

**Are your MRI contrast agents cost-effective?**  
Learn more about generic **Gadolinium-Based Contrast Agents**.



**AJNR**

**Intractable hiccups: the role of cerebral MR in cases without systemic cause.**

K Marsot-Dupuch, V Bousson, J Cabane and J M Tubiana

*AJNR Am J Neuroradiol* 1995, 16 (10) 2093-2100

<http://www.ajnr.org/content/16/10/2093>

This information is current as of February 9, 2025.

# Intractable Hiccups: The Role of Cerebral MR in Cases without Systemic Cause

K. Marsot-Dupuch, V. Bousson, J. Cabane, and J. M. Tubiana

**PURPOSE:** To look for central nervous system abnormalities as possible causes of intractable hiccups. **METHODS:** Of a series of 50 patients with chronic (ie, lasting more than 48 hours) hiccups, a prospective study identified a subgroup of 9 patients with no clinical or gastroesophageal abnormalities (according to endoscopy, pH monitoring, and manometry). We performed in all 9 patients brain and upper cervical cord MR examination with precontrast and postcontrast T1- and T2-weighted sequences. A study of the last cranial nerves was done with thin T2-weighted imaging (constructive interference in a steady state sequence). The cervical cord and parapharyngeal space were systematically explored using coronal T2- and sagittal T1-weighted imaging. **RESULTS:** Five of these 9 patients had definite MR abnormalities located in the temporal lobe (3 cases), cerebellopontine angle (1 case), or areas of high signal intensity compatible with demyelination (1 case). The relationship between hiccups and infratentorial abnormalities in 2 cases was doubtful (vascular loop and prominent posterior condylar canal). MR findings in 2 cases were considered normal. **CONCLUSIONS:** Brain MR is a useful investigation in patients with chronic hiccups when gastroesophageal lesions are either excluded or too mild to account for an intractable hiccup.

**Index terms:** Brain, abnormalities and anomalies; Brain, magnetic resonance; Magnetic resonance, indications

*AJNR Am J Neuroradiol* 16:2093–2100, November 1995

Acute hiccup (singultus) is a benign, frequent, and transient phenomenon most commonly caused by overdistension of the stomach from overeating, eating too fast, alcohol ingestion, tobacco use, or sudden changes of gastrointestinal temperatures. It is an involuntary spasmodic contraction of the inspiratory muscles associated with an upper airway closure causing a peculiar sound.

In contrast, intractable hiccup is an uncommon, chronic, and incapacitating disturbance defined as hiccup bouts lasting more than 48 hours or recurring despite various treatments

and affecting male subjects more than female (81% in a retrospective study of the Mayo Clinic carried out on 220 patients) (1). This rare clinical symptom often results (93%) from an underlying serious pathologic process (2). Therefore, looking for a cause by a systematic diagnostic approach is mandatory for effective treatment of persistent hiccups. Gastrointestinal diseases emerged recently as the most frequent causes to search for, because approximately two thirds of those patients have a gastroesophageal reflux (3).

Our purpose was to perform brain magnetic resonance (MR) in a selected group of patients with chronic hiccups in whom other causes were ruled out, to evaluate for intracranial disease as the possible cause of the chronic hiccups, and to characterize and locate such central nervous system disease.

## Materials and Methods

Nine patients were evaluated with MR in this study between September 1993 and July 1994. All were referred

---

Received October 25, 1994; accepted after revision April 24, 1995.

From the Department of Radiology (K.M.-D., V.B., J.M.T.) and Service de Médecine Interne du Pr Imbert (J.C.), Hôpital Saint-Antoine, Paris, France.

Address reprint requests to Dr K. Marsot-Dupuch, Département de Radiologie, Hôpital Saint-Antoine, 184 Rue du Faubourg Saint-Antoine, 75571 Paris Cedex 12, France.

*AJNR* 16:2093–2100, Nov 1995 0195-6108/95/1610-2093

© American Society of Neuroradiology

for attacks of hiccups intractable to various therapeutic approaches lasting from 12 days to 30 years (average, 7 years).

