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Laryngeal and vocal evaluation in untreated growth hormone deficient adults

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Abstract

OBJECTIVE—To evaluate the consequences of lifetime, severe and untreated isolated growth hormone deficiency (IGHD) on vocal and laryngeal function.

STUDY DESIGN—Cross-sectional.

SUBJECTS AND METHODS—A total of 23 IGHD adult subjects and 22 controls were administered a questionnaire about vocal complaints and harmful voice habits, and underwent video-laryngostroboscopic examination, voice evaluation by perceptual-auditory analysis with GRBAS scale including grade of dysphonia, roughness, breathiness, asthenia and strain items, objective voice evaluation by maximum phonation time (MPT), and acoustic analysis.

RESULTS—There was no difference in vocal complaints between IGHD subjects and controls. Vocal abuse and smoking were more frequent in IGHD subjects. IGHD subjects presented higher values for roughness, breathiness, and strain. Laryngopharyngeal reflux (LPR) signs and laryngeal constriction were more frequent in IGHD individuals. MPT was similar in the two groups. Fundamental frequency was higher in IGHD females and males. Harmonic to noise ratio was higher in IGHD in both genders and shimmer was lower in IGHD females.

CONCLUSIONS—IGHD subjects have higher prevalence of signs of LPR and laryngeal constriction, with high pitch in both genders, which suggests a prominent role of IGHD on these parameters.

Growth hormone (GH) has an important role not only on somatic growth but on several other functions such as body composition, intermediate metabolism, bone apposition, and regulation of blood pressure. In addition, GH is known to influence voice quality. For instance, in acromegaly, a GH hypersecretory state, the fundamental frequency (*f0*) is lower than normal,

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AUTHOR CONTRIBUTION

Valéria M. P. Barret, writer, data collection; **Jeferson S. D'Ávila**, writer, data collection; **Neuza J. Sales**, writer, data collection; **Maria Inês R. Gonçalves**, writer, data collection; **Juliane Dantas Seabra**, writer, data collection; **Roberto Salvatori**, writer, data collection; **Manuel H. Aguiar-Oliveira**, writer, data collection, statistics.

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probably due to an increase thickness of the vocal folds.[1] Conversely, data on voice quality in GH deficiency (GHD) are scarce.

In Itabaianinha County, in the Northeastern Brazilian state of Sergipe, we have identified an extended kindred of patients with familial isolated GHD (IGHD), with approximately 100 affected subjects over seven generations. In this population, IGHD is caused by a homozygous mutation in the splice donor site of intron 1 (IVS1+1G→A) of the GH-releasing hormone receptor (GHRHR) gene (*GHRHR*), resulting in very low serum levels of GH that fail to respond to secretion stimuli, and of its principal mediator insulinlike growth factor-I (IGF-I).[2,3] These subjects present severe dwarfism with adult height ranging between 105 to 135 cm, frontal bossing, underdeveloped nose, vertical facial and cranial volume reduction, central obesity, and increased systolic blood pressure without evidence of premature atherosclerosis.[4,5] Data obtained in four male subjects with another *GHRHR* mutation suggested "high pitch and disordered spectral quality of voice,"[6] but no data are available on laryngeal status in IGHD. Here we have compared a large number of IGHD individuals of both genders from the Itabaianinha kindred with adults of normal stature with the use of a protocol that included recording of vocal complaints, harmful habits, voice, and laryngoscope evaluation.

METHODS

Subjects

Twenty-three IGHD GH-naive adults, 43 ± 19.43 years old (17 females, 44.2 ± 21.5 and six males, 40.5 ± 14.15 years old), and 22 controls, 45 ± 19.23 years old (16 females, 46 ± 18.52, and six males, 42.33 ± 22.6 years old) were studied. IGHD subjects were recruited by an ad placed in the local dwarfs' association building located in Itabaianinha and by word of mouth. All the IGHD subjects were homozygous for the same *GHRHR* (IVS1+1G→A) mutation.[2] The serum IGF-1 levels of these subjects are invariably at the lowest limits of sensitivity of the assay. Controls were recruited in Aracaju, the capital of Sergipe State, by an ad placed at the University Hospital of the Federal University of Sergipe. Both groups included two teachers, whereas housewife and farm worker were the other predominant professions. All subjects were Portuguese-language native speakers. The study design was cross-sectional, and the inclusion criteria were: mental and physical ability to answer the questionnaire and to perform the protocol; no history of GH replacement therapy; no history of laryngeal surgeries, intubation, or speech therapy procedures. The protocol was approved by Ethics Committee of the Federal University of Sergipe. All subjects signed a written informed consent.

Questionnaire

Twenty-two of the 23 IGHD subjects (16 females) and all 22 controls (16 females) were administered a questionnaire on vocal complaints and main habits known to be harmful to vocal health.

