Intractable hiccup caused by spinal cord lesions in demyelination disease

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Objective: This study aimed to summarize the clinical features of patients who presented intractable hiccup (IH) without brain and medulla oblongata (MO) lesions.

Method: This study included six patients who were diagnosed with inflammatory demyelinating myelitis, categorized as neuromyelitis optica (NMO), multiple sclerosis (MS), and myelitis. Patients who presented IH with cervical lesions but without MO lesions were also included. Clinical profiles, laboratory data, and magnetic resonance imaging findings were analyzed.

Results: Three out of six patients were diagnosed with NMO, whereas the remaining three were diagnosed with acute myelitis, recurrent myelitis, and MS, respectively. The duration of hiccup was from 2 to 23 days (average = 9.33 ± 8.64 days). Five patients (83.33%, patients 1–5) had long segmental lesions and one had a patchy lesion. None of these patients had any MO lesions. Half of them were successfully treated with high-dose methylprednisolone combined with gamma-aminobutyric acid (GABA) inhibitor.

Conclusion: IH occurred in patients without MO lesion. However, the mechanism remained unclear. Immune factors of demyelinating neuropathy stimulated the hiccup reflex arch. Cervical cord lesions may activate the hiccup center. In general, IH can be controlled by IVMP combined with GABA inhibitor. Unilateral phrenic nerve block may elicit no effect.

Keywords: Intractable hiccup, Demyelinating disease, Myelitis, Multiple Sclerosis, Neuromyelitis optica

Hiccup is a repetitive, involuntary, spasmodic, and temporary contraction of the diaphragm accompanied by sudden closure of the glottis.¹ In general, the hiccup and vomiting centers are located in the medulla oblongata (MO).² Hiccup and vomiting are common symptoms of neuromyelitis optica (NMO), which have been also reported in some cases of multiple sclerosis (MS). Reports on intractable hiccup (IH) without MO lesions are rare, but cervical spinal lesions can also cause hiccup. However, the mechanism remains unclear. In this study, six patients with different diseases, all of whom presented with IH without MO lesion found in the magnetic resonance imaging (MRI) scan, were investigated. To our knowledge, this report is one of a few reports about such condition. We summarized the clinical features of these patients and provided a brief review of literature.

Methods

IH is characterized by hiccup and nausea that last for more than 48 hours² even with common therapeutic management. Inflammatory demyelinating diseases, including NMO, MS, as well as acute and recurrent myelitis were considered in this study. The diagnosis of NMO was based on the revised diagnostic criteria,³ whereas the diagnosis of MS was based on the revised 2005 McDonald Criteria.⁴ Acute and recurrent transverse myelitis were diagnosed based on clinical characteristics and MRI findings.

The study retrospectively investigated patients who were diagnosed and treated accordingly depending on these inflammatory demyelinating diseases at the Department of Neurology in West China Hospital from May 2009 to November 2011. Our database from December 2008 to December 2012 contained 329 patients with NMO and 232 patients with MS. The patients presented IH as one of the main manifestations, and their MRI intensive scans of the brain as well as cervical and thoracic spinal cord (1.5 or 3.0 T) were obtained, which created 5-mm thick slices. Cervical spinal demyelinating lesions were responsible for IH. Their demographic characteristics, clinical profiles,

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laboratory data, MRI findings, and treatments were also collected.

The inclusion criteria used were as follows: (i) hiccup and nausea for central nervous system; (ii) treatment failure for common therapeutic management with symptoms lasting for at least 48 hours; and (iii) MRI intensive scans of the head as well as cervical and thoracic spinal cord (1.5 or 3.0 T), showing that spinal lesion was responsible for IH. The exclusion criteria used were as follows: (i) patients who received any medication that may cause hiccup and nausea before onset; (ii) hiccup and nausea caused by digestive diseases, medication, mediastinum, and/or any reason not associated with the central nervous system; (iii) lesions found in the cervical and thoracic spinal cord; (iv) lesions found in the spinal cord considered as non-inflammatory diseases; and (v) patients who did not sign an informed consent. Patients who experienced hiccup must meet a gastroenterologist beforehand to exclude IH caused by gastric problems.

MRI examinations were performed using the Siemens Sonata 1.5 T, Siemes Avanto 1.5 T, Siemens Trio 3.0 T, or Philips Achieva 3.0 T MRI scanner at West China Hospital to create 5-mm thick slices. Two neuroradiologists and a neurologist blindly evaluated each scan to make radiological diagnose.

Results

Six patients were included in this study, of which five were female. The age at IH onset ranged from 16 to 32 years. Three patients were diagnosed with NMO, whereas the other three were diagnosed with acute myelitis, recurrent myelitis, and MS, respectively. The disease durations of inflammatory myelitis varied from 1 to 74 months (average 33.5 ± 24.38 months). Their hiccups lasted from 2 to 23 days (average: 9.33 ± 8.64 days). Only one patient suffered from vomiting at the same time. None of these patients presented nausea during onset. Four patients experienced limb weakness, three had abnormal discomfort, and two had urinary

retention. None had a manifestation attributed to the brainstem, cerebellum, or cerebrum.

