and CI are presented in order to demonstrate the auditory outcomes of each method and to convey the most successful management techniques which improve hearing and speech outcomes in these cases. Moreover, eligible research studies were assessed to evaluate the auditory outcomes of CI in children with AN. Cochlear implantation, as a treatment modality in AN individuals, has shown to achieve satisfactory speech perception and development probably because the electric stimulation through the CI is adequate to overcome the existing dyssynchrony. The data presented evaluates the success rate in achieving satisfactory understanding of speech and improved language development after CI in children diagnosed with AN. Furthermore, the studies displayed asses the likelihood of success in auditory outcomes in implant recipients, according to the site of the lesion causing AN. Moreover, the research studies assessed present the necessary diagnostic workup in order to ascertain the site of lesion and discern the poor and good implant candidates. The literature reviewed also identifies and explores the etiologies, of poor auditory outcomes and speech perception after CI in children with AN. These etiologies include lack of neural synchronization and/or concurrent medical and cognitive comorbidities in these children diagnosed with AN.

Quantitative analysis of the data was not performed due to the diversity of the study designs and the heterogeneity of the data. The checklist PRISMA 2009 was implemented for this systematic review.

3. Results

Application of the initial search strategy to the databases PUBMED, EMBASE and ERIC using the terms pertaining to “auditory neuropathy”, “auditory, neuropathy spectrum disorder”, “auditory dyssynchrony”, and AN linked with key words such as “epidemiology”, “etiology”, “pathophysiology”, “diagnosis”, “therapy”, “management” and “cochlear implants”, provided a total of 748 articles, for the allocated time period from January 1990 to January 2019. The final search was conducted on the 16th January 2019. Figure 3 shows the flow chart of the literature research selection. A thorough search of the COCHRANE CENTRAL database was also conducted in order to discover randomized control trials (RCTs) on auditory neuropathy for the abovementioned time frame. This investigation detected only 5 relevant RCTs encompassing auditory neuropathy in general and of the five only 2 were applicable RCTs addressing AN and cochlear implantation. A total of 732 studies were gleaned from the Pubmed database, 9 articles from Embase, 2 studies from ERIC and 5 articles were derived from Cochrane library. After a thorough inspection of the titles of the abovementioned articles, 16 studies were found to be repeated references in more than one database and thus were excluded. A further exclusion of 100 articles was conducted due to the language exclusion criteria, as these studies were not in the English or Greek language. Case reports and case studies were not included in this systematic review of the literature, therefore, 106 studies were excluded following assessment of the study type. Similarly the search identified 8 letters to the editor which were also excluded from this literature review. Consequently, 518 studies remained to be assessed for subject matter relevance by their titles and abstracts. A thorough evaluation of the study summaries and titles led to an exclusion of 222 citations as they were deemed irrelevant to the topic analyzed in this literature review. A further 3 studies were included after appraisal of the included study references. Thus, a total of 299 studies that illustrate their insight on the diagnosis, pathophysiology, epidemiology, the risk factors and the etiology of AN were finally included in this literature review. The articles were examined and critically appraised in their entirety for their relevance to the subject tackled in this review of the literature and were evaluated in order to be further classified. Quantitative analysis of the data was not performed due to the diversity of the studies in terms of study design, outcome measures, quality and the heterogeneity of the data illustrated in each citation.

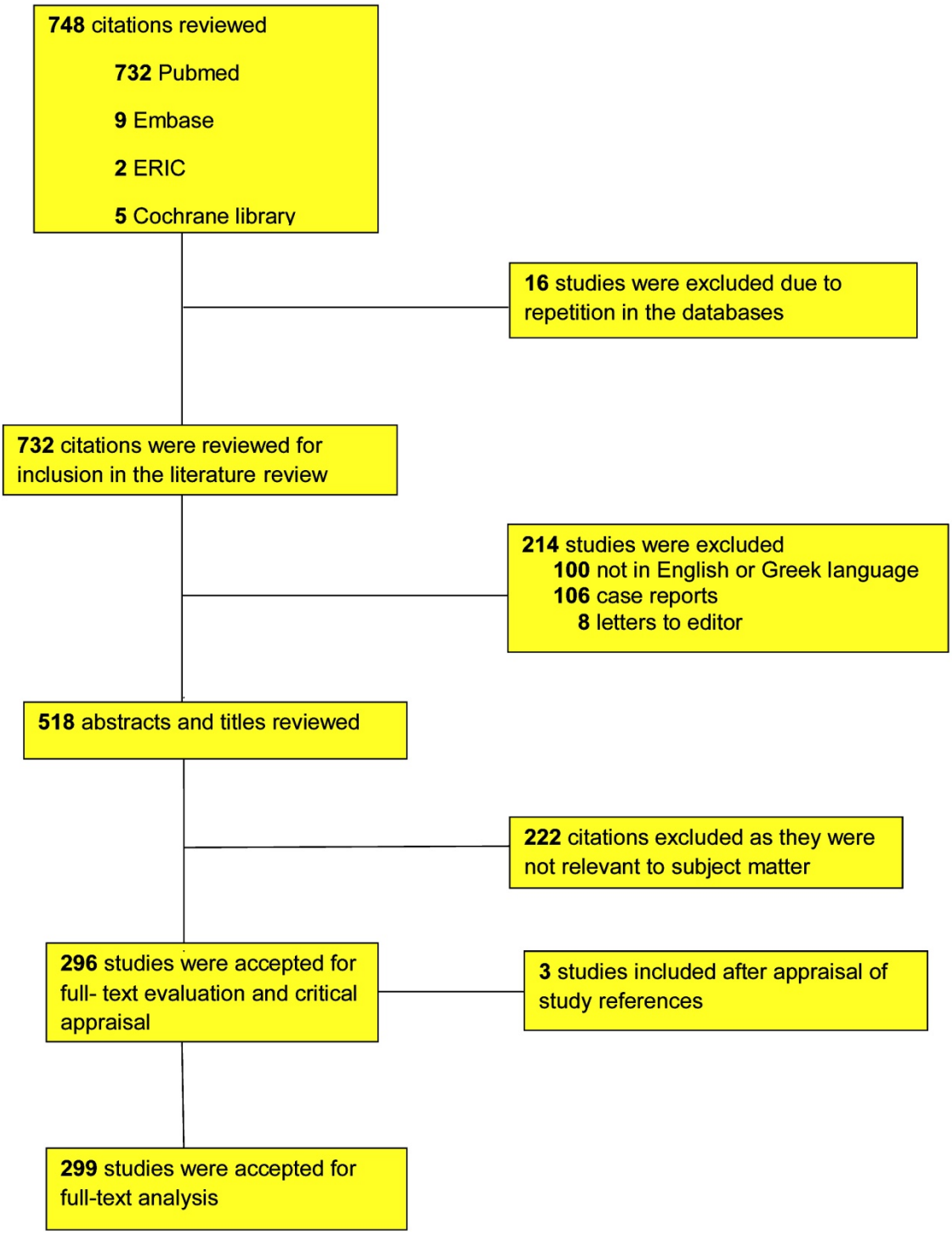

Figure 3. Auditory neuropathy. Literature search selection and identification process for inclusion in the systematic literature review.

The above-mentioned research articles were thoroughly assessed and evaluated to glean the relevant information regarding the prevalence of auditory neuropathy in the adult and pediatric population (Table 1). Until recently, AN was considered to be a very rare disease, however, current evidence demonstrates that this disorder is much more frequent than initially

anticipated. 14 of the articles, included in this review, assessed the prevalence of different adult and pediatric populations in order to discern the distribution and determinants of AN.

Table 1. Classification of Research Articles

Epidemiology	1. Penido & Isaac (31) 2. Bielecki et al (38) 3. Foerst et al. (45) 4. Mittal et al. (46) 5. Maris et al. (47) 6. Tang et al. (48) 7. Duman et al. (156)	8. Lotfi et al. (157) 9. Boudewyns et al. (158) 10. Rosenhall et al. (159) 11. Kumar et al. (160) 12. Vignesh et al. (161) 13. Sanyelbhaa et al. (162) 14. Kirkim et al. (163)
Etiology and Risk Factors	1. Sivera et al. (12) 2. Attias et al. (17) 3. Attias et al. (20) 4. Buchman et al. (23) 5. Starr et al (24) 6. Beutner et al. (25) 7. Coenraad et al. (26) 8. Psarommatis et al. (42) 9. Rajput et al. (49) 10. Shapiro & Nakamura (50) 11. Saluja et al. (52) 12. Akman et al. (53) 13. Liu et al. (54) 14. Kim et al. (55) 15. Xoinis et al. (56) 16. Rance et al. (57) 17. Acar et al. (58) 18. Sawada et al. (69)	19. Ye et al. (73) 20. Olds & Oghalai (74) 21. Starr et al. (146) 22. Rance et al. (164) 23. Shapiro & Popelka (165) 24. Menezes et al. (166) 25. Can et al. (167) 26. Dowley et al. (168) 27. Amin et al. (169) 28. Huang et al (170) 29. Amin et al. (171) 30. Martínez-Cruz et al. (172) 31. May et al. (173) 32. de Paula-Vernetta et al. (174) 33. Rance et al. (175) 34. Shaia et al. (176) 35. Olds & Oghalai (177)
Genetics basis of auditory neuropathy	1. Santarelli (10) 2. Starr et al. (30) 3. Del Castillo et al. (59) 4. Rodrı´guez-Ballesteros et al. (60) 5. Varga et al. (61) 6. Wang et al (62) 7. Kim et al. (63) 8. Manchaiah et al. (65) 9. Varga et al (66) 10. Lang-Roth et al. (67) 11. Morlet et al (178) 12. Rodríguez-Ballesteros et al. (179) 13. Runge et al. (180) 14. Matsunaga et al. (181) 15. Santarelli et al. (182) 16. Han et al. (183) 17. Santarelli et al. (184) 18. Wang et al. (185) 19. Liberman et al. (186)	20. Tang et al. (187) 21. Yildirim-Baylan et al (188) 22. Bae et al. (189 23. Carvalho et al. (191) 24. Gilels et al. (192) 25. Bong et al. (193) 26. Zong et al. (194) 27. Delmaghani et al. (195) 28. Chiu et al. (196) 29. Romanos et al. (197) 30. Grati et al (198) 31. Chang et al. (199) 32. de Carvalho et al (200) 33. Wang et al. (201) 34. Chen et al. (202) 35. Tranebjærg et al. (203) 36. Wang et al. (204) 37. Schoen et al. (205) 38. Silva et al. (206)