Voice and Video-laryngostroboscopic Evaluation

Voice evaluation through perceptual-auditory analysis was performed in 22 (16 females), maximum phonation time (MPT) and acoustic analyses in 19 (15 females), and video-laryngostroboscopic (VLS) examination in 21 (15 females). All the evaluations were performed by two speech therapists and 2 otorhinolaryngologists experienced in this type of assessments. Given the evident dwarf phenotype of the IGHD subjects, they could not be blinded to the group the subjects belonged to.

Subjects' perceptual-auditory analysis was assessed with a GRBAS scale, in which the voice properties, such as the grade of the severity of dysphonia (G), roughness (R), breathiness (B),

asthenia (A), and strain (S), are scored on a four-point scale: 0 = normal, 1 = mild deviance, 2 = moderate deviance, and 3 = severe deviance.[7]

We defined as normal a voice with socially acceptable quality, not interfering with speech understanding, and adequate with respect to fundamental frequency, loudness, modulation, and projection, considering gender and age of the speakers and without disagreement to listeners during selection emissions, as defined in Brazil on Portuguese-speaking individuals.[8]

Maximum phonation time (MPT) was determined by measuring the duration of /a/ vowel produced at a comfortable amplitude and pitch level of voice after maximum inspiration and the s/z ratio.

Computer acoustic analysis was performed as reported [9] in a room with a noise level below 40 dB, with Multi Speech Program, Model 3700, from Kay Pentax (Whippany, NJ).The microphone used was a Shure SM 48 dynamic, and it was kept at a fixed distance of 5 cm in front of the subject's mouth. For each subject, we studied 3-second sustained /ε/ vowel emission. The individuals were asked to say the sustained vowel one time before recording it, to verify that they understood the task and that the vowel quality was perceptual-auditory similar in all emissions. Discrepancies were discharged and the subjects were asked to record again as close to the habitual voice as possible. In Portuguese language, the vowel /ε/ is the best vowel to voice and laryngeal evaluation. We analyzed: 1) computer analysis of fundamental frequency (*f0*), which corresponds to the number of vocal fold vibration cycles in one second; 2) jitter (J), which indicates the variability of *f0* in the short run; 3) shimmer (S), which measures the phonation stability and indicates the variability of sound wave amplitude in the short run; 4) harmonic-to-noise ratio (HNR), which relates the harmonic component to the noise component of the sound wave.

VLS examination was performed with the following devices: 8.0 mm rigid laryngeal telescope at 70° (Machida, Orangeburg, NY); 3.2 mm flexible nasofibrolaryngoscope (Machida); light xenon source 350 watts (Stroboview, Rotterdam, The Netherlands); micro-camera (Toshiba CCCD IK-M30AK, Japan); videocassette (Sony Trinitron model PVM-14N5U, Japan); videomonitor (LG flat screen, Korea); VHS tape. The examinations were carried out under topical anesthesia with 2 percent lidocaine spray. We instructed the subjects to produce deep breathing, comfortable production of sustained vowels /e/ and /i/, and inspiratory phonation. The reflux finding score (RFS) was used to assess laryngopharyngeal reflux (LPR) signs (subglottic edema, ventricular obliteration, erythema/hyperemia, vocal fold edema, diffuse laryngeal edema, posterior commissure hypertrophy, granuloma, and others). A score greater than 11 was strongly considered suggestive of LPR.[10]

Statistics

All the continuous variables are expressed in mean and standard deviation. Categorical variables were analyzed by Fisher's exact test. The two groups were compared by the independent *t* test for all the continuous variables unless HNR distribution was not normal and therefore Mann-Whitney test was used. In order to avoid possible influence of pathologies and the results of their acoustical analysis, tests were repeated to compare the individuals with and without laryngeal diseases in both groups. Probability values of 0.05 or less were considered statistically significant.

RESULTS

Table 1 shows the vocal complaints and harmful habits in IGHD and controls. There was no difference in any of the vocal complaints between the two groups. Among the harmful habits,

vocal abuse and smoking were more frequent in IGHD than in controls ($P = 0.009$ and $P = 0.006$, respectively).

Table 2 shows the results on perceptual-auditory analysis (GRBAS scale). It revealed higher values for roughness (R) ($P = 0.001$), breathiness (B) ($P = 0.002$), and strain ($P < 0.0001$) in IGHD subjects. Asthenia of moderate grade was found in only one GHD female and in none of the controls.

Table 3 shows results of MPT analysis. There was no difference between the two groups. Results of the acoustic analyses are shown in Table 4. F0 was higher in IGHD than control in females ($P = 0.029$) and more markedly in males ($P < 0.0001$). HNR were higher in both genders ($P = 0.037$ and $P = 0.01$ in females and males, respectively). Shimmer was lower in IGHD than control females ($P = 0.029$). These results did not change when we analyzed separately individuals with and without laryngeal diseases (nodules, cysts, and granuloma).