During the study period 50 patients with chronic hiccups were treated by a multidisciplinary research team devoted to the study of hiccups. This team included a pneumologist, a gastroenterologist, an ear, nose, and throat specialist, and a neurologist and was under the responsibility of a medical internist professor. The patients were investigated according to a standardized three-step protocol to look for the main known causes of hiccups. The first stage was to gather the medical history, the chronology of hiccup bouts, and the associated present symptoms. The patients underwent physical examination including blood tests and chest x-ray. Second, gastroesophageal investigations were systematically performed including manometry, pH monitoring, and endoscopy. Furthermore, we performed a cervicothoracic computed tomographic scan to look for thoracic hiccup causes that may occur along the course of the phrenic or vagus nerves. The majority of our patients were treated at this stage, because the gastroesophageal disorders are the main cause of hiccups. The third-stage brain MR was performed only for those patients in whom either stages 1 and 2 yielded no satisfactory results, maximum esophageal treatment failed to cure the hiccups, or associated neurologic symptoms (paresthesia, seizures, etc) were present at the initial clinical examination. Thus only 9 patients were included in the present study.

All examinations were performed on a 1-T superconductive MR scanner. The noncontrast MR included axial, coronal, and sagittal spin-echo T1-weighted images (500/15/2 [repetition time/echo time/excitations]) and axial T2-weighted images (3500/19,93/2). Thin coronal T2-weighted images were performed to study the cervical cord. Postcontrast T1-weighted images in axial and coronal views were obtained immediately after intravenous injection of 0.2 mmol/kg gadoterate dimeglumine using identical precontrast parameters. Fine study of root entry zone of 9th, 10th, and 11th cranial nerves was always performed, using a three-dimensional Fourier transform constructive interference in steady state sequence (50/20/8/2), allowing contiguous 0.7-mm T2-weighted images. This gradient-echo sequence delineates the pathway of nerves as a fine, linear hypointense structure surrounded by the high signal of cerebrospinal fluid. Computed tomography was performed only when bone abnormalities or brain calcifications were suspected by MR. All imaging investigations were evaluated by two unblinded neuroradiologist reviewers, looking for brain abnormalities, cerebellopontine angle diseases, cervical cord abnormalities, and parapharyngeal lesions especially close to the jugular foramen.

## Results

The main features characteristic of the nine patients studied with MR are depicted in Table

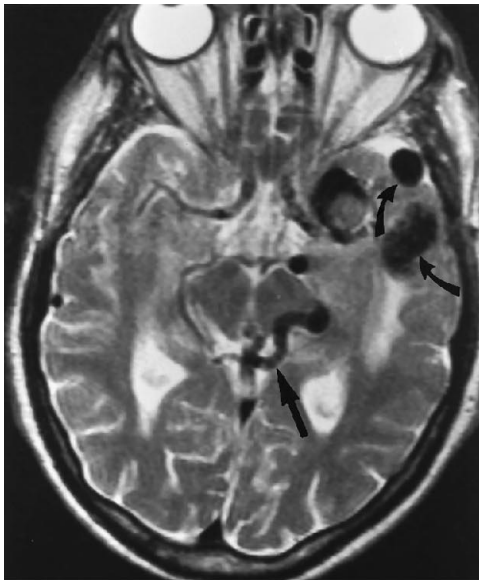
1. All were men. They were 34 to 83 years of age with a mean of 57 years. The onset of hiccups was always sudden. In three cases, hiccups appeared simultaneously with a first attack of seizures (case 5), *Listeria* meningoen-cephalitis (case 9), or after a C1–2 herpes zoster (case 8). All these nine patients had a long invalidating history of hiccups (average, 7 years), except one case (case 7), in which hiccups lasted only 12 days and spontaneously disappeared with no recurrence until now. In two cases, hiccups were at the origin of a severe weight loss (more than 12 kg; cases 3 and 9), and in one, it caused a severe mental stress (case 5). Associated neurologic symptoms were found by clinical examination in four cases: attacks of inferior limb paresthesia (case 1), seizures (case 5), *Listeria* meningoen-cephalitis (case 9), and C1–2 herpes zoster (case 8). Six cases had associated digestive diseases: three hiatus hernia (cases 2, 3, and 4) and four gastro-intestinal reflux (cases 3, 4, 7, and 9).

