Unilateral congenital hearing loss in children: challenges and potentials

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Abstract

The estimated incidence of sensorineural hearing impairment (> 40 dB HL) at birth is 1.86 per 1000 newborns in developed countries and 30-40% of these are unilateral. Profound sensorineural unilateral hearing impairment or single sided deafness (SSD) can be treated with a cochlear implant. However, this treatment is costly and invasive and unnecessary in the eyes of many. Very young children with SSD often do not exhibit language and cognitive delays and it is hard to imagine that neurocognitive skills will present difficulties with one good ear. In the current paper we review the most recent evidence on the consequences of unilateral hearing impairment for auditory and neurocognitive factors. While data of both adults and children are discussed, we focus on developmental factors, congenital deafness and a window of opportunity for intervention. We discuss which etiologies qualify for a cochlear implant and present our multi-center prospective study on cochlear implants in infants with one deaf ear. The large, state-of-the art body of research allows for evidence-based decisions regarding management of unilateral hearing loss in children.

Keywords: single sided deafness, children, congenital, neurocognition, cochlear implant

Contents

1. Introduction

Humans are equipped with two ears for effective communication. Good coordination between the two ears facilitates, among other things, sound localization, speech in noise understanding, spatial awareness, ease of listening, and spoken language development (e.g. Boons et al., 2012 a,b; Van Deun et al., 2010; Jacobs et al., 2016, Litovsky and Gordon, 2016). The estimated incidence of sensorineural hearing impairment > 40dBHL at birth is 1.86 per 1000 newborns in developed countries of whom 30-40% are unilateral (Morton et al., 2006, Van Kerschaever and Stappaerts, 2011; Giardina et al., 2014 for SSD; Fitzpatrick et al., 2017). Lack of binaural input and diminished audibility negatively impact the abovementioned factors, thereby affecting communication and quality of life (e.g., Harkönen et al., 2015; Roland et al., 2016; Sladen et al., 2017b).

Newborn hearing screening (NHS) programs are pivotal to the diagnosis of congenital hearing impairment (HI) at birth. Following diagnosis of profound bilateral HI, treatment is offered early in life to enable exposure to sound for the development of speech and language. Although the brain is able to adapt to experiences throughout life, its plasticity is greatest during the first few years (Kral and Sharma, 2012). Most children with bilateral HI and two cochlear implants outperform peers with one cochlear implant in hearing and in spoken language, and the younger the age of implantation the better their performance (Van Deun et al., 2010; Boons et al., 2012b). Bilateral stimulation provided at a young age may, therefore, also be beneficial for children with profound unilateral hearing loss (UHL).

In Belgium, as in many other countries worldwide, there is no standard care for children with UHL, thereby assuming that the normal ear provides sufficient sensory cues for speech understanding. However, an increasing body of research shows that children with UHL not only experience difficulties localizing sounds and understanding speech in noise, but also have difficulty mastering complex skills for spoken language (Anne et al., 2017). Even mild HI places a child at risk for lasting language delays (Carew et al., 2017), although it is also true that language impairments are not an inevitable consequence of mild/moderate HI (Halliday et al., 2017).

Mild and moderate sensorineural HI in children are often managed with hearing aids, while conductive hearing loss can be treated with a bone anchored hearing aid (e.g. Snik et al., 2008; Nelissen et al., 2016). Profound sensorineural HI in one ear, also termed single sided deafness (SSD) could be treated by a cochlear implant (CI), especially if it is provided at a young age to maximize learning opportunities. Over the past decade, an increasing number of adults and

children with SSD have received a CI. The reported performance is often variable, presumably due to small sample sizes, different onsets of hearing loss, and different ages at implantation. Moreover, most research focusses on spatial and binaural hearing, not on neurocognitive factors, such as spoken language and executive functioning. In order to draw evidence-based decisions on whether or not to provide a CI to children with SSD, it is important to consider the functional and neural consequences of UHL, as well as the window of opportunity for cochlear implantation to maximize performance of the child.

2. Objectives of the current review

The objectives of this paper are threefold. The first objective is to discuss the importance of two ears for speech perception and communication, and the consequences of UHL on several performance factors in the developing child. Inevitably, the presented difficulties in spatial hearing, speech understanding and spoken language will be much more subtle for children with UHL than for children with profound bilateral HI. It is expected that children with SSD, the most prominent form of UHL, will show similar patterns of performance as children with other degrees of asymmetric hearing. In addition to the behavioral performance data we review the brain research on SSD, i.e. the extent to which SSD affects the cortical structures, especially in congenital deafness, and the importance of early intervention. A second objective of the paper concerns the current evidence on the efficacy of a CI as a treatment for SSD. Based on distribution of etiologies known from NHS data of the university hospitals in Antwerp and Leuven, we present an estimate of the number of children with UHL who qualify for a CI. Subsequently, we review current evidence on spatial and speech in noise understanding in adults and children with SSD and a CI reported in the literature. The final and third objective is to present our ongoing multi-center study on treatment of infants with SSD and a CI in Belgium.

3. The importance of two ears for speech perception and communication

In normal hearing, a specialized circuitry of neurons in the brainstem and midbrain processes the binaural cues presented to the two ears based on well-aligned input from the periphery (Colburn et al., 2006; Grothe et al., 2010). These interaural time and level cues are used to identify and separate sound sources. Thereby, they improve the signal-to-noise ratio (SNR) and, hence, provide cues for the development of communication skills. In the case of UHL the sensitivity to these cues is significantly reduced. The mechanisms through which (profound) UHL affects language, cognitive and academic performance relate to impaired spatial abilities and binaural hearing. In the next section the main binaural hearing mechanisms are discussed.

3.1 Binaural hearing mechanisms

The main processes involved in spatial hearing and binaural advantage are the head shadow effect, binaural unmasking and binaural summation. The head shadow effect refers to the ability to listen with the ear with the more favorable signal-to-noise ratio (SNR). It is a monaural, physical, effect, in which the head acts as an acoustic barrier and causes a level difference between the ears (Dillon, 2001). A person able to listen with both ears can potentially benefit from the head shadow effect by attending to the ear with the better SNR, regardless of the position of the noise source. A person with (profound) UHL, however, can detect speech and noise mostly or only on the side contralateral to the deaf ear. Because of the head shadow effect, the level of the signal can decrease up to 15-20 dB as it travels from one side of the head to the other side. This makes speech more difficult to understand, especially in the presence of noise. In addition, it is difficult for a person with (profound) UHL to compare interaural time and level cues associated with each source to improve the SNR, a mechanism termed binaural unmasking. Binaural unmasking can provide a 2- to 4.9-dB improvement in speech recognition threshold (Bronkhorst et al., 1988). Finally, binaural summation refers to an increase in the perception of loudness when listening binaurally rather than monaurally to a certain stimulus. The additive effect by higher-order processing centers usually results in a 2-3 dB improvement in speech intelligibility compared to the monaural condition (Dillon, 2001).