Table 1. Classification of Research Articles (continued)

Diagnosis

1. Zeng et al. (2)
2. Starr (4)
3. Rance et al. (6)
4. Rance et al. (7)
5. Zeng et al. (8)
6. Doyle et al. (15)
7. Rance et al. (19)
8. Berg et al (21)
9. Madden et al. (22)
10. Buchman et al. (23)
11. Soares et al. (29)
12. Rance (34)
13. Vlastarakos et al. (36)
14. Mittal et al. (46)
15. Maris et al. (47)
16. Nickisch et al. (51)
17. Akman er al. (53)
18. Kumar & Jayaram (71)
19. Attias et al. (76)
20. Berlin et al. (78)
21. Deltenre et al. (79)
22. Starr et al. (80)
23. Abdala et al. (81)
24. Santarelli R, Arslan (82)
25. Stuermer et al. (83)
26. Gibson & Sanli (85)
27. Ranve et al. (86)
28. Alvarenga et al. (87)
29. Ji & Yang (88)
30. Hood (89)
31. Caldas et al. (90)
32. Rance et al. (93)
33. Shivashankar et al. (94)
34. Sinha et al. (96)
35. Sujeet et al. (97)
36. Roche et al. (101)
37. Mohammadi et al (103)
38. Berlin (105)
39. He et al. (108)
40. Sharma et al. (111)
41. Hayes et al. (115)
42. Shallop et al. (130)
43. Jeong et al. (155)
44. Emara et al. (207)
45. Berlin et al. (209)
46. Jafari et al. (210)
47. Muluk et al (211)
48. Chandan et al (212)
49. Mo et al. (213)
50. Dimitrijevic et al. (214)
51. Takata et al (215)
52. Ngo et al. (216)
53. Berlin et al. (217)
54. Michalewski et al. (218)
55. Sahu et al. (219)
56. Sinha et al (220)
57. Shi et al. (221)
58. Wang et al. (222)
59. James et al. (223)
60. Sharma & Cardon (224)
61. Apeksha & Kumar (225)
62. Shetty & Kooknoor (226)
63. Gardner-Berry (227)
64. Franck et al. (228)
65. Narne et al. (229)
66. Narne & Vanaja (230)
67. McMahon et al. (231)
68. He et al. (232)
69. Wang et al. (233)
70. Riggs et al. (234)
71. Sinha et al. (235)
72. Wynne et al. (236)
73. Oda et al. (237)
74. Wang et al. (238)
75. Michalewski et al. (239)
76. Santarelli et al. (240)
77. He et al. (241)
78. Hood et al. (242)
79. Sanyelbhaa Talaat et al. (243)
80. Cardon et al. (244)
81. Prabhu & Chandan (245)
82. Yalçinkaya et al. (246)
83. Psarommatis et al. (247)
84. Emami & Farahani (248)
85. Lee et al. (249)
86. Prabhu et al. (250)
87. Kumar & Jayaram (251)
88. Apeksha & Kumar (252)
89. Narne (253)
90. Vinay & Moore (254)
91. James et al . (255)
92. Wang et al. (256)
93. Lu et al. (257)
94. Narne et al. (258)
95. Shaheen et al. (259)
96. Zhang et al. (260)
97. Sazgar et al. (261)
98. Sheykholeslami et al. (262)
99. Gates et al. (263)

Pathophysiology

1. Moser & Starr (5)
2. Rance & Starr (11)
3. Cacace & Pinheiro (14)
4. Rance (34)
5. Starr et al. (68)
6. Sawada et al. (69)
7. El-Badry & McFadden (70)
8. Matsumoto et al. (264)
9. Salvi et al. (265)
10. Hong & Kang (266)
11. Rapin & Gravel (267)
12. Lepcha et al. (268)
13. Cowper-Smith et al. (269)
14. Wang et al. (270)

Table 1. Classification of Research Articles (continued)

Management

1. Berlin et al. (3)
2. Rance & Starr (11)
3. Rance et al. (16)
4. Attias & Raveh (20)
5. Madden et al. (22)
6. Buchman et al. (23)
7. Harrison et al. (27)
8. Pham (28)
9. Berlin et al. (33)
10. Teagle et al. (35)
11. Vlastarakos et al. (36)
12. Raveh et al. (37)
13. Madden et al. (39)
14. Zeng & Liu (40)
15. Sininger & Trautwein (41)
16. Psarommatis et al. (42)
17. Pelosi et al. (43)
18. Budenz et al. (44)
19. Rodrıguez-Ballesteros et al. (60)
20. Santarelli et al (72)
21. Boo (75)
22. Gibson & Sanli (85)
23. Alvarenga et al. (87)
24. Hood (89)
25. Declau et al. (102)
26. Walton et al. (104)
27. Roush et al. (106)
28. Gardner-Berry et al. (107)
29. Rance & Barker (109)
30. Cardon & Sharma (110)
31. Hood et al. (112)
32. Nikolopoulos (113)
33. Jeon et al. (114)
34. Hayes et al. (115)
35. Peterson et al. (117)
36. Breneman et al. (118)
37. Jeong et al. (119)
38. Kontorinis et al (120)
39. Humphriss et al. (121)
40. Fernandes et al. (122)
41. Sarankumar et al. (123)
42. Dean et al. (124)
43. Carvalho et al. (126)
44. Shallop (127)
45. Buss et al. (128)
46. Mason et al (129)
47. Runge-Samuelson et al. (131)
48. Fulmer et al. (132)
49. Gibson & Graham (133)
50. Bradley et al. (134)
51. Fontenot et al. (135)
52. Wu et al. (136)
53. de Carvalho et al (137)
54. Ji et al. (138)
55. Nayagam (139)
56. Chen et al. (140)
57. Hang et al. (141)
58. Kim et al (142)
59. Chisholm et al. (144)
60. Liu et al. (145)
61. Daneshi et al. (147)
62. Zdanski et al. (148)
63. Ji et al (149)
64. Neary & Lightfoot (150)
65. Ching et al. (151)
66. Greisiger et al. (152)
67. Jeong et al. (155)
68. Runge et al.(153)
69. Liu (154)
70. Santarelli et al. (184)
71. Giraudet & Avan (190)
72. Kumar & Jayaram (251)
73. Ramirez & Mann (271)
74. Nassiri et al. (272)
75. Stuermer et al. (273)
76. He et al. (274)
77. Pelosi et al. (275)
78. Fernandes et al. (276)
79. de Carvalho et al. (277)
80. Wang et al. (278)
81. Yuvaraj & Jayaram (279)
82. Kaga (280)
83. Attias et al. (281)
84. Mathai (282)
85. Walker et al. (283)
86. Ji et al. (284)
87. Anderson et al. (285)
88. Kim et al. (286)
89. He et al. (287)
90. Shallop et al. (288)
91. Hong et al. (289)
92. Yuvaraj & Mannarukrishnaiah (290)
93. Adams et al. (291)
94. Balan & Maruthy (292)
95. Prabhu & Barman (293)
96. Prabhu & Barman (294)
97. Hosoya et al. (295)
98. Kaga et al (296)
99. Nash-Kille & Sharma (297)
100. Gökdoğan et al. (298)
101. Ji et al (299)
102. Young et al. (300)
103. Narne & Vanaja (301)
104. Mathai & Appu (302)
105. Narne & Vanaja (303)
106. Lee et al. (304)
107. Rance et al. (305)
108. Rance & Barker (306)
109. Narne & Vanaja (307)

Table 1. Classification of Research Articles (continued)

Vestibular Involvement	1. Sinha et al. (96) 2. Sheykholeslami et al (98) 3. Prabhu & Jamuar (99) 4. Fujikawa & Starr (100) 5. Sazgar et al. (261) 6. Nash et al. (310)
AN and Depression	1. Prabhu (311)

Of these research articles 35 bestowed insights on the different etiological factors that may play a role in the development of AN and also shed light on the underlying risk factors associated with this disorder. The etiologies of auditory neuropathy are largely unknown and appear to be diverse, thus, these studies contribute to the evaluation of the independent etiologic factors and the relative contribution of each independent risk factor predisposing individuals to AN.

Moreover, to further enlighten our knowledge on the etiological factors associated with AN, 38 of the studies included, analyze the genetic basis of AN in order to identify the causative genes predisposing to this disorder. One of the challenges contributing to the understanding of the molecular bases of the different phenotypes of hearing loss is the identification of genetic alterations responsible for AN. The above-mentioned studies highlight some of the defective genes that have been found to be related to the pathological auditory alterations.

The complex pathophysiological mechanisms of AN have yet to be fully understood and it has still not been elucidated how lesions in the auditory nervous system from the hair cell to the brainstem and cerebrum contribute to the development of AN. The intricate pathophysiological mechanisms of AN using various approaches such as experimental animal models with AN in order to provide insights into the basic molecular mechanisms of the disorder, was analyzed in 14 research articles. In order to establish the diagnostic assessment required to detect and identify the disease in the adult and pediatric population, 99 research papers investigated the clinical and electrophysiological features of AN. These studies portray the typical physiological and behavioral test results and variations encountered in patients with AN and demonstrate additional investigations that may need to be incorporated to the assessment algorithm, in order to identify concomitant peripheral neuropathies or radiologic

abnormalities helpful in distinguishing among various conditions. The management of patients diagnosed with AN continues to be a challenge as there is no standard treatment due to its heterogeneity and associated concomitant non-auditory factors. The different treatment modalities and management approaches in individuals diagnosed with AN was evaluated in 109 research studies.

