Critical Review: Are There Successful Predictors of Cochlear Implant Outcomes in Children with Auditory Neuropathy Spectrum Disorder (ANSD)?

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This critical review examines literature that has addressed the question: Are there successful predictors of cochlear implant outcomes in children with auditory neuropathy spectrum disorder (ANSD)? Through a search of the current literature, four studies were included for critical analysis. Study designs included one nonrandomized retrospective cohort study, one nonrandomized longitudinal cohort study, one nonrandomized between groups retrospective study and one case study. Three different potential predictors of cochlear implant success were investigated amongst the studies: Magnetic Resonance Imaging (MRI), Electrocochleography (ECochG) and Genetic mutations (OTOF). Overall, the evidence provided by these studies suggests that MRIs, specifically identification of cochlear nerve deficiency, may be a potential predictor of cochlear implant success. However, no support was found for the use of ECochG and genetic mutations as predictors as a result of small sample sizes, and limited related research available. Future research is warranted in all three predictor areas with a focus on increasing the number of subjects, appropriate methodology and increased reliability.

Introduction

Auditory Neuropathy Spectrum Disorder (ANSD) is a term used to describe a patient who presents with the audiological condition of normal outer hair cell function as measured through either otoacoustic emissions (OAEs) or cochlear microphonic (CM), and an abnormal functioning of the neural conduction along the auditory pathway as measured though an absent or abnormal auditory brainstem response (ABR). While the diagnosis of this condition can be easily determined through the above electrophysiological measures, the perceptual consequences, etiologies, as well as treatment options are much less definitive. Individuals who suffer from ANSD present with a variety of audiological features including varying and fluctuating pure tone thresholds, speech discrimination scores that do not correlate with pure tone averages, as well as a variety of radiological findings. This multitude of audiological findings may be a result of differing sites of lesion along the auditory pathway. Based on recent research, a variety of different pathologic sites have been determined along the auditory pathway in individuals with ANSD. As a result, ANSD has been separated into two main streams: lesions associated with the demyelination and axonal loss of the cochlear nerve, and lesions associated at sites including the inner hair cells, tectorial membrane and synapse between inner hair cells and spiral ganglion cells.

It is estimated that 10-14% of all children with a severe to profound sensorineural hearing loss present with ANSD. In Ontario, children with this diagnosis are initially fit with hearing aid technology, following confirmation of behavioural hearing thresholds, and then followed closely to determine their degree of success. While research has shown that in some cases hearing aid technology can be an appropriate treatment option, other cases have suggested quite the opposite (Rance, Beer, Cone-Wesson, Dowell, King, Rickards & Clark, 1999). This varying degree of success is also true for those individuals provided with a cochlear implant (Buss, Labadie, Brown, Gross, Grose & Pillsbury, 2003; Rance et al., 1999). The mixture of success with regards to conventional hearing aid technology and cochlear implant technology is most likely a result of the different sites of lesion and provides a substantial dilemma for both the audiologist and patient. Determining which form of treatment would be most beneficial for the patient becomes quite difficult and an improper decision may impose enormous detrimental implications on the patient.

The ability to determine, at an early age whether hearing aid technology or cochlear implantation would provide the greatest benefit for a patient would be of huge advantage. Hearing aids can be fit on all individuals, however if little success is obtained in prelingual children, then the development of speech and language may be severely impaired and/or fail all together. While the decision for cochlear implantation may be the only viable option for individuals who present with a permanent profound sensorineural hearing loss, individuals with a fluctuating or less severe hearing loss have a much more difficult decision, as surgery often results in the elimination of all residual hearing which in the instance of no improved benefit from the implant, would leave them in a complete world of silence. The ability to predict the amount of benefit a child with ANSD may receive with cochlear implants would be of significant importance since it would provide information regarding what treatment options would be the most ideal for the child and ultimately assist in

providing the best approach to support speech and language development.