3.2 Consequences of unilateral hearing impairment

3.2.1 Spatial hearing and binaural processing

A vast number of clinical studies demonstrates the difficulties in spatial and binaural hearing that children with (profound) UHL encounter. While the mean localization error ranges between 4-6° for normally hearing (NH) children (Van Deun et al., 2009), it increases to 28° for children with SSD (Reeder et al., 2015). The inability to accurately localize sources not only affects the development of neurocognitive factors but also jeopardizes safety, e.g. in traffic. Moreover, children (6-14 yrs) with profound UHL require a more advantageous listening condition (between 2.5 – 8 dB SNR) to perform equally as well as their NH peers to identify sentences and nonsense syllables (Ruscetta et al., 2005; Noh and Park, 2012). Lieu et al. (2013) reported significantly poorer word recognition scores in quiet and in babble noise using CID W-22 word lists in a large sample of 107 children with UHL. Reeder et al. (2015) reported reduced word recognition of twenty 6 to 17 year old children compared to NH controls, even when words

were presented in quiet. Hearing impaired and NH children performed equally well when noise was presented from the front. However, when the noise moved to the right or left, the NH children benefited from spatial unmasking, while the children with moderately severe to profound UHL only exhibited better word understanding in noise when the noise was moved towards the deaf ear. As expected, localization performance was significantly poorer and more varied for children with UHL compared to age matched NH peers.

For young children with HI these results are disturbing, as they are exposed to many hours of environmental noise each day (Busch et al., 2017a). With the exception of very young children, most people spend at least 4 hrs/day (understanding speech) in noise. Listening in noise is bound to affect learning, also because children require a higher SNR than adults irrespective of noise to achieve comparable speech recognition scores (e.g. Corbin et al., 2016). In addition to improving the design of the classroom environments and addressing auditory distraction (for an overview see Clark and Sörqvist, 2012), it is important to improve the SNR of children with (profound) UHL through bilateral hearing, in order to provide optimal conditions to acquire (new) knowledge and learn. In an excellent review, Kral and colleagues (2016) discuss sensory loss as a connectome disease due to abnormal changes in individual wiring and coupling patterns in the brain. These changes profoundly affect the development of spoken language and higher-order cognitive skills in congenitally deaf children.

3.2.2 Neural processing

A child's brain is highly sensitive to loss of auditory input (Kral and O'Donoghue, 2010; Kral and Sharma, 2012; Kral, 2013). Cortical growth and synaptic development, which continue to develop up to sexual maturity (Kral et al., 2005), differ in persons with different degrees of congenital and acquired UHL. Changes in auditory and other brain structures, as a result of imbalanced auditory input, have been reported for both adults and children with UHL (Khosla et al., 2003; Schmithorst et al., 2005; Hanss et al., 2009; Propst et al., 2010; Burton et al., 2012; Kral et al., 2013; Liu et al., 2015; Tillein et al., 2016; Laugen Heggdal et al., 2016). For example, Propst et al. (2010) reported decreased activation of attention networks for children with profound UHL compared to NH children, and Zhang et al. (2016) reported changes in default mode network functioning. Furthermore, children with UHL demonstrated several differences in functional connectivity between brain networks involved with executive functioning, cognition and language comprehension (Jung et al., 2017). These results, as well as those of the other studies in adults and/or children with UHL, are consistent with the

connectome model presented by Kral et al. (2016), in that no part of the brain works in isolation, but that HI, whether uni- or bilateral, has a cascading effect on other neurocognitive skills.

In summary, changes in peripheral hearing impact upon cortical speech processing networks, with cascading effects for the neural processes supporting both perceptual and higher-level cognitive functions. Although changes in neuroplasticity also occur after acquired UHL (Maslin et al 2013a,b), those as a result of congenital deafness pose severe challenges for the maturation of the brain (Kral and O'Donoghue, 2010; Kral and Sharma, 2012). In the next section we review the literature on development of neurocognitive factors in children with UHL and SSD.

3.3 The development of neurocognitive factors

3.3.1 Spoken language: infancy

The consequences of unilateral sensory deprivation for the development of language are often difficult to grasp in very young children. Caregivers of children with SSD may not even notice hearing problems during the first year of life, especially as the environment can be relatively quiet (Busch et al., 2017a). Moreover, infants sleep a lot and sound production and perception are very much one-to-one at a short distance from their caregiver. Without neonatal hearing screening one may only start noticing hearing deficiencies when the child starts walking and the distance to the sound stimuli changes and/or when the child is exposed to more noise (such as in kindergarten). Yet, Kishon-Rabin and colleagues (2015) clearly showed that, compared to NH peers, 21% of 34 infants with UHL (median age 9.4 mo) demonstrated delays in auditory behavior and 41% showed delays in preverbal vocalizations. These data corroborated previous findings that infants with SSD demonstrated an average delay of 5 months to produce two-word phrases compared to NH peers (Kiese-Himmel, 2002) and, a bit later in life, delays in preschool language development (Borg et al., 2002). These data also underscore the need for appropriate intervention and rehabilitation at a very early age. Spoken language is acquired unconsciously, and diminished auditory input and lack of binaural summation affect access to relevant acoustic information from natural listening conditions that enables incidental learning, which, in turn, may result in impoverished vocabulary, language rule formation, and generalized knowledge about the surrounding environment (Saffran et al., 1996).

3.3.2 Spoken language: tapping into grammatical skills

In general, relatively few studies have focused on language difficulties in school age children with (profound) UHL (for a systematic review on language outcomes see José et al., 2011; Anne et al., 2017; Appachi et al., 2017). Klee and Davis-Dansky (1986) reported similar language

scores for a group of NH children aged 6 to 13 yrs compared to a group of same-aged children with a UHL of at least 45 dB HL. Despite similarity in language scores between the two groups, the authors argued that these HI children may still present with language difficulties, since verbal IQ scores were significantly lower for the children with UHL and the battery of language tests may not have been sensitive enough to demonstrate differences in performance. Subsequently, over the past years, research by Lieu and colleagues has shed some light on language difficulties in children with different degrees of UHL. They showed that children with UHL (aged 6-12) demonstrated significantly lower scores on receptive and expressive language tests when compared with their NH peers (Lieu et al., 2010). When 46 of the children with UHL in the latter study were monitored longitudinally, oral language scores improved significantly over time, but parent- or teacher-identified problems with school did not change (Lieu et al., 2012). A follow-up study, including 107 children (6-12 yrs) with permanent UHL matched to NH ones, yielded lower mean vocabulary, verbal sum, lower full-scale IQ scores, and lower mean oral language scores. In a following study, Fischer and Lieu (2014) also reported that adolescents did not catch up and that receptive and expressive language proficiency remained poorer compared to NH adolescents.