The recent literature has mentioned the term audio-vestibular neuropathy, hence 6 articles included in this literature review, also assessed the prevalence and likelihood of vestibular involvement in individuals diagnosed with auditory neuropathy. Only 1 study was found that evaluated the severity of depression and anxiety in the individuals that were diagnosed with this disorder.

3.1 Results for cochlear implantation in auditory neuropathy

The search strategy to the above-mentioned databases for the benefits of cochlear implants in auditory neuropathy patients yielded a total of 211 articles for the allocated time period from January 1990 to January 2019. Figure 4 shows the flow chart for the search selection and strategy for inclusion of studies. Due to the language barrier, 21 studies were immediately excluded as they were not in the English or Greek language. A further 39 research articles were also not included as they were case reports and case studies, leaving a total number of 151 studies to be scoped for subject matter relevance. Following the assessment of the titles and abstracts of the remaining studies, 71 articles were further excluded as they were irrelevant to the subject matter tackled in this review of the literature. Therefore, a total of 80 articles remained to be reviewed and evaluated for relevance in order to answer the posed question in this literature review. A thorough research and analysis of the references of the above-mentioned articles gave another 14 research studies that were applicable to the subject matter of this review report, and therefore were included. Hence, the total of 94 articles was included for assessment and evaluation. A thorough analysis of the full text of each study led to a further 19 exclusions due to unrelated subject matter or studies that did not apply to the posed question. Hence, a total of 75 studies were finally included in the literature review that were applicable to answer the question; what effect does cochlear implantation have on hearing and communication skills in patients diagnosed with auditory neuropathy? A meta-analysis of study findings was not deemed appropriate due to the heterogeneity of the identified studies in terms of design, outcome measures, and quality.

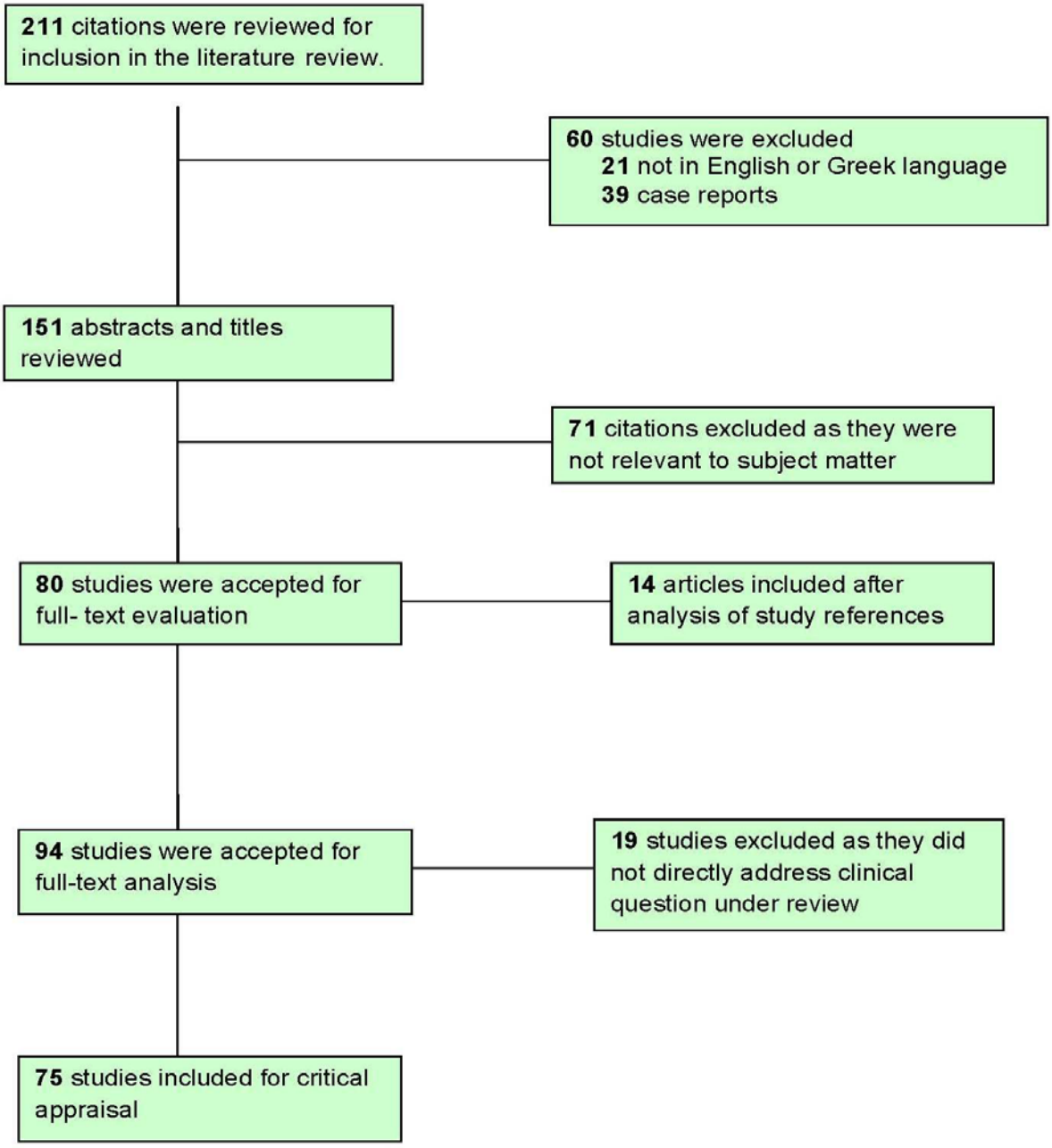

Figure 4. Cochlear implantation in patients with auditory neuropathy. Search selection and strategy for inclusion in the systematic literature review.

The above-mentioned research articles were thoroughly assessed and evaluated to glean the relevant information regarding their results on how cochlear implants affected the hearing and communication skills in patients with AN. Variable conclusions were drawn from different research protocols on the efficacy of CI in AN patients (Table 2.). Regarding the performance of hearing skills in the AN population that underwent CI, the majority of the research studies reported remarkable hearing improvement and speech perception skills. That is to say that a total of 57 articles that were analyzed in this review of the literature, reported a significant advantage in the management of AN with CI.

Table 2. CI outcomes in AN individuals: Substantial benefit.

Substantial benefit from CI	References
Favorable outcomes regarding speech perception skills and audibility in isolated AN individuals	33, 37, 40, 44, 72, 86, 110, 116 -119, 123, 125-129, 136, 142-147, 152
AN/CI children were benefited in the acquisition of hearing skills: sound detection, discrimination, and recognition of words and sentences, with good communication skills.	22, 33, 40, 44, 72, 75, 115, 117-122, 124-127, 129, 132, 133, 136, 142- 147
Implanted AN children performed at a comparable level to their SNHL peers, regarding speech perception and production.	37, 44, 86, 116-119, 120, 122, 123, 132, 142, 143, 151
Changes in pure-tone thresholds in implanted AN individuals.	119, 128, 129
Implanted AN patients demonstrated synchronous neural response to the stimulation delivered through the implant, thus ameliorating temporal processing.	40, 41, 110, 117, 118, 123, 125, 128,129, 132, 146, 152, 190
Aiding the contralateral non-CI ear increases the benefit of CI.	153
Gene related positive CI outcome results.	60, 72, 136
CI is a valid therapeutic alternative in the management of AN.	28, 36, 41, 43, 106, 121, 122, 128, 141, 154,

AN: auditory neuropathy, CI: cochlear implantation, SNHL: sensorineural hearing loss, HA: hearing aid, CND: cochlear nerve deficiency.

The remaining 17 studies demonstrated that although CI offers the possibility of speech perception and improved hearing skills to subjects with AN, the benefit depends on the site of the lesion and confounding disorders. From the total of articles included, 25 reported the inclusion of AN patients without any co-morbidities and 9 studies examined a heterogeneous group of AN subjects with isolated AN and with co-morbidities.

Results indicating positive efficacy of CI in AN patients, from these 57 research studies, included demonstrated; improvement in speech recognition and communication skills, improved hearing thresholds over speech frequencies, elicitation of electrophysiological responses such as electrically evoked auditory brains stem responses (EABRs), evoked compound action potentials (ECAPs), or electrical stapedius reflexes (ESRs). Many studies actually combined the above-mentioned categories of criteria to evaluate CI efficacy in patients of AN in a more comprehensive manner. Hence, 32 studies demonstrated that patients with AN that underwent CI benefited in the acquisition of improved hearing skills (Table 2.). The auditory skills that were developed by these patients were sound detection, discrimination and recognition of words and improvement in sentence understanding. Furthermore, they acquired improved communication skills. Fourteen of the 57 studies compared speech perception in children with AN versus children with SNHL, who were both CI users, and reported that the AN children's progress was near to matched SNHL patients' progress as far as auditory performance was concerned. Changes in pure-tone thresholds in individuals with AN managed with a CIs was reported in 3 of the 57 articles. Furthermore, 13 of these research studies demonstrated that electric signals from the cochlear implant may improve synchronization within the auditory pathway, thus ameliorating temporal processing in AN patients. Thus, the research data portrayed that the elicitation of electrophysiological responses such as EABRs, ECAPs, or ESRs measured postoperatively indicate the of presence of neural synchrony in implanted AN patients. Moreover, 2 studies noted that robust ECAPs measured after CI in AN individuals correlate with development of open-set speech perception. One research article even went one step further and contemplated that an increased benefit of CI in AN patients may be gained by aiding the contralateral non-cochlear implantation ear. Ten reviews of the literature analyzed the up to date published data and concluded that the major body of evidence suggests that cochlear implantation is a valid therapeutic alternative in the management of auditory neuropathy for the improvement of auditory and communication skills in these patients. However, patient selection should be taken with caution in order to achieve optimum post-implantation results.

