Laryngeal Manifestations of Neurofibromatosis

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No sponsorships or competing interests have been disclosed for this article.

Abstract

Objectives. To describe the range of findings in patients with neurofibromatosis (NF) presenting to a laryngology clinic and to analyze the etiologic factors of vocal fold dysfunction in this cohort.

Study Design. Case series with chart review.

Setting. Tertiary laryngology practice.

Subjects and Methods. All cases of NF presenting to an academic laryngology practice were retrospectively reviewed (August 2005 to May 2014), with a total of 34 cases. Demographic data, symptoms, and endoscopic examination findings were reviewed. Etiologic factors of laryngeal complaints were analyzed with reference to NF-associated pathologies and surgical history.

Results. Thirty-four patients with NF-1 or NF-2 were evaluated, and 28 of these patients (6 NF-1 and 22 NF-2) had laryngeal pathology. The most common presenting symptoms were vocal weakness (n = 21), dysphagia (n = 5), and globus (n = 4). Three patients had NF-related vocal fold masses on examination, including 2 neurofibromas and 1 schwannoma. Unilateral vocal cord paralysis was seen in 17 patients; bilateral paralysis was observed in 5 patients. Of patients with unilateral or bilateral paralysis, 20 had intracranial masses (vestibular schwannoma, meningioma, or skull base tumors), and 16 had previously undergone surgery for these lesions. Of the patients with NF-associated intracranial tumors, 87.0% presented with vocal cord paralysis, whereas only 40.0% of those without intracranial masses had paralysis (P = .0560). Seven patients underwent medialization procedures.

Conclusion. Neurofibromatosis patients may present to laryngology clinic with primary laryngeal tumors or, more commonly, unilateral or bilateral paralysis. Otolaryngologists should be keenly aware of vocal fold paralysis caused by the NF-associated tumors, with particular attention to bilateral paralysis in NF-2.

Keywords
neurofibromatosis, neurofibroma, NF-1, NF-2, vocal cord paralysis

Received October 5, 2015; revised November 25, 2015; accepted December 17, 2015.

Neurofibromatosis (NF) is an autosomal dominant neurocutaneous syndrome characterized by aberrant growth of tumors (neurofibromas, neuromas, and schwannomas) in the skin and central nervous system. NF-1 and NF-2 are phakomatoses that are relevant to otolaryngologists. NF-1 is characterized by cutaneous neurofibromas, café au lait spots, ocular hamartomas, and skeletal abnormalities. It presents in the head and neck in 20% of cases.1 NF-2 is a less common disorder in which patients develop gliomas, meningiomas, ependymomas, and bilateral vestibular schwannomas, with fewer cutaneous findings.2,3 Primary tumors of the larynx associated with NF are exceedingly rare and have been characterized in several small case series.4-13 As a whole, however, laryngeal manifestations of NF have not been characterized, including vocal fold paralysis. Here, we aim to characterize the range of symptoms, medical histories, and examination findings in patients with NF presenting to an academic laryngology clinic and to analyze the etiologic factors of vocal fold dysfunction in this cohort.

Methods

Approval of this study was obtained through the Massachusetts Eye and Ear Infirmary’s Institutional Review Board. All patients with the recorded diagnosis of NF-1 or NF-2 were identified in our laryngology clinic’s medical record via a Boolean search of the following terms:

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This article was presented at the 2015 AAO-HNSF Annual Meeting & OTO EXPO; September 27-30, 2015; Dallas, Texas.

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“neurofibroma,” “neurofibromatosis,” “NF,” “NF-1,” “NF-2.” Only patients who had documented videolaryngoscopic examinations were included. Dates were limited from August 2005 through May 2014. All patients were evaluated by 1 of 2 fellowship-trained laryngologists (P.C.S., R.A.F.). Separate evaluations by speech and language pathologists were included, but this was not required for inclusion in the study.

Each patient’s full demographic, medical, and surgical history was reviewed. Data relevant to the patient’s laryngologic history were recorded, including presenting complaint and presence of neck, thoracic, spinal, and intracranial tumors, as well as interventions related to these conditions. Videolaryngoscopy for each patient was reviewed for laryngeal pathology, including visible lesions or weakness. The number and timing of laryngeal interventions were noted. Comorbidities were recorded, including diabetes, hypothyroidism, psychiatric conditions, neurologic disorders, and cardiovascular disease.

Data were analyzed with Microsoft Excel (Microsoft Corp, Redmond, Washington) and JMP11 statistical software (Cary, North Carolina). Standard descriptive statistics are reported. Unpaired Student’s t tests and Fisher’s exact tests were used for relevant variables to analyze statistical trends. Level of significance was set at $P < .05$.

