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MAIN ARTICLE

Laryngeal sensory neuropathy in patients with diabetes mellitus

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Abstract

Objective: To determine the prevalence of laryngeal sensory neuropathy in patients with type 2 diabetes mellitus.

Methods: A cross-sectional study was performed, comprising 50 patients diagnosed with type 2 diabetes mellitus and 36 healthy controls. In the diabetic group, glycaemic control level, disease duration and presence of neuropathy were assessed. Participants were diagnosed with laryngeal sensory neuropathy if they had a cough, globus pharyngeus or throat clearing lasting for more than six weeks, in the absence of laryngopharyngeal reflux disease, allergies, asthma, angiotensin-converting enzyme inhibitor intake or psychogenic disorders.

Results: In the diabetic group, the mean age ± standard deviation was 44.66 ± 10.07 years. Sixty per cent of patients were male, 42 per cent had had diabetes for more than five years and 52 per cent had average to poor glycaemic control. The prevalence of laryngeal sensory neuropathy was 42 per cent in the diabetic group, compared with 13.9 per cent in controls; this difference was statistically significant ($p = 0.005$). There was no association between the prevalence of laryngeal sensory neuropathy and glycaemic control level, disease duration or presence of neuropathy.

Conclusion: Laryngeal sensory neuropathy is more common in patients with type 2 diabetes mellitus than in controls.

Key words: Diabetes Mellitus, Type 2; Cough; Pharyngeal Diseases; Laryngeal Nerves

Introduction

Diabetes mellitus, defined as a derangement in glucose metabolism, is one of the most common endocrine disorders worldwide. If left untreated, end organ damage and morbid complications may occur.[1–3] Diabetic neuropathy is one of the common complications intimately related to glycaemic control. Poor glycaemic control results in metabolic changes that can lead to nerve degeneration, with ensuing demyelination and poor nerve conduction.[4] Diabetic neuropathy can affect any part of the neurological system, including the maxillofacial region.[5–7]

The most commonly reported neuropathy is peripheral sensory neuropathy, in which patients experience numbness, pain or severe hyperaesthesia. Peripheral sensory neuropathy is commonly associated with myopathy, muscle inflammation, ischaemia and necrosis, leading to a reduction in total muscle mass, especially in the extremities.[8,9] In the head and neck region, multiple cranial nerves may be involved simultaneously. Ophthalmoplegia involving cranial nerves II, IV and VI may occur, and trigeminal neuralgia with involvement of the oculomotor and maxillary divisions may prevail. Wong *et al.* reported simultaneous unilateral multiple cranial neuropathies involving both divisions of the trigeminal nerve in a poorly controlled diabetic patient.[10]

Despite the wealth of literature on diabetic neuropathy, and particularly on sensory neuropathy, there are no reports of laryngeal sensory neuropathy in patients with type 2 diabetes mellitus.[11–13] Laryngeal sensory neuropathy is characterised by the presence of persistent laryngopharyngeal symptoms, such as throat clearing, coughing and globus pharyngeus, in the absence of laryngopharyngeal reflux disease, allergy, asthma, psychiatric disorders or intake of angiotensin-converting enzyme (ACE) inhibitors. The diagnosis is made after excluding the aforementioned confounding diseases. It is usually acute in onset following an upper respiratory tract infection, or an insult to the recurrent laryngeal nerve, superior laryngeal nerve or vagus nerve.[14]

A literature review identified no study comparing the prevalence of laryngeal sensory neuropathy in diabetic patients to non-diabetic controls. This investigation therefore aimed to determine the prevalence of

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laryngeal sensory neuropathy in patients with type 2 diabetes mellitus, and to assess possible correlations with clinical parameters such as disease duration, glycaemic control level and diabetic neuropathy. We hypothesised that diabetic patients with neuropathy are more likely than non-diabetics to exhibit laryngeal sensory neuropathy.

Methods

A total of 50 consecutive patients diagnosed with type 2 diabetes mellitus by a primary endocrinologist were referred to the Hamdan Voice Unit of the American University of Beirut Medical Center for evaluation. Exclusion criteria included a recent history of upper respiratory tract infection or laryngeal manipulation, such as microlaryngeal surgery, direct laryngoscopy or endotracheal intubation. All participants agreed to participate in the study. A group of 36 healthy participants served as controls.

