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Case Report
Relato de Caso

Mitochondrial myopathy and sensorineural hearing loss: case study

Miopatia mitocondrial e deficiência auditiva neurossensorial: estudo de caso

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Keywords

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ABSTRACT

Mitochondrial myopathy is caused by the absence and/or insufficiency of L-carnitine, a quaternary enzyme responsible for transporting free fatty acids into the mitochondria. The primary function of the mitochondria is to produce energy, contributing to proper cell functioning. Muscular lipidosis causes abnormalities in enzymes that metabolize fat, resulting in the accumulation of harmful amounts of fats in tissues. The aim of this study was to present the case study of patient B.D., a 37-year-old woman diagnosed with muscular lipidosis with L-carnitine deficiency at 6 years old, and describe the speech-language follow-up performed at a hearing care clinic. The first entry in the patient's medical chart was on 03/05/1989, with continuous use of 2g/day of L-carnitine prescribed by a neurologist. The mother reported that B.D. had difficulty hearing and was inattentive, which became more evident when she started school. In 1988 the patient was diagnosed with moderate bilateral sensorineural hearing loss and began using behind-the-ear (BTE) hearing aids in 1989, after which her academic performance and communication improved. In 1998 she switched to Completely in Canal (CIC) hearing aids, which are more discreet, provided better sound localization and greater high frequency gain, although her hearing thresholds worsened slightly. She completed her graduate studies and currently works at a large financial institution. It was concluded that early neurological diagnosis and speech-language intervention enabled adequate language development in the patient.

Descritores

Perda Auditiva
Carnitina
Doenças Mitocondriais
Audiologia
Miopatias Mitocondriais

RESUMO

A miopatia mitocondrial é causada pela ausência e/ou insuficiência de uma enzina quaternária, L-carnitina, responsável por transportar ácidos graxos livres para a parte interna da mitocôndria. A função da mitocôndria é produzir energia, contribuindo para o bom funcionamento das células. A Lipidose Muscular é uma doença que provoca anomalias em enzimas que metabolizam gordura e por consequência causa acúmulo de toxinas de subprodutos com gordura nos tecidos. O objetivo deste trabalho é apresentar o estudo de caso da paciente B.D., 37 anos, diagnosticada com Lipidose Muscular aos seis anos, com deficiência de L-Carnitina e relatar o acompanhamento fonoaudiológico realizado em um serviço de saúde auditiva. A abertura de prontuário da paciente foi realizada em 05/03/1989. Foi prescrito pelo neurologista o uso contínuo de 2g/dia de L-carnitina. A mãe relatou que B.D. apresentava dificuldades em ouvir, pois era muito desatenta, o que foi mais evidente quando começou a frequentar a escola. Em 1988, a paciente foi diagnosticada com perda auditiva neurossensorial de grau moderado bilateral e começou a fazer uso de aparelhos de amplificação sonora individual retroauriculares em 1989. O desempenho escolar e comunicação melhoraram. Em 1998, passou a utilizar aparelhos tipo micro canal, o que a favoreceu esteticamente, promoveu melhora da localização sonora e maior ganho em altas frequências. Os limiares de audibilidade apresentaram uma leve piora e a paciente atualmente é pós-graduada e trabalha em uma grande instituição financeira. Conclui-se que o diagnostico neurológico e a intervenção fonoaudiológica precoces possibilitaram o adequado desenvolvimento de linguagem da paciente.

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INTRODUCTION

L-carnitine belongs to a group of dietary components known as non-nutrients, which can be produced in the body and consumed in food. Since its discovery, the scientific literature has reported its main function in the body as transporting fatty acids into the mitochondria, providing a wide range of benefits in the treatment of different diseases and harmful effects when absent or insufficient[1].

Mitochondria are complex organelles surrounded by two membranes (inner and outer) and are present in almost all eukaryotic cells. Their primary function is to provide cells with energy via cellular respiration[2].They also produce free radicals for specific purposes within the cell (cell signaling and inflammatory processes) and act in the detoxification of these same radicals in other situations.

The production of energy (adenosine triphosphate – ATP) occurs in the respiratory chain. Glucose, obtained from food (or via photosynthesis in autotrophic organisms) is converted into carbon dioxide and water, producing ATP, which is used in different cell activities. Complete glucose breakdown involves different molecules, enzymes and ions and occurs in three stages: glycolysis, the Krebs cycle and oxidative phosphorylation[3].

