

ORIGINAL ARTICLES

Lesional location of intractable hiccups in acute pure lateral medullary infarction

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Abstract

Background & Objective: Hiccups is a disabling condition of lateral medullary infarction (LMI). Unlike other symptoms of LMI, the anatomical lesions of hiccups are not well known. Few studies have evaluated the relationship between the lesional location of LMI and hiccups. We performed this study to correlate hiccups and magnetic resonance imaging (MRI)-based lesional location in pure LMI. **Methods:** Between January 1997 and February 2013, we identified 24 patients with pure LMI who presented with hiccups in addition to typical lateral medullary syndrome. Sixty six pure LMI patients without hiccups were included as a control group. Clinical and radiologic findings were compared between the two groups. MRI-identified lesions were classified rostrocaudally as rostral, middle and caudal, and horizontally as typical, ventral, large, lateral and dorsal. **Results:** The pure LMI patients with hiccups had significantly more frequent aspiration pneumonia ($P = 0.001$) and longer hospital stay ($P = 0.03$). The patients with hiccups significantly more often had dorsal rather than ventral lesion at horizontal levels ($P = 0.012$). But, there were no rostro-caudal differences at vertical levels ($P = 0.162$).

Conclusions: We suggest that pure LMI associated with hiccups often locates in the dorsal medulla at horizontal correlation. This MRI-based comparative study has advanced the understanding of the neural substrate for hiccups in LMI, and indicates that hiccups become predictable when specific lesional locations in the lateral medulla are considered.

INTRODUCTION

Lateral medullary infarction (LMI), known as Wallenberg syndrome, constitutes about 2% of cases of acute cerebral infarction¹, and is the most well-known syndrome of cerebral infarction occurring in the territories of the vertebralbasilar artery. LMI displays a variety of clinical symptoms and signs. The common symptoms are dizziness or vertigo, dysarthria, hoarseness, dysphagia, numbness, ataxia, and hiccup (singultus). The frequent signs include contralateral hemibody sensory change, ipsilateral facial sensory change, Horner syndrome, skew deviation, nystagmus, and laryngopharyngeal and vocal cord paralysis.²⁻⁴ Dysphagia and hiccups are among the various symptoms that cause aspiration pneumonia and respiratory exhaustion, which result in poorer prognosis.^{5,6} Thus, dysphagia and hiccups are

important symptoms to observe and pay attention to in the rehabilitating part of cerebral infarction. Swallowing is associated with the solitary nucleus, the nucleus ambiguus in the medulla oblongata. The anatomical areas that are associated with hiccups are mostly located in the medulla and widely in cerebellum and thalamus.⁶⁻¹²

Recently, the relationship between medullary infarction and dysphagia or aspiration has been reported.^{6,12} But, little is still known of the association of acute LMI with hiccup.¹³ The reports concerning dysphagia and medullary infarction did not provide statistical analysis, calling for further clarification.

In view of the reports of medulla lesions that has provoked hiccups in several animal studies⁷⁻⁹, we proceeded to analyze statistically structural lesions causing intractable hiccups in patients diagnosed as acute LMI.

METHODS

We screened 5,889 records of patients seen between January 1997 and February 2013 in the stroke registry of our university and selected 134 patients identified clinically and radiologically as acute (visited within 7 days after developing symptoms) LMI. We excluded 26 patients having several scattered acute infarct lesions in midbrain, pons, cerebellum, or cerebrum. One hundred and eight patients were diagnosed to have acute pure LMI (Pure LMI; LMI without concomitant midbrain, pontine, cerebellar, or cerebral infarction). Among 108 patients, we excluded 5 patients with endotracheal intubation, 4 patients confirmed with severe bronchitis or pneumonia through chest x-ray or chest computed tomography, and 5 patients with esophagitis, gastritis, or gastric ulcer as indicated by gastrofibroscopy. We selected 28 patients with intractable hiccups (defined as hiccups persisting beyond 48 hours despite medical treatments^{5,10}). Among the 28 patients, 4 patients in whom hiccups subsided after changing or removing nasogastric tube were excluded. Finally, 24 patients formed the study group (Pure LMI with hiccup group) and 66 patients not having intractable hiccups formed the control group (Pure LMI without hiccup group).

