Cochlear implantation in children with Autism Spectrum Disorder (ASD): Outcomes and implant fitting characteristics

Mancini Patrizia [a], Mariani Laura [a,*], Nicastri Maria [a], Cavicchiolo Sara [b], Giallini Ilaria [a], Scimemi Pietro [c], Zanetti Diego [d], Montino Silvia [e], Lovo Elisa [e], Di Berardino Federica [d,1], Trevisi Patrizia [e,1], Rosamaria Santarelli [c,1]

[a] *Department of Sense Organs, University Sapienza of Rome, Italy* [b] *Audiology Unit, Department of Clinical Sciences and Community Health, University of Milan, Italy* [c] *Department of Neuroscience, University of Padua, Padua - UOSD Otolaryngology and Audiology, Santi Giovanni e Paolo Hospital, Venice, Italy* [d] *Department of Specialistic Surgical Sciences, Foundation IRCCS Ca' Granda Maggiore Hospital, Milan, Italy* [e] *Department of Neuroscience, University of Padua, UOC Otolaryngology, Padua Hospital, Italy*

[1] The Authors equally contributed to the study.

* Corresponding author. Department of Sense Organs, University Sapienza of Rome, Viale dell'Universit`a 31, 00161, Rome, Italy. *E-mail address:* l_mariani@pec.it (M. Laura).

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ABSTRACT

Background: Little is known regarding fitting parameters and receptive and expressive language development in cochlear-implanted children (CCI) with profound sensorineural hearing loss (SHL) who are diagnosed with Autism Spectrum Disorder (ASD). The aim of the study was to evaluate a group of ASD CCI users in order to describe their ASD clinical features and CCI outcomes; report on the average electrical charge requirements; and evaluate the possible correlations between electrical and psychophysical outcomes with ASD characteristics.

Materials and Methods: A multicentre observational study of 22 ASD children implanted in four cochlear implant (CI) centres. Data concerning profound SHL diagnosis, ASD diagnosis, CI timing and CI compliance were collected. Sound Field (SF) was assessed through repeated behavioural measurements. Categories of Auditory Perception (CAP) and Categories of Language (CL) were used to evaluate speech perception and language skills at short (≤2 yrs), medium (5 yrs) and long term (>10 yrs) follow-up. Fitting parameters such as comfortable thresholds, pulse-width (pw, μsec) and clinical units converted into units of charge/phase were collected. The diagnosis of ASD was acquired by the referral neuropsychiatric department and severity was assessed through the Diagnostic and Statistical Manual of Mental Disorders (DSM-V) and the Childhood Autism Rating Scale (CARS).

Results: At the final follow-up session the median SF threshold for CI outcomes was 30 dB HL (min 15 – max 60). CAP score was extremely variable: 45.5 % showed no improvement over time and only 22% of children reached CAP scores of 5-7. CL 45.5% showed no improvement over time and score was 1-2 in the majority of ASD children (72.7%), while only 18.2% reached the highest level of language skills. There were no statistically significant differences at each follow-up between subjects with or without comorbidities. CAP and CL were inversely correlated with DSM-V A and B domains, corresponding to lower speech and language scores in children with more severe ASD symptoms, and maintained their correlation at mid and long follow-ups whilst controlling for age at CI. Electrical charge requirements did not correlate with SF or age at implant but did inversely correlate with ASD severity. With regards to CI compliance: only 13.6% children (3) with severe DSM-V A/B levels and CARS score were partial/intermittent users.

Conclusion: The present study is a targeted contribution to the current literature to support clinical procedures for CI fitting and audiological follow-up in children with ASD. The findings indicate that the outcomes of CI use and the fitting procedures are both influenced by the severity of the ASD symptoms rather than the demographic variables or associated disorders.

Keywords: cochlear implantation, children, autism spectrum disorders, outcomes, fitting

Introduction

Autism Spectrum Disorder (ASD) is an umbrella term, which includes Autism (A), Asperger Syndrome (AS), Pervasive Developmental Disorder not otherwise specified (PDD-NOS), and Childhood Disintegrative Disorder (CDD) as described in the latest revision to the Diagnostic and Statistical Manual of Mental Disorders (DSM-V). ASDs involve persistent deficits in social communication and social interaction across multiple contexts and restricted/repetitive patterns of behaviour, interests, or activities that significantly affect quality of life [1]. The severity, intensity and frequency of ASD core deficits vary significantly between patients, leading to heterogeneous manifestations. For some individuals, having an ASD means a life of constant care and supervision with minimal opportunities for independent living; for others it is associated with many lasting challenges but does not hinder the acquisition of independent living skills, meaningful employment and/or the development of close relationships [1]. Furthermore, although developmental trajectories vary across individuals as a result of ageing and clinical interventions, ASD could be considered a lifelong disability for most patients, with a substantial degree of persistence of core ASD features throughout their lifetime [2].

Worldwide prevalence of ASD is 0.62–0.70%, with a male to female ratio of 4-5:1 and frequently presents as a comorbidity with other impairments or disorders [3]. One of the conditions frequently associated with ASD is profound sensorineural hearing loss (SHL) [4,5,6], although data on prevalence of hearing loss in autistic children remain controversial [7]. Szymanski et al. reported a prevalence of ASD in a group diagnosed as deaf or hard of hearing (DHH) as high as 6-7% by the time the children reached 8 years of age [5]. The percentage, however, does seem to increase in conditions such as TORCH infections, meningitis, prematurity and neonatal hypoxia traditionally considered organic causes for both ASD and deafness [8, 9]. Genetics and epigenetics seem to play a role in the aetiology of ASD in association with these primary environmental factors [10]. In fact, studies on twins and families [11,12,13] have suggested that autism has a high heritability, and it is also known that some genetic syndromes can combine with ASD, including Rett, Fragile X, Prader-Willi, Angelman and CHARGE.

The combination of ASD and deafness in children is challenging for clinicians as it makes management decisions more complex, impacting on both the diagnosis of ASD and on the audiological choices required in terms of appropriate hearing device selection, fitting procedures and outcomes.

