Molecular Genetics and Metabolism xxx (xxxx) xxx–xxx

Contents lists available at ScienceDirect

Molecular Genetics and Metabolism

journal homepage: www.elsevier.com/locate/ymgme

Research Article

Neurophysiology of hearing in patients with mucopolysaccharidosis type IV

Kyoko Nagao[a,b,c,*], Thierry Morlet[a,b,d], Elizabeth Haley[e], Jennifer Padilla[f], Julianne Nemith[c], Robert W. Mason[a], Shunji Tomatsu[a,g,**]

[a] Department of Biomedical Research, Nemours Alfred I. duPont Hospital for Children, Wilmington, DE, United States
[b] Department of Linguistics and Cognitive Science, University of Delaware, Newark, DE, United States
[c] College of Health Sciences, University of Delaware, Newark, DE, United States
[d] Georges Osborne College of Audiology, Salus University, Elkins Park, PA, United States
[e] Department of Communication Science & Disorders, University of Pittsburgh, Pittsburgh, PA, United States
[f] Siemens Healthcare Diagnostics Inc, Newark, DE, United States
[g] Department of Pediatrics, Thomas Jefferson University, Philadelphia, PA, United States

ARTICLE INFO

Keywords:
Mucopolysaccharidosis IV
Auditory system
Electrophysiology
Audiological testing
Hearing impairment/loss

ABSTRACT

Background: Hearing impairment is a common problem in patients with mucopolysaccharidosis IV (MPS IV) throughout their life. Many of the adult patients with MPS IV exhibit permanent or severe hearing loss. However, there has been no systematic review of detailed audiological test results in MPS IV.

Materials and methods: Fourteen individuals with MPS IV (13 MPS IVA and 1 MPS IVB; aged between 12 and 38 years old) participated in the current study. We obtained auditory neurophysiological responses (auditory brainstem responses and otoacoustic emissions test) in addition to pure-tone audiometry and middle ear function tests (tympanometry and acoustic reflexes).

Results: The results indicated various levels and types of hearing loss with abnormal neurophysiological responses even in those patients with MPS IVA with normal pure tone thresholds. We also found a strong relationship between height (short stature is an indicator of skeletal severity) and hearing sensitivity as well as a strong relationship between height and outer hair cell function in the inner ear (measured by otoacoustic emissions) among MPS IVA patients.

Conclusion: The strong correlation between reduced height and hearing loss indicates that patients with severe skeletal dysplasia may be at higher risk of developing more severe hearing loss. More importantly, the spectrum of hearing disorders indicates that MPS IV patients should have annual neurophysiological hearing tests in addition to audiometric testing from an early age regardless of their skeletal severity to more carefully monitor disease progression.

1. Introduction

1.1. General characteristics of mucopolysaccharidosis IV

Mucopolysaccharidosis IV (MPS IV), also known as Morquio syndrome, is an autosomal recessive lysosomal storage disorder. MPS IV includes two types of disorders, MPS IVA (OMIM 253000) and MPS IVB (OMIM 253010), due to a deficiency of two different lysosomal enzymes, *N*-acetylgalactosamine-6-sulfate sulfatase (GALNS) and β-galactosidase, respectively. The majority of patients (95%) exhibit Type A [1]. MPS IV is characterized by a unique skeletal dysplasia caused by excessive accumulation of keratan sulfate (KS) and/or chondroitin 6-sulfate (C6S). Although most patients with MPS IV appear normal at birth, patients show skeletal abnormality within a few years of age or even at birth.

Patients with MPS IV have a wide spectrum of clinical manifestations [2–4] including growth impairment and progressive spondyloepiphyseal dysplasia frequently resulting in limited ambulation or complete wheel-chair bound condition. Patients with a severe phenotype of MPS IVA often do not survive beyond the second or third decade

Abbreviations: MPS, mucopolysaccharidosis; ABR, auditory brainstem response; DPOAE, distortion products of otoacoustic emission; MEMR, middle ear muscle reflex; PTA, pure tone average; C6S, chondroitin-6-sulfate; ERT, enzyme replacement therapy; GALNS, *N*-acetylgalactosamine-6-sulfate sulfatase; KS, keratan sulfate; GAG, glycosaminoglycan; ADL, activity of daily living; CNS, central nervous system; CT, Computed tomography; MR images, Magnetic resonance images

* Correspondence to: K. Nagao, Nemours Biomedical Research, Nemours Alfred I. duPont Hospital for Children, 1600 Rockland Rd., Wilmington, DE 19899-0269, United States.
** Correspondence to: S. Tomatsu, Skeletal Dysplasia Lab, Nemours Biomedical Research, Nemours Alfred I. duPont Hospital for Children, 1600 Rockland Rd., Wilmington, DE 19899-0269, United States.
E-mail addresses: kyoko.nagao@nemours.org (K. Nagao), stomatsu@nemours.org (S. Tomatsu).

https://doi.org/10.1016/j.ymgme.2018.02.002
Received 5 February 2018; Accepted 5 February 2018

of life. Patients with a mild form of MPS IVA may survive until the seventies [4]. Recent advancements in medical and surgical treatment and management as well as early awareness of the disease have led to extended life expectancy [5] in the patients with MPS IVA [6]. In general, patients with MPS IVB have a milder skeletal dysplasia with taller stature.