Demographic data between Pure LMI with hiccup group and Pure LMI without hiccup group were compared to ascertain the relationship between intractable hiccups and symptoms and signs of LMI (including dizziness or vertigo, nystagmus, nausea and vomiting, headache, hoarseness, dysphagia, dysarthria, Horner syndrome, skew deviation, gait ataxia, limb ataxia, and diplopia). Additionally, the etiology of cerebral infarction was classified into large-artery atherosclerosis (LAA), small vessel occlusion (SVO), cardioembolism (CE), and undetermined. We also examined the relationship between intractable hiccups and the etiological classification of cerebral infarction. Brain magnetic resonance imaging (MRI) was performed for all patients with cerebral infarction within 7 days following development of neurological symptoms. A Gyroscan Intera 1.5 Tesla MRI scanner (Philips Medical Systems, Best, The Netherlands) was used (5 mm slice thickness; 2.5 mm interslice gap; 23 axial slices; 230 mm field of view). MRI including T1 weighted image (TR/TE 550/11 ms), T2 weighted image (TR/TE 4442/100 ms), fluid attenuated inversion recovery (FLAIR; TR/TI/TE 11000/2800/140 ms), and diffusion-weighted magnetic resonance imaging (DWI; TR 4,032

msec, TE 80 msec; matrix number of 192 × 192; two b values of 0 and 1,000 sec/mm²), and apparent diffusion coefficient (ADC) map were generated. MRI-based lesion size and location were evaluated through T2-weighted images and FLAIR images by two neurologists and one neuroradiologist who were blinded to the patients' clinical findings. Lesional classification was subdivided into rostral, middle, and caudal parts vertically. The rostral medulla was characterized by posterolateral bulging of the restiform body, the middle medulla was characterized by nodular lateral surface due to the olivary nucleus, and the lower medulla was characterized by a relatively round figure with closed fourth ventricle.¹⁴ Horizontal lesions were classified into five lesions as previously described.¹⁵ Diagonal band-shaped lesions sparing the most dorsolateral portion were the most common and were therefore designated as 'typical type'. Similarly shaped, but more ventrally situated lesions involving some portion of the inferior olive and sparing relatively large portions of the dorsolateral area were classified as 'ventral' type. Large lesions extending ventrally so as to involve some portion of the olivary nucleus and dorsally to involve most (or all) of the dorsolateral area were classified as 'large type'. Lesions restricted to the most dorsal or dorsolateral portion were classified as 'dorsal type'. Some lesions, usually at the caudal medulla, were restricted to the lateral, superficial area without extending dorsally and were classified as 'lateral type' (Figure 1).

Statistical analysis

Clinical findings were compared between PLMI with hiccup group and PLMI without hiccup group. MRI-examined lesional locations were fractionized vertically and horizontally, and analyzed by cross tabulation. Pearson chi-square test was used to compare sex, symptoms and signs, stroke etiological classification, lesional location in categorical variables. Student's t-test was used for continuous variables. *P* values < 0.05 were regarded as indicating significance.

RESULTS

The Pure LMI with hiccup group comprised 24 patients (22 men and 2 women; mean age 59.8±13.3 years) and the Pure LMI without hiccup group comprised 66 patients (37 men and 29 women; mean age 61.1±12.1 years). There was no statistically significant difference in the age of the two groups. The mean MRI scanning time

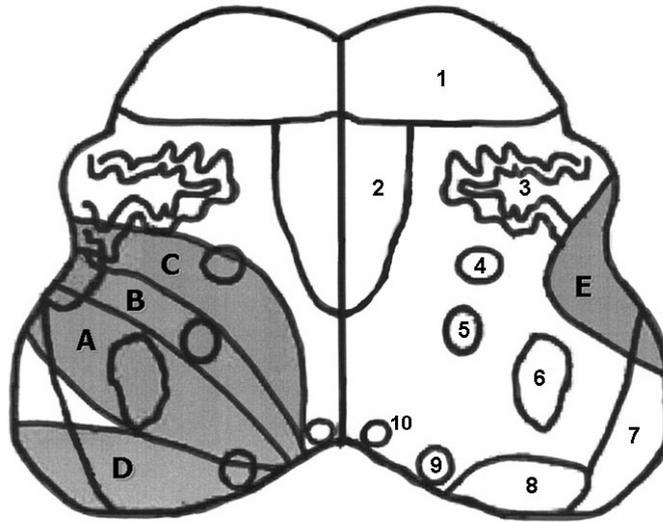


Figure 1. Schematic drawing of important medullary structures in medulla. Shaded areas are indicated as various patterns of medullary infarction. 1, pyramidal tract; 2, medial lemniscus; 3, inferior olivary nucleus; 4, ascending trigeminal tract; 5, nucleus ambiguus; 6, descending trigeminal tract; 7, inferior cerebellar peduncle; 8, vestibular nucleus; 9, nucleus solitarius; 10, hypoglossal nucleus; A+B=typical, B+C=ventral, A+B+C=large, D=dorsal, E=lateral (reproduced from Kwon et al., 2005¹²)