Early recognition of ASD - from 12 months of age for more severe forms and at around 2-3 years for mild forms - and prompt treatment are essential to positively modify the symptoms' frame of reference, to decrease tendency to isolation and the difficulties in achieving the best possible social

learning [14] as well as to improve the quality of life of people with ASD including their families. Diagnosis of coexisting SHL could potentially delay ASD diagnosis for up to 5 years thereby concealing atypical childhood development of language skills [15]. With the introduction of the latest hearing screening and the lowering of the age at CI, ASD diagnosis often follows cochlear implantation, as signs of ASD are rarely detected in the first 18 months of life in SHL children [16]. The delay in ASD diagnosis postpones the onset of rehabilitation needed for specific treatment and potentially limits the benefit of early intervention. On the other hand, when these two conditions are contemporaneously diagnosed in a child, the presence of ASD becomes a reason for greater caution when making CI selection in this category of patients. This is also linked to major difficulties with communication and spoken language development in ASD patients as well as to sensory integration difficulties [17]. While, in the past, these concerns often resulted in a contraindication to CI surgery or in delayed implantation, more recent studies have highlighted how early implantation is beneficial to SHL children with associated ASD, despite extremely variable outcomes. The procedure does not interfere with the evolution of ASD symptoms, and even in the worst hearing and language outcomes it might help the child to recognize sounds and produce vocalizations more often than without a CI [17,18,19,20,21,22,23].

Despite this, CI in this setting is still a difficult challenge, linked to both behavioural disorders and to sensorial hypersensitivity, in particular to sounds. CI compliance may be a concern in this population as some studies have reported variable incidences of non-users or partial users of hearing technology [17,19,20,24,25]. The reason for the failure of implant use or for poor tolerance to loudness in ASD children has been hypothesized by Brandy et al. [26] and has been driven by auditory hypersensitivity, although it is not clear whether it originates from a central or peripheral auditory deficit. While the diagnosis of SHL can be reached using objective methods, CI programming can also be very challenging. Fitting sessions are often based on Electrically Evoked Compound Action Potential (ECAP) thresholds [27] and on the observation of children's behaviour [19]. These tests may vary from one session to another because they are influenced by children's willingness to undergo tests. Finally, there is a lack of information concerning CI fitting parameters, except for limited case reports [28].

Based on these premises and considering the small body of literature available concerning outcomes after cochlear implantation in children diagnosed with ASD, a uniform body of information was retrospectively collected for a group of 22 implanted ASD children with the aim to: 1) describe the clinical characteristics of ASD CI children, 2) evaluate CI outcomes; 3) identify average electrical charge requirements in this special population; 4) identify possible correlations between outcomes,

CI use, and the specific characteristics of children with ASD and CI (severity, presence of comorbidities).

Deepening our knowledge of clinical characteristics can also help highlight possible factors that limit successful outcomes. Describing the extent of improvements after cochlear implantation and identifying factors that could impact them can be helpful for clinicians to orient families and discuss with them the possible expected development trajectories. Finally, better understanding of the electrical charge requirements and relating them to ASD characteristics could help clinicians to prevent device abandonment.

Materials and method

Study Group

The present study was a multi-center retrospective analysis of ASD profoundly deaf children, who underwent CI. Data concerning deafness diagnosis, CI timing, psychophysical measurements and ASD diagnosis were collected. The information obtained was analysed in accordance with the principles and later amendments to the Declaration of Helsinki (1964) and approved by the Policlinico Umberto I- Rome Ethics Committee (n. 259/2020).

The study group included 22 patients identified in 4 CI centres: 1) Policlinico Umberto I Department of Sense Organs, Rome; 2) Foundation IRCCS Ca' Granda Maggiore Hospital Department of Specialistic Surgical Sciences, Milan; 3) Padua Hospital Department of Neuroscience UOC Otolaryngology; 4) Santi Giovanni e Paolo Hospital, Venice UOSD Otolaryngology and Audiology Department. The children enrolled in the study had a median range at assessment of 10.8 years (min 3.1 – max 18.5; IQR=9.4) and a median duration for CI use of 102 months (min 24-max 180; IQR= 92) Median ages at diagnosis were respectively 8 months (min 1-max 50; IQR= 7.5) for severe/profound SHL and 42 months (min 36-max 120; IQR=17.3) for ASD. All patients had ASD diagnosis after referral by the neuropsychiatric department of each CI centre, and it was completed after severe/profound SHL was assessed, with a median between the two diagnoses of 35 months (range 12-115). Fourteen ASD children (63.6%) presented with associated comorbidities [Table 1], of which 36.4% (8) were genetic disorders. All children underwent CT and MRI imaging, all showing normal inner ear anatomy, with the exception of one child with Mondini malformation. For those patients with cytomegalovirus (CMV) association (19%) [Table 1], the MRI scan showed lesions such as; white matter hyperintensities (WMH), atrophy of the hippocampus and/or the temporal lobes and periventricular and/or white matter calcifications. Median age at CI was 34 months (10-144; IQR= 26.25), and between diagnosis and surgery 21 months (min 3 – max 135). Sixteen children

were unilateral CI users and 6 of the 22 children received simultaneous bilateral implantation, bringing the total number of ears to 28. The device for implantation was determined by the parents and the implanting center. Ten ears were implanted with Advanced Bionics Devices (AB) (CI/HighFocus, 2; 90K/HighFocus, 8), 1 with a MedEl Concerto and 17 with Cochlear Devices with perimodiolar electrode carrier (CI24R 2; CI24RE, 6; CI512, 3; CI532, 6). All children were wearing 'behind the ear' speech processors. The child with the Mondini malformation received a Cochlear CI24RE device.

Speech perception and language evaluation

Sound Field (SF) was assessed through behavioural measurements and the final assessment was collected and used for statistical analysis. Data for speech perception and language skills were collected at short (≤2 yrs), medium (5 yrs) and long term (> 10 yrs) follow-up.

Italian standardized speech perception and language tests were selected by the audiologist and speech-language pathologist according to their feasibility. Where the cognitive level of the child and/or the severity of ASD didn't allow the use of standardised tests, parents' reports such as the Meaningful Auditory Integration Scale [29], the Infant-Toddler Meaningful Auditory Integration Scale [30] or the Italian version of the MacArthur-Bates Communicative Development Inventories [31] were used, together with structured observations carried out by the speech pathologist using the Listening Progress Profile [32] or the Tait video analysis [33]. Alternatively, children with adequate compliance were tested utilising Italian standardised tests, routinely employed in clinical practice, to assess pediatric patients after CI, such as the "Common Protocol of Evaluation in Rehabilitation Audiology [34] for speech perception, the Peabody Picture Vocabulary Test (PPVT) for lexical comprehension [35], and the Test for Reception of Grammar (TROG-2) [36] for morpho-syntactic comprehension. In order to have a uniform approach to describe outcomes, information from the two different assessment methodologies were collected during the evaluation of the CI fitting and children were classified using the Categories of Auditory Perception (CAP) [37] and the Categories of Language (CL) [23,38] [Table 2].

Psychophysical measurements

Fitting parameters for participants using their last observed measurements were collected. Follow-up median value was 78 months (min 24 – max 180). Each center has extensive experience in CI programming. Mapping procedures were performed by an experienced audiologist, adapted subjectively and based on a combination of ECAP measurements and behavioural responses to Ling and environmental sounds.

