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Voice disorders in residual paracoccidioidomycosis in upper airways and digestive tract

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ABSTRACT

Background: Paracoccidioidomycosis (PCM) is a systemic mycosis of acute and chronic evolution, caused by species belonging to the genus *Paracoccidioides*. It is considered the most prevalent systemic endemic mycosis in Latin America, with cases in the tropical and subtropical regions. Residual PCM refers to the fibrotic scar sequelae resulting from the disease treatment which, when associated with collagen accumulation, leads to functional and anatomic alterations in the organs.
Aims: The aim of this study was to evaluate the vocal function of patients with residual PCM in upper airways and digestive tract.
Methods: We performed a cross-sectional study in 2010 in a cohort of 21 patients with residual PCM in upper airways and digestive tract.
Results: The average age was 49.48 ± 9.1 years, and only two (9.5%) patients were female. The study was performed in the 1–113 month-period (median 27) after the end of drug treatment. Five (23.8%) patients had alterations in the larynx as a sequela of the disease. However, all patients had vocal changes in vocal auditory perceptual analysis by GRBASI scale. The computerized acoustic analysis using the software Vox Metria, showed that 11 patients (52.4%) presented alterations in jitter, 15 (71.4%) in shimmer, 8 (38.1%) in F0, 4 (19%) in glottal to noise excitation (GNE), 7 (33.3%) in the presence of noise and 12 (57.1%) in the presence of vibratory irregularity.
Conclusions: The great frequency of alterations in residual PCM suggests that the patients in such phase could benefit from a multidisciplinary treatment, offering them integral monitoring of the disease, including speech rehabilitation after the PCM is healed.

Trastornos de la voz en paracoccidioidomicosis residual en las vías respiratorias superiores y el tubo digestivo

Palabras clave:
Paracoccidioidomicosis
Laringe
Disfonía
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Calidad vocal

RESUMEN

Antecedentes: La paracoccidioidomicosis (PCM) es una micosis sistémica de evolución aguda y crónica causada por especies que pertenecen al género *Paracoccidioides*. Se considera que es la micosis sistémica endémica de mayor prevalencia en América Latina, con casos en las regiones tropicales y subtropicales. La PCM residual se refiere a las secuelas de las cicatrices fibróticas que provoca el tratamiento de la enfermedad; cuando se asocia con la acumulación de colágeno, conduce a alteraciones funcionales y anatómicas en los órganos.

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Objetivos: El objetivo de este estudio fue evaluar la función vocal de los pacientes con PCM residual en las vías respiratorias superiores y el tubo digestivo.
Métodos: En 2010 se realizó un estudio transversal con una cohorte de 21 pacientes con PCM residual en las vías respiratorias superiores y el tubo digestivo.
Resultados: La media de edad fue 49,48 ± 9,1 años y solo dos pacientes (9,5%) eran mujeres. El estudio se realizó durante un período entre 1 y 113 meses (mediana: 27) después de finalizado el tratamiento farmacológico. Cinco pacientes (23,8%) presentaban alteraciones en la laringe como secuela de la enfermedad. Sin embargo, se encontró que todos los pacientes tenían alteraciones vocales en el análisis de percepción auditiva vocal por la escala GRBASI. El análisis acústico computarizado con el software Vox Metria mostró que 11 pacientes (52,4%) presentaron alteraciones en la variación ciclo a ciclo de la frecuencia fundamental (parámetro denominado *jitter*), 15 (71,4%) en la variación ciclo a ciclo de la amplitud de la señal vocal *(shimmer)*, 8 (38,1%) en la frecuencia fundamental (F0), 4 (19%) en la relación señal-ruido (*glottal to noise excitation* - GNE), 7 (33,3%) en la existencia de ruido y 12 (57,1%) en la existencia de irregularidad vibratoria.
Conclusiones: La gran frecuencia de alteraciones en la PCM residual indica que los pacientes en dicha fase podrían beneficiarse de un tratamiento multidisciplinario con vigilancia integral de la enfermedad que incluyera la rehabilitación del habla tras la curación de la PCM.

