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A case report of Vagus nerve stimulation for intractable hiccups

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ABSTRACT

INTRODUCTION: Intractable hiccups frequently result from an underlying pathology and can cause considerable illness in the patients. Initial remedies such as drinking cold water, induction of emesis, carotid sinus massage or Valsalva manoeuvre all seem to work by over stimulating the Vagus nerve. Pharmacotherapy with baclofen, gabapentin and other centrally and peripherally acting agents such as chlorpromazine and metoclopramide are reserved as second line treatment. Medical refractory cases even indulge in unconventional therapies such as hypnosis, massages and acupuncture. Surgical intervention, although undertaken very rarely, predominantly revolves around phrenic nerve crushing, blockade or pacing. A novel surgical strategy is emerging in the form of Vagus nerve stimulator (VNS) placement with three cases cited in literature to date with varying degrees of success. Here the authors report a case of VNS placement for intractable hiccups with partial success, in accordance with SCARE-2018 guidelines. **PRESENTATION OF THE CASE:** An 85-year-old gentleman with a 9-year history of intractable hiccups secondary to pneumonia came to our hospital. The hiccups were symptomatic causing anorexia, insomnia, irritability, depression, exhaustion, muscle wasting and weight loss. The patient underwent countless medical evaluations. All examinations and investigations yielded normal results. The patient underwent aggressive pharmacotherapy, home remedies and unconventional therapies for intractable hiccups but to no avail. He also underwent left phrenic nerve blocking and resection without therapeutic success. The patient presented to our hospital and decision for VNS insertion was taken for compassionate reasons considering patient morbidity. The patient demonstrated significant improvement in his symptoms following VNS insertion.

DISCUSSION: A temporary hiccup is an occasional happening experienced by everyone. However, intractable hiccups are associated with significant morbidity and often mortality. Several medical, pharmacological, surgical and novel treatment options are available for intractable hiccups.

CONCLUSION: VNS insertion is a novel surgical option for the treatment of intractable hiccups.

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1. Introduction

Hiccup is a widely experienced and less understood phenomenon. Although much is known about the afferent and efferent limbs of the hiccup reflex pathway, no definitive consensus exists on the hiccup centre generating this reflex. Even the word “hiccup” is an onomatopoeic for the sound the reflex arc produces [1]. The hiccup reflex arc can be categorised as having afferent and efferent limbs and a central connection. The afferent limb is composed of the Vagus and phrenic nerves, and the lower sympathetic (T6–12) segments. The efferent pathway is constituted by the phrenic nerve (C3–5) innervating the diaphragm, plexal branches to the scalene muscles (C5–7), recurrent laryngeal nerve to the glottis and the intercostal nerves (T1–11) innervating the intercostal muscles [2,3].

The hiccup central connection is believed to be spinal cord segments rostral to medulla oblongata (C3–5) in the reticular formation in the middle and dorsolateral segment, connecting to the hiccup rhythm centre in the Pre-Botzinger complex, nucleus ambiguus, lateral reticular nucleus, hypothalamus and mesial temporal lobes [2–5]. Gama-aminobutyric acid (GABA) and dopamine act as neurotransmitters for this reflex. It is speculated that the hiccup centre and the respiratory centre although separate may interact with one another through the various neuronal connections [2,5]. When the hiccup reflex is triggered there is synchronous contraction of the inspiratory thoracic muscles and the diaphragm. This is followed, in 35 milliseconds, by an abrupt glottal closure producing the typical “hic” [6].

There is no conclusive knowledge on how this reflex is triggered but a safe idea would be that any mechanism which irritates or damages the components of the reflex arc, the central nuclei, the Vagus, phrenic or other nerves of the autonomic system can trigger a hiccup. Of these the Vagus is particularly important. The “wan-

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Table 1
Possible Causes of Hiccups adapted from Steger et al.

