Annals of Clinical and Medical Case Reports

Case Report

ISSN 2639-8109 | Volume 13

First Case in Italy of a Patient with Sifrim-Hits-Weiss Syndrome [Sihiwes] Described from an Audiological and Neuropsychological Point of View

Laria C[1], Rodio A[1], Casarella A[1], Scala I[2], Auletta G[1] and Fetoni AR[1]

[1]Institute of Audiology, Dept. of Neurosciences, Reproductive Sciences and Dentistry, University of Naples Federico II, Naples, Italy

[2]Unit of Clinical Pediatric Genetics, University of Naples Federico II, Naples, Italy

***Corresponding author:**

Carla Laria,
Institute of Audiology, Department of Neuroscience, Reproductive and Odontostomatological Sciences, University of Naples "Federico II", Via Pansini 5, 80131 Naples, Italy

Received: 26 Feb 2024
Accepted: 06 Apr 2024
Published: 12 Apr 2024
J Short Name: ACMCR

Citation:

Laria C, First Case in Italy of a Patient with Sifrim-Hits-Weiss Syndrome [Sihiwes] Described from an Audiological and Neuropsychological Point of View.
Ann Clin Med Case Rep. 2024; V13(10): 1-6

Keywords:

Sifrim-Hitz-Weiss Syndrome; Hearing loss; CHD4; Neuropsychological Testing

1. Abstract

Sifrim-Hitz-Weiss syndrome [SIHIWES] is a multi-systemic neurodevelopmental disorder caused by heterozygous missense variants in chromodomain helicase DNA-binding protein 4 [CHD4]. This condition is part of an increasingly recognized group of Mendelian disorders involving chromatin remodeling abnormalities. We describe the audiological and perceptive evaluations in a patient with SIHIWES [1]. We hope that this report will broaden knowledge on the audiological and perceptive aspects of these patients with a very rare syndrome and on the possible rehabilitation path to be undertaken that is effective in improving long-term outcomes.

2. Introduction

The initial publications on individuals with de novo variants in CHD4 were described since 2016. SIHIWES is a rare multi-systemic neurodevelopmental disorder characterized by macrocephaly or microcephaly, ophthalmic abnormalities such as strabismus, hypermetropia and astigmatism, fundoscopic anomalies, facial dysmorphism such as asymmetrical ears, drooping eyelid, long philtrum and downturned mouth, congenital heart defects, ventriculomegaly, hypotonia, motor delays, global developmental retardation, intellectual disability in the mild-to-moderate range, autism, conductive and/or sensorineural hearing loss [2,3], however the complete description of the audiological phenotyping is lacking. CHD4 is implicated in the repression of lineage-specific genes during differentiation and is required for the establishment and maintenance of more compacted chromatin structures. CHD4 mutations have a high incidence in some carcinomas and in thyroid and ovarian cancers. Mutations in CHD4 have also been implicated in intellectual disability syndromes [4,5]. De novo missense mutations in CHD4 are also associated with an intellectual disability syndrome with distinctive dysmorphisms. Mutations observed in patients with this syndrome are located in PHD finger 2 [Cys467Tyr] and predominantly in ATPase lobe 2 [Ser851Tyr, Gly1003Asp, Arg1068His, Arg1127Gln, Trp1148Leu, Arg1173Leu, and Val1608Ile] [2,3,4,5]. We mapped the sites of these mutations into our Clinic and attempted to predict the effects of the mutations as far as possible. In this report, we present the multidisciplinary work up in a case of a patient with SIHIWES that shows a moderate-severe hearing loss, low intellectual disability, convergent strabismus, hypothyroidism and scoliosis. We want to describe the audiological and neuropsychological characteristics of a patient with SIHIWES following a correct and early stimulation with hearing aids.

