Vocal Tract Abnormalities in Patients with Two Genodermatoses: Lipoid Proteinosis and Neurofibromatosis Type 1

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ABSTRACT

Objectives: We aimed to investigate the abnormalities of the oral cavity, pharynx, and larynx of patients with two Genodermatoses: lipoid proteinosis (LP) and Neurofibromatosis type 1 (NF1)

Study Design: Cross-sectional study.

Patients and Methods: Twenty-five patients with genodermatoses were recruited from the Genodermatoses clinic, NRC, eighteen cases with NF1 and seven cases with LP, where precise cutaneous and oro-dental examinations were done for all patients followed by Naso-pharyngo-laryngeoscopic examination done in the phoniatric unit, faculty of medicine, Cairo university.

Results: Oral, pharyngeal, and laryngeal abnormalities were detected in twenty-three, twenty, and seventeen patients respectively. Malocclusion was the main oro-dental abnormality in patients with NF1, while in patients with LP lingual and labial abnormalities were the most common oro-dental abnormalities. Reddish and white-yellowish oropharyngeal swellings were the chief pharyngeal abnormality in patients with NF1 and LP respectively. Congested and thick hypertrophic laryngeal structures are the main laryngeal abnormalities in patients with NF1 and LP respectively. Vocal fold paralysis is not uncommon finding in patients with NF1.

Conclusion: Oral, pharyngeal, and laryngeal abnormalities are very common in NF1 and LP. Precise Oro-dental examination and Naso-pharyngo-laryngeoscopic evaluation are recommended for all patients with genodermatoses, especially NF1 and LP. Periodic follow-up by a multidisciplinary team is essential to detect any newly developed lesions or changes in current detected lesions.

Key Words: Cutaneous manifestations, laryngeal abnormalities, lipoid proteinosis, neurofibromatosis type1, Oral abnormalities, pharyngeal abnormalities.

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INTRODUCTION

Genodermatoses refers to a group of genetic disorders that affect the structure and/or function of the skin. They are characterized by an association between cutaneous and extracutaneous abnormalities commonly including vocal tract abnormalities which may develop at any age causing difficult breathing, feeding, or vocalization. Early identification, treatment, and proper follow-up of vocal tract abnormalities particularly those carrying a risk of malignant transformation is critical in management decisions.

The vocal tract is a container of air extending from the lips, traveling down through the pharyngeal cavity, and terminating at the laryngeal cavity. The oral cavity performs variable functions essential for life, including speech, respiration, mastication, taste, digestion, and swallowing.

The pharynx is divided into the nasopharynx, the oropharynx, and the hypopharynx or the laryngopharynx, it is considered as a junction to five tubular pathways: It communicates with the nasal cavity through the choanae, the middle ear through the pharyngotympanic tube, the oral cavity through the oropharyngeal isthmus, the larynx through the laryngeal inlet, and the esophagus through the mouth of the esophagus.

The larynx is a complex neuromuscular structure that extends from the tip of the epiglottis down to the inferior border of the cricoid cartilage i.e., the entrance of the
trachea, where it continues into the trachea. The larynx can be divided into the supraglottis, the glottis, and the subglottis.\textsuperscript{[9,10]}

Among the genodermatoses reported to affect the vocal tract are Neurofibromatosis type 1 (NF1) and Lipoid proteinosis (LP). NF1 is a fully penetrant autosomal dominant (AD) genodermatoses with up to 50% incidence of de novo mutations, it has a prevalence of 1/4000 and incidence that varies between 1/2558 and 1/3333 live births independent from ethnicity, race, and gender.\textsuperscript{[11]} NF1 is caused by mutations in the tumor suppressor gene neurofibromin located in the long arm of chromosome 17 (17q11.2) resulting in reduced levels of neurofibromin, a cytoplasmic protein involved in controlling the cell cycle and acting as a negative regulator of the cell growth.\textsuperscript{[12]}