Despite the hiccup bouts, MR examination was always of enough quality to identify the brain abnormalities in T1- and T2-weighted sequences. Thin T2-weighted images were of poor quality in three cases because of patient movement or pulse artefacts. MR study depicted brain abnormalities in seven cases. Supratentorial lesions were found in four patients, three in the temporal lobe (left side, two; right side, one), and one had diffuse high-signal-intensity T2 lesions in the white matter. The temporal lesions were an arteriovenous malformation (case 4, Fig 1), an intracranial neoplasm with features suggesting an oligodendroglioma (case 5), and a scar of *Listeria* encephalitis (case 9, Fig 2). Infratentorial abnormalities were depicted in three patients, one with a brain stem lesion (case 3, Fig 3) infiltrating the root entry zone of the last cranial nerves and one with a bone variant compressing inferomedially the 9th and 10th nerve bundle, in the cerebellopontine angle (case 2, Fig 4). The latter presented with small brain stem infarcts and a vascular loop of the vertebral artery close to the root entry zone of the cranial 9th and 10th nerves (case 8, Fig 5). All these three last anomalies were well depicted on thin T2-weighted images. Demyelinating disease correlated to clinical symptoms and perturbed cerebrospinal fluid analysis suggesting multiple sclerosis was seen in case 1. The cervical cord

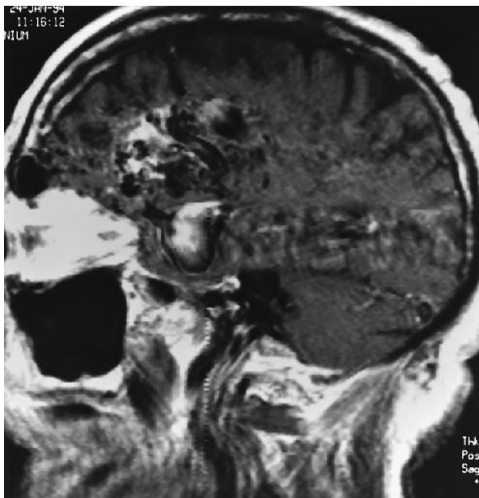
TABLE 1: Duration of hiccups and brain MR findings

Case	Sex	Age, y	Duration of Hiccups	History	Associated Signs	Brain Imaging	Location	Evoked Diagnosis
1	M	34	3 y	...	Lower limb paresthesia Hiatal hernia	Multiple high-intensity lesions on T2	Supratentorial white matter	Multiple sclerosis
2	M	80	15 mo	...	Hiatal hernia	Bony compression of the IX, X, XIth nerves	L jugular foramen	Prominent postcondylar canal
3	M	41	15 y	L cerebellar "cavernoma" operated on 9 y ago; gastric schwannoma	Cerebellar signs, 20-kg weight loss, hiatal hernia and GE reflux GE reflux	Infiltrating lesion showing gadolinium enhancement, calcifications (CT)	L retroolivary area	Choroid plexus papilloma? ependymoma?
4	M	78	3 y	...	GE reflux	Serpentine areas of signal voids	L temporal lobe	Arteriovenous malformation
5	M	41	2 y	...	Epilepsy, GE reflux	Cystic and tissular process, partial gadolinium enhancement, irregular calcifications	L temporal lobe	Oligodendroglioma?
6	M	55	30 y	Gastrectomy	Barret esophagus	Ventricles, cortical sulcus dilatation	Supratentorial and infratentorial	None
7	M	58	12 d		GE reflux	Mega cisterna magna	Infratentorial	None
8	M	83	1 y	C1-2 herpes zoster 12 mo before	Sinusitis	Multiple punctuate high-intensity lesions on T2, vertebral artery loop, cerebral atrophy	Supratentorial and infratentorial	Vascular loop atrophy, ischemia
9	M	43	7 y	Listeria encephalitis	12-kg weight loss, GE reflux	Hyperintense triangular lesion on T2 without gadolinium enhancement	R temporal lobe	Scar tissue

Note.—GE indicates gastroesophageal.



