Neural Correlates of Hiccups in Patients with Lateral Medullary Infarction

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Abstract
Background: Hiccups is a known presentation of lateral medullary infarction. However, the region in the medulla associated with this finding is not clearly known. In this study, we aimed to study the neural correlates of hiccups in patients with lateral medullary infarction (LMI).
Methods: This retrospective study included all patients who presented with lateral medullary infarction between January 2008 and May 2018. Patients with hiccups following LMI were identified as cases and those with no hiccups but who had LMI were taken as controls. The magnetic resonance imaging of the brain was done viewed and individual lesions were mapped manually to the template brain. Voxel-based lesion-symptom mapping employing nonparametric permutation testing was performed using MRICron.
Results: There were a total of 31 patients with LMI who presented to the hospital during the study period. There were 11 (35.5%) patients with hiccups. Using the voxel-based lesion-symptom mapping analysis, the dorso-lateral region of the middle medulla showed significant association with hiccups.
Conclusion: In patients with LMI, we postulate that damage to the dorsolateral aspect on the middle medulla could result in hiccups.

Keywords
Lateral medullary syndrome, Hiccups, Lesion mapping, Lateral medullary infarction, Voxel-based lesion

Introduction
Hiccups is an involuntary inspiration against a closed glottis. Hiccups is also known as singultus, which in Latin refers to the sharp intake of breath that occurs while crying.1 Hiccups occur because of many causes which can be broadly divided into central and peripheral causes. Among these, lateral medullary infarction (LMI) is one of the central causes for hiccups. Intractable hiccups which can occur in LMI may lead to aspiration pneumonia, oesophagitis, exhaustion, malnutrition, dehydration, and in severe cases, respiratory depression and death.1,2 Previous lesion-based studies have shown that the dorsolateral region of the lateral medulla is associated with hiccups.3,4 In this study, we aimed to identify the neural correlates of hiccups in patients with LMI, by using voxel-based lesion-symptom (VLSM) mapping.5

Methods
Subjects
This retrospective study was done in the neurology department of Christian Medical College, Vellore in South India. The study was approved by the Institutional Review Board and ethics committee. All consecutive patients admitted under neurology with a diagnosis of lateral medullary infarction

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between January 2008 and May 2018 were identified by searching the inpatient records using a computerized database. Details of history and neurological examination findings of all patients were recorded on a standard data collection sheet. The following characteristics were extracted: demographics, clinical features, comorbidities, and duration of hospital stay. Patients with hiccups caused by an acute lateral medullary infarction were taken as cases. Exclusion criteria included (a) nonavailability of neuro-imaging and (b) poor image resolution because of which lesion boundaries could not be delineated. Controls included those patients with LMI but no hiccups.

Lesion Mapping

All patients had a brain magnetic resonance imaging (MRI) scan within seven days from the time of admission to hospital (Siemens 3T Skyra scanner, Siemens, Erlanger, Germany). MRI images were reviewed by a neurologist trained in lesion mapping and diffusion-weighted imaging and T2-weighted and fluid-attenuated inversion recovery sequence were used for lesion mapping. The individual lesions were mapped onto the Montreal Neurological Institute (MNI) space manually using MRICron (https://www.nitrc.org/projects/mricron). Nonparametric mapping toolbox from the MRICron software package (May 2016) was used to test the statistical contribution of the lesion location to hiccups. Voxel-wise nonparametric testing was done using the Liebermeister with the presence of hiccups as the dependent variable. Voxels were required to be affected in at least five patients to be included in the VLSM analysis. To correct for multiple comparisons, the results were threshold at a 5% false discovery rate. The resultant statistical map was color-coded and displayed on the MNI template. The location of these voxels was further categorized into anatomical sites such as the rostral, middle, and caudal parts of the medulla, as described by Kim et al.

Data Availability

Data can be made available on request.

Results

During the study period from January 2008 to May 2018, 31 patients with LMI were admitted under neurology unit and were included for analysis. The baseline characteristics of the patients with LMI are shown in Table 1. The mean age of the patients was 48 years. There was male predominance (90.3%) and the most common comorbidity present was hypertension (67.7%), followed by smoking (45.1%), diabetes mellitus (35.4%), and alcohol (22.5%). There were 11 (35.5%) patients with intractable hiccups. The clinical findings of the patients with hiccups are given in Table 2. The clinical features other than hiccups included dysphagia (96.8%), dysarthria (100%), ataxia (96.8%), Horner’s syndrome (64.5%), facial palsy (29%), loss of gag (66.7%), pain (19.4%), and sensory loss (80.6%). The average duration of hospital stay was 13 days.