NF1 affects multiple systems presenting mostly with cutaneous, and neurologic manifestations as major features that might lead to significant morbidity or mortality.\textsuperscript{[13]} It is characterized by marked variable expressivity, even within the same family, ranging from very mild to severe life-threatening phenotype making anticipatory guidance difficult.\textsuperscript{[13,14]}

LP is a rare multisystem genodermatoses with approximately 400 cases reported in the literature with no gender or ethnic preference.\textsuperscript{[15,16]} LP is inherited as an autosomal recessive (AR) disorder, occurring more frequently in countries with higher rates of consanguineous marriages.\textsuperscript{[17]} However, few studies proposed that LP may occur due to sporadic mutations.\textsuperscript{[18]}

LP is caused by loss of function mutations in the extracellular matrix protein 1 (ECM1) gene located on the long arm of chromosome 1 (1q21.2) involved in maintaining the structural integrity of the skin.\textsuperscript{[19,20]} Mutation in the ECM1 gene leads to infiltration of amorphous hyaline-like material in the skin and mucous membrane with underproduction of pro-collagen type I which impairs tissue healing resulting in atrophic scarring and overproduction of some structural proteins of the basement membrane causing nodular lesions.\textsuperscript{[19,17]}

The purpose of this study is to detect and describe the vocal tract anomalies within NF1 and LP patients to help with early detection and proper management.

**PATIENTS AND METHODS:**

This cross-sectional study included twenty-five patients (18 NF1 and 7 LP) recruited from the Genodermatoses clinic, National Research Centre, Egypt. All patients were presented with skin lesions with or without dysphonia. After obtaining informed written consent following thorough explanation according to the Helsinki Declaration of 1975, as revised in 1983, all included patients were evaluated thoroughly:

**Clinical evaluation.**

- Detailed medical history recording including three generations pedigree analyses, demographic data, history of present illness, and disease progression.

- Thorough clinical examination with emphasis on dermatological status, and neurologic affection.

- Imaging studies mainly brain neuroimaging, as well as ophthalmological and auditory evaluation studies, were recorded.

- Patients were diagnosed based on each disease’s cardinal diagnostic manifestations:

  In cases of NF1, patients were diagnosed based on the presence of at least two of the diagnostic clinical features stated by the National Institutes of Health (NIH) (Table 1).\textsuperscript{[12]}

  For LP patients, acneiform scarring and the hyperkeratotic verrucous lesions were described in detail.

- Complete Oro-dental examination was carried out next with a full description of any abnormalities affecting the lips, dentition, alveolus, buccal mucosa, floor of the mouth, tongue, soft palate, and/or hard palate.

- Laryngoscopic evaluation: All patients were examined using a flexible fiberoptic laryngoscope. The following structures were examined, and photo documented: nasopharynx, valleculae, epiglottis, vocal folds, pyriform fossae, arytenoids, inter-arytenoids region, anterior commissure, ventricular folds (VFs), aryepiglottic folds, and post-cricoid region. The items to be noticed were the mucous membrane, vocal folds configuration, vocal folds gross mobility (adduction and abduction), loss of tissue or atrophy, symmetry of the glottis, ventricular bands girth, and position on phonation and glottic closure.
Table 1: National Institutes of Health (NIH) diagnostic criteria of NF1

Six or more café-au-lait macules (CALMs)  
Axillary freckling or freckling in inguinal regions  
Two or more neurofibromas of any type or one or more plexiform neurofibromas  
Two or more Lisch nodules  
Bone lesion with sphenoid bone dysplasia or thickening of the cortex of the long bones with or without pseudoarthrosis  
An optic pathway glioma  
A first-degree relative with neurofibromatosis type 1 diagnosed by the above criteria

RESULTS:

I. Clinical results:

The twenty-five studied patients included 6 males and 19 females whose ages ranged from 15 months - 39 years. Pedigree analyses revealed positive consanguinity in 100% of LP pedigrees and in only 27.8% of NF1 also similarly affected family members were detected in 83% of NF1 and 57% of the LP pedigrees (Table 2). All included patients were diagnosed clinically based on their different characteristic cutaneous manifestations (Fig. 1) which were the main complaint in all patients (Table 3) coupled with dysphonia in all cases of LP patients and with a history of at-birth surgical excision of laryngeal neurofibroma in one NF1 patient who suffered from difficult breathing.

