

Critical Review:

Can individuals with hearing impairment associated with Usher Syndrome benefit from a cochlear implant?

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This critical review examines the evidence on the topic of cochlear implant benefit among individuals with hearing impairment associated with Usher syndrome. Study designs include two retrospective cohort studies, one case control and one case series. Overall, the evidence of this critical review seems to agree on improved benefit from earlier age of implantation. Recommendations for clinical implications are provided.

Introduction

Usher syndrome is an autosomal recessive genetic condition, differentiated into three types (Vivero, Fan, Angeli, Balkany & Liu, 2010). It was described in 1858 by von Gaefe, and later characterized in 1914 by Charles Usher. It involves impairments in both the visual and auditory systems. The hearing impairment is sensorineural in type. Usher syndrome is also characterized by progressive retinitis pigmentosa which can lead to the degeneration of the retina. Approximately 3 to 6 % of children born deaf can have their impairment be associated with Usher syndrome gene mutations (Liu, Angeli, Rajput, Yan, Hodges, Eshraghi, Telischi & Balkany, 2008). The three types of Usher syndrome are defined by the degree of severity and progression of the hearing loss and the presence of vestibular dysfunction. Type I, which can be considered the most severe, involves a severe to profound congenital hearing loss, the presence of vestibular dysfunction that can lead to motor delays and progressive loss of vision leading to blindness in adolescence. Type I is also subcategorized (subtypes 1B, 1C, 1D, 1E, 1F, 1G and 1H). Type II can be described as a moderate to severe sensorineural hearing impairment, no vestibular dysfunction and visual impairment beginning in the second decade of life (Liu et al., 2008). Some individuals are able to preserve useful vision into middle age. Individuals with Usher syndrome type II can benefit from amplification by hearing aids (Vivero et al., 2010). Type III can be classified by a progressive hearing impairment (moderate to profound), loss of vision beginning in late childhood or adolescence and variations in the extent of the vestibular dysfunction (Liu et al., 2008; Loundon, Marlin, Busquet, Denoyelle, Roger, Renaud & Garabedian, 2003).

Usher syndrome Type I can account for approximately 30 to 40% of Usher syndrome (Vivero et al., 2010). It is often recommended for individuals

with Usher syndrome type I to receive a cochlear implant due to the severity of the hearing loss and progressive nature of the visual impairment (Vivero et al., 2010; Loundon et al., 2003). Sign language may only be a temporary solution for these individuals given the associated loss of vision. Moreover, a cochlear implant can help facilitate oral communication. Specific criteria exist for candidature to receiving a cochlear implant. Moreover, not all individuals with a hearing impairment will benefit from one making it difficult to predict the outcome of a cochlear implant. However, individuals with Usher syndrome (type I and III) are can be candidates for a cochlear implant.

Thus far, several genetic mutations have been identified to cause certain types and subtypes of Usher syndrome (Millán, Aller, Jaijo, Blanco-Kelly, Gimenez-Pardo & Ayuso, 2011). For type I, genetic mutations in the gene *MYO7A* has been linked to subtype 1B, *USH1C* has been linked to subtype 1C, *CDH23* has been linked to subtype 1D, *PCDH15* has been linked to subtype 1F and *USH1G* has been linked to subtype 1G. Type II has been linked to mutations in the genes *USH2A*, *GPR98* and *DFNB31*. Lastly, type III has been linked to a mutation in the gene *USH3A*.

One genetic mutation involving the *USH1C* gene, causing Usher syndrome type IC, is predominant in the Acadian population (Ebermann, Lopez, Bitner-Glindzicz, Brown, Koenekoop & Bolz, 2007). Given that a large proportion of the Acadian population is located in Canada, it is important that Canadian health professionals understand the diagnosis and treatment options for Usher syndrome type I.

Reviewing the literature available on this topic will enable audiologists to make an informed decision on (re)habilitation options. This can also help provide individuals and parents with the information allowing

them to make an informed decision on their available options.

Objectives

The primary objective of this paper is to provide a critical evaluation of the available literature regarding the outcome of a cochlear implantation in individuals with hearing impairment associated with Usher syndrome. In addition, a secondary objective is to present evidence-based recommendations for clinical practice and future research.

Methods

Search Strategy

Articles related to this topic were collected from the following computerized databases: PubMed, CINAHL and Scopus. The keywords used for searching through PubMed and Scopus were “Usher syndrome” and “Cochlear implant outcome”. The keywords used for searching through CINAHL were “Usher syndrome” and “Cochlear implant”. The search was limited to articles written in English.