3. Case Presentation

We report the first documented case in Italy of a 13-year-old girl affected by SIHIWES, born to non-consanguineous parents, after 38 weeks of gestation. Pregnancy was complicated by pregnancy hypertension [intake of S-adenosyl methionine] and intrauterine growth restriction [IUGR] from the 12 weeks. She performed

emergency C-section for fetal distress. Among pre-perinatal risk factors, we found the low birth weight at 2,360kg, TORCH complex tests were negative, no ototoxic drugs have been administered; APGAR values were 1' 6, 2' 7. The first 15 days she was hospitalized in Neonatal Intensive Care Unit [NICU] for hypotonia, without the need for respiratory assistance or artificial nutrition. During the stay in NICU the diagnosis of congenital hypothyroidism was made and early treated with replacement therapy, the echocardiogram showed the presence of a 13mm wide interatrial defect [IAD] treated surgically at the age of 4 years old. Girl underwent to the Universal Hearing Screening Program, the neonatal otoacoustic emission testing performed in the NICU was bilaterally refer. She underwent to Auditory Brainstem Responses [ABR] at the age of 3 months and the diagnosis of moderate to severe sensorineural hearing loss was made as below described, and she early underwent to hearing aids rehabilitation at the age of 4 months. Since she was 3 months old the young patient underwent bilateral power hearing aids with non-linear amplification and prescriptive method NAL-2. During the growth up she underwent to speech therapy for speech disorder and mild intellectual disability as showed below, while motor retardation with neuropsychomotricity. The convergent squint was treated with bandages, myopia with corrective lenses, for the flat foot uses orthopedic orthotics and practice corrective gymnastics therapy. For the developmental milestones, she held her head at 5 months, the first steps at 18 months and the first words 12 months of age. Remarkably the syndrome's diagnosis was made at the age of 9 years old because of the progressive onset of signs of disease and mainly for the later genetic diagnosis despite the earlier rehabilitation of the incoming signs as described below. Thus, New Generation sequencing [NGS] analysis showed the following de novo variant in heterozygous of exon 24 of the CHD4 gene: c.3568A>G, p.Lys1190Glu de novo missense variants of the CHD4 gene which has been associated to SIHIWES presenting clinical signs comparable to those present in the patient.

4. Results

We describe the facies and the overall signs at 13 years of age. Clinical examination showed short stature, facial dysmorphism, convergent strabismus, motor delays, hypothyroidism and scoliosis, hemidactyly, bilateral valgus knee, flat foot, prominent forehead with imbibition of the subcutaneous, synophria, blue sclerae, helix slightly curled low implant, fistula under nasal [blind bottom], nasal bridge widened bifid, high palate, hypoplastic nipples, feet overlap of the II on III, IV on III. Right lumbar back hump convex (Figure 1). Otoscopy was normal. Audiological assessment was characterized by sensorineural hearing loss that was moderate to severe in the right ear and moderate in the left ear (Figure 2A,2B). Speech audiometry using bysyllabic word list showed in left ear a threshold of detection at 40 dB HL, threshold of perception at 55 dB HL and intelligibility at 80 dB HL. In the right ear detection threshold at 50 dB HL of perception at 65 dB HL and intelligibility at 90 dB HL (Figure 2C). Verbal perception tests were performed in the noise, ITA matrix, in binaural listening with and without hearing aids. The Speech recognition thresholds [SRT50] without hearing aids is 13.3 dB HL and with -1.5 dB HL hearing aids. This results in fairly correct listening skills with hearing aids. Tympanogram was type A in left ear and type As in right ear. The stapedial reflexes were bilaterally absent. The perceptive evaluation was performed through the common evaluation protocol in rehabilitative audiology [Burdo, 1996] shows speech recognition 100% of correct responses, phrases recognition 100% of correct responses, consonant recognition [vocal-consonant-vocal /vcv/ configuration] 95% of correct responses (Figure 3A) [6]. In the neuropsychological protocol [BVN 12-18] the direct digit span used to evaluate the short-term memory [MBT] was 4 [Z= -1.82ds] that means an attention request, the inverse digit span to study working-memory was 3 [Z= -1.26ds] this was a sufficient performance. In the spoonerism test used to assess phonological awareness [Marotta et al., 2008], established values Benso middle schools, the patient obtained 0 correct answers therefore falls below the 5° percentiles. For the evaluation of planning and problem-solving tests the Tower of London test was used. The Tower of London test [Vio, 2006] is a test used in applied clinical neuropsychology for the assessment of executive functioning specifically to detect deficits in planning, which may occur due to a variety of medical and neuropsychiatric conditions. It is related to the classic problem-solving puzzle known as the Tower of Hanoi. The results were [Z= -1.94ds] therefore falls below the 5° percentiles (Figure 3B). The result is a weakness both in short-term verbal memory and in verbal working memory, as well as in visuospatial planning. For the evaluation of the learning, the following diagnostic protocol was administered: MT3 tests [Cornoldi C., 2016], battery for the Evaluation of Dyslexia and Disortography Evolutive-2 [DDE2] [G. Sartori, 2007], battery for evolutionary dyscalculia [BDE2] [A. Biancardi, 2016]. MT3 Tests are a battery to assess reading skills in speed and correctness and understanding. The DDE2 allows you to assess the level of proficiency acquired in both reading and writing. The BDE2 is a fundamental tool to ascertain the presence of a disturbance of numerical processing and computation. The survey areas are three: the area of number, calculation and "sense of number" to indicate the semantic processing skills of numerical information and calculation. In all three areas the child is below the 5° percentile. Since in all the batteries administered the girl is below the 5 percentiles has been diagnosed nonspecific disorder of learning [7,8,9]. Since the application of the hearing aids and subsequent adjustments over time the free-field audiometry revealed a mean value of pure tone [average of 0.25, 0.5, 1, 2 and 4 kHz] of 15 dB HL bilaterally. The binaural tonal audiometry performed in the free field showed a good hearing aids recovery (Figure 4A). The speech recognition threshold using bysillabic word list voice audiometry in the free field showed in binaural listening a threshold