Demographic data included age, gender and smoking status. The authors ensured that the prevalence of smoking was comparable in patient and control groups, in view of its confounding effect.

For the diabetic group, glycaemic control level, disease duration and presence of neuropathy were assessed. Glycaemic control was considered good when the glycated haemoglobin (HbA1c) level was less than 7 per cent, average when HbA1c was equal to or above 7 but less than 9 per cent, and poor when HbA1c was 9 per cent or above. The presence of diabetic neuropathy was defined by a previous change in neuropathy. Positive sensory symptoms included limb numbness, pricking sensation, aching pain, burning pain and at least one of the following neurological changes: (1) decreased pressure or pain sensation (positive monofilament test); (2) decreased light touch sensation (positive cotton wool swab test); and (3) decreased tendon reflexes.

Participants were asked about the presence or absence of any of the following symptoms: cough, globus pharyngeus and throat clearing. In line with Halum *et al.*, laryngeal sensory neuropathy was defined as the presence of one or more of those symptoms, lasting for at least six weeks, in the absence of: laryngopharyngeal reflux disease; allergy or asthma; ACE inhibitor intake; or psychogenic disorder.[14] The presence of laryngopharyngeal reflux disease was determined based on a Reflux Symptom Index score of more than nine using the scale designed by Belafsky *et al.*[15] The presence of allergy was confirmed using a validated questionnaire developed by Bauchau.[16]

Frequencies and means (± standard deviation) were used to describe categorical and continuous variables, respectively. The Pearson chi-square test was used for categorical variables. All analyses were conducted using IBM SPSS Statistics software version 19.0 (Armonk, New York, USA). For two-tailed tests, a p value of less than 0.05 was considered statistically significant.

Results

Demographic data

A total of 50 patients with type 2 diabetes mellitus were enrolled in this study. The mean age was 44.66 ± 10.07 years. Sixty per cent of patients were males. The prevalence of smoking was 20 per cent. Forty-two per cent of patients had had diabetes for more than five years, and 52 per cent had average to poor glycaemic control. Diabetic neuropathy was present in 22 per cent of patients (Table I).

Prevalence of laryngeal sensory neuropathy

The prevalence of laryngeal sensory neuropathy was 42 per cent in the diabetic group, compared with 13.9 per cent in the control group. The difference between the two groups was statistically significant ($p = 0.005$). To examine the possible confounding effect of smoking, we also calculated the prevalence of laryngeal sensory neuropathy in smokers and non-smokers in both the diabetic and control groups. There was no significant difference in disease prevalence among smokers and non-smokers in either group ($p = 0.886$ for diabetic patients and 0.829 for controls) (Table II).

TABLE I
DEMOGRAPHIC DATA

Parameter	Group	
	Control	DM
Participants (*n*)	36	50
Age (mean ± SD; years)	33.03 ± 11.39	44.66 ± 10.07
Gender (% males)	52.8	60.00
Smoking (%)	16.7	20.00
Diabetes duration (%)		
– <5 years	–	58.00
– 5–10 years	–	10.00
– >10 years	–	32.00
Glycaemic control (%)		
– Good	–	48.00
– Average	–	24.00
– Poor	–	28.00
Presence of neuropathy (%)	–	22.00

DM = diabetes mellitus; SD = standard deviation

TABLE II
PREVALENCE OF LSN IN SMOKERS AND NON-SMOKERS

Group	LSN (%)		*p*
	Smokers	Non-smokers	
DM	40	42.5	0.89
Controls	16.7	13.3	0.83

LSN = laryngeal sensory neuropathy; DM = diabetes mellitus

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TABLE III
ASSOCIATION BETWEEN LSN AND GLYCAEMIC CONTROL, DIABETES DURATION AND NEUROPATHY

Parameter	LSN (%)		*p*
	Yes	No	
Glycaemic control			
– Good	43	52	0.71
– Average	33	17	0.31
– Poor	24	31	0.67
Diabetes duration			
– <5 years	57	59	0.96
– 5–10 years	10	10	0.93
– >10 years	33	31	0.90
Neuropathy			
– Present	24	21	0.83
– Absent	76	79	0.93

LSN = laryngeal sensory neuropathy

Laryngeal sensory neuropathy and clinical parameters

The prevalence of laryngeal sensory neuropathy was not associated with glycaemic control, disease duration or neuropathy (Table III).

