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The Effects of Delayed Hearing Rehabilitation in a Patient with Myhre's Syndrome during COVID-19 Pandemic

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Abstract

Hearing loss (HL) is observed among pathologies in patients affected by Myhre syndrome and it is predominantly conductive and sometime sensorineural or mixed. Hearing loss if not treated properly can have impacts on cognitive behavioural and communicative language. We describe the benefits of hearing rehabilitation by using hearing aids in a patient with conductive HL, that carries a mutation (c.1498A>G; p.lle500Val) within the SMAD4 gene as detected by whole exome sequencing [1]. Despite the relevant delay of hearing aid and language rehabilitation in this baby girl because of the COVID-19 pandemic restrictions, we demonstrate the positive impact of the hearing rehabilitation on listening skills, on cognitive abilities and working memory in syndromic HL which is characterized by behavioural disorders and mild to moderate intellectual disability, thus improving quality of life.

Keywords: Hearing Loss; Hearing Aids; Myhre Syndrome; SMAD 4 Gene; Working Memory

Introduction

Myhre syndrome (MS) is a rare genetic autosomal dominant connective tissue disorder, first observed in 1981 [2], has thus far been reported in about 80 patients worldwide [1]. It is characterized by developmental delay, characteristic facial features, various bone and joint abnormalities, distinctive cardiovascular, ophthalmological and ear, nose and throat manifestations including deafness, in association with mild to moderate intellectual disability and autism or autism spectrum disorder-like behaviour [1,3-5]. Although MS is a rare syndrome, in almost all cases reported an intellectual deficit of varying degrees which may be life-threatening, while limited intellect and autism spectrum disorder-like behaviour may affect the capability of having normal social interactions [1,6]. Behaviour was reported as abnormal with difficult social interaction, attention deficit, repetitive/stereotypic activities and depressive traits [1,6]. Hearing loss is observed in about 80% of subjects affected by MS [7] and it is predominantly conductive even if cases of sensorineural or mixed HL have been observed. Of note, most infants pass the universal newborn hearing screening. The HL loss usually becomes evident in early childhood and is typically present in adults, its underlying aetiology is often unclear or unknown; often patients have a history of bilateral myringotomy tube placement. The diagnosis of MS is established corroborating the clinical findings with SMAD4 heterozygous mutation identified in most of the patients. SMAD4 gene mutations result in abnormal TGF-β signalling in several cell types, which affects the development of several body systems and leads to the specific phenotype of MS [1].

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Considering the gain-of-function mutations responsible for MS and the consequent proliferative response seen in tissues, it has been suggested that HL depends by the abnormalities of the cartilaginous and bony structures of the ossicular chain and bony labyrinth even otospongiotic abnormalities [6]. We underly the importance to hearing aids rehabilitation in counteracting the cognitive developmental impairment that is a phenotype character of MS and improving quality of life.

