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THE BENEFITS OF EARLY COCHLEAR IMPLANTATION FOR SPEECH DEVELOPMENT IN CHILDREN WITH USHER SYNDROME: LITERATURE REVIEW

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Contributions:
A Study design/planning
B Data collection/entry
C Data analysis/statistics
D Data interpretation
E Preparation of manuscript
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Abstract

Introduction: Usher syndrome (USH) is a rare autosomal recessive genetic disorder characterized by sensorineural hearing loss (SNHL), vision loss (retinitis pigmentosa), and occasional balance impairment. Depending on the severity and onset of hearing loss and coexisting vestibular dysfunction, USH is divided into three clinical types – USH1, USH2, USH3 – as well as atypical USH which combines features of all these three. The purpose of this review is to present the impact of cochlear implantation on speech development in children diagnosed with all types of Usher syndrome.

Material and methods: All relevant publications published in from 2013 to 2023 were retrieved from PubMed based on the keywords *Usher syndrome*, *Usher syndrome diagnostics*, *Usher syndrome hearing loss*, *Usher syndrome cochlear*, and *Usher syndrome speech*. Exactly 67 papers were selected.

Results: Bilateral cochlear implantation in children with Usher syndrome is beneficial for audiological and verbal development provided that hearing loss is detected early and implantation done promptly. In USH1 the preferred age is before 3 in the case of severe to profound congenital SNHL; in USH2 and USH3 the optimal time for implantation is hampered by the difficulty of estimating when hearing loss occurred and its rate of progression. After bilateral cochlear implantation, studies showed improvements in the categories of auditory performance (CAP), speech intelligibility rate (SIR), meaningful auditory integration scale (MAIS), meaningful use of speech scale (MUSS), and speech reception score (SRS), together with good development of speech perception and verbal communication.

Conclusions: Early diagnosis (before the onset of vision loss) and early bilateral cochlear implantation in children who have suffered severe to profound SNHL due to Usher syndrome reduces disability and maximizes auditory–oral communication skills, significantly increasing their quality of life.

Keywords: Usher syndrome • diagnostics • hearing loss • cochlear • speech

KORZYŚCI Z WCZESNEJ IMPLANTACJI ŚLIMAKOWEJ W ROZWOJU MOWY U DZIECI ZE WSZYSTKIMI TYPAMI ZESPOŁU USHERA. PRZEGLĄD LITERATURY

Streszczenie

Wprowadzenie: Zespół Ushera (USH) jest rzadką chorobą genetyczną dziedziczoną w sposób autosomalny recesywny, charakteryzującą się odbiorczym ubytkiem słuchu (SNHL), utratą wzroku (zwyrodnienie barwnikowe siatkówki), czasami z zaburzeniami równowagi. W zależności od stopnia zaawansowania ubytku słuchu i jego momentu wystąpienia oraz współistniejącej dysfunkcji przedsionkowej zespół Ushera dzieli się na trzy typy kliniczne – USH1, USH2, USH3 oraz atypowy zespół Ushera, który łączy w sobie cechy wymienionych typów. Celem pracy jest przedstawienie wpływu wszczepienia implantu ślimakowego na rozwój mowy u dzieci ze zdiagnozowanymi wszystkimi postaciami zespołu Ushera.

Materiał i metody: Wszystkie istotne publikacje pobrano z bazy PubMed, z wykorzystaniem słów kluczowych takich jak *Usher syndrome*, *Usher syndrome diagnostics*, *Usher syndrome hearing loss*, *Usher syndrome cochlear*, *Usher syndrome speech*. Ostatecznie wybrano 67 prac. Wszystkie badania zostały opublikowane w ciągu ostatnich dziesięciu lat (2013–2023).

Wyniki: Badania wykazały, że obustronna implantacja ślimakowa u dzieci z zespołem Ushera korzystnie wpływa na rozwój słuchowy i werbalny. Jedynym warunkiem jest odpowiednio wczesne wykrycie niedosłuchu i wykonanie implantacji – najlepiej przed 3 rokiem życia w przypadku głębokiego lub ciężkiego wrodzonego SNHL w USH1. Optymalny czas implantacji w USH2 i USH3 jest utrudniony ze względu na niemożność

oszacowania momentu wystąpienia i tempa postępu ubytku słuchu. Badania wykazały poprawę w kategoriach sprawności słuchowej (CAP), wskaźnika zrozumiałości mowy (SIR), skali znaczącej integracji słuchowej (MAIS) i skali znaczącego wykorzystania mowy (MUSS) oraz wyniku odbioru mowy (SRS) po obustronnym wszczepieniu implantu ślimakowego oraz rozwojem prawidłowego postrzegania mowy i komunikacji werbalnej u dzieci z zespołem Ushera.