Central/Peripheral Nervous System	Gastrointestinal	Thoracic	Ear, Nose & Throat (ENT)	Metabolic	Pharmacologic/ Toxic	Surgical	Psychosomatic
Ischemic/haemorrhagic stroke	Gastric Distension	Cardiac Ischemic Injury	Infection	Hypo/Hyper-Glycaemia	Alcohol	Thoracic Surgery	Anxiety
Tumours	Gastro-oesophageal Reflux Disease	Cardiac Infection	Inflammation	Hypo/Hyper-Natremia	Chemotherapy/ Radiotherapy	Abdominal Surgery	Stress
Traumatic Brain Injury	Hiatus Hernia	Cardiac Inflammation	Foreign Body	Hypo/Hyper-Kalemia	Steroids	Ear, nose, throat Surgery	Excitement
Infection	Gastrointestinal tumours	Pulmonary Infection	Tumours	Hypo/Hyper-Calcemia	Inhalational Oxygen	Endoscopy	Fear
Inflammation	Infection	Pulmonary Inflammation		Hypocapnemia	Benzodiazepines	Pharyngeal Intubation	
Demyelinating diseases	Inflammation	Thoracic Tumours		Hypo/Hyper-Uraemia	Dopamine Agonists	Placement of Central Venous Catheter	
Auto-immune diseases	Obstruction	Aneurysms		Metabolic Diseases	Opioids	Iatrogenic Injury	
Neuro-transmitter abnormalities	Haemorrhage	Auto-immune diseases		Hypo/Hyper-Thermia	Barbiturates		
Vascular abnormalities				Smoking	Anti-biotics		
Anatomical Abnormalities					Anaesthetic Agents		

Table 2
Various Treatments of Hiccups adapted from Steger et al.

Vagal Stimulation	Respiratory Manoeuvres	Centrally Acting Pharmacological	Peripherally Acting Pharmacological	Surgical	Alternative Treatment
Intra-Nasal application of Vinegar	Valsalva Maneuver	Chlorpromazine	Metoclopramide	Phrenic Nerve Blockage or Crushing	Hypnosis
Inhalation of Smelling Salts/Strong Odours	Breath Holding (Inspiration, Expiration)	Phenytoin	Domperidone	Phrenic Nerve Pacing	Acupuncture
Swallowing Ice Water	Re-Breathing (Hyper-capnia)	Haloperidol	Nifedipine	Percutaneous Phrenic Nerve Stimulation	Massage
Splashing Cold water Or Cold Compress On Face		Baclofen		Cervical Epidural Block	
Induce Vomiting		Gabapentin		Implantation of Vagal Nerve Stimulator	
Induce Fright		Pregabalin			
Carotid Massage		Carbamazepine			
Pressure Over Eyeball		Sodium Valproate			
Digital Rectal Massage		Amitriptylline			
Induce Orgasm					

derer” has such immense distribution throughout the body that the reflex can be triggered by any number of odd reasons such as irritation of the ear drum, rapid change in body temperature, over distension of stomach, irritation of the respiratory tractor stroking of hair [7,8]. As such most initial remedies seem to centre on over stimulating the Vagus nerve [9,10]. In cases of known underlying pathology treatment of the causative factor may help relieve the symptoms [11]. Table 1 enlists the various causes of a hiccup. Gastro-oesophageal reflux disease (GERD) has been shown to be both a cause of as well as a consequence of hiccups [1]. Although GERD can induce hiccups via the irritation of the Vagus nerve, long standing hiccups in themselves can cause reduction in the oesophageal motility as well as lowering of oesophageal-gastric sphincter pressure thus favouring GERD [1,6]. Hiccups are classified as temporary (<48 h), persistent (48 h-1 month) or intractable (>1 month), depending on their duration [3]. Intractable hiccups may cause debilitating problems such as insomnia, anorexia, fatigue, exhaustion, weight loss, depression, opening of surgical wounds, development of hernia and haemorrhoids, inability to undergo imaging such as MRI and even death. In such cases active management is required. Numerous medical and alternative therapies

are available for the treatment of hiccups. Rarely surgical interventions are employed [2,8,12]. Table 2 provides an overview of the different treatment modalities for hiccups (Table 3).

2. Case report

An 85-year-old Caucasian gentleman with a 9-year history of intractable hiccups came to National Hospital for Neurology and Neurosurgery, a 244-bed quaternary care hospital, after numerous unsuccessful traditional medical and alternative treatments.