On the one hand, language acquisition requires the integration of perceptual information (see also Kral et al., 2017), and even minimal hearing loss can interfere in this process. On the other hand, normal variation from one child to another can obscure the effect of HI in childhood language acquisition. Several children with UHL appear to do as well as NH children (e.g. Fitzpatrick et al., 2015, based on questionnaires). However, composite expressive and receptive language scores do not really inform us about more specific language skills, such as grammar, that may negatively affect language development in children with mild/moderate HI or SSD. If composite language scores improve over time, but school performance remains poor, it may be appropriate to have a look at more specific deficiencies that may not be visible in composite scores.

To date, specific language deficiencies have not been studied in detail in children with SSD. However, formal language aspects reported to be affected in children with mild-to-moderate HI (Delage and Tuller, 2007; McGuckian and Henry, 2007; Tomblin et al., 2015) such as phonology and morphology, should be studied in children with SSD too. The acquisition of these complex linguistic skills is tied to critical periods in language development (Newport, 2002) and is very challenging for a child with any degree of HI. Morphology is a branch of linguistics that deals with the internal structure of words (such as inflection, derivation, and

compounding), and the way they are put together to form sentences (syntax). In order to be able do so, children need to master the phonology of the language, i.e. to learn to segment the speech stream and to distinguish the speech sounds from each other. Persistent delays in phonology are expected to affect morphology, such as the accuracy of verb tense marking. In typical development, tense marking begins at two and a half years of age (Rispoli, et al. 2009), and all of the forms are mastered by three years (Hadley and Holt 2006; Rispoli et al., 2009).

Several studies have reported delays in phonological skills by children with mild and moderate HI (e.g. Briscoe et al., 2001; Eisenberg et al., 2007 for a review). Delage and Tuller (2007) identified disorders in phonology and morphosyntax in half of their French-speaking adolescents, aged 11-15 yrs (n = 19) with mild and moderate HI. McGuckian and Henry (2007) showed that young children (7 yrs) with mild or moderate HI experienced difficulties in producing possessives and plurals (although they did not lag behind in the production of progressive –ing articles and irregular past tenses). In addition, Koehlinger et al. (2013) reported that some 3-6 yr old HI children yielded similar performance for allomorph production and sentence position as their NH peers, despite an overall lower accuracy rate. However, better hearing skills and better articulation skills were related to improved morpheme production (Koehlinger al., 2015). Their studies showed that any degree of HI places children at risk for producing shorter utterances and being less capable of producing verb-related grammatical morphology.

Sangen et al. (2017) were among the first to study complex linguistic skills in children with SSD. Results indicated significantly lower scores on tests of morphology, syntax and vocabulary, presumably due to disrupted auditory input during the time of normal language acquisition. The correct use of the past participle and of pronouns seemed to be challenging for several children with SSD. Formulating sentences was also more difficult compared to normal hearing children, as they made more mistakes in grammar and semantics.

It is unclear whether delays in phonology and morphosyntax resolve with age. Adults who acquired their language with more severe auditory limitations have been found to be more at risk of persistent problems with morphosyntax in written language production than adults with a lower degree of hearing loss in childhood (Huysmans et al., 2017).

3.3.3 Working memory, executive functioning and schooling

Alterations in the brain due to auditory deprivation not only influence language development but also affect general neurocognitive functioning (Kral et al., 2015; Pisoni et al., 2016).

Children with UHL were found to present lower (verbal) IQ scores than their NH peers (Niedzielski et al., 2006; Martinez-Cruz et al., 2009; Lieu et al., 2013; Purcell et al., 2016), although verbal IQ also improved in some children in the course of time (Lieu et al., 2012). Ead et al. (2013) reported significant deficits in a complex verbal working memory task in children with UHL. They had difficulty maintaining verbal information while processing irrelevant verbal information (impaired executive control function). Furthermore, the children demonstrated reduced accuracy and efficiency associated with phonological processing, especially when listening to unfamiliar verbal information, such as nonsense words.

The abovementioned challenges are likely to affect behavior and academic performance (Lieu, 2004; Tharpe, 2008; for a review see Krishnan et al., 2016). Although children with UHL often function satisfactorily at a young age (Kuppler et al., 2013), many experience difficulties at school, with up to 35% repeating a grade compared to 3.5% of their normal hearing peers and with significantly more of them requiring individualized education plans (Lieu et al., 2004, 2010). These children are also at risk for social and emotional problems (e.g. Borton et al., 2010), as are children with very mild losses (Bess et al., 1998). Recently, Netten et al. (2017) reported that children with moderate hearing loss have more difficulty understanding other people's intentions, desires and beliefs than their hearing peers. Effective management of UHL, whether mild or profound, should result in meaningful improvements in social skills and educational performance. In addition to (considering) intervention, care should be taken to optimize listening conditions in daily life, e.g. in the classroom. Previously, it has been shown that children and adolescents with moderate to profound UHL needed a seating position of 4.35 meters from a target to reach the same speech discrimination performance as NH adults seated at a 10 meter distance (Noh and Park, 2012). Even with a CI, classroom seating should be considered carefully, as well as the difficulties due to degraded exposure (due to noise, reverberation). In addition, more support and guidance are essential for families in the early stages of learning about hearing impairment (Fitzpatrick et al., 2016; Grandpierre et al., 2017).

In summary, limited audibility and atypical auditory experience affects listening skills and one good ear is not sufficient to promote the development of normal auditory, linguistic, and cognitive functions. Linguistic deficiencies in children with (profound) UHL are not as severe/pronounced as in children with bilateral deafness, and may especially show up in the emergence of morphology (Moeller et al., 2010). Importantly, research also demonstrates that the developmental gap between children with UHL and children with NH does not disappear

as children grow older (Fischer and Lieu, 2014). Therefore, in the next section, we will discuss the window of opportunity for intervention.

3.4 Congenital deafness and the window of opportunity for intervention

Behavioral and brain findings support the need for early intervention to optimize auditory exposure. As the neural circuitry for binaural processing is inborn and functional at birth (Tillein et al., 2010), the neural consequences of congenital SSD should not be underestimated. With congenital deafness, mutual interconnections cannot mature during the first years of life, as is demonstrated by a reduced corticocortical functional coupling between primary and secondary cortical auditory areas, both in the bottom-up and top-down information streams (Kral et al., 2017). In addition to deprivation-induced dystrophic changes beyond the primary auditory cortex (Berger et al 2017), bottom-up driven learning is not sufficiently effective if the periods of juvenile plasticity have already expired (Kral and Sharma, 2012).

