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ARTICLE

An Analysis of Hearing Outcomes in Children with Hutchinson-Gilford Progeria Syndrome

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Abstract

Aims/Background Few hearing loss studies have been conducted in patients with progeria, and only the possibility of low-frequency conductive hearing loss has been mentioned. The primary objective of this study is to perform a comprehensive analysis of the clinical audiological characteristics of children with Hutchinson-Gilford progeria syndrome (HGPS), and the secondary objective is to analyse the causes of their hearing loss and what can be done to enable them to hear as well as possible.

Methods Ten children with HGPS underwent impedance audiometry (tympanogram), otoacoustic emissions, and pure-tone audiometry tests. Otoscopic examination and imaging were also performed in the patients with abnormal hearing.

Results Five patients had normal hearing, while the other five had varying degrees of hearing impairment manifesting as mild to moderate low-frequency or full-frequency conductive hearing loss. Otoscopic examination of those patients with abnormal hearing showed a narrowing of the external auditory canal, a thinning of the tympanic membrane, and a distorted cone of light. Further, computed tomography of one patient showed a poorly defined temporal bone morphology with scant pneumatization of the mastoid process.

Conclusion Patients with HGPS differ from normally aging individuals with a predominant conductive pattern of hearing loss as opposed to sensorineural deafness, with more lower-frequency hearing impairment due to poor pneumatization of the mastoid process and the possible formation of osteophytes in the temporal bone.

Key words: Hutchinson-Gilford progeria syndrome; hearing abnormality; children; conductive hearing loss

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Introduction

Hutchinson-Gilford progeria syndrome (HGPS) is a rare disorder with a disseminated autosomal dominant inheritance (Capell et al, 2005). HGPS is induced by premature aging and can serve as a model for studying the normal process of aging (Goldman et al, 2004). HGPS mainly affects children, with a prevalence of 1 in 8 million (Ahmed et al, 2018). The main features of children with HGPS include severe growth retardation, alopecia, subcutaneous fat thinning, scleroderma, and dysmorphic facial features, such as a disproportionately large head, narrow nasal ridge, narrow nasal tip, thin upper and lower lips, small mouth, and small jaw (Gordon et al, 2014).

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In this study, we evaluated 10 children with HGPS experiencing varying degrees of hearing loss. We found that their hearing patterns differed significantly from the pattern of senile deafness. To date, there are only a few reports in the literature describing the possibility of low-frequency conductive hearing loss in progeria, without mentioning the specific hearing tests that should be performed, the possible causes of hearing loss in patients with progeria, and the methods that should be taken to improve hearing (Ahmed et al, 2018; Guardiani et al, 2011). Therefore, we conducted a case study in children with HGPS diagnosed according to clinical phenotype and genetic analysis at the Children's Hospital of Zhejiang University School of Medicine to answer the above questions.

Methods

Study Population

This study followed the World Medical Association Code of Ethics (Declaration of Helsinki). It was approved by the Ethics Committee of the Children's Hospital of Zhejiang University School of Medicine (No. 2020-IRB-158), and informed consent was obtained from each child's parent(s) or legal guardian(s).

The inclusion criteria were as follows:

1. Clinical signs with typical facial features, including a disproportionately large head, narrow nasal ridges, narrow nasal tip, thin vermilion upper and lower lips, small mouth, posterior and small jaws. Common features include decreased subcutaneous fat, delayed eruption and loss of primary teeth, abnormal skin with small bumps on the abdomen and upper thighs, alopecia, nail dystrophy, hip exostosis, and progressive joint contractures.

2. Patients with a mutated locus by genetic testing. The diagnosis of classical or non-classical genotypes of HGPS was established in pre-diagnosed patients with characteristic clinical features, classical genotypes of HGPS are inherited in an autosomal dominant manner and tend to be disseminated, whereas non-classical genotypes of HGPS often show autosomal recessive inheritance. The molecular mechanism is due to a point mutation in the lamin (*LMNA*) gene encoding the A/C-type nuclear fibrillar protein on chromosome lq. (Gonzalo et al, 2017). The HGPS disease mutation locus is located in exon 11, and 90% of classical HGPS is associated with the heterozygous mutation G608G in the *LMNA* gene, and that non-classical HGPS may be associated with mutations in the K542N and R527C loci of the *LMNA* gene. This does not result in an amino acid change but activates a cryptic splice site, resulting in the production of abnormal lamin A (Navarro et al, 2005). Lamin A plays an important role in the structural integrity and shape of the inner nuclear membrane; therefore, accumulation of the mutant protein leads to defects in nuclear architecture and function. This is hypothesized to be the cause of the premature ageing phenotype of HGPS patients (Goldman et al, 2004).

The exclusion criteria were patients lacking clinical signs or genetic test results.

Ten children with a clinical diagnosis of Hutchinson-Gilford progeria syndrome (HGPS) augmented by genetic analysis who were admitted to our nephrology department from January 2018 to December 2022 were included in this study. Five

were typical HGPS cases (c.1824 C>T), and five were atypical HGPS. The patients comprised five males and five females, aged 1–17, with a mean age and standard deviation of 8.3 ± 5.2 years old.

