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Vocal Cord Paralysis as Primary and Secondary Results of Malignancy. A Prospective Descriptive Study

Roi Knudsen, MD; Maria Q. Gaunsbaek, MD, PhD; Joyce H. Schultz, MD; Anna Christine Nilsson, MD; Jonna S. Madsen, MD, PhD; Nasrin Asgari, MD, PhD

Objective: Vocal cord paralysis (VCP) may be caused by a primary malignancy and associated immune cross-reactivity. We aimed to illuminate underlying causes of VCP and to assess if onconeural antibodies occur in association to VCP as an early predictor of cancer.

Methods: A prospective study was performed in patients with newly diagnosed VCP from 2014 to 2016. All patients underwent fiberoptic laryngoscopy, ultrasound of the neck and computed tomography (CT) of the neck and thorax. Patients with idiopathic VCP underwent neurological examination, positron emission tomography/CT, and serum analysis for onconeural antibodies. All patients were offered a one-year clinical follow-up.

Results: In total 53 patients fulfilled the inclusion criteria. Left VCP occurred in 37 (70%), right in 15 (28%), and bilateral in one patient (2%). The cause of VCP was cancer in 27 (51%) patients, of those 15 (56%) had VCP as the primary symptom, including all cases with laryngeal and esophageal cancer. Median time interval between VCP and cancer was 7 days (range 1–30). In 12 (23%) VCP was a secondary symptom. Lung cancer was the most common etiology, 14 of 27 (52%), 12 patients (86%) with non-small cell lung cancer. Idiopathic VCP was diagnosed in 18 (34%) patients, of those nine patients had a neurological examination and were screened for well-known onconeural antibodies, which were not detected. Reactions against Purkinje cell nuclei were seen in three patients, none showed symptoms or signs of cancer at follow-up.

Conclusions: The causes of VCP were described. VCP was frequently the primary symptom, and also occurred as a secondary symptom of cancer. Exclusion of malignancy is important in patients with VCP.

Key Words: Vocal cord paralysis, cancer, immunology, paraneoplastic neurological disorders.

Level of Evidence: 1b

INTRODUCTION

The recurrent laryngeal nerves innervate all laryngeal muscles with the exception of the cricothyroid muscle. On the right side the recurrent laryngeal nerve arises from the vagus nerve and loops behind the right subclavian artery and ascends to the larynx. On the left side the recurrent laryngeal nerve arises from the vagus nerve in the superior mediastinum, where it loops around the aortic arch before returning to the larynx. Any damage to the vagus nerve or the recurrent laryngeal nerve (RLN) may cause vocal cord paralysis (VCP). The symptoms, which vary in severity, may appear as voice alteration, aspiration, and respiratory problems. Because of its longer course in the mediastinum, the left RLN is more commonly affected than the right and more commonly affected than the vagus nerve itself. Bilateral VCP is less common. VCP may be due to various causes such as neoplastic, traumatic (most commonly surgical) and inflammatory entities, as well as occur as idiopathic VCP.1

The paraneoplastic neurological syndromes (PNS) are regarded as autoimmune reactions against the malignant tissues.2–4 An underlying tumor may produce antigens, which are normally expressed in the nervous system.3 Antibodies, known as onconeural antibodies, are produced against these antigens, cross-reacting with components of the nervous system.3,5 The detection of onconeural autoantibodies aids the diagnosis of PNS.5 PNS can be of great clinical significance, as they may appear prior to symptoms of a cancer,2,6 but these conditions are rare and often difficult to diagnose.

Patients with VCP are diagnosed by flexible fiberoptic laryngoscopy or videostroboscopy. These examinations are supplemented with an ultrasound scan of the neck and a computed tomography (CT) scan of the neck and thorax. If no pathology is found a magnetic resonance imaging (MRI)
or a (18) F-fluorodeoxyglucose positron emission tomography / computed tomography (PET/CT) scanning can be performed.\(^7\) If no underlying pathology can be identified, the patient is categorized with idiopathic VCP.

The purpose of the current study was to evaluate the distribution of underlying etiology to VCP and to assess, if VCP may be caused by a primary malignancy.