Carnitine is a quaternary ammonia that exists in three forms (acetyl-L-carnitine (ALCAR), L-carnitine and propionyl-L-carnitine)[4], and is physiologically important as a cofactor in transporting long-chain fatty acids (LCFA)from the cytoplasm into mitochondria. These LCFA are then oxidized within the mitochondria and used as an energy source in the Krebs cycle. Changes in these activities due to mutations in mitochondrial DNA (mtDNA) result in cell dysfunction or even cell death in mitochondrial diseases.

The stria vascularis in the inner ear is a highly vascularized structure with a large concentration of mitochondria, which are vital in maintaining potassium in the endolymph. In the event of insufficient glucose supply, fat is mobilized to provide energy[5].

Among other functions, carnitine helps protect the receptor cells of sensory neurons that receive and interpret sound waves, allowing signals to be transmitted from cochlear hair cells to neurons in the central auditorynervous system. The enzyme is known to improve mitochondrial bioenergetics and the efficiency of fatty acid transport across the mitochondrial membrane[6].

Changes in L-carnitine homeostasis have been associated with progressive cardiomyopathy, encephalopathy and muscle weakness, which, when left untreated can lead to death from heart failure[7,8].Mitochondrial dysfunction due to carnitine deficiency can also cause sensorineural hearing loss and labyrinthine anomalies[5].Hearing loss caused by mtDNA mutation accounts for 0.5 to 1% of all genetic hearing problems[9].

In cases of L-carnitine deficiency, pharmacological intervention may prevent and/or improve hearing thresholds according to the amount in the body and its replacement time[5,10].

The aim of this study was to present the case study of a patient with L-carnitine deficiency due to muscular lipidosis diagnosed in 1989, and describe the speech-language follow-up performed at a hearing care clinic in the municipality of São Paulo, Brazil.

CLINICAL CASE PRESENTATION

This is a retrospective study that involved analyzing medical charts from the Clinical Neurology (Department of Neurology) and Hearing Disorders courses (Department of Speech Therapy) at the Universidade Federal de São Paulo.

The patient's treatment began on March 5, 1989 and annual follow-up has continued at Hospital São Paulo, in clinics belonging to the Speech and Auditory Therapy and Neurology Departments.

The study was approved by the Research Ethics Committee of the Universidade Federal de São Paulo under protocol number 1207/2016 and the patient provided written informed consent.

Clinical case

B.D., female, born in Recife, Pernambuco state (PE), on 01/31/1983, preterm, weighing 2520 kg with a body length of 50 cm, currently 37 years old and diagnosed with muscle lipidosis at the age of 6 years.

In 1989, a muscle biopsy detected insufficient L- carnitine levels and the patient has undergone replacement therapy at a dose of 2g/day since then.

Past history of the current complaint: B.D. was born by C-section with no pregnancy complications and received oxygen for two hours following delivery (the mother was unable to provide further details). The patient exhibited muscle weakness in early childhood, which prevented breastfeeding and execution of movements expected in the first few months of life. She also showed delayed motor development, crawling at 11 months and walking at 16 months, but with frequent falls. Her mother reports no family history. As a result, B.D. underwent physiotherapy from the age of 14 months until 2018.

She also did hydrotherapy for six years, global postural reeducation (GPR), Pilates and acupuncture for one year, and currently practices yoga. In 1986 at the age of three years, the patient began speech therapy at a private facility in her hometown of Recife due to speaking difficulties (articulation and voice).

In 1988, B.D.'s mother noticed signs indicating possible hearing loss: the child was inattentive, which became more evident when she started school, and she constantly watched her mother's face and mouth for clues to understand what was being said, to the point of understanding verbal commands only by gestures, when her mother spoke to her without making sounds. Based on the mother's observations, B.D.'s speech therapist at the time conducted an audiometry exam, which indicated moderate bilateral sensorineural hearing loss[11].