All 10 children underwent a full physical examination and an audiological evaluation by acoustic impedance (AI) and distortion product otoacoustic emission (DPOAE). In addition, pure-tone audiometry (PTA) was conducted for children older than 5 years who could cooperate with the subjective evaluation. All audiological examinations were performed in a soundproof room.

Acoustic Impedance (AI)

AI was conducted using a hearing test platform (model Titan, GE Healthcare, Chicago, IL, USA). Tympanograms were classified according to Jerger's criteria as type A, As, B, or C (Jerger, 1970). Normal peak compensated static compliance and middle ear pressure represented by Type A, there was reduced static compliance with normal middle earpressure represented by Type As, flat tympanograms represented by Type B, negative middle ear pressure represented by Type C. The parameters were as follows: tympanogram type A, peak normal range: –100 daPa~100 daPa, peak amplitude 0.3–1.6 mL. Type As: peak normal range: –100 daPa~100 daPa, peak amplitude less than 0.3 mL. Type B: tympanic ventricular acoustic conductance was flat with a peak value of less than 0.1 mL (Farinetti et al, 2018).

Distortion Product Otoacoustic Emission (DPOAE)

DPOAE was conducted using the Otodynamics Echoport Otoacoustic Emission System MADSEN Capella (No. 988442, Otometrics, Taastrup, Denmark). DPOAE was often missing at low frequencies 125 Hz–500 Hz due to elevated background noise, so the initial frequency was tested from 750 Hz. DPOAE was tested from 750 Hz to 8 KHz. It was determined as an acceptable response by a signal-to-noise ratio (SNR) of ≥6 dB and a signal sound of >–5 dB at the frequency point. If the two conditions were not or could not be met simultaneously, the frequency display failed (El-Sayed El-Sayed Gaafar et al, 2022).

Pure-Tone Audiometry (PTA)

The test equipment used by the PTA was MADSEN Astera (No. 948641, Otometrics, Taastrup, Denmark). Pure-tone hearing threshold was measured from 125 Hz to 8 KHz, with both air and bone conduction thresholds. The reference standard was based on the WHO hearing impairment grading scale of 2021 (mean thresholds of 0.5, 1, 2, and 4 KHz): mild hearing loss was defined as 20 to <35 dBHL; moderate hearing loss was defined as 35 to <50 dBHL; moderate to severe hearing loss was defined as 50 to <65 dBHL; severe hearing loss was defined as 65 to <80 dBHL; very severe hearing loss was defined as 80 to <95 dBHL; and total deafness was defined as >95 dBHL (Chadha et al, 2021).

Genetic Analysis Procedures

DNA from EDTA-anticoagulated peripheral blood was extracted using the Blood Genomic DNA Extraction Kit (Lot: C742408001, BOIER Nucleic Acid Extraction or Purification Reagent: MagaBio plus Universal Genomic DNA Purification Kit

II, Guangzhou, China), and capture probes designed to cover 4500 genes related to hereditary diseases (Lot: 2000007955, Roche Hybridisation Reagent: Kapa Whole Exome Probe V2, Shenzhen, China) were used to capture the target region using the DNBSEQ-T7 sequencer (Lot: WLC24005, UW T7 onboard reagent: DNBSEQ-T7RS High-Throughput Sequencing Reagent Kit, App-AFCL PE150 v3.0, Shenzhen, China) for high-throughput sequencing. Data were down-sequenced using BWA software (http://bio-bwa.sourceforge.net/) to align the filtered sequences to the human genome reference sequence (hg19). Single nucleotide variation (SNV) and insertions and deletions (INDEL) were analysed using GATK software (https://software.broadinstitute.org/gatk/). All variants were then annotated by ANNOVAR software (http://annovar.openbioinformatics.org/en/latest/). Variants with frequencies less than 0.05 in the gnomAD human genetic variant database were screened. Missense mutations were used for pathogenicity prediction and conservatism prediction using SIFT, PolyPhen-2, MutationTaster, and GERP++, and alterations at the shear site were predicted for pathogenicity using HSF, SpliceAI, and other software. Comprehensive analyses were performed with disease inheritance patterns and clinical characteristics of patients along the family line to screen for suspected candidate variants.

Results

Genetic Testing

Eight of the ten children had heterozygous variants in the *LMNA* gene while the other two (No.1 and No.9) had pure variants in the *LMNA* gene. The amino acid changes caused by the LMNA mutation sites and the pathogenicity of the variants were classified according to the American College of Medical Genetics (ACMG) guidelines (Richards et al, 2015). Details of pathogenicity are shown in Table 1.

Physical Examination

An otolaryngologist completed the physical examination. All 10 patients aged 1–17 years old had stiff auricles, cartilage deformities, thin skin with a transparent and shiny appearance, a significant reduction in earlobe size due to loss of subcutaneous fat, and poor elasticity of the external auditory canal (Fig. 1).

Hearing Evaluation

Five of the ten children had abnormal hearing results, with two showing mild to moderate low-frequency conductive hearing loss on pure-tone audiometry and the other three failing DPOAE in both ears at 750 Hz–1.5 KHz (abnormal hearing at low frequencies) but passing at 2–8 KHz (normal hearing at mid and high frequencies). Case 7 did not have accurate behavioural audiometric data because she could not cooperate. The 226 Hz acoustic conductance tympanogram results showed that among the 20 ears of the 10 patients, one ear had a flat tympanogram (10%), seven ears were bimodal (35%), and the rest had normal tympanograms (Table 2).