Wnioski: Wczesna diagnostyka i obustronna implantacja ślimakowa u dzieci z głębokim i ciężkim SNHL pozwala na redukcję niepełnosprawności i maksymalizację rozwoju umiejętności komunikacji słuchowo-ustnej u dzieci z zespołem Ushera (przed wystąpieniem utraty wzroku), co znacząco zwiększa komfort ich życia.

Słowa kluczowe: zespół Ushera • diagnostyka • niedosłuch • ślimak • mowa

Introduction

Usher syndrome (USH) is an autosomal recessive genetic disorder that causes hearing and vision dysfunction, sometimes with balance difficulties [1]. It occurs with an incidence of 1/10,000 and is the most common cause of combined deafness and blindness [2].

Depending on the severity and onset of hearing loss and coexisting vestibular dysfunction, Usher syndrome can be divided into three clinical types [3]. The most severe, Usher syndrome type I (USH1), involves inborn deafness (profound congenital bilateral and prelingual sensorineural hearing loss, SNHL) and serious balance problems. In many cases, vision loss due to retinitis pigmentosa (RP) appears within 10 years of birth and progressively constricts the field of vision (so-called tunnel vision) and reduces visual acuity, ultimately leading to complete blindness. Congenital hearing loss and vestibular dysfunction in USH1 cause severe developmental difficulties in children: there is delay in psychomotor development and, in the absence of intervention, halting verbal communication [3–6]. Type 2 (USH2) is characterised by congenital and bilateral SNHL of mild to moderate severity (affecting the low frequencies) or, more often, severe to profound SNHL affecting the higher frequencies, usually without vestibular dysfunction or with variable vestibular response. Visual problems usually start in adolescence and are progressive. Due to the clinical similarity of USH1 and USH2 – early hearing and vision loss – it is difficult to distinguish the types, but in USH2 vestibular function is often preserved [3,6–8]. Ramos et al. [9] also report possible olfactory dysfunction in patients with USH1 and USH2: they saw significantly lower olfactory threshold and shallower olfactory sulcus depth. In type 3 (USH3), the child is born with normal hearing, but in their teenage years, progressive SNHL with variable vestibular abnormalities begin. Vision loss often starts with night blindness [3]. Velde et al. [10] also distinguish Usher syndrome type 4 (USH4), where there is late-onset RP and SNHL, but no vestibular dysfunction. Finally, atypical Usher syndrome involves early and progressive SNHL without vestibular involvement and mild RP [11,12]. **Table 1** summarises the four types.

In Usher syndrome type 1 there are, depending on the mutation, six genetic subtypes: subtype 1B (mutation in myosin VIIa, *MYO7A*), subtype 1C (mutation in harmonin, *USH1C*), subtype 1D (mutation in cadherin 23, *CDH23*), subtype 1F (mutation in protocadherin 15, *PCDH15*), subtype 1G (mutation in scaffold protein containing ankyrin repeats and sam domain, SANS), and subtype 1J (mutation in calcium and integrin-binding family member 2, CIB2) [12–17]. The predominant subtype is 1B, which accounts for more than 50% of USH1 cases [18].

As for Usher type 2, Nisenbaum et al. [19,20] claim that its basis is a mutation in *CDH23* (similar to the mutation identified in USH1), as well as *USH2A* (usherin), *GPR98* (very large G protein–coupled receptor 1, also known as *VLGR1*), *WHRN* (whirlin, also known as *DFNB31*), and *ABHD12* (alpha/beta-hydrolase domain containing 12). Davies et al. [8] list four genetic subtypes of Usher syndrome type 2: 2A (mutation in usherin), 2B (mutation in *ADGRV1*), 2C (mutation in *VLGR1*), and 2D (mutation in whirlin). Stemerdink et al. [21] estimate that mutations in *USH2A* comprise 50% of the total number of cases of Usher syndrome type 2.

For USH3, the evidence is that mutations in *CLRN1* (clarin-1), *HARS* (histidyl-tRNA synthetase), and ABHD12 are typical.