Objectives

The primary objective of this paper is to critically evaluate the current body of research addressing the question of whether or not there are any successful predictors of cochlear implant outcomes in children with auditory neuropathy spectrum disorder.

Methods

Search Strategy

Computerized databases including GoogleScholar, PubMed and Medline, were searched using the following search strategy: [(auditory) OR (hearing) AND (dyssynchrony) OR (neuropathy) AND (cochlear implants) AND (predictors)].

The search was limited to journal articles that were peer reviewed and written in English. Reference lists in acquired sources were also reviewed to find additional related journal articles.

Selection Criteria

Studies selected to be included in this critical review were required to examine some outcome of cochlear implantation in children with ANSD and compare their results to a measure obtained pre implantation. No limit was set with regards to what the type of cochlear implantation outcome measure was used, the type of predictor evaluated or the way in which the research was conducted.

Results

Data Collection

Results of the literature search produced the following types of studies consistent with the above mentioned selection criteria: nonrandomized retrospective cohort study (1), nonrandomized longitudinal cohort study (1) nonrandomized between groups longitudinal study (1), and case study (1). In accordance with the Oxford Centre for Evidence-Based Medicine Levels of Evidence (2009), the level of evidence for these studies has been evaluated as: 2b (Walton, Gibson, Sanli & Prelog, 2008), 2b (Teagle, Roush, Woodard, Hatch, Zdanski, Buss & Buchman, 2010), 2c (McMahon, Patuzzi, Gibson & Sanli, 2008) and 4 (Rouillon, Marcolla, Roux, Marlin, Feldmann, Couderc, Jonard, Petit, Denoyelle, Garabedian, & Loundon, (2006).

Retrospective Nonrandomized Cohort Study: Magnetic Resonance Imaging and Electrical Auditory Brainstem Response Predictors

Walton, Gibson, Sanli and Prelog (2008) examined the outcome of cochlear implantation in children with auditory neuropathy spectrum disorder and cochlear nerve deficiency through magnetic resonance imaging (MRI) examination of the cochlear nerve in the internal auditory canal (IAC). All children younger than 15 years of age at the Syndey Cochlear Implant Centre (SCIC) from 1997-2006 with a diagnosis of ANSD, a referral for cochlear implantation, and who met the inclusion criteria were included in the study. Pre-implantation MRI scans of each child were examined by a radiologist blinded to the cochlear implant outcome. The cochlear nerve was classified into three different groups: 1) normal if it was the same size as or larger than the facial nerve; 2) deficient if it was smaller than the facial nerve; 3) rudimentary if there was unbranching of the vestribulocochlear nerve complex; and 4) absent if it was not seen on any of the images.

Electrical auditory brainstem response (EABR) data was recorded for each child from all channels of the cochlear implant (Ch22-Ch1) immediately after electrode array insertion. The EABR was classified based on waveform morphology and was marked a score of three for the best result and zero for the worst result, for all of the channels for a maximum score of 66 across all channels. The authors conducted a validation pilot phase study that indicated that subjects with EABR scores of 56-66 were likely to develop open-set speech perception scores $\geq$4 using the Melbourn Speech Perception Score (MSPS) instrument compared to those who had EABR scores of 55 or lower.

Based on the MRI findings the cohort was divided into two groups: deficient cochlear nerve (Group A) and normal cochlear nerve (Group B). Speech perception and EABR results were compared between the two groups.

A Mann-Whitney U Test for nonparmetric data indicated that individuals in Group A had significantly lower MSPS and EABR scores than the children in Group B which suggests that children with ANSD and cochlear nerve deficiency have poorer cochlear implant outcomes than those with normal cochlear nerves and furthermore that MRI scans can aid in predicting cochlear implant benefit in children with ANSD.