Discussion

Laryngeal sensory neuropathy is a disease entity in which a reduced laryngeal sensory threshold leads to abnormal laryngeal behaviour.[14,17–19] This decreased sensory threshold is accompanied by abnormal afferent feedback to the higher neural system, leading to alterations in laryngeal functions, with subsequent spasm, coughing and throat discomfort. It is sometimes accompanied by motor involvement, with impaired mobility of the vocal fold. As such, the most common presentation is an intractable cough, throat clearing and/or globus pharyngeus, with or without vocal fold paralysis or paresis. A variety of clinical problems may arise, ranging from abnormal glottic reflexes to dysphonia and aspiration. The pathogenesis is unknown, but is thought to involve metabolic damage, viral infection or mechanical trauma. The initiating insult may be to the internal branch of the superior laryngeal nerve, the recurrent laryngeal nerve or the vagus nerve.

Laryngeal sensation can be evaluated using fibreoptic endoscopy, with sensory testing performed by applying regulated puffs of air to elicit a glottic closure reflex. Subtle alterations in laryngeal sensation can be detected using this technique.[20] In patients with suspected neuromuscular motor abnormalities, such as irregularities in vocal fold position and glottic movement, laryngeal electromyography can help diagnosis.[19] Laryngeal electromyography may document acute changes such as fibrillation potentials and fasciculations, and chronic changes such as giant potentials and reduced recruitment. Another non-invasive diagnostic test for laryngeal sensation involves evaluating surface evoked laryngeal sensory action potential ('SELSAP') waveforms. Bock *et al.* showed that neuropathic participants have statistically significant differences in baseline amplitude, conduction velocity and intra-subject side-to-side amplitude ratio of surface evoked laryngeal sensory action potential waveforms, compared with controls.[21]

A diagnosis of laryngeal sensory neuropathy is often made by excluding confounding conditions, namely allergy, reflux, psychiatric disorders and intake of ACE inhibitors. In our investigation of patients with type 2 diabetes mellitus, a diagnosis of laryngeal sensory neuropathy was made based on the presence of throat clearing, globus pharyngeus and/or coughing for more than six weeks, in the absence of any of the aforementioned diseases. The results of this study indicate that patients with type 2 diabetes mellitus have a significantly higher prevalence of laryngeal sensory neuropathy compared with controls ($p = 0.005$). Laryngeal sensory neuropathy was not associated with level of glycaemic control, disease duration or presence of diabetic neuropathy.

The significantly higher prevalence of laryngeal sensory neuropathy in the diabetic group than in the control group is not surprising because various types of neuropathy have been described in these patients. Reported neuropathies include peripheral sensory and motor neuropathy, cranial neuropathy, and, specifically, vagal dysfunction. Though uncommon, cranial neuropathy and vagal dysfunction are reported complications of diabetes mellitus.[5–7,10] When present, the differential diagnosis of cranial neuropathy includes vasculopathy secondary to hypertension, autoimmune diseases such as systemic lupus erythematosus, or cranial aneurysm.[16,22] Diabetic patients with ocular involvement may present with symptoms of diplopia, impaired ocular movement and eyelid ptosis. When the trigeminal nerve is affected, patients present with facial and/or non-odontogenic pain. Similarly, vagal autonomic neuropathy is commonly reported in patients with long-standing diabetes, especially in poorly controlled cases. This is supported by the high prevalence of gastrointestinal disorders in this patient group. In a survey of 136 diabetic out-patients, Feldman and Schiller reported that 76 per cent had at least 1 gastrointestinal symptom attributed to gastrointestinal dysmotility secondary to diabetic autonomic dysfunction. Elevated gastrin concentration has been reported in diabetic patients, commonly following vagotomies.[23] Gastroparesis and a higher prevalence of gastroesophageal reflux disease have been described in diabetic patients. These findings are also associated with diabetic neuropathy.[24] Bytzer *et al.* used a questionnaire to determine the frequency of 16 gastrointestinal symptoms and 5 symptom complexes in 9000 diabetic patients. These authors concluded that diabetes mellitus is associated with an increased prevalence of both upper and lower gastrointestinal symptoms, which may be linked to the level of glycaemic control.[25] The presence of autonomic neuropathy, and in particular vagal involvement, has been substantiated in a study by Jamali and Mohseni.[4] Using an animal model of diabetes, these authors showed that

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hypoglycaemia induces degenerative alterations in the large myelinated axons of the vagus nerve and recurrent laryngeal nerve.