In atypical Usher syndrome, a number of mutations characteristic of the three previously mentioned types have been identified (*MYO7A*, *USH1G*, *USH2A*, *GPR98*, *HARS*, *ABHD12*) as well as other mutations – *CEP250* (C-Nap1),

Table 1. Severity of hearing loss and presence of vestibular dysfunction in types of Usher syndrome [3–9,11,12]

Type of Usher syndrome	Severity of hearing loss and vestibular dysfunction
USH1	Profound congenital sensorineural hearing loss or complete deafness; severe vestibular dysfunction
USH2	Congenital sensorineural hearing loss at low frequencies (from mild to moderate); at higher frequencies, from severe to profound; no vestibular dysfunction or variable vestibular responses
USH3	Progressive sensorineural hearing loss since adolescence (from normal to severe); variable vestibular responses
Atypical USH	Progressive sensorineural hearing loss since adolescence; no vestibular dysfunction

Table 2. Detected mutations in Usher syndrome [12–20]

Type of Usher syndrome	Detected mutations
USH1	*MYO7A, USH1C, CDH23, PCDH15, SANS, CIB2*
USH2	*CDH23, USH2A, GPR98, WHRN, ABHD12*
USH3	*CLRN1, HARS, ABHD12*
Atypical USH	*CEP250, CEP78, ARSG, MYO7A, USH1G, USH2A, GPR98, HARS, ABHD12*

CEP78 (centrosomal protein 78), and *ARSG* (arylsulfatase g) [8,19]. The PDZ domain-containing protein 7 (*PDZD7*) is considered a modifier for the retinal phenotype and the severity of Usher syndrome [8,19,22,23]. **Table 2** summarises detected mutations in all types of Usher syndrome.

It is estimated that hearing loss affects approximately 1.1–3.5 per 1000 newborns screened [24]. Auditory privation significantly impacts on a child's psychosocial development, and can include delays in speech and language development, depression, anxiety, low self-esteem, problems with self-acceptance, and reduced academic performance [24–26]. Depending on when hearing loss occurred, the loss can be classed as prelingual, which occurs before the development of speech (Usher syndromes types 1 and 2), or postlingual, which occurs after speech has been acquired (Usher syndrome type 3) [25]. To avoid the long-term consequences of hearing loss, early diagnosis (hearing screening) and treatment are crucial [24,25].

The degree of hearing impairment in Usher syndrome increases with age, but it is impossible to predict the rate of progression: in some people it progresses quickly to complete deafness, while in others the rate of progression is almost imperceptible. However, it has been noticed that the most rapid progression of hearing loss occurs within the first two decades of life [8].

Currently, the only treatments for hearing loss associated with Usher syndrome are hearing aids or cochlear implantation [27]. Hearing aids are often preferred in such patients, but in the case of USH1 (and some people with USH2 and USH3) they may prove ineffective (since good speech recognition is required), and then a cochlear implant (CI) is needed. CIs are frequently used in the treatment of profound hearing loss in children with Usher syndrome and allow children to achieve proper speech and language development [8,12,28,29]. According to Hoshino et al. [30], auditory stimulation in a child with congenital deafness restored before the age of 3 1/2 allows the child to acquire natural developmental abilities, and so early implantation in a case of Usher syndrome can enable proper speech and verbal communication skills.

According to Davies et al. [8], children with Usher syndrome type 1 are perfect candidates for a CI because they are usually born with prelingual deafness in which low-frequency hearing is preserved. Hence, early and bilateral implantation has the potential to confer significant audiological benefits – hearing and speech intelligibility can often be excellent. In USH2, however, hearing aids used from early childhood are usually the first choice, although if there are poor speech detection and communication problems in patients with severe and progressive hearing loss, then a CI is indicated. For patients with USH3, a CI may also be a suitable way to improve hearing, but only if the hearing loss is severe (otherwise there is a risk of damaging residual hearing) [8]. According to Koenekoop et al. [4], non-implanted children with USH1 often fail to develop speech.

In this review we present the benefits of receiving an early CI on the speech development of children diagnosed with Usher syndrome.

Material and methods

Aim

The purpose of this review is to summarise the impact of early cochlear implantation on speech development in children diagnosed with Usher syndrome.

Eligibility criteria

We analysed studies published within the last 10 years. The core focus was Usher syndrome, its impact on speech development, and the role of CIs in such children. We considered all types of observational studies.

Search strategy

The search was conducted in PubMed. Keywords were *Usher syndrome* (686 results), *Usher syndrome diagnostics* (338 results), *Usher syndrome hearing loss* (343 results), *Usher syndrome cochlear* (88 results), and *Usher syndrome speech* (17 results). The last time the source texts were reviewed was on 15/09/2023. The inclusion criteria used in the review were publication date (last 10 years), papers with full text available, English language, on-topic, approval of a bioethics committee, and high reliability. We excluded older studies, animal studies, pharmacological models, studies in languages other than English, studies with low reliability, and those without bioethics committee consent.