The ECAP measurements represent a synchronous response from electrically stimulated auditory nerve fibres recorded via the intracochlear electrodes of the implant in at least 5 different electrodes, to represent the whole array (electrodes number 22, 16, 11, 6 and 1 for Cochlear; 1, 5, 8, 11 and 15 for AB 90K; 1, 3, 6, 9 and 12 for Med-El). For all devices, these potentials are mainly used to set maximum stimulation profiles (referred to as C level for Cochlear devices, M level for Advanced Bionics and Med-El devices). For Cochlear devices with ACE strategy, the average ECAP threshold drops to approximately 67% of the dynamic range [39]. For the AB HiRes strategy, the single-electrode ECAP falls on average to 110-115% of M-level for paediatric users [40]. ECAP for Med-El devices are primarily used to estimate only the M level profile [41]. Additionally, ECAP, although useful as a starting point for stimulation levels, show a wide variability in their relationship to mapping levels across the electrode array and across subjects. Clinical most comfortable thresholds were therefore verified and corrected observing behavioural responses to environmental sounds and Ling sounds [6, 42]. The number of active electrodes and pulse-width (pw) adopted in children's maps were the same as the standard software implementation. In particular: Cochlear devices are usually fitted with 8 maxima, 25 µsec pw; Advanced Bionics devices implement 16 active electrodes with a minimum pw of 18 µsec; Med-El devices have 12 active channels with a minimum pw of 13.7 µsec.

As all data were collected after a minimum of 24 months of CI follow-up and the M/C levels reported were stable since at least 6 months prior data collection. Clinical units (which are a product of electrodes charge, frequency of stimulation per phase and pw) were converted to units of charge/phase (nCoulomb, nC) using the formulas provided by the manufacturer [Table 3].

ASD Severity Assessment

The diagnosis of children with ASD was undertaken by experienced pediatric neuropsychiatrists utilising assessment instruments including parent/caregiver interviews, direct observation of the patient and a detailed clinical assessment that encompassed: the Autism Diagnostic Interview–Revised [43], the Autism Diagnostic Observation Schedule (ADOS) [44] and the Childhood Autism Rating Scale (CARS, [45]. Additionally, a review of family history for ASD or other neurodevelopmental disorders was conducted. Assessment of the degree or level of intellectual disability was measured through administration of the Developmental Disability-Child Global Assessment Scale (DD-CGAS) [46]. The ADI-R [43] is a structured interview procedure developed for parents with questions relating to their child's symptomatic behaviours and playing activities. It is a diagnostic tool that allows analysis of ASD according to DSM and International Classification of Diseases (ICD) criteria and is usually used as a complement to ADOS [44]. ADOS is based on a

direct and standardized observation of a child for a duration of about 45 minutes allowing for a diagnosis of ASD. It is structured around modules that explore social behaviour in natural communication contexts. The Childhood Autism Rating Scale (CARS) [45] is a popular scale that is frequently used to assist in the diagnosis of ASD in children [47]. It is consequently widely used in neuropsychiatric services in Italy and was used with children's families during the final follow-up session. CARS consists of 14 domains assessing behaviours associated with autism, with a 15th domain rating the overall impression of autism. Each domain is scored on a scale ranging from one to four; higher scores are associated with a higher level of impairment. Total scores can range from a minimum of 15 to a maximum of 60; scores below 30 indicate that the individual is in the non-autistic range, scores between 30 and 36.5 indicate mild to moderate autism, and scores from 37 to 60 indicate severe autism. It can be administered to children from 2 years of age upwards through to adulthood. In the study ASD was classified according to DSM-V classification [1] which emphasizes the dimensional concept of ASD, identifying two areas within which to look for signs and symptoms: domain A, persistent deficits in social communication and social interaction in multiple contexts, and domain B, restricted and repetitive patterns of behaviour [Annex 1]. Three levels of severity are described ranging from requiring minimal to very substantial support. These symptoms should not be explained solely through the prism of intellectual disability (intellectual developmental disorder) or through global developmental delay. Intellectual disability and ASD frequently co-exist. Nevertheless, the diagnostic process employed must specify whether ASD is accompanied by an intellectual disability or other neurodevelopmental disorder. In fact, to make comorbid diagnoses of ASD and intellectual disability, social communication should not be rated as highly as that expected for a general developmental level.

Statistical Analysis

Subjective demographic, audiological and psychophysical data were reported as median (min – max) or mean (SD) values where appropriate. The Shapiro-Wilk normality test was first applied to the dataset under investigation. Depending on the result of the normality test, parametric or non-parametric analysis of variance (ANOVA) was used. To determine the strength / magnitude of the experimental effect, the Cohen effect size was calculated (the larger the effect size, the stronger the relationship between two variables). The univariate analysis was adopted to compare data between unilateral and bilateral users and different CI strategies. Concerning CI electrical charge requirements, after conversion to nC, mean values were compared to those reported in Zwolan et al. and used as a reference (nCref) [48]. nCref were calculated on 188 CI children (192 ears), enrolled from 6 different cochlear implant centers [Table 3]. Similar to the present study, children had a mean

age at implantation of 62 months (7-62),and were implanted with devices marketed by the 3 main manufacturers. In this analysis mean values were calculated separately for normal and malformed cochleae, and univariate analysis of variance between centers was not found to be statistically significant. Average C/M levels were calculated by the authors in an effort to provide clinicians who do not have access to large data sets a guide for assessing channel availability and C/M level stability during the first 24 months use of the device. More specifically, the maps collected were stable in terms of the number of active channels, electrical impedance, pulse-width and C/M and T levels. In order to make group statistical analysis possible, differences between ASD-CI patients' nC (nCasd) and those reported in the literature (nC-ref) were calculated as % difference ($nC_{\Delta\%}$) following the formula: (nC-ref – nCasd)*100)/nC-ref. Simple Spearman's rank order correlations was performed to understand the relationship between subjective, audiological and ASD variables, while partial correlation (rp) was performed to evaluate the relationship between speech perception and language outcomes whilst controlling for Age at CI. Statistical significance was set at p=0.05. Statistical analysis was conducted using IBM SPSS® version 25 software.