Table 1. Demographic and Clinical Characteristics of Patients with Lateral Medullary Infarction

| Characteristics                        | Total Number of Patients with LMI | LMI with Hiccups | LMI Without Hiccups | P Value |
|----------------------------------------|----------------------------------|------------------|--------------------|---------|
| Number of subjects                     | 31                               | 11               | 20                 |         |
| Age (years) Mean(SD)                   | 48 (17.4)                        | 54.4 (18.2)      | 44.5 (16.4)        | .132    |
| Sex, male/female                       | 28/31                            | 10/1             | 18/2               | .79     |
| Hypertension                           | 21                               | 7                | 14                 | .510    |
| Diabetes mellitus                      | 11                               | 6                | 5                  | .106    |
| Smoking                                | 14                               | 10               | 4                  | .364    |
| Alcohol use                            | 7                                | 4                | 3                  | .180    |
| Dysphagia                              | 30                               | 10               | 20                 | .355    |
| Dysarthria                             | 31                               | 11               | 20                 | 1.000   |
| Ataxia                                 | 30                               | 10               | 20                 | .355    |
| Horner’s syndrome                      | 20                               | 10               | 10                 | .047    |
| Facial weakness                        | 9                                | 4                | 5                  | .683    |
| Impaired gag                           | 2                                | 0                | 0                  | .118    |
| Hemi-sensory loss                      | 25                               | 8                | 17                 | .553    |
| Pain                                   | 6                                | 2                | 4                  | .646    |
| Severe dysphagia requiring Nasogastric | 18                               | 9                | 9                  | .052    |
| tube                                   | Duration of hospital stay (days) | 13               | 17.8 (15.0)        | 10.4 (5.6) | .061 |

Source: From authors’ own research.
Table 2. Neurological Findings in Patients with Hiccups and Lateral Medullary Infarction

| S. no. | Age | Gender | Risk Factors | Neurological Findings | Side |
|--------|-----|--------|--------------|-----------------------|------|
| 1      | 68  | Male   | DM, HTN, smoking, alcohol | Hiccups, dysphagia, dysarthria, Horner’s syndrome, and ataxia. | R    |
| 2      | 44  | Male   | DM, HTN | Hiccups, dysphagia, dysarthria, Horner’s syndrome, facial palsy and loss of gag, crossed hemisensory loss, and ataxia. | R    |
| 3      | 60  | Male   | DM, HTN | Hiccups, dysphagia, dysarthria, and Horner’s syndrome | L    |
| 4      | 54  | Male   | HTN, alcohol | Hiccups, dysphagia, dysarthria, Horner’s syndrome, and ataxia. | L    |
| 5      | 80  | Male   | DM, HTN, smoking | Hiccups, dysphagia, dysarthria, Horner’s syndrome, crossed hemisensory loss, and ataxia. | BL   |
| 6      | 56  | Male   | DM, HTN, smoking, alcohol | Hiccups, dysphagia, dysarthria, Horner’s syndrome, facial palsy crossed hemisensory loss, and ataxia. | R    |
| 7      | 73  | Male   | – | Hiccups, dysphagia, dysarthria, Horner’s syndrome, crossed hemisensory loss, and ataxia. | R    |
| 8      | 30  | Male   | – | Hiccups, dysphagia, dysarthria, facial sensory loss, Horner’s syndrome, facial palsy, and ataxia. | L    |
| 9      | 70  | Male   | DM, HTN | Hiccups, dysphagia, facial sensory loss dysarthria, Horner’s syndrome facial palsy, and ataxia. | L    |
| 10     | 25  | Male   | Smoking, alcohol | Hiccups, dysphagia, Horner’s syndrome, facial sensory loss, dysarthria, and ataxia, | R    |
| 11     | 38  | Female | – | Hiccups, dysphagia, crossed hemisensory loss dysarthria, and ataxia | L    |

Source: From authors’ own research.

Notes: DM, Diabetes Mellitus; HT, Hypertension; R, right; L, left.

Results of the Voxel-Based Lesion-Symptoms Analysis

Location of the lesions in 31 patients is given as a lesion overlay map in Figure 1A. This includes 11 cases and 20 controls. The lesions were distributed across the caudal, middle, and rostral medulla. The results of the VLSM analysis are shown as a statistical map in Figure 1B. The color scale denotes the z-scores from the Liebermeister test that shows the association of a given voxel to hiccups at a false discovery rate level of 5%. The MNI coordinates for the area maximally associated with hiccups was (x = –4, y = –40, z = –58). This region was located at the dorsolateral region of the middle medulla.

Discussion

The hiccup reflex is characterized by sudden inspiration immediately followed by an active closure of the glottis. The reflex arc for hiccups involves phrenic, glossopharyngeal, vagal, and sympathetic pathways as afferents, a central pattern generator in the lower brainstem, and motor neurons that supply the diaphragm and the other respiratory muscles as the efferent. The neurotransmitters involved in hiccups include gamma-aminobutyric acid (GABA), dopamine, and serotonin, and hence, blocking these has proved to be useful in the treatment of hiccups. There are central and peripheral causes for hiccups. Cerebrovascular accidents, trauma, and space occupying lesions include some of the central causes, and peripheral causes include gastro-esophageal reflux, lesions along the afferent pathway such as tumors, herpes infection or myocardial ischemia and drugs like steroids, anti-Parkinsonism and chemotherapeutic agents. Medullary lesions are known to result in hiccups, and lateral medullary infarction is an important cause for intractable hiccups.