Data collection

First, papers were selected and then abstracts and full articles for chosen studies were read. The extracted data included the following information: clinical features, hearing disorders, speech development, and type of CI. There were 1472 papers from the PubMed database which were retrieved. Papers were searched using the above keywords and duplicates were removed. There were 243 articles whose titles were relevant to the topic. After reading their abstracts, 155 of them appeared to be highly reliable. We checked the papers in terms of quality of the results,

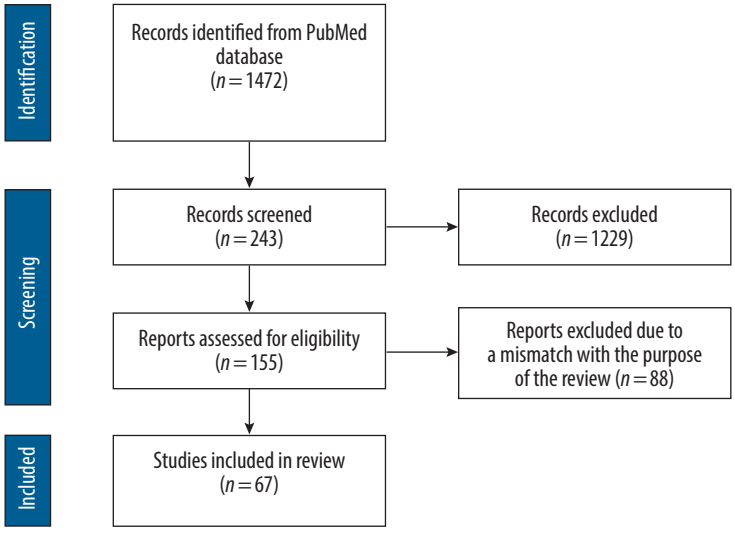

Figure 1. The search process PRISMA diagram

the type of technique used, the intervention and, finally, if they met our inclusion criteria, the full article was read. Finally, 67 articles were selected as being relevant to the topic. **Figure 1** illustrates the search process.

Results

Time and lateralisation of CIs in children with Usher syndrome

The literature recommends bilateral implantation in children with USH1 at the earliest opportunity. This will have the greatest developmental benefits for the child in terms of hearing, speech, and development. It has been found that in children with USH implanted before the age of 3, verbal communication is better developed than in children who received a CI at a later age [8,31]. In the case of USH2 and USH3, the optimum time for implantation is hampered by the inability to estimate when hearing loss began and its rate of progression [8]. Several authors document how early implantation in children allows them to develop speech, and the earlier the child receives a CI, the better will these skills be [8,12,28,32].

Bilateral implantation produces significantly better effects than unilateral implantation and better sound localisation (due to brain plasticity and bilateral noise blocking), and so children implanted early show faster development of speech and psychosocial skills than children with SNHL but no CI. This is especially important in people with disabilities, such as those with Usher syndrome, who develop RP in their teenage years [8,12]. Moreover, analysis by Davies et al. [8] showed that bilateral implantation at an early age (defined as less than 3 years) allowed children to develop better verbal communication skills than patients implanted later (defined as age above 13 years) who tended to have suboptimal speech reception scores. Among children with various subtypes of USH and implanted before the age of 9, the best effects in postoperative speech perception were achieved by children operated on before the age of 3. Nevertheless, findings show that receiving a CI within the first 20 years of life still allows for measurably better hearing results [8]. Of course, it is important for auditory rehabilitation to follow on from implantation, as it effectively improves communication skills [8].

Alsanosi [33] concludes that early, simultaneous bilateral implantation in patients with Usher syndrome with congenital profound bilateral deafness allows age-appropriate audiological results. For example, implantation in a 5-month-old boy with Usher syndrome, probably USH1, shows what is possible [33]. Hoshino et al. [30] find that late implantation in patients with USH1 allows speech recognition, but only in patients who have received previous hearing stimulation, because full development of the auditory pathway and central processes is necessary. Without prior central hearing skills, there is difficulty adapting to the CI and it often leads to failure [30].

Benefits of a CI in children with Usher syndrome

The benefits of a CI in children diagnosed with Usher syndrome were investigated by Nair et al. (2020) in a group of 27 patients aged 1–6 years with bilateral profound sensorineural hearing loss [34]. The control group were 30 implanted people of similar age, but without Usher syndrome. In both groups, the categories of auditory performance (CAP) and speech intelligibility rate (SIR) were examined after 3, 6, 9, and 12 months after the procedure. Both in the study and control groups, improvement in verbal communication was noted, but in the USH group it was less developed, which may have been affected by RP as part of Usher syndrome. The paper emphasises the importance of audio-verbal therapy after a CI, the significance of an individualised approach, and the need for early intervention, which will protect the child from severe impairment and enable appropriate development [34].