Table 1. Basic information of the patients.

Patient number	Gender	Age (Y)	Mutation site	Amino acid change	ACMG pathogenicity assessment
1	F	17	c.1579C>T	p.Arg527Cys	Likely pathogenic (PS4+PM2+PP3+PP4)
2	F	8	c.1822G>A	p.Gly608Ser	Likely pathogenic (PS3+PM2+PP4+PP5)
3	M	4	c.1824 C>T	p.Gly608Gly	Pathogenic (PS3+PS4+PP4)
4	M	15	c.1453-1454delins AG	p.Pro485Arg	Uncertain significance (PM2+PP4)
5	M	10	c.1824 C>T	p.Gly608Gly	Pathogenic (PS3+PS4+PP4)
6	M	9	c.1824 C>T	p.Gly608Gly	Pathogenic (PS3+PS4+PP4)
7	F	1	c.1824 C>T	p.Gly608Gly	Pathogenic (PS3+PS4+PP4)
8	F	7	c.1824 C>T	p.Gly608Gly	Pathogenic (PS3+PS4+PP4)
9	M	2	c.1579 C>T	p.Arg527Cys	Likely pathogenic (PS4+PM2+PP3+PP4)
10	F	10	c.1968+5 G>A	No amino acid changes	Likely pathogenic (PS3+PM2+PP4+PP5)

ACMG, American College of Medical Genetics; F, female; M, male.

Table 2. Hearing test results.

Patient number	PTA (Degree of hearing loss)		Nature of hearing loss	226 Hz AI tympanogram classification (L/R)	DPOAE
	Left ear (L)	Right ear (R)			
1	Mild hearing loss	Moderate hearing loss	Conductive hearing loss	B/B	Left ear, 750 Hz to 2 KHz failed, 3–8 KHz passed; Right ear 750 Hz –8 KHz failed
2	Mild hearing loss	Mild hearing loss	Conductive hearing loss	As/A	Both ears ear 750 Hz to 1.5 KHz failed, 2–8 KHz passed
3	Not measured	Not measured	Normal	A/A	Binaural 750 Hz to 8 KHz passed
4	Normal	Normal	Normal	A/A	Binaural 750 Hz to 8 KHz passed
5	Normal	Normal	Conductive hearing loss at 250 Hz	A/A	Both ears ear 750 Hz to 1.5 KHz failed, 2–8 KHz passed
6	Normal	Normal	Conductive hearing loss at 125–250 Hz	A/A	750 Hz to 1 KHz failed for both ears, 1.5–8 KHz passed
7	Not measured	Not measured		A/A	750 Hz to 1 KHz failed for both ears, 1.5–8 KHz passed
8	Normal	Normal	Normal	As/As	Binaural 750 Hz to 8 KHz passed
9	Not measured	Not measured	Normal	As/As	Binaural 750 Hz to 8 KHz passed
10	Normal	Normal	Normal	A/A	Binaural 750 Hz to 8 KHz passed

AI, acoustic impedance; DPOAE, distortion product otoacoustic emission; PTA, pure-tone audiometry. Tympanograms were classified according to Jerger's criteria as type A, As, B, or C (Jerger, 1970). Normal peak compensated static compliance and middle ear pressure represented by Type A. There was reduced static compliance with normal middle ear pressure represented by Type As. Flat tympanograms represented by Type B. Negative middle ear pressure represented by Type C.

Table 3. Summary information on the children with hearing disorders.

Patient number	Mutation site	Age (Y)	PTA (Degree of hearing loss)	DPOAE	226 Hz acoustic impedance tympanogram classification	Nature of hearing loss
1	c.1579C>T	17	L: Mild hearing loss	L: 750 Hz to 2 KHz failed	B	Conductive hearing loss
			R: Moderate hearing loss	R: 750 Hz–8 KHz failed	B	Conductive hearing loss
2	c.1822G>A	8	L: Moderate hearing loss	L: 750 Hz–1.5 KHz failed	As	Conductive hearing loss
			R: Moderate hearing loss	R: 750 Hz–1.5 KHz failed	A	Conductive hearing loss
5	c.1824 C>T	10	L: Conductive hearing loss at 250 Hz	L: 750 Hz–1.5 KHz failed	A	Normal
			R: Conductive hearing loss at 250 Hz	R: 750 Hz–1.5 KHz failed	A	Normal
6	c.1824 C>T	9	L: Conductive hearing loss at 125–250 Hz	L: 750 Hz–1 KHz failed	A	Normal
			R: Conductive hearing loss at 125–250 Hz	R: 750 Hz–1 KHz failed	A	Normal
7	c.1824 C>T	1	unknow	L: 750 Hz–1 KHz failed	A	Normal
			unknow	R: 750 Hz–1 KHz failed	A	Normal

Pure tone hearing thresholds were the average of 500 Hz, 1000 Hz, 2000 Hz, and 4000 Hz hearing values.