The different dermatological manifestations are presented in (Table 4) where café au lait macules (CALMs) were the predominant skin lesion in all NF1 patients (n=18), followed by freckles in 10/18 then neurofibromas in 7/18 cases, while the facial acneciform scaring and the hyperkeratotic verrucous lesions were the chief skin lesions presenting in all patients with LP (7/7) followed by moniliform blepharosis in 4/7 and waxy deposits in 2/7 cases.

II. Oral abnormalities were evident in 23 patients:

II.a. NF1 patients: Dental malocclusion was the most common oral abnormality in patients with NF1 affecting 15/18 patients from which 2 patients had also dental hypo-calciﬁcation. Fissured tongue with abnormal coating comes next affecting 6/18 patients one of them had a painless ulcer on the dorsum of the tongue and another had macroglossia. Two patients had fissured thick lips, one had a thick upper labial frenulum. Three patients had racial gingival and mucosal pigmentation and two had high arched palate. One patient had plexiform neurofibroma arising from the floor of the mouth giving the impression of a second tongue.

II.b. LP Patients: Stiff tongue with limited protrusion and thick fissured lips were the most common oral abnormality; presented in all patients (n=7) with thick lingual frenulum in 5 patients. Oral mucosa was firm in 5 patients with whitish deposits. Three patients had long uvula, two patients had broad uvulæ, and one patient had whitish depostions on the palate and oral surface of the uvula. The gingiva was the least affected area; showing hypertrophy in one patient.

III. Pharyngeal abnormalities were evident in 20 patients:

Orropharynx was the most affected region (n=20), hypopharynx (n=13), and nasopharynx (n=1). Both oral and pharyngeal detected abnormalities within our cohort are presented in (Table 6 and Fig. 2 & 3).

III.a. NF1 patients: multiple reddish nodular swellings were the main finding affecting mainly the oropharynx (n=13) while the nasopharynx showed no abnormalities. A relatively large pulsatile mass in the right side of the posterior oropharyngeal wall was detected in one NF1 patient.

III.1.b. LP patients: whitish yellowish deposits were the chief predominant pharyngeal finding affecting the oropharynx in all patients (n=7), hypopharynx (n=6), and nasopharynx (n=1). Whitish deposition in the inlet of the esophagus was noticed in one patient.

IV. Laryngeal abnormalities were evident in 17 patients:

Detected laryngeal abnormalities are documented in (Table 7 and Fig. 4).

IV.a. NF1 patients: mucosal congestion was the main abnormality found in the larynx affecting arytenoids (n=9), intra arytenoid region (n=3) and aryepiglottic folds (n=2). In four NF1 patients vocal fold abnormalities were detected in the form of; bilateral symmetrical swelling in the middle of the membranous part of the vocal folds (n=2), unilateral vocal fold paralysis after surgical excision of laryngeal plexiform neurofibroma (n=1) and unilateral vocal fold paralysis accidentally discovered during this study (n=1).

IV.b. LP patients: Hypertrophic thick mucosa was the predominant laryngeal finding detected in vocal folds, arytenoid, and intra-arytenoids (n=7), aryepiglottic fold
(n=5), and ventricular folds (n=2). Two patients had whitish deposition in the arytenoids and intra-arytenoid area. One patient had bilateral asymmetrical vocal fold whitish deposits.

Only one patient in this study shows no abnormalities in the oral cavity or pharynx nor larynx. The percentage of affection for the oral cavity, pharynx, and larynx among the patients in this study are summarized in (Tables 5 and 6).