of detection at 20 dB HL, threshold of perception at 35 dB HL and intelligibility at 60 dB HL (Figure 4B). The evaluation of linguistic and cognitive outcomes over time has shown improvements in all domains explored. In particular, the girl at the age of 10 years had a cognitive delay, important phonetic-phonological difficulties, poor vocabulary, a discreet selective attention to the task and a mild prolonged attention. Nowadays she is 13 years old, has a slight cognitive delay, good verbal perceptual skills, a distinct intelligibility of speech, a vocabulary still poor in age, a short-term verbal memory [MBT] and work partially lawful [12,13,14].

Figure 1: Patient's picture

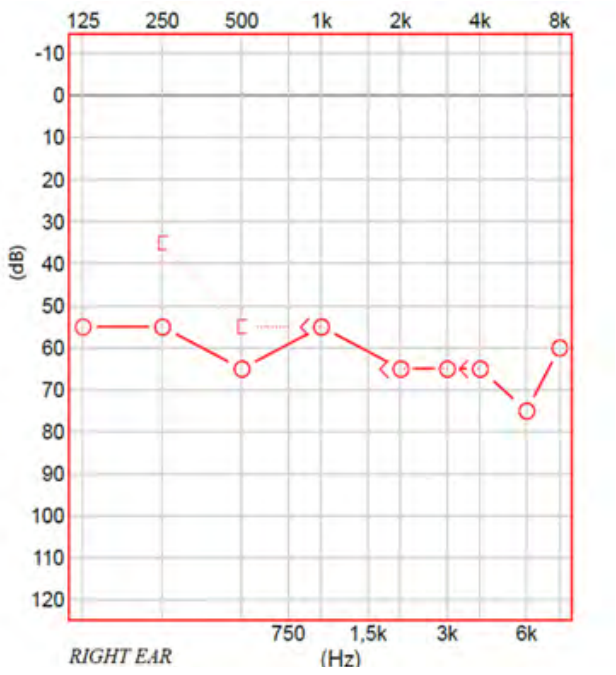

Figure 2A: Tonal audiometry in headphones right ear

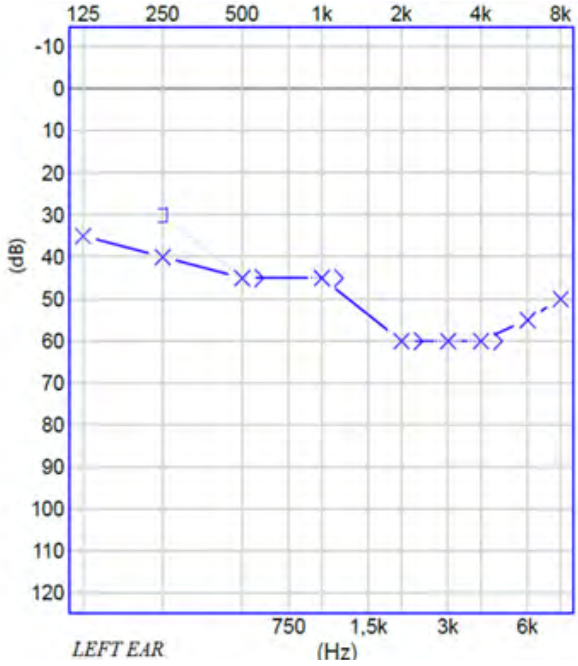

Figure 2B: Tonal audiometry in headphones left ear

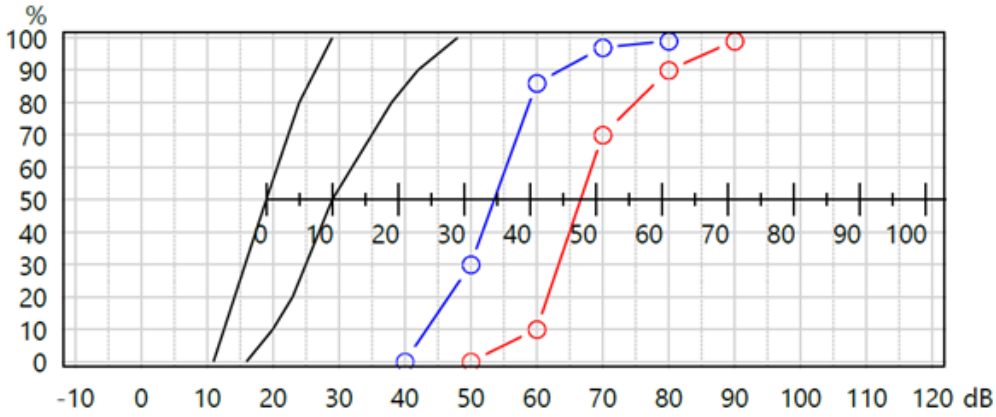

Figure 2C: Speech audiometry in headphones left ear and right ear

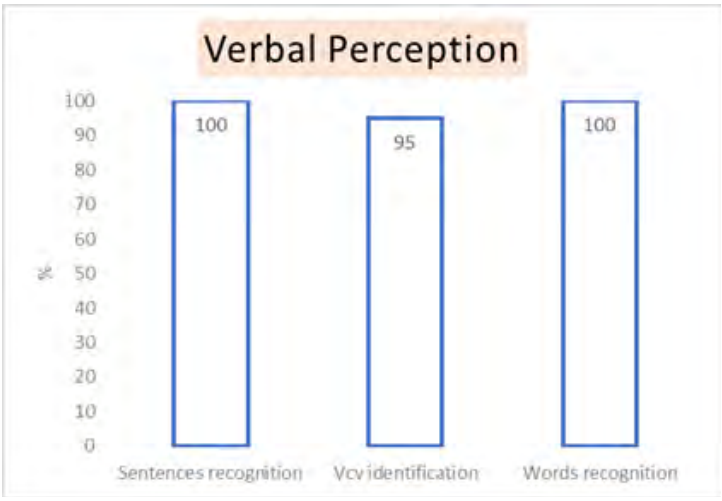

Figure 3A: Verbal Perception

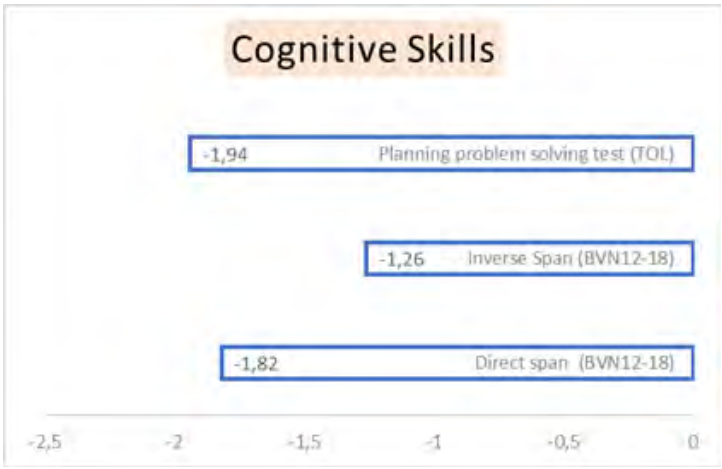

Figure 3B: Cognitive skills

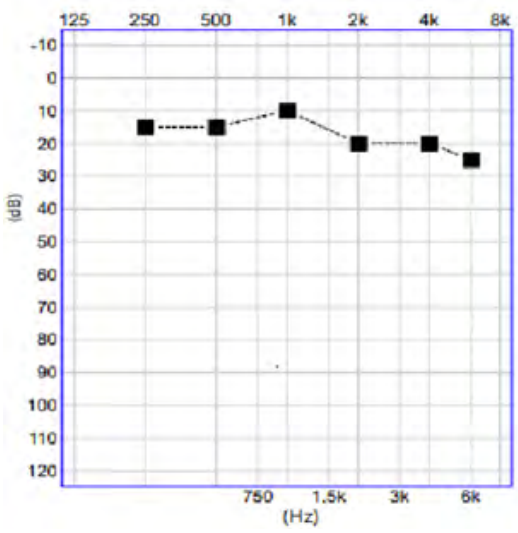

Figure 4A: Tonal audiometry free field with HA

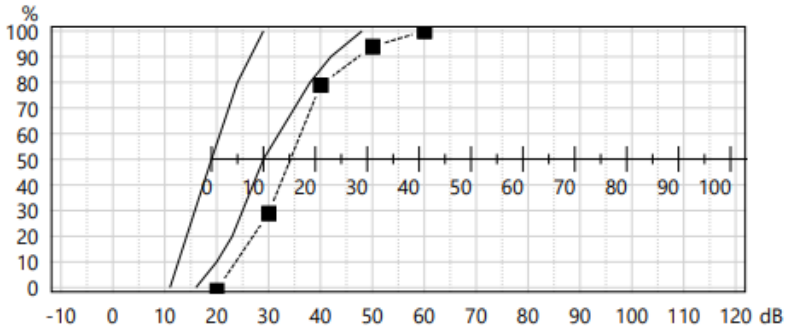

Figure 4B: Speech audiometry free field with HA

5. Discussion