The mother's cousin, a nurse who was studying for her Master's in Nursing at the Universidade Federal de São Paulo at the time, encouraged her to seek treatment for B.D. at the

health service affiliated with her cousin's graduate program. Since B.D. was experiencing muscle weakness, she initially saw a neurologist. At the time, she presented with facial paresis, eyelid ptosis (referred to an ophthalmologist), delayed bone age, weakness of the deep neck flexor muscles, and dental arch alterations (referred to an orthodontist). Following a diagnostic hypothesis of congenital myopathy, the patient was diagnosed with muscular lipidosis in March 1989, at the age of six. A muscle biopsy detected insufficient L-carnitine levels in B.D.'s system and in April 1989, she began L-carnitine replacement therapy, with a significant improvement in the symptoms listed after eight months. Weekly follow-ups were performed for the first 10 years, switching to annual follow-up thereafter, funded by the National Health System (SUS).

The results of the previously mentioned audiometry exam prompted the mother to seek treatment for B.D. at the hearing health clinic of the same hospital service as her neurological follow-up, where she continues to receive treatment to this day.

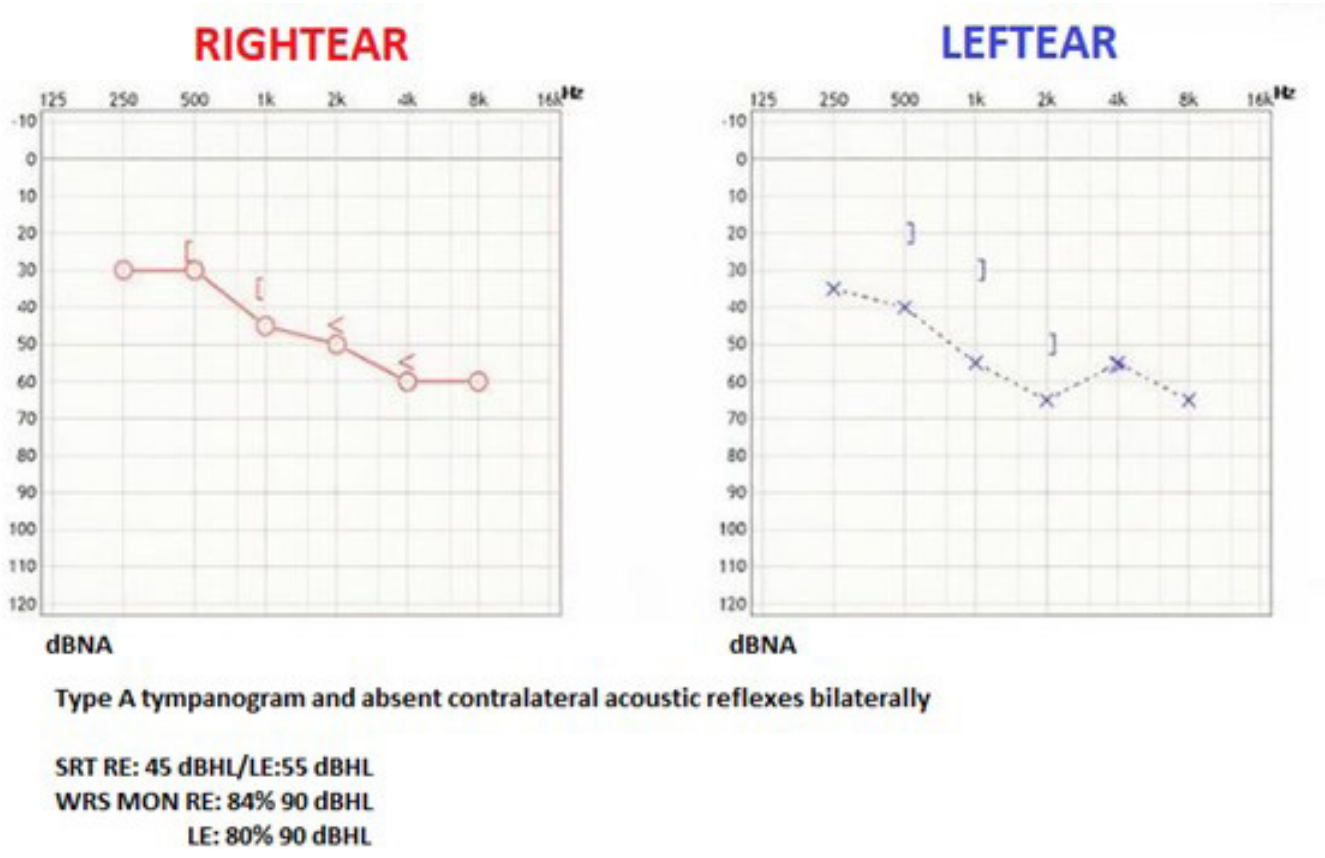
Her mother believes that the delay in diagnosing her hearing loss compromised her academic performance and literacy in the first grade.