Results

CI outcomes

No differences were found in univariate analysis between children with or without comorbidities with regard to age at SHL diagnosis (p=0.36), age at CI (p=0.9), age at ASD diagnosis (p=0.3) and SF (p=0.56). For Spearman correlation, age at SHL diagnosis was correlated to age at CI (r=0.5, p=0.008) and to age at ASD diagnosis (r=0.47, p=0.03). Median SF threshold was 30 dB HL (min 15 – max 60 IQR=16.25). Table 4 shows the outcomes for CAP and CL for short (≤2 yrs), medium (5 yrs) and long term (> 10 yrs) follow-up. Fig.1 shows the percentage of ASD CI Children for each CAP and CL level, assessed at each follow-up. In particular, CAP scores at the final follow-up session were extremely variable. Overall, 13.6% of patients at the last follow-up showed no benefit in terms of speech recognition (CAP score 0; 23.7% had a minimal benefit (CAP score 1-2). For acquiring the awareness of environmental and speech sounds; 31.8 % improved to the level of identification of environmental sounds or recognition of speech sounds (CAP scores 3-4) and 22.5% reached speech perception understanding at variable degrees (score 5-7). With regard to language development 45.5% of children showed no improvement over time (score 1). CL score was 1-2 for the majority of ASD children (72.7%), while only 18.2% reached the highest level of language skills. Four patients (18.2%) developed the use of one-word (holophrase) or two/multiple word sentences and were able to identify environmental sounds or speech sounds in auditory mode only (CAP 3-4). The remaining 12 patients (54.6%) failed to develop oral language skills. There were no statistically significant

differences at all follow-ups between subjects with or without comorbidities ($p>0.072$). Augmentative alternative communication, gestures or simple signs supported their communication. Standardized language measures were available for 6 patients only. Six patients reached a fluent oral language competence after cochlear implantation (CL 4 or 5) and achieved contextually higher CAP scores (categories 5-7) [Table 4, Table 5].

Implant variables and electrical charge requirements

All children, except for four, were habitually hyperactive during fitting sessions. electrically evoked compound action potential and impedance measurements were, however, collected in all patients and, where possible, fittings were verified based on behavioural responses. Electrical charge fitting parameters were collected at the final follow-up session (median 180 months, range 24-102). All children had full electrode insertion, with the exception of one child who had an extra-cochlear electrode which was switched off. Six Cochlear users had one electrode switched off because of high impedance (open circuits) along the middle section of the array. The remaining 15 children had all channels active. Impedance values for the active electrodes, which are typical for each device, were comparable to those reported in the literature, and were <10 kOhm in all arrays. Average M level values were 197 (SD=77.5) CU for AB and 224 CU for the one MedEl device. Average C level value for Cochlear devices was 171 (SD=18.1) CU. Once conversion formulas were applied, the nC HiRes mean value was 15.48 nC (SD=5.46), ACE mean value was 10.25 nC (SD=3.5). A parametric statistic was adopted to compare mean values with those reported by Zwolan et al. [48]. One sample Z test was run separately for HiRes (10 ears) and ACE (17 ears) electrical charge: HiRes ASD users Z value was -1.73 with a p= .08 and a Cohen's effect size= .52; ACE ASD users Z value was -3.7, with a p<0001, and a Cohen's effect size= 97. The only ASD child who was an FS4 user reported a median 14.2 nC value for the 12 active channels, while for the same device an average of 24.48 nCref was reported. The child with a Mondini malformation implanted with a cochlear device had an average electrical charge of 22.14 nC. In malformed cochlea with comparable devices, an average of 46.42 nCref was reported. The group as a whole showed mean 35.7 (SD=23.4) $nC_{\Delta\%}$ [Table 5]. Univariate analysis of $nC_{\Delta\%}$ between HiRes and ACE devices showed a significantly larger deviation from the data reported by Zwolan et al. for the Cochlear group [Table 3]. Mean SF was 34.9 (SD=11.7) dB. No significant differences in SF were recorded for different listening modes and strategies [Table 6]. Bivariate analysis did not show any SF correlation with age at ASD diagnosis, age at CI (p range=0.3-0.7) or overall electrical charge requirements.

ASD severity and correlation with audiological and implant variables.

DSM-V levels and CARS ratings were not uniformly distributed [Table 5]. ASD severity for the 22 patients in the Social Communication domain was as follows: level 1 27.3% (n=6), level 2 27.3% (n=6) and level 3 45.5% (n=10). ASD severity in the Behaviours domain was level 1 31.8% (n=7), level 2 31.8% (n=7) and level 3 36.4% (n=8) [Table 7]. With regard to CARS, the study group showed a median score of 43 (min 31 – max 60; IQR=21,25). Overall, 31.8% (7) of children presented with a mild/moderate score and 68.2% (15) with a severe score. 81.8% (n=18) of children were diagnosed as having an intellectual disability (QI≲70).

With respect to speech perception and language outcomes, ASD severity for DSM-V A and B domains were inversely correlated with CAP (p ranging from 0.001 to 0.038; r ranging from -0.39 to -0.65) and CL (p ranging from 0.001 to 0.038; r ranging from -0.39 to -0.63) outcomes in all follow-ups. DSM-V A and B maintained their correlation at mid and long follow-ups with CAP (r_p = -0.68 to -0.68, p= 0.001 to 0.004; r_p= -0.55 to -0.58, p= 0.005 to 0.02) and CL outcomes (r_p= -0.054 to -0.57, p= <0.001 to 0.007; r_p= -0.05 to -0.57, p= <0.001 to 0.02), whilst controlling for age at CI. Similarly, CARS rating was inversely correlated at mid and long-term follow-up with CAP (r_p = -0.63 to -0.66, p= 0.003 to 0.005; r_p= -0.55 to -0.58, p= 0.005 to 0.02) and CL outcomes (r_p= -0.054 to -0.57, p= <0.001 to 0.007; r_p= -0.058 to -0.62, p= <0.006 to 0.012) while controlling for age at CI. The direction of correlation indicates that the most severe ASD symptoms corresponded to lower CAP and CL levels.

Three subjects (13.6%) with both severe CARS scores and DSM-V levels were partial/intermittent users. Subjects S1-2 were partial users and being bilaterally implanted only accepted one processor. Subject S17, unilateral CI, only intermittently used his processor, and the episodes of temporary non-use differed significantly with wide variations in the onset, length, and frequency (from a few days to weeks or months). We were unable to identify any defining factor(s) that were associated with partial/intermittent CI use. All three subjects presented with level 2-3 DSM-V and a CARS rating of >43, indicating a severe form of ASD disorder.

Differences in ASD severity and SF were not significant between HiRes and ACE users (p>0.37). Equally, $nC_{\Delta\%}$ for both HiRes and ACE strategies were not significantly different between levels of DSM-V A (p=0.18) and B (p=0.4) domains or CARS scores (p=0.86). Bivariate Spearman analysis between patients' audiological characteristics and ASD outcomes is reported in Table 7. Additionally, age at CI was correlated both to age at SHL (r=0.55, p=0.008) and to ASD diagnosis (r=0.473, p=0.03), underlying a delayed rehabilitative approach in older children diagnosed in regions where neonatal universal screening was not yet routinely adopted. CARS rating was closely correlated to DSM-V A-B levels (r=0.9; p<0.001).

