■ Clinical commentary

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Clinical management of voice and breathing problems in two patients with vagus nerve stimulation therapy

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ABSTRACT – We report two cases highlighting the diversity of vagal nerve stimulation (VNS)-related effects on voice and breathing in patients with refractory epilepsy. The patients had both implantation and stimulation-related side effects, which lasted for several months, impacting on their quality of life. The adverse effects appear to be due to recurrent laryngeal nerve paralysis-related vocal cord hypofunction and stimulation-related vocal fold spasms, however, their inter-relationship is complex. In one of the patients, we were able to utilize the novel programming capabilities of the VNS device to reduce the laryngeal side effects without compromising therapeutic efficacy. [*Published with video sequences*].

Key words: vagal nerve stimulation (VNS); side effect; voice and breathing problems

VIDEOS ONLINE

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Vagus nerve stimulation (VNS) has been available as a treatment option for refractory epilepsy for more than 20 years with well-established efficacy; at least 50% of patients experience a 50-60% reduction in seizure frequency [1]. Although VNS therapy is generally well tolerated, the known adverse effects, such as vocal cord palsy, cough, throat pain, dysphagia and breathing and voice disorders, can be distressing [2-4]. These laryngeal side effects are induced by either implantation surgery-related trauma to the vagus nerve or electrical stimulation via the vagus and recurrent laryngeal nerve to the larynx and pharynx [5].

The implantation can cause transient or permanent vocal cord paralysis and occurrence varies extensively, from 5% to 79% [6-8]. Most adverse effects are reported to occur when the stimulator is delivering a pulse, and they are often noted to be proportional to the duration, frequency and current amplitude of the stimulation (*e.g.* see references [9, 10]). The electrical impulse can cause spasmodic contraction of the ipsilateral intrinsic laryngeal muscles, presenting as an immobile left vocal fold in the paramedian to median position during stimulation, usually with a higher stimulation energy [3, 11]. However, a correlation between stimulation parameters and different visible laryngeal patterns or audible voice change is not always evident [3, 6].

Most patients rapidly habituate to the symptoms and reprogramming of the parameters often results in a satisfactory outcome even in those patients whose symptoms persist (*e.g.* see references [9, 10]).

This study describes two cases illustrating the diversity of the clinical presentation and therapeutic implications

of laryngeal side effects of VNS. The patients received VNS treatment for their refractory epilepsy in the neurological outpatient clinic of Tampere University Hospital in 2018-2019. The multidisciplinary assessment and details of the side effects are discussed.

Case studies

The evaluation of voice and breathing, including flexible fibreoptic endoscopy, were performed by two specialist speech-language pathologists (SA, TM) who assessed the signs and symptoms before and during initial VNS device activation and four times during the follow-up periods of 22 and 13 months (*tables 1 and 2*). The assessment included self-evaluation of breathing and voice by systematic interview and the VHI (Voice Handicap Index [12]). Further, the voice quality was evaluated perceptually for Patient 1. For Patient 2, it was possible to conduct acoustic voice analyses using AVQI (Acoustic Voice Quality Index 03.01 [13]), because adequate audio recordings were available.
A specialist nurse (SH) programmed the stimulator parameters and monitored the patient with frequent out-patient visits. The neurologist devised the individual care plan (JP).
In both patients, antiepileptic medication was not changed during follow-up (*tables 1 and 2*). The VNS output current was increased weekly with 0.25 mA increments from the time of activation. Frequency (20 Hz) and pulse width (250 µs) were held constant from the onset of stimulation.

Case 1

Patient 1 was a 51-year-old, passionate amateur athlete with a 17-year history of refractory epilepsy. The aetiology of his epilepsy was right hemisphere temporo-parietal cavernoma, which was resected without any meaningful effect on seizure frequency or severity. The patient was implanted with a VNS AspireSR® M106, manufactured by LivaNova PLC. Post-operatively, the patient experienced hoarseness, inability to shout and laboured breathing during exercise.
After the implantation, the patient had left vocal cord paralysis, causing breathing and voice dysfunction. His maximum output current (1.75 mA/magnet 2.0 mA) was reached three months post-operation. At seven months, the quality of his voice was better when the stimulator was active. At 10 months, his breathing was still troubled during exercise. He had gained some movement in the paralysed vocal fold, and therefore his voice was now more normal when the stimulation was off and hoarser when the stimulator was firing. At 11 months, the patient's breathing difficulties occurred only during high-intensity exercise, and he exhibited only transient stimulus-related dysphonia. At 22 months, the patient's breathing and voice symptoms remained stable. He felt that he could manage with his voice and he changed his exercise routine. He now avoided very-high-intensity exercise and sports, such as swimming, which were too demanding for his breathing capacity. At this point, the patient had a Class IIIA response (<50% reduction in seizure frequency but improved ictal severity) to VNS therapy [14].