was 3.7 ± 2.4 days since neurological symptoms developed. The mean period of hospital stay was 38.0 ± 42.1 days in the PLMI with hiccup group and 21.1 ± 31.6 days in the PLMI without hiccup group; the difference was statistically significant ($P=0.03$). In aspiration pneumonia, significant difference existed ($P=0.001$), with 12 patients (50.0%) having aspiration pneumonia in the Pure LMI with hiccup group and 9 patients (13.6%) diagnosed with aspiration pneumonia in the Pure LMI without hiccup group. There were no statistically significant differences in several sensory symptoms of LMI (ipsilateral trigeminal, contralateral trigeminal, bilateral trigeminal, isolated limb body, and isolated trigeminal). The other symptoms and signs of LMI (Horner syndrome, hoarseness, dysphagia, dysarthria, gait ataxia, limb ataxia, dizziness, vertigo, nausea and vomiting, nystagmus, headache, neck pain, diplopia, and facial palsy) had no statistically significant differences in the two groups. The etiological classifications of pure LMI did not significantly differ. The clinical findings and MR lesion images of pure LMI co-existing intractable hiccups are summarized in Table 1.

The lesional distributions of 24 patients in the Pure LMI with hiccup group were subdivided vertically into rostral ($n=4$), rostral-middle ($n=3$), middle ($n=6$), middle-caudal ($n=7$), caudal ($n=4$), and rostral-middle-caudal ($n=1$) (Table 2). There

were 7 rostral lesions, 16 middle lesions, and 12 caudal lesions (Table 3). Classifications of the horizontal lesions comprised typical, vertical, large, dorsal, and lateral forms. Horizontal lesions were arranged numerically irrespective of vertical distribution. That is, horizontally distributed lesions were numerized including all rostral, middle, and caudal medullary lesions. In the horizontal distribution of the Pure LMI with hiccup group, the lesional number of the typical form, large form, dorsal form, lateral form, and vertical form was 9, 11, 14, 5, and 0, respectively (Table 4). There were no statistically significant differences in vertical distribution in the two groups ($P=0.162$), but the horizontal distribution was significantly different ($P=0.002$). There were more hiccups horizontally in the dorsal lesion of the Pure LMI with hiccup group, but less hiccups in the ventral lesion of the same group.

DISCUSSION

In this study, we define pure LMI as patient with LMI with no other lesions in midbrain, pons, cerebellum, or cerebrum except medulla. We found a significant correlation between intractable hiccups and lesion location at dorsal medulla.

Hiccup occurs when there is sudden closure of the glottis within 30-40 milliseconds after an unexpected inspiration from an involuntary,

Table 1: Clinical and radiological features of 24 patients of pure lateral medullary infarction with hiccups

No	Sex	Age	HS	RF	SS	GA	D/V	HS	N/V	DA	DP	LA	HA	NP	D	FP	AP	ET	Brain MRI
1	M	57	7	HT	1	Y	Y/N	N	N	Y	Y	N	N	N	N	Y	N	1	
2	M	60	18	HT	4	Y	Y/Y	N	Y	Y	Y	N	Y	N	N	N	Y	1	
3	M	62	13	DM, HT, S	1	N	Y/N	N	Y	N	Y	N	Y	N	N	Y	Y	1	
4	M	65	27	DM, HT	1	Y	Y/Y	Y	Y	N	Y	Y	N	N	Y	N	Y	4	
5	M	72	132	HT, S, HL	1	Y	Y/Y	N	Y	Y	Y	Y	Y	N	N	N	Y	3	
6	F	64	26	HT, HL	1	Y	Y/N	N	Y	N	Y	N	Y	N	N	N	Y	4	
7	M	58	12	DM, HT, HL	2	Y	Y/N	Y	Y	Y	Y	Y	N	N	N	N	Y	5	
8	M	50	15	HT, S	5	Y	Y/Y	N	Y	Y	Y	N	Y	Y	N	Y	N	1	
9	M	70	139	DM, HT	4	Y	Y/Y	N	Y	Y	Y	N	N	N	N	Y	Y	4	
10	F	57	12	DM, HT	4	Y	Y/N	N	Y	N	N	N	Y	N	N	N	N	3	
11	M	70	55	HT, S	1	Y	Y/N	Y	N	Y	Y	N	Y	N	N	Y	Y	1	
12	M	64	19	S	4	N	Y/Y	N	Y	N	N	N	N	N	N	N	N	1	
13	M	51	19	S	1	Y	Y/Y	N	Y	N	N	Y	N	N	N	Y	N	1	
14	M	68	20	None	1	Y	N/N	N	N	Y	Y	N	N	N	N	N	Y	3	
15	M	40	56	HT	1	Y	Y/Y	N	Y	N	Y	N	N	N	N	N	Y	3	
16	M	77	36	HT, DM	1	Y	Y/Y	N	Y	Y	Y	Y	Y	N	N	Y	Y	3	
17	M	60	60	HT, S	1	N	Y/Y	Y	N	Y	Y	N	N	N	N	N	Y	5	
18	M	63	18	HT	1	Y	Y/N	N	N	N	Y	N	N	N	Y	N	N	3	
19	M	36	7	HT	1	Y	N/N	Y	N	Y	N	Y	Y	N	N	Y	N	3	
20	M	87	12	HT, DM, S, HL	4	Y	Y/N	N	Y	N	N	Y	Y	N	N	N	N	1	
21	M	73	15	HT, S	1	Y	Y/N	N	Y	Y	N	Y	N	N	N	N	N	1	
22	M	35	8	S	1	Y	Y/Y	N	N	Y	N	N	N	N	N	Y	N	3	
23	M	60	33	HT	2	Y	Y/N	N	N	N	N	Y	N	N	N	N	N	1	
24	M	36	170	HT, S, HL	2	Y	Y/Y	Y	Y	N	N	Y	N	N	N	N	N	1	