Paracoccidioidomycosis (PCM) is a systemic mycosis of subacute or chronic evolution, caused by species belonging to the genus *Paracoccidioides*.[16] It is considered the most prevalente systemic endemic mycosis in Latin America, with cases in the tropical and subtropical regions.[13] Brazil is considered an endemic zone of this disease, concentrating about 80% of the world cases within its south, southeast, center-west and north regions. Since it is not a disease of compulsory notification the number of cases is underestimated and, therefore, based on hospital records, literature reports and precarious official data.[23]

Hospitalization due to PCM is concentrated in few municipalities, and the disease records in official databases are inadequate, with no interoperability or standardization amongst the data sets, with almost half of hospitalization and death numbers being mistakenly codified as blastomycosis.[9]

The disease PCM is subdivided into three forms: acute/subacute, being this clinical form more frequent in children with no gender prevalence; chronic (unifocal and multifocal), and residual. The chronic form in the most frequent, corresponding to about 90% cases, with prevalence on adult males, mainly between 30 and 50 years of age. Once it affects individuals in the most productive phase of their lives, this disease results in social and economic impacts.[21,23] Therefore, PCM represents an important problem in public health due to its disabling potential and the amount of premature death when the cases are not properly diagnosed and treated, especially in specific social segments such as rural workers who meet great difficulties to access and obtain support from the health care network.[21] PCM is acquired through the inhalation of infectious propagules.[7] Its evolution is related to fungal load, to the amount of inhaled infectious particles and the infected individual's general state,[4] with no transmission from man to man.[17] PCM involves the lungs because of the inhalation, and it can disseminate to several organs and systems, originating secondary lesions in the lymph nodes, skin, adrenal glands and, mainly, mucosae.[4] Mucous lesions are located most frequently on the lips, gingiva, tongue, jugal mucosa, palate, uvula, tonsillar pillars, floor of the mouth, nose and larynx.[24] Usually the clinical condition of mucosal involvement by PCM is associated with sialorrhea, odynophagia, dysphonia and shortness of breath. Pain on swallowing and on oral hygiene contribute effectively to jeopardize the nutritional condition of the patient.[22] When there is laryngeal involvement (PCML), the vocal folds are the most affected structures, and consequently high degrees of dysphonia and even aphonia are the main complaints.[2,4]

Residual PCM refers to the fibrotic scar sequelae resulting from the disease treatment which, when associated with collagen accumulation, leads to functional and anatomic alterations in the organs. The process of fibrosis in the airways can lead to dysphonia, due mainly to the thickening of the vocal folds, besides dyspnea, due to stenosis of the larynx and the trachea, and pulmonary emphysema, among others.[10,24] The aim of this study was to evaluate the vocal function of patients with residual PCM in upper airways and digestive tract (UADT).

Materials and methods

Between 1997 and 2010, 471 patients were diagnosed with PCM in the National Institute of Infectious Diseases Oswaldo Cruz Foundation, INI/FIOCRUZ, Rio de Janeiro RJ, Brazil, from whom 81 had UADT involvement. All patients were recruited to participate in the study; however, some died or changed their addresses. In 2010, a cross-sectional study with 21 patients with residual PCM in UADT was performed. The retrospective clinical, laboratorial and therapeutic data from these patients were obtained through active research within the records. The selected individuals had a proven mycological infection, confirmed through the observation of *P. brasiliensis* in biological samples, and had also already healed UADT mucosa lesions. All patients underwent anamnesis and otorhinolaryngologic examination by Karl Storz's 30° optical rigid nasal endoscopy and 70° rigid optical videolaryngoscopy (Tuttlingen, Germany). The auditory-perceptual evaluation was performed through the GRBASI scale, which evaluates the overall grade of hoarseness (G), considering the level of roughness (R), breathiness (B), asthenia (A), strain (S) and instability (I), which are classified as follows: (0) no alteration, (1) slightly altered, (2) moderately altered and (3) severe alteration.[18]