Longitudinal Nonrandomized Cohort Study: Magnetic Resonance Imaging

In 2010, Teagle, Roush, Woodard, Hatch, Zdanski, Buss & Buchman conducted a longitudinal study of 52 children with ANSD who received cochlear implants. With each implanted child, the patient's characteristics, preoperative MRI profiles, surgical outcomes, and postoperative performances were evaluated and

compared using individual t-tests. A variety of patient characteristics were identified stressing the enormous medical differences found amongst children with ANSD. Preoperative imagings through MRIs were completed and results suggested that abnormal findings were evident in 18 of the 48 images taken. Speech perception testing was completed in six month intervals post implantation for those who had worn the cochlear implant for greater than six months. The remaining children were separated into two groups: Group B: those who used their cochlear implants for > six months but were unable to participate in the open-set speech perception testing due to their young age and developmental delays (n=15; 29%) and Group C: those who used their implants for > six months and could participate in open-set word recognition testing (9n=26; 50%). In Group B, Infant-Toddler Meaningful Auditory Integration Scale (IT-MAIS) scores were used to document parental perception of their child's use of sound and were compared pre and post implantation. Results suggested significant improvements in IT-MAIS scores with the mean scores being 79% (SD=16%, range 48 to 96%) post implantation compared with only 26% (SD =21%, range 5 to 63%) before implantation.

In Group C, large variability in cochlear implant performance was seen across the children. The mean Phonetically balanced kindergarten (PBK) word and phoneme test scores for the entire group were 76% and 54% respectively. Research by Moog & Geers (2003) has suggested that cochlear implant performance is correlated with age at the time of testing, duration of implant experience, best ear pure-tone-average, and gender. To determine if the variance among the PB-K and phoneme test scores was a result of these factors a multiple regression analysis was completed. The results of the analysis however, indicated that these five factors were poor predictors of PB-K word scores in the Group C children. To determine whether factors other than the above conditions contributed to differences in speech perception performance amongst these children, the residuals from the multiple regression were submitted to a series of t-tests. Three separate t-tests were performed with Welch's correction for unequal variance to determine if medical comorbidiites, ECAPs, and MRI findings were correlated with the speech performance outcomes. These tests indicated a significant difference in speech perception performance between groups characterized by robust versus absent or atypical (i.e. abnormal) ECAP ($t_{15.5}$ = 3.80, $p<0.01$), a difference between those with normal versus abnormal MRI findings ($t_{13.0}$ = 3.20, $p<0.01$), and a distinction between presence versus absence of medical comorbidiites ($t_{15.4}$ = 2.29, $p<0.05$).

The study also found that many children with abnormal Electrical Compound Action Potentials (ECAP) testing also had abnormal findings on preoperative MRI. Using t-test measures, results of MRI and speech perception tests were compared. The mean PB-K word score for children with normal MRI was 61% and 18% for those with an abnormal MRI. This difference was found to be highly significant ($t_{15.1}$=4.63, $p<0.001$).

While the authors suggested that caution should be exercised when extrapolating any of the above results, they continued to suggest that abnormities on MRIs specifically when cochlear nerve deficiency is identified may act as a predictor of poor performance for children with ANSD who may or may not have already received a cochlear implant.

Nonrandomized Between Groups Retrospective Study: Electrocochleography Predictor

In 2008, McMahon, Patuzzi, Gibson and Sanli investigated the site of lesion of ANSD in 14 children using frequency specific electrocochleography (ECochG). ECochG results were then compared with each child's EABR measured after cochlear implantation.

The subjects consisted of seven males and seven females and were diagnosed with ANSD between three and 24 months. A majority of the children presented with a variety of neonatal problems such as prematurity, jaundice, rubella and cytomegalovirus, however no complications were found in 50% of the subjects. All subjects were fit with hearing aid technology within their first nine months and cochlear implantation took place between four and 53 months after hearing aids were worn.

The round window ECochG was recorded via a posterior myringotomy. Frequency specific tone pips between 250 and 8000Hz were presented via a TDH-39 headphone. All subjects were later implanted with a Nucleus cochlear implant with 22 electrodes. EABR measures were conducted immediately after insertion of the implant and were classified into three categories: present, absent, or poor waveform morphology based on wave V of the EABR.