The 17 research articles that showed skepticism on the efficacy of CI in AN patients (Table 3.) and demonstrated that some patients showed suboptimal performance on auditory

evaluation and hearing skills, mostly stressed the importance of the identification of the site of lesion in order for the benefits of acuity to be gained.

Table 3. CI outcomes in AN individuals: Etiology for limited benefit.

Limited benefit from CI	References
AN/CI children showed no progress in speech recognition, and no subject demonstrated effective social communication.	27, 35, 85,138, 148-150
Significantly better speech perception results in the implanted children with SNHL than the AN subjects.	85, 109
No significant difference in performance levels between AN children who received CI intervention compared to a group who received HA intervention.	109
The presence of another cognitive or developmental disorder significantly adversely affects the CI outcome in AN subjects.	22, 35, 43,44, 75, 120, 124, 132, 151
Anatomical abnormalities of the temporal bone, including CND and enlarged vestibular aqueduct were negatively associated with achievement of speech perception in implanted AN patients.	23, 35, 85, 104, 106, 134, 135, 144, 155,
A reliable prediction of functional outcomes for implanted AN children is presently not possible.	11, 27

AN: auditory neuropathy, CI: cochlear implantation, SNHL: sensorineural hearing loss, HA: hearing aid, CND: cochlear nerve deficiency.

Two of the 17 abovementioned articles noted extremely poor speech perception results in AN patients after CI and further depicted that in comparison with CI users with SNHL, better speech recognition results were gleaned from the SNHL group. The general hypothesis surmised from these studies for the poor efficacy of CI in AN patients is that success of implantation is closely related to the exact site of the lesion responsible for the AN. Limited benefit from CI in AN individuals was reported in 8 research articles as they portrayed that, in spite of fairly good behavioral audiometric thresholds, the patients did not progress appropriately with speech and language development post-implantation. The studies demonstrated that none or limited improvement in speech recognition was achieved and no effective social communication was developed in the AN patients after intervention with CI.

One study compared the efficacy of CI versus HA use in patients with AN and the authors concluded that although CI offers the possibility of speech perception to subjects with AN, some of these individuals can be benefited adequately through the use of HA. Thus, it was duly noted that some individuals with AN do as well with hearing aids as the average implantee. A significant determinant of CI results in AN patients was the presence of another cognitive or developmental disorder which was depicted in 9 of the abovementioned studies. The authors demonstrated that AN individuals with another cognitive or developmental alteration have significant adverse outcomes after CI, and the presence of such a confounding disorder makes it significantly more likely that the subject will not achieve oral modes of communication after implantation and will continue to rely on a non-oral mode of communication. Nevertheless, AN patients with cognitive or developmental disorders do derive some benefit from CI in the form of sound awareness expectations. Nine studies revealed that AN patients presenting with any anatomical abnormalities of the temporal bone, including cochlear nerve deficiency and enlarged vestibular aqueduct, gleaned from magnetic resonance imaging (MRI) and high-resolution computed tomography (CT) scans, were negatively associated with achievement of open-set speech perception after CI. Various pathologies from the auditory nerve to the cerebral cortex, places the site-of-lesion proximal to the IHCs in many of these AN patients. Moreover, 2 reviews of the literature state that a reliable prediction of functional outcomes after CI for patients with AN is presently not possible due to the heterogeneity of the disease, the wide range of functional severity in AN subjects and the developmental and behavioral co-morbidities that may be present.

4. Discussion

4.1. Epidemiology

Initially, AN was considered to be a rare form of SNHL with a frequency of occurrence estimated between 0.23% and 1.3% for the “at risk” clinical population (19, 45). However, recent literature demonstrates that AN prevails in 8% of the newly diagnosed cases of hearing loss in children each year (36). Among children with confirmed diagnosis of permanent SNHL the prevalence of AN reaches 7% and 11% (19, 34, 45) and even as high as 14% (46) and 19% (47). A study conducted in Hong Kong demonstrated that the frequency of occurrence of AN in children attending schools for the hearing impaired was estimated to be 2.44% (48). In a study conducted by Psarommatis et al. 2.2% of high risk infants met the AN profile, of which 14.1% corresponded to infants who failed initial ABR (42). These studies demonstrate that AN is a comparatively common disorder in the population of hearing-impaired individuals which may have been significantly underestimated and undertreated in the past.

4.2. Etiology and Risk Factors

The factors predisposing a child to AN are largely unknown and some of the literature has even indicated that AN can occur in the absence of any other apparent medical condition. Many researchers have come to the conclusion that AN comprises a spectrum of risk factors and associated problems affecting the auditory pathway, rather than being a single etiological entity (25).

The most prevalent etiological risk factors of AN in neonates seem to be hyperbilirubinemia, prematurity and anoxia, as has been repeatedly demonstrated in the literature (19, 22, 39, 49, 50, 51, 52). Akman et al. evaluated whether a correlation between increased serum bilirubin and neuron-specific enolase (NSE) assays (a biochemical index of neuronal damage) and AN exists. He reported a high incidence with 7 out of 19 infants with severe jaundice had findings of AN (53). Madden et al. reported that hearing thresholds can spontaneously improve in certain cases of AN neonates with hyperbilirubinemia, thus, this risk factor may be associated with such a transient behavior of the disease (22).

Cochlear nerve deficiency (CND) may be another significant cause of AN, particularly in the unilateral cases, which may be detected by electrophysiological evidence and MRI of the internal auditory canal (54, 55). CND may present a relatively common diagnosis as denoted

by Buchman et al. (23). Another pathogenetic mechanism of AN in high risk infants seems to be central nervous system immaturity associated with low birth weight (42, 56), hence a study conducted in Honolulu, suggested that a greater risk for AN exists in the smallest, most premature infants (56). Finally, another risk factor for the development of AN in adults and children is diabetes mellitus (57, 58). Rance et al. recently investigated adults with type I diabetes mellitus and performed audiological evaluations. This study demonstrated that 6/10 with Type I diabetes mellitus fit the clinical definition for AN (57).

4.3. Underlying Genetic Basis of Auditory Neuropathy

40% of AN is estimated to be due to an underlying genetic basis with autosomal-dominant, autosomal-recessive, mitochondrial and X-linked inheritance all being reported (59). Even though transmission of these genetic disorders is heterogeneous, the predominant form of transmission is the autosomal recessive mode (22, 60, 61). Some research has also discovered X-linked recessive and autosomal dominant patterns of genetic transmission in AN, but these individuals present with a more delayed symptom onset (62, 63).

At present, four causative genes associated with non-syndromic AN have been mapped, although other genetic aetiologies will surely be unmasked in the future. The known genes are: the otoferlin (OTOF) gene, the pejvakin (PJVK) gene, the diaphanous-3 (DIAPH3) gene and AUNX1, linked to chromosome X. Furthermore, mutations of connexin 26 (GJB2) have also been linked with the disease (64, 65).

Genetic research has demonstrated that non-syndromic recessive auditory neuropathy (NSRAN) is linked with mutations in the otoferlin gene, which encodes the protein otoferlin at the molecular level, with the ensuing hearing loss (66). A study conducted by Kim et al. found the first locus responsible for autosomal dominant AN (63). In 2017, a second locus for autosomal-dominant AN (AUNA2) was discovered which is also associated with a slowly progressive postlingual hearing loss without any evidence for additional symptoms in other organ systems (67).

4.4. Pathophysiology of Auditory Neuropathy

The pathophysiological mechanisms and the underlying lesion(s) in AN are the basic points needed to understand and treat this disorder, however, the up to date evidence remains

ambiguous and, in some cases obscure. Most of the data gleaned from clinical and electrophysiological research portray that AN is a spectrum of pathologies and not a single disease entity (25).

4.4.1. Presynaptic mechanisms of auditory neuropathy

The cochlear IHCs are the initial point of contact between the auditory nerve and sensory mechanism. Thus, the loss or disorders of cochlear IHCs would likely compromise and degrade neural synchrony. This in turn leads to changes in temporal patterns of discharge and overall amplitude alterations, which are plausible pathophysiological mechanisms accounting for the electrophysiological and psychoacoustic changes found in AN (68). Experimental animal studies have also demonstrated IHC- susceptibility to mild, long-term hypoxia, which in turn, may be an etiologic factor in the presentation of AN, particularly in high-risk birth infants (69). It is interesting to note however, that El-Badry et al. demonstrated that substantial IHC and auditory nerve fiber losses do not produce dys-synchrony of CAP or ABRs, and are therefore unlikely to be sufficient pathologies underlying AN (70).

Disorders involving the IHC ribbon synapses could involve alterations in the timing and magnitude of transmitter release and/or the availability of receptor sites on the nerve terminals of the afferent nerve (68). Therefore, a major cause of abnormal ABRs in neonates diagnosed with AN is the shortfall of neurotransmitter release from the IHC ribbon synapses (59). Furthermore, an abnormal hair cell/VIIIth nerve functional unit may cause a perisynaptic synchronization disorder which in turn will lead to temporal processing deficits (71).

4.4.2. Postsynaptic mechanisms of auditory neuropathy

Impairment of auditory nerve function can occur at multiple sites along the auditory nerve. An example of terminal dendritic abnormality, due to OPA1 gene mutation, portrays a pattern of objective measures similar to those outlined for ribbon synapse disorders, thus consistent with AN (72). Another possible pathologic mechanism responsible for AN is the inadequate myelination of neural fibers of the auditory nerve. Although these nerve fibers are ultimately capable of conducting action potentials, they are characterized by delayed excitation and impaired capacity to transmit high-frequency neural signals, due to prolonged refractory periods of transmission (11, 36).

