Hiccups

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Introduction

Overview

Hiccups are inappropriate respiratory muscle contractions that can occur due to gastrointestinal, respiratory, neurologic, and general systemic disorders as well as a sequel to surgery or adverse reaction to drugs. Among the neurologic lesions that can cause persistent hiccups, brainstem lesions figure prominently. Benign posterior fossa tumors can cause hiccups by compression of the brainstem. This is relieved following the removal of the tumors. This article describes the differential diagnosis and management of hiccups. If no lesion is found, hiccups can be controlled by some pharmacologic agents such as baclofen and gabapentin. Unconventional methods and surgical procedures to relieve hiccups are also described.

Key points

• Hiccups are inappropriate respiratory muscle contractions.

• Hiccups may due to several systemic as well as gastrointestinal and neurologic disorders such as brainstem lesions.

• Diagnosis of idiopathic hiccups is made after exclusion of identifiable causes.
Historical note and terminology

Hiccuping (singultus) derives from the Latin “singult,” meaning “to catch one’s breath while sobbing.” It is a common occurrence, but little is known about its pathophysiology. Although vomiting and coughing are protective reflexes of the gastrointestinal and the respiratory systems respectively, hiccuping seems to have no survival value. It may be a vestigial reflex in mature persons as a remnant of a primitive sucking reflex, as fetal hiccuping is a normal phenomenon, which has been demonstrated by ultrasonography in utero. Hiccuping may be serving a useful purpose by maintaining the activity of the respiratory muscles, which are superfluous at that stage of development.

The classification of hiccups is by their duration. Acute hiccups are less than 48 hours duration, persistent over 2 days, and intractable over a month. Idiopathic chronic hiccup is defined as recurring hiccup attacks that last for longer than 1 month, and for which no organic cause can be found. It is also called diabolic hiccup.

Hiccups were a mystery to early physicians, and some of the folklore methods of treatment have survived in modern practice such as breath-holding, gargling with water, or inducing sneezes. These may work by temporary halting the rhythm of respiration.

Clinical manifestations

Presentation and course
• Hiccups are a distinct sound caused by contraction of the inspiratory muscles terminated abruptly by closure of the glottis.

• Hiccuping is usually a benign self-limiting condition and does not produce any serious sequelae unless there is an underlying cause.

Hiccups are a distinct sound caused by contraction of the inspiratory muscles terminated abruptly by closure of the glottis. Short, sharp contractions of the diaphragm and inspiratory intercostal muscles occur, coupled with transient closure of the glottis. These events occur from 10 to 30 times per minute. Hiccups are usually transient but may persist.

**Prognosis and complications**

Hiccuping is usually a benign self-limiting condition and does not produce any serious sequelae. Intractable hiccups may cause insomnia, interference with speech and eating, exhaustion, and even death. The prognosis depends on the underlying cause, if any. In a series of 24 patients with a high incidence of organic lesions such as gastrointestinal cancers, mortality was more than 50% during follow-up (33).

**Clinical vignette**

A 35-year-old female with known diagnosis of multiple sclerosis was admitted to the hospital with intractable hiccups of 3 weeks’ duration. Previous MRI scan had shown lesions in the cerebral hemispheres, but none in the brainstem. There were no neurologic signs suggestive of brainstem involvement, but MRI showed a new lesion in the ventral paramedian portion of the medulla oblongata. Hiccups were controlled with baclofen.

**Biological basis**
• Center for hiccups lies in brainstem.

• Hiccups is a syndrome of inappropriate respiratory muscle contraction.

• A large number of causes involving various systems of the body may underly hiccups.

