International Journal of Pediatric Otorhinolaryngology 100 (2017) 107–113

Contents lists available at ScienceDirect

International Journal of Pediatric Otorhinolaryngology

journal homepage: http://www.ijporlonline.com/

Hearing loss in children with growth hormone deficiency

John S. Muus [a, *], Forest W. Weir [a], Kathryn L. Kreicher [a], Deborah A. Bowlby [b], Christopher M. Discolo [a], Ted A. Meyer [a]

[a] Department of Otolaryngology-Head & Neck Surgery, Medical University of South Carolina, Charleston, SC, United States
[b] Department of Endocrinology, Medical University of South Carolina, Charleston, SC, United States

ARTICLE INFO

Article history:
Received 6 April 2017
Received in revised form
26 June 2017
Accepted 30 June 2017
Available online 1 July 2017

Keywords:
Growth hormone deficiency
Pituitary dwarfism
IGF-1
Children
Hearing loss
Audiogram
Conductive hearing loss
Sensorineural hearing loss

ABSTRACT

Objective: Although insulin-like growth factor 1 (IGF-1) has been shown to be important for inner-ear development in animal models, little is known about the otologic and audiologic findings of children with growth hormone deficiency (GHD). The goal of this study is to evaluate the prevalence, type, and severity of hearing impairment in children with GHD.

Methods: Audiologic, otologic, and demographic data were recorded for children with a diagnosis of GHD in the AudGen database. Data for each patient were selected based on the first encounter with available complete audiometric data or the first encounter with a type of hearing loss documented. The patients were then stratified by type and severity of hearing loss, and otologic issues were documented. A separate cohort comprised of children with GHD without hearing loss was compared as a control.

Results: 209 children with GHD met inclusion criteria. 173 (83%) of these patients had hearing loss. 79% of losses were bilateral and 21% were unilateral (309 total ears with hearing loss). 293 of the 309 ears with hearing loss had audiograms with ear-specific thresholds; 47 had conductive, 24 had sensorineural, 65 had mixed and 157 had undefined hearing loss with incomplete audiograms. Pure-tone averages (PTA) were higher among patients with mixed hearing loss compared to patients with all other loss types.

Conclusion: Hearing loss is prevalent in children with GHD with a predisposition to be bilateral. These findings suggest the need for increased awareness and routine hearing screening for patients with GHD. Further studies may elucidate the etiology of the hearing impairment in children with GHD to better aid pediatricians, endocrinologists, otolaryngologists and audiologists when assessing and managing these children.

1. Introduction

Growth hormone deficiency (GHD) is a rare endocrine disorder characterized by short stature and diminished growth hormone production [1,2]. The disease is synonymous with pituitary dwarfism and isolated growth hormone deficiency and is estimated to affect 1 in 4000 children [1]. GHD is typically diagnosed during infancy or early childhood [1–3]. GHD in affected children is classified as either congenital or acquired, both of which present clinically with growth failure and delayed bone age [1]. Children with congenital GHD can also present with perinatal asphyxia and hypoglycemia at birth [4]. Acquired GHD develops secondary to brain injury or another diagnosis [1].

Due to the potential inaccuracy of diagnostic testing and substantial cost of growth hormone therapy, the diagnosis and management of GHD in children are controversial [1,3]. The Growth Hormone Society recommends a multifactorial diagnostic approach involving assessment of the child's growth chart, mid-parental height, height velocity and presence of intracranial lesions, followed by laboratory and radiologic testing [2]. The vast majority of children diagnosed with GHD receive regular human growth hormone (somatropin) injections throughout their growth period [1–3].

Insulin-like growth factor 1 (IGF-1) is the central mediator of growth hormone action and is typically present at low serum

* Corresponding author. Medical University of South Carolina, Department of Otolaryngology-Head & Neck Surgery, 135 Rutledge Ave, MC550, Charleston, SC 29425, United States.
E-mail addresses: muus@musc.edu (J.S. Muus), weir.forest@gmail.com (F.W. Weir), kreicher@musc.edu (K.L. Kreicher), bowlbyd@musc.edu (D.A. Bowlby), discolo@musc.edu (C.M. Discolo), meyerta@musc.edu (T.A. Meyer).

http://dx.doi.org/10.1016/j.ijporl.2017.06.037
0165-5876/

concentrations in patients with GHD [5,6]. Multiple animal models have shown IGF-1 plays a critical role in otologic neurogenesis, maturation and survival [5,7,8]. Additionally, clinical data have supported an association between adults with hearing loss and various symptoms of growth hormone deficiency, such as short stature and low IGF-1 concentration [8–10]. Welch and Dawes described the longitudinal audiologic outcomes in 1037 patients with short stature, showing a strong association between higher hearing thresholds and lower serum concentration of IGF-1 [9]. Several case studies of patients with IGF-1 deficiency displayed sensorineural hearing loss or deafness [11], suggesting that compromised function of IGF-1 results in cochlear abnormalities due to the role of IGF-1 in inner-ear development.