In Cochlear devices nC values were correlated with age at ASD diagnosis (r=-0.58, p=0.03) and to both CARS (r=-0.65, p=0.01) rating and DSM-V B domain (r=-0.64, p=0.02), underlying an inverse relationship between electrical charge requirements and ASD severity. No similar correlation was found for HiRes users.

Discussion

Cochlear implants are effective and beneficial for hearing impaired populations with ASD although, despite early access to hearing aid amplification or cochlear implantation, hearing and language skill development may be lower when compared to children implanted without additional disabilities and extremely variable [17,20,22,23]. ASD is characterized by deficits in social communication and interaction along with restricted, repetitive patterns of behaviour, interests, or activities. Difficulties with communication and language present significant clinical challenges with regard to choosing CI candidacy, notwithstanding central hearing processing issues which are inherent features of ASD, for example, when evaluating outcomes, and ultimately achieving effective CI programming. Above all, there is a lack of information concerning the strategies necessary for CI adaptation/regulation in ASD CI children, for compliance with device use, and specific actions towards setting CI parameters as described in one case reports [28]. For this reason, the present retrospective study describes clinical characteristics and CI outcomes, the average electrical charge requirements in this special population and highlights possible correlations between outcomes, CI use, and the specific characteristics of ASD CI children.

Clinical characteristics and outcomes in the studied sample

Children included in the present study showed severe to profound deafness whose etiology was either genetic or related to CMV infection in 36% and 19 % of patients respectively. The association between ASD and other genetic disorders is not an unusual finding. Meinzen-Derr et al. [17] reported 25% ASD in syndromic children with hearing loss. Recently, increased knowledge of the genetic bases of ASD suggests that a common disorder could be the sum of many different disorders, although this genetic landscape may not be apparent at first clinical evaluation [49]. Coexistence of CMV infection with ASD diagnosis has already been described [50] and it is usually associated with severe psycho-neurological symptoms and delays in language development. Accordingly, 3 out of 4 children with CMV related deafness required substantial support in both social and behavioural DSM-V domains. Additionally, premature birth is another well-established risk factor for ASD with overall prevalence rates of 7% [51]. The risk of ASD is greatest in exceptionally preterm infants and is likely to be compounded by prematurity associated complications, such as anoxia and hypoglycaemia. A

similar prevalence was found in the present study, where two children had substantial support in both A and B DSM-V domains.

ASD severity

ASD severity was not evenly distributed and the majority of children in the present study were diagnosed as requiring substantial (level 2) or very substantial (level 3) support both in social and behavioural domains. In addition, most of the participants were identified with autism several months after cochlear implantation. The median time between implantation and diagnosis of autism was 34 months. Delayed diagnosis of autism in children with hearing loss has been reported in other studies. Meinzen-derr et al. [17] reported that the average age at ASD diagnosis was 66.5 months, although children with profound HL and CI were diagnosed sooner than children with lesser degrees of hearing loss. Deafness may play a role in delaying the diagnosis of ASD [17,52] and the number of children in whom autism is only diagnosed after they receive an implant has slowly increased. Due to a widespread consolidation of universal neonatal hearing screening programs, there has been a steady decrease in the age at which children are evaluated and implanted and, consequently, more than 50% of deafness established in the present study group was diagnosed prior to 6 months of age. The wide timespan elapsing between deafness and ASD confirmation bear witness to the challenges associated with performing a dual diagnosis, given the complexities of determining whether speech/language and social delays are attributable to the hearing deficit, or whether these delays are indicative of a concomitant neurodevelopmental disorder [17,20,25,52]. This is a significant time impediment that needs to be shortened as we know that prompt prognosis of ASD is linked to early intervention [20]. The age at ASD diagnosis was inversely correlated with the severity of ASD at the B domain of the DSM-V. To achieve early ASD identification observations made during assessments such as unusual or stereotyped behaviours, inflexible routines, intense and restricted interest and sensorial hyper- or hypo-reactivity should be considered indicators that require timely assessment and intervention. On the contrary, ASD diagnosis arrived later when behavioural signs are more shaded, expose the risk that when communication alteration alone prevails, ASD diagnosis is more likely to be confused with typical difficulties related to hearing deprivation. In clinical practice, more attempts should be made to identify assessment tools capable of differentiating these challenges.

CI outcomes

The median SF threshold was 30 dB HL, whilst CAP score at the final follow-up was extremely variable, with most children have some form of benefit, ranging from environmental sound awareness to the ability to sustain a conversation without lip-reading. Language skills in the majority of children

varied from no improvement to the use of simple phrases, while only 18% reached the highest level of language skills. These findings are consistent with prior research, which describes extremely variable improvements in speech perception and expressive vocabulary, although no statistical analysis correlating outcomes to ASD severity was attempted [17,18,19,20,21,22,23]. Delays in language development and impairments in the ability to communicate constitute a defining feature of ASD. However, these language and communication impairments can vary significantly and become more severe in the presence of deafness [53]. Factors that appear to influence verbal language skills include the severity of the disorder, age at implantation, age at ASD diagnosis, the presence of comorbidities, and the availability of multidisciplinary support. Meinzer-Derr et al. [17] observed how outcomes and expectations for children with ASD and CI are as variable as outcomes and expectations for children with ASD who have normal hearing. Thus, the severity of ASD may also influence communication outcomes.

In the present study DSM-V A and B and CARS scores show an inverse correlation with CAP and CL outcomes at mid and long follow-ups, whilst controlling for age at CI. The direction of correlation was inverted, meaning that the most severe symptoms for DSMV A-B level corresponded to lower CAP and CL levels. The absence of significance in partial correlation analysis for short term ($\leq$2 years) follow-up data is probably related to the large number of children implanted <2 years where signs and symptoms of ASD had not yet been diagnosed [16]. It is a natural consequence that these children endure, in the first two years, a greater delay in the acquisition of speech and language skills and their outcomes are generally poorer.

CAP and CL scores were previously used in the literature to measure ASD children speech and language outcomes. Mikic et al. [18] assessed the development of auditory perception and speech intelligibility in implanted children with profound congenital hearing loss who were later diagnosed with ASD compared to those who were developing normally. In their finding, the CAP and Speech Intelligibility Rating showed that ASD children with CI had slower auditory processing development, often confined to the identification of environmental sounds or discrimination of speech sounds, whilst speech intelligibility showed very little or no progress.

