CASE REPORT

Persistent Hiccups (Singultus) as the Presenting Symptom of Medullary Cavernoma

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SUMMARY

Background: Singultus (hiccup) is common, usually transient, and only rarely indicative of disease. If it persists, it can be highly bothersome, potentially interfering with sleep and leading to depression and physical exhaustion. It is presumed to be due to a disturbance in a reflex arc that includes the brainstem, the phrenic nerve, the vagus nerve, and the sympathetic chain. It can be induced by mechanical irritation (e.g., gastric distention), metabolic or toxic irritation (e.g., alcohol, cigarette smoke), infectious processes, emotional disturbances, and, rarely, neurological diseases.

Case description: The patient presented with persistent singultus (by definition, singultus lasting more than 48 hours). Initial diagnostic tests failed to reveal the cause, and the hiccups failed to respond to medications and other attempted treatments. Finally, an imaging study revealed a medullary cavernoma. After neurosurgical resection of this lesion, the patient was asymptomatic and returned to work.

Conclusion: This case shows that singultus, though it may seem trivial, deserves to be taken seriously, particularly when it persists and does not respond to medications. Its cause can be discovered in timely fashion by means of a thorough clinical history, physical examination, and ancillary testing.

► **Cite this as:**

Eisenächer A, Spiske J: Case report: Persistent hiccups (singultus) as the presenting symptom of medullary cavernoma. *Dtsch Arztebl Int* 2011; 108(48): 822–6. DOI: 10.3238/arztebl.2011.0822

Singultus (Latin: sobbing, gasping) is a well-known, usually short-term phenomenon. Hiccupping is a reflex inspiratory movement that leads to sudden closure of the vocal cords. It is thought to be a disruption to the swallowing reflex arc. This involves the phrenic nerve, the vagus nerve, the sympathetic nervous system, and the brainstem (1, 2). Specifically, the reflex arc can be divided into three parts:

- The afferent branch: this consists of the nerve fibers of the phrenic nerve, the vagus nerve, and the thoracic sympathetic nervous system (Th6–Th12).
- The central connection: the neuronal connection between the brainstem and the hypothalamus with involvement of various cranial nerve nuclei.
- The efferent branch: innervation of the diaphragm by the phrenic nerve (C3–C5), innervation of the anterior scalene muscles (C5–C7), innervation of the intercostal muscles (Th1–Th11), and finally innervation of the glottis by the recurrent branch of the vagus nerve.

It is important to distinguish between acute and chronic, or persistent, singultus. Acute hiccups usually last only a short time and are self-limiting. Potential causes include strong distension of the stomach, sudden temperature changes, chemical substances (e.g. alcohol, smoking), and psychogenic alterations. If they persist for longer than 48 hours, they are described as persistent hiccups. This results in an extremely bothersome situation for the patient, which may result in sleep disturbances, depression, and exhaustion (2).

Persistent singultus can indicate a number of different abnormal processes in the reflex arc. It is therefore important to perform comprehensive diagnostics. *Table 1* shows the possible causes and necessary diagnostic measures, in line with the recommendations of Kuhn et al., Vecellio et al., and Guelaud et al. (3–5). According to Guelaud et al., gastrointestinal etiology accounts for approximately two thirds of cases (5). However, singultus can also be the primary symptom of an intra-abdominal, intrathoracic, or cranial disease.

The authors intend the following case report to indicate a rare cause of singultus that can be identified in differential diagnosis and treated.

TABLE 1

Causes and diagnostic measures for chronic singultus (according to the recommendations of Kuhn et al., Vecellio et al., and Guelaud et al. [3–5])

Cause		Diagnostic measures
Gastrointestinal etiology	Diaphragmatic hernia/tumor, esophageal carcinoma, esophageal ulcer, reflux esophagitis	Endoscopy pH manometry 24-hour pH monitoring CT of abdomen and chest
Infection	Syphilis, pneumonia, pleurisy, myocarditis, empyema	Laboratory testing Bronchoscopy
Operation and anesthesia	Status following thoracic, abdominal, or cranial surgery	Medical history Bronchoscopy Pulmonary function test
Neurological etiology	Cranio-cerebral injury, syringomyelia, astrocytoma, encephalitis/meningitis, neurosyphilis, multiple sclerosis, cerebrovascular diseases, tabes dorsalis, stroke, giant cell arteritis	(Contrast) MRI Electroencephalography Lumbar puncture Laboratory testing
Metabolic and toxic etiology	Diabetes mellitus, uremia, hyponatremia, hypokalemia, alcohol, hypocapnia	Laboratory testing
Drugs	Barbiturates, diazepam, alpha-methylidopa, dexamethasone	Medical history
Psychogenic	Stress, conversion reaction	Medical history
Idiopathic		Medical history