Part of the cortical reorganization involves an increased representation of the NH ear compared to the deaf one, also termed ‘aural preference’. This preference, which has been demonstrated in cats (Kral et al., 2013b) and in humans (Gordon et al., 2015), results in a biased input to higher-order cortical areas and cognition. This is especially true if the onset of unilateral deafness is before or around the peak of functional synaptogenesis. Past a certain early sensitive period, the reorganization is less severe (Kral et al., 2009; 2013a,b). Recent research in rats with SSD shows that the unimpaired ear takes over the function of the impaired ear and stimulates the ipsilateral cortex (Lee et al., 2017). Moreover, the reorganization of the brain continues with increasing duration of SSD. The abovementioned consequences of congenital deafness strongly support early intervention, as the capacity for reorganization is greatest in the juvenile brain. Timing of treatment is thus essential and should be provided within the early critical period, to impede further preference for the stronger ear, and, possibly, to reverse or restore cortical reorganization (Kral and Sharma, 2012; Gorden et al., 2013; Jiwani et al., 2016).

4. Neurosensory restoration of the deaf ear combined with a normal hearing ear

A cochlear implant (CI) offers the potential to (partially) restore binaural hearing, whereas other interventions such as the CROS hearing aids or bone anchored hearing aids do not. While cochlear implantation (CI) has been standard of care and a life changing opportunity for bilaterally deaf adults and children for several decades (O’Donoghue, 2013), it has only gained attention for persons with SSD after treatment for incapacitating tinnitus by Van de Heyning et al. (2008). Due to stimulation of the auditory nerve and higher neural structures, the CI is the

only treatment option capable of providing hearing in the profoundly deaf ear in SSD, thus facilitating source localization, binaural hearing, and speech perception in noise. However, not all children with profound UHL will benefit from a CI to improve communication skills. Therefore, the second objective of this review paper was to examine the prevalence and etiologies of congenitally deaf children based on the data sets from the university hospitals of Antwerp and Leuven. In the subsequent parts we discuss the current evidence of CI as an option to provide binaural hearing to (adults and) children with SSD.

4.1 Prevalence and etiology: who qualifies for a CI?

On a yearly basis approximately 60 (out of ~ 68000) neonates have UHL in Flanders, of whom about 20 to 25 neonates with profound UHL (> 90 dB HL, Van Kerschaever and Stappaerts, 2011). Depending on their etiology of UHL, some children qualify for a CI. Here we review the etiologies of 237 neonates with UHL documented during the past 17 years.

Between 1999 and 2016, 139 neonates with UHL were in follow-up at the University Hospital in Antwerp (UZA). For 118/139 children, 54 boys and 64 girls, an etiological work-up, including high resolution MRI imaging, was performed (Declau et al., 2008). In the same period, UHL was confirmed in 118 children at the University Hospital Leuven (UZL), 59 boys and 59 girls. However, MRI scans were only available for 56% of the children with profound HI in the UZL cohort. Based on the entire data set approximately 22% (56/258) of children suffered from conductive hearing loss related to microtia/outer ear canal astresia. These figures were similar in both centers (n=30 for UZA, n=26 for UZL). Congenital aural atresia or microtia occurred in approximately 1 per 10.000 live births as part of syndromic or non-syndromic disorders (Alasti and Van Camp, 2009). Unilateral aural atresia was found in approximately 70% of cases of microtia (Schuknecht, 1989). As microtia leads to a stable conductive HI of about maximally 60 dBHL, these patients usually do not qualify for cochlear implantation unless there are associated inner ear anomalies.

The remaining 78% of all children suffered from different degrees of congenital sensorineural HI. Because of the difference in work-up between the two hospitals the distribution of etiologies for sensorineural HI are presented separately for the UZA (n=88) and UZL (n=92) in Table I.

Table I: distribution of etiology of congenital unilateral sensorineural HI (given in percentage) for University hospital Antwerp (UZA, n=88) and University Hospital Leuven (UZL, n=92) separately. The data are presented for different degrees of HI (Mild=41-50 dBHL, moderate=51-70 dBHL, severe = 71-90 dBHL, profound>=91 dBHL). The etiology can be

syndromal, congenital cytomegalovirus (cCMV) infection, cochlear nerve deficiency (CND), meningitis, neurological, inner ear malformation (IEM), CMV+CND or unknown.

	Mild	**Moderate**	**Severe**	**Profound**
	UZA/UZL	UZA/UZL	UZA/UZL	UZA/UZL
Etiology UZA/UZL(n=88/92)	%/%	%/%	%/%	%/%
Syndromal (4/2)	1.1/1.1	2.3/-	-/-	1.1/1.1
cCMV (21/26)	1.1/-	4.6/1.1	2.3/4.3	15.9/22.6
CND (23/7)	-/-	-/-	-/-	26.1/7.5
Meningitis (1/0)	-/-	-/-	-/-	1.1/-
Neurological (1/7)	-/-	-/4.3	1.1/1.1	-/2.2
IEM (3/7)	-/-	1.1/-	1.1/2.2	1.1/5.4
CMV + CND (1/0)	-/-	-/-	-/-	1.1/-
unknown(34/43)	9.1/2.2	13.6/9.7	4.6/9.7	11.4/24.7
Total	**11.4/3.2**	**21.6/15.1**	**9.1/17.2**	**57.9/63.4**

4.1.1 Cochlear nerve deficiency

On average, approximately 60% of children presented with a profound sensorineural HI in the affected ear, which corresponded to 51 and 59 children for UZA and UZL, respectively. Cochlear nerve deficiency (CND) was the most commonly identified cause, with 26% for UZA being more representative than 7.5% for UZL because of the complete work-up in the former hospital. Cochlear nerve deficiency may be an isolated finding or may be associated with other inner ear anomalies or syndromes. The cochlear nerve (CN) is hypoplastic if it is smaller than the facial nerve (cochlear nerve hypoplasia) or if it is absent (cochlear nerve aplasia). Hearing impairment has been found to be more severe for CN aplasia compared to CN hypoplasia, but the significant variability in hearing thresholds are not explained entirely by CN size (Clemmens et al., 2013). Because of the difficulty of detecting small nerves, non-visualisation of the CN in MRI does not necessarily imply complete absence of nerve fibers (Clemmens et al., 2013). CND has been associated with poor outcomes following CI (Walton et al., 2008). Teagle et al. (2010) reported that none of the children with CND achieved open-set speech perception abilities. Altogether, a relatively large percentage of children with profound

congenital UHL, i.e. 45% in our data and more than 50% in the study by Arndt et al. (2015), did not qualify for a CI because of CND as the underlying etiology.