Case 2

Patient 2 was a 40-year-old journalist with refractory temporal epilepsy since childhood. He was not a candidate for resective surgery because of his inoperable right-sided cortical occipitotemporal dysplasia. He was implanted with a VNS SenTiva™ M1000, manufactured by LivaNova PLC. After the operation, the patient experienced difficulties when speaking; his voice was hoarse, whispery and easily broken. About two weeks after the implantation, he also began to experience pain in the neck area.
The patient had left vocal cord paralysis due to the implantation, causing him subjective swallowing difficulties and mild dysphonia (*table 2*). Operation-related symptoms recovered spontaneously within three months although minimal dysfunction in the left vocal cord persisted for six months.
At two to three months after implantation, 1.25 mA stimulation current was associated with breathing and voice problems. The patient experienced mild dysphonia, but the acoustic analyses were within normal range. The endoscopy revealed abnormal left vocal cord function with OFF-stimulation and vocal cord spasm with 1.25 mA stimulation. The stimulation with 1.50 mA again provoked a stronger vocal cord spasm, which restricted his breathing and induced significant voice dysfunction.
At six months, he still had stimulus-related swallowing and breathing discomfort. The higher the stimulation energy, the worse were his laryngeal problems. In particular, the unpredictability of his voice disturbed him. At eight months, the stimulation of 1.25 mA still caused discomfort and hampered his work, so the current was tapered down to 1.0 mA for daytime use (10am to 6pm), whereas at night (6pm to 10am), the current remained at 1.25 mA. In order to intensify the VNS therapy, the OFF-time for the night cycle was decreased to 3 minutes, whereas in the daytime, OFF-time was kept at 5 minutes. The patient was satisfied; the discomfort and the voice changes were more subtle. At 10 months, the discomfort

▼ **Table 1.** Laryngeal functions and VNS parameters in Patient 1.

		Post-operation 1 month	**1st follow-up 7 months**		**2nd follow-up 10 months**		**3rd follow-up 11 months**			**4th follow-up 22 months**		
		VNS activation	VNS OFF	1.75mA	VNS OFF	1.75mA	VNS OFF	1.0mA	1.75mA	VNS OFF	1.0mA	1.75mA
Larynx	Endoscopy	Left vocal cord immobile	Left vocal cord immobile	Left vocal cord static near midline	Slight movement in left vocal cord	Left vocal cord static near midline	Moderate movement in left vocal cord	left vocal cord static near midline	Left vocal cord static near midline	Moderate movement in left vocal cord	Left vocal cord static near midline	Left vocal cord static near midline
		Restricted glottis	Restricted glottis	Restricted glottis	Restricted glottis	Restricted glottis	Mildly restricted glottis	Restricted glottis	Restricted glottis	Mildly restricted glottis	Restricted glottis	Restricted glottis
Breathing	Self-evaluation	Labored breathing and Shortness of breath while exercising	Labored breathing and severe panting in aerobic exercise		Choking during aerobic exercise		Choking during intense aerobic exercise			Choking during intense aerobic exercise		
Voice	Self-evaluation (VHI)	-	Moderate handicap=46/120		Moderate handicap=41/120		Mild handicap=14/120			Mild handicap=14/120		
	Perceptual evaluation	Hoarse and rough, somewhat breathy and strained	Hoarse, and rough, somewhat breathy and strained	Normal	Somewhat hoarse and rough	Somewhat hoarse, rough and strained	Normal	Somewhat hoarse and rough	Somewhat hoarse, rough and strained	Normal	Somewhat hoarse and rough	Somewhat hoarse, rough and strained
VNS	Activation time/ day		11%		13%		13%			24%		
	ON/OFF time	30s/5min	30s/5min		30s/5min		30s/5min			30s/1.8min		
	Threshold for autostimulation	off	20%		30%		30%			30%		
Antiepileptic medication	Eslicarbazepine acetate 1200mg x1, levetiracetam 500mg x2, perampanel 6 mg x1											

VHI: Voice Handicap Index (scale 0-120, 0-30 mild handicap, 31-60 moderate handicap, 60-120 severe handicap); -: not assessed.