For our knowledge, this is the first case described in literature on the audiological and perceptive findings in a young girl with the rare SIHIWES. Despite, in the literature both conductive and sensorineural hearing loss have been described [2]; herein the audiological feature and audiological work up have been firstly described together with the genetic profile. Interestingly, the two mutations observed in the patient was de novo variant in heterozygous of exon 24 of the CHD4 gene: c.3568A>G, p. Lys1190Glu. CHD4 encodes an ATP-dependent chromatin remodeler, a core component of the nucleosome remodeling and histone deacetylation [NuRD] complex. This complex is widely expressed and acts mainly, but not exclusively, as a transcriptional repressor. CHD4, as well as CHD3 and CHD5, belong to the CHD subfamily II, which is characterized by the presence of PHD fingers and chromodomains, in addition to the SNF2-like ATPase/ helicase core. These three paralogs incorporate into the NuRD complex in a mutually exclusive manner, and each enzyme was found to have distinct roles in the cortical development of mice. CHD4 and NuRD act mainly but not exclusively through transcriptional repression. Several studies have shown that CHD4 has a role in DNA damage response and cell cycle progression either independently or as part of the NuRD complex, and it may also function as an oncogene, a tumor suppressor, or both. CHD4 and NuRD act mainly but not exclusively through transcriptional repression. Similarly, to CHD4, de novo variants in CHD3 are associated with a neurodevelopmental syndrome [4]. Frequent included findings are the history of developmental delay, hypotonia, mild to moderate intellectual disability, and hearing loss. According to our patient phenotype, physical exam was significant for macrocephaly, palatal abnormalities, and similar facial dysmorphisms [e.g., wide-spaced eyes, a square-shaped face, and external ear anomalies] [3]. In order to addressed the genetic diagnosis toward this syndrome, both audiology and ophthalmologic evaluations are recommended. Thanks to the early rehabilitation and the follow up, the overall evaluation performed at age of 13, the teenager showed has good relational skills. Since the linguistic point of view, she looks a good intelligibility of the speech, with only slight phonetic distortions. At the neuropsychological testing the spoonerism and the Tower of London [TOL] tests demonstrated a weakness in short-term verbal memory, verbal working memory and visuospatial planning [11]. Our patient had an audiological diagnosis and early treatment with hearing aids and speech therapy; thus, the delay in the development of language and cognitive-curricular skills could be related to the syndrome rather than to the hearing loss. Her expressive and curricular skills, although delayed compared to peers, allow her to achieve good school results, through the use of compensatory and dispositive tools. The degree of archived independence allows her to have good social skills.