The audiological diagnostic tests conducted in April 1989 at the hearing health service where B.D. is still treated revealed moderate sensorineural hearing loss in the right ear and moderate mixed hearing loss in the left[11].Her speech reception threshold (SRT) was 45dBHL for the right ear and 55 dBHL for the left, with a word recognition score (WRS) for monosyllabic words of 84% and 80% for the right and left ears, respectively, obtained at the most comfortable level (MCL) for both ears. Immittance testing showed type A tympanograms[12] and absent contralateral acoustic reflexes bilaterally (Figure 1).

In 1989, the patient began wearing behind-the-ear (BTE) hearing aids with linear amplification. Linear amplification provides the same gain for different input sound levels, that is, the same gain for soft, moderate (speech) and loud sounds. B.D.'s first BTE hearing aids were Widex ES6 with skeleton earmolds.

After adjusting to the hearing aids, both B.D. and her family reported better hearing levels, which improved her academic and social performance.

Due to technical issues, in 1994 these devices were replaced with Bernafon hearing aids (C2H), also with linear amplification. The patient's hearing loss had remained stable since diagnosis and as such, the recommendation of hearing aids for moderate hearing loss was maintained[11].



Caption: SRT = Speech Reception Threshold; MON = Monosyllables; WRS = Word Recognition Score; RE = right ear; LE = left ear
Figure 1. Audiology assessment at six years old, in 1989

In addition to wearing hearing aids, B.D. continued to undergo speech therapy twice a week in Recife, until 1996 when, at the age of 13, she began home-based sessions to correct phoneme distortions, under the supervision of a speech therapist and with assistance from her mother.

In 1998, she switched to Siemens bilateral Completely in Canal (CIC) hearing aids, with nonlinear amplification, which provides different gains for different input sound levels, that is, greater gains for soft sounds, slightly lower for speech sounds and low gains for loud sounds. This change resulted in better acceptance of the devices because of the improved sound quality and for esthetic reasons. Additionally, the fact that the microphone is located inside the ear canal enables better acoustics and sound localization, as well as greater gains at high frequencies (2000 to 5000 Hz).

Since then, these benefits have been taken into account when replacing her hearing aids and the same adaptations have been maintained to date.

In 2003, a speech therapist at the same facility where B.D. undergoes audiology and neurology follow-up suggested that she resume speech therapy. In 2006, she began treatment with an oral and maxillofacial specialist at the Dentistry Department of the Universidade de São Paulo, and was fitted with a palatal lift prosthesis to improve palatopharyngeal incompetence, essential in speech production.

In 2008, she switched to Phonak Extra 11 CIC hearing aids and currently uses the Cassia 10 Petite model (Phonak), adjusted in 2014. The thresholds obtained with amplification are shown in Table 1. It should be enphasized that the thresholds were obtained for soft sounds. The patient's most recent consultation was in August 2017 and the results obtained in the audiology exam are presented in Figure 2.

In situ assessment was conducted with a Verifit 1 device and acoustic gain adjusted according to the NAL N/L1 fitting method. The Speech Intelligibility Index (SII) was determined using amplification at 65 dBSPL and the International Speech Test Signal (ISTS)[13], obtaining values of 54 and 55% for the right and left ears, respectively. The results are shown in Figures 3 and 4.

Table 1. Individual air conduction hearing thresholds obtained for the left and right ears, with and without CIC hearing aids

Threshold	250 Hz	500 Hz	1000 Hz	2000 Hz	3000 Hz	4000 Hz	6000 Hz	8000 Hz
RE AC without CIC	45 dBHL	50 dBHL	55 dBHL	70 dBHL	70 dBHL	80 dBHL	90 dBHL	85 dBHL
RE AC with CIC		45 dBHL	25 dBHL	20 dBHL	35 dBHL	55 dBHL		
LE AC without CIC	45 dBHL	55 dBHL	65 dBHL	65 dBHL	60 dBHL	75 dBHL	105 dBHL	90dBHL
LE AC wih CIC		40 dBHL	30 dBHL	20 dBHL	30 dBHL	55 dBHL		