Although IGF-1 has been shown to be important for inner-ear development in animal and human studies, no studies have described the otologic and audiologic findings of children with growth hormone deficiency. We identified only one small-scale study to date characterizing audiologic outcomes of patients with GHD, where adults with lifetime, untreated GHD showed increased hearing thresholds compared to controls [6]. Using the AudGen Database, this study provides what we believe to be the largest analysis of hearing outcomes and audiometric data in 173 children with GHD and hearing loss.

2. Methods

2.1. Subjects

The AudGen Database is an NIH (NIH-NIDCD R24DC012207) funded resource containing information on approximately 100,000 pediatric patients populated from the electronic medical records of the Children's Hospital of Philadelphia and has been previously used to look at other medical conditions and hearing loss [12–14]. With over 185,000 audiograms, 105,000 tympanograms and 180,000 encounters of patients between the ages 0 and 21, the Audgen Database is the largest pediatric audiological database currently available.

The patients in this study were drawn from a query for children with a diagnosis of GHD under either the diagnosis and/or problem list sections (both of which are populated via ICD-9 coding). Patients with GHD were then cataloged by age, gender, ethnicity, and availability of audiometric data.

2.2. Audiologic evaluation

Pure-tone air and bone conduction audiometry as well as sound-field testing were used to evaluate hearing outcomes. When available, ear-specific air-conduction thresholds were obtained at octave frequencies of 0.25–8.0 kHz and at interoctave frequencies of 3.0 and 6.0 kHz. Both masked and unmasked bone-conduction thresholds were analyzed when available at octave frequencies of 0.25–4.0 kHz and at the interoctave frequency of 3.0 kHz. For audiograms lacking complete information, for example audiograms without bone-conduction testing or non-ear-specific sound-field audiograms, the hearing loss was designated as “undefined.” The pure-tone average (PTA) was calculated for air conduction thresholds bilaterally using the four frequencies 0.5, 1.0, 2.0, and 4.0 kHz.

To analyze change in hearing loss over time, change in PTA was calculated from the patient's first audiogram to their last available audiogram in patients with at least one year between extremal dates. Cases were stratified by “PTA Outcome” (classified as improved, unchanged, or worse) with “unchanged” defined as an absolute change in PTA $\leq$ 5 dB HL.

We analyzed all available audiograms for each patient for evidence of elevated hearing thresholds at any frequency. Patients with greater than a 15 dB HL threshold at any frequency by pure tone audiometry or greater than 20 dB hearing level at any frequency by sound-field testing were classified as having hearing loss. The audiogram that demonstrated the earliest evidence of hearing loss was used to describe hearing loss type, severity and laterality for each patient. When describing hearing loss type, the mean HL was reported with the standard deviation (represented by the symbol “±”).

2.3. Hearing loss type and severity

For audiograms tested by pure-tone audiometry, type of hearing loss was classified as:

1. Conductive: Normal bone-conduction thresholds, air conduction thresholds greater than 15 dB HL and an air-bone gap of 10 dB HL or more at any recorded frequency
2. Sensorineural: Bone-conduction thresholds of greater than 15 dB HL with an air-bone gap of less than 10 dB HL at any recorded frequency
3. Mixed: Conductive and sensorineural hearing loss were present together at any recorded frequency or were both present but at different frequencies
4. Undefined: Air conduction thresholds greater than 15 dB, however, insufficient bone-conduction thresholds to determine loss type

For audiograms obtained in a sound-field using noise or warble tones, hearing loss was defined as any threshold greater than or equal to 20 dB HL (due to the use of 20 dB as a baseline starting threshold) and the loss type was classified as “undefined.” The severity of the hearing loss was established using the pure-tone average (PTA) when possible, via the following guidelines: normal (PTA $\leq$ 15 dB HL), slight (16–25 dB HL), mild (26–40 dB HL), moderate (41–55 dB HL), moderately severe (56–70 dB HL), severe (71–90 dB HL), and profound (90 + dB HL) [12–14].

Hearing loss was also described as unilateral (one ear with hearing loss) or bilateral (two ears with hearing loss). Data describing loss type and severity was summarized by ear to more effectively characterize the sample population, as seen in previous studies evaluating hearing in patients with GHD [6]. Throughout the text, *N* is used to denote number of patients and *n* is used to denote number of ears.

2.4. Medical conditions

Various medical conditions are recorded in Audgen, populated from ICD-9 codes. In children who met the inclusion criteria of a GHD diagnosis, all other ICD9 codes were accessible for analysis. Among the numerous medical conditions populated for each patient, diagnoses typically prevalent in children with GHD include short stature, hypothyroidism, asthma, hypoglycemia, intellectual disability, critical and noncritical heart defects. For each patient with GHD, various otologic factors were documented, including the total counts of acute and chronic otitis media, the presence of Eustachian tube dysfunction, and the number of tympanostomy tube procedures performed.

2.5. Statistical analysis

All statistical analyses were performed in R version 3.2.4 [15]. Welch's independent *t*-test and one-way analysis of variance (ANOVA) were used to analyze the relation between PTA (and change in PTA) and a number of variables including gender, ethnicity, hearing loss type, hearing loss severity, and laterality of