▼ **Table 2.** Laryngeal functions and VNS parameters in Patient 2.

		Post operation 1 month	**1st follow-up 3 months**			**2nd follow-up 6 months**			**3rd follow-up 10 months**				**4th follow-up 13 months**			
		VNS OFF	VNS OFF	1.25mA	1.50mA (trial)	VNS OFF	1.25mA	1.50mA (trial)	VNS OFF	1.0mA (day-time)	1.25mA (night-time)	1.5mA (trial)	VNS OFF	1.0mA (day-time)	1.25mA (night-time)	1.5mA (trial)
Larynx	Endoscopy	Mild left vocal Cord dysfunction	Mild left vocal cord Dysfunction	Left vocal cord static near Midline	Left vocal cord static near midline	Normal vocal cord function	Left vocal cord static near midline	Left vocal cord static near midline	Normal vocal cord function	Left vocal cord static near midline	Left vocal cord static near midline	Left vocal cord static near midline	Normal vocal cord function	Left vocal cord static near midline	Left vocal cord static near midline	Left vocal cord static near midline
		Mild vocal cord dyscoordination	Normal	Restricted glottis	Restricted glottis	Normal	Restricted glottis	Restricted glottis	Normal	Restricted glottis	Restricted glottis	Restricted glottis	Normal	Restricted glottis	Restricted glottis	Restricted glottis
Breathing	Self-evaluation	No symptoms	Restricted	Restricted	Restricted	No symptoms	Restricted	Very restricted	No symptoms	No symptoms	Restricted	Very restricted	No symptoms	Restricted	Restricted	Restricted
Voice	Self-evaluation (VHI)	Mild handicap=15/120	Mild handicap=18/120			Mild handicap=27/120			Moderate handicap=43/120				Moderate handicap=42/120			
	Acoustic analysis (AVQI)	Dysphonia =1.97	Normal =1.48	Normal =1.75	Dysphonia = 2.78	normal =0.55	Dysphonia = 2.09	Dysphonia = 2.38	Normal =0.94	Dysphonia =2.34	Dysphonia =2.63	Dysphonia =2.94	Normal =0.15	Normal =1.42	Normal =1.41	Dysphonia =2.26
VNS	Activation time/ day		10%			12%			16%				16% Day-time 30s/5min Night-time 30s/3min			
	ON/OFF time		30s/5 min			30s/5min			30s/5min							
	Threshold for autostimulation		Off			40%			30%				30%			
Antiepileptic medication	Lacosamide 100mg x2, lamotrigine 200mg x2, levetiracetam 500mg x2															

AVQI: Acoustic Voice Quality Index 03.01 (threshold for Finnish speakers is 1.83), VHI: Voice Handicap Index (scale 0-120, 0-30 mild handicap, 31-60 moderate handicap, 60-120 severe handicap); - : not assessed.

and the voice changes were more subtle in the day-time, but there were no signs of adaptation to the night-time current of 1.25 mA or the magnet current 1.50 mA. Finally, at 13 months, the patient coped with the minor stimulation-related voice changes. According to the acoustic analyses, he had also adapted to the 1.25 mA current, which no longer caused him dysphonic hoarseness. The patient had a Class IIB response (more than 50% reduction in seizure frequency but without any change in ictal or post-ictal severity) to VNS therapy [14].

Discussion

Both operation and stimulation related side effects occurred in these patients and lasted for several months. Recurrent laryngeal nerve paralysis-related vocal cord hypofunction and stimulation-related vocal fold spasm accounted for the adverse effects, but the experienced voice and breathing problems and the adaptation to stimulation were distinctive.