The mutation site, age, and audiological performance of the children with hearing abnormalities are shown in Table 3. Except for one 1-year-old patient with likely low-frequency hearing loss (DPOAE binaural 750 Hz–1 KHz failed), the rest of the patients with hearing loss were older than 8 years, and most of them had mild to moderate low-frequency conductive hearing loss.

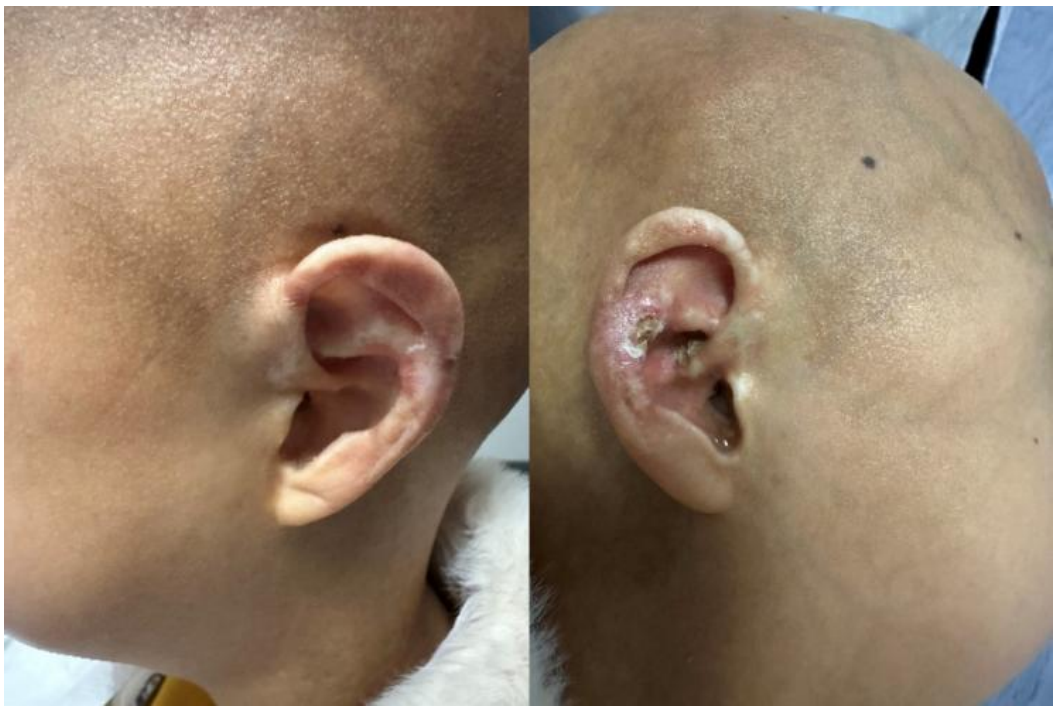


Fig. 1. The physical examination was completed by an otolaryngologist. All 10 patients had transparent skin, significantly reduced earlobes, hard external auditory meatus, and poor elasticity.

Causes of Hearing Loss

To understand the cause(s) of hearing loss in the children with progeria, we performed thin-section computed tomography (CT) of the temporal bone (c.1579C>T), carried out a detailed otoscopic examination, and tested the stapedius muscle reflexes of the oldest patient, specifically case 1, a 17-year-old with atypical HGPS (pure variant in the *LMNA* gene) with hearing loss. Pure-tone audiometry in this patient revealed predominantly low-frequency conductive hearing loss in the left ear, with moderate conductive hearing loss in the right ear (Fig. 2). On DPOAE testing, the left ear failed at 750 Hz to 2 KHz but passed at 3–8 KHz; the right ear failed at 750 Hz to 8 KHz (Fig. 3).

The 226 Hz sound-probe acoustic conductance tympanometry revealed an As-type tympanogram for the left ear, and a B-type tympanogram for the right ear. Ipsilateral acoustic emissions revealed the following features: left ear 500 Hz, 2 KHz threshold 4 KHz lead, 1 KHz unleaded; right ear 2 KHz lead only, 500 Hz, 1 KHz, 4 KHz unleaded (Fig. 4).

Otoscopy revealed external auditory canal stenosis bilaterally, atrophy or thinning of the right tympanic membrane, and an indistinct cone of light (Figs. 5,6).

