Hiccups due to Central Nervous System Disease: Analysis of 71 Inpatients

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Can. J. Neurol. Sci. 2010; 37: 870-872

In bypassing the lungs to direct water to their gills, our tadpole ancestors may have bequeathed hiccups to man[1]. Central nervous system (CNS) lesions presumably disinhibit this primitive synkinesis in which the diaphragm is joined in a coordinated movement by intercostal and accessory respiratory muscles, as well as pharyngeal (rarely mentioned but easily observed) and laryngeal muscles. While hiccup is usually a transient problem associated with minor gastro-esophageal perturbation, rare persistent hiccups often portend serious illness—of CNS origin in 17% of patients[2].

As no general clinical study of hiccups from CNS lesions is available, I reviewed my experience.

Patients

This study was based on inpatients seen in neurology consultation (with emphasis on neuro-ophthalmological, brainstem, and unusual neurological findings) on the wards of a large public hospital, the Los Angeles County/University of Southern California Medical Center, during a 37-year-period. Symptoms, signs, and diagnoses of each patient of interest were recorded and cross-referenced. Photographs of patients and their radiographs, as well as autopsy reports, supplemented the clinical notes.

Those with persistent hiccups (≥ 1 day) originating at the onset or with worsening of intracranial disease were analyzed. None had hiccup as the chief complaint; all had multiple neurological signs; and none had gastric or esophageal problems as an alternative cause.

Etiology and location were determined by history and examination, aided by laboratory and cerebrospinal fluid (CSF) studies, contemporary contrast studies and computed scans, and biopsy and autopsy, as clinically indicated. Computed tomographic scanning was available from the 20th consecutive patient and magnetic resonance imaging with the 44th. Of 17 patients known to have died, ten underwent postmortem examination.

Results

Of 71 patients with hiccups of CNS origin (0.5% of all patients in my files), 59 (83%) were men. The mean age was 50 with a range of 20 to 85. Most hiccups resolved within 1 week. Medical therapy for hiccups [usually chlorpromazine] was used only occasionally, with little effect.

Infarcts, present in 50 cases (70%), were the most common cause and the medulla, involved in at least 47 cases (66%), was the most frequent location (Table 1). The 40 cases with lateral

Table 1: Location and cause of CNS lesions associated with hiccups in present study

CAUSE	LOCATION [Number (%)]					
	MEDULLA	PONS	MIDBRAIN	CEREBRUM	SAS	TOTAL
INFARCT	40*	7*[2]	1	2	0	50 (70)
TUMOR	5	1	1	2	0	9 (13)
HEMORRHAGE	0	2	3*	0	1	6 (8)
MS/NMO	2	2	0	0	0	4 (6)
MENINGITIS	0**	0	0	0	2*	2** (3)
TOTAL	47 (66)	12 (17)	5 (7)	4 (6)	3 (4)	71

CNS=central nervous system, SAS=subarachnoid space, MS=multiple sclerosis, NMO=neuromyelitis optica; *includes cases with unusual hiccups; **2 of 4 cases of meningitis are listed as lateral medullary infarcts

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Received April 27, 2010. Final Revisions Submitted June 3, 2010.
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medullary infarcts (LMIs)—one bilateral--comprise 56% of hiccup cases and 25% of all LMIs in my files. Two LMIs resulted from meningitis and two followed surgery for posterior inferior cerebellar artery aneurysms.

Nine tumors (13% of cases) included three brainstem gliomas, two metastatic tumors (lymphoma and squamous carcinoma) invading the floor of the fourth ventricle, two large clival masses (chordoma and plasmacytoma) compressing the medulla, and two large supratentorial meningiomas (one on the left convexity with papilledema and the other a left falx-subfrontal tumor accompanied by seizures). Of six hemorrhages (8% of cases), three involved the thalamus or midbrain, two were large pontine lesions, and one was a subarachnoid hemorrhage arising from a large deep right cerebral arteriovenous malformation (Table 1).

The four patients (6% of cases) diagnosed as multiple sclerosis (MS) were seen prior to the modern radiological-immunological delineation of neuromyelitis optica (NMO), and at least two might better fit that diagnosis. Meningitis in four cases (6%) included two cases (syphilis and unknown subacute meningitis) which presented with LMIs and two others (coccidiomycosis and listeria) with no apparent brainstem lesions.

Unusual hiccups occurred in five cases with severe brainstem involvement (three were comatose and two initially locked-in) and involved end-inspiratory hiccups in two, repeated strings of one to five hiccups as the sole means of spontaneous respiration in two, and hiccups independent of inspiratory gasps in one. The causes were bilateral pontine infarcts in two cases and one each bilateral medullary infarction, left basal ganglion-thalamic hemorrhage with tentorial herniation, and listeria meningitis.