**MATERIAL AND METHODS**

**Patients**

A fast-track program for patients with suspicion of head and neck cancer (HNC) was introduced in Denmark in 2007.\(^8\) The program was based on so called "package solutions" including pre-booked consultations for outpatient evaluation, imaging, and diagnostic surgical procedures.\(^8\) Between July 2014 and May 2016, 53 consecutive adult patients (>18 years of age) with newly diagnosed VCP were referred to the Department of Otolaryngology, Vejle Hospital from practicing ear nose and throat (ENT) specialists or from other departments. The diagnosis of VCP was based on flexible fiberoptic laryngoscopy with the objective finding of an immobile vocal cord. The patients then entered into the HNC fast-track program consisting of thorough (ENT) examination including flexible fiberoptic laryngoscopy and ultrasound of the neck as well as diagnostic CT scan of the neck and thorax. Patients with no obvious cause of VCP were offered a PET/CT scan. By the HNC fast-track program patients were diagnosed within 14 days. The etiologies were divided into 1) Cancer, 2) Iatrogenic, 3) Idiopathic, or 4) Other. A total of 18 patients were diagnosed with idiopathic VCP, and after informed consent nine of these accepted to participate in a clinical neurological examination and blood testing for PNS-associated antibodies at the Department of Neurology, Vejle Hospital (Fig. 1). The patients were all offered a one-year clinical phoniatric follow-up and rehabilitation.

**Determination of Other Autoantibodies/ Laboratory Tests**

**Indirect immunofluorescence test**

Screening for IgA, IgG, and IgM antibodies associated with paraneoplastic neurologic syndromes was done by indirect immunofluorescence test (IFT) using monkey cerebellum sections as substrate (Euroimmun Medizinische Labordiagnostika AG, Lübeck, Germany). Sera were screened at a 1:10 and a 1:100 dilution and assayed according to the protocol provided by the manufacturer.

**Immunoblotting**

Sera were tested for antibodies (IgG) by immunoblotting using the Neuronal Antigens Profile coated with 12 recombinant antigens (ampiphysin, CRMP5 [CV2], PNMA2 [Ma2/Ta], Ri [Nova1], CDR2/Yo, HuD, recoverin, SOX1, titin, Zic4, GAD65, and Tr [DNER]) from Euroimmun Medizinische Labordiagnostika AG (Lübeck, Germany). Sera were diluted 1:10 and assayed according to the protocol provided by the manufacturer.

**Standard Protocol Approvals, Registrations, and Patient Consents**

The patients provided oral and written informed consent before participating in the study. As the study was based on quality assurance, permission to obtain patient information was given from the Department of Otolaryngology, Vejle Hospital. The part of the project regarding screening for PNS associated antibodies was approved by The Committee on Biomedical Research Ethics for the Region of Southern Denmark (Project-ID: S-20130026). The project was reported to the Data Inspectorate and followed the regulations of the Personal Data Protection.
RESULTS

Demographic Characteristics

In total 53 patients with newly diagnosed VCP were included in the study with a median time of onset of hoarseness/alteration in voice until the diagnosis of VCP was made of 28 days (range 0–1095) with a female:male ratio of 1:1.5. Of these, 37 (70%) patients presented with left VCP, 15 (28%) with right VCP, and one (2%) with bilateral VCP. The mean age at the time of diagnosis was 66 years (range 26–87 years). The median follow-up time was 163 days (range 6–365) (Table I).

Causes of VCP

Of the 53 participants, iatrogenic injuries as a result of mediastinoscopy (1), general anesthesia with intubation (1) or cervical spondylitis surgery (1) occurred in three (6%) patients. In addition, five (9%) patients had other diseases, which explained the VCP; aortic arch aneurysm, amyotrophic lateral sclerosis, rheumatoid arthritis, benign neoplasm of the thyroid gland, and eosinophilic granulomatosis with polyangiitis (Churg-Strauss Syndrome). In 18 (34%) of patients there was no obvious cause of VCP, leading to a diagnosis of idiopathic VCP. In 27 (51%) of the cases, VCP was due to malignancy.