Table 2: Basic Demographic data

<table>
<thead>
<tr>
<th>Patients, n (%)</th>
<th>NF1 (n=18)</th>
<th>LP (N=7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>2 (11.1)</td>
<td>4 (57.1)</td>
</tr>
<tr>
<td>Women</td>
<td>16 (88.9)</td>
<td>3 (42.9)</td>
</tr>
<tr>
<td>Consanguinity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>5 (27.8)</td>
<td>7 (100)</td>
</tr>
<tr>
<td>No</td>
<td>13 (72.2)</td>
<td>0</td>
</tr>
<tr>
<td>Similarly affected family members</td>
<td>15 (83.3)</td>
<td>4 (57.1)</td>
</tr>
<tr>
<td>Yes</td>
<td>3 (16.7)</td>
<td>3 (42.9)</td>
</tr>
</tbody>
</table>

Table 3: Main complain upon presentation

<table>
<thead>
<tr>
<th>Patients, n (%)</th>
<th>NF1 (n=18)</th>
<th>LP (N=7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin lesions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Since birth</td>
<td>13 (72.2)</td>
<td>4 (57.1)</td>
</tr>
<tr>
<td>Childhood</td>
<td>4 (22.2)</td>
<td>3 (42.9)</td>
</tr>
<tr>
<td>Adulthood</td>
<td>1 (5.6)</td>
<td>0</td>
</tr>
<tr>
<td>Dysphonia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Since birth</td>
<td>0</td>
<td>6 (85.8)</td>
</tr>
<tr>
<td>Childhood</td>
<td>0</td>
<td>1 (14.2)</td>
</tr>
<tr>
<td>Adulthood</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Table 4: The type of the skin lesions

<table>
<thead>
<tr>
<th>Patients, n (%)</th>
<th>NF1 (n=18)</th>
<th>LP (N=7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Café au lait Macules</td>
<td>18 (100)</td>
<td>0</td>
</tr>
<tr>
<td>Freckles</td>
<td>10 (55.6)</td>
<td>0</td>
</tr>
<tr>
<td>Neurofibromas</td>
<td>7 (38.9)</td>
<td>0</td>
</tr>
<tr>
<td>Acneiform scaring</td>
<td>0</td>
<td>7 (100)</td>
</tr>
<tr>
<td>hyperkeratotic lesions</td>
<td>0</td>
<td>7 (100)</td>
</tr>
<tr>
<td>Moniliform blepharosis</td>
<td>0</td>
<td>4 (57.1)</td>
</tr>
<tr>
<td>Waxy deposits</td>
<td>0</td>
<td>2 (28.6)</td>
</tr>
</tbody>
</table>

Table 5: Percentage of affection of the oral cavity, pharynx and the larynx

<table>
<thead>
<tr>
<th>Patients, n (%)</th>
<th>NF1 (n=18)</th>
<th>LP (N=7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral cavity</td>
<td>16 (88.9)</td>
<td>7 (100)</td>
</tr>
<tr>
<td>Pharynx</td>
<td>13 (72.2)</td>
<td>7 (100)</td>
</tr>
<tr>
<td>Larynx</td>
<td>10 (55.5)</td>
<td>7 (100)</td>
</tr>
</tbody>
</table>

Table 6: Oral and Pharyngeal abnormalities

<table>
<thead>
<tr>
<th>Patients, n (%)</th>
<th>NF1 (n=18)</th>
<th>LP (N=7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral abnormalities</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dental</td>
<td>5 (83.3)</td>
<td>5 (71.4)</td>
</tr>
<tr>
<td>Lingual</td>
<td>6 (33.3)</td>
<td>7 (100)</td>
</tr>
<tr>
<td>Labial</td>
<td>3 (16.7)</td>
<td>7 (100)</td>
</tr>
<tr>
<td>Mucosa</td>
<td>3 (16.7)</td>
<td>5 (71.4)</td>
</tr>
<tr>
<td>Gingival</td>
<td>3 (16.7)</td>
<td>1 (14.3)</td>
</tr>
<tr>
<td>Palatal</td>
<td>2 (11.1)</td>
<td>6 (85.7)</td>
</tr>
<tr>
<td>Pharyngeal abnormalities</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nasopharynx</td>
<td>0</td>
<td>1 (14.3)</td>
</tr>
<tr>
<td>Oropharynx</td>
<td>3 (72)</td>
<td>7 (100)</td>
</tr>
<tr>
<td>Hypopharynx</td>
<td>7 (38.9)</td>
<td>6 (85.7)</td>
</tr>
</tbody>
</table>