A



B

Fig 1. Case 4, MR axial T2-weighted image (3500/93/1) (A) and postcontrast sagittal T1-weighted image (500/15/2) (B) show left frontotemporal round and serpentine areas of signal void (*curved arrows*) (A and B) with a large draining vein (*arrow*) leading into the vein of Galen (A): frontotemporal arteriovenous malformation.

and the upper parapharyngeal space appeared normal in all the patients.

## Discussion

Although rare, persistent hiccups can be a very unpleasant and even debilitating disease causing mental stress, dehydration, weight

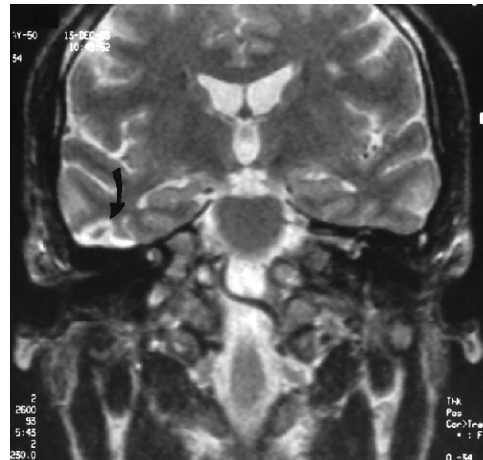


Fig 2. Case 9, coronal T2-weighted MR image (2600/93/2) shows a high-intensity triangular area (*curved arrow*) in the right temporal lobe: sequela of a listeria encephalitis.

loss, and even death (4). This largely neglected symptom was only recently evaluated by a careful investigation led by a specialized medical team devoted to chronic hiccups. Large prospective studies on the affected population can be the clue to an improved knowledge and understanding of the causes and the treatment of hiccups.

Until recently, many physiopathogenic hypotheses in the genesis of hiccups were considered, such as seizures, fetal breathing or gasping, chronobiological disturbance, or a postanoxic syndrome (1, 2). Today, even if its physiopathology remains unclear, hiccups is thought to be related to a stimulation, probably by damage or irritation, of one or more portions of the so-called hiccup reflex arc (Fig 6). The central coordination of hiccupping is not well defined. A brain stem hiccup center near the respiratory center in the medulla has been postulated by some authors. More recent studies attributed it to a nonspecific anatomic location in the spinal cord between C-3 and C-5 segments. Furthermore, supratentorial areas likely play a role in the genesis of hiccups by a stimulation of this reflex arc or by a decrease of normal inhibition(s) of hiccup neurons. The main reported key zones seem to be the hypothalamus (5), the temporal areas (6), and the reticular activating substance (5, 7). Therefore, any process occurring along this reflex arc can promote chronic hiccups. The length of this arc suggests the multitude of possible pathologic organic processes in question (Table 2).