Case Presentation

We report the case of a 7-year-old girl affected by Myhre syndrome, born to non-consanguineous parents, after 38 weeks of gestation, complicated by intrauterine growth retardation and a prenatal diagnosis of tetralogy of Fallot, confirmed by echocardiogram at birth. Among pre-perinatal risk factors we found the low birth weight at 2.2 Kg (3rd percentile, than 5 ibs), the TORCH complex was negative throughout pregnancy, no ototoxic drugs have been administered. On the third and nineteenth day of life due to the dilation of the pulmonary balloon, a cardiac catheterization was carried out with subsequent placement of coronary stent in the right ventricular outflow tract to increase pulmonary blood flow. At 7 months of age, there was complete surgical resolution of the TOF with closure of the ventricular septum, trans-annular lung patch and repair of the left pulmonary artery. She underwent to two surgeries at 10 months and 24 months of age for correction of the obstruction of the right ventricular flow. Since birth the weight, height and circumference of the head were maintained below the 5 percentile. Around 10 months of age she was able to sit, walk alone at 20 months of age. The first words were spoken at 16 months of age. The diagnosis of the syndrome was made at the age of 22 months of age. Sequence analysis of protein-coding genes using whole-exome analysis revealed heterozygous missense variant of SMAD4, c.1498A>G, p. (Ile500Val). The baby girl was the second of three sisters, after the diagnosis of SM, familial genotyping (father, mother, and older sister) was also performed and it was negative. According to the genetic test results the detected variant was confirmed as a de novo variant. Despite the genetic diagnosis, the patient did not undergo to audiological evaluation. From a phenotypic point of view the girl presents esotropy, displacement of the pupil of the eye from its normal and central position (e.g. chorectopy) more evident in the left eye, short eyelid fissures, hypertelorism, flat nasal bridge, arched palate and brachidactilia. At 4 years of age, she carried out the audiological assessment with air conduction (AC) and bone conduction (BC) Auditory Brainstem Response for click signals which resulted in the presence of AC threshold up to 50dBnHL bilaterally and BC ABR threshold at 20dBnHL indicating the conductive origin of hearing impairment which can be estimate as a moderate hearing loss for the mid-high frequencies, however hearing rehabilitation has been not prescribed. The girl underwent to speech therapy from 3 to 5 years of age due to cognitive, perceptual-linguistic and curricular difficulties. Since five years of age because of the pandemic from COVID -19 speech therapy has been interrupted. The baby girl at 7 years of age arrived to our observation with severe delay for audiological diagnosis and treatment. She carried out the audiological evaluation at the Audiology Unit of the University of Naples "Federico II". The otoscopy was normal. The pure tone audiometry demonstrated medium-severe at low frequencies and moderate at high frequencies conductive hearing loss (figure 1). The audiometric speech test using bisyllabic words list for children reached a threshold of perception (50%) at an input intensity of 60 dB bilaterally and never reached the intelligibility threshold. Tympanometry shows bilaterally normal (type A), the stapedial reflexes were bilaterally absent. High resolution temporal bone CT scan was requested to evaluate ear malformations. No malformation and /or signs of inflammatory diseases or osteospongiotic lesions were observed. In addition, the evaluation of perceptual-linguistic and cognitive results was carried out. Furthermore, the assessment of perceptual-linguistic and cognitive outcomes was performed. The Common Assessment Protocol in Rehabilitative Audiology was administered (8), for the assessment of fluid intelligence Raven's coloured progressive matrices (CPM Protocol) were used, for the assessment of verbal memory the Neuropsychological Evaluation Battery (Protocol BVN5-11) were used, the evaluation test of metaphonological capabilities (Protocol CMF) and linguistic balance were used (9,10,11). Follow-up (3 months from application hearing aid) was performed to monitor perceptual and cognitive-linguistic abilities. The baby girl underwent to hearing rehabilitation with bilateral BTE hearing aids. The reduction of clinical activities to focus the resources on COVID-19 cases and the lockdown restrictions caused the relevant delay from in the diagnosis and management of hearing loss and hearing aid rehabilitation. The restrictions also have limited the access to speech and language rehabilitation. As known in (figure1A) BTE hearing aid application significantly improved hearing threshold, both on tonal audiometry and speech audiometry. The improvement of the hearing abilities in silent environment, both in terms of power and frequency analysis was observed. Due to the partial cooperation, it was not possible to perform speech tests in noise. A significant improvement was also evident in verbal acoustic perception (figure 2 A), performed with unrecorded voice, regardless of the reactive used (words of full meaning, sentences, consonants). The assessment of cognitive abilities (figure 2 B, C) showed a significant improvement in both fluid intelligence (CPM Protocol - Reference Values sec. Russo), which in 4 months varied from Merit Class III- (25 percentile) to Class III+ (25-50 percentile) as well as of the memory to the verbal attentive span (Protocol BVN5-11-Direct Span of numbers), from 3 (80 percentile) to 4 (100 percentile) (11). Expressive language is characterized by a phonetic disorder, with correct pronunciation only phones