Table 7: Laryngeal abnormalities

<table>
<thead>
<tr>
<th>Patients, n (%)</th>
<th>NF1 (n=18)</th>
<th>LP (N=7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vocal folds</td>
<td>4 (22.2)</td>
<td>7 (100)</td>
</tr>
<tr>
<td>Arytenoids</td>
<td>9 (50)</td>
<td>7 (100)</td>
</tr>
<tr>
<td>Intra-arytenoid area</td>
<td>3 (16.7)</td>
<td>7 (100)</td>
</tr>
<tr>
<td>Aryepiglottic folds</td>
<td>2 (11.1)</td>
<td>5 (71.4)</td>
</tr>
<tr>
<td>Ventricular folds</td>
<td>0</td>
<td>2 (28.6)</td>
</tr>
</tbody>
</table>

DISCUSSION

Genodermatoses are a heterogeneous group of rare genetic disorders with dermatological diagnostic clues, that are characterized by association between cutaneous and extracutaneous abnormalities. Thorough phenotypic analyses of rare disorders could provide clues to diagnostic as well as managerial procedures. Studying abnormalities in the oral cavity, pharynx, and larynx among genodermatoses patients could be critical for accurate diagnosis and proper management of several of these disorders.\[21\]

The current study included 25 cases; eighteen NF1 patients with NF1 presented to the Genodermatoses Clinic, NRC complaining of Café au lait macules (CALMs) which is the earliest cutaneous manifestation of NF1.\[13\]

The other seven patients were presented with dysphonia coupled with skin lesions. Dysphonia is the first and most striking manifestation in LP patients presenting usually at birth or infancy followed by skin scarring.\[19,22,23\] Contrary to previous reports, one of our cohort of LP patients developed skin lesions since birth followed by dysphonia during childhood however, in their report, Srinivas et al., described a similar presentation in one of their six studied LP cases.\[24\]

Gingiva is considered part of the dermatological examination and accordingly, oral manifestations are common clinical features in genodermatoses, they are detected in up to 92% of NF1 patients following the detection of cutaneous manifestations.\[21\] Santoro et al. & Aşkın et al. reported the tongue as the primary site to be affected in patients with NF1.\[12,21\] Sixteen of our NF1 cohort had oral abnormalities however, lingual abnormalities were the second most common type following dental malocclusion. Mucosal and gingival pigmentation which are also considered among common clinical features in NF1 cases were detected in 3/18 of our NF1 patients.\[14,23\] Plexiform neurofibroma arising from the floor of the mouth giving the impression of a second tongue was detected in one NF1 patient. Plexiform neurofibroma is a very rare finding inside the oral cavity, apparently originating from the fifth cranial nerve and its branches.\[26,27,14\] A close follow-up is mandatory for this oral neurofibroma to detect any symptomatic growth or malignant transformation and accordingly provide proper intervention when needed.

Oral manifestations are also considered as predominant clinical feature in patients with LP. Thick-fissured lips and stiff tongue with limited protrusion were the chief predominant complaints as well as thick

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Fig. 3: Pharyngeal abnormalities: (A): Multiple reddish nodular swellings in patient with NF1. (B): Multiple yellowish white swellings in patient with LP.

Fig. 4: Laryngeal abnormalities: In patients with NF1 (A-b): A: Congested arytenoids and intra-arytenoid area and bilateral symmetrical vocal fold masses. B: Forward tilting of the left arytenoid. In patients with LP (C-D) C: Thick hypertrophic glottic and supraglottic region. D: Whitish deposition in the arytenoid and intra arytenoid area.
lingual frenulum noticed in five/seven of LP studied patients. In the current study, tongue and lingual frenulum abnormalities were notably high: 100% and 71.4% compared to 55.6% and 48.1%, respectively, reported in a systemic literature review of eighty-one LP patients in Middle East and North Africa. That review included only one Egyptian LP patient which may point to possible higher prevalence of those clinical features within the Egyptian population. This is an important clinical finding particularly for the phoneticians and dentists who may be the first physicians to encounter LP patients for early identification.