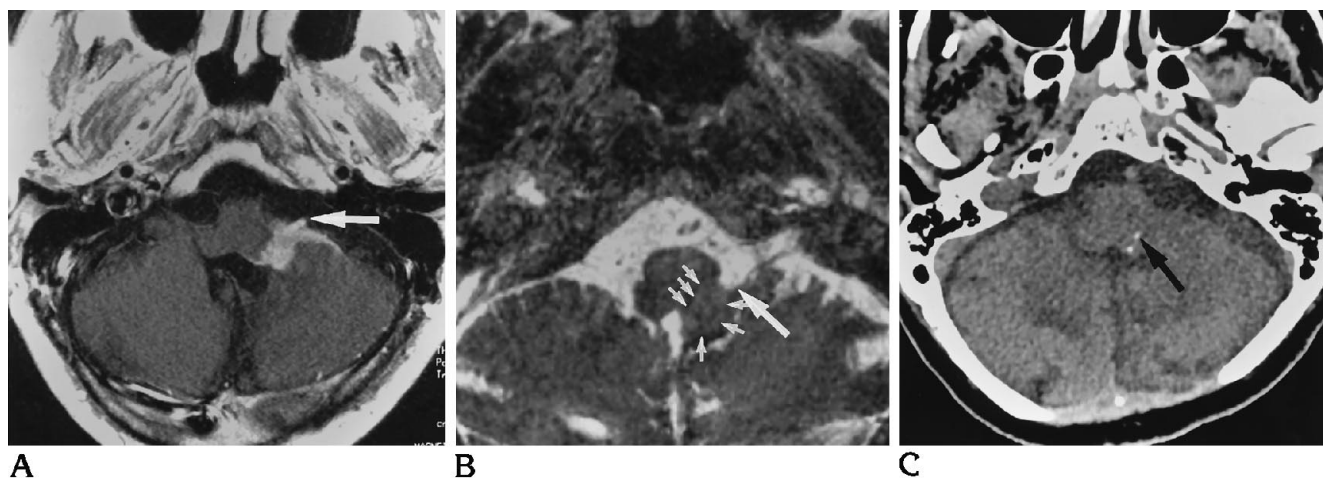


Fig 3. Case 3, postcontrast axial T1-weighted MR image (450/5/5) (A), 1-mm T2-weighted 3-D Fourier transform constructive interference in steady state MR sequence (50/20/8/1) (B), and computed tomographic scan, 2-mm thickness, soft window setting (C). A large extraaxial enhancing process spreads within the left lateral recess of the fourth ventricle. There is compression of the fourth ventricle with an enhancement of the last cranial nerves (arrow) (A). T2-weighted image (B) shows the relationship between the brain stem mass (small arrows) and the root entry zone of the last cranial nerves (arrow). Note the small calcifications (arrow) depicted by computed tomography (C) and the large posterior postsurgical scar from a previous cerebellar tumor removal (cavernoma).

Gastroesophageal disorders (mainly reflux esophagitis) are by far the most frequent causes of chronic hiccups (7, 8). The frequency of the other causes of hiccups is unknown. In fact, to our knowledge, the literature contains mainly anecdotal reports of chronic hiccups. We hypothesized that brain abnormalities could be prevalent among patients with hiccups, especially those without esophageal explanation. Previous literature already stressed that hiccups might be the sole or prevalent manifestation of intracranial processes (2, 6–10). This hypothesis seems to be validated by our results. According to them and to the literature, brain MR studies in patients with hiccups should include the brain, the brain stem, the cervical cord, and the root entry zone of the last cranial nerves.

Therefore the coronal plane is mandatory to analyze all these key areas in a same sequence. The 3-D Fourier transform constructive interference in steady state sequence, thanks to its thin T2-weighted axial contiguous sections, may depict the root entry zone of the 9th, 10th, and 11th nerves and any vascular or bone structures that could give rise to a nervous compression of the last cranial nerves.

Our data (seven abnormalities of nine investigated patients) suggest that central nervous system diseases are encountered in a significant number of patients with hiccups. The lesions varied in location and appearance. Two key zones appeared more affected: the temporal lobe area and the bulbopontine sulcus, close to the retroolivary area. These lesions were sig-