**Anatomic localization**

Three components of the reflex arc involved in hiccups are:

1. **The afferent limb including phrenic, vagus, and sympathetic nerves.**
2. **The center in brainstem.**
3. **The efferent limb consists of phrenic nerve to the diaphragm and accessory nerves to the intercostal muscles.**

The central elements and efferent limbs of the hiccup reflex are better characterized than the afferent limb. Neurotransmitters such as dopamine, gamma-amino-butyric-acid (GABA), serotonin, glutamate, and glycine can regulate this central mechanism, whereas the hiccup arc has modulatory input from catecholaminergic and serotonergic afferents (37). Idiopathic chronic hiccups may result from chronic stimulation of the supraspinal "hiccup center" by impulses originating from receptors in the gastrointestinal tract. This hypothesis implies the possibility of treating idiopathic chronic hiccups by correcting the gastrointestinal abnormalities or suppressing the "hiccup center" (via GABA-ergic effects of baclofen or gabapentin). In experimental animals, a hiccup-like reflex can be elicited by electrical stimulation of the nucleus raphe magnus within the medullary reticular formation. Hiccup-like response can be suppressed by microinjection of baclofen in this area, indicating that it has GABA-B receptors. The hiccup can be considered as an involuntary medullary reflex influenced by, but independent of, the respiratory center of the medulla. Dysfunction of the inferior olivary complex, due to a lesion in that area, has been implicated in the pathogenesis of hiccups. Unilateral lesion of nucleus tractus solitarius in the brainstem has also been associated with intractable hiccups. Plaques in the ventral paramedian portion of the medulla oblongata have been demonstrated in multiple sclerosis patients with hiccups. Medulla oblongata lesions involving bilateral nucleus tractus solitarius as a cause of intractable hiccups were reported on autopsy in a patient with neuromyelitis optica (26). Although brainstem is localized as the region of the brain involved in hiccups, persistent
Hiccups have been reported as a sole manifestation of right cortical infarction without apparent brainstem lesion (52).

**Pathophysiology**

The pathogenesis of hiccups is not clear. Hiccuping is a syndrome of inappropriate respiratory muscle contraction. Hiccups can be considered as a myoclonus of the diaphragm generated by repetitive activity of the "inspiratory solitary nucleus" due to release of higher nervous system inhibitory and regulatory control. EMG studies during persistent hiccups have demonstrated a synchronous respiratory muscle activity in the diaphragmatic and inspiratory (external intercostal) muscles. Coincidental inhibition occurs of expiratory intercostal muscles, and closure of glottis follows immediately with marked reduction in air exchange. These events occur 10 to 30 times per minute. The inspiratory efferents are more vigorously activated during a hiccup than during cyclical respiration.

The commonly observed induction of hiccups by distention of the stomach can be explained by the observation that sudden rapid stretch of the mechanoreceptors in the proximal esophagus can trigger the hiccup reflex in normal subjects. Only rapid distention above a determined volume threshold will predictably induce hiccups in a subject.

Variation in heart rate is often observed during hiccups. Laboratory studies on subjects during hiccups show variations in R-wave-R-wave interval, suggesting that some phasic autonomic efferent activity is associated with hiccups.

Various causes of hiccups are shown in Table 1.

**Table 1. Causes of Hiccups**

**Causes in the gastrointestinal tract and abdomen**

- Distention of the stomach
- Intra-abdominal processes
- Gastroesophageal reflux disease
- Peptic ulcer: *Helicobacter pylori* hiccup
- Pancreatic cancer
- Pharyngitis
• Renal dysfunction (39)

Causes in the chest and the respiratory system

• Excessive smoking
• *Herpes zoster* laryngitis
• Irritation of the diaphragm by a tumor or an inflammatory process
• Mediastinitis or infiltration of the mediastinum by tumor
• Phrenic nerve schwannoma (18)
• *Sarcoidosis* involving mediastinal lymph nodes (40)
• Vagus nerve irritation

Cardiovascular disorders

• Pericarditis
• Myocardial infarction (13)
• Chronic myocardial ischemia
• Cardiac tamponade (11)

Systemic causes

• Acquired immune deficiency syndrome
• Diabetes
• Fever
• Hyponatremia
• Metabolic derangements: uremia
• Primary antiphospholipid syndrome
• Pulmonary *embolism* (22)
• Systemic infections