Consistent with these findings, Nasralla et al. [23] observed that only 64% of children were able to detect sounds without discrimination and were unable to develop speech. However, those patients who managed to progress in their CAP score also observed an evolution in their spoken language CL score. Results from the present study agree with findings in the literature and further, for the first time, show a significant correlation between ASD severity and perceptive and language outcomes despite the small study group. These results, backed by a medium-high effect size, were likely

supported by the use of categorical scores, the homogeneous ASD diagnostic classification and by data completeness.

CI electrical and psychophysical characteristics

The assessment of electrical charge requirements in the ASD population has not been addressed before in this category of patients. Zwolan et al. [48] reported the average psychophysical responses for a large, heterogeneous population of paediatric CI recipients. The mapping data reported for each device brand (Cochlear, AB and MedEl) showed that there was no significant difference in average electroacoustic charges, across CI centers that participated in the study. The authors claim that homogeneous data observed in such a large cohort could provide observations that can be adopted by and reflect the real-world practices of various clinical providers. It is indeed common practice to assess C/M levels and T levels through multiple recording of postoperative ECAP, which are then verified by the observation of subjective behavioural responses. C/M and T levels are mostly stabilized within 24 months of CI activation. The greatest change in C/M levels took place between device activation and the 6-month post-activation visit for all devices, but it tended to be more stable for AB and Cochlear devices after the 12-month visit [48]. Similar values for Cochlear device users were described by Incerti et al. [54] in a group of 65 children with no additional disabilities, while higher values were reported in other children with cochlear malformations. In Incerti et al. study, fitting of devices was accomplished using standard, age-appropriate, audiological behavioural techniques, and objective measures such as ECAP and Electrical Auditory Brainstem Responses in conjunction with behavioural measures were typically adopted in infants with and without cognitive deficits.

Likewise, Baudhuin et al. [55] while studying the fitting parameters of a group of children tested to evaluate the effects of parameter settings on detection and speech recognition, describes for AB devices an average M level similar to that reported by Zwolan et al [48]. ASD children in the present study showed on average 35% lower nC electrical CI charge when compared to that reported in the literature for CI children without ASD.

The one sample Z test differed significantly when compared to Zwolan et al. data only for Cochlear devices, which had a larger deviation from literature values when compared to AB devices. Data for AB devices were not significantly different, probably owing to the smaller study group, which did not support the analysis (lower effect size). The only ASD child FS4 user and the child with a Mondini malformation also showed lower electrical charge requirements when compared to that reported in the above cited literature. Electrical charge requirements for the present study group did not correlate with SF or age at implant, whilst showing an inverse correlation with ASD severity in Cochlear users.

This data might be linked to various factors, such as the poor response by the child to the stimuli or difficult interpretations of behavioral responses as well as incidences of hypersensitivity to sounds or more general sensorial stimulation.

It has been reported how CI fitting might be particularly challenging in very young children and children with additional disabilities to the point where thresholds could be at excessively high levels; lack of participation by the child, absence of adverse responses to sound, no continuity of care (clinicians unfamiliar with the patient may not see subtle variations in the child's behaviour), misconceptions that "louder" is better and clinician inexperience in the processes or products or in fact a combination of all of these factors [56]. In the present study group, where neither C/M levels nor ASD severity were found to be correlated to FF thresholds, it seems more likely that ASD severity, due to the absence of reliable behavioural responses and/or the presence of loudness intolerance, may possibly be the principal factors influencing M level regulation.

In the present study, C/M were based on electrically evoked compound action potential thresholds and behavioural responses observation. Programming progressed conservatively and was always preceded by reports from parents concerning CI use at home and children's behaviour with respect to speech and environmental sounds. The children’s willingness to undergo these tests changed from session to session and fittings were mainly based on their cooperation. In most cases, their cooperation during sessions was such that behavioural responses were considered reliable by the audiologists. Nevertheless, responses were verified, wherever possible, through behavioural audiometry, detection, and discrimination of Ling sounds. In children with more severe ASD symptoms assessments were carried out in more than one session. However, in the most severe cases their answers could not be considered as reliable. These outcomes are consistent with reports in the literature. Tharpe et al. [57] found that the majority of children with autism demonstrated elevated behavioural SF thresholds despite normal objective measures of auditory function, and warned against the risk of over-estimating hearing thresholds due to difficulties in measuring reliable responses at low stimulus levels. Lachowska et al [19] recommended caution when fitting sound processors owing to the possibility of heightened sensitivity to sounds. Nevertheless, specific structured activities together with multiple observations of patients by specialized professionals have proved to be effective in most cases in assessing functional listening [6].

Finally, one of the study objectives was to assess electrical charge requirements and correlate them to ASD characteristics and the condition of the CI user/non user to avoid device abandonment.

In the present study group only 3 subjects (13.6%) with severe DSM-V A/B levels and CARS scores were partial (2 bilateral implanted CI children who dropped the use of one CI) or intermittent (1 child who dropped the use of the only CI device for days-weeks) users. Of these, two children presented

electric charge requirements below the average whilst one had values in line with that reported in the literature. The number of children in this cohort is too small to draw any firm conclusions, although, taken together all of the explored factors indicate that intermittent/partial CI use seems more likely correlated to ASD severity than to fitting characteristics. Higher percentages of non-users or partial/intermittent users of hearing technology have already been reported in the literature and, although a statistical analysis was not performed, this phenomenon has been described as being more frequent in patients with more severe ASD symptoms. Rodriguez Valero et al [24] specifically studied CI compliance in children subsequently diagnosed with ASD. Over 22 implanted children, 2/22 (9%) were partial users. Overall, 13/22 (59%) children with ASD experienced episodes of intermittent CI usage. The factor(s) that precipitated these episodes were not identified and temporary non-use differed significantly between patients with wide variations in the onset, length and frequency of temporary rejections. Eshraghi et al. [20], in a cohort of 15 patients of whom 9 were CI users, reported an intermittent CI use in only 1 child (11%). Fitzpatrik et al. [25] identified 22 deaf ASD children using hearing aids, with 27% reporting intermittent use of the device. Meinzen-Derr et al. [17] reported 21% of non-users (permanent reject of CI use).