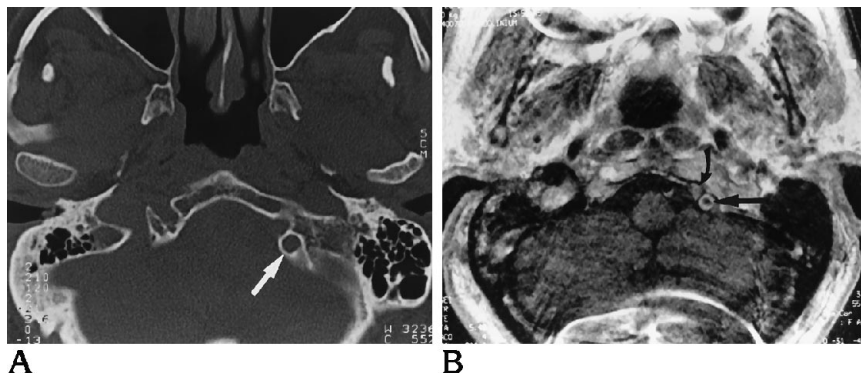
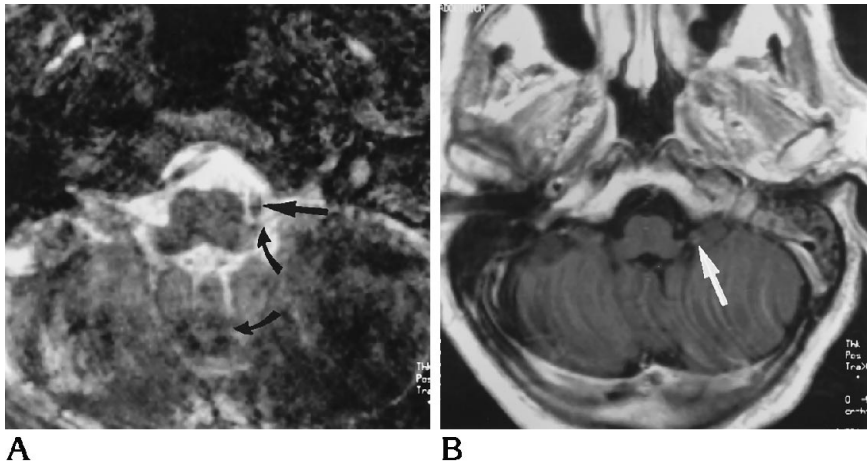


Fig 4. Case 2, CT scan (A), bone window setting, and postcontrast axial (B) T1-weighted MR images (540/15/4). Axial CT (A) shows a left round foramenlike hole (arrow), suggesting a prominent unilateral posterior condylar canal. Postcontrast T1-weighted image (B) shows a bright peripheral enhancement (arrow) with a low-signal-intensity area suggesting flow within the posterior condylar canal. Note the enhancing linear structure located medially (curved arrow) and the asymmetry of size of the jugular veins.

Fig 5. Case 8, 1-mm axial T2-weighted, 3-D Fourier transform constructive interference in steady state MR sequence (A) shows a left vertebral artery loop (arrow) close to the root entry zone of the last cranial nerves (curved arrow). Postcontrast T1-weighted MR image (500/15/2) (B) depicts a small round enhancing mass (arrow) caused by the vascular structures crossing the nerves.



nificantly predominant on the left side (five of six, 83%). Different lesions were found: arteriovenous malformations, neoplasms, demyelinating disease, and a scar of encephalitis. The other illustrated processes were debatable in the pathogeny of hiccups: vascular loop, small

brain stem infarcts, and bone abnormality compressing the root entry zone of the last cranial nerves. Common lesions such as atrophy and mild occipitocervical junction abnormalities were not considered because of their frequency in everyday patients of the same age. In con-