Another potential pathologic mechanism accountable for AN is axonal neuropathy of the auditory pathways (34). It is of significance to note that myelin and axonal impairments that

can lead to the development of AN often occur as part of generalized neuropathic disorders, such as Charcot-Marie-Tooth disease, which typically presents with a delayed onset of symptoms (11, 36). Moreover, another potential mechanism resulting in AN is the loss of SGNs. SGNs may be affected as both a primary and a secondary effect of gene mutations (68) or may be compromised by hyperbilirubinaemia in neonates, due to their susceptibility to adverse metabolic factors (73, 74).

Irrespective of the etiology of the AN phenotype, it appears that a common pathophysiologic mechanism predominates. More insights into basic molecular mechanisms of AN will be gained with the continual research of experimental animal models which in turn will lead to the development of adequate treatment strategies.

4.5. Diagnosis

The AN profile is defined by the OHC integrity in evoked OAEs and/or CMs in conjunction with the inability to record evoked neural activity at the level of the VIII nerve (CAP) and brainstem (absence of ABR waveforms), altered acoustic reflexes and impaired speech perception, disproportional to the PTA. For timely detection and intervention in children, both OAE and ABR should be carried out on all newborns and infants. Similarly, these same tests should be carried out in children and adults complaining of having difficulty in understanding speech (75). Although, it should be noted that even with the above diagnostic protocol an accurate diagnosis is not always easy.

ASSR (auditory steady-state responses) to multiple simultaneous stimuli is another examination normally carried out on children, which ordinarily correlates well with hearing thresholds in cases of normal hearing and SNHL (76, 77), however, the same does not occur in AN individuals (3, 4). Even though the definition of AN is widely accepted in principle, some exceptions and variations in electrophysiological testing have been depicted in the AN patient population. Firstly, CM's in patients with AN have been observed to be explicitly prominent and to persist several milliseconds after a transient click stimulus (78), findings not detected in normal-hearing individuals. Secondly, up to 30% of ears, which otherwise fulfill criteria for AN, may not present with transient evoked otoacoustic emissions (TEOAEs) (4, 19, 79). Thirdly, AN subjects also exhibit gradations of the degree of hearing impairments, as approximately 20% of these individuals may present with a low-amplitude wave V in their ABRs, which in turn indicates the partially preserved neural synchrony seen in these patients (80).

Regarding the absence of OAE's it is significant to note that behavioral audiograms do not seem to deteriorate with the absence or disappearance of OAEs (79), thus no correlation exists between presence or absence of OAEs and behavioral hearing thresholds in AN children (19, 80). Moreover, the disappearance of OAE's during the course of AN has been noted in the literature (79, 80) thus, the presence or absence of OAE's alone is not necessarily linked with the existence of potentially contributing factors (24). A more specific method to differentially diagnose AN is with contralateral suppression using white noise, where the reduction in either DPOAE or TEOAE amplitude is unequivocally absent in these patients (4, 81). Another useful diagnostic tool that may be implemented to diagnose AN subjects is electrocochleography (ECochG). Electrocochleography measures the electrical potentials that are generated in the auditory pathway after sound stimulation. Three response components are recorded in ECochG: 1) CMs, 2) summating potential— SP, 3) CAP. This procedure is reliable in evaluating the auditory peripheral function in the presence of a desynchronized ABR (82). ECochG is the most appropriate method for evaluating cochlear function, and thus assisting CM identification which in turn reflects the integrity of cochlear hair cells, therefore, supports an audiological diagnosis of AN (34, 82, 83). OHC pathology cannot be excluded, especially in the absence of recordable OAEs, thus, OHC integrity should not necessarily be deduced from the presence of the CMs alone (84). A study conducted by Gibson et al. using round window electrocochleography and EABR discovered that the presence of an atypical waveform representing an early positive SP, combined with an absence of EABR responses, depicts children most likely experiencing a true neuropathy (85).

Additionally, other studies used cortical auditory evoked potentials to determine the relationship between these responses and speech perception in AN individuals (86, 87). The P1 component of long latency auditory evoked potentials can serve as a marker of central auditory cortical development and a predictor of the child's potential for speech perception; therefore, it could be utilized as a clinical tool in AN subjects, to guide management interventions and to evaluate the effectiveness of the treatment modality (87).

The least informative measures in the evaluation of AN patients are pure-tone thresholds and speech recognition, especially in quiet. Audiometric findings among AN subjects, reported in the literature, vary from mild and moderate in most cases (19, 88, 89) to profound in others (90). AN patients with mild to moderate audiometric findings, tend to have word recognition scores, especially in the presence of noise, disproportionately poorer than expected by audiometric thresholds (91). The data gleaned from the recent literature demonstrate that speech recognition abilities in individuals diagnosed with AN can range from poor to fairly good recognition ability (7, 33, 92). Both adults and children with AN have severely affected

speech perception in noise skills (93) and data has shown significantly poor performance on the dichotic digit test in children able to manage auditory stimuli in quiet conditions (94).

The classic clinical triad of audiological findings in AN is further supplemented by the absence, or threshold elevation of acoustic reflexes to both ipsilateral and contralateral tones (3, 46, 89). In neonates and infants up to six months of age the presence of reflexes at levels near 90 dB HL should not result in a diagnosis of AN, as they are not deemed reliable at such a young age (33, 95).

Vestibular involvement in AN patients has also been reported in the literature and authors have demonstrated that it is likely that auditory neuropathy involves both the cochlear and vestibular nerve and its innervated structures, thus vestibular evaluation may be appropriate in certain AN cases (96- 100).

The up to date literature has strongly suggested that MRI evaluation be incorporated in the assessment algorithm of all children diagnosed with AN, as many of the CNS findings identified in MRI can alter the treatment and prognosis for these children (101, 102). Mostly, the imaging characteristics in AN are typically normal, yet Roche et al. reported that up to 18% of their child population diagnosed with AN, showed evidence of cochlear nerve disorders in MRI examination (101). A significant need to implement MRI as a diagnostic tool arises, when there is a syndromic profile present and when there is electrophysiological evidence of unilateral AN in association with a profound hearing loss, as there is a distinct possibility of CND in these patients (23, 103).

Finally, genetic testing for mutations of the OTOF gene may be proposed to supplement the assessment algorithm, especially in cases of prelingual children presenting with the AN phenotype in the absence of a neurological syndrome (60). These cases of non-syndromic AN can be detected at a molecular level and finding the genetic cause has important implications for treatment options and prognosis (10, 61).

It has been made clear that it is imperative for diagnostic techniques to be developed in order to better identify both the site of lesion and degree of abnormality in each AN patient, which in turn will lead to optimum treatment options and outcomes in these patients. MRI is helpful for children with hypoplasia, but is not diagnostically practical for other types of AN. Even though EABR measurement does not identify the site of lesion and the patient must have already undergone the invasive procedure of CI, a positive response is strongly associated with favorable CI outcomes (104), thus, making this examination necessary in AN implant patients.

4.6. Treatment modalities and outcomes

Due to the variation in clinical presentation across individuals with AN, the need for individualized and refined management strategies arises (19). The development of auditory and communication skills in children with prelingual onset of AN is of utmost importance, but the implementation of the appropriate treatment interventions are very challenging for the clinician. Having all of the above in mind, many studies aimed to glean the potential of optimum outcomes from the various management interventions such as; ameliorating signal-to-noise ratio, the amplification of the acoustic signal and improvement of speech audibility with the use of conventional HAs, improvements in hearing skills and development of auditory and speech skills in children using CIs.

4.6.1. Amplification

The American Academy of Audiology (AAA) Pediatric Amplification guidelines state that children with AN should undergo a HA trial when the evaluated auditory thresholds are inadequate to support speech perception at levels of conversation. However, very few studies, examining speech perception, or literacy outcomes for children with AN who use HAs, have been published and some of these reports have observed poor outcomes with this intervention. A study conducted by Berlin even advised that HA are not adequate treatment for AN subjects simply because they are designed to compensate for missing OHCs and in this disorder OHCs are presumably normal (105). Thus, there may be an improvement in sensitivity (86) but no improvement in speech or language acquisition as AN subjects have temporal processing difficulties, which are strongly related to speech discrimination ability (7). Current HA technology has not been able to enhance the temporal envelope of the speech signal to compensate for temporal processing deficits associated with AN. Regardless of the lack of elucidating evidence at present (106), the general practice is to implement a trial of amplification with HA in order to provide appropriately audible signals for AN individuals who display reduced threshold sensitivity. Determining threshold sensitivity in young infants is a challenge, thus clinicians rely on ABR data and lately cortical responses seem to show promise in this evaluation (107, 108). Unlike the published data by Deltenre et al. (79) and Rance et al. (109) which stated favorable outcomes with the use of HA in quiet, only 15% AN-hearing aid users were successful in a study conducted by Berlin et al. (33). There seems to be a subset of children, yet to be determined, who show improvement in puretone detection thresholds, and who furthermore benefit in their speech-perception abilities from HAs (106), probably due to some preserved neural synchrony (110). A significant finding in a study by Sharma et al. was that a third of the AN patient population with HAs continued to exhibit

abnormal auditory cortical development, as was depicted in their cortical auditory evoked potential (CAEP) latencies. This in turn enhances the notion that these children had more severe auditory neural dys-synchrony, therefore did not benefit from the amplification of sound by HAs (111)

Thus, after having adequately informed the parents about the child's condition, the tremendous variations possible among patients, and the alterations that may appear in some children's audition over time (3), it is justified to suggest and provide conventional amplification to enhance lucid speech as an initial intervention, or during a trial period before CI (15, 19).

4.6.2. Frequency Modulation Systems

Similarly, the use of FM systems alone or in conjunction with other devices in noisy surroundings, such as classrooms or restaurants might be helpful to AN subjects. This management intervention provides an improved signal-to-noise ratio, whilst presenting minimal risks to surviving OHCs, thus aiding the AN listener with poor speech perception in noise (39, 112).