4.1.2 Congenital cytomegalovirus

The prevalence of congenital cytomegalovirus (cCMV) infection was also high, i.e. about 1 in every 100-200 live births (Kenneson et al., 2007). The overall incidence of CMV related-hearing loss was 12.6%, of which about 28.8% of symptomatic and 56.9% of asymptomatic cCMV cases developed UHL (Goderis et al., 2014). At UZA and UZL, 16% and 23% of children with profound UHL had cCMV, respectively, thereby explaining nearly 36% of the profound HI etiologies.

Performance of bilaterally deaf children with cCMV and a CI varied. For 15 children implanted at a median age of 24 months (range 14-36 months) median word recognition scores were 74% on closed-set speech and 48% on open-set testing (Laccourreye et al., 2015). However, 20% of the children remained unintelligible. Insufficient progress was associated with bilateral vestibular areflexia and/or brain abnormalities. Philips et al. (2014) compared outcomes in cCMV children and matched peers deafened bilaterally by a mutation of the Connexin 26 gene (CX26). The cCMV children received their CI(s) 8 months (range 4-14 months) after diagnosis of bilateral profound HI. The mean age at implantation (2y9m range) was higher than the CX26 peers, because 6 out of 12 cCMV children had delayed onset of HI. A follow-up after 5 years showed that the cCMV children with abnormal MRI scans lagged behind on speech production compared to their matched peers. These findings are in contrast to those published by Lyutenski et al. (2016) who concluded that the severity of brain lesions on its own does not predict performance of bilaterally deaf cCMV implanted children. Most poor performers also presented other factors, such as bilingualism, late age at implantation or additional handicaps. Although cCMV children with SSD qualify for a CI, and intervention should be considered, because UHL due to cCMV may progress to bilateral HI, it seems prudent to counsel parents that outcomes could be less than expected and to recommend auditory rehabilitation and speech therapy.

4.1.3 Congenital inner ear malformation

Congenital inner ear malformation (IEM) was determined only in few of our newborns, while it has been reported to occur in 35.5% of patients with unilateral profound hearing loss (Lin et al., 2017) and in 28.9% of 322 children with unilateral sensorineural hearing loss (Song et al., 2009). In the latter study CT scans most often showed an incomplete partition type II (28 cases), followed by a narrow internal auditory canal (23 cases) and an enlarged vestibular aqueduct (17

cases). In children with profound hearing loss, the incidence of malformations was significantly higher (31,6 %, Song et al, 2009). Cochlear implantation may be technically challenging in children with congenital inner ear malformations, with an increased risk of complications (Isaiah et al., 2017; Bille et al., 2017).

Clinical outcomes are variable and partially depend on the type of the malformation. Isaiah et al. (2017) reported that children with cochlear dysplasia, vestibular dysplasia and cochlear nerve hypoplasia failed on both closed and open set speech testing, whereas 65% of children with enlarged vestibular aqueduct achieved open set speech recognition. Bille et al. (2017) described 18 children with cochlear malformation and a CI (17 had an incomplete partition, 1 had a common cavity malformation). Ten children were prelingually deafened, and all had been treated with hearing aids for a varying period before receiving their CI. At least 3 years after the first implant, performance scores of children with inner ear malformations and a control group were similar. When considering CI in children with cochlear malformations parents should be counseled accordingly.

UHL may progress to BHL due to inner ear abnormalities, such as enlarged vestibular aquaeduct that affect both sides but initially presents with UHL. Previous studies have shown that between 7 and 11% of patients with UHL developed bilateral hearing loss over time (Lin et al., 2017; Uwiera et al., 2009; Haffey et al., 2013; Fitzpatrick et al., 2014).

4.1.4 Bacterial and viral meningitis

Based upon data from a recent systematic review, the incidence of profound hearing loss following bacterial meningitis is 5% (Rodenburg-Vlot et al., 2016). Among those with profound hearing loss, 30% present unilateral hearing loss, 60% bilateral hearing loss, and 10% asymmetric hearing loss. In our data only 1 child became deaf on one side, as a result of meningococcal meningitis at 4 months of age (Table 1). HI in this child is not congenital. However, given the good performance outcomes of bilaterally deaf meningitis children with CIs (e.g. Boons et al., 2012a,b) there is no contra-indication to provide a cochlear implant here. The only concern is that bacterial meningitis may result in ossification of the cochlea, especially at the basal turn thus hampering full insertion of the electrode-array. In this case, a specially designed double array implant and an adapted surgical procedure may be required to achieve optimal outcomes (Lenarz, 2001).

Other less common causes of UHL in children include auditory neuropathy spectrum disorder (ANSD), and sudden idiopathic hearing loss. ANSD is a particular kind of hearing disorder

characterized by normal outer hair cell function and abnormal or absent auditory brainstem responses. It usually presents as a bilateral condition and has been associated with perinatal insults such as hyperbilirubinemia requiring exchange transfusion, perinatal intracranial haemorrhage, perinatal asphyxia, and neurological conditions such as Friedereichs ataxia or peripheral neuropathies (Sanyelbhaa Talaat et al., 2009). Boudewyns et al. (2016) reported a 6.5% prevalence of ANSD in well babies identified through NHS. In otherwise healthy children, ANSD may be related to mutations in the gene encoding otoferlin (OTOF) or to cochlear nerve deficiency (Rodriguez-Ballesteros, 2008). Boudewyns et al. (2016) reported abnormalities on MRI in 6 out of 13 infants, of whom 5 had CND (1 bilateral and 4 unilateral). These children would not qualify for a CI.

Sudden idiopatic hearing loss is defined as hearing loss of at least 30dBHL in 3 adjacent frequencies, developing over 3 days or less (Schreiber et al., 2010). The hearing impairment may be associated with vestibular symptoms, aural fullness or tinnitus, is usually unilateral and the underlying mechanism is unknown. Sudden idiopatic hearing loss is a common condition in adults with an estimated incidence of 5-30 cases per 100.000 per year (Schreiber et al., 2010). It is a rare condition in children and seems to happen mainly postlingually.

4.1.5 Unknown etiology

Of the children with congenital profound sensorineural UHL the underlying cause could not be identified in 11.4% and 24.7% for UZA and UZL, respectively. The higher percentage for UZL is probably due to the absence of a complete etiological work-up and counterbalances the relatively low incidence of CND at UZL. In the future, UZL will also include imaging in a complete work-up to determine the etiology as precisely as possibly. Unknown etiology also involves perinatal factors and missed cCMV cases (the sensitivity of Real-Time Polymerase Chain Reaction Assays on dried blood spots may be as high as 95% to 96% in a high risk population, but depends on the size of the dried blood spot used, the assay and the population under test (Leruez-Ville et al., 2011).