Caption: CIC = completely-in-canal hearing aid; RE = right ear; LE = left ear; AC = air conduction

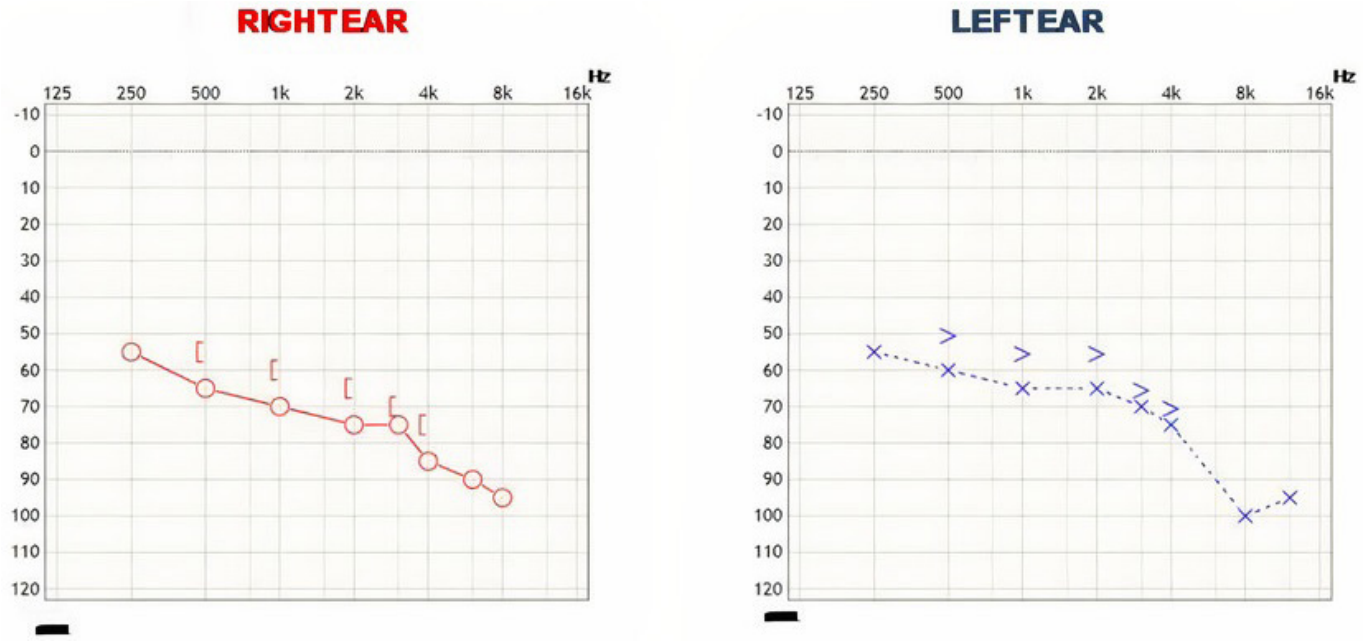
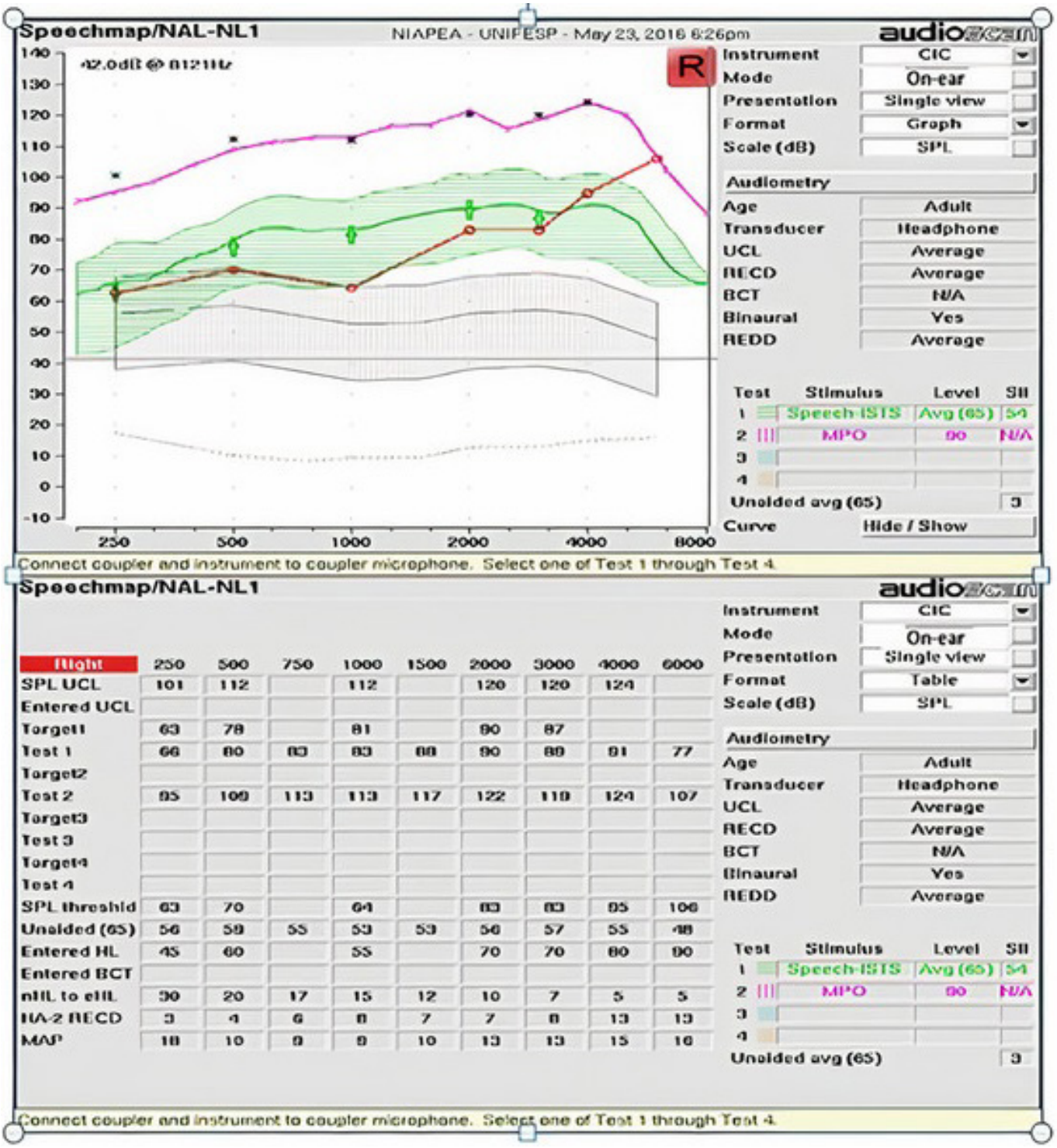