4.6.3. Cochlear Implantation

A continuously increasing plethora of evidence suggests significant advantages of CI in the management of AN (39, 113, 114, 115). Research has portrayed that both child and adult populations with AN demonstrate significant benefit from cochlear implants (Table 4.), as they present with improved sound detection and discrimination, enhanced recognition of words and sentences, thus improved speech perception in quiet and in noise and better communication skills (40, 116, 117, 118). Presently, the management of AN with cochlear implantation has become widely accepted, even though the evidence is still quite sparse and limited to case series with limited or no controls (28). Successful outcomes were portrayed in all the studies that examined audibility and speech perception progress in isolated AN patients, that is without the presence of comorbidities (33, 40, 72). Peterson et al. reported that 9 out of the 10 implanted children with isolated AN, displayed considerable improvement according to parental report using the IT-MAIS (Infant-Toddler Meaningful Auditory Integration Scale) or MAIS (Meaningful Auditory Integration Scale) questionnaire. The authors reported that the 10nth child lived in a foreign country and thus did not have post-operative data (117).

Table 4. Substantial benefit from CI in AN patients.

Citation	N	Risk Factors/Comorbidities	Previous interventions	Reported outcomes	Remarks
Berlin et al. (33)	AN-CI: 49 Total: 260	Hyperbilirubinemia/anoxia/ prematurity (n-74) Genetic (n-41), Peripheral neuropathies (n-20)	HA (27/49 implanted patients)	a) Improvement in speech comprehension & language acquisition in 85% (42/49) of implanted patients, b) 4/49 recently implanted so no outcome data available yet.	13/260 (5%) required NO intervention for hearing or developing speech and language, although all reported trouble hearing in noise.
Zeng & Liu (40)	AN-CI: 7 Total: 13	Hereditary (n-2) Hyperbilirubinemia (n-1) Peripheral neuropathies (n-2)	Not mentioned	81% and 67% correct scores in clear and conversational speech perception in quiet, respectively. 84% and 66%, respectively in noise.	Binaurally combined acoustic and electric stimulation yielded significantly better speech scores in quiet backgrounds, but not in noisy backgrounds.
Budenz et al. (44)	AN-CI: 26 SNHL (control): 17	Hyperbilirubinemia (n-10) Prematurity (n-13) Global developmental delay, autism, microcephaly & cerebral palsy (n-9)	HA (all patients)	a) AN patients with cognitive or developmental disorders (9/26) performed significantly poorer as compared with those of children with isolated AN (17/26), b) Isolated AN subjects performed comparably to their peers with SNHL in speech perception category scores.	AN subjects with cognitive or developmental disorders did derive some benefit from CI in the form of sound awareness.
Madden et al. (22)	AN-CI: 4 Total: 22	Hyperbilirubinemia (n-11) Prematurity (n-10) Hereditary (n-8) Anoxia (n-8) Cerebral palsy: (n-2) Ototoxic drug exposure: (n-9)	HA &/or FM system (16/22 patients)	Significant improvement in auditory and communication skills.	a) No amplification required in 4/22 (18%) due to spontaneous improvement, b) 2 subjects too young to determine intervention required.

AN: auditory neuropathy, CAP: categories of auditory performance, CI: cochlear implants, ECAP: electrically evoked compound action potential, ESP: early speech perception, FM: frequency modulated system, HA: hearing aids, MAIS: meaningful auditory integration scale, OPA1: Optic atrophy 1, SGN: spiral ganglion neurons, SNHL: sensorineural hearing loss, SRT: speech recognition thresholds.

Table 4. Substantial benefit from CI in AN patients (continued).

Citation	N	Risk Factors/Comorbidities	Previous interventions	Reported outcomes	Remarks
Santarelli et al. (72)	AN-CI: 8	OPA1 missense mutations (n-8)	Not mentioned	a) Mean disyllable recognition scores (in quiet) increased from 16% before CI to 72% after 1-year's experience with CI (7/8), b) Mean disyllable recognition scores (in noise) increased from 7% before CI to 53% after 1-year's experience with CI (7/8).	a) OPA1 mutation causes degeneration of terminal dendrites early in the disease, b) Demyelination & axonal loss may become prevalent at an advanced stage.
Peterson et al. (117)	AN-CI: 10 SNHL (control): 10	None mentioned	Not mentioned	a) 18/20 children made progress on the post- operative ESP test.6 AN children and 5 SNHL control children moved from 0% to 100 % at least within one subtest of the ESP, b) No major differences in speech perception measures between the two groups.	a) 1 AN child spoke only Arabic, so could not take the test, b) 1 SNHL control child had not yet reached a language age to be able to take the test.
Breneman et al. (118)	AN-CI: 35 SNHL (control): 35	Hyperbilirubinemia (n-16) Genetic (n-7) Prematurity (n-1) Infections (n-1)	HA (all patients)	a) 32 (91%) AN children achieved some degree of open-set word recognition ability, b) Similar long-term outcomes on measures of speech recognition between AN and SNHL groups.	5 AN children (8%) made on-going progress with hearing aids.
Jeong et al. (119)	AN-CI: 9 SNHL (control): 12	Hyperbilirubinemia (n-2) Abnormal vestibular results (n-8)	HA (all patients)	Postoperative speech perception abilities in AN children are comparable to SNHL children (CAP, p: 0.1200; Common Phrases test, p: 0.3337).	SGN cells may be comparable in the two groups as ECAP amplitude growth functions (p: 0.970) are similar among them.

AN: auditory neuropathy, CAP: categories of auditory performance, CI: cochlear implants, ECAP: electrically evoked compound action potential, ESP: early speech perception, FM: frequency modulated system, HA: hearing aids, MAIS: meaningful auditory integration scale, OPA1: Optic atrophy 1, SGN: spiral ganglion neurons, SNHL: sensorineural hearing loss, SRT: speech recognition thresholds.

Table 4. Substantial benefit from CI in AN patients (continued).

Citation	N	Risk Factors/Comorbidities	Previous interventions	Reported outcomes	Remarks
Buss et al. (128)	AN-CI: 4	Mondini dysplasia (n-1)	HA (all patients)	Speech data were comparable with those obtained from the general pediatric population receiving CI	Relatively poor performance on auditory tasks of one subject due to the parents' continuous use of manual communication after implantation.
Kontorinis et al. (120)	AN-CI: 27	Cognitive disorders(n-4) Autism (n-3) Dyspraxia (n-1). Hemiplegia (n-1)	HA (all patients)	a) All AN patients demonstrated improved speech perception scores following CI, even in the long run, b) No statistical difference between CI outcomes in patients with and without AN	a) Cognitive disorders are a significantly negative prognostic factor for CI outcome, b) Three subjects had fluctuating post-CI outcomes.
Dean et al. (124)	AN-CI: 27	Hyperbilirubinemia (n-5) Prematurity (n-5) Perinatal hypoxia (n-1) Enlarged vestibular aqueduct (n-1) Hydrocephalus (n-2) Autism (n-1) Congenital anomalies (n-1) Plagiocephaly/microcephaly (n-1) Developmental delays (n-3)	HA (all patients)	a) Improved speech perception performance after CI in 20 (74%) AN patients, b) Several medical comorbidities that were examined showed no statistically significant difference between the good and bad CI performers	a) Poor performers had later age of implantation, lower socioeconomic status, and lack of family support, b) Bilateral implantation in the poor performing AN patients may prove beneficial.

AN: auditory neuropathy, CAP: categories of auditory performance, CI: cochlear implants, ECAP: electrically evoked compound action potential, ESP: early speech perception, FM: frequency modulated system, HA: hearing aids, MAIS: meaningful auditory integration scale, OPA1: Optic atrophy 1, SGN: spiral ganglion neurons, SNHL: sensorineural hearing loss, SRT: speech recognition thresholds.

Table 4. Substantial benefit from CI in AN patients (continued).

Citation	N	Risk Factors/Comorbidities	Previous interventions	Reported outcomes	Remarks
Shallop et al. (125)	AN-CI: 5	None mentioned	HA (all patients)	a) Significant improvements in sound detection, speech perception abilities and communication skills in all of the implanted AN children, b) All implanted children moved from category 1 ESP preoperatively, to category 4 postoperatively, c) Children were able to talk on telephone	No comorbidities or additional neurological disorders present.
Carvalho et al. (126)	AN-CI: 18	Neonatal diseases (n-9) Congenital rubella (n-1)	HA (all patients)	a) Significant improvements in hearing abilities in 94% implanted AN subjects, b) Closed set speech recognition - 61% of subjects; open set speech recognition - 33% of subjects; and detection of sounds only in 6% of subjects.	Speech perception results were better the longer the CI were used.
Mason et al. (129)	AN-CI: 6	Measles encephalitis (n-1) Hyperbilirubinemia (n-2) Ototoxic drug exposure (n-1) Genetic (n-1) HIV & cryptococcal meningitis (n-1)	HA (all patients)	a) Improved speech awareness and developing speech skills in 4/6 AN patients after implantation, b) 2/6 patients have not been implanted yet.	a) Post-implantation outcomes not available for all reported subjects, b) Auditory perception on promontory stimulation is valuable in adult patient evaluation before CI.

AN: auditory neuropathy, CAP: categories of auditory performance, CI: cochlear implants, ECAP: electrically evoked compound action potential, ESP: early speech perception, FM: frequency modulated system, HA: hearing aids, MAIS: meaningful auditory integration scale, OPA1: Optic atrophy 1, SGN: spiral ganglion neurons, SNHL: sensorineural hearing loss, SRT: speech recognition thresholds.

Table 4. Substantial benefit from CI in AN patients (continued).