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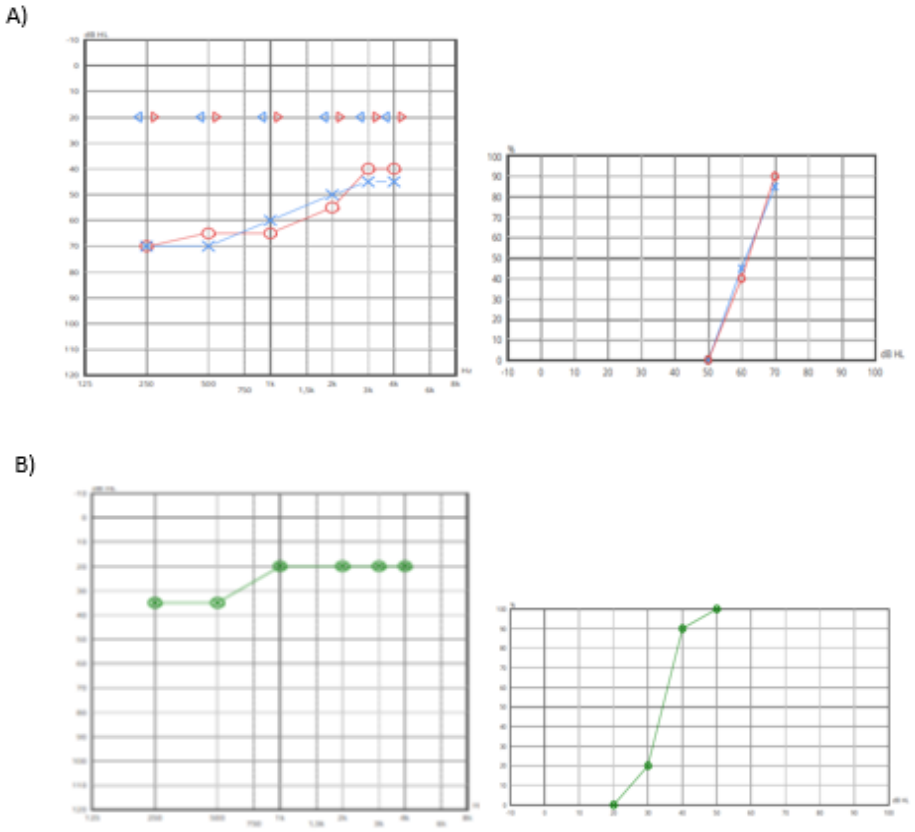

Figure 1: A) Tonal and speech audiometry with headphones pre application HA. B) Tonal and speech free field audiometry post application HA (4 months).

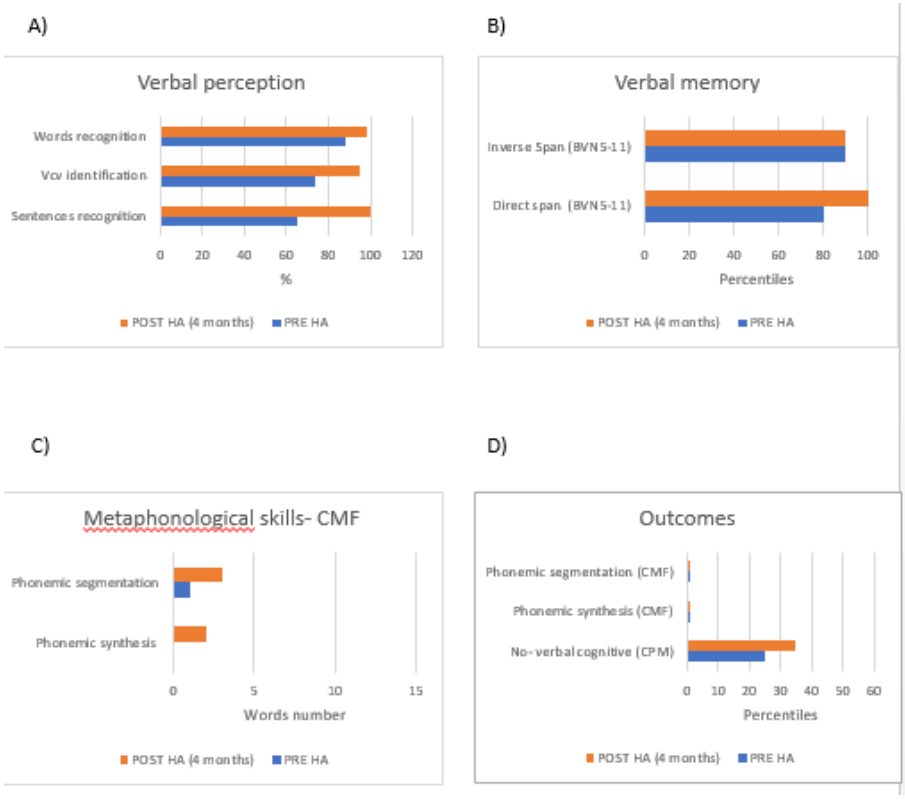

Figure 2: A) Verbal perception, B) Verbal memory, C) Metaphonological skills – CMF, D) Outcomes.