HS, hospital stay, days; RF, risk factors; SS, sensory symptoms, 1: ipsilateral trigeminal, 2: contralateral trigeminal, 3: bilateral trigeminal, 4: isolated limb/body, 5: isolated trigeminal; GA, gait ataxia; D/V, dizziness / vertigo; HS, Horner syndrome; N/V, nausea / vomiting; DA, dysarthria; DP, dysphagia; LA, limb ataxia; HA, headache; NP, neck pain; D, diplopia; FP, facial palsy; AP, aspiration pneumonia; ET, etiology, 1: large artery atherosclerosis, 2: cardioembolism, 3: small vessel disease, 4: unknown, 5: two or more; Brain MRI, All lesions are presented in the right side; M, male; HT, hypertesion; DM, diabetes mellitus; HL, hyperlipidemia; S, smoking; Y, yes; N, No

intermittent spasmodic contraction of the diaphragm and external inspiratory intercostal muscles.¹⁶ The excitatory-inhibitory mechanism of the glottis closure complex (GCC) and the inspiratory complex (IC) operates during hiccups. The important mechanism of hiccup generation is the dysfunction of reciprocal inhibition between the GCC and the IC. Hiccups represent a neurologic valve dysfunction between the GCC and the IC. When the IC is activated, diaphragm, external intercostal muscle, sternocleidomastoid

muscle, serratus anterior muscle, and scalene muscles all contract, and air is inspired. After 30-40 milliseconds, the GCC is operative. At this time, the epiglottis extends backward, the larynx is pulled upward, the hyoid and pharyngeal superior constrictor contract, and the esophageal sphincter muscle relaxes. Simultaneously the glottis closes abruptly. Consequently, the inspiratory tonic closure of the glottis results in a hiccup.¹¹ A neurogenic reflex arc is involved in this process. The reflex arc consists of three

Table 2: Distribution of the vertical and horizontal lesions in 24 patients of pure lateral medullary infarction with hiccup

Patient	Rostral	Middle	Caudal
1			large+dorsal+lateral
2		typical	large
3	typical		
4		large+dorsal+lateral	
5	typical	large	lateral
6		typical+dorsal	typical+dorsal
7		large	typical
8		large+dorsal	typical
9	typical		
10			typical
11	large+dorsal	large+dorsal	
12		large+dorsal	
13		dorsal	typical
14		typical	lateral
15		typical+dorsal	
16	typical+dorsal		
17	typical+dorsal		
18		large	
19			large+dorsal
20	dorsal	typical	
21		typical	
22		typical	
23		typical+dorsal	lateral
24			typical

parts: an afferent limb, a central connection, and an efferent limb. The afferent pathway is composed of multiple branches of the vagus nerve, phrenic nerve, and sympathetic plexus arising from T6 through T12. The efferent portion is the phrenic nerve innervating the glottis and external intercostal muscles. The less well-defined central connection is primarily located in the brainstem, and partially in the cerebellum, thalamus, and hypothalamus.^{11,16} The solitary nucleus, nucleus ambiguus, and circumferential respiratory control area seem to play important roles in generating hiccup.^{6,13,17,18}