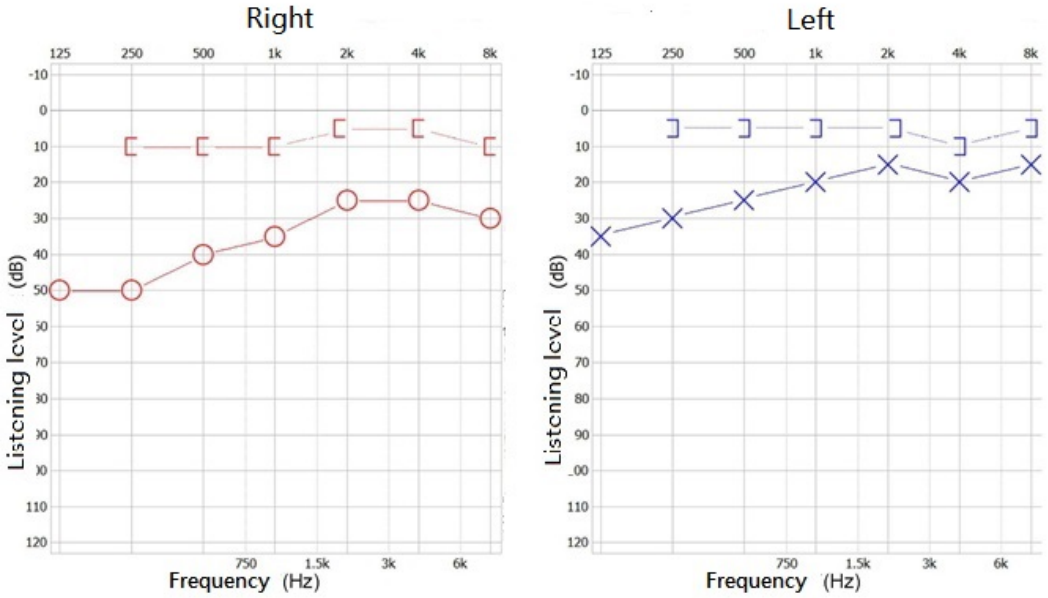


Fig. 2. PTA results. Predominantly low-frequency conductive hearing loss in the left ear, with moderate conductive hearing loss in the right ear.

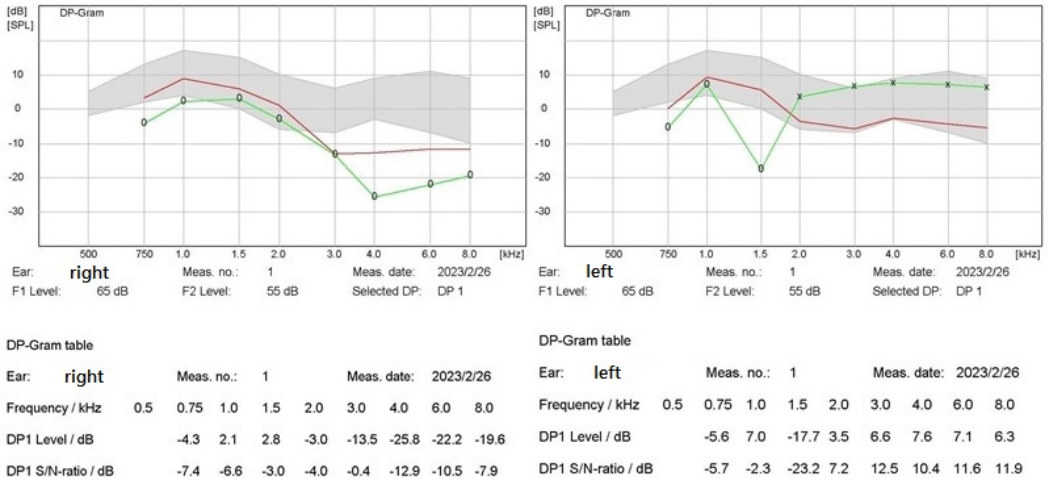
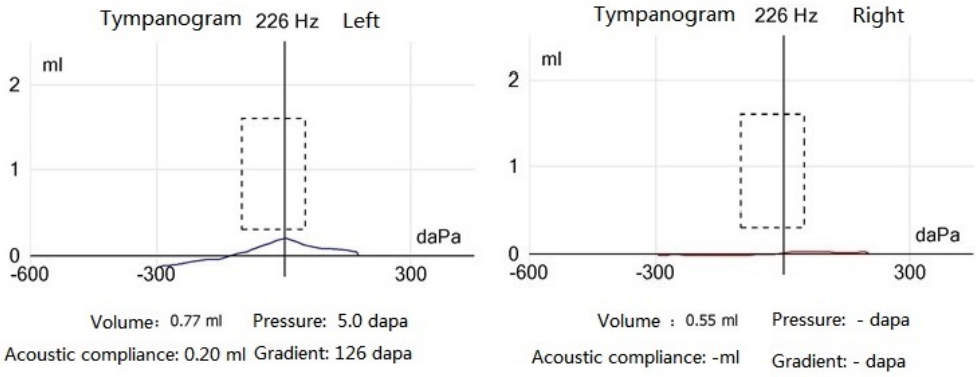


Fig. 3. DPOAE results. The left ear failed at 750 Hz to 2 KHz but passed at 3–8 KHz; the right ear failed at 750 Hz to 8 KHz.

CT temporal bone plain scan with 3D reconstruction revealed the following features.

The temporal papillae were poorly pneumatized bilaterally, with plate-barrier-type papillae; the bony cortex of the posterior wall of the right papillary atrium was discontinuous, and the bony cortex of the lateral wall of the left papillary atrium was discontinuous, with some pneumatization seen in its marginal soft tissues (Fig. 7). The vestibular aqueduct was enlarged bilaterally, the size of the enlarged vestibular aqueducts was 2.2 mm (Fig. 8).