The results of the round window ECochG measures were separated into three groups: a) flat line, indicating an absent summating potential (SP) or compound action potential (CAP) components; b) large SP was present which often had a prolonged latency and was followed by a residual CAP; and c) normal latency SP waveform followed by a negative potential.

EABRs were measured immediately after cochlear implantation and results included three varying morphologies: a) normal waveform, with the presence of waves II-V; b) absent waveform; and c) a waveform showing poor waveform morphology for wave V.

Results indicated that when comparing the types of ECochG waveforms, SP latencies and EABR waveforms, children who presented with ECochGs that consisted of both a SP and a dendrite potential (DP) showed SP latencies of less than 1.0msec after the stimulus onset and either absent EABR waveforms, or poor wave V morphology. Children however who had an SP but no DP showed normal EABR waveforms (eight out of nine ears).

Not only does this study suggest that pre and postsynaptic mechanisms of ANSD exist but it suggests that in individuals with a delayed latency SP with or without a residual CAP have presynaptic ANSD and produce ideal EABR waveforms which has been correlated with good Melbourn Speech Perception Scores.

Case Study: Genetic Predictor

In 2006, Rouillon, Marcolla, Roux, Marlin, Feldmann, Couderc, Jonard, Petit, Denoyelle, Garabedian & Loundon conducted case studies involving two children who presented with mutations in the OTOF gene which has been classified as an isolated subclass of ANSD.

The first child was diagnosed with ANSD at 22 months of age with an absent ABR and positive TEOAE. Through genetic testing, double heterozygous mutations in OTOF were identified; a missense mutation as well as a stop mutation. The child received a cochlear implant at the age of 35 months. Outcome measures were completed 35 months post operation and then compared to audiometric measures taken pre-implantation. Audiometric thresholds in free field testing (250 – 4000Hz) improved from 75 dB when wearing hearing aids, to 37 dB post implantation. Speech perception results were also said to improve with the child identifying 100% of open-set words and 60% of open-set sentences post implantation, however no pre-implantation scores were provided for comparison. The Meaningful Auditory Integration Scale (MAIS) score was also said to improve increasing from 4/40 to 40/40 at follow-up. The child also had spontaneous oral communication and intelligibility of speech was graded as four on the Nottingham scale.

The second child was diagnosed with ANSD at ten months of age with absent AEP and positive TEOAEs. Double heterozygous mutations were identified in OTOF: a slice mutation as well as a stop mutation. Cochlear implantation of the child occurred when she was four years of age. At 18 months post implantation the child was evaluated. She was currently wearing her implant all of the time, and her mean audiometric threshold (250-4000Hz) had improved from severe-profound pre-implantation to moderate post implantation.

Rouillion, et al. (2006) explained that OTOF deafness is a form of auditory neuropathy that unlike all cases of ANSD result in excellent speech perception performance post cochlear implantation.

Discussion

Through an extensive investigation of the current literature it is clear that there are very few studies that evaluate whether cochlear implant outcomes in children with ANSD can be predicted. Of those that do, sample sizes are small and while there have been several potential predictors identified, there is little overlapping evidence to encourage their use clinically.

It is essential that more research be completed in all areas of potential cochlear implantation predictors: MRI, ECochG and genetic associations. Of all predictors however, MRI and identification of cochlear nerve deficiency seems to be the most valid and presents with the highest degree of evidence. The studies conduction by both Walton et al. (2008), and Teagle (2010) had substantial power over the other two studies as they contained a high sample size (n=39);(n=52), appropriate methodology such as suitable blinded measures, validation pilot phases and validated post implantation outcome measures. Both studies also consisted of children who had a varying degree of comorbidities such as prematurity, Down syndrome, CHARGE syndrome, jaundice, etc., and thus were good representations of real world ANSD populations.