His symptoms started in October 2010 when he suffered from pneumonia which caused severe respiratory compromise and fever. Prompt hospitalization and medical management attained full recovery, however a few days later the patient developed hiccups. Patient had a past medical history of ischaemic heart disease of 10 years, hypertension and hypercholesterolemia, both of which were very well controlled with amlodipine and rosuvastatin and had no symptoms of hiccups prior to the pneumonia in 2010. Patient neither consumed alcohol nor smoked and did not indulge in recreational drugs. Initially the hiccups were for intermittent onset, about 2–3 per day with months of remission between suc-

Table 3
Functional Components of the Vagus Nerve.

20% Efferent				80% Afferent				
General Visceral Efferent (Pre-Ganglionic Parasympathetic)		Special Visceral Efferent		General Somatic Afferent	General Visceral Afferent			Special Visceral Afferent
Dorsal Motor Nucleus	Nucleus Accumbens	Motor Innervation	Reflexes	Sensory	Sensory	Receptors	Reflexes	Sensory
Thoracic Organs	Cardio-inhibitory Function	Soft Palate	Gag Reflex	Pharynx	Abdominal Organs	Aortic Arch Baroreceptors	Reflex Regulation of Gastrointestinal Tract	Epiglottis
Abdominal Organs		Pharynx	Cough Reflex	Larynx	Thoracic Organs	Carotid Sinus Baroreceptors	Reflex Regulation of Cardiovascular System	Taste Buds
		Larynx	Peristaltic Reflex	Oesophagus		Chemoreceptors	Reflex Regulation of Respiratory System	
		Upper Part of Oesophagus		Trachea				
				Bronchi				
				External Auditory Meatus				
				Tympanic Membrane				
				Concha				

cessive episode. Gradually they became more consistent, occurring daily with a frequency of about 50–100 per day. Patient was still able to carry out his daily routine and used home remedies such as drinking cold water, re-breathing in a paper bag, pressure over eyeballs, Valsalva manoeuvre and splashing cold water on face to treat his hiccups.

However, the hiccups progressively worsened in frequency, rate, intensity and magnitude. In 2013 patient developed GERD, possibly as a consequence of the ongoing hiccups and underwent Nissen fundoplication. Fundoplication completely resolved GERD but the hiccups continued to worsen. 3 years ago, they became non-stop occurring every 5 s and continued during sleep. They were symptomatically disabling and scored 9/10 on a 10-point subjective patient scale. They caused severe distress to the patient who became progressively anorexic, irritated, short tempered, fatigued and depressed. He became emaciated over the years and found it hard to talk. Even normal breathing was upset with sensations of choking secondary to glottis spasms. Patient underwent countless medical evaluations; physical and neurological examinations including ENT, chest and abdomen; laboratory investigations including blood urea nitrogen; imaging including magnetic resonance imaging (MRI) of brain and neck, computed tomography (CT) of abdomen and thorax and even upper gastrointestinal endoscopy and bronchoscopy. All examinations and investigations yielded normal results. In the absence of a definitive underlying cause an aggressive pharmaco-medical treatment was started. These medical therapies including prochlorperazine, metoclopramide, levetiracetam, baclofen, chlorpromazine, omeprazole, domperidone, gabapentin, carbamazepine, lansoprazole and Maalox plus remained ineffective. Patient also tried acupuncture, massage and hypnosis but to no avail. In April 2018 the patient underwent left phrenic nerve blocking which provided temporary relief for half a day. Following this, in June 2018 the patient underwent left phrenic nerve resection which cured the hiccups for only 2 days.

Patient became progressively unwell and lost half of his body weight. Furthermore, the disquieting symptoms were temporarily relieved for approximately 30 min. only by the induction of vomiting. Patient induced vomiting about 15 times in a day to experience relief from the hiccups.