**Results**

From 2005 to 2014, 34 patients with NF-1 or NF-2 presented to our academic laryngology clinic for a comprehensive voice examination. Twenty-eight of these patients had documented pathology on videolaryngoscopy. Of these, 22 patients presented with NF-2 and a 6 with NF-1. The average age was 39.0 years (range, 18.4-63.8), with 14 men and 14 women. All patients had a preexisting diagnosis of NF-1 or NF-2, with no cases being diagnosed according to endoscopic examination. Table 1 lists the basic demographics and comorbidities, including diabetes, hypothyroidism, psychiatric conditions (bipolar, depression, schizophrenia), and neurologic conditions (epilepsy, Parkinson’s, multiple sclerosis, sleep disturbance, chronic headache).

Table 2 documents the presenting laryngeal symptoms of patients with NF. Notably, hoarseness was the predominant chief complaint in both groups (NF-1, 83.3%; NF-2, 72.7%) and was seen in 75.0% of patients overall. Also reported were dysphagia and globus (17.9% and 14.3%, respectively). Differences in presenting symptoms between NF-1 and NF-2 patients did not reach a level of statistical significance (hoarseness, $P = 1.00$; dysphagia, $P = .553$; globus, $P = 1.00$). Three patients were asymptomatic at presentation but had previously had hoarseness as documented by their referring physicians; all of these patients had demonstrable findings on laryngoscopy.

Table 3 shows the preoperative tumor burden of the patients presenting for laryngoscopic evaluation, with a focus on masses known to be associated with vocal cord dysfunction. In the NF-1 group, 4 of 6 patients had previous tumors (2 cervical, 1 thoracic, 1 intracranial), all of which were pathologically shown to be neurofibroma after excision. In the NF-2 group, 100.0% of patients were found to have previous history of intracranial masses, consistent with the natural history of this disease. The majority of these patients (81.8%) had undergone previous surgery. Spinal masses were also common in the NF-2 group (86.4%). Patients with NF-associated intracranial tumors presented with vocal cord paralysis in 87.0% of cases, whereas 40.0% of patients with exclusively extracranial manifestations presented with vocal cord paralysis; this difference was not significant ($P = .0560$). Of these patients, most (80.0%) had onset of paralysis after surgical therapy for their intracranial or skull base masses. The presence of other associated tumors (thoracic, cervical, spinal) and their removal were not associated with vocal cord paralysis.

Table 4 shows these laryngoscopic findings in detail. There were 3 NF-related tumors of the larynx: 2 neurofibromas in the NF-1 group and 1 schwannoma in the NF-2 group. Only 2 patients underwent resection (both with neurofibromas of the vocal fold). Unilateral cord paralysis was the most commonly observed pathology on scope examination. In the NF-2 group, 63.6% of patients had unilateral paralysis, and 22.7% had bilateral paralysis. Notably, all 5 patients with bilateral vocal fold paralysis had bilateral

**Table 1. Basic Demographic Data.**

<table>
<thead>
<tr>
<th>Demographic</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total patients</td>
<td>28</td>
</tr>
<tr>
<td>Men</td>
<td>14 (50.0)</td>
</tr>
<tr>
<td>Women</td>
<td>14 (50.0)</td>
</tr>
<tr>
<td>Age, y</td>
<td>39.0* (18.4-63.8)</td>
</tr>
<tr>
<td>Comorbidities</td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>1 (3.6)</td>
</tr>
<tr>
<td>Hypothyroid</td>
<td>6 (21.4)</td>
</tr>
<tr>
<td>Psychiatric conditions</td>
<td>9 (32.1)</td>
</tr>
<tr>
<td>Neurologic conditions</td>
<td>9 (32.1)</td>
</tr>
<tr>
<td>Time of follow-up, mo</td>
<td>42.7* (0.0-114.2)</td>
</tr>
</tbody>
</table>

*Average (range).

**Table 2. Chief Complaints upon Presentation.**

<table>
<thead>
<tr>
<th>Patients, n (%)</th>
<th>NF-1 (n = 6)</th>
<th>NF-2 (n = 22)</th>
<th>Total (N = 28)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hoarseness</td>
<td>5 (83.3)</td>
<td>16 (72.7)</td>
<td>21 (75.0)</td>
</tr>
<tr>
<td>Globus</td>
<td>1 (16.7)</td>
<td>3 (13.6)</td>
<td>4 (14.3)</td>
</tr>
<tr>
<td>Dysphagia</td>
<td>0 (0.0)</td>
<td>5 (22.7)</td>
<td>5 (17.9)</td>
</tr>
<tr>
<td>Cough</td>
<td>0 (0.0)</td>
<td>1 (4.5)</td>
<td>1 (3.6)</td>
</tr>
<tr>
<td>Shortness of breath</td>
<td>1 (16.7)</td>
<td>1 (4.5)</td>
<td>2 (7.1)</td>
</tr>
<tr>
<td>Throat clearing</td>
<td>0 (0.0)</td>
<td>2 (9.1)</td>
<td>2 (7.1)</td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>0 (0.0)</td>
<td>3 (13.6)</td>
<td>3 (10.7)</td>
</tr>
</tbody>
</table>

Abbreviation: NF, neurofibromatosis.
high incidence of vocal cord weakness in NF patients, with 18% showing bilateral paralysis. These results indicate a majority of patients had unilateral vocal fold paralysis, with another reporting hoarseness as the chief complaint. Approximately 61% than breathing or swallowing, with 75% of patients reporting major chief complaints were related to voice, rather than more durable options, such as transcervical implant, particularly in patients with known bilateral paralysis or bilateral intracranial or skull base masses.

