Hiccup: Mystery, Nature and Treatment

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Hiccup is the sudden onset of erratic diaphragmatic and intercostal muscle contraction and immediately followed by laryngeal closure. The abrupt air rush into lungs elicits a “hic” sound. Hiccup is usually a self-limited disorder; however, when it is prolonged beyond 48 hours, it is considered persistent whereas episodes longer than 2 months are called intractable. A reflex arc involving peripheral phrenic, vagal and sympathetic pathways and central midbrain modulation is likely responsible for hiccup. Accordingly, any irritant in terms of physical/chemical factors, inflammation, neoplasia invading the arc leads to hiccups. The central causes of hiccup include stroke, space occupying lesions and injury etc, whereas peripheral causes include lesions along the arc such as tumors, myocardial ischemia, herpes infection, gastroesophageal reflux disease and applied instrumentations on human body etc. Besides, various drugs (eg, anti-parkinsonism drugs, anesthetic agents, steroids and chemotherapies etc) are the possible etiology. An effective treatment of persistent hiccup may be established upon the correct diagnosis of lesion responsible for the serious event. The pharmacotherapy of hiccup includes chlorpromazine, gabapentin, baclofen, serotonergic agonists, prokinetics and lidocaine. Non-pharmacological approaches such as nerve blockade, pacing, acupuncture and measures to hold breathing are also successful. Finally, alternative medicines and remedies are convenient to treat hiccups with uncertain effect. In conclusions, hiccup is likely to result from lesions involving the hiccup reflex arc. The lesion may need to be localized correctly for ablative treatment in patients with intractable hiccup. Apart from lesion ablation, drugs acting on reflex arc may be effective, while some other conventional measures may also be tried. (J Neurogastroenterol Motil 2012;18:123-130)

Key Words
Complementary therapies; Gabapentin; Hiccup; Myoclonus; Reflex arc

Introduction

Both functional belching and hiccup are abnormal physiological behavior activated by the air movement. Functional belching results from venting of excessive gas from stomach and it is often accompanied with gastroesophageal reflux disease (GERD). It belongs to one of the functional gastrointestinal disorders. In contrast, hiccup is the sudden onset of erratic diaphragmatic and intercostal muscular myoclonus which are followed immediately by laryngeal closure, hence the abrupt air rush into lungs induces the vocal cords to close leading to a “hic” sound. Hiccup or singultus is derived from the Latin word singultus, which means “the act of catching one’s breath while sobbing.”

Hiccup occurrence is not only confined to the adults but also observed among the infants and children. It is usually a self-limited disorder meaning many episodes would subside spontaneously without any clinical significance. The self-limited...
Hiccup is believed to be induced by the rapid stomach distension and irritation in terms of overeating, eating too fast, ingesting spicy food, drinking carbonated drinks, aerophagia and sudden change in ingested food temperature (eg, hot or cold drinks, a cold water shower, using alcohol and excessive smoking etc). Persistent hiccup means episode lasting for 48 hours or more, whereas those longer than 2 months are considered intractable. Severe and prolonged hiccup may lead to exhaustion, fatigue, malnutrition, weight loss, dehydration and even death in the extreme situations. Persistent hiccup means episode lasting for 48 hours or more, whereas those longer than 2 months are considered intractable. Severe and prolonged hiccup may lead to exhaustion, fatigue, malnutrition, weight loss, dehydration and even death in the extreme situations. Unfortunately, there is no guideline available to direct treating this serious disorders effectively. Chlorpromazine is approved by the US Food and Drug Administration as the only drug to treat hiccup until now. However, using chlorpromazine to treat hiccup without correct diagnosis of lesion responsible for hiccup may lead to missing potentially serious conditions that may cause this symptom. Literature suggests that measures ranging from conventional remedies, alternative medicines to emerging therapies may treat hiccups successfully. The authors attempt to review current understanding of pathophysiology and management of hiccup.

**Pathophysiology**

The pathophysiological mechanism of hiccup is related to lesions in its reflex arc shown in Figure. The hiccup reflex arc consists of 3 components, the afferent limb including phrenic, vagus and sympathetic nerves to convey somatic and visceral sensory signals, the central processing unit in the midbrain and the efferent limb traveling in motor fibers of phrenic nerves to diaphragm and accessory nerves to the intercostal muscles, respectively. Central process of hiccup remains poorly understood, it may not only be confined to the medulla but may also involve other parts of central nervous system (CNS) located between brainstem and cervical spine. The hiccup central component usually refers to chemoreceptors probably located in the peri-aqueductal gray matter and sub-thalamic nuclei. Among the neurotransmitters involved in the process of hiccup, both dopamine (D) and gamma-aminobutyric acid (GABA) have been documented. The above pathophysiological basis explains why some inhibitors of these substances may be employed in treatment of hiccup. Accordingly, any physical and chemicals irritants and inflammatory and neoplastic conditions involving the hiccup reflex may cause hiccup. In addition, hiccup may be transient in many patients as spontaneous resolution of the stimuli that caused it might lead to its disappearance. Unfortunately, owing to the long trajectory of afferent and efferent nerves and the diffuse central processes involving the hiccup reflex arc, the accurate diagnosis of lesions in the arc and trying to terminate the pathological processes in the intractable events are often very difficult. As several types of lesion located along the hiccup reflex arc may cause it, hiccup is common and has been described as case reports in association with several conditions and has been treated with various types of treatment, which might confuse readers.

**Etiology of Persistent and Intractable Hiccups**

In the review of recent literature, too many causes of hiccups have been reported. Some are well known to invade the hiccup reflex arc, whereas many others remain unexplained why they would elicit persistent or intractable hiccups since no obvious invasion to the hiccup reflex pathway was confirmed. According to the sites of lesion, hiccup may originate either from central or peripheral pathways. Briefly, Table 1 summarizes the reported etiology of persistent and intractable hiccups. Their details are further illustrated in the following.

**Cerebral Vascular Accidents**

Brain ischemia or stroke is not rare among the individuals with intractable hiccup and in some patients cerebrovascular cause was correctly diagnosed months later. If a correct diagnosis is made, intractable hiccup may resolve after initiation of anticoagulant therapy. In addition, hiccup did occur in the patient