In the vocal acoustic analysis, all patients underwent voice recording in a quiet environment, directly into the computer for a better capture of the voice by the software VoxMetria (CTS Informática, Pato Branco, Brazil). A Plantronix A-20 model microphone was used within a distance of 10 cm to the mouth, during the emission of the/e/sustained vowel at common condition.[3] The following parameters were analyzed in the present study: jitter, that indicates the variability of the fundamental frequency perturbation in the short term, with normal pattern up to 0.6%; shimmer, that indicates the variability of the amplitude of the vocal note in the short term and with normal values up to 6.5%; measures of

Table 1
Clinical and voice characteristics of 21 patients with residual paracoccidioidomycosis of the upper airways and digestive tract. Evandro Chagas National Institute of Infectious Diseases, Oswaldo Cruz Foundation, 2010.

N	Smoking/ Alcoholism	Active lesion site	Site of the active lesion in larynx	Anatomic sequela site	Dysphonia	Voice quality alteration	General grade of hoarseness
1	Yes/No	Pharynx and oral cavity	-	Oral cavity	Yes	Yes	Moderate
2	Yes/No	Larynx and oral cavity	Vocal folds and arytenoids	Oral cavity	Yes	Yes	Moderate
3	Yes/Yes	Larynx and oral cavity	Arytenoids and interarytenoid region	-	No	Yes	Moderate
4	Yes/No	Larynx	Vocal folds	-	Yes	Yes	Moderate
5	Yes/Yes	Larynx, pharynx, oral cavity and nasal mucosa	Epiglottis	Oral cavity	No	Yes	Slight
6	No/No	Oral cavity and nasal mucosa	-	Oral cavity	No	Yes	Moderate
7	Yes/No	Larynx and oral cavity	Vocal folds	Oral cavity	Yes	Yes	Moderate
8	Yes/No	Larynx	Vocal folds	Larynx	Yes	Yes	Severe
9	Yes/Yes	Larynx, oral cavity and nasal mucosa	Vocal folds and epiglottis	Oral cavity	No	Yes	Moderate
10	Yes/No	Oral cavity	-	Oral cavity	No	Yes	Moderate
11	Yes/No	Oral cavity and nasal mucosa	-	Oral cavity	No	Yes	Moderate
12	Yes/Yes	Larynx, oral cavity and nasal mucosa	Vocal folds and arytenoids	Oral cavity and nasal mucosa	Yes	Yes	Moderate
13	Yes/No	Larynx and oral cavity	Vocal folds and arytenoids	-	No	Yes	Moderate
14	No/No	Larynx	Vocal folds	-	Yes	Yes	Moderate
15	No/No	Larynx	Vocal folds	Larynx	Yes	Yes	Moderate
16	No/No	Larynx, oral cavity and nasal mucosa	Vocal folds	-	Yes	Yes	Severe
17	Yes/No	Larynx	Vocal folds	Larynx	Yes	Yes	Moderate
18	Yes/Yes	Larynx and pharynx	Epiglottis	Larynx	No	Yes	Moderate
19	Yes/Yes	Larynx, pharynx, oral cavity and nasal mucosa	Vocal folds and epiglottis	Pharynx	No	Yes	Moderate
20	Yes/Yes	Larynx, oral cavity and nasal mucosa	Vocal folds	-	No	Yes	Moderate
21	Yes/No	Larynx, pharynx, oral cavity and nasal mucosa	Vocal folds and epiglottis	Larynx	Yes	Yes	Moderate

Table 2
Voice disorders in GRBASI[a] scale in 21 patients with residual paracoccidioidomycosis in upper airways and digestive tract. Evandro Chagas National Institute of Infectious Diseases, Rio de Janeiro, Brazil, 2010.