4.1.6 Children with SSD who qualify for a cochlear implant

In summary, CND and cCMV infection are the most common underlying etiologies in children with congenital SSD. Children with unilateral deafness caused by CND do not qualify for a CI. In our prospective study (see further), syndromal children and children with neurological problems are also excluded from cochlear implantation. Early provision of a CI in a unilateral deaf child with cCMV may prove beneficial, and also necessary if the contralateral normal

hearing ear is expected to decline too. However, potential abnormalities of the central nervous system or associated neurological comorbidity may negatively affect performance outcomes. Altogether, after etiological work-up for sensorineural hearing loss, the data of UZA (n=88) showed that only about 30% of the children with SSD (n=26) qualified for a CI in terms of degree of HI and etiology (after removal of CND, syndromal and neurological etiologies). Each year, between 20-25 babies are born with unilateral profound hearing loss in Flanders (Van Kerschaever and Stappaerts, 2011). Therefore, we estimate that about 5 to 10 newborns with SSD qualify for a CI each year in Flanders.

4.2 Performance of adults with SSD and a CI

The emerging research on postlingually deafened adults with SSD show that a CI in the deaf ear not only reduces tinnitus (Van de Heyning, 2008; Blasco and Redleaf, 2014; Mertens et al., 2013, 2016a), but also improves sound localization and speech understanding in quiet and in noise in some persons (Buechner et al., 2010; Arndt et al., 2011; Firszt et al., 2012 a,b; Hansen et al., 2013; Giardina et al., 2014; Távora-Viera et al., 2015; Harkonen, 2015; Mertens et al., 2015; 2016b; Kitoh et al.,2016; Grossmann et al., 2016; Hassepass et al., 2013, 2016; Sladen et al., 2017; Thomas et al., 2017).

A meta-analysis by Vlastakaros et al. (2014) on 108 SSD CI users in 17 studies reported highly consistent use of the CI, improved tinnitus and better sound localization. Speech perception in noise improved when speech came from the side of the implanted ear or from the front, when noise came either from the front or from the NH ear. Results from other signal-to-noise configurations were inconclusive. Data from the speech, spatial and qualities of hearing scale confirmed perceived improvements in localization and speech perception in daily life, but no improvement in other qualities of hearing. The systematic review by van Zon et al. (2015) supported these conclusions, despite certain methodological shortcomings of the reviewed studies. These included, for instance, non-randomization, small sample sizes, possible self-selection bias in participant inclusion, short follow up and lack of statistical analyses in some studies.

Participant satisfaction among implanted adults was generally high. Using a semi-structured questionnaire Finke et al. (2017b) investigated the main reason(s) for 19 individuals with postlingual onset of SSD to choose for a CI. Four main reasons were reported: 1) poor sound localization, including wanting to feel more safe in the traffic, 2) seeking release from tinnitus and noise sensitivity, 3) the desire to improve quality of life, and 4) out of fear to lose the second

ear. Importantly, all participants reported that they had made the right decision by choosing for a CI. Louza et al. (2017) also evaluated subjective CI benefit one year after implantation in ten postlingually SSD individuals using four standardized questionnaires. Although overall quality of life did not improve for all persons, significant improvements were reported for subscales of spatial hearing, speech intelligibility and basic sound perception.

Most of the adults with SSD acquired their HI postlingually. Távora-Vieira et al. (2013) reported 12-month post implant speech-in-noise performance with different spatial configurations as well as subjectively rated CI benefit. The improvements in speech perception in noise were likely due to the CI subjects being able to exploit the head shadow (Bernstein et al. 2016; Sladen et al. 2017). Bernstein et al. (2016) showed that auditory input via the CI facilitated the perceptual separation of speech from a target talker from competing talkers, in 7 adults with postlingual SSD tested 6 months post implantation. Sladen et al. (2017) demonstrated that a CI improved speech perception in quiet and in noise in a group of adults (and one child) with a relatively short duration of SSD (idiopathic sudden SNHL). In that study, noise was presented from all around, instead of to one of both ears, or from the front, as in other studies. The improvements found with this arrangement, therefore, do not only reflect a mere head shadow effect but are indicative of true binaural hearing, i.e. binaural unmasking and/or binaural summation. Mertens et al. (2015) tested a group of 22 patients with acquired UHL and asymmetric HI 36 months post implantation, and also reported improved speech perception in noise with CI compared to a CI off condition.

Most studies evaluated the two ears together. When solely analyzing the ear with the CI in post lingual SSD adults, Hansen et al. (2013) reported a 28% increase in word scores and a 40% increase in sentence scores when comparing unilateral free-field audio stimulation pre-implantation to electrical CI stimulation 6 months post-implantation, with the majority of participants demonstrating significant improvements in speech perception in the CI ear. Finke et al. (2017a, 2017b) also reported improved open speech set understanding with the CI in isolation using the direct connection for 13 out of their 19 postlingually deafened SSD participants. Compared to the scores of the second CI of bilaterally fitted participants, those of SSD CI users were lower, which is, according to the authors indicative of the dominance of the NH ear (Finke et al., 2017a).

Localization ability of SSD patients with CI has been reported less frequently in the literature than the ability to understand speech in noise. Localization skills seemed to improve to some

extent with a CI, albeit after some time (Hansen et al, 2013), as the brain needs experience in order to integrate acoustic and electric signals.

4.3 Performance of children with SSD and a CI

Hassepass et al. (2012) were among the first to observe benefits of CI in children with acquired SSD. Two postlingually deafened children (10 and 11 yrs) demonstrated improved speech recognition in noise in a condition with speech presented to the CI ear and noise to the NH ear and improved sound localization ability at 6 and 12 months post implantation. Data from the speech, spatial and qualities of hearing scale were indicative of perceived improvement in hearing ability in a variety of everyday listening situations 12 months post implantation.

Arndt et al. (2015) later tested three groups of children with different onsets of SSD. Nine children with postlingual onset of deafness demonstrated significant improvements on speech understanding, localization and subjective benefit at 12 months post implantation, and all children used their device daily. Results of two perilingually deafened children differed from each other: one performed well, while the other showed only marginal benefits. Two children with congenital SSD showed significantly poorer results in sentence understanding in noise when the signal was presented to the good ear and noise to the CI ear, compared to pre implantation. Performance was similar between the two time points when both signal and noise were presented from the front, and when the signal was presented to the CI ear and noise to the good ear. Moreover, localization ability did not improve and one child became a non-user. Another child with congenital SSD was implanted at 21 months of age. Although too young for formal testing, the authors reported that this child did seem to exhibit clinical evidence of binaural integration through behavioral responses to sounds and willingness to wear the CI all the time (Arndt et al., 2015), as was corroborated by data of Távora-Vieira and Rajan (2015). Later, Tavora-Vieira and Rajan (2016) reported 36 month follow up data; the child had a maximum score on a free field speech perception test with the normal hearing ear masked with speech noise and could correctly lateralize sounds presented at -90 and 90 degrees. Spatial acuity could not be tested yet.