During the follow-up period, 10 (56%) patients with idiopathic VCP had spontaneous recovery. The other eight patients had no change in vocal cord mobility. The patient with VCP after mediastinoscopy also had spontaneous recovery and two of the patients with lung cancer had recovery after chemotherapy.

Presence of VCP in Association to Neoplasms

VCP as the primary symptom of malignancy

After clinical examination and imaging, 15 of 27 (56%) patients with VCP as the primary symptom were diagnosed with malignancies. Lung cancer was detected in five patients, one with SCLC and four with non-small cell lung cancer (NSCLC). Interestingly, all cases with laryngeal cancer (four patients) and esophageal carcinoma, (three patients) had VCP as primary symptom. In addition two patients had a pharyngeal cancer and disseminated colon cancer was detected in one patient (Fig. 2). The median time interval between diagnosis of VCP and diagnosis of cancer in these 15 patients was 7 days (range 1–30).

VCP as a secondary symptom of malignancy

Of the 53 patients, 12 presented with VCP as the secondary symptom of malignancy. They had an existing cancer diagnosis with mediastinal metastases, attributed to VCP: nine patients had lung cancer (one with SCLC and eight with NSCLC), one patient disseminated breast cancer, another pharyngeal cancer, and one patient had a marginal zone lymphoma.

The total distribution of cancer in the study group is illustrated in Figure 2.

Screening for Onconeural Antibodies

A total of nine patients with idiopathic VCP had a full neurological examination with serum testing for onconeural antibodies. They had normal ENT examination and diagnostic CT scan of the neck and thorax, as well as PET/CT

<table>
<thead>
<tr>
<th>Cause Characterization</th>
<th>Cancer Primary symptom</th>
<th>Secondary symptom</th>
<th>Idiopathic</th>
<th>Iatrogenic</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects, n (%)</td>
<td>15 (28%)</td>
<td>12 (23%)</td>
<td>18 (34%)</td>
<td>3 (6%)</td>
<td>5 (9%)</td>
</tr>
<tr>
<td>Gender, (F:M)</td>
<td>4:11</td>
<td>4:8 (1:2)</td>
<td>10:8 (5:4)</td>
<td>1:2</td>
<td>2:3</td>
</tr>
<tr>
<td>Age (median [range])</td>
<td>66 (48–83)</td>
<td>67 (55–87)</td>
<td>65 (26–82)</td>
<td>66 (45–82)</td>
<td>79 (45–87)</td>
</tr>
<tr>
<td>Side of VCP</td>
<td>L-11, R-3, Bilat-1</td>
<td>L-9, R-3</td>
<td>L-12, R-6</td>
<td>L-2, R-1</td>
<td>L-3, R-2</td>
</tr>
<tr>
<td>Median interval (days)</td>
<td>between onset of symptom and diagnosis of VCP</td>
<td>21 (0–365)</td>
<td>21 (0–547)</td>
<td>28 (10–365)</td>
<td>75 (0–93)</td>
</tr>
<tr>
<td>Median interval (days)</td>
<td>between diagnosis of VCP and diagnosis of cancer</td>
<td>7 (1–30)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

VCP = vocal cord paralysis.
scan without abnormalities. Except for the presence of VCP, the nine patients with idiopathic VCP did not show apparent neurological symptoms or clinical signs. No onconeural antibodies were detected. In three patients, weak neural specific reactions on IFT were seen at a dilution 1:10, with a positive staining of the nuclei in Purkinje cells and a rim-like staining of nuclei in cells of the cerebellar molecular layer was seen in all three patients (Fig. 3). All patients were negative on immunoblotting. Two out of the three patients had full recovery of vocal cord function at follow-up, but in one VCP persisted. None of the patients were diagnosed with cancer during follow-up.