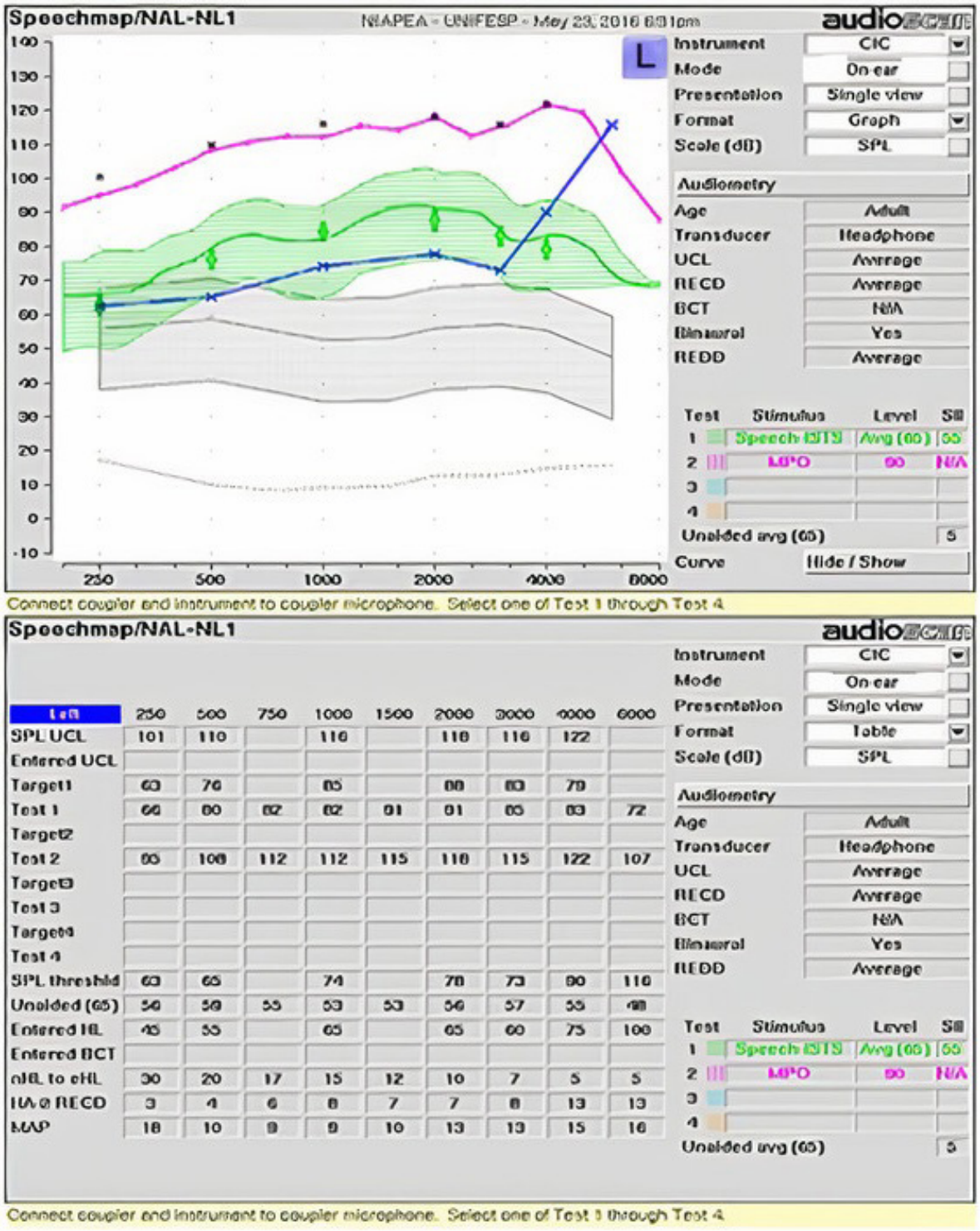
Figure 2. Pure-tone audiometry threshold at 34 years old

