

Persistent Singultus as an Early Symptom in Primary Central Nervous System Lymphoma: A Case Report

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Article Information

Article Type:	Case Report	*Corresponding author:	Citation: Brian Walter (2020) Persistent Singultus as an Early Symptom in Primary Central Nervous System Lymphoma: A Case Report. <i>J Neuropsychiatr Neurodis</i> , 2(2);1-5
Journal Type:	Open Access	Brian Walter, DO	
Volume: 2	Issue: 2	Larkin Community Hospital	
Manuscript ID:	JNN-1-106	7031 SW 62 nd Ave South Miami	
Publisher:	Science World Publishing	FL 33124	
		Phone: +1 901-283-0049	
Received Date:	09 August 2020	Email: bwalter@larkinhospital.com	
Accepted Date:	26 August 2020		
Published Date:	28 August 2020		

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ABSTRACT

Introduction: Persistent singultus is a rare, debilitating clinical symptom that has multiple etiologies which includes central nervous system pathology. Regarding central nervous system pathology, brainstem lesions have been found to be most associated with singultus. The present study reports a unique case of persistent singultus as one of the early signs of primary B cell lymphoma of the central nervous system with a lesion localized to the frontal lobe with extension into basal ganglia and cerebral peduncle. Pathophysiologic processes mediating the hiccup reflex arc are explored in this report. Additionally, management of refractory singultus is detailed with attention to pharmacological approach.

Case Presentation: Patient is a 46-year-old Hispanic male who initially presented to the emergency department with a 4-day history of disruptive hiccups and fever. Hiccups were reported to start shortly after finishing a 10-day course of doxycycline for the right axillary abscess. The persistent singultus was occurring 8-13 per minute and causing significant impairment to his quality of life and affecting his daily functions including breathing. Patient underwent significant testing and was found to have multiple comorbidities. His complicated hospital course included being diagnosed and treated for Human Immunodeficiency Viruses (HIV)/acquired Immunodeficiency Syndrome (AIDS), disseminated histoplasmosis, central nervous system Epstein Barr Virus (EBV) infection, Cytomegalovirus (CMV) pneumonia in addition to primary B cell lymphoma of the brain.

Conclusion: Diagnostic evaluation for space occupying lesions should be considered in patient's presenting with persistent singultus. Furthermore, refractory singultus may be successfully treated with a multi-regimen pharmacological approach. Our case study also provides clinical support for use of gamma knife radiosurgery in treatment of primary B cell lymphoma of the central nervous system.

INTRODUCTION

Singultus, also known as hiccup, is a natural, involuntary process in which inhalation of breath triggers spasm of the diaphragm and intercostal muscles that is followed by rapid glottis closure [1]. Singultus is generally a benign, transient self-limited condition. Prolonged singultus can have debilitating effects on quality of life and can disrupt daily functions. Physical exhaustion, malnutrition, and reduced breathing performance can arise due to prolonged singultus. Singultus is classified according to duration. Acute hiccups are defined as lasting less than 48 hours. Persistent hiccups are defined as over 2 days and intractable hiccups are defined as lasting over one month [2]. The hiccup reflex arc is composed of several neural pathways [3]. The afferent limb includes sensory branches from phrenic and vagus nerves as well as the sympathetic chain. Central processing is not well defined but postulated to involve brainstem, especially midbrain, respiratory centers, phrenic nerve nuclei, medullary reticular formation, and hypothalamus. Studies have shown electrical stimulation of a localized area of medullary reticular formation can induce singultus [4]. Chemoreceptors located in the peri-aqueductal gray matter and sub-thalamic nuclei are thought to be involved in the pathway [3]. The efferent limb includes the phrenic nerve with accessory efferent neural connections to the glottis and inspiratory intercostal muscles. Figure 1 shows a generalized accepted pathway of hiccup reflex arc. Studied neurotransmitters involved in the hiccup pathway include dopamine and gamma-aminobutyric acid [5].

Singultus has multiple etiologies, both central and peripheral nervous system causes. Central nervous system etiologies include diseases of the brain and the spinal cord including strokes, neoplasms, infections and demyelinating diseases such as multiple sclerosis. Peripheral etiologies involve diseases at the phrenic nerve level. Most common causes are gastrointestinal related, including gastroesophageal reflux and hiatal hernia [6]. Additional precipitating factors include stomach distension and gastrointestinal irritation from overeating, spicy food, or even ingestion of air while eating. [1