Patient 1 was an enthusiastic athlete; thus, breathing difficulties restricted his performance in sports. His breathing gradually eased along with recovery of his vocal cord paralysis and adaptation to stimulation. However, some difficulty remained. The VNS parameters were not radically changed because of two main reasons. First, the effect on seizure control was modest, and lowering the overall stimulation energy was not considered appropriate. Second, at some point, the stimulation energy was useful for the paralysed left vocal cord. In retrospect, it could have been beneficial to customize an "exercise setting" for him, for example, by lowering the current for a couple of hours during the day. Nevertheless, his devise, AspireSR® M106, does not include this option. Eventually, he started to avoid the most demanding sports as a compensatory strategy.

Because the implantation had evoked vocal cord paralysis, his voice at first improved while the stimulator was firing. Later, when the paralysis recovered to some extent, the stimulation caused his voice to worsen; stimulation is known to tend to trigger spasms in functioning vocal cords [3]. To our knowledge, similar cases on which stimulation temporarily benefitted voice production have not been documented before. However, the phenomenon is understandable as indirect or direct neuromuscular electrical stimulation may be effective as an adjunctive treatment for some cases of pharyngo-laryngeal dysfunction [15].

Patient 2, the journalist, suffered from poor voice quality. For several months, he experienced significant voice problems, especially at higher currents. Unlike most previously published cases (for example, see [9, 10]), his adaptation to the stimulation currents took much longer. During the follow-up, the patient's VNS parameters were adjusted in order to enhance his performance at work, especially when talking on the phone. Because his VNS device (SenTiva™ M1000) enabled settings to be customised, it was possible to decrease the current during working hours in daytime while maintaining a higher current and shorter stimulation OFF-time at night. In this way, the patient could use his voice during working hours, but the overall therapeutic effect for his seizures was not compromised.

These two cases are good examples of how, in some individuals, even seemingly mild voice and breathing problems may impair quality of life. Therefore, specific and up-to-date knowledge of VNS complications is required to ensure good individualized care.

Currently, there are no established assessment protocols for voice and breathing problems of VNS patients. More systematic research is needed to determine the most sensitive assessment tools and the best care practices. However, it is important to at least differentiate patients with vocal fold paralysis from those with only stimulation-related side effects. We recommend using multiple assessment methods, including systematic self-evaluation such as VHI, acoustic or perceptual analysis of voice and endoscopy or even stroboscopy, to enhance investigation of laryngeal functions. We suggest using AVQI as an acoustic measure. AVQI relies on the detection of hoarseness as an indicator of overall voice quality and is therefore well suited for a population whose voice disorders are mainly classified as hoarse, due to vocal cord paralysis or unilateral vocal cord dysfunction. In the future, it may also be possible to record VNS-induced laryngeal motor evoked potentials, as suggested by Vespa *et al*. [16].

Considering the recommendations for the management of laryngeal problems, there is no definite indication for delaying the increase of output current due to vocal cord paralysis. It is possible that, at therapeutic levels, the stimulation may protect paralysed vocal cords from atrophy [6] and assist in regaining function. The spectrum of suitable VNS candidates is expanding with development in care. In VNS patients, whose occupation, hobbies or social life require intact voice control or who want to undertake strenuous physical exercise, the capabilities of the new VNS devices, enabling customized stimulation cycles, should be acknowledged and exploited. ■

Disclosures.
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Legends for video sequences

Video sequence 1

Initiation of vagus nerve stimulation at 1.50 mA in Patient 2. Note the left vocal cord (on the right).

Video sequence 2

Termination of vagus nerve stimulation at 1.50 mA and release of the glottis to its normal open position in Patient 2. Note the left vocal cord (on the right).

Key words for video research on www.epilepticdisorders.com

Phenomenology: voice and breathing dysfunction
Localization: larynx
Syndrome: left vocal cord spasm
Aetiology: VNS

TEST YOURSELF

(1) Name the known laryngeal side effect of VNS therapy.

(2) What are the main causes of adverse effects of VNS therapy?

(3) How may these side effects be relieved?

Note: Reading the manuscript provides an answer to all questions. Correct answers may be accessed on the website, www.epilepticdisorders.com, under the section "The EpiCentre".