MRI scans were obtained for each patient as they were experiencing IH before high-dose methylprednisolone (IVMP) was administered. All of the patients had lesions in the cervical spinal cord. Five patients (patients 1–5) had longitudinal lesions and the remaining patient had a patchy lesion. Three patients (patients 1, 3, and 5) had long lesions extending to the thoracic segment with thoracic cord lesions. The sagittal and axial MRI views showed that the lesions involved the central canal, pericanal regions, and bilateral anterior horn. None of these six patients had any new lesions in MO where the hiccup center was located (Table 1 and Fig. 1). Only one patient had an old lesion in the brainstem, but he had never had hiccups before onset.

IH in three patients (patients 1, 2, and 4) was successfully treated with IVMP combined with a gamma-aminobutyric acid (GABA) receptor inhibitor. Patient 5 was administered with IV immunoglobulin treatment after IVMP failed, although the hiccup was partially controlled. The hiccup was completely controlled with ritalin, baclofen, clonazepam, gabapentin, and chlorpromazine. The symptoms of patients 3 and 6 could not be controlled with the aforementioned therapeutic treatments. These two patients received unilateral phrenic nerve block, but the result was unsatisfactory. The symptom of these two patients subsided spontaneously with muscle strength recovery.

Discussion

IH is a common feature in inflammatory demyelinating diseases. Sato and Fujihara⁵ found that almost 20% of the patients had at least one short period of IH, and numerous studies on NMO have confirmed these results.^{1,2,6–8} A previous study suggested that the afferent nerves of the hiccup reflex include vagus, phrenic, and sympathetic nerves of T6–T10. The reflex center is located at C3–C5 anterior horn and MO; the efferent nerves include phrenic and vagus nerves.^{2,9} The reflex

Table 1 Clinical profile and MRIs of lesions in six cases

Cases	Age/sex	Onset duration (minutes)	Diagnosis	Hiccup duration (days)	MRI finding	
					Range	Classification
1	23/F	74	NMO	4	C2–T2	Long longitudinal
2	42/F	1	AM	2	C3–C7	Long segment
3	30/M	19	NMO	23	C2–C6 T2–T7	Long segment
4	37/F	41	RM	3	C3–C5	Long segment
5	29/F	35	NMO	7	C3–T4	Long segment
6	16/F	31	MS	17	C1–C2	Patchy like

NMO, neuromyelitis optica; AM, acute myelitis; RM, recurrent myelitis; MS, multiple sclerosis.

Figure 1 MRI features of NMO with IH cases when patients were admitted. The photograph on the left shows C2–C6 longitudinal lesion with T2-hyperintense signal (A), axial section of cervical spinal cord (C: T1-weighted), and T2-weighted image of MO (D) in patient 3. The photograph on the right shows C3–T4 longitudinal lesion with T2-hyperintense signal (B), axial section of cervical spinal cord (E: T1-weighted) and T2-weighted image of MO (F) in patient 5.

center is also regulated by the cerebral cortex, the limbic system, and the hypothalamus. Although IH rarely occurs in patients with cervical spinal lesions without brain and MO lesions, Takahashi *et al.*¹⁰ reported on 15 patients who collectively experienced 35 onsets of IH, 20 of which did not involve MO. All of these patients were diagnosed as NMO with anti-AQP-4 antibody positive.

IH occurs in various diseases, including those that affect the brainstem and the cervical cord. The MRIs of six patients in this study only had demyelinated lesions with

edema in the cervical or the cervicothoracic spinal cord from C2 to T7 without MO lesion. Hinson *et al.*¹¹ indicated that the serum IgG of patients with NMO affects the cell membrane expressing aquaporin-4 (AQP-4). Although MRI did not show lesions in the brain stem, previous findings can partly explain that anti-AQP4 antibody potentially affects the hiccup center located in the pericanal region of MO where the blood–brain barrier is anatomically not observed.¹ In our study, only three patients had NMO. Aside from the anti-AQP-4 antibody, other

factors of humeral immunity associated with demyelinated neuropathy stimulate the hiccup reflex loop, which results in IH.

Glucocorticoids can relieve inflammatory reaction, and GABA inhibitor can inhibit abnormal electrical activities of nerves. Previous studies suggested that IVMP combined with GABA inhibitor can usually control IH.^{2,12–14} The result of this is consistent with previous results. IH was controlled by therapeutic treatment in approximately half of the patients, but few cases were intractable. We also administered unilateral phrenic nerve block to treat IH, but the results were unsatisfactory, suggesting that unilateral block may not control the attacks effectively. However, bilateral phrenic nerve block possibly causes ventilator paralysis. We considered that phrenic nerve block may ineffectively control IH. Thus, further investigation is required.

Some studies on the relationship of IH and the relapse of inflammatory demyelinating disease have indicated that IH may be an initial manifestation relapse in these diseases.¹⁵ Hence, IH should be promptly identified and controlled to treat and evaluate inflammatory demyelinating diseases.

Conclusion

IH can occur in patients without MO lesion, but the mechanism was unclear. Immune factors of demyelinating neuropathy stimulated the hiccup reflex loop and cervical spinal lesions may activate the hiccup center. In general, IH can be controlled by IVMP combined with GABA inhibitor. However, the effectiveness of unilateral phrenic nerve block requires further investigation.

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