Citation	N	Risk Factors/Comorbidities	Previous interventions	Reported outcomes	Remarks
Fulmer et al. (132)	AN-CI: 10 SNHL (control): 10	Mondini dysplasia (n-1) Hyperbilirubinemia (n-3) Hypoxia (n-3) Prematurity (n-4) Autism (n-1) Perinatal infection (n-1)	Not mentioned	Comparable SRTs in quiet and in noise in children with AN compared to children with SNHL.	Slower neural recovery observed in some AN subjects.
Wu et al. (136)	AN-CI: 10 SNHL (control): 183	Biallelic OTOF mutation (n-10) Biallelic *GJB2* mutations (n-25) Biallelic *SLC26A4* mutations (n-23)	Not mentioned	Mean speech discrimination score in AN patients, 3years post-implant was 77.5±37.1, which was comparable to patients in the control group.	a) No spontaneous recovery in hearing thresholds or ABR with age in the OTOF mutation AN patients, b) CI should be performed in these patients without delay.
Kim et al. (142)	AN-CI: 6 SNHL (control): 4	None mentioned	Not mentioned	a) Comparable ECAP recovery function in children with AN and children with SNHL, b) Robust ECAP responses presented with good speech perception scores	Implanted AN subjects with robust ECAP responses performed as well as or even better than the 78 implanted children with SNHL
Schramm & Harrison et al. (143)	AN-CI: 16 SNHL (control): 32	NICU admission (n-10) Genetic (n-2) Syndromic (n-2)	HA (all patients)	Similar outcome results in auditory skills and speech perception among AN subjects and age-matched SNHL patients	CI should be considered in AN patients if conventional amplification fails

AN: auditory neuropathy, CAP: categories of auditory performance, CI: cochlear implants, ECAP: electrically evoked compound action potential, ESP: early speech perception, FM: frequency modulated system, HA: hearing aids, MAIS: meaningful auditory integration scale, OPA1: Optic atrophy 1, SGN: spiral ganglion neurons, SNHL: sensorineural hearing loss, SRT: speech recognition thresholds.

Table 4. Substantial benefit from CI in AN patients (continued).

Citation	N	Risk Factors/Comorbidities	Previous interventions	Reported outcomes	Remarks
Chisholm et al. (144)	AN-CI: 5	Thin or small cochlear nerve (n-5)	Not mentioned	Delayed development of spoken speech and language in some AN children (4/5) with compromised auditory nerves may be achieved after CI	Results beyond 2 years were not available for one of the children.
Shallop (127)	AN-CI: 10 (children) AN-CI: 2 (adults)	None mentioned	HA (1 adult patient)	a) 8 to 91% improvement in MAIS for all the AN children, b) Improved speech recognition and communication in the AN adults	CI restores neural synchrony in AN patients who then progress in their speech and language skills development
Liu et al. (145)	AN-CI: 10	None mentioned	Not mentioned	All implanted AN children developed time-related auditory perception and speech skills	AN children implanted before 24 months tended to acquire better auditory and speech skills than children implanted after 24 months
Starr et al. (146)	AN-CI: 3 Total: 5	Genetic (n-5)	HA (all patients)	Improved speech recognition in all implanted AN patients	Conclusions should be viewed as suggestive due to the small number of patients implanted
Daneshi et al. (147)	AN-CI: 136	Not documented in the study	HA (all patients)	a) Significant improvement in auditory perception ability in implanted AN individuals, b) No significant difference between CI outcomes in patients with and without AN.	a) Auditory performance and speech production depend on age of implantation, b) Long-term outcomes not available for all patients, due to the retrospective nature of study.

AN: auditory neuropathy, CAP: categories of auditory performance, CI: cochlear implants, ECAP: electrically evoked compound action potential, ESP: early speech perception, FM: frequency modulated system, HA: hearing aids, MAIS: meaningful auditory integration scale, OPA1: Optic atrophy 1, SGN: spiral ganglion neurons, SNHL: sensorineural hearing loss, SRT: speech recognition thresholds.

The results from a study by Breneman et al. on 35 subject pairs demonstrated that children with AN can definitely benefit from CI and that their long-term outcomes are equivalent to matched peers with SNHL, on speech recognition measures (118). This research article excluded the AN patients with significant cognitive and global developmental delays from their implant population, in order to glean the outcome results of isolated AN subjects, but they did note that even these patients benefit from CI as it provides awareness of sound and improves quality of life according to the parents. Jeong and colleagues also excluded comorbidities such as mental retardation and developmental disorders in their AN patient population and denoted that CI outcomes regarding speech perception abilities in these patients were similar to non-neuropathic SNHL subjects (119).

Among the studies reviewed in this literature review, some compared speech perception in CI-children with AN versus children with SNHL. The majority of these studies denoted that auditory performance in AN patients after CI was comparable to that of the children with SNHL using CI, presenting with similar results in speech perception tests. Successful outcomes have been shown in a study conducted by Kontorinis et al. where 27 children implanted at a mean age of 35.4 months had statistically significant improvement in speech perception and language development similar to implanted children with SNHL (120). The authors did note, however, that their 4 patients with cognitive disorders (3-autism, 1-dyspraxia, 1-hemiplegia) performed worse than children with isolated AN, even though they did gain some benefit from implantation (120).

Humphriss et al. conducted a systematic review that concluded that most children with AN achieved open-set speech after implantation and that the resulting outcomes were comparable to implanted SNHL individuals. Nevertheless, the authors denoted that although currently available evidence demonstrates favorable outcomes from CI in AN children, the data is weak and stronger evidence is needed to support the effectiveness of this intervention (121). A systematic review, conducted by Fernandes and colleagues, evaluated the performance of hearing skills in children with AN after CI, and after the appraisal of 18 articles and two dissertations, concluded that noteworthy improvement in speech perception skills, equivalent to cochlear implantation outcome of children with SNHL, is denoted in the literature (122). Finally, a recent study by Sarankumar et al. demonstrated that CI, in the 10 AN children that were assessed, showed significant benefit in hearing perception and speech outcomes at one year post-surgery. The authors also displayed that the speech outcomes after CI in AN children are comparable with children having profound cochlear loss (123).

On the other hand one study demonstrated that AN patients presented with poorer auditory performance than SNHL patients after implantation. This report by Rance et al. denoted that the children with SNHL using CI performed significantly better ($p = 0.02$) compared to the three groups of children with AN (CI users, HA users, and CI + HA users). Thus, the authors concluded that even though CI offers the possibility of speech perception to subjects with AN; some individuals may benefit from conventional amplification with HAs (109). The vast majority of the studies published in the literature, to date, indicate that AN children implanted with CI are benefited in the acquisition of hearing skills, which in turn leads to improved communication skills (124, 125). An early study by Shallop et al. demonstrated that the 5 children with isolated AN, managed with CIs had successful outcomes, as they showed improved communicative abilities after implantation (125). Encouraging results were also gleaned from a study conducted by de Carvalho et al. as it was noted that the hearing abilities of 94% of their 18 study subjects improved significantly and that speech perception results were better the longer the CIs were used (126). A retrospective review by Berlin et al. evaluated and summarized the management data of 260 AN patients, of which 85 of these subjects had HA and 49 patients tried CI. The authors reported that 85% of patients who were implanted presented with improved speech comprehension and language acquisition, whereas only 15% reported some benefit from HA. It was also noted that normal speech and language developed without intervention in approximately 5% (13/260) of the total population (33). Teagle et al. included 140 patients with AN in their study and reported that 50% of their subjects successfully achieved open set speech recognition after CI. It is of significance to note that 42% of the studied patient population was born prematurely and suffered from a variety of medical comorbidities and 38% had abnormal findings on preoperative MRI of the brain and inner ear. Thus, it is feasible that the authors concluded that poor outcomes were accounted for by the concurrent medical and cognitive comorbidities in the patient population and the lack of neural synchronization (35). It is important to note that definitive conclusions cannot be made, regarding speech perception outcomes in CI-AN subjects, as studies varied greatly in type of speech perception measures reported and the heterogeneous patient populations included, thus, making it difficult to interpret the results among studies.

It is of interest to mention that even AN patients with mild to moderate pure-tone threshold average, yet poor speech intelligibility, benefit from CI in significantly improved conversational speech discrimination post-surgically. A study by Zeng and Liu (40) demonstrated that in their AN patient population with CI one patient suffered from poor speech intelligibility (60% clear speech, 45% conversational speech), even though the pure-tone threshold average (31-40dB) was mild to moderate, benefitted significantly from CI in clear and conversational speech discrimination (80% clear speech, 70% conversational

speech). Furthermore, these results were further improved in quiet backgrounds with binaurally combined acoustic and electric stimulation. There is a scarcity of published data specifically regarding AN patients with milder hearing loss undergoing CI, but if residual hearing with good audibility is ultimately not useful in facilitating communication, it is reasonable to suggest that these patients might improve with CI (115). Shallop also reported a patient with mild to moderate hearing loss in both ears, who received a CI unilaterally and demonstrated improved word recognition scores and better speech discrimination in noisy environments post-surgically (127).

Theoretically, the electric signals from the CI may improve synchronization within the auditory pathway in AN subjects, as is evident with the synchronous neural responses in EABRs and neural response telemetry (40, 41, 128, 129), thus ameliorating temporal processing in these patients. The evoked potential measures, taken in the pre-operative, intraoperative, and postoperative settings, demonstrate that the restoration of neural synchrony or the increased number of responding neurons probably occur at multiple levels of the auditory pathways in AN individuals . The extent to which cochlear implants can overcome poor neural synchrony, however, is still under investigation (130, 131, 132). The literature has deemed the implementation of intraoperative electrophysiological measures, such as ECAP and EABR, competent measures to predict the expected outcome of CI surgery in AN children (35, 104, 118). Although, it is of significance to note that the presence of normal EABR/ECAP measurements does not necessarily guarantee success with implantation as these measures reflect an intact auditory pathway at the level of the brainstem and do not measure higher cortical responses (118). A study by Gibson and Sanli portrayed better speech perception scores in AN CI-candidates than their SNHL peers at 1 and 2 years post-CI when AN subjects displayed normal intraoperative electric ABR waveforms ($p < 0.01$ and 0.05, respectively) and significantly worse outcome results when the intraoperative EABR waveforms were abnormal (85). Gibson and Graham in an editorial elucidating the myths and facts of cochlear implantation in AN subjects, stated that normal EABR waveforms indicate that in most ears (75%), the disorder is due to loss of IHC with survival of OHC leading to dys-synchrony of the basilar membrane, therefore benefitting from CI. In the other 25% the hair cell dys-synchrony correlates to an abnormality of the neural pathway, thus achieving only limited speech perception scores post-CI (133).