The abovementioned studies seem to support the idea that there is a window of opportunity for CI implantation for children with congenital SSD. However, it is very difficult to test young children and draw solid conclusions regarding potential development delays due to listening with one ear. It is unlikely that a binaural advantage will be restored completely, as the signal provided by a CI is degraded compared to normal hearing. However, reintroduction of cross

inhibition leads to changes in central gain mechanisms beneficial for binaural hearing (Gordon et al., 2015; Hansen et al., 2013, Mertens et al., 2016a). Through restoration of auditory input, the CI is, however, expected to partly restore the quality and precision of phonetic and phonological representations that are important for the development of neurocognitive skills.

It is possible that (few of the) older congenital SSD children who showed no improvement from pre to post CI in speech in noise tests, may have developed coping strategies in the years prior to CI. Rahne & Plontke (2016) reported that all children with SSD benefitted from a CI in different hearing conditions, and that even those with a long period of deafness can improve after cochlear implantation. Results of Thomas et al. (2017) showed moderate but significant audiological and subjective benefits in 14 children with congenital SSD implanted between the ages of 3;6 and 11yrs. Performance of 7 children implanted below 6 yrs of age was similar to that of 7 children implanted at a later age. The authors therefore speculate that maybe one NH ear is able to prolong the sensitive period for brain plasticity in the auditory pathways into adolescence (Thomas et al., 2017). In order to be able to draw solid conclusions regarding age of implantation in children it is necessary to control for other factors, such as cCMV, which are associated with poor outcomes after cochlear implantation.

Due to heterogeneous findings, small sample sizes, and lack of high level evidence findings, no firm conclusions can be drawn on the effectiveness of CI in children with UHL yet (Peters et al., 2016). Recently, Polonenko et al. (2017) reported that children with SSD did consistently use their CI upon activation in a variety of environments, and Thomas et al. (2017) confirmed that most of the children in their study accepted the CI, and some demonstrated positive behavior changes, with improvement of academic performance, and better acoustic orientation. However, in the study by Thomas et al. (2017), some children reported increased irritability at higher sound levels. These were mostly children implanted at a later age, and they were possibly more aware of their SSD than the children implanted at a young age. Therefore, despite positive outcomes in most children, limited use and non-use (approx. 4/20), due to lack of benefit and a feeling of stigmatization, should not be ignored (Thomas et al., 2017).

5. Cochlear implant in infants and toddlers with one deaf ear

The above-mentioned reviewed data indicate that several developmental factors are compromised in children with unilateral hearing and that these may, to some extent, be mitigated by a CI in the deaf ear. Given this, as well as the importance of early implantation, a

multicenter project has been initiated to provide a cochlear implant in infants with one congenitally deaf ear.

The main objective of the multicenter collaboration (Leuven, Antwerp, Gent) is to fundamentally investigate the development of spoken language, cognition, and spatial/binaural hearing longitudinally in ten monolingual Dutch speaking children with one profound, sensorineural, congenital deaf ear who receive a cochlear implant (Cochlear Ltd). Performance is compared to age-matched children with SSD who do not receive a CI (either because they do not qualify or because their parents do not want it) and age-matched NH peers. Children receive the CI in their deaf ear before 36 months of age. It is hypothesized that provision of the CI at a very young age will result in near-normal binaural processing in the following years and hence yield the best conditions for (near-) normal development of spatial hearing skills, cognition, language and learning in general. The study was approved by the Ethical Committee of all participating centers.

5.1 Protocol and testing materials

Children are followed up longitudinally 2 times a year with regard to hearing, cognition, language and quality of life during their first 4 to 5 years with a CI (and possibly beyond). The time line of the protocol is depicted in Figure 1. At a very young age, development in the different domains is monitored via parent questionnaires, in addition to LENA analyses. The LENA system (Xue et al., 2008) automatically analyzes the speech environment of a child by estimating the amount of adult words the child is exposed to, the amount of vocalizations of the child, the amount of conversational turns and the electronic media that the child is exposed to. Its reliability has recently been validated for the Dutch language (Busch et al., 2017b).

From the age of 2 years onwards, receptive and expressive language and cognition are tested with standardized, differentiating and age-appropriate materials, see figure 1. At four years of age also spatial and binaural hearing skills are investigated longitudinally in order to explore hearing abilities with and without the CI. Localization tests and spatial hearing are carried out with an array of single-cone loudspeakers spaced 15° apart from -90° to +90° in the frontal horizontal plane at 1 m from the subject. A child-friendly procedure with smurfs will be applied (Van Deun et al., 2009). Language and cognitive development are also assessed in children under the age of 2 with standardized tests, to the extent that it is possible to monitor progress at this young age. The young age of the children in this study brings along several challenges for testing. Due to the nature of the tests (one test for a large age range, with items in ascending

order of difficulty), young children can often only complete a limited number of items before they reach their potential at that moment of testing. Consequently a few wrong or absent answers can significantly affect the final score. With increasing age, more items can be administered and performance becomes more stable. Furthermore, motivation, energy level, wellbeing and shyness influence performance.

5.2 Participants

Currently 8 out of 10 children have been implanted, of whom 6 of the children as a result of cCMV infection, 1 of cochlear malformation (incomplete partition type II) and 1 of a fall thereby fracturing his left petrous bone. These children act as their own control (tested with and without CI). In addition, the children are age-matched with 10 children with SSD without a CI and with a group of normal hearing children. If possible the cCMV children with a CI will be matched to cCMV controls.

The mapping of the CI is done by two clinical audiologists. During visual reinforcement audiometry, the NH ear of the child poses a challenge, compared to such sessions with bilaterally deaf children. While the mapping of a child with bilateral CIs is usually checked in free field, the one of a child with SSD is assessed using a personal audio cable coupled to the CI speech processor to prevent listening with the NH ear. As with very young bilaterally HI children, several mapping sessions are needed to reach satisfying threshold and comfort levels. The exact number of sessions depends on the age of the child, its wellbeing, motivation to cooperate and understanding of the reinforcement paradigm (‘getting conditioned’ to search for visual reinforcement when hearing the sound). The audiologists also monitor the use of the CI through datalogging.