The results of the Nair et al. (2020) study [34] confirm similar research carried out by Remjasz-Jurek et al. (2023) in which auditory performance and speech intelligibility after a CI in children with Usher syndrome were also

Table 3. Summary of findings from research studies and case reports included in review

Authors	Type of USH	Number of patients (n) implanted with USH	Type of cochlear implantation	Conclusion
Henricson et al. (2018) [28]	USH1	*n* = 7	unilateral	Children with Usher syndrome implanted after the age of 2 achieve similar outcomes (memory capacity, phonological and lexical skills) to children implanted with congenital deafness
Hoshino et al. (2017) [30]	USH1	*n* = 10 average age at implantation = 18.9 years (5–49)	unilateral	Late cochlear implanttation in patients with USH1 allows speech recognition, but only in patients having previous hearing stimulation
Jatana et al. (2013) [32]	non-defined	*n* = 712 average age at implantation = 3.3 years	bilateral	Bilateral CI in children with USH permits development of open speech perception in 92% and verbal communication in 69%
Broomfield et al. (2013) [36]	non-defined	*n* = 9 Average age at implantation: early = 2.7 years late = 12.7 years	unilateral	Results achieved after a CI are usually satisfactory (higher reception scores and speech perception ability), but may differ in patients with the same genetic syndrome
Alsanosi (2015) [33]	non-defined	*n* = 1 (case report) age at implantation = 5 months	bilateral	Simultaneous bilateral implantation in children aged several months is recommended when performed by an experienced team, which allows for age-appropriate audiological results
Remjasz-Jurek et al. (2023) [35]	non-defined	*n* = 35 average age at implantation = 6.3 years (0.3–17.6 years)	unilateral	USH patients had marginally worse post-implant outcomes than asymptomatic implanted patients, CI significantly improved the hearing and speech intelligibility of children with Usher syndrome. Particular advancement was noticed in children who received a CI under the age of 3 years
Nair et al. (2020) [34]	non-defined	*n* = 27 average age at implantation = 2.9 years (11 months – 4.7 years)	unilateral	Both in the study and control groups, improvement in verbal communication was noted, but in the USH group it was less developed than in the control group

assessed [35]. The research group was 35 children aged 0.3–17.6 years (average age of implantation was 6.3) diagnosed with Usher syndrome (without specifying the type), whose results were compared to a control group of 46 implanted children without symptoms. Average PTA thresholds were 25.0 dB HL in the group of children with Usher syndrome, while in the control group it was 28.4 dB HL. Categories of auditory performance (CAP) was 5.3, compared to 5.1 in the study group. Speech intelligibility rate (SIR) in the study group was 4.1 and in the control group 3.9. The *Meaningful Auditory Integration Scale* (MAIS) in the Usher syndrome group was 82.3% and in the control group 80.5%, while the *Meaningful Use of Speech Scale* (MUSS) in the study group was 81.8% and in the control group 76.6%. The results showed that although USH patients had marginally worse post-implant outcomes than asymptomatic implanted patients, a CI significantly improved the hearing and speech intelligibility of children with Usher syndrome. Particular advancement was noticed in children who received a CI under 3 years of age. In general, better speech therapy results were achieved in children who were implanted early [35].

Jatana et al. (2013) evaluated the benefits in speech perception and movement after bilateral cochlear implantation in 712 children with USH (also without determination of USH subtype) [32]. Children were implanted at ages from 6 months to 11.6 years (average 3.3 years). Observations were carried out from 10 months to 15.6 years after implantation – an average of 7.8 years. The study showed that the vast majority of children (92%) developed open speech perception and more than half the children (69%) used verbal communication. The authors conclude that bilateral CIs in children with severe to profound SNHL with Usher syndrome is crucial for proper speech development [32]. Another study by Broomfield et al. (2013) demonstrated increased Bench–Kowal–Bamford (BKB) speech reception scores and speech perception ability using the

Table 4. Summary of findings from other papers included in review [1–27,29,31,37–67]