Acoustic reflex F: 226 Hz P: -4 daPa

Probe	Stimulate	Threshold
Left	500 Hz Ipsilateral	100 dB HL
Left	1 kHz Ipsilateral	> 100 dB HL
Left	2 kHz Ipsilateral	100 dB HL
Left	4 kHz Ipsilateral	80 dB HL

Acoustic reflex F: 226 Hz P: -237 daPa

Probe	Stimulate	Threshold
Right	500 Hz Ipsilateral	> 100 dB HL
Right	1 kHz Ipsilateral	> 100 dB HL
Right	2 kHz Ipsilateral	95 dB HL
Right	4 kHz Ipsilateral	> 100 dB HL

Fig. 4. 226 Hz probe tone AI tympanogram and stapedius muscle reflex results. Tympanogram revealed an As-type for the left ear, and a B-type for the right ear. Ipsilateral acoustic emissions revealed left 1 KHz unleaded, right 500 Hz, 1 KHz, 4 KHz all unleaded.

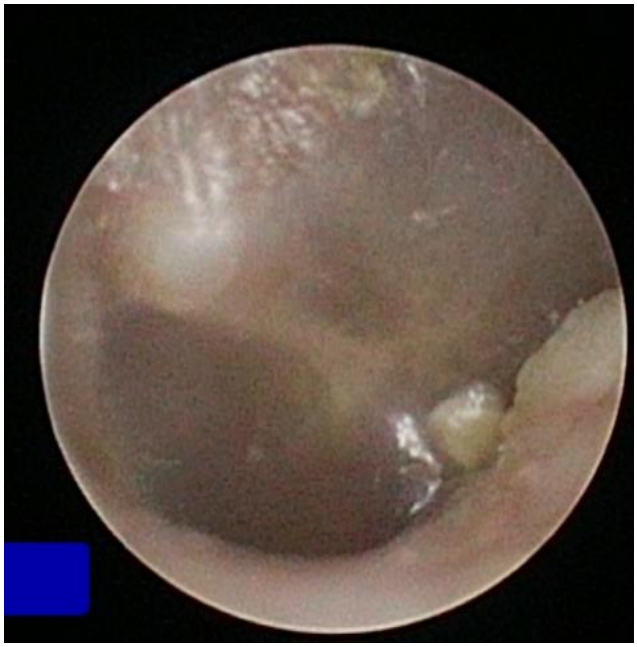


Fig. 5. Otoscopy, left (Case 1).

Discussion

The rate of aging in children with HGPS is 5 to 10 times higher than that of normal children. The child appears normal at birth, but by 1–2 years of age, symptoms of progeroid aging begin to appear, with characteristic bone changes such as osteoporosis, resorption and fibrosis of the clavicle, resorption of the ends of the toes, hardening of the metacarpal joints, nail hypoplasia, thinning of the ribs, arrested development of the jaw, stiffness of the large joints, restricted joint movements, knee

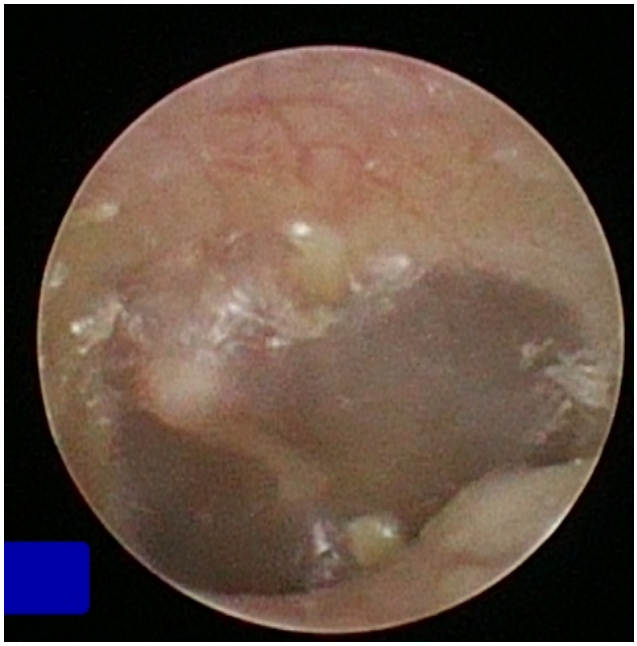


Fig. 6. Otoscopy, right (Case 1). External auditory canal stenosis bilaterally, atrophy or thinning of the right tympanic membrane, and an indistinct cone of light.