Although there is no formal rehabilitation in our study, parents are encouraged to promote language growth, by speaking to and reading with their child. The children are encouraged to listen for about half an hour, a few days per week, to an auditory-visual children’s story presented only to the CI device from a tablet through a mini mic (Cochlear Ltd) provided through the project. In addition, a binaural training game is being developed to help the child to learn to use acoustical and electrical binaural cues in an engaging manner. Studies have shown improvements with auditory training, e.g. in children with bilateral CI (Kuhn-Inackers, 2004), adults with postlingual SSD and a CI (Nawaz et al. (2014) and in NH subjects with prolonged unilateral ear plugging (Kumpik et al., 2010; Irving and Moore, 2011). Also, different programs exist that are designed to promote phonological, comprehension and

language skills. Intervention efforts need to consider approaches that provide supportive educational environment to empower them as much as possible.

6. Summary

This paper focusses on the consequences of UHL for several factors, including spatial perception, speech intelligibility (in noise), and (the development) of spoken language. The reviewed literature on (adults and) children with (profound) UHL clearly demonstrates deficiencies in several domains, which do not appear to resolve with age without hearing intervention (Lieu, 2015; Rohlfs et al., 2017).

It is very important to obtain a good understanding of the consequences of reduced auditory input on specific developmental trajectories in children with HI. In children with (profound) UHL potential deficiencies are much more subtle than in persons with bilateral HI. Subtle, persistent, deficiencies in complex linguistic areas may not be picked up by composite scores. Therefore, research should focus on potential difficulties in the development of phonology and morphology as well as on cognitive skills (working memory, sequential processing, executive functioning).

A cochlear implant offers the potential to (partially) restore binaural hearing in children with SSD and it seems to be a promising solution for some children with congenital SSD. The reviewed animal and human studies provide ample evidence that a CI should be provided as early as possible after detection of HI in order to be able to exploit the sensitive period of maturation of the central auditory pathways, and to remove barriers to cognitive, academic and psychosocial development. Given the current evidence on auditory plasticity, we have opted for a maximum time window of 36 months after birth for cochlear implantation in our prospective multicenter study. As yet, the ages of the 8 implanted children range between 8 to 26 months. A CI in a child with SSD may not be beneficial for all children, but possibly for those who need to expend a lot of mental effort in the challenging listening situations. Long-term observation of the implanted infants and toddlers on language, cognition and auditory skills, compared to children without CI, will be of key importance to draw conclusions regarding audiological benefit, improvement in spoken language, schooling, quality of life and type of treatment/training.

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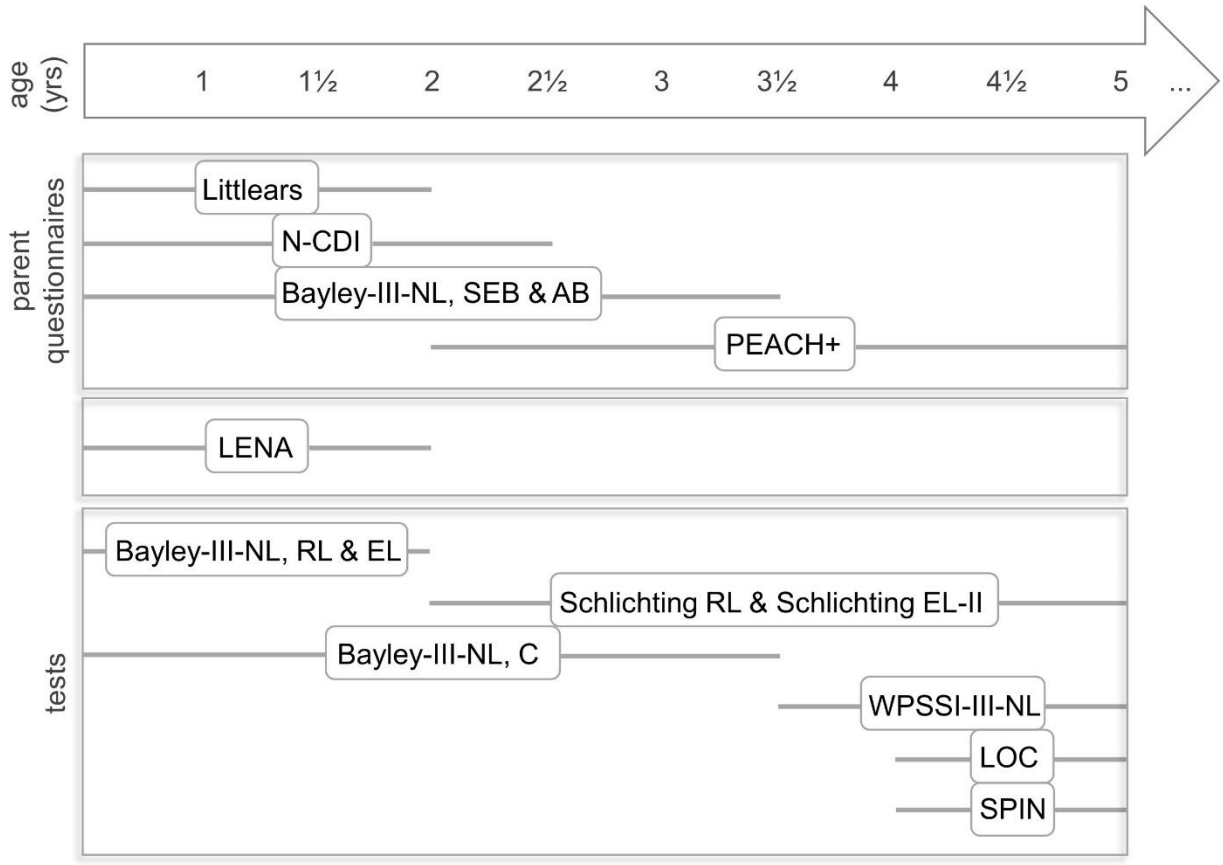

Figure 1. Timeline of the multicenter research studying the development of very young children with SSD with and without a CI. Upper box: parent-questionnaires: Littlears (Kuehn-Inacken et al., 2003); Communicative Development Inventory (N-CDI; Zink and Lejaegere, 2002); Bayley Scales of Infant and Toddler Development III-NL questionnaire Social Emotional Behavior and Adaptive Behavior (Baar et al., 2014). Middle box: Language ENvironment Analysis system (LENA; Xue et al., 2008). Lower box: behavioral tests: Bayley-III-NL subscales Receptive Language (RL), Expressive Language (EL) and Cognition (C); Schlichting tests of Receptive (RL) and Expressive language (EL) (Schlichting and Lutje Spelberg, 2010a, 2010b), Wechsler Preschool and Primary Scale of Intelligence III-NL (WPPSI-III-NL, Hurks et al., 2010), sound localization test (LOC) and speech understanding in noise test (SPIN).