DISCUSSION

In the present study the distribution of underlying etiology to VCP was evaluated prospectively. The most frequent cause of VCP was cancer, constituting 27 patients (51%). Lung cancer was the most common neoplastic etiology (52%) dominated by NSCLC (86%). Remarkably, VCP was the primary symptom of cancer in more than half of the cases with a median time interval between diagnosis of VCP and diagnosis of cancer 7 days (range 1–30), including all cases with laryngeal cancer and with esophageal carcinoma. Idiopathic VCP was the second most common cause, accounting for 18 (34%) of the cases. These findings indicate that VCP can be the first symptom of cancer or occur in association with a previously diagnosed cancer.

Several studies have previously reported the distributions of underlying etiology of VCP.1,9–11 In a retrospective study of 291 patients the cause were reported to be surgical in 40.2%, neoplastic in 29.9%, and idiopathic in 10.7%.1 Thyroidectomy represented the most common surgical trauma and lung cancer was the most common neoplastic etiology.1 Another retrospective study, including 100 patients with VCP collected over two decades, showed almost the same frequency of cancer as the present study, with 50% of the cases due to malignancy, mainly of the lung.9 In two retrospective Danish studies10,11 one reported that 34% of the cases were due to cancer, mainly lung cancer and idiopathic VCP 24%. In the other the most frequent cause of VCP was trauma (39%), of which 35% were due to iatrogenic causes, in particular thyroid surgery, whereas idiopathic VCP constituted 27%, and malignancy 22%. These numbers probably reflect the patient uptake characteristics and degree of specialization of the particular ENT department, as the latter study was carried out in a hospital with highly specialized function as thyroid and cancer surgery including collaboration with departments of thoracic and parenchymal surgery, an obvious cause of the high frequency of iatrogenic etiologies. Furthermore, the variation between studies may be the result of evolution of diagnostic methods or differences in the definition of VCP and differences in the completeness of case ascertainment. In the present prospective study with a one-year follow-up, a high incidence of cancer (51%) was observed as the cause of VCP and the primary symptom of malignancy in a considerable proportion of patients (28%). Consequently, an early illumination of the underlying cause of VCP may be important for the demonstration of malignancy.

PNS is a group of rare autoimmune diseases.5 In general, the detection of neural-reactive autoantibodies aids the diagnosis of organ-specific autoimmune neurologic disorders.5 VCP as the presenting sign of PNS has been described in a case report.12 The patient presented with bilateral VCP and tested positive for anti-Hu and was subsequently diagnosed with SCLC. In the present study no onconeural antibodies were detected in a subgroup of patients with idiopathic VCP. In three patients, neural specific reactions against the nuclei of Purkinje cells and of the cells in the molecular layer was observed by IPT, but immunoblotting was negative, and the clinical significance is uncertain. To our knowledge, this reaction pattern has not previously been described in relation to VCP. None of the patients had any clinical signs or symptoms compatible with a PNS or cancer at the final follow-up. Further research is needed to determine if PNS screening is beneficial in patients with VCP.

A notable strength of this study was the prospective design and the involvement of a neurologist in the evaluation of a possible PNS cases in patients with idiopathic VCP. A further strength was the performance of all antibody tests in a blinded fashion. A possible limitation of our study could derive from the inclusion of patients with high risk for cancer, especially those with lung cancer suspicion, as our hospital has an ongoing fast track program for lung cancer in cooperation with departments of pulmonology and oncology.

CONCLUSION

The study shows the importance of excluding malignancy in patients with VCP, mainly lung cancer, which accounted for more than half of the cases in this study. VCP was observed as a first and secondary symptom of cancer. Ability to detect an underlying cancer at an early
stage may lead to better treatment options and prognosis. Further studies are needed for clarification.

AUTHOR CONTRIBUTIONS

RK: Study design, acquisition of data, interpretation of results and writing of manuscript.

MQG: Acquisition of data, statistical analysis, interpretation of results and writing of manuscript.

JHS: Study design, acquisition of data, interpretation of results, revising manuscript and approving final version.

ACN: Determination of antibodies, revising manuscript and approving final version.

JSM: Interpretation of results, revising manuscript and approving final version.

NA: Study design, acquisition of data, interpretation of results, revising manuscript and approving final version.

BIBLIOGRAPHY