Table 2: Reported causes of central nervous system hiccups

Infarcts (**lateral medullary**, bilateral medial medullary, bilateral thalamic, other)
Demyelinating diseases (**NMO**, multiple sclerosis, ADEM, Alexander's disease)
Tumors (**medullary**, others)
Chiari malformations and syringes
Hemorrhage (**medullary**, especially from **cavernous angiomas**, other)
Brainstem encephalitis (lethargica, listeria, herpes simplex & zoster, Japanese, EB virus)
Meningitis (syphilis, listeria, coccidiomycosis, other)
Abscess (bacterial, paracoccidiodomycosis)
Tuberculoma
AIDS (HIV encephalopathy, toxoplasmosis, PML)
Lupus encephalopathy and its treatment with steroids
Parkinson's disease and its treatment
Sarcoidosis
Cysticerosis
Tetanus
Dolichoectasia of the vertebral artery
Degos disease
Star fruit encephalopathy in uremic patients

Bold type is used for common causes; NMO=neuromyelitis, ADEM=acute disseminated encephalomyelitis, EB=Epstein Barr (virus), AIDS=acquired immune deficiency syndrome, HIV=human immunodeficiency virus, PML=progressive multifocal leukoencephalopathy

Discussion

Hiccup appears to represent a vestigial bulbar synkinesis, coordinated in or near the nucleus of the solitary tract, which is disinhibited most often by ascending vagal impulses.[1] Hiccups of CNS origin usually arise from direct medullary damage. However, occasional reports of persistent hiccups attributed to cerebral lesions, the four cerebral cases in the present study, and an 11% incidence of hiccups following pallidotomy[3,4] all suggest that descending medullary influences may evoke hiccup on occasion. The pitfalls of coincidence and undiscovered medullary lesions aside, cerebral lesions also might produce hiccups through brainstem distortion or a secondary gastric effect.

Historically, some of the few older textbooks to consider CNS causes of hiccups mention hysteria and "various diseases of the central nervous system"[5]; hysteria[6]; hysteria, neuritis and acute pontine disease[7]; cerebral hemorrhage and myelitis of the upper cord[8]; tonsillar herniation compressing the medulla, encephalitis, and hysteria[9]; and epidemic encephalitis, tabes dorsalis, syringomyelia, hysteria, intracranial tumors, and "bulbar causes"[10]. Modern textbooks, while giving less credence to hysteria, are little more enlightening and many fail even to index hiccups. For all its ubiquity, hiccup—apart from treatment concerns--is a remarkably neglected subject.

A 1968 study at the Mayo Clinic found 220 patients (82% men) with intractable hiccups (≥48 hours) in a 29-year-period[2]. Of 38 patients (17%) with neurological causes, 26 had strokes, three encephalitis, two degenerative disease, and one each syphilis, syrinx, pituitary adenoma, glioma, medullary metastasis, meningioma, and hemangioendothelioma.

C. Miller Fisher briefly reviewed his experience with protracted hiccups (≥24 hours) in 39 cases (97% men) and found at least 12 with CNS causes (11 strokes, 1 head trauma)[11]. A smaller review of 24 patients with persistent hiccups (96% men) was complicated by the presence of multiple potential causes in many patients but did include 2 LMIs[12].

Hiccups occur in about 15%[13] to 25%[14], present study of LMIs, making it the leading CNS cause of hiccups. A famous 1926 case of "the streptococcus of epidemic singultus," proposed as a hiccupogenic forme fruste of encephalitis lethargica, actually resulted from a secondary LMI[15]. For unknown reasons, persistent hiccup is a disease of men (82%[2], 83%present study, 96%[12], 97%[11]).

Early reports of hiccups in MS may have conflated MS and NMO, as a recent study found persistent hiccups rare in MS (0/130 cases) but common in NMO (8/47 cases-17%, 88% women)[16]. Indeed, persistent hiccup in demyelinating disease, often heralding an attack, favors a diagnosis of NMO in children[17] as well as adults[18], with autoimmune disorders being common accompaniments[18].

https://doi.org/10.1017/S0317167100051611 Published online by Cambridge University Press

Many other CNS causes of persistent hiccups have been reported, usually as single cases affecting the medulla (Table 2).

In the present study, two-thirds of the lesions were medullary, 17% were located in the pons (where some may have extended into the medulla), and 17% were in the midbrain, cerebrum or subarachnoid space (Table 1). All four cerebral lesions (two meningiomas, two carotid territory infarcts) as well as a basal ganglion hemorrhage were left-sided, but there is little in the way of previous cerebral localization for comparison.

In summary, persistent hiccups of CNS origin are rare, occur mostly in men, result from a plethora of causes usually affecting the medulla, and are especially common with LMI and NMO. In the acute neurological inpatient, hiccup is one of the few signs offering the examiner a clue to etiology and location before entering the patient's room.

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https://doi.org/10.1017/S0317167100051611 Published online by Cambridge University Press