CNS disorders

• Brainstem lesions
• *Multiple cranial nerve palsies*
• Neoplasms

  - Metastatic tumor at dorsal surface of medulla oblongata (05)
• Vascular lesion
  - **Cavernous angioma** in medulla oblongata
  - **Dolichoectasia** or dissection of the vertebral artery with brainstem compression
  - Lateral medullary syndrome
  - Basilar artery **aneurysm**
  - Primary **medullary hemorrhage**

• Infectious granulomas: tuberculoma
• Covid-19 (03)
• Sarcoidosis involving the brain
• Syringobulbia associated with a Chiari I **malformation**
• Neuromyelitis optica with periaqueductal lesions (area postrema syndrome)
• **Encephalitis**
  - Bilateral carotid artery dissection
• **Meningitis**
• **Movement disorders**: orofacial **dyskinesia**, **Parkinson disease**
• **Migraine**: hiccups as symptom of migraine aura (10)

**Drug-induced hiccups**

• Alcohol
• Anesthetics
• Antibiotics: beta-lactams, macrolides, fluoroquinolones
• Atypical antipsychotic: clozapine
• **Benzodiazepines**
• Barbiturates
• Chemotherapy
• Corticosteroids
• **Digitalis**
• Dopamine agonists used for Parkinson disease
• Intrathecal morphine infusion (31)
• Nicotine gum
• Opioids, eg, tramadol (17)
• **Phenytoin** (06)
• Sedatives
• **Selective serotonin reuptake inhibitors**, eg, sertraline (07)
• Tricyclic antidepressants

**Epidemiology**

There are approximately 4000 admissions for hiccups each year in the United States.

**Differential diagnosis**

**Confusing conditions**

Transient hiccups cannot be confused with any other symptoms and are not a reason for a neurologic consultation. They usually subside with simple remedies or on their own. Differential diagnosis involves determination of the cause from the list in Table 1.

Among the general causes of hiccups, the first conditions to be ruled out are those of the

**Surgery and minimally invasive procedures**

• Abdominal surgery
• Complication after laparoscopic fundoplication for gastroesophageal reflux disease
• Chest surgery
• Dental implant surgery (42)
• **Epidural** injections: bupivacaine, steroid injection (25)
• Gastrointestinal endoscopy under midazolam sedation (30)
• General anesthesia with laryngeal mask airway
• Intrathecal morphine infusion therapy
• Lumboperitoneal shunt complication due to migration of peritoneal catheter and contact with diaphragm; hiccups relieved by repositioning of catheter (57).
gastrointestinal system and the chest. Systemic diseases can be ruled out by concomitant findings. History of drugs suspected to cause hiccups should help to determine the possibility of drug-induced hiccups and can be confirmed if hiccups subside after discontinuation of the offending medicine. Hiccups started in an adolescent with attention deficit and hyperactivity disorder as well as a conduct disorder after adding aripiprazole (an antipsychotic) treatment to extended-release methylphenidate but were relieved only by discontinuation of methylphenidate and not aripiprazole, leading to the conclusion that the cause was concurrent use of methylphenidate and aripiprazole (28). History of recent surgery would indicate the possibility of a cause related to surgery.

The differential diagnosis includes other syndromes of inappropriate respiratory muscle contraction, such as myoclonus of the diaphragm in which spasmodic contractions of the diaphragm occur, but no upper airway closure. Respiratory dyskinesia is an abnormal asynchronous pattern of breathing involving all the respiratory muscle groups and is usually associated with facial and limb muscle dyskinesia. Severe spasmodic contractions of all respiratory muscle groups associated with hypoventilation may occur in status epilepticus, tetanus, and strychnine poisoning but lack upper airway closure.

Among the neurologic lesions that can cause persistent hiccups, brainstem lesions figure prominently. Initially, hiccuping may be the only symptom at the start of a lesion close to the various areas in the brainstem that have been linked to hiccups.

Area postrema syndrome, a part of the neuromyelitis optica spectrum of disorders, can present solely with nausea, vomiting, and hiccups but no neurologic signs. Cases of this syndrome have been reported that can present atypically with aquaporin-4 IgG antibody negativity (positivity is usually required for diagnosis) and lesions on MRI in the area postrema, which is an emetogenic center targeted by the antibodies (08).