A well conducted study was also completed by McMahon et al. (2008) which provided evidence for the potential application of round window ECochG in identifying subtypes of ANSD and ultimately cochlear implant outcomes. Seven of the eight subjects who showed a delay in the SP waveform showed good EABR waveforms indicating its potential use as a cochlear implant predictor. It is important however, to address the fact that EABRs used in this study as well as in Walton et al. (2008) only suggest that there is neural integrity along the auditory pathway up to the brainstem. The EABR cannot address cortical processing which may also play a significant role in speech perception.

ANSD can have a variety of origins i.e. congenital, infections and idiopathic. While the study conducted by Rouillon et al (2008) suggests that children who present with the subtype of ANSD associated with mutations in the OTOF gene should be implanted for optimal benefit, the fact that the study consisted of only two individuals, each of which did not have identical mutations, is quite worrisome. Again, more research with an increased number of subjects is needed for this genetic predictor to be used clinically. Furthermore, speech perception outcomes were poorly described and the way in which their data was collected is unknown thus affecting the validity of this study.

Conclusions and Future Considerations

Overall, predicting the success of cochlear implantation in children with ANSD cannot be completed with any kind of confidence. MRI with the identification of cochlear nerve deficiency currently serves as the predictor with the highest degree of evidence but the studies discussed here do not warrant its use clinically with 100% certainty.

Children who present with ANSD represent a heterogeneous group with a variety of impairments. While the number of children who present with ANSD and are implanted are low in number, it is essential that cochlear implant teams document all pre and post evaluations of the child in hopes that increased subject numbers, audiological profiles and predictors can be used in future research. It may also be largely beneficial if cochlear implant programs used similar outcome measurement protocols so that performance outcomes could be compared in a valid way. The ability to predict cochlear implantation outcomes in these children would be invaluable and perhaps continued research in the areas of MRI, ECochG and genetic mutations is the start of that essential milestone.

References

Buss. E., Labadie, R.F, Brown, C.J., Gross, A.J., Grose, J.H. & Hillsbury, H.C. (2002). Outcome of Cochlear Implantation in Pediatric Auditory Neuropathy. *Otology & Neurology*, 23, 328-332.

Gibson, W.P., & Sanli, H. (2007). Auditory Neuropathy: An Update. *Ear & Hearing*, 28 (2) 102S-106S.

McMahon, C.M., Patuzzi, R.B., Gibson, W.P., & Sanli, H. (2008). Frequency Specific Electrocochleography Indicates that Presynaptic and Postsynaptic Mechanisms of Auditory Neuropathy Exist. *Ear & Hearing*, 29: 314-325.

Moog, J.S., & Geers, A.E. (2003). Epilogue: Major Findings, conclusions and implications for deaf education. *Ear & Hearing*, 24, 121S-125S.

Rance G, Beer D.E, Cone-Wesson B, Robert, S., Dowell, R.C., King, A., Rickards, F.W. & Clark, G.M. (1999). Clinical findings for a group of infants and young children with auditory neuropathy. *Ear and Hearing*, 21: 238-252.

Rouillon, I., Marcolla, A., Roux, I., Marlin, S., Feldmann, D., Couderc, R., Jonard, L., Petit, C., Denoyelle, F., Garabedian E.N., Loundon, N. (2006). *International Journal of Pediatric Otorhinolaryngology*, 70, 689-696.

Starr, A., Sininger, Y.S., & Pratt, H. (2000). The varieties of auditory neuropathy. *The Journal of Basic Clinical Physiology and Pharmacology*, 11, 215-230.

Teagle, H.F.B., Roush, P.A., Woodard, J.S., Hatch, D.R., Zdanski, C.J., Buss, E. & Buchman, C.A. (2010). Cochlear Implantation in Children with Auditory Neuropathy Spectrum Disorder. *Ear & Hearing*, 31,325-335.

Walton, J., Gibson, W.P., Sanli, H., & Prelog, K. (2008). Predicting Cochlear Implant Outcomes in Children with Auditory Neuropathy. *Otology & Neurotology*, 29: 302-309.