The patient is currently undergoing continuous use of 2 g/day of L- carnitine, follow-up with an oral maxillofacial specialist and effective use of amplification (more than 17 h/day). The combination of these factors and treatments has provided good communication and social performance, and B.D. successfully completed graduate and undergraduate courses and is currently employed.



Legend: R = Right; CIC = Completely in Canal; SPL = Sound Pressure Level; UCL = Uncomfortable Loudness; RECD = Real Ear to Coupler Difference; BCT = Bone Conduction Threshold; REDD = Real Ear Dial Difference; MPO = Maximum Power Output; ISTS = International Speech Test Signal; HL = Hearing Level; MAP = Minimum Audible Pressure; eHL = Estimated Hearing Level; nHL = Normalized Hearing Level; avg = average; dB = decibels; Hz = Hertz; N/A = not applicable; SII = Speech Intelligibility Index

Figure 3. Amplified Speech Mapping of the Right Ear – Phonak Cassia Petite 10 CIC hearing aid



Left	250	500	750	1000	1500	2000	3000	4000	6000
SPL UCL	101	110		110		110	110	122	
Entered UCL									
Target1	60	70		65		60	60	70	
Test 1	60	60	62	62	61	61	65	63	72
Target2									
Test 2	60	100	112	112	115	110	115	122	107
Target3									
Test 3									
Target4									
Test 4									
SPL threshld	60	65		74		70	73	90	110
Unaided (65)	50	50	55	53	53	56	57	55	48
Entered HL	45	55		65		65	60	75	100
Entered BCT									
nHL to eHL	30	20	17	15	12	10	7	5	5
HA @ RECD	3	4	6	8	7	7	8	13	13
MAP	18	10	9	9	10	13	13	15	16