Cerebellar hemangioblastoma has been reported to cause hiccups due to compression of the brainstem at the level of the medulla oblongata (35). Hiccups were relieved after excision of the tumor. Intractable hiccup was the presenting symptom of a medullary cavernoma diagnosed by brain imaging and was relieved after resection of this lesion (14).

There is a case report of an elderly patient that presented with persistent hiccups and vomiting and who was found to have unilateral palsies of cranial nerves V, VII, VIII, IX, and X due to herpes zoster virus without skin lesions (56). Varicella zoster virus-DNA was positive on CSF examination using polymerase chain reaction, and the patient responded well to treatment with intravenous acyclovir and steroids.
Neurologic examination would usually reveal other neurologic signs, and the diagnosis can be confirmed by brain imaging studies. Nonlocalizing neurologic lesions such as meningitis and encephalitis may be associated with hiccups, but they also have several other signs and symptoms, such as neck stiffness and headache, in the case of meningitis. Persistent hiccups in a patient known to have multiple sclerosis indicate the appearance of a new lesion in the brainstem. Intractable hiccups and nausea are unique symptoms in neuromyelitis optica and are early indicators of exacerbation of the disease (48).

Hiccups may be the symptom of a more serious non-neurologic disorder. A patient who presented with hiccups was ultimately diagnosed to have renal abscesses (15).

The diagnosis of idiopathic chronic hiccup is made by excluding identifiable causes. Diagnosis of psychogenic hiccup also requires the exclusion of physical causes and the detection of an abnormal psychological state.

**Associated or underlying disorders**

These are included in Table 1.

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**Diagnostic workup**

**Key tests and procedures**

- Thorough medical and neurologic examination
- Complete blood count and blood chemistry
- Chest and abdominal x-rays
- Brain imaging for suspected CNS lesion
A patient with persistent hiccups requires a thorough medical and neurologic examination to detect underlying pathology. The basic laboratory work-up should include a complete blood count and blood chemistry to rule out metabolic disorders such as uremia. Chest and abdominal x-rays are indicated to rule out dilatation of the stomach, abnormalities of the diaphragm or chest, and abdominal lesions. X-ray of the upper gastrointestinal tract following barium swallow should be done for suspected gastrointestinal reflux disease. This may be supplemented by upper endoscopy, ultrasonic examination, and CT scan. For suspected neurologic lesions, the investigations are done according to the suspected lesion. MRI scan should detect most of the brainstem lesions associated with hiccups.

Management

- Correction of the underlying cause if detected
- Pharmacotherapy
- Nonpharmacological approaches
- Unconventional methods

Various methods of management of hiccups are listed in Table 2.

Table 2. Management of Hiccups

Treatment of the cause if identified
• Correction of metabolic abnormality
• Treatment of gastroesophageal reflux disease
• Decompression of the distended stomach by intubation
• Discontinuation of the offending drug in drug-induced syncope
• Removal of posterior fossa tumor causing brainstem compression

**Pharmacotherapy**

• Amitriptyline
• **Anticonvulsants:** carbamazepine, valproic acid
• Dexmedetomidine
• GABA-ergic medications: baclofen, gabapentin (51)
• Dopamine agonists: pramipexole
• **Neuroleptics:** chlorpromazine (intravenous), haloperidol
• Lidocaine: intravenous or oral
• Non-narcotic analgesic: nefopam
• Nonpolarizing muscle relaxant: cisatracurium
• Methylphenidate
• Prokinetic drugs
• Selective serotonin reuptake inhibitor: sertraline
• Combination therapy: 2 or more of the above agents

**Nonpharmacological approaches**

• **Acupuncture**
• Carbon dioxide inhalation
• Carotid massage
• Heart rate variability biofeedback (23)
• **Hyperventilation**
• Hypnosis
• Kinesio taping

**Unconventional methods**

• Pressure on the eyeballs
• Rapidly swallowing water on ice chips
• Stimulation of pharynx with a catheter introduced through the nose
• Stimulation of the root of the tongue
The cause of hiccup, if identified, should be treated. For example, the offending drug may be discontinued, or its administration may be modified. For example, a randomized, multicenter, phase 3 trial showed that hiccup intensity was significantly lower when the antiemetic corticosteroid was rotated from dexamethasone to methylprednisolone without a change in emesis intensity than that when dexamethasone was maintained (19).