Table 5 shows the data of VLS evaluation. LPR signs and laryngeal constriction were more frequent in IGHD individuals than controls ($P < 0.0001$ and 0.001, respectively). RFS was higher than 11 in 11 of the 14 IGHD and in 1 of the 3 controls who presented LPR signs ($P = 0.001$). There was no difference in the rate of nodules and vocal cysts between the two groups. Only one male IGHD and none in the controls presented a single laryngeal granuloma.

DISCUSSION

High pitched voice is the common finding reported to be present in untreated GHD or GH resistance.[2,11] Due to the well-known effect of gonadal steroids and thyroid hormones on voice,[12] a careful analysis of the effects of GHD can only be performed in patients with GHD and otherwise normal pituitary function (IGHD). As IGHD is a rare disease, and most patients in the developed countries are treated with GH replacement during childhood, it is difficult to generate data on the effect of GH on voice. Therefore, the Itabaianinha kindred offers a unique opportunity as it allows us to study adult subjects with lifetime, severe IGHD, who have never received GH replacement therapy.

The vocal complaints of the IGHD subjects were similar to controls and to what has been previously reported in normal individuals.[13,14] Among the three harmful habits investigated (vocal abuse, smoking, and alcohol abuse), the first two were more frequent in IGHD subjects. Although we cannot rule out that IGHD itself (or the severe short stature) causes such difference, it is more likely that they are due to the higher level of education of the controls, who reside in the state's capital, compared with the residents of the rural Itabaianinha environment.

In perceptual-auditory analysis, IGHD subjects presented an abnormal voice with higher values for roughness, breathiness, and strain. More strain, possibly necessary for vocal self-assurance, could contribute to the observed higher prevalence of laryngeal constriction.

There was no statistical difference between the two groups in the MPT of the vowel /a/ and s/z ratio. As for the MPT of the vowel /a/, the control group presented values below the average values previously reported in a Brazilian Portuguese-speaking population.[9] This probably explains why we did not find a statistical difference between the two groups. It is important to point out, however, that we do not have data on MPT specifically for the Aracaju and Itabaianinha regions. Despite the observed anatomic differences, both groups presented similar s/z proportion, which indicates equilibrium between airflow and vocal fold vibration.

Fundamental frequency (*f0*) was similar in female and male IGHD subjects (221.06 Hz and 204.66 Hz, respectively), and higher than in controls (200.25 ± 23.37 and 130.47 ± 13.56 in

females and males, respectively). Such difference was more marked in males, likely related to the clinical observation of small size and reduced glottic proportion (relationship between phonatory and respiratory larynx) of their larynx. In addition, our IGHD individuals have reduced craniofacial dimensions, a fact that could also contribute to the alterations in *f0*. In agreement with our findings, high pitch voice has been reported in four male Pakistani IGHD subjects with a different *GHRHR* mutation (Glu72X) (the Dwarfs of Sindh[15]), who had *f0* ranging from 174 Hz to 266 Hz.[6] Three of them presented breathiness and one creaky voice, attributed to small laryngeal size.[6] We did not find any subject who appeared to have creaky voice. This difference could be related to laryngeal functional variation due to ethnic or language differences.

We did not observe any difference in jitter between the two groups, and the values of both groups were similar to normative Brazilian data.[9] IGHD females presented lower shimmer than controls, which suggests lower phonation stability, but values are in the lower part of normal range. The harmonic-noise ratio was higher in IGHD individuals than controls, but still in lower range of normal, and therefore of dubious clinical significance.[9]

Vocal abuse is the most common cause of inflammatory laryngeal lesions.[16] LPR and laryngeal constriction where more frequent in IGHD than controls. However, there was no difference in the rate of nodules and vocal cysts between the two groups, with frequencies apparently lower than the ones of most surgical studies, where rates of nodules vary from 8 percent to 50 percent, and of vocal cysts from 20 percent to 29 percent.[17] Such low prevalence is not unexpected, as this is a healthy population not referred for evaluation because of clinically evident complaints. Although specific anatomic measurement could not be obtained due to technical difficulties related to the small size of the larynx, clinical observation of the IGHD individuals suggests that both females and males present reduced glottic configuration and smaller glottic proportion (relationship between phonatory and respiratory larynx). As there is a high risk of laryngeal nodule development in women and children with reduced glottic proportion,[18] we would have expected a higher prevalence of nodules in IGHD individuals exposed to vocal abuse. It is possible that the GHD status has somehow a protective effect on the development of nodules, but we cannot rule out environmental or additional genetic factors associated with the mutated *GHRHR* allele.