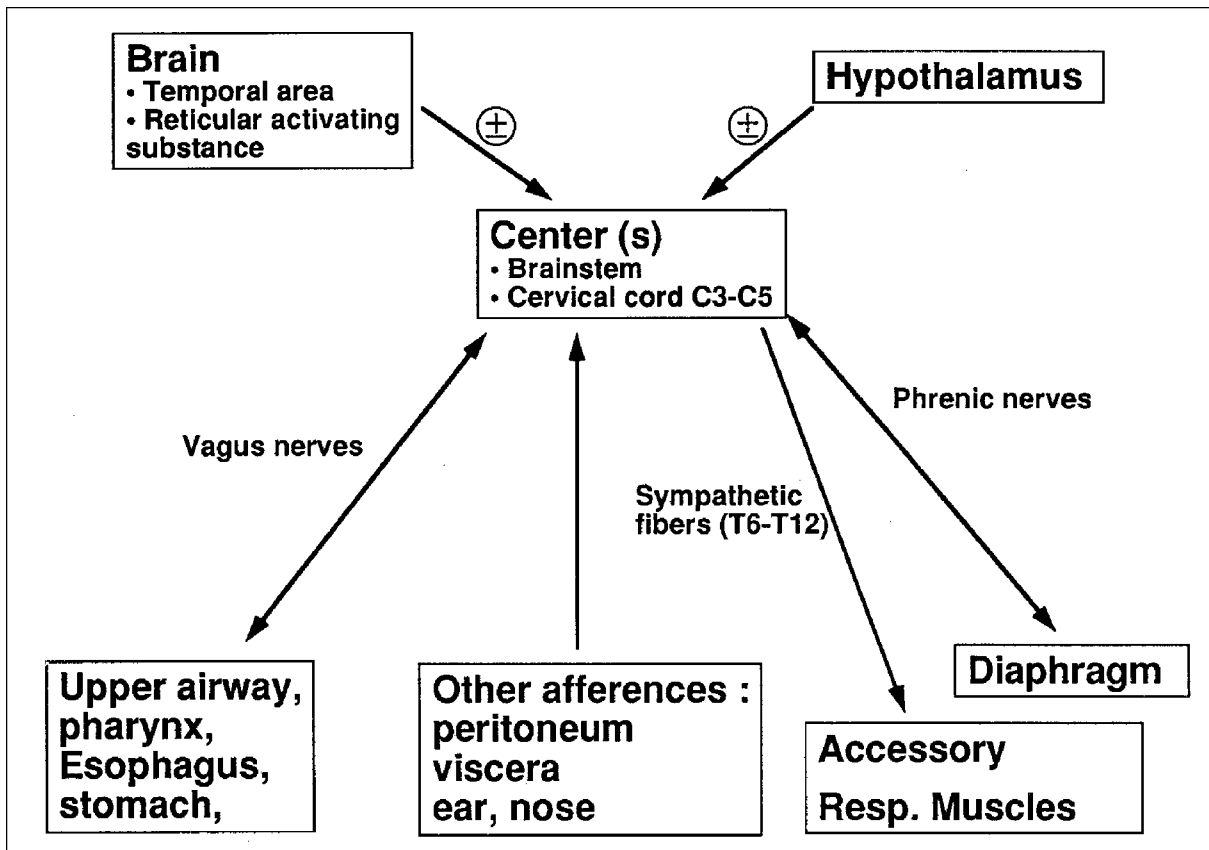


Fig 6. Physiology of the hypothetical reflex arc of hiccups includes afferent input coming mainly from the diaphragm, the stomach, the esophagus, and the ear and nose. The main routes are the phrenic and vagus nerves and the sympathetic fibers (T-6 to T-12). The hiccup center(s) are thought to be located either in the brain stem close to the inspiratory centers or in the cervical cord between C-3 and C-5. The efferent path is mainly represented by the phrenic and vagus nerves.

TABLE 2: Main causes of hiccups

Central nervous system
Craniocerebral injury
Neoplastic diseases
Cerebrovascular diseases
Infectious diseases
Spinal cord processes
Psychiatric
Metabolic, toxic and infectious
Renal failure, hyponatremia, herpes zoster
Ear, nose, and throat diseases
Thoracic
Pneumonia
Pleuritis
Mediastinitis
Myocardial infarction
Esophagus diseases
Diaphragm abnormalities
Abdomen
Gastric disorders
Pancreatic disorders
Hepatobiliary disorders
Subphrenic abscess
Abdominal aortic aneurysm

trast with the literature, no lesion in our series was seen in the cervical cord or in the parapharyngeal space. Association with mild gastrointestinal disease noted in seven of nine patients corroborates the previous data of the literature; a person can be affected by one or more lesions (2, 11). The therapeutic trial with potent medical treatment enabled us to differentiate hiccups caused by esophagitis and hiccups inducing esophagitis (3, 12).