1.2. Hearing in MPS IV

Although hearing impairment does not directly contribute to mortality, hearing impairment does have significant contribution to development of speech and language, and quality of life [2]. Recurring ear infections and hearing loss are common symptoms in MPS [7–9]. Because skeletal deformities are usually not apparent in the first couple of years of life, it is common for patients with MPS to see otolaryngologists before their diagnosis of MPS. Although commonly reported hearing loss in MPS IVA is conductive in nature [10,11], sensorineural hearing loss has also been documented in some patients [12]. However, because MPS IVA is such a rare disorder, previous studies on hearing loss in MPS IVA were based on very small sample sizes, and detailed descriptions of the types and degree of hearing impairment are sparse. Based on a few studies, it is suggested that hearing loss in MPS IVA is bilateral and progressive in general [13,14] similar to other MPS types [7,15], and its severity ranges from mild to moderate [4,16]. Riedner and Levin [13] reported that conductive hearing loss was observed in patients under eight years old, but that mixed and sensorineural hearing loss were also found in older patients. Permanent hearing loss has not been observed until adolescence [17]. Abnormal auditory brainstem response (ABR) results were also reported, but systematic chart review or study to correlate the auditory function to skeletal dysplasia in MPS IVA have not been made until now. Last, the majority of studies are based on MPS IVA. So far, two patients with MPS IVB were reported as having no hearing loss [18,19].

The aims of this study are to examine hearing function in patients with MPS IV (mainly MPS IV A) and to correlate auditory phenotype with skeletal severity (measured as short stature) and/or activity of daily living.

2. Materials and methods

The current study was approved by the Nemours Institutional Review Board (Local Board Reference Number: 458707 and 750932).

2.1. Participants

Fourteen participants (5 males and 9 females) aged between 12 and 38 years old, who had been diagnosed biochemically with MPS IV (13 patients for MPS IVA; one patient for MPS IVB), participated in the study. They were recruited by referrals from the Departments of Orthopaedics and Genetics at the Nemours/Alfred I. duPont Hospital for Children or fliers distributed through the Carol Ann Foundation. The study was conducted at the Nemours/Alfred I. duPont Hospital for Children, Wilmington, Delaware, after obtaining the informed consent of each participant. Demographic information about the participants is summarized in Table 1. Skeletal (clinical) severity of the disease was determined by the height as described previously [20–22]. Eight of the patients with MPS IVA had received enzyme replacement therapy (ERT) for 1 to 5 years.

2.2. Procedure

Following otoscopic inspection, middle ear function was assessed by tympanometry and middle ear muscle reflexes (MEMR) (Titan, Interacoustics, Inc). MEMR thresholds were recorded at 0.5, 1, 2, and 4 kHz for those who did not have pressure equalization tubes. Distortion products otoacoustic emissions (DPOAE) were collected from each ear to obtain an objective measure of the function of the cochlear outer hair cells. DPOAE were recorded at 12 different f2 frequencies varying from 1 to 10 kHz (Titan, Interacoustics, Inc). To assess the brainstem nervous pathways, auditory brainstem responses (ABRs) were obtained using 100 μsec air-conduction clicks at a rate of 27.7/s and at levels ranging 40 to 90 dBHL (SmartEP, Intelligent Hearing System, Inc). The responses to the clicks at 80 dBHL or 90 dBHL were reported in this study. To obtain behavioral hearing data, we conducted audiometry and speech perception test. Pure tone air conduction thresholds at 125, 250, 500, 1, 2, 3, 4, 6, 8 kHz were obtained in each ear using insert earphones. All air conduction audiometry was conducted without masking because none of our participants indicated > 40 dB threshold difference between the ears. Pure tone bone conduction thresholds were obtained for some participants with suspected conductive hearing loss with and without masking. Speech reception thresholds were obtained using spondee words, and word recognition scores were obtained using the Central Institute for the Deaf (CID) W22 word list. These two speech perception tests were conducted using insert earphones without hearing aids. All the audiological data were obtained in a sound proof booth. The participant's demographic information, medical/health history including frequency of ear infection, and functional activity of daily living (ADL) [23,24] were obtained with a questionnaire.

2.3. Data analysis

The types of hearing loss (conductive, sensorineural, and mixed) were categorized by an audiologist based on all the tests results. The severity of hearing loss was based on the pure tone average (PTA) values of 0.5, 1, and 2 kHz (per ear) [25].

For each of the 12 frequencies, DPOAE was considered present when the DPOAE amplitude level was −10 dB SPL or above, and the signal to noise ratio at least of 6 dB SPL. The percentage of present DPOAE (per 12 frequencies) was calculated for each ear. Responses were classified as abnormal when only < 25% of the DPOAE frequencies were present and partially abnormal when the percent was between 26 and 75%.

The ABR was categorized as normal or abnormal by two experienced clinicians. Waveforms were judged as abnormal when waves I, III, and V were absent, delayed, of low amplitude or with an atypical morphology.

Pearson's correlation coefficients were obtained to analyze relationships between hearing test results and other measures only with the MPS IVA data. We excluded the MPS IVB data from correlation analysis because the mild skeletal severity associated with MPS IVB could have biased the results.

3. Results

3.1. Ear infection

All but one participant reported that they had multiple ear infections in the past. Five participants had chronic ear infections. Half of the participants in this study had one or more sets of ear pressure equalization tubes, and two patients (both adults) had pressure equalization tubes at the time of our data collection. Despite the history of frequent ear infections in most patients, only two participants reported speech/language delays when they were young. The results are consistent with previous descriptions of normal speech/language skills in MPS IV. We should point out that recurring middle ear infection in patients with MPS IV persists even after young childhood.

3.2. Audiological test results

Table 1 lists the audiometry results in all participants. All participant exhibited normal tympanometry. All but two participants (S10 and