Laryngeal examination revealed multiple reddish nodular pharyngeal swellings affecting mainly the oropharynx in thirteen of the studied NF1 patients which are mostly lymphatic inflammatory reactions. An unclear link between neurofibromas and the inflammatory environment that is critical for its development and progression was suggested in some studies. In one of the studied NF1 patients, a relatively large pulsatile mass was detected on the right side of the posterior oro-pharyngeal wall for which a CT scan was requested. Both aberrant course of ICA and cervical ICA aneurysm could be a life-threatening explanation for this endoscopic finding.

Pharyngeal whitish-yellowish deposits were endoscopically noted in all LP patients involved in this study which are considered a constant finding in LP. Whitish deposition on the esophageal inlet, was detected in one of our studied LP patients. Multiple yellowish nodules throughout the esophagus were detected in an upper GIT endoscopy for a Brazilian patient. This was considered a very rare clinical finding in LP. In 2017, one LP patient was diagnosed with absent esophageal peristalsis which was explained by infiltration of hyaline materials in the muscular layer of the esophagus, although histological examination was not done to confirm this explanation. Upper GIT endoscopy may be of beneficial value in patients with LP particularly those complaining of dysphagia.

Congested laryngeal structure, mainly the arytenoids, was significantly noticed in our cohort of NF1 patients, and congested gastrointestinal tract mucosa was reported in NF1 patients in different studies. Also, two patients had bilateral symmetrical vocal fold swelling between the anterior third and posterior two third of the vocal folds. These bilateral vocal fold swellings are most probably vocal fold nodules (VFNs). VFNs are bilateral benign growths of variable size found at the midpart of the membranous vocal cords at the junction between the anterior and middle third of the vocal folds that develop secondary to repetitive mucosal injury due to laryngeal hyperfunction and vocal abuse. Neurofibroma arising from the glottis is a very rare finding and is usually unilateral.

In the current study, one patient had a history of laryngeal neurofibroma since birth that originated from the right aryepiglottic fold causing respiratory obstruction, necessitating surgical excision that was complicated by unilateral vocal fold paralysis. The aryepiglottic folds are considered the most common laryngeal site to be affected by neurofibromas followed by the arytenoids due to the rich nerve supply by the superior laryngeal nerve and its anastomosis with recurrent laryngeal nerve. Unilateral vocal fold paralysis was also detected in another NF1 patient in our cohort. Vocal fold paralysis due to neurofibroma -either in the larynx or elsewhere- was found to be a more common fibro-endoscopic finding than laryngeal neurofibromas in NF1 patients.

Among our studied LP patients, thick hypertrophic laryngeal structure was the main detected laryngoscopical finding. Arytenoids, intra-arytenoid area, and the vocal folds were the main affected regions. Yukkaldiran et al. considered thickening, and hypertrophy of laryngeal structure a constant clinical finding in LP patients. Two patients had whitish depositions on the arytenoids and intra-arytenoid area and one patient had similar depositions on vocal folds. Whitish deposition in the larynx of LP patients was reported in different studies before.

**CONCLUSION**

In conclusion, phenotypic variability and several rare findings were detected among studied patients as well as common abnormalities in the oral cavity, pharynx, or larynx in patients with Genodermatoses. Precise Oro-dental examination and Flexible Naso-pharyngo-laryngoscopic evaluation are recommended for all genodermatoses patients to reach an early precise diagnosis. Periodic follow-up by a multidisciplinary team is essential to detect any newly developed lesions or changes in current detected lesions for early prevention and proper management.

**CONFLICT OF INTEREST**

There are no conflicts of interest.

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