In the light of these studies, our finding of a significant difference in the prevalence of laryngeal sensory neuropathy between the diabetic and control groups suggests dysfunction in either the recurrent laryngeal nerve or the superior laryngeal nerve branch of the vagus nerve. However, this hypothesis needs further investigation.

Notably, there is no association between laryngeal sensory neuropathy and glycaemic control, disease duration and/or diabetic neuropathy. Diabetic neuropathy causes several types of polyneuropathy, the development and extent of which are related to the degree of glycaemic control and duration of the disease.[26,27] The lack of a significant correlation between laryngeal sensory neuropathy and glycaemic control or disease duration in our patient group, despite a correlation in other diabetic neuropathies, can be attributed to two factors. Firstly, sensory roots are less strongly affected than motor roots. Mohseni reported the effect of dysglycaemia on sensory and motor neurons at root and/or perikaryal levels.[28] Electron microscopy examination showed normal qualitative morphology, and a normal number of unmyelinated and myelinated axons in dorsal roots, whereas there were marked to moderate signs of pathological changes and axonal degeneration in ventral roots. Secondly, compared with the vagus nerve, peripheral nerves may exhibit different changes in response to dysglycaemia. MacLean demonstrated differences in neuropeptide behaviour in peripheral nerves versus the vagus nerve.[29] This author reported that the content and transport of both somatostatin and substance P differ between the vagus and sciatic nerves in diabetic rats. There is increased transport of both peptides in the vagus nerve, and decreased transport in the sciatic nerve. In addition, Jamali and Mohseni showed that hypoglycaemia, rather than hyperglycaemia, induces degenerative changes in the vagus nerve, and that the signs of neuropathy are less obvious in unmyelinated and small myelinated nerves.[4]

- **Laryngeal sensory neuropathy prevalence was investigated in type 2 diabetes mellitus patients**
- **Fifty patients with type 2 diabetes mellitus and 36 healthy control participants were recruited**
- **Glycaemic control, disease duration and presence of neuropathy were assessed**
- **Laryngeal sensory neuropathy prevalence was significantly higher in the diabetic group**
- **Laryngeal sensory neuropathy was not associated with glycaemic control, disease duration or presence of neuropathy**

This study has one main limitation: the absence of an objective diagnostic test for laryngeal sensory neuropathy such as the surface evoked laryngeal sensory action potential waveform, or laryngeal electromyography in patients with evidence of sensory or motor neuropathy. Notably, a diagnosis of laryngeal sensory neuropathy is often made by exclusion.

This is the first study to investigate laryngeal sensory neuropathy in type 2 diabetes mellitus patients, and the first to report a significantly higher prevalence in these patients compared with healthy controls. The clinical implications of this finding are important for the management of intractable symptoms of laryngopharyngeal reflux disease in diabetic patients. Diabetic patients with laryngeal sensory neuropathy may benefit from treatment with an array of medications, including amitriptyline, gabapentin and pregabalin. There have been many reports of laryngeal sensory neuropathy responding favourably to neuromodulating agents, despite their sedative effect.[14,17,18] Both gabapentin and pregabalin act centrally by binding to the α2δ subunits of presynaptic voltage channels, thus causing a decrease in neurotransmitters including glutamate, substance P and noradrenaline. As a result of these potent physiological changes, symptoms such as chronic cough are markedly suppressed. In a study by Norris and Schweinfurth on the management of recurrent laryngeal sensory neuropathic symptoms using amitriptyline hydrochloride and gabapentin, most patients improved, with a mean time of two months from the initiation of therapy to a complete response.[30] Similarly, Lee and Woo reported symptomatic relief using gabapentin in 68 per cent of patients with chronic cough as a sign of laryngeal sensory neuropathy.[19] These reports indicate that physicians should consider including neuromodulating agents in the treatment of laryngeal sensory neuropathy in type 2 diabetic patients with non-specific symptoms such as cough, globus pharyngeus and throat clearing.

Conclusion

Laryngeal sensory neuropathy is more common in type 2 diabetes mellitus patients than controls. The persistence of certain symptoms (such as cough, globus pharyngeus and/or throat clearing) that do not respond to anti-reflux treatment should alert the physician to possible laryngeal sensory neuropathy. Treatment with neuromodulating agents is recommended.

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