Authors	Conclusions in terms of diagnosis and treatment by a CI
Koenekoop et al. (2023) [4,7] Fuster-García et al. (2021) [5] Ramos et al. (2019) [9] Velde et al. (2022) [10] Gilmore et al. (2023) [13] Donaldson et al. (2018) [14] Miyasaka et al. (2013) [15] Chen et al. (2022) [16] Emptoz et al. (2017) [17] Toms et al. (2020) [18] Nisenbaum et al. (2022)[19] Stemerdink et al. (2022) [20] Blanco-Kelly et al. (2015) [21] Zou et al. (2014) [22] Bonnet et al. (2016) [23] de Joya et al. (2021) [27] Whatley et al. (2020) [66] Toualbi et al. (2020) [67]	Bilateral CI in patients with USH is, next to hearing aids, currently the best option for hearing rehabilitation, despite the detection of many mutations in USH and the dynamic development of gene therapies
Castiglione et al. (2022) [1] McKinney et al. (2017) [43] Miyamoto et al. (2018) [44] Karltorp et al. (2020) [45] Dettman et al. (2021) [46] Szyfter et al. (2019) [47]	In children with USH1, early CIs (age 6–12 months) is recommended to ensure normal development of hearing, speech, and social skills
Delmaghani et al. (2022) [2] Koenekoop et al. (2023) [4,7]	CIs and hearing aids may provide significant benefits in auditory-sensory orientation in most patients with USH
Davies et al. (2021) [8] Health Quality Ontario. Bilateral Cochlear Implantation: A Health Technology Assessment (2018) [48] Gifford et al. (2020) [50] Kumari et al. (2018) [51] Bae et al. (2019) [52]	When children affected by USH (severe to profound SNHL) are implanted bilaterally, they have better sound localisation, speech perception, language development, and greater vocalisation in preverbal communication compared to unilateral implantation. Additionally, children with bilateral CIs achieve better results at school and communicate more effectively with others
Tsang et al. (2023) [6] Cejas et al. (2015) [31] Virzob et al. (2023) [49]	Most patients with USH have better speech perception after CI, but the development of verbal communication depends on their age (the sooner the implantation, the better the speech perception). This is especially important in USH1 patients with prelingual deafness
Nolen et al. (2020) [3] Fowler et al. (2021) [11] Mathur et al. (2015) [12]	Most children with USH who received a CI early are able to develop verbal communication. SNHL occurring in atypical USH usually requires hearing aids only
Sommerfeldt et al. (2023) [24] Young et al. (2023) [25] Verstappen et al. (2023) [26] Korver et al. (2017) [29] Position Statement from the Joint Committee on Infant Hearing (2019) [37] Park et al. (2021) [40] Fitzpatrick et al. (2015) [41] Koffler et al. (2015) [53] Arias-Peso et al. (2023) [54] Stiff et al. (2020) [55]	Lack of early intervention (diagnosis and treatment, including CI) for hearing loss in people with USH can lead to serious developmental delays in children, including speech and language development. Thus early detection of hearing loss and then treatment remains crucial
Magliulo et al. (2015) [62] West et al. (2015) [63] Kletke et al. (2017) [64]	Newborn hearing screening (OAE, ABR) is a key to early detection of hearing loss. In the diagnosis of hearing loss, ECOG and assessment of speech may be helpful, while when assessing vestibular function key tests are VEMPs, vHIT, as well as Fitzgerald–Hallpike caloric test, rotary chair testing, ENG, posturography
Yoshimura et al. (2021) [56] Medina et al. (2021) [57] Ramzan et al. (2018) [58] Lenarduzzi et al. (2015) [59] Aparisi et al. (2014) [60] Magliulo et al. (2017) [61] Ambrosio et al. (2021) [65]	Comprehensive genetic tests are costly, but necessary for a definite diagnosis of USH (and differential diagnosis), and can help to detect the USH even before the appearance of ophthalmological symptoms

Table 4 continued. Summary of findings from other papers included in review [1–27,29,31,37–67)

Authors	Conclusions in terms of diagnosis and treatment by a CI
Sharma et al. (2020) [38] Warner-Czyz et al. (2022) [39]	To maximise the benefits of CIs in deaf children (USH1), support is essential. The greatest speech benefits from CIs are achieved by children with USH who have no other comorbidities and where intervention was begun quickly
Varadarajan et al. (2021) [42]	The benefits of CIs in children with USH depend on the degree of hearing loss, asymmetric or bilateral hearing loss, presence of residual hearing, inner ear malformation, and cochlear nerve deficiency

Speech Reception Score (SRS) in a group of 38 implanted children – 9 with Usher syndrome and 29 with other genetic syndromes with severe hearing impairment [36].

Table 3 and **Table 4** summarise the findings from the papers included in this review.