Degree of alteration	G		R		B		A		S		I	
	n	(%)	*n*	(%)	*n*	(%)	*n*	(%)	*n*	(%)	*n*	(%)
Slight	1	(4.7)	7	(33.3)	13	(61.9)	0	(0)	16	(76.2)	20	(95.2)
Moderate	18	(85.7)	13	(61.9)	7	(33.3)	0	(0)	5	(23.8)	1	(4.7)
Severe	2	(9.5)	1	(4.7)	1	(4.7)	0	(0)	0	(0)	0	(0)
Total	21	(100)	21	(100)	21	(100)	0	(0)	21	(100)	21	(100)

[a] GRBASI: G – grade of hoarseness; R – roughness; B – breathiness; A – asthenia; S – strain; I – instability.

Glottal to Noise Excitation Ratio (GNE), which is an acoustic measure to assess noise in a pulse train that is typically generated by the oscillation of the vocal folds, with normal values above 0.5 (dimensionless); Fundamental Frequency (F0), which is affected by gender and age, in which the rates observed in young male and female adults vary from 80 to 150 Hz and 150 to 250 Hz, respectively; similar to jitter and shimmer, normal voices have a certain amount of expected noise, related to the production of voice disorders, with normal values from 0 to 2.5 dB and vibratory irregularity, that can be defined as asymmetry in the vibration pattern of the vocal folds, usually associated with hoarseness, with normal values from 0 to 4.75 Hz.[3] The frequencies of the categorical variables were calculated. The normality of the numerical variables was tested through the Shapiro–Wilk test. Means and standard deviation were calculated for the numerical variables with normal distribution (age, time of evolution, irregularity and mean F0) and median and interquartile range (IIQ) for the numerical variables without normal distribution (jitter, shimmer, GNE and noise).

This project was approved by the Committee of Ethics in Research (CEP-INI) under protocol number 0055.0.009.000-09. All participants signed a free and informed consent form.

Results

All 21 patients studied aged between 36 and 66 years (average = 49.48 ± 9.1 years). Only two (9.5%) were women, seven (33.3%) reported use of alcohol, and 18 (85.7%) were smokers.

Amongst the comorbidities, chronic obstructive pulmonary disorder was reported by 10 (47.6%) patients, diabetes by one (4.8%) and HIV also by one (4.8%). The time of evolution of the lesions until diagnosis varied from 8 to 300 months (mean = 133.43 ± 68.77 months). The larynx was the main site of mucosae lesions (81%) in the active phase of the disease and the vocal folds were the most frequent lesion site at larynx (82.4%) (Table 1). All patients presented at least one method of diagnostic confirmation, with the histopathology being positive in 11 (52.4%), culture in 10 (47.6%) and direct examination in 6 (28.6%). The serologic test used was double immunodiffusion targeting the gp43 glycoprotein, being positive in 19 (90.5%). Concerning treatment, the most prescribed drug was itraconazole (52.4%), followed by sulfamethoxazole + trimethoprim (42.8%) and ketoconazole (4.7%). The study was conducted over one to 113 months (median = 27) after the end of drug treatment.

After drug treatment, five patients (23.8%) presented alteration in the larynx as a disease sequela and 11 (52.4%) complained of dysphonia (Chart 1). However, all patients presented voice disorders on the vocal auditory-perceptual analysis through the GRBASI scale (Table 2). The computerized acoustic analysis using the software VoxMetria showed that 11 patients (52.4%) presented alterations in jitter (median = 0.6%; IIQ = 0.20–1.29), 15 (71.4%) in shimmer (median = 7.12%; IIQ = 5.70–15.34), eight (38.1%) in F0 (mean = 136.42 Hz ± 62.11), four (19%) in GNE (median = 0.72%; IIQ = 0.54–0.80), 7 (33.3%) in the presence of noise (median = 1.39 dB; IIQ = 1.08–2.14) and 12 (57.1%) in the presence of vibratory irregularity (mean = 4.93 Hz ± 1.49).