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/p/, /v/, /m/, /n/, /[/, /e/, /r/ on repetition of simple syllables, words or in spontaneous production. Moreover, phonological disorganization and praxic oral difficulties persist, consequent to the muscular hypotonia of the phonatory district, which makes the speech partially intelligible. There was a delay of language characterized by poor receptive and expressive vocabulary and a lack of use of complex syntactic structures. School learning was severely delayed in all formal domains: the girl attended her first year of primary school with support, with modest decoding and encryption skills. Furthermore, slight improvement on verbal working memory was also observed following the hearing aid application such as inverse span of numbers, metaphonological abilities. However, after 6 months of hearing aids fitting the related abilities were still lacking (<5 percentile), despite a slight improvement (i.e. phonemic fusion improved from 0 to 2 words and phonemic segmentation improved from 1 to 3 words) (figure 2 D). Accordingly, to the other cases previously reported [5] a mild intellectual disability was measured, despite no severe disability or autism spectrum disorders were evaluated. Thus, she passed by a level of fluid intelligence at the lower limits of the norm (class III-) to a class III+ (subject of intelligence in the norm) after wearing hearing aids. This finding underlines the effectiveness on cognitive development, speech and language skills, learning development and social interaction in early, at about 6 months after hearing aids application. Longer follow up will be helpful to demonstrate the beneficial effects of hearing aids. The baby girl is currently enrolled in a follow up program for the risk of progression of hearing loss.

Discussion

We described a rare case of MS caused of de novo variant in heterozygous missense mutation MAD4, c.1498A>G, p. (Ile500Val) of SMAD4 gene. Although the rarity of syndromic disease, typical clinical picture of SM was observed in our case including developmental delay with mild intellectual disability, characteristic short stature, facial and ophthalmological dysmorphisms, cardiovascular malformations and deafness [1,3-5]. However, in this case we describe the impact of delated diagnosis and treatment of HL mainly due to the poor consideration of Clinicians of this impairment among different clinical manifestations of disease and secondly for the difficulty in accessing the multiple facilities required for diagnosis the rehabilitative process during COID-19 pandemic. Despite the advancement in understanding genetic causes, there is still limited consensus on management of paediatric syndromic patients with HL. In this case, the genetic diagnosis was appropriately done in infant, however the moderate conductive hearing loss was untreated for 4 years and speech therapy was unsuitably performed in child who did not adequately undergo to hearing aid rehabilitation. Likely, the family was not enough informed and denied the cure of their baby girl. The attitude of parents with syndromic children could be to reject the possibility of genetic stigma. Indeed, major goals in the management of paediatric patients with HL are timely and proper diagnosis and determining appropriate aural rehabilitation and familiar counselling (Belcher et al., frontiers pediatric 2021). Thus, the aim is to optimize communication and language development in these children especially in cases with associated multisensory, developmental, and cognitive comorbidities. Prompt and adequate hearing rehabilitation is crucial especially in these children. Deaf children with conventional hearing aids can benefit of speech therapy in improving language skill and cognitive development (landolfi et al., 2022). Thus, the delay in hearing aid prescription is a key point for the rehabilitation of a SM child who is affected by intellectual disability and behavioural dysfunctions. In agreement with the few cases associated with progressive HL [6], we found a typically conductive HL likely related to the otospongiotic abnormalities even if the CT scan did not showed morphological abnormalities. Interestingly, despite the late hearing aid fitting the baby girl showed an early improvement of speech and language skills which can positively affect cognitive development and social interaction. The early effect on the outcome of rehabilitation, even in this case of SM associate a variable cognitive defects, suggests more attention in the management of mild to moderate HL in these patients who must to be insert in a long term surveillance program for risk of late onset or progression to severe and profound HL reaching the indication to cochlear implant [6]. Finally, this case highlights the risk of delay the diagnosis and treatment of severe syndromic patients because of the COVID-19 pandemic consequences including ‘‘social distancing,’’ prolonged lockdowns, cancelling elective procedures, and limiting nonessential services. Given critical period for language development and the long-term impact of auditory deprivation, especially in syndromic children, audiologic and speech disorders Services should be considered essential. In conclusion, we describe a case of SM with a typical presentation in which HL rehabilitation was severely delayed demonstrating the positive impact of hearing aids on acoustic and perceptive skills and, also, on all cognitive and communicative performances (verbal and non-verbal), with beneficial outcomes even in the early stages of the hearing aids wearing [8-13].

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