The low compliance to acoustic/electric stimulation in some ASD children could be explained by hypersensitivity to acoustic changes. Hyperacusis is one form of auditory hypersensitivity, which also includes phonophobia and auditory recruitment. It is not clear whether hyperacusis originates from a central or peripheral auditory deficit [26]. Studies using parental questionnaires reported a prevalence of 16-100% for auditory hypersensitivity [58], and hyperacusis being present in 18-63% of children with ASD [4]. Loudness intolerance does not seem to depend so much on recruitment as on higher order neuron neurophysiological mechanisms unique to ASD. Research employing a battery of physiologic auditory tests has shown that the peripheral auditory characteristics of children with normal hearing who have ASD are comparable to those of typically developing children. However, whilst objective audiological measures produced similar results in children with and without ASD, the group with ASD responded differently when applying behavioural audiological measures [57]. Central neural mechanisms involving negative emotional reactions to sound seem to reside in the limbic system and in its connection to the auditory system [59]. The number of patients in the study group with low compliance for CI is relatively small compared to that reported in the literature and no children dropped the CI permanently, reiterating how the majority of ASD DHH children might benefit from this procedure.

Contributions and limitations of the present study

The present study contributes to the body of knowledge available on outcomes after implantation in ASD children and is the first report focused on different time periods of follow-up. Altogether, there is a significant correlation between ASD severity and perceptive and language outcomes despite the small study group. Most of the improvements were recorded in the mid-term period and continued into long term follow up. ASD CI children with less severe clinical pictures were able to reach good listening and linguistic skills, while children with an increased degree of severity show positive but limited benefits. Most likely, the outcomes that ASD CI children obtain after cochlear implantation correspond to the maximum level of competencies they would have reached on the basis of severity anyway [60]. These two data sets could be used by clinicians to counsel families in what they can expect after cochlear implantation, helping them to understand that improvements in ASD populations are possible in the long run but slow and to set realistic and achievable goals [61]. Furthermore, the findings on electrical charge requirements explains and supports Tharpe et al [57] and Lachowska et al. [19] who cautioned against the risk of over-estimating hearing thresholds and/or heightened sensitivity to sounds. In fact, the CI children evaluated in the present study diagnosed with ASD showed an average of 35% lower nC electrical CI charge when compared to CI peers without ASD.

Some limitations of the study, however, need to be taken in account.

Results reported in this study are obviously qualified by being retrospective in nature. The small study size has limited our ability to make statistical inferences amongst many variables. Because this was a retrospective review of clinical data, we were limited to data available in medical charts.

Furthermore, there were only 3 partial/intermittent CI users (3 subjects) and there were no cases of CI abandonment: this data did not allow us to perform any analysis useful to understanding the possible reasons for differences in CI tolerance (e.g differences in electrical charge settings) nor to identify any specific procedures and strategies necessary in order to stabilize CI use. Future research could focus on these unanswered questions, helping the scientific community to gather new knowledge that could help improve clinical practice.

Conclusion

SHL children diagnosed with ASD are challenging for clinicians and require complex management including audiological selection, fitting procedures and ongoing clinical management. Results reported in the present retrospective study show that CI is effective and beneficial for hearing impaired ASD children, although outcomes in speech perception and language development lag behind

those reported in the literature being typical of implanted children with no additional disabilities. A limited improvement in language skills was found in most ASD CI children with more severe symptomatology. This shows the importance of integrating audiological and communicative assessments (with ASD diagnostic criteria) alongside a series of standardized tools such as CARS, in order to define the gravity of ASD on which to calibrate outcomes and expectations after cochlear implantation. The electrical charge settings tended to be lower than the values reported in the literature for CI children without additional needs. This finding when linked to the severity of ASD symptoms constitutes a warning against the risk of over-estimating hearing thresholds and/or heightened sensitivity to sounds.

Further studies are needed to broaden clinical understanding in this specific research field.

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Subjects	Age at DHH diagnosis months	Age at CI months	Age at ASD Diagnosis months	Comorbidities
S1	30	38	60	no
S2	11	14	36	CMV
S3	5	15	120	Baraitser Winter
S4	13	41	40	Congenital
S5	6	14	36	Usher type I
S6	12	39	42	no
S7	4	22	38	CMV
S8	6	65	42	no
S9	9	144	44	prematurity
S10	11	57	56	GJB2
S11	50	77	62	Usher type I
S12	1	14	36	CMV
S13	3	10	39	CMV
S14	30	40	42	no
S15	1	15	62	no
S16	7	28	40	Mondini
S17	4	44	50	no
S18	14	42	60	no
S19	12	33	48	GJB2
S20	7	35	42	no
S21	9	17	42	GJB2
S22	5	26	43	prematurity

Table 1: subjective and audiological characteristics of the study group.

CAP			
0	No awareness of environmental sounds	5	Understanding of common phrases without lip-reading
1	Awareness of environmental sounds	6	Understanding of conversation without lip-reading
2	Responds to speech sounds	7	Use of telephone with known listener
3	Identification of environmental sounds	8	Follows group conversation in a reverberant room or where there is some interfering noise, such as a classroom or restaurant
4	Discrimination of some speech sounds without lip-reading	9	Use of phone with unknown speaker in unpredictable context

CL	
1	The child does not speak and may present undifferentiated vocalization
2	The child speaks only isolated words
3	The child builds sentences of two or three words
4	The child builds sentences of four or five words, and begins to use connective elements (pronouns, articles, prepositions)
5	The child construct sentences of more than five words, using connective elements, conjugating verbs, using plurals, etc. He/she is fluent in oral language.

Table 2: Categories of Auditory performance (CAP), classifies listening outcomes in 10 categories of increasing difficulty. Categories of Language (CL) classifies speech production in 5 categories of language performances.

Device	Formula	Reference nC values by device
Advanced Bionics M levels	(µAmp/0.0128)/1000	17.49 (8.79-28.07) n=47
Cochlear C levels	(µAmp*pw)/1000 Clinical units are arbitrary and µAmp conversion was provided by the manufacturer	18.39 (6.37-58.89) n=87
MedEl M levels	(µAmp*pw)/1000	24.48 (8.42-74.84) n=25

Table 3: Formulas used to convert clinical units to charge per phase (nCoulomb). Reference mean (min – max) nC values for Electric charge requirements in nC reported by Zwolan et al (2008) in children with normal and malformed cochlea were reported.