TABLE 2

Drug-based treatment

Drug	Dose
Baclofen	3 × 5 to 20 mg PO
Gabapentin	3 × 300 to 600 mg PO
Chlorpromazine	3 × 25 to 50 mg PO or 25 mg IV
Carbamazepine	3 × 100 to 300 mg PO
Metoclopramide	3 × 10 mg PO or 10 mg IV
Haloperidol	3 × 1 to 4 mg PO
Amitriptyline	3 × 10 to 25 mg PO
Lidocaine	1 to 2 mg/kg body weight IV
Nimodipine	3 × 30 mg PO
Valproate	Incremental rises up to 20 mg/kg body weight

After diagnosis, treatment should follow primarily causal lines. However, if causal diagnostics prove unsuccessful, various drug-based and non-drug-based treatments can be used. *Tables 2 and 3* (5–7; 9–13) provide an overview of the various treatment options. Drug-based treatment may include a combination of various drugs, e.g. haloperidol plus metoclopramide (7). Petroianu et al. recorded complete remission of singultus in 40% of all patients treated with a combination of 3 × 10 mg cisapride, 20 mg omeprazole, and 3 × 15 mg baclofen (8). If no improvement can be achieved using the selected medication, treatment should promptly be stopped (3). Following non-drug-based treatment, such as drinking iced water or breathing into a bag, Becker (9) states that additional improvement can be achieved by increasing CO₂ partial pressure. If both conservative, non-drug-based treatment and medication fail to provide any relief, surgery, e.g. partial resection of the phrenic nerve, can be considered as a last resort.

However, most of the available information is in the form of small case studies or case reports, which makes evidence-based treatment recommendations impossible to provide. Treatment is therefore dependent on the empirical experience of each treating physician.

TABLE 3

Non-drug-based treatment

Treatment	Possible measures
Respiratory maneuver	Holding breath, Valsalva maneuver, hyperventilation, breathing into a bag, supra-supramaximal inhalation (10)
Nasal and pharyngeal stimulation	Pressure on root of nose or upper lip, inhalation of stimulants, gargling water, drinking iced water quickly, sneezing, stimulation of roof of mouth
Vagus nerve stimulation	Pressure on eyeball, carotid massage
Evacuation of the stomach	Induced vomiting, stomach probes, fasting
Calming the phrenic nerve	Cooling or massaging of the upper abdomen, block or partial resection of the phrenic nerve
Psychiatric treatment	Behavioral therapy, hypnosis
Acupuncture	Acupuncture at points PC6 (Nei Guan), ST36 (Zu San Li), DU9 (Chih Yang) (11)
Electrotherapy	Faradic and galvanic current, electrophrenic stimulation

Case description

A 26-year-old soldier in the German Army attended an appointment with an armed forces physician with persistent singultus that had not improved following self-treatment (drinking cold water). The singultus was described as dependent on the physical activity and affected by consumption of small amounts of food. The patient had no history of neurological or other complaints. Physical examination yielded no findings indicative of a possible cause.

Initial treatment involved oral and intravenous metoclopramide, but no improvement was achieved. Initial diagnostics involved the following procedures:

- Gastroscopy
- Laboratory testing to determine gastrointestinal parameters and infection parameters
- Blood count
- Abdominal computed tomography (CT).

These measures also failed to yield useful findings. Following consultation with the on-site specialized neurological and psychiatric unit, promethazine was administered, but did not lead to improvement. The patient subsequently reported a recurring lack of concentration and dizzy spells. He also reported a feeling of no longer being able to focus on the distance while driving.

Further diagnostic measures included inpatient admission to the Berlin Forces' Hospital. Internal medical status on admission included a slight bilateral kinetic tremor, reported double vision, and paresthesia in both arms (more pronounced in the left arm than the right). Neurological examination revealed altered sensitivity in the region of the C4 dermatome on the left-hand side and a slight alteration in the C5 reflex contraction, which was more pronounced on the left. Gabapentin was administered but achieved no significant improvement.