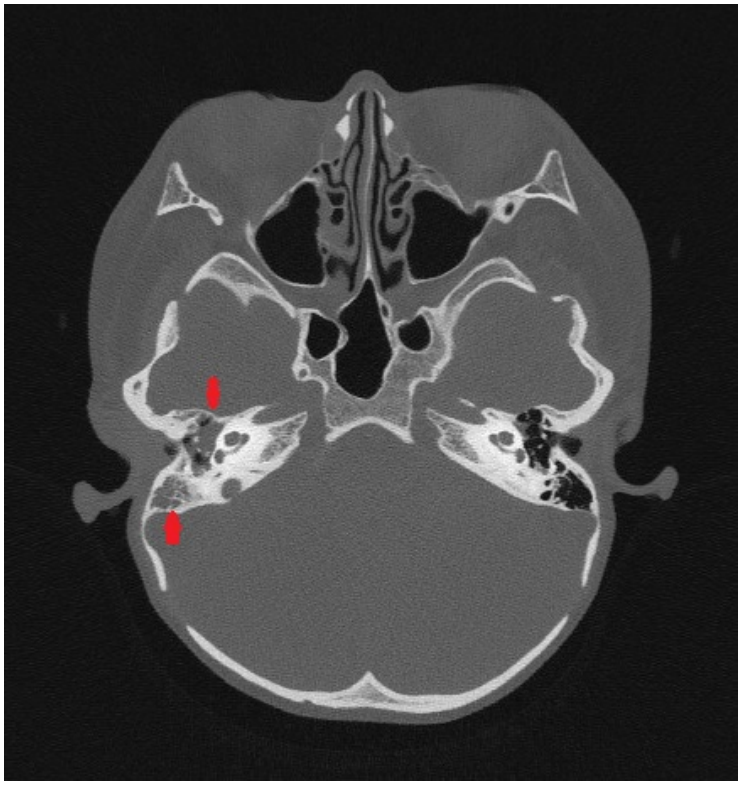


Fig. 7. Plain computed tomography (CT) scan of the temporal bone. Red arrows point to the temporal papillae were poorly pneumatized bilaterally, with plate-barrier-type papillae.

spasms, and a horse-like posture (Sato-Kawano et al, 2017), but with normal or age-appropriate intellectual and cognitive development. In some individuals, the kidney, gastrointestinal, neurological, and immune systems continue to function

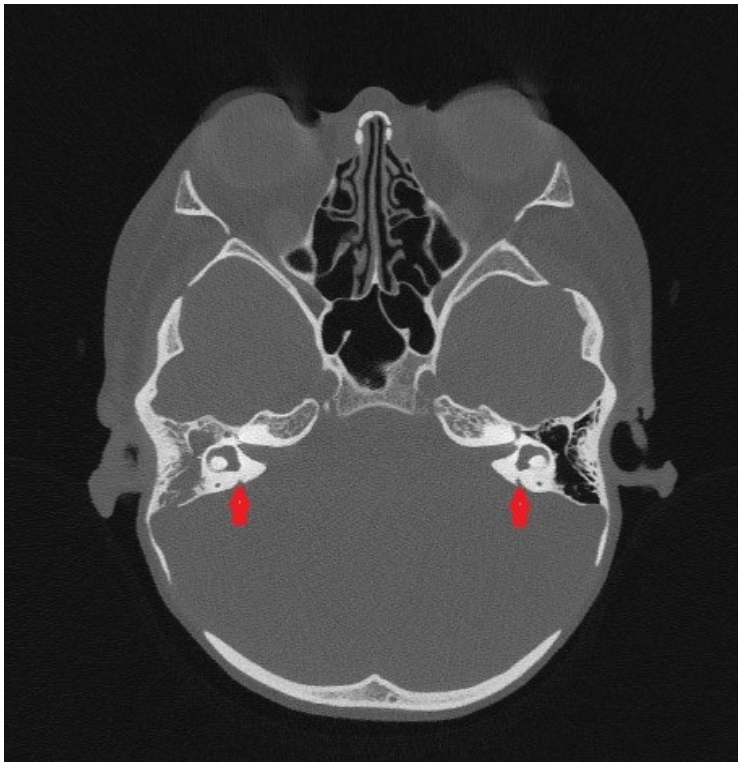


Fig. 8. CT plain scan of the temporal bone. Red arrows point to the vestibular aqueduct was enlarged bilaterally, the size of the enlarged vestibular aqueducts was 2.2 mm.

normally, leading to 'partial' senility (segmental progeroid syndromes) (Gordon et al, 2014). In all affected individuals, the disease follows a course of accelerated atherosclerosis, congestive heart failure, myocardial infarction, and other serious sequelae. Most affected children die from cardiovascular disease or stroke, with the typical lifespan ranging from 7 to 27 years, and an average of 13 years (Sarkar and Shinton, 2001).

Guardiani et al (2011) and Gordon et al (2014) observed that conductive hearing loss is very common in HGPS patients of all ages, with low-frequency conductive hearing loss more prevalent than high-frequency conductive hearing loss. In our study, we observed that most patients with hearing loss were older than 8 years, with only one (25%) patient younger than 1 year of age. We also observed that 50% of our patients with HGPS had normal hearing and 50% had mild to moderate bilaterally symmetrical low-frequency conductive hearing loss. Five of the ten patients passed the DPOAE 750 Hz to 8 KHz test, while four patients passed the DPOAE 2–8 KHz test, and one patient did not pass the DPOAE test all frequencies, although the patient showed normal bone conduction thresholds on pure-tone audiometry, suggesting good cochlear function and no sensorineural hearing loss. In contrast, Guardiani et al (2011) observed sensorineural hearing loss in a 16-year-old patient. We will continue to follow-up our five patients with normal hearing for the possibility of delayed hearing loss.