In the literature, SIHIWES is described both as cases of moderate to severe cognitive delay and real autistic syndromes. Our patient presents a cognitive situation that differs from the cases described above. Audiological work up and early rehabilitation may have played a key role in cognitive and behavioural aspects. In fact, the child is autonomous in all aspects of everyday life and in interpersonal relationships. This allowed her, despite her deafness, to live an almost normal life with her peers. Early rehabilitation becomes crucial regardless of pathology. Even such a severe cognitive syndrome can greatly benefit in terms of outcomes from timely and early rehabilitation. This case report testifies how early audiological rehabilitation can reduce the effects of cognitive retardation in patients with this rare syndrome, improving the quality of life of the same who are partly aware of their difficulties, that of their family

References

1. Weiss K, Lazar HP, Kurolap A, Martinez AF, Paperna T, Cohen L, et al. The CHD4-related syndrome: a comprehensive investigation of the clinical spectrum, genotype-phenotype correlations, and molecular basis. Genet Med. 2020; 22(2): 389-397.
2. Farnung L, Ochmann M, Cramer P. Nucleosome-CHD4 chromatin remodeler structure maps human disease mutations. Elife. 2020; 9: e56178.
3. Zhou X, Wang Q, Liu Y, Liu J, Yuan H. Clinical and genetic analysis of a novel CHD4 gene variant in a Chinese patient with Sifrim-Hitz-Weiss syndrome. 2021; 38(1): 63-66.
4. Weiss K, Terhal PA, Cohen L, Bruccoleri M, Irving M, Martinez AF, et al. De Novo Mutations in CHD4, an ATP-Dependent Chromatin Remodeler Gene, Cause an Intellectual Disability Syndrome with Distinctive Dysmorphisms. Am J Hum Genet. 2016; 99(4): 934-941.
5. Sifrim A, Hitz MP, Wilsdon A, Breckpot J, Turki SH, Thienpont B, et al. Distinct genetic architectures for syndromic and nonsyndromic congenital heart defects identified by exome sequencing. Nat Genet. 2016; 48(9): 1060-5.
6. Burdo S. Common Evaluation Protocol in Rehabilitative Audiology I Care, 1996.
7. Cornoldi C, Carretti B. Prove MT 3 Clinica. Giunti Edu. 2016.
8. Sartori G, Job R, Tressoldi PE. DDE-2 Batteria per la Valutazione della Dislessia e della Disortografia Evolutiva-2. Giunti psycometrics. 2007.
9. Biancardi A, Bachmann C, Nicoletti C. BDE2. Developmental dyscalculia battery Test for the diagnosis of numerical processing and calculation disorders in developmental ages 8-13 years. 2016.
10. Garel C, Cont I, Alberti C, Josserand E, Moutard ML, Ducou le Pointe H. Biometry of the Corpus Callosum in Children: MR Imaging Reference Data American Journal of Neuroradiology September 2011.
11. Sannio Fancello G, Vio C, Cianchetti C. TOL. Tower of London. Test to evaluate executive functions (planning and problem solving). 2021.

12. Marciano E, Laria C, Malesci R, Iadicicco P, Landolfi E, Niri C, et al. Newborn hearing screening in the Campania region (Italy): early language and perceptual outcomes of infants with permanent hearing loss. Acta Otorhinolaryngol Ital. 2013; 33(6): 414-7.
13. Malesci R, Del Vecchio V, Bruzzese D, Burattini E, Auletta G, Errichiello M, et al. Performance and characteristics of the Newborn Hearing Screening Program in Campania region (Italy) between 2013 and 2019. Eur Arch Otorhinolaryngol. 2022; 279(3): 1221-1231.
14. Landolfi E, Lilli G, Marciano E, Laria C. The development of language in babies and the role of the family. J Matern Fetal Neonatal Med. 2011; 24 Suppl 1: 120-1.