Needless to say, if there is a presynaptic lesion or at the hair cell level, CI will have comparable outcomes to non-AN deaf patients, but subjects who present with a pathology involving the cochlear nerve and higher in the auditory pathway will have limited benefit with CI (134). This is depicted in many studies that utilized MRI and high resolution CT scans to

analyze the associated abnormalities in the inner ear in patients diagnosed with AN. A study by Walton et al. demonstrated that AN patients with CND presented with abnormal EABR response and poor auditory performance, when measured by speech perception score, after implantation (104). Fontenot and colleagues also made reference to several risk factors associated with AN and other comorbidities such as anatomical abnormalities of the temporal bone, including CND and enlarged vestibular aqueduct in their cohort study. The authors disclosed that these findings in individuals diagnosed with AN were negatively associated with achievement of open-set speech perception after CI (135). A study by Teagle et al. portrayed that 9 of the 16 children with absent or abnormal ECAP measures had abnormal findings in their imaging examinations. The authors demonstrated that there is a strong correlation between poor auditory performance and abnormal MRI as well as absent or abnormal ECAP after CI. The authors concluded that poor open-set-speech perception outcomes after CI are often the case, especially when CND is identified (35).

The literature has also demonstrated that patients with non-syndromic recessive AN may benefit from CI (60, 61). Thus, AN individuals with OTOF mutations have successful outcome results after implantation, presenting optimum clinical responses and electrophysiological tests postoperatively (60, 136). A recent study evaluating the post-implant outcome results in patients carrying another mutation associated with AN, the OPA1mutation, concluded that CI in these individuals is successful. The underlying hearing disorder in these OPA1 patients is a dys-synchrony in auditory nerve fibre activity occurring due to neural degeneration affecting the terminal dendrites, therefore, the authors denoted that electrical stimulation via the CI is capable of improving synchronous activity in auditory brainstem pathways, hence hearing thresholds and speech perception (72).

Certain cases of patients, diagnosed with AN, present with a fluctuating course of hearing disability which needs to be taken into account when management intervention with CI is considered (42). Caution should be taken when considering AN subjects as possible candidates for CIs, as several patients displayed significant auditory improvement on extensive follow-up in a study conducted by Attias et al. (20). AN cases need to have an adequate chance to spontaneously retrieve useful hearing levels by ongoing auditory pathway maturation (39), therefore, the decision regarding intervention with a CI after failure of conventional rehabilitation, should not be made before the patient reaches 1 year of life and repeated follow-up measures have displayed negligent signs of improvement (37).

A report by de Carvalho et al. evaluated the satisfaction of AN individuals one year after CI, using the SADL questionnaire (Satisfaction with Amplification in Daily Life), and concluded

that these patients were satisfied with the CI intervention as the average of the overall satisfaction score (Likert scale, ranging 0–10) was 8 (137).

The literature has also depicted AN cases with variable outcome results after CI, however, the variability observed in AN individuals is possibly related to the uncertainty regarding the site of lesion, which could result in unpredictable performance after implantation (11,138). A study by Ji et al. concluded that CI benefits prelingual AN children to different extents, as some of their patient population showed improved speech recognition and others gained effective speech recognition in noisy environments, whereas others made no progress whatsoever and furthermore, no patient displayed effective social communication (138). A review by Harrison et al. stated that it is imperative for AN to be subdivided into more discrete disease entities, in order for reliable prediction of functional outcome results with CI, to be gained (27). Moreover, children diagnosed with AN associated with other cognitive or developmental anomalies may show limited benefit from CI but are more likely to continue to rely on other methods of communication after implantation, as was portrayed in a study by Budenz et al. This study compared CI-outcomes in children with isolated AN to 9 AN children with confounding cognitive or developmental co-morbidities and concluded that the latter had significantly poorer outcomes after implantation (44). The knowledge derived from these studies is valuable as the identification of the correct etiology is crucial in order to identify potential co-morbidities at an early stage which in turn will significantly help in predicting the prognosis and outcome of hearing rehabilitation, therefore, direct optimum patient management.

It is clear that AN is a disease category with many different etiologies and includes patients with a wide range of functional severity, co-morbidities and anatomical abnormalities, in addition to the range of functional impairments from the isolated neuropathy. The up-to-date literature that focuses on patients with isolated AN is meager, yet the majority of these publications denote favorable outcomes regarding speech perception skills and audibility in implanted AN individuals (Table 4.). On the other hand, the research articles that have heterogeneous AN patient populations with subjects that present with concomitant non-auditory factors such as autism, CNS abnormalities, cognitive disorders and developmental delays portray a percentage of poor CI outcomes which they attribute to these factors (Table 3.) A study by Dean et al. duly noted that even though their AN patient population also consisted of several medical co-morbidities (2-hydrocephalus, 1-autism, 1-congenital anomalies, 1-plagiocephaly/ microcephaly, 3-developmental delays) the speech perception outcomes in the implanted individuals showed no statistically significant difference between the good and poor performers (124).

Determination of CI suitability is a challenge for AN patients and due to the heterogeneity of the participants, the varied outcomes reported and the methodological limitations of the studies, definitive conclusions cannot be drawn in order to guide the clinician. Thus, it is imperative that high-quality research studies, such as well-controlled, longitudinal prospective studies with homogeneous grouping of study participants are undertaken to evaluate the efficacy of CI and the impact of various co-morbidities on auditory, speech, language, and learning outcomes of these individuals. Undeniably, in the interest of promoting evidence-based practices, there is also a need for further published data regarding CI in AN patients with mild to moderate hearing acuity in order to discern the benefits in speech discrimination abilities. No studies up to date have reported social, emotional or academic outcomes for AN subjects with CI, and the literature is still lacking on the management interventions for AN children with mild to- moderate pure-tone thresholds. Further research and advances in technology will provide more lucid answers regarding etiology and predicted outcomes as well as means to meliorate audibility and speech clarity for AN individuals in the future.

4.6.4. Innovative Treatment Methods for Auditory Neuropathy

Promising clinical implications for patients with AN are presented in research studies that investigate the viability of various stem cell types for the replacement of auditory neurons in impaired cochleas (139). A recently reported discovery by Chen and colleagues, demonstrated 46% success in restoration of hearing thresholds in a rodent AN model, after transplantation of human pluripotent stem cells. The authors relayed that improved hearing function correlated with new synapse formation in the peripheral and central aspects of the auditory system (140). These encouraging results and further investigations will bring us closer to the clinical application of stem cells for the management AN in the future.

5. Conclusion

Auditory neuropathy is a more frequent disorder than was speculated in the past. Major risk factors such as hyperbilirubinemia and immaturity are being associated with this disorder and recent investigations have led to important information involving the genetic substrate responsible for the AN phenotype in certain cases. Although the underlying lesion(s) and the pathophysiologic mechanisms in AN are fundamental in understanding and treating the disorder, the related evidence is still obscure, thus continued research is essential in order to elucidate the true pathology resulting in this disease entity. The most likely underlying pathophysiologic mechanisms leading to impairment in the subjects' temporal processing abilities are synaptic deficiency and dys-synchrony of neural discharge, which in turn lead to

hindered auditory skills and spoken language abilities. Consequently, a thorough diagnostic regime is of utmost importance in order to attain an accurate diagnosis of AN in these patients. The diagnostic protocol should include OAEs and CMs in individuals with absent or severely atypical ABR waveforms, bearing in mind that fluctuations in audiometric findings are quite possible in these children. Furthermore, genetic testing might be feasible to be included in the diagnostic work-up as well as MRI or high resolution CT scans, in order to unmask comorbidities and CND especially in CI-candidates.

The management of these individuals is very challenging, and consensus regarding amplification and optimum auditory rehabilitation has yet to be reached. The main goal of any treatment modality implemented on children is to provide adequate hearing ability in order to develop auditory skills and oral communication. Serial clinical and audiometric evaluations should be implemented in young children before CI is considered, as spontaneous recovery of hearing is not uncommon in some of these AN subjects. Focusing on the management of children with AN; it is of paramount importance that diagnosis and intervention be executed rapidly and modified according to each child's needs and progress. Firstly, the parents must be notified of the child's condition and what realistic expectations can be harbored in each treatment intervention, regarding speech perception performance. Secondly, conventional amplification, tailored with meticulous speech and language therapy is currently the cornerstone of management strategies for children with AN. Hearing aids are still a justified management option, hence are implemented in all AN children initially, as a subpopulation of AN patients do benefit from it by improving clear speech, and during the assessment period before CI in order to ascertain that speech development is hindered. In order to achieve oral communication a child must be able to gain auditory skills to discriminate speech and thus replicate it. Thus, the third step in the management strategy is to improve synchronization within the auditory system, which is made feasible with CI which is currently the intervention option of choice for AN patients with severe auditory processing difficulties.

The data gleaned in this review of the literature support the conclusion that cochlear implantation positively affects hearing and communication skills in AN individuals. Mounting evidence suggests that CI is a justified management intervention in the treatment of AN as it has been remarkably successful in adult and child populations as they present with significant perceptual benefits and speech perception performance post-surgically. However, due to the heterogeneity of this disorder, patient selection should be cautious in order to identify the subjects that will have successful hearing and speech outcomes with CI. Thus, comorbities need to be identified and electrophysiological testing that may predict post-surgery outcome results may be utilized. Nevertheless, an essential number of AN children

with concomitant non-auditory pathologies, receiving CI, may still benefit considerably from implantation, either by achieving open-set speech or acquiring environmental sound awareness, improved quality of life, or satisfaction of the child and family. Cochlear implantation in such AN children needs to be tailored for each patient and family and requires realistic expectations for post-CI performance and appropriate counseling (141).

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