**Pharmacotherapy.** The approach to management is to try simple maneuvers, and if unsuccessful, a trial of pharmacotherapy is made. Gastroesophageal reflux disease should be treated with a proton pump inhibitor as the first-line therapy (43).

Chlorpromazine had been the classic drug of choice for persistent hiccups and remains the only drug for hiccups approved by the U.S. Food and Drug Administration. It acts as an antagonist on multiple central and peripheral neurotransmitter sites including dopamine, serotonin, histamine receptors, alpha-adrenergic receptors, and muscarinic receptors.

Baclofen is the most used and the most effective drug for hiccups. If no response occurs, then combination therapy may be considered. Baclofen combined with intravenous steroids was
used to successfully treat a patient with recurring episodes of **convulsive syncope** following intractable hiccups resulting from pharyngitis (46). The hiccups also improved and disappeared 6 days thereafter. A systematic review of studies of pharmacotherapy of hiccups found no high quality data on which to base treatment recommendations. With the limited information available, baclofen and gabapentin remain as first-line therapy for persistent and intractable hiccups (45). In a case series of 4 patients, improvement or resolution of intractable hiccups by use of gabapentin was reported in a **stroke** rehabilitation setting (20).

The efficacy of cisapride, omeprazole, and baclofen for treatment of idiopathic chronic hiccup has been proven in several studies. The combination is considered, at present, to be the "therapy of choice" for this condition. In cases where the results are not entirely satisfactory, the addition of gabapentin should be considered. Idiopathic hiccup can be managed with **alpha-2-delta ligand, pregabalin**. Intractable hiccups in patients with ischemic lesions of the medulla respond to a short course of gabapentin with immediate disappearance of the hiccups.

Carvedilol, a drug with several pharmacologic effects including nonspecific beta blockade, alpha-1 blockade, and calcium channel inhibition, has been used for the treatment of hiccups. The exact mechanism of action in hiccups is not known.

Dexmedetomidine, a sedative analgesic that acts as an agonist of alpha2 receptors in the spinal cord has been reported to be beneficial for intraoperative hiccups induced by general anesthesia with laryngeal mask airway (27). Dexmedetomidine is also used for prevention of persistent postoperative hiccups (32).

Intravenous lidocaine has been used for treatment of hiccups. An oral preparation containing 2% lidocaine in a gel formulation has been reported to be effective for control of hiccups (38).

Metoclopramide has been shown to control migraine-associated hiccups (21). The mechanism is restoration of esophageal smooth muscle function by competitive dopaminergic antagonism and a prominent cholinergic agonist activity of metoclopramide.

Drug-induced hiccup may be managed by replacement of the offending drug with an alternative in the same therapeutic category. Dexamethasone, used for the prevention of chemotherapy-induced **nausea and vomiting**, may cause hiccups, which has been relieved in several cases by switching to prednisolone (24).
High doses of a prokinetics, drugs for gastroesophageal reflux disease, have been used to successfully treat persistent hiccups after chemotherapy for metastatic colorectal cancer (53). A patient with lung cancer who suffered from persistent hiccups due to chemotherapy with cisplatin, pemetrexed, and bevacizumab was successfully managed with pregabalin after other treatments failed and was able to continue chemotherapy without recurrence of hiccups (36).

A chronic case of chronic idiopathic intractable hiccups was successfully treated with cisatracurium, a nondepolarizing muscle relaxant, under intravenous general anesthesia (55). When hiccups recurred 2 weeks later, the procedure was repeated with success, and the patient was hiccup free for at 6 months follow-up.