Subjects	SF dB	CAP				CL			
		Pre-CI	short	mid	long	Pre-CI	short	mid	long
S1	35	0	0	1	1	1	1	1	1
S2	30	0	1	2	3	1	1	1	2
S3	25	0	4	5	7	1	2	4	5
S4	30	0	2	3	3	1	1	2	2
S5	30	0	1	5	7	1	1	3	5
S6	15	0	0	4	4	1	1	2	2
S7	50	0	0	2	3	1	1	1	1
S8	40	0	0	1	1	1	1	1	1
S9	30	0	3	3	5	1	2	3	4
S10	30	0	2	3	4	1	2	2	3
S11	25	0	0	2	2	1	1	1	1
S12	20	0	2	4	-	1	2	2	-
S13	25	0	4	-	-	1	2	-	-
S14	35	0	1	-	-	1	1	-	-
S15	45	0	0	0	1	1	1	1	1
S16	60	0	1	2	-	1	1	2	-
S17	59	0	0	-	-	1	1	-	-
S18	30	0	1	5	6	1	1	3	5
S19	30	0	2	4	6	1	1	4	5
S20	45	0	0	1	1	1	1	1	1
S21	45	0	0	1	1	1	1	1	1
S22	55	0	0	0	0	1	1	1	1

Table 4: subjective and audiological characteristics of the study group. Categories of auditory performances (CAP) (Archbold et al, 1995) and Categories of Language (CL) (Bevilacqua, 1996; Nasralla, 2018) were assessed pre-CI and at short (<2 yr) medium (5 yr) and long term (> 10 yr) follow-up.

S22	M	user	3	2	52	2

Table 5: ASD DSM-V domains levels (see table 1) and CARS rating and severity of symptoms. CARS severity= 1, mild/moderate and 2, severe. CI compliance: user (daily use>8 hrs), partial user (bilaterally implanted only accepted one processor) and intermittent user (the episodes of temporary non-use differed with wide variations in the onset, length, and frequency).

		SF		$nC_{\Delta\%}$	
Variables		dB HL	(p)	%	(p)
Strategy	HiRes	31.82 [8.7]	(0.3)	20.54 [24.12]	(**0.007**)
	Ace	37 [13.1]		44.68 [18.36]	
Listening mode	Unilateral	37.4 [13.4]	(0.4)	28.9 [24.7]	(0.1)
	Bilateral	31.6 [8.7]		36.8 [21.3]	

p value significant at a level≤ 0.05 (bold); standard deviation [SD].

Table 6: Univariate analysis of strategy and listening mode outcomes for sound field (SF) and nCΔ%

	Age at CI months	Age at ASD diagnosis months	SF dB HL	$nC_{\Delta\%}$	HiResolution nC	ACE nC
	Rho (p)	**Rho (p)**	**Rho (p)**	**Rho (p)**	**Rho (p)**	**Rho (p)**
DSM-V domain A	0.08 (0.9)	-0.2 (0.2)	0.7 (<**0.001**)	-0.05 (0.8)	-0.4 (0.3)	-0.4 (0.1)
DSM-V domain B	-0.001 (0.9)	-0.39 (**0.04**)	0.6 (<**0.001**)	-0.06 (0.7)	-0.04 (0.9)	-0.06 (0.7)
CARS rating	0.01 (0.9)	-0.3 (0.07)	0.6 (**0.001**)	0.09 (0.6)	-0.06 (0.8)	-0.54 (**0.02**)

Table 7: Spearman's Rho and p values between DSM-V A (Social communication) and B domains (Behaviour), CARS rating and children characteristics (22 patients, 28 implanted devices). Significant correlations in bold.

ASD			
		A: Social communication domain	**B: Restricted, repetitive behaviours domain**
Severity Level	**Level 1 "Requiring support"**	Without support in place, deficits in social communication cause noticeable impairments. Difficulty initiating social interactions, and clear examples of atypical or unsuccessful responses to social overtures of others. May appear to have decreased interest in social interactions. For example, a person who is able to speak in full sentences and engages in communication but whose to-and-fro conversation with others fails, and whose attempts to make friends are odd and typically unsuccessful.	Inflexibility of behaviour causes significant interference with functioning in one or more contexts. Difficulty switching between activities. Problems of organization and planning hamper independence.
	Level 2 "Requiring substantial support"	Marked deficits in verbal and nonverbal social communication skills; social impairments apparent even with supports in place; limited initiation of social interactions; and reduced or abnormal responses to social overtures from others. For example, a person who speaks simple sentences, whose interaction is limited to narrow special interests, and who has markedly odd nonverbal communication.	Inflexibility of behaviour, difficulty coping with change, or other restricted/ repetitive behaviours appear frequently enough to be obvious to the casual observer and interfere with functioning in a variety of contexts. Distress and/ or difficulty changing focus or action
	Level 3 "Requiring very substantial support"	Severe deficits in verbal and nonverbal social communication skills cause severe impairments in functioning, very limited initiation of social interactions, and minimal response to social overtures from others. For example, a person with few words of intelligible speech who rarely initiates interaction and, when he or she does, makes unusual approaches to meet needs only and responds to only very direct social approaches.	Inflexibility of behaviour, extreme difficulty coping with change, or other restricted/ repetitive behaviour markedly interfere with functioning in all spheres. Great distress/ difficulty changing focus or action.

Annex 1: Severity levels for Autism Spectrum Disorders (ASD), according to the Diagnostic and Statistical Manual of Mental Disorders DSM-V. **Domain A**, Persistent deficits in social communication and social interaction across contexts, not accounted for by general developmental delays, and manifest by 3 of 3 symptoms. **Domain B**, restricted, repetitive behaviours domain, and manifest by at least 2 of 4 symptoms, for ASD diagnosis.

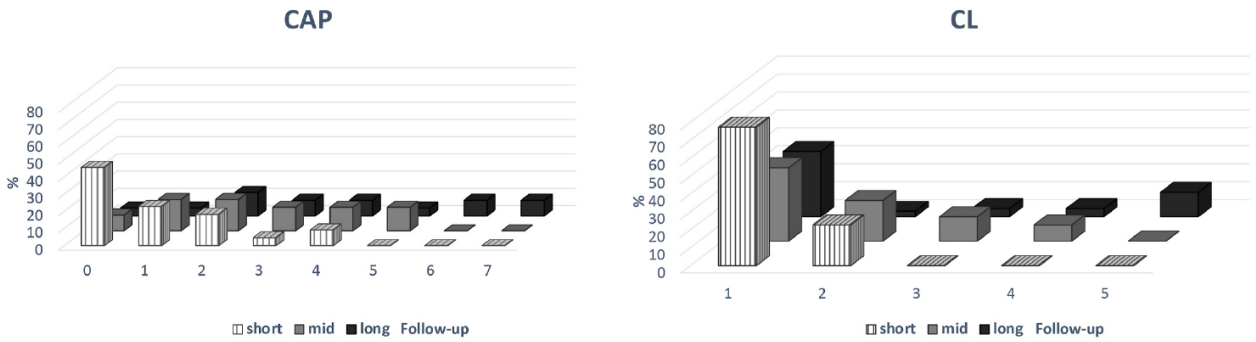

Fig. 1. Percentage of ASD CI Children by levels of Categories of Auditory Performances (CAP) and Categories of Language (CL) assessed at short (<2 yr) medium (5 yr) and long term (>10 yr) follow-up.

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