Detection of space-occupying lesions is an important point not only for correct treatment of hiccups itself, but also for treatment of the brain lesion. Treatment of the brain lesion can eliminate or decrease the hiccups. Unfortunately, a prolonged history of hiccups (more than 30 days) can be a poor prognostic factor and is often associated with self-perpetrating hiccups, even if their presumed initial cause is radically treated (13). This underlines the fact that investigations must be rapidly carried out as soon as the first month when a bout of hiccups persists more than 48 hours.

Identification of the brain lesion is an important point for the treatment of the patient. The clinical history, the cerebrospinal fluid analysis, and/or the follow-up allow a correct diagnosis in cases of demyelination or vascular diseases (cases 1 and 8). In expansive or compressive

nervous lesions, a biopsy or surgery should be performed, and radical therapy should be carried out if necessary. This opinion is promoted by Souadjian and Cain (1). Unfortunately, neither surgery nor biopsy was performed in our patients, because the brain process was considered inoperable (cases 3, 4, and 5), or because the patient's benefit from surgical procedures in cases of vascular loop, bone compression, or scar tissue (cases 2, 8, and 9) was doubtful.

We point out that this study is a preliminary work. Further studies should explore the possibility of brain lesions in other patients with hiccups, that is, those responding to the treatment of esophagitis.

In conclusion, intractable hiccups is a symptom most often related to gastroesophageal diseases (two of three of the cases). The data in our study validate our hypothesis that after excluding the responsibility of esophagitis, a brain abnormality has to be searched for. But because no surgery was carried out on the lesions, the cause-effect relationship between hiccups and brain abnormalities is not proved. To confirm our hypothesis, functional MR can be of value to locate the brain centers involved in hiccups. Conversely, we should consider that hiccups can be absent in patients presenting with known tumors in the same areas, such as the temporal lobe or cerebellopontine angle. However, to find seven brain abnormalities out of the nine MR studies performed is much higher than expected. It is probable at least that some of the lesions play a role in the pathogenesis of hiccups.

Brain MR seems, therefore, to be indicated as a second-line investigation for patients with no esophageal abnormalities or when esophageal treatment fails to reduce hiccups. A systematic brain MR screening for all patients with hiccups would not be a cost-effective approach.

## References

1. Souadjian JV, Cain JC. Intractable hiccup: etiologic factors in 220 cases. *Postgrad Med* 1968;43:72-77
2. Kolodzik PW, Eilers MA. Hiccups (singultus): review and approach to management. *Ann Emerg-Med* 1991;20:565-5733
3. Launois S, Bizec JL, Whitelaw WA, et al. Hiccup in adults: an overview. *Eur J Respir Dis* 1993;6:563-575
4. Fabricant ND. The distressing hiccup. *Eye Ear Nose Thr Monthly* 1962;41:216



5. Askenasy JJM. About the mechanism of hiccup. *Eur Neurol* 1992; 32:159-163
6. Mac Failing DA, Susae JO. Hoquet diabolique: intractable hiccup as a manifestation of multiple sclerosis. *Neurology* 1979;29:797-801
7. Wagner M, Staksynski J. Persistent hiccups. *Ann Emer Med* 1982; 11:124-126
8. Anthony TR, Anthony SL, Anthony DJ. On temporal structures of human hiccup etiology and chronobiology. *Int J Chronobiol* 1978;5:477-482
9. Stotka VL, Barcay SJ, Bell HS, Derenne JP. Intractable hiccup as the primary manifestation of brain stem tumor. *Am J Med* 1962; 32:313-315
10. Jansen PMP, Josten EMG, Vingerhoets HM. Persistent periodic hiccups following brain abscess: a case report. *J Neurol Neurosurg Psychiatry* 1990;53:83-84
11. Marshall D, Nathan MD, Robert T, et al. Intractable hiccups. *Laryngoscope* 1980;90:1612-1617
12. Shay SS, Myers RL, Johnson LF. Hiccups associated with reflux esophagitis. *Gastroenterology* 1984;87:204-207
13. Triadafilopoulos G. Hiccups and esophageal dysfunction. *Am J Gastroenterol* 1989;84:164-169