**Unconventional methods.** Several of these methods, such as breath-holding, have inconsistent performance with no studies to confirm their effectiveness. The forced inspiratory suction and swallow tool (FISST) for stopping hiccups consists of a rigid drinking tube with an inlet valve that requires suction effort to draw water from a cup into the mouth and has been patented as “HiccAway.” Suction through the tube generates high negative intrathoracic pressure, leading to contraction of the diaphragm, which is followed immediately by closure of the epiglottis and cessation of hiccups. A clinical study showed that FISST stopped hiccups in approximately 92% of cases and was more effective than other home remedies (02).

**Acupuncture.** Successful use of acupuncture for control of hiccups has been reported (59; 54). Acupuncture has been used for control of persistent postoperative hiccups. Near-infrared irradiation, applied on custom-set acupuncture points, was shown to be effective in the treatment of intractable hiccups (09). A systematic review of clinical trials suggests that acupuncture may be an effective treatment for patients suffering from hiccups following stroke when used as an adjunct to medical treatment (58). However, no definitive conclusion can be reached because of poor methodology of trials, and rigorously designed clinical trials are required.

**Carbon dioxide retention.** An experimental study on normal human volunteers for inducing CO2 retention by rebreathing determined that to successfully obstruct the mechanisms causing hiccups, it is necessary that the level of inspired CO2 not only increase at the same level as expired CO2, but also reach approximately 50 mm Hg (41). After demonstrating the safety of this approach, by rebreathing in a 20 L air-filled plastic bag, it was used successfully to stop hiccups in 2 patients.
**Kinesio taping.** This is a taping technique in alternative healthcare and is used in physiotherapy by specially trained professionals to treat musculoskeletal conditions. Anterior and posterior diaphragm kinesiology taping was applied successfully in an attempt to inhibit diaphragm spasm and intractable hiccups in a patient with acute infarction in the territory of the posterior inferior cerebellar artery where pharmacologic interventions had failed (16).

**Anesthesia.** A large variety of interventions have been proposed for the treatment of hiccups during anesthesia and sedation. However, no treatment is "evidence-based," and no valid recommendations for the treatment of hiccups can be derived. Short-term anesthesia has been used to stop persistent hiccups. General anesthesia with positive-pressure ventilation and muscle relaxation has been used for the termination of chronic hiccups has been described. Persistent hiccups in a patient awakening from anesthesia did not respond to deepening of anesthesia but was controlled with propofol, a short-acting intravenous anesthetic (47).

**Nerve blocks.** Blocking of the glossopharyngeal nerve and sphenopalatine ganglia have been used. Ultrasound-guided continuous phrenic nerve block has been used successfully for persistent hiccups (44). Three patients who developed hiccups following abdominal surgery were successfully treated with sphenopalatine ganglion block to stop the hiccups (29).

**Surgery.** Apart from removal of the offending lesions, surgical procedures are the last resort (49).

In one patient with intractable hiccups, computed tomography showed an exostosis originating from the costochondral junction of the left fourth rib. Removal of a 2 cm rib segment including the exostosis was followed by relief of hiccups (01). Neurosurgical decompression of lesions compressing the dorsal medullary region may relieve intractable hiccups originating from this area (04). Intractable hiccups due to a cavernous malformation of the medulla oblongata resolved after resection of the lesion (50). Decompression surgery is an appropriate method for relieving intractable hiccups as the main symptom of Chiari type I malformation (12).

**Concluding remarks.** According to a systematic review of clinical trials, there is insufficient evidence to assess the efficacy of treatment of persistent or intractable hiccups by either pharmacological or non-pharmacological methods (34). Because of the relative rarity and unpredictable onset of the symptom, it would be difficult to plan clinical trials or recruit enough patients. Moreover, the clinical trials would need to be multicenter and possibly multinational.
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Contributors

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Dr. Jain is a consultant in neurology and has no relevant financial relationships to disclose.
SEE PROFILE

Patient Profile

Age range of presentation

0 month to 65+ years