Guardiani et al (2011) also observed a shortened ear canal and stiff auricular cartilage in patients with HGPS, they reported that the skin of the bony external auditory canal is very thin and there are few hairs and sebaceous glands. Toyoda et

al (2009) reported that the dermal sebaceous glands are underdeveloped in HGPS patients, resulting in dry, hard wax in most patients, leading to poor elasticity of the external auditory canal skin. This appears as a flattened 226 Hz sound-probe acoustic conductance tympanogram and an elevated stapedius muscle reflex threshold. In addition, Merideth et al (2008) suggested that a bimodal pattern of the 226 Hz sound-probe tympanogram is typical of a mass-dominated middle-ear system, such as in those with sclerosis of the tympanic cavity or excessive scar-tissue formation. A case report by Hall and Denneny (1993) suggested that fibrous abnormalities of the stapes footplate and adhesions of the incudostapedial joint could explain the increased mass of the middle-ear system. In the study by Guardiani et al (2011), five patients underwent acoustic reflex testing, and three (60%) showed acoustic abnormalities; one 17-year-old patient also showed deficits or increased thresholds in otoacoustic emissions at all frequencies. When sensorineural deafness is more than 30 dB HL, the acoustic reflex becomes difficult to elicit (Fan and Cheng, 2016), so if the HGPS patient is too young to undergo subjective testing, the stapedius reflex can be used in addition to the DPOAE to predict the presence of mild to moderate hearing loss. Guardiani et al (2011) also reported that 90% of their patients had a normal DPOAE at a frequency of 750 Hz to 8 KHz, whereas in our study, only 50% had a normal DPOAE. This may be due to the differences in the frequencies used for testing. The external ear canal should be cleaned before DPOAE is performed so that the results are not affected by cerumen plugs or impacted cerumen. In addition, the diagnosis may be missed if only the middle and high frequencies are tested.

Ahmed et al (2018) observed a case of HGPS with osteolysis of the clavicle, mandible, skull, and distal pha-langes, and reported that osteolysis may cause poor mastoid pneumatization. This could account for the slightly higher incidence of otitis media. Pichichero (2000) further calculated that 29% of patients had recurrent otitis media, and the age of recurrence was 7–12 years, compared to a 20% recurrence rate in the general population. This, of course, underlies mastoid pneumatization's important role in developing otitis media, especially in children, but the converse is also true. Lu et al (2020) suggested that otitis media in childhood can lead to poor papillary pneumatization. The CT findings in the case of our 17-year-old patient with HGPS suggested bilateral otitis media with poorly pneumatized mastoid processes in the temporal bone, with numerous, albeit small, air spaces indicating plate-barrier mastoids. We hypothesize that the poorly pneumatized mastoids may be due to osteolysis or recurrent otitis media and, combined with poor sound conduction because of the effects of auricular contracture and external auditory canal stenosis, which would result in the conductive hearing loss seen in these patients. The degree of mastoid pneumatization could also be genet-ically determined (Lu et al, 2021). Duan et al (2017) reported the presence of LMNA synonymous variants in one patient with abnormal hearing, suggesting this may be due to shearing defects. However, they did not elucidate an association with HGPS (Duan et al, 2017). At present, we have only one case of an HGPS patient with hearing abnor-malities who underwent CT of the temporal bone, so more patients need to be investigated to further determine whether the platysmal papillae are associated with *LMNA* gene

variants. Otolaryngology experts recommend that HGPS patients with hearing loss should undergo an added thin-layer temporal bone CT scan and endoscopic examination to document and record the progression of the disease.

The presence of other structural malformations or genetic abnormalities should also be considered in patients with HGPS. For example, the 17-year-old patient we observed with complete audiological and imaging data had a congenital malformation of enlarged vestibular aqueducts, which could also contribute to hearing loss. However, unlike the typical mixed hearing loss with enlarged vestibular aqueducts, this patient had not yet developed sensorineural hearing loss at the most recent follow-up. A larger sample size is needed for additional studies to explore whether there is an association between the *LMNA* gene variant and the structural malformations of the cochlea observed in typical HGPS patients.

Conclusion

HGPS patients have widely different patterns of hearing loss and associated ear problems. Methods such as softening and removing the cerumen regularly in children with hard and inflexible external auditory canals should greatly relieve the conductive hearing loss seen in this condition, thus improving the patient's quality of life. Further studies will help answer whether other genetic variants accompany deafness in HGPS patients and possibly pave the way for precision medicine.

Key Points

- Patients with progeria have normal or predominantly low-frequency conductive hearing loss across full frequencies, and the degree of hearing loss is mild or moderate.
- Low-frequency hearing loss is more likely to occur in patients older than 8 years, with hearing loss centered on 125–250 Hz.
- It is recommended that after otitis media is ruled out by acoustic impedance testing, the hearing level of patients with progeria should be assessed using both pure tone audiometry and otoacoustic emission.
- CT of the temporal bone in older patients with progeria shows bilateral temporal bone mastoid pneumatization of a platysmal barrier mastoid, alerting for other inner ear malformations such as enlargement of the vestibular aqueduct.

Availability of Data and Materials

Data used to support the findings of this study are available from the corresponding author upon request.

Author Contributions

JS, JJW and JB designed the research study. JS and JJW performed the research. JB drafted the manuscript. JS analysed the data. All authors contributed to

important editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

This study was approved by the Ethics Committee of the Children's Hospital of Zhejiang University School of Medicine (No. 2020-IRB-158). Informed consent was obtained from each child's parent(s) or legal guardian(s).

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Conflict of Interest

The authors declare no conflict of interest.

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