The next diagnostic step taken was magnetic resonance imaging (MRI) of the head. This revealed a space-occupying lesion measuring 2.2 cm in the medulla oblongata, apparently compatible with cavernoma and multiple hemorrhaging (*Figure 1*). Neurosurgical intervention was decided on for definitive treatment. One day before the day on which surgery was scheduled the patient experienced a sudden deterioration in consciousness and respiratory failure. An emergency CT showed hemorrhaging into the medullary cavernoma. Emergency, but complication-free, neurosurgery was performed: using microsurgical osteoplastic suboccipital craniotomy. This successfully removed the hematoma and the cavernoma. The double vision that had occurred before surgery resolved completely. Follow-up examination showed no significant abnormalities or focal neurological deficits, and the singultus had resolved completely. The patient reported only slight tingling in the soles of the feet, which did not limit his activities.

Neurosurgical follow-up using imaging diagnostics and determination of the definitive scope of care were performed following an eight-week convalescence

Figure 1: Head MRI showing a cavernoma measuring approximately 2.2 cm with multiple hemorrhaging in the medulla oblongata

Figure 2: Follow-up head MRI 8 weeks after surgery

KEY MESSAGES

- Chronic hiccupping is defined as singultus lasting more than 48 hours and representing an extremely bothersome situation for the patient, often associated with sleep disturbances, depressive moods, or physical exhaustion.
- Singultus can indicate a number of different abnormal processes in the reflex arc. This consists of the afferent branch, the central connection, and the efferent branch.
- Following successful diagnosis, treatment should follow primarily causal lines.
- If drug-based and non-drug-based treatment that has generally proved beneficial fails to achieve an improvement, rarer causes should be considered and investigated using further diagnostic procedures.

period. Head MRI revealed scar tissue resulting from the removal of the cavernoma from the medulla oblongata in the left paramedian region (*Figure 2*). There was no indication of a further space-occupying lesion in the form of residue, bleeding, or ischemia.

Discussion

Persistent or chronic singultus is a sign of a disruption to the complex reflex arc, involving the above-mentioned nerves and regions of the brain. The diagnostic work-up must therefore be multifaceted and interdisciplinary. Because Guelaud et al. state that etiology is gastrointestinal in a majority of cases, this should be considered during initial diagnosis (5). Medical history and physical examination often provide important clues to etiology. Laboratory diagnostic tests should be performed promptly, as these alone can narrow down differential diagnosis. If parameters are normal, a toxic, metabolic, or infectious etiology can often be ruled out. Machine-based (e.g. CT of the chest and abdomen) or if necessary invasive (e.g. gastroscopy, bronchoscopy) diagnostic measures should then be taken. All these steps and symptomatic drug-based treatment may prove unsuccessful, so rarer causes must also be considered during differential diagnosis.

In the case reported here, isolated, persistent singultus that did not respond to drug-based treatment was the only symptom. Initial diagnosis revealed neither abnormal laboratory findings nor helpful findings following esophagogastrosocopy. Only when rarer causes were considered and diagnostic measures were taken as a result was it possible to detect a cavernoma that had bled multiple times in the region of the medulla oblongata.

An animal study by Musumeci et al. (12) revealed that the region of the medulla oblongata lateral of the obex is partly responsible for the singultus reflex, and that the nucleus raphe magnus contains GABA-active cells (GABA: gamma-aminobutyric acid) with singultus-inhibiting functions. Compression in this region can sometimes induce chronic singultus. Hassler et al. (13)

base a model for persistent singultus on interactional dysfunction of various regions of the brainstem. According to Askenasy (14), the locus of the dysfunction is in the olivar area and the posterolateral regions of the reticular formation.

Individual cases described by Musumeci et al. (12) and Mattana et al. (15), however, showed cavernoma in the region of the medulla oblongata in patients with persistent singultus. Overall, singultus is only rarely described in the context of a tumor in the region of the medulla oblongata (16). Despite the everyday phenomenon of “hiccupping,” there are few studies concerning its incidence and prevalence. Soudjian et al. (6) investigated 181 male and 39 female patients in a retrospective study in 1968 with chronic hiccups. This revealed that there was an organic etiology in 93% of male patients. In contrast, a psychogenic cause was detected in most female patients.

Summary

This case shows that even primary care physicians’ daily practice can include rare neurological disorders presenting with isolated, persistent hiccups as their primary symptom. However, if neurological symptoms occur during disease progression, head MRI should be performed promptly. If cavernoma is revealed to be the cause of singultus, prompt neurosurgical removal of the tumor should be performed, followed by neurological rehabilitation.

Conflict of interest statement

The authors declare that no conflict of interest exists.

Manuscript received on 16 March 2011, revised version accepted on 29 August 2011.

Translated from the original German by Caroline Devitt, MA.

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