Discussion

When performing voice evaluation of the 21 patients with residual paracoccidioidomycosis in the upper airways and digestive tract, we could observe that all of them remained with alteration of this function, even with absence of active lesions in the larynx and presence of little or no visible structural scar alteration in UADT.

Gender and age of the patients within our group were not different from other studies, showing prevalence of males, with average age around 40 years.[2,4,6,8,11,17,22] Studies indicate that the frequency of chronic cases is very low among women, and that is related to the inhibitory action of estrogen over the fungus transformation from mycelium, the infective form, to yeast, parasitic phase.[11]

As in other diseases, PCM patients present alcoholism and smoking as associated factors.[14] Smoking and alcoholism are frequent in PCM patients, being considered risk factors for the disease, once they interfere in the agent–host relationship.[5,8,17,22] Smoking jeopardizes clinical and functional recovery of the patients and alcoholism results on depression of the patient's nutritional condition, which compromises the immune system's defense due to its immunosuppressive effects.[15]

All of our patients have had mycological confirmation of PCM. Fungus isolation by culture and direct examination of biologic fluids or biopsy samples are considered the gold standard for PCM diagnosis. The serologic test was double immunodiffusion, which resulted positive in over 90% of the patients, and is useful for diagnosis, evaluation of the disease's complexity and clinical monitoring.[20] Other studies have also shown the high sensitivity (around 80%) of serologic tests for the detection of PCM.[1,20]

Large scale usage of itraconazole in our institute is justified because it is a reference center for infectious diseases and therefore we have easy access to such drug. In Brazil, usually, the combination sulfamethoxazole + trimethoprim has a good cost benefit ratio.[13]

The vocal alterations present in PCM are categorized as organic, i.e., dysphonias that are not dependent on voice use and that can be caused by several processes, as the alterations derived from the communication organs.[3] Dysphonia is a frequent symptom after cicatrization of the mucosal lesions in the UADT, occurring even in patients with no larynx lesions. The association of dysphonia with other anatomic sites suggests that the occurrence of compensatory mechanisms caused by the presence of lesions on the UADT leads to an alteration on voice quality.[18,19]

In our study, we observed that the larynx was the most affected site during the active phase, and the second site of anatomical sequelae of the disease. The scar lesions on the larynx caused by *Paracoccidioides brasiliensis* are described as extensive and causing functional restrictions in most cases.[11] The vocal folds' mucous membranes, when affected by the infection, become more rigid, which alters its function and may create an asymmetry in the vibration of the vocal folds.[18]

In the GRBASI scale analysis, the most observed voice disorder was roughness in a moderate degree, consistent with the most affected anatomic site, the vocal folds. Roughness was also the most observed disorder on the study by Weber et al.[24] who analyzed the voice quality of 15 patients with residual laryngeal PCM. This modification in the glottal source can lead to vibratory irregularities and reduction of the abduction capacity of the vocal folds, in addition to the reduction of glottal resistance, justifying the dysphonia.[3] Concerning the acoustic analysis, the parameter that showed the highest alteration was shimmer, pointing out a disturbance in the mucosal wave amplitude, substantiating the hoarseness, differing from the study by Weber et al.[24] which identified jitter as the mostly altered vocal parameter. The permanence of dysphonia in 52.4% and the voice quality alteration in all of the patients treated for PCM suggest that these alterations may start during the active phase of the disease and continue due to the scarring process of the lesions or to functional adjustment mechanisms developed during the voice limitation phase.[12] Therefore, the great frequency of this alteration in residual PCM suggests that the patients in such phase could benefit from a multidisciplinary treatment, offering them integral monitoring of the disease, including speech rehabilitation after the PCM is healed.

Conflict of interest

The authors declare no conflict of interest.

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