Caption: L = Left; CIC = Completely in Canal; SPL = Sound Pressure Level; UCL = Uncomfortable Loudness; RECD = Real Ear to Coupler Difference; BCT = Bone Conduction Threshold; REDD = Real Ear Dial Difference; MPO = Maximum Power Output; ISTS = International Speech Test Signal; HL = Hearing Level; MAP = Minimum Audible Pressure; eHL = Estimated Hearing Level; nHL = Normalized Hearing Level; avg = average; dB = decibels; N/A = not applicable; SII = Speech Intelligibility Index
Figure 4. Amplified Speech Mapping of the Left Ear – Phonak Cassia Petite 10 CIC hearing aid

DISCUSSION

This case study demonstrates the importance of a multidisciplinary team and observations by family members in child development, since issues raised by the patient's mother and investigation by a multidisciplinary team enabled early intervention, which favored good development in the patient. Annual testing and regular speech therapy follow-up indicated stable hearing thresholds bilaterally and satisfactory language development.

The patient's hearing thresholds remained relatively stable since L-carnitine supplementation helps protect the receptor cells of sensory neurons that receive and transmit sound waves throughout the central auditory nervous system. Several studies have been conducted on the use of antioxidants targeting mitochondria to treat hearing loss. In research with animals, L-carnitine reduced aminoglycoside-induced ototoxicity[10].In another study, acetyl-L-carnitine (ALCAR) played an important role in reducing tinnitus after 30 days[4].

In addition to hearing aids use, B.D. received guidance, counseling and therapy to ensure adequate language development. More recently, procedures such as speech mapping have been introduced in the routine assessment of hearing aid performance. This assessment was carried out to adjust acoustic gain according to the NAL N/L1 fitting method and obtain the Speech Intelligibility Index (SII).

The SII was determined by electroacoustic evaluation using the International Speech Test Signal (ISTS). The ISTS stimulus is used worldwide, with measurements taken by a probe-tube microphone inserted in the patient's ear canal. It is a collection of short segments of six languages (French, English, Mandarin, Arabic, Spanish and German) and was created based on the need for a standard test signal that included as many of the most relevant properties of natural speech as possible and allowed reproducible measurements. The recordings are based on natural speech sounds, but are largely unintelligible due to segmentation and remixing. The signal reflects a single voice for all six languages[13].In the case of B.D., the SII results for the right and left ears were 54 and 55%, respectively, while wearing hearing aids, and zero without the devices. This indicates that the adjustments to the hearing aids have given the patient access to more than 50% of the phonemes in both ears for medium-intensity speech sounds. The substantial hearing improvement provided by amplification, combined with the patient's use of visual cues since childhood, have allowed her to develop into a competent adult in terms of communicating and expressing herself.

Analysis of the patient's current clinical picture shows that the early diagnosis and intervention by the teams in the Clinical Neurology and Speech Therapy Departments were beneficial to overall development. B.D. is now able to perceive speech sounds, has more defined muscle movements, adequate static and dynamic balance, nonrecurring headaches and better quality development. This highlights the importance of the speech therapy diagnosis and monitoring that the patient received from the age of six years in terms of her hearing, balance and oral motricity.

B.D.'s treatment was only possible because of the Brazilian National Health System's (SUS) Nationwide Treatment policy (TFD in Portuguese). The TFD was created on 02/24/1999 by Ministry of Health Ordinance 55[14], which guarantees medical treatment via the SUS for patients with diseases that cannot be treated in their hometown due to lack of technical resources. The policy also stipulates that users of the SUS or SUS-affiliated health services and their caregivers be given access to transportation and financial assistance, provided the treatment location is at least 50 km from their place of residence. Although ideally all Brazilian citizens should have access to the necessary health care in their hometown, some specialist treatments are still only available at large referral hospitals. As such, public policies such as the TFD are vital in that they allow patients to travel to treatment locations and remain there for as long as necessary. In the present case in particular, the TFD ensured B.D. had access to specialist treatment and was able to establish important relationships for successful multidisciplinary care, which continues to this day. In a rehabilitation process, good practices are essential and relationships decisive in ensuring treatment adherence and successful rehabilitation.

FINAL COMMENTS

Early diagnosis with adequate treatment intervention and annual follow-up contributed to ensuring that the patient achieved satisfactory overall performance, stable hearing loss, greater comfort due to the technology available, and better quality of life.

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Author contributions

RS participated in data collection, writing, data analysis and submission for publication; MRFS participated in writing, supervision anda data collection; ASBO participated in the supervision and data collection; MCMI, as study supervisor, participated in the study design, review and supervision.