The function of hiccups continues to remain poorly understood. Phyllogenetically, hiccups are similar to the gill ventilation that occurs in fish and tadpoles. In tadpoles, gill ventilation precedes lung ventilation which is similar to that of humans where, embryologically, hiccups occur during the latter part of gestation, even before the onset of fetal respiration. It is postulated that hiccups may be the expression of archaic motor patterns of gill ventilation which may persist in mammals for other useful functions of the pharynx and chest wall muscles, such as sucking or eupneic breathing. There are numerous other theories on the pathophysiology of hiccups. One of the important theories suggests that hiccups are caused by the failure of the reciprocal inhibition of the valve control of the pharynx and larynx. This dynamic valve function is achieved by alternating excitation-inhibition of two structures: The glottis closure complex and the inspiratory complex. Imbalance between inspiration and expiration as because of destruction of the expiratory center and destruction of the dorsal motor nucleus...
of vagus and nucleus ambiguus which innervate the diaphragm are other postulated mechanisms.\textsuperscript{17,18}

Neuroanatomical correlates on the sites that produce hiccups have been studied widely in animals and in few limited human studies.\textsuperscript{4,10,14} Studies done in cats have shown that the area associated with hiccups is in the solitary tract nucleus in the dorsal medulla and the reticular formation lateral to the nucleus ambiguus, at the rostrocaudal level between 1.0 mm and 2.5 mm rostral to the obex.\textsuperscript{10,13} In a lesion-based study in patients with LMI, Park et al. found that the dorsolateral region of the middle lateral medulla was involved in patients with hiccups.\textsuperscript{3} Another study done by Moon et al. in 2014 showed that in patients with LMI, those that had hiccups often had dorsal rather than ventral lesions.

In our study on patients with LMI, using the method of VLSM, we demonstrated that the area associated with hiccups was on the dorsolateral aspect of the middle medulla. Based on this location we postulate that the involvement of nucleus of solitary tract, nucleus ambiguus, associated reticular formation, fifth cranial nerve nuclei, and their connections with the middle part of the medulla are necessary for the development of hiccups (Figure 2). The MNI coordinates for the area maximally associated with hiccups was at \((x = -4, y = -40, z = -58)\). This region was located at the dorsolateral region of the middle medulla. The association of hiccups with clinical findings of severe dysphagia and Horner’s syndrome suggests the anatomical proximity of the pattern generator of hiccups to the location of the nucleus of solitary tract and sympathetic tract.\textsuperscript{3,19} The major strength of our study is that it is a lesion-symptom mapping study powered with statistical testing, unlike previous lesion-based studies on hiccups and LMI.

**Figure 1.** (A) Lesion Overlay Map of Lesions of All 31 Patients with Lateral Medullary Infarction. All Lesions were Flipped to the Left Side. Maps were Overlaid on a T1-Template in Montreal Neurological Institute (MNI) Space. The Color Scale Denotes the Number of Patients with a Lesion in a Particular Voxel. (B). Statistical Map of the Results From the Voxel-Based Lesion-Symptom Mapping Displaying Voxels with a Significant Association with Hiccups. The Colour Scale Indicates the z-Statistics From the Results of the Liebermeister Test at a 5% False Discovery Rate. The Areas in Red Indicate a Significant Association with Hiccups. The MNI Coordinate for the Peak Area Associated with Hiccups was \((x = -4, y = -40, z = -58)\). This Region was Located at the Dorsolateral Region of the Middle Medulla.

**Source:** From authors’ own research.

**Figure 2.** Axial Slice of the Medulla Oblongata at the Level of the Olive Showing the Various Nuclei and Tracts. The Circle in the Dorsolateral Region Denotes the Lesion Location Identified by the VLSM Analysis that was Associated with Hiccups. Neuroanatomical Structures that are Involved in this Region Includes the Nucleus of Solitary Tract (NTS), Nucleus Ambiguus, Associated Reticular Formation, Fifth Cranial Nerve Nuclei, Vestibular Nucleus and the Posterior Spinocerebellar Tract.

**Labels:** (a) Pyramid, (b) Inferior Olive, (c) Medial Lemniscus, (d) Spinothalamic Tract, (e) Tectospinal Tract, (f) Spinal Tract of Vth Nerve, (g) Nucleus Ambiguus, (h) Medial Longitudinal Fasciculus, (i) Hypoglossal Nucleus, (j) Dorsal Nucleus of Vagus, (k) Solitary Nucleus, (l) Medial Vestibular Nucleus, (m) Inferior Vestibular Nucleus, (n) Posterior Spinocerebellar Tract.

**Source:** From authors’ own research.
Conclusion

In patients presenting with LMI, we postulate that damage to the dorsolateral aspect on the middle medulla could result in hiccups.

Statement of Ethics

The study was approved by the Ethics committee and IRB of CMC Vellore, Tamil Nadu, India.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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