VLS findings revealed a high incidence of signs of LPR and laryngeal constriction. LPR is the most common extra esophageal expression that leads to dysphonia.[19] It is possible that the nearness of organs caused by the severe short stature may lead to increased risk of laryngopharyngeal reflux and laryngeal constriction. LPR (together with vocal abuse) is a risk factor for posterior laryngeal granuloma, mainly in males.[20] Although IGHD individuals presented more LPR signs and laryngeal strain, the frequency of granulomas was low. Similar to the issue of nodules, we do not have a clear explanation for this finding.

Laryngeal constriction may be a compensatory event in dysphonic patients being associated with functional dysphonia, nodules, cysts, vocal fold palsy, and LPR.[21] We postulate that the cause of higher prevalence of constriction is related to the presence of LPR rather than to the IGHD status itself. None of the VLS findings seems to be peculiar to untreated IGHD.

CONCLUSIONS

Adult individuals with severe short stature due to congenital and untreated IGHD present higher prevalence of signs of LPR and laryngeal constriction. Their voice is abnormal, with a high pitch pattern, particularly evident in males, which suggests a prominent role of GHD on this parameter.

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Table 1

Vocal complaints and harmful habits (vocal abuse, smoking and alcohol abuse) in 22 IGHD and 22 controls (significant *P* values are in bold)

	IGHD		Controls		
Variables	**N**	**%Total**	**n**	**%Total**	***P***
Hoarseness	7	31.8	7	31.8	0.579
Vocal fatigue	8	36.3	9	40.9	0.420
Sore throat	6	27.2	7	31.8	0.421
Neckache	6	27.2	8	36.3	0.259
Aphonia	4	18.1	2	9.0	0.130
Phonatory pain	5	22.7	3	13.6	0.170
Vocal abuse	16	72.7	10	45.4	**0.009**
Smoking	8	36.3	3	13.6	**0.006**
Alcohol abuse	0	0	0	0	NA
Total	22	100	22	100	

NA, Not applicable.

Table 2

Perceptual assessment of voice quality according to GRBAS scale in IGHD subjects and controls (significant *P* values are in bold)

	IGHD		Controls		
Variable	**n/Total**	**%Total**	**n/total**	**%Total**	***P***
Grade of severity Dysphonia	16/22	72.7	8/22	36.4	**0.001**
Roughness	15/22	68.2	8/22	36.4	**0.002**
Breathiness	15/22	68.2	6/22	26.1	**<0.0001**
Asthenia	1/22	4.5	0	0	NA
Strain	16/22	72.7	6/22	26.1	**<0.0001**

NA, Not applicable.

Table 3

Maximum phonation time in seconds in IGHD individuals and controls (number of subjects studied is in parentheses)

Variables	Gender	IGHD (n)	Controls (n)	*P*
a	F	8.6 ± 3.68 (15)	10.37 ± 3.3 (16)	0.158
	M	7.5 ± 5.6 (4)	11.00 ± 4.38 (6)	0.275
s/z	F	1.19 ± 0.52 (15)	1.21 ± 0.43 (16)	0.902
	M	0.96 ± 0.22 (4)	1.04 ± 0.2 (6)	0.563

Table 4

Acoustic analysis in IGHD individuals and controls (number of subjects studied are in parentheses. Significant *P* values are in bold)

Variables	Gender	IGHD (n)	Controls (n)	*P*
Frequency- *fo* (Hz)	F	221.06 ± 26.55 (15)	200.25 ± 23.37 (16)	**0.029**
	M	204.66 ± 20.96 (4)	130.47 ± 13.56 (6)	**<0.0001**
Jitter (%)	F	2.31 ± 1.48 (15)	2.99 ± 3.12 (16)	0.448
	M	3.55 ± 1.15 (4)	2.31 (6)	0.798
Shimmer (dB)	F	0.71 ± 0.36 (15)	1.49 ± 1.27 (16)	**0.029**
	M	0.74 ± 0.28 (4)	0.56 (6)	0.578
HNR	F	2.58 ± 4.71 (15)	0.22 ± 0.10 (16)	**0.037**
	M	3.80 ± 2.99 (4)	0.24 ± 0.89 (6)	**0.01**

HNR, Harmonic-to-noise ratio.

Table 5

Laryngeal evaluation of IGHD and controls (significant *P* values are in bold)

	IGHD		Controls		
Variables	**n/total**	**%**	**n/total**	**%**	***P***
Laryngopharyngeal reflux signs	14/21	66.6	3/22	13.6	**<0.0001**
Laryngeal constriction	11/21	52.4	4/22	18.2	**0.001**
Vocal nodules	5/21	23.8	3/22	13.6	0.196
Vocal cysts	2/21	9.5	1/22	4.5	0.368