In February 2020 the patient was referred to our neurosurgery department for evaluation. All physical and neurological examina-

tions, relevant imaging and blood investigations were normal. No underlying cause was ascertained. VNS is currently not approved for the indication of intractable hiccups but given the fact that the patient had failed multiple lines of treatment and was disconsolate, after meticulous consideration and careful review of literature a decision was made for VNS insertion as a compassionate indication. Patient was positioned supine under general anaesthesia. The procedure was performed by senior consultants Ms Misericocchi and Mr McEvoy. Livanova VNS electrode was wrapped around the left Vagus nerve of the patient and a pulse generator was implanted on the left chest above the pectoralis muscle 2–3 cm below the collar bone. The surgery and post-operative period were uneventful. After 2 weeks of rest, the device was switched on with automatic current settings of amplitude between 1–2 mA, frequency between 10–30 hertz, pulse width between 250–750 microseconds and duration of between 20–60 seconds. Pharmaco-medical treatment for the hiccups was discontinued. There was no hoarseness or change in voice of the patient and no chest pain or any sign of cardiac compromise.

This provided complete remission for few hours after which the hiccups returned but were infrequent with episodes lasting for up to 15 min, with a rate of 1 hiccup per second, every 4–6 hours, thus demonstrating a much-decreased rate and magnitude. Patient and his family noted the intensity to be 5/10 on a subjective scale with marked improvement in speech. Due to the coronavirus (Covid-19) outbreak the patient is currently awaiting a follow up appointment to review prognosis and revise the automatic current settings.

We therefore document partial success with the surgical placement of Vagus nerve stimulator for the treatment of intractable hiccups at our centre with short term results. As seen with epilepsy, VNS tends to continue to improve prognosis up to 1–1.5 years. We will continue to monitor the patient and present a follow up report with long term results.

3. Discussion

Although temporary hiccups are a benign occurrence having no significant impact on the life of a person but intractable hiccups are a serious and debilitating pathology and often lead to dire consequences [1–3,7]. The world record of longest hiccups is 69 years with notable people such as Pope Pius XII dying from the ailment

[13]. Therefore, symptomatic intractable hiccups warrant medical and surgical treatment [1].

The Vagus nerve forms a significant component of the hiccup reflex arc and can explain several odd triggers as well as the basis for most initial remedies [4,9,10]. In fact hiccups most frequently occur during inspiration when lung inflation impedes vagal afferents known to suppress hiccups [6]. The Vagus nerve, also referred to as the “wandering” nerve or the “vagabond” nerve, greatly innervates multiple organs of the body and forms a part of several bodily reflexes [4,7,10]. Its stimulation has demonstrated varied functional outcomes the exact mechanism of most of which are not clearly understood [7]. VNS is an acknowledged treatment for epilepsy and depression [2].

Medical therapy for intractable hiccups comprises of GABA-derivatives, baclofen, dopaminergic antagonists and anticonvulsants. Non-traditional treatments such as acupuncture, massages and hypnosis are also widely used. Non-pharmacological options such as phrenic nerve blocking, crushing and pacing, percutaneous phrenic nerve stimulation and cervical epidural block have shown limited success due to the occasional presence of an accessory phrenic nerve as well as the bilateral diaphragmatic contraction aetiology of centrally originated hiccups [2,3,7,13].

Recently surgical placement of Vagus nerve stimulators have been undertaken for chronic hiccups with varying degrees of success [2,5,7,10]. We report a case of intractable hiccups secondary to pneumonia, treated with VNS placement at our centre with short term results demonstrating partial success, in accordance with SCARE-2018 guidelines [14]. Since the thorax is of immense anatomical importance in the hiccup reflex, it is reasonable to consider that infections of the chest can lead to hiccups [1]. Seeing as no validated questionnaires have been formulated to document the intensity of hiccups [1], a 10-point patient subjective scale was employed.

Very little research is available on the cure of hiccups and even the pathogenesis of hiccups is less understood. Due to the lack of a physiological relevance in adults and the observation of hiccups in fetuses along with the efficacy of baclofen in arresting gill-ventilation in tadpoles, it is speculated that hiccup is a phylogenetical reflex [2,4,6,13]. Future research will help us better understand this phenomenon and its treatment.

Declaration of Competing Interest

The authors have no conflict of interest. We confirm that where other sources of information have been utilised and cited, it is with the permission of the corresponding authors.

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Consent

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Author contribution

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Ms Anna Miserocchi: Supervision, Project administration.

Mr Andrew McEvoy: Supervision, Project administration.

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