Discussion

Quick intervention helps proper speech development

The result of a CI depends on the age at which the hearing loss began and when it was diagnosed, whether the implant was done prelingually or postlingually, the age of implantation, the method of communication before and after intervention, rehabilitation, as well as motivation to learn and support from the family. The above studies agree that the earlier the implantation, the greater the chances for proper development of speech skills. However, for children with Usher syndrome, no clear guidelines exist from scientific societies specifying the appropriate age for implantation. Among the studies cited, most recommend an age of under 3 years for a child with USH1 to receive a CI. In other types of Usher syndrome, the best time depends on the level of hearing impairment.

The age of implantation is affected by when the hearing loss was detected, and here hearing screening programs play a major role. The current recommendations of the Joint Committee on Infant Hearing from 2019 include the need to perform a hearing screening by the age of 1 month, to identify hearing loss by 3 months, and to enroll for appropriate therapeutic intervention by 6 months. However, the committee encourages a 1–2–3 approach: a hearing screening by month 1, identifying hearing loss by month 2, and beginning therapy by month 3 [37,38]. Early use of hearing aids is also encouraged, and if progress is not achieved there is time for early referral to determine candidacy for a CI. This is particularly important in younger children so that they can develop verbal communication [38,39]. Delays in receiving a CI lead to poorer outcomes [40]. Significant problems hindering early implantation are diagnostic delays, the presence of residual hearing, comorbidities, family hesitancy and geographical location [38,39]. Fitzpatrick et al. (2015) point out that delays in implantation in children result from a failure to continually test audiological performance, and so it is important to constantly monitor children with hearing loss [41].

Although CIs are a proven method of treating sensorineural hearing loss in children and adults, better technology allows the indications for implantation to be expanded. This ensures that all children will have access to sounds and develop language and communication skills [39,42]. As set out in [42], the current FDA indications for receiving a CI in children depend on the degree of hearing loss. However, there is good evidence of successful implantation below these indications [33,43–46]. Furthermore, another study [45] has shown that in children implanted at 5–11 months, the level of speech recognition and vocabulary range was significantly better than in children implanted at 12–29 months (and there was no indication of an increase in surgical complications due to the lower age). Based on the Categories of Linguistic Performance (CLIP) analysis, another study found that children who received a CI before 9 months had better language development than children implanted later [46].

Bilateral cochlear implantation in children is still under discussion worldwide [47–51]. According to Szyfter et al. (2018), this solution should be used in children with visual impairment (Usher syndrome), with initial cochlear obstruction and insufficient audiological results from unilateral implantation [47]. In the case of bilateral congenital deafness, implantation should not be postponed for longer than 12 months. An assessment made by Health Quality Ontario demonstrated that in children with severe to profound SNHL, they had improved sound localisation, speech perception, language development, and greater vocalisation in preverbal communication when implanted bilaterally compared to unilaterally. The Canadian group concluded that bilateral implantation is effective and willingly used by patients [48]. Virzob et al. [49] reach similar conclusions, emphasising that the age at implantation, the level of language peformance before surgery, the duration of implant use, and auditory rehabilitation are key to achieving good results. Gifford et al. (2020) believe that residual hearing at low frequencies is not an obstacle to bilateral implantation after a trial period with bimodal stimulation [50]. Kumari et al. (2018) encourage the use of bilateral implantation as standard in severe prelingual bilateral SNHL in children; in their study mean CAP and SIR scores were significantly higher in children implanted bilaterally than in children implanted unilaterally [51].

A study by Bae et al. (2019) showed that children with bilateral prelingual deafness and a CI received between 1 and 3 years of age are more likely to attend mainstream schools than similar children without an implant [52]. They note that the rate of attending a tertiary institution of people with CIs is the same as in the general population.

Diagnosis of USH and importance of early detection

The differential diagnosis of Usher syndrome is a key. It is estimated that there are about 40 disorders in which vision and hearing are impaired (e.g. Alport syndrome, Stickler syndrome, Baraitser–Winter syndrome), but more than half the cases are Usher syndrome [53–55]. Typically, audiological symptoms precede vision loss in patients with USH [8]. To make a diagnosis, thorough ophthalmological and otorhinolaryngological examinations are needed, but genetic tests are crucial to confirm the diagnosis and make a prognosis [53–55].

Yoshimura et al. (2021) point out that although Usher syndrome is diagnosed based on clinical symptoms, comprehensive genetic tests can detect the disease before the appearance of ophthalmological symptoms [56]. Medina et al. (2021) emphasise that, when Usher syndrome is uncertain, it is important to do genetic testing for genes responsible for hearing and vision loss although a combination of genetic deafness and blindness does not always mean Usher syndrome [57]. According to these authors, the genes responsible are *ALMS1*, *TUBB4B*, *CEP78*, *ABHD12*, and *PRPS1*.