Hiccups have a variety of group of causes. Firstly, pharyngitis, gastritis, ulcer disease, abdominal distension, pneumonia, and pleurisy that stimulate the vagus nerve. Secondly, gastric

distension, hiatal hernia, hepatosplenomegaly, or subdiaphragmatic abscess that irritate the diaphragm. Thirdly, causes related to the central nervous system are tumor-like structural lesion, encephalitis or meningoencephalitis, cerebral infarction, cerebral hemorrhage, and multiple sclerosis. Fourthly, causes related to surgery. This include anesthetic effect and irritation of the laryngopharynx and glottis due to endotracheal intubation. Fifthly, toxic or metabolic causes. These are e.g., alcoholic intoxication, uremia, diabetic acidosis, and electrolyte imbalance. Lastly, psychiatric problems, emotional upset or stress.^{10,16,19-23} In the present study, we excluded as much as possible causes of hiccups other than cerebral infarction, based on past medical history, physical examination, blood investigations,

Table 3: MRI-identified lesions of medulla were classified as rostral, middle, and caudal in vertical levels, where there were no significant rostro-caudal differences

	Rostral	Middle	Caudal	Total	P-Value
PLMI with Hiccup	7 (20.0)	16 (45.7)	12 (34.3)	35	0.162
PLMI without Hiccup	19 (24.4)	45 (57.7)	14 (17.9)	78	

The numbers in **parentheses** refer to percentage.
($P = 0.162$, Pearson chi-square)

gastroscope, abdominal or chest computed tomography.

The present results echo those of a previous study. Based on seven cases of pure LMI and hiccups, Park *et al.*¹³ reported that the lesions were mostly located in the middle area vertically or dorsolateral area horizontally of the medulla. We conclude similarly that the associated lesions were in the dorsolateral area horizontally, and in the middle area vertically, the latter was not statistically significant.

When comparing our study with that of Kwon *et al.*¹², which investigated the relationship between dysphagia and pure unilateral medullary infarction, and with the study of Kim *et al.*⁶ concerning the association between aspiration and pure medullary infarction, there were some differences and some similarities. Kwon *et al.*¹² reported that dysphagia occurred when the lesions are mostly in the vertical rostral part. However, the horizontal location was non-specific (i.e., not the dorsal or lateral portions). Hiccups mostly develop owing to the incoordination of inspiratory respiration center and swallowing center¹¹, although the intractable hiccups are related to dysphagia to some extent. We may conclude that the anatomical lesional location and mechanism causing dysphagia is different from that of hiccup. Kim *et al.*⁶ found aspiration to be commonly associated with dysphagia, when they analyzed 10 pure LMI and aspiration patients. They concluded that many aspirations occur when the lesion was located in the middle

part of the medulla. Our results support this view. Our patients with intractable hiccups had their lesion mainly in the middle part of the medulla. Thus, there appear to be a correlation of lesional location between aspiration and hiccup. Lastly, in the present study the Pure LMI with hiccup group had more cases of aspiration pneumonia and prolonged hospital stay. The Pure LMI with hiccup group may thus had greater morbidity than the Pure LMI without hiccup group.

Hiccups is more frequent when the infarcted lesion is in the dorsal area of the medulla. Vagus nerve, respiratory center, solitary nucleus, nucleus ambiguus, central sympathetic tract, and spinal tract of trigeminal nucleus generating hiccup^{2,3,12} are all located in the same area. These lesions may result in a dysfunction of the vagus nerve, sympathetic nerve, and an incoordination between GCC and ICC.

In contrast with previous studies, we tried to correlate intractable hiccups with brain MRI lesion statistically. However, there were some limitations in this study. Firstly, the number of patients is small. Secondly, evidence about the dysfunction of glottis and laryngeal structures was less objective, since the video-fluoroscopic swallowing test (VFSS) was not performed to evaluate the disharmony of respiration and swallowing. Thirdly, we may have overlooked extremely small lesions because of the 5mm thickness of brain MRI slices. To overcome these limitations, future study will need to involve patients from different institutes, more precisely

Table 4: MRI-identified lesions of medulla were classified as typical, ventral, large, dorsal, and lateral in horizontal levels, with significant differences

	Typical	Ventral	Large	Dorsal	Lateral	Total	P-Value
PLMI with Hiccup	19 (38.8)	0 (0.0)	11 (22.4)	14 (28.6)	5 (10.2)	49	0.002
PLMI without Hiccup	26 (27.7)	24 (25.5)	17 (18.1)	14 (14.9)	13 (13.8)	94	

The numbers in **parentheses** refer to percentage.
($P = 0.002$, Pearson chi-square)

evaluate the state of patient, and more precisely determine the lesional locations vertically or horizontally using higher capacity MRI.

In conclusion, patients with dorsal lesion of medulla in acute pure LMI may experience intractable hiccups more frequently.

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