Asymptomatic patients with NF may have subclinical voice deficits. A recent study of NF-1 without a history of voice issues, laryngeal surgery, or vocal weakness reported that these patients can have narrower vocal range and reduced voice intensity when compared with controls. While the cause of this may be related to vocal fold lesions, such lesions are quite rare. Weakness from skull base masses (especially those affecting the jugular foramen), paraspinal nerve root tumors altering respiratory muscle innervation, and alterations in neural architecture are also likely to contribute to vocal dysfunction. For example, diffusion tensor imaging shows quantifiable radiographic differences in NF-1 patients relative to controls that likely reflect basic and diffuse alterations in cerebral microstructure. With high-resolution computed tomography and magnetic resonance imaging, imaging of peripheral nerve lesions continues to improve and may ultimately reveal the etiology of vocal fold weakness, which is currently considered idiopathic.

Direct involvement of visible mass lesions in NF is rare but well described in NF-1 and NF-2. Of the neurogenic tumors that affect the larynx, schwannomas are thought to be more common than neurofibromas. Neurofibromas are rare in NF-2, with only 1 case reported in the literature. These benign nerve sheath tumors can present with sleep apnea, stridor, airway obstruction, and voice complaints and are seen more often in children. A 2014 review identified 62 worldwide cases of pediatric laryngeal NF. These patients often presented with stridor (44%), dysphagia (15%), and dysphonia (12%). Lesions most often occurred in the supraglottis (specifically the aryepiglottic fold), which is rich with nerve plexuses, and they were very rarely found incidentally. Rarely, neurofibromas can become malignant. Approximately 30 cases exist in the adult literature.

Primary lesions of the larynx associated with NF are now commonly treated in an endoscopic, rather than open, manner, with the goal of preserving laryngeal function. The plexiform subtype neurofibromas arise from multiple nerve bundles and are typically larger and more infiltrative; these are often more difficult to excise. In our series, neither of the 2 neurofibromas was plexiform in nature, and both were excised endoscopically. There were 4 vocal fold lesions (granuloma, nodules, cyst) that were not thought to be primarily related to voice complaints. Although overall incidence of vocal cord weakness in NF patients cannot be drawn from these data, this study nonetheless suggests that otolaryngologists should have a high suspicion of vocal fold weakness in patients with NF. Furthermore, we conclude that bilateral vocal fold paralysis, which is rare in our overall clinic population, is a concern in NF-2 patients, particularly those with compressive skull base or cerebellopontine angle masses. Medialization procedures should thus be approached with caution in NF-2 patients, as growth of intracranial masses can lead to vocal fold paralysis and airway narrowing over time. We therefore recommend the use of temporary injection laryngoplasty rather than more durable options, such as transcervical implant, particularly in patients with known bilateral paralysis or bilateral intracranial or skull base masses.
the underlying pathogenesis of NF but rather were secondary lesions in the setting of cord paralysis.

There are several limitations to this study. Foremost, we have compiled these cases retrospectively, which makes ascertaining the overall incidence of laryngeal weakness and voice complaints in patients with NF quite difficult. By definition, patients presenting to our laryngology clinic have an airway, swallowing, or voice complaint. Nevertheless, characterizing this population is essential, and several authors recommend laryngologic evaluation for any NF patient with airway, voice, or swallowing symptoms. For this reason, we have chosen to include both NF-1 and NF-2 patients in this study, despite the relative predominance of NF-2 patients. Another limitation is that laryngoscopic findings are subject to interpretation by physicians, rather than being purely objective in nature. Finally, because NF is rare, this study has a relatively small sample size.

Conclusions

NF patients may present to laryngology clinic with various complaints and pathologies. Whereas primary vocal fold lesions associated with NF should be considered, vocal fold paralysis is more common and is associated with previous surgery and intracranial tumors. Bilateral paralysis in NF-2 is a particular concern, and these patients should be managed conservatively with regard to medialization procedures. Otolaryngologists must be keenly aware of vocal fold paralysis caused by the NF-associated tumors and their management, and direct visualization of the larynx should be performed in all NF patients with voice, swallowing, or airway complaints.

Acknowledgments

We thank William Goedicke of the Massachusetts Eye and Ear Infirmary for his thoughtful approach to database management.

Author Contributions

Matthew R. Naunheim, design, data collection, data analysis, drafting, editing, final approval, accountability for all aspects of the work; Scott R. Plotkin, conception of work, data collection, editing, final approval, accountability for all aspects of the work; Ramon A. Franco, conception of work, data collection, editing, final approval, accountability for all aspects of the work; Phillip C. Song, conception of work, design of study, data analysis, drafting, editing, final approval, accountability for all aspects of the work.

Disclosures

Competing interests: None.

Sponsorships: None.

Funding source: None.

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