Precise genetic diagnosis is hampered by the genetic heterogeneity of Usher syndrome, its high cost, and the long time required to undertake multiple testing procedures [58,59]. So far, mutations in 11 genes responsible for USH have been described, but many patients have the condition without a specific mutation being identified [58]. There is hope that many previously unexplained genetic mutations will be detected by next-generation sequencing (NGS) using targeted panel sequencing and clinical exome sequencing (CES) and genome sequencing [58–60]. Ramzan et al. (2018) highlight the role of CES in identifying the genetic cause of hearing loss [58]. According to them, this method is accurate and allows rare genetic diseases such as Usher syndrome to be detected. Aparisi et al. (2014) designed a custom HaloPlex panel for Illumina platforms to capture exons of 10 Usher syndrome causative genes – *MYO7A*, *USH1C*, *CDH23*, *PCDH15*, *USH1G*, *CIB2*, *USH2A*, *GPR98*, *DFNB31*, and *CLRN1* – and the related genes *HARS* and *PDZD7* and candidate genes *VEZT* and *MYO15A* [60]. Among 44 patients with Usher syndrome participating in the study (11 in the control group with known mutations, and 33 in the study group without a detected mutation), the panel confirmed mutations in 40 of them (8 from the control group and 32 from the study group). Sequencing using the panel allowed 53 different mutations to be detected at the same time – both point mutations and large rearrangements, including the detection of mutations in previously genetically undiagnosed patients. According to the authors, genetic diagnosis of Usher syndrome using a panel allows for more genetic causes of USH to be detected and minimises the cost of testing [56]. According to Lenarduzzi et al. (2015), it is important to investigate all possible causative genes to detect mutations and direct treatment [59].

Newborn hearing screening remains crucial, especially in the diagnosis of Usher syndrome type 1. A child with an abnormal result of otoacoustic emissions (OAEs) or auditory brainstem response (ABR) can be subsequently tested by otoscopy, cytomegalovirus (CMV) testing, temporal imaging, and possible genetic testing [4,8]. Electrocochleography (ECOG) and, in older children, assessment of speech may also be added [4]. Vestibular function can be evaluated using caloric testing, cervical vestibular evoked myogenic potentials (cVEMPs), ocular vestibular evoked myogenic potentials (oVEMPs), video head impulse test (vHIT), rotary chair testing, electronystagmography (ENG), and posturography [8,60]. According to several authors, VEMP and vHIT remain the most sensitive tests for detecting hidden vestibular damage in USH2; both tests are recommended to assess vestibular nerve deficit in patients with USH, which also helps determine the type of USH [4,61,62].

Ophthalmological diagnosis of children with profound to severe preverbal SNHL is often essential in the diagnosis of Usher syndrome [63,64]. West et al. (2015) mention the necessity of performing an electroretinogram (ERG) in those patients with SNHL and a CI or with ophthalmological symptoms (retinal dystrophy) [63]. According to Kletke et al. (2017), in children with congenital SNHL and co-occurring vestibular disorders, the risk of USH is increased, and so performing an ophthalmological examination (including an electroretinogram) and genetic tests for USH are recommended, because they will speed up diagnosis and treatment [64]. When diagnosing Usher syndrome in children with SNHL, Ambrosio et al. (2021) recommend, as well as performing an electroretinogram, determination of the dark-adapted threshold [65]. However, in all cases, genetic testing is necessary for a definite diagnosis of Usher syndrome.

Identification of genes responsible for Usher syndrome and the development of gene therapies provide opportunities for cures and for improving the quality of life of patients with USH. However, even though hearing aids and CIs improve hearing and allow good speech development, there is currently still no treatment for retinitis pigmentosa [27,66,67].

Limitations

Many of the available publications do not determine the type or subtype of Usher syndrome, often because there may be blurring of symptoms between the different types. Additionally, due to the small database of records from the last 10 years, some of the chosen studies were carried out on small groups, and so there is a need for further research to confirm the results, particularly on the impact of a CI on improving children's speech.

Conclusions

Early cochlear implantation in children with severe to profound SNHL and Usher syndrome reduces their disability and maximises their auditory and oral communication skills, significantly increasing their quality of life. The earlier the implantation, the greater the chances that the child will develop good speech and be able to effectively communicate verbally, provided of course that there is adequate auditory–verbal rehabilitation. If Usher syndrome is detected early and treated appropriately (including cochlear implantation), children with USH can be rehabilitated even before the onset of vision loss.

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