Selection Criteria

The studies that were selected for inclusion in this critical review were required to review the outcome of cochlear implantation in individuals with Usher Syndrome. Articles classified as literature reviews were excluded from this critical review.

Data Collection

The results of the literature search yielded four articles that corresponded to the aforementioned selection criteria. Two studies followed a retrospective cohort study design. One study employed a non-randomized retrospective between groups case control design. Lastly, one study used a case series with pre- and post-test design.

Results

Study #1

Liu et al. (2008) performed a case series with pre- and post-test evaluations to examine the potential effects of four Usher syndrome type I genes (*MYO7A*, *USH1C*, *CDH23* and *PCDH15*) and other factors on the outcome of cochlear implantation. The participants consisted of 9 individuals classified with Usher syndrome type I and all were recipients of a cochlear implant. The age of implantation ranged from 2 to 11 years. The post-implantation evaluations were conducted periodically for a minimum of 1 to 2 years. Audiologic evaluation involved a battery of speech perception tests administered both pre- and

post-implantation which varied based on the individual's age and cognitive ability. Also, two qualitative scales (Categories of Auditory Performance and Qualitative Assessment of Cochlear Implant Use) were used to assess post-implantation outcome.

The authors found through pre-implantation evaluation that all subjects were pre-linguistically profoundly deaf. The nine individuals were placed into either one of two groups based on age of implantation: group 1 consisted of those implanted at age 3 years or younger and group 2 consisted of those implanted at age 6 years and older.

Group 1 had four individuals. Greatest improvements were found in this group for closed-set and open-set monosyllabic word recognition. Group 2 consisted of the remaining five individuals. A mean closed-set monosyllabic score of 54% was found, and only one individual was able to provide a score for open-set word recognition.

The authors were unable to provide significant evidence of speech perception improvement due to the small sample and the different preoperative modes of communication employed (including oral communication, sign language and total communication). All individuals in the sample showed significant improvements on the post-operative Categories of Auditory Performance scale.

Mutational analysis of the type I genes included a screening of DNA samples. Only five of the nine patients had blood samples for this analysis. The mutation analysis demonstrated that three out of the nine individuals were confirmed with a diagnosis of Usher syndrome type I (genes *CDH23* and *PCDH15*).

The authors stated that they believe early intervention and specific genetic testing could potentially improve most of the developmental and behavioral difficulties that children with hearing impairment often exhibit. Genetic testing in individuals with Usher syndrome is important as several gene mutations have been associated with different types of the disorder. This can be crucial in early identification and choosing the type of intervention by providing information on future symptoms to the audiologist and the family.

This study showed several limitations and flaws. The cochlear implant devices found in the nine individuals were not all from the same make which could introduce some differences in the performance (e.g. differences in the processing of the device). All individuals did not utilize the same mode of communication pre-operatively varying from oral, sign language and total communication.

Inconsistencies in the documented age range of implantation were also present.

Although pre-implantation data was collected, the authors did not provide this information.

No statistical analyses were used.

With respect to determining the Usher etiology, the authors also did not include a screening for all known Usher syndrome type I genes in the mutation analysis. This may have helped confirm the diagnosis in more individuals. These are important factors that significantly limit the credibility and results of this study.

Based on an adaptation by the Oxford Centre for Evidence-based Medicine Levels of Evidence (March 2009) and NHMRC additional levels of evidence and grades for recommendations for developers of guidelines (June 2009), the case series with pre- and post-test study design has a level of evidence of 3. However, the level of evidence provided by this study is not very compelling due to the study's limitations and flaws, as described above.

Study #2

Damen, Pennings, Snik & Mylanus (2006) conducted a retrospective non-randomized, between groups case-control to examine the quality of life, audibility and visual abilities of individuals with Usher syndrome type I. These were compared within two groups: individuals with a cochlear implant and without (control group). These two groups were further differentiated by age of implantation (children and adults). Twenty eight individuals with Usher syndrome type I were used for this study.

Audibility was evaluated through the principle of Equivalent Hearing Level (EHL). Quality of life was evaluated through three questionnaires: the Nijmegen Cochlear Implant Questionnaire (NCIQ), the Usher Lifestyle Survey and the Standard Medical Outcome Study Short-Form 12 (appropriate for adult individuals only). The latter is a more generic questionnaire (non-disease specific).

The data was statistically analyzed using the nonparametric independent sample Mann-Whitney U test, the χ^2 test and the Spearman's correlation.

The authors found that individuals with a cochlear implant had better EHL scores: adults had a mean score of 107.1 dB HL and children had a mean score of 84.4 dB HL. This was compared to the non-cochlear implant user group who were all profoundly deaf with EHL scores of 130 dB HL.

Quality of life results for the NCIQ were found to be significantly better for the cochlear implant user group compared to the non-cochlear implant user group. Within the cochlear implant group, children seemed to show better results than

adults. The Usher Lifestyle Survey showed an overall trend of individuals with a cochlear implant being able to maintain independence more easily than those without cochlear implantation. The authors found no significant differences or trends among the adult individuals in the Standard Medical Outcome Study Short-Form 12.

Correlation analysis demonstrated a significant relation between the EHL and the NCIQ. This was present in two domains of the NCIQ: sound perception basic and sound perception advanced. However, these decrease significantly when the hearing impairment worsens (increasing EHL score).

Overall, the authors state that cochlear implantation can help individuals with Usher syndrome type I maintain their independence and can improve their quality of life especially with their hearing abilities. They mention that benefit from cochlear implantation can be present in specific areas. Also, they suggest that quality of life should be measured separately in specific (e.g. hearing) and generic categories because often it is assumed that deaf-blind cochlear implant recipients will have a significant improvement in quality of life. The authors provide evidence that this is not always true.

The study design was good, and appropriate statistical analyses were used. The authors discussed areas in their study that could introduce bias (e.g. differing methods of answering the questionnaires). Based on the same scale of level of evidence previously mentioned, the non-randomized, between groups case control research design has a level of evidence of 2b. Overall, the level of evidence for this study could be considered moderate, and the results should be carefully considered because of this limitation.

Study #3

Pennings, Damen, Snik, Hoefsloot, Cremers & Mylanus (2006) performed a retrospective cohort study to observe the benefit and performance of a cochlear implant in individuals with Usher syndrome type I. They also examined whether variations in genotype could have an effect on the cochlear implant performance. Fourteen individuals with Usher syndrome type I who received a cochlear implant were divided into three separate groups differentiated by age of implantation. Group 1 consisted of those implanted below 10 years of age, group 2 consisted of those implanted between the ages of 10 and 19 years, and group 3 consisted of those implanted over the age of 20 years.

Audiologic performance was assessed using the Equivalent Hearing Level (EHL), and cochlear implant benefit was evaluated using the Glasgow Benefit Inventory (GBI) and the Glasgow Children's

Benefit Inventory (GCBI). Statistical analyses included linear regression and non-linear regression (to acquire satisfactory curve fits).

Mutation analysis for type I genes was performed on blood samples from each individual. This analysis did not include a screening for all exons of USH1 genes which can introduce a limitation to this study (as mentioned in study #1). The authors identified gene mutations in two type I genes: *MYO7A* and *CDH23*. Six individuals had pathogenic mutations in *MYO7A* and one individual demonstrated a mutation associated with the *CDH23* gene. The remaining 7 individuals did not demonstrate mutations in the genes screened in this study.

Significantly lower EHL scores were found in group 1 (in 5 of 7 individuals). The group had a mean EHL score of 84 dB HL. In group 2, the youngest individual (of 3 individuals) also had a significantly lower EHL score. The mean score for this group was 97 dB HL. The 4 individuals in group 3 did not show any significant improvement in hearing post-implantation. They had a mean score of 115 dB HL.

Linear regression analyses were used to assess relationships between age and different performance criteria post-implantation. A linear regression analysis (GCBI and age of implantation) showed that performance of a cochlear implant could have significantly increased benefit when implanted at a younger age. The authors suggested the best performance occurred when individuals were implanted within the first two decades of life. One individual displayed negative GCBI scores; however, these were attributed to other associated complications.

Likewise, a linear regression analysis (EHL scores and age of implantation) showed that there was a significant improvement in audiologic performance in individuals that were implanted at an earlier age.

A linear regression analysis (GCBI and EHL scores) showed a negative relationship between EHL scores and cochlear implant performance: when hearing ability decreased (increased EHL scores), cochlear implant benefit significantly decreased (lower percentage score). No relationship between varying genotype for Usher syndrome type I and cochlear implant benefit was found based on the results from the mutational analysis.

Overall, Pennings et al. were able to demonstrate that early implantation can be linked to improved audiologic performance. Although the statistical analyses used can help predict relationships between the two variables, regression analysis does not provide causality (Greenhalgh, 1997). Therefore

the results the authors have demonstrated should be considered cautiously. The sample of participants in this study was the same used in the Damen et al. (2006) study which could have introduced a bias in this study. Based on the same scale of level of evidence previously mentioned, the cohort study design has a level of evidence of 2b. Overall, this study gives a moderate level of evidence.

Study #4

Loundon et al. (2003) conducted a retrospective cohort study to evaluate which specific symptoms can lead to clinical diagnosis of Usher syndrome and the quality of life outcome after cochlear implantation in individuals with Usher syndrome (n=X), selected from a cohort of 210 patients who received a cochlear implant between January 1989 to December 2001. Of these patients, 13 individuals were diagnosed with Usher syndrome: 11 with type I, 1 with type III and 1 unclassified. These individuals were divided into 3 groups based on age of implantation: group 1 consisted of individuals implanted before 3 years of age (4 individual), group 2 consisted of those implanted between the ages of 3 and 9 years (6 individuals) and group 3 consisted of those implanted beyond 18 years old (3 individuals). Speech tests were conducted pre- and post-operatively. These assessed four domains: perception of sound, speech perception, speech production and intelligibility. Speech perception was evaluated through word recognition in closed and open sets. Speech production was assessed either through a test for the deaf children (GAEL; comprehension and expression for ages 3 to 6 years) or hearing children (Chevrie-Muller; comprehension and expression for ages 5 to 8 years). Those over the age of 9 years were tested based on academic level. The speech production scores were divided into five levels: complex sentences, simple sentences, grammatical sentences, spared words and no production.

The statistical analyses included the χ^2 test and the Student's *t* test.

In group 1, the results for speech perception showed there was a significant improvement in closed-set words. Only one individual showed improvements in open-set words. In group 2, 5 individuals demonstrated significant improvements in closed and open set words. In group 3, all 3 individuals had improvements in closed and open set words. The closed-set words scored had statistically significant improvement.

The results for speech production demonstrated that 8 individuals had production of at least simple sentences. In group 1, all individuals progressed from no production to spared words or

simple sentences. In group 2, 5 individuals evolved from no production to at least spared words. Four of the 5 individuals had simple or complex sentences, and this showed statistically significant improvement. In group 3, all 3 individuals had complex sentence production before receiving a cochlear implant, and this remained stable post-implantation.

Loundon et al. concluded that the benefit of a cochlear implant in this population was indisputable. They also stated the importance of earlier age of implantation due to the progressive nature of the visual system. This in addition to speech therapy can help develop the auditory-oral communication.

Based on the same scale of level of evidence previously mentioned, the cohort study design has a level of evidence of 2b. Overall, this study seems to provide a moderate level of evidence.

Discussion

Individuals with Usher syndrome have an additional visual impairment than those with a hearing loss. A cochlear implant can help an individual use oral communication by providing auditory cues. Early diagnosis can provide support and increase the outcome benefit. Genetic mutation analysis can help with early identification and the diagnosis of the type of Usher's which can be crucial in determining the appropriate intervention.

Overall, the studies reviewed offer variable evidence on the outcome of cochlear implantation in people with Usher syndrome. All but one study were able to demonstrate that earlier implantation can have a significant impact on hearing and quality of life. No study has yet been able to report better improvement linked to a different type or subtype of Usher syndrome, or to a specific causative genetic mutation.

It can be difficult to make conclusions with such small study samples as this disorder is rare. Moreover, with this type of population, it is difficult to conduct certain types of study designs (e.g. randomized clinical trials) that could perhaps lend more confidence to evidence due to ethical reasons.

Conclusion

Currently, it is believed that the best cochlear implant outcome regarding speech is related to earlier age of implantation. The studies presented in this critical review also agree with this statement. Individuals with a hearing impairment associated with Usher syndrome seem to benefit from a cochlear implant in terms of quality of life including improved audiologic performance, speech perception and production, and maintaining independence.

Clinical Implications

Recommendations based on this topic include:

- 1) Audiologists must consider the benefits of a cochlear implant for individuals with Usher syndrome especially due to the possibility of progressive visual impairment which can affect their mode of communication.
- 2) Audiologists must understand the role of genetic mutation analysis and early diagnosis of Usher syndrome. Specific testing can provide information on the type of Usher syndrome which can help determine the appropriate treatment option.
- 3) Audiologists must be aware of the increased benefit of an early age of implantation on speech perception, speech production and quality of life.
- 4) Additional research is needed in the future regarding cochlear implant benefit. If possible, researchers should try finding larger sample sizes and should try employing a study design that offers a stronger level of evidence.

This critical review offers an overall moderate level of evidence on the topic of cochlear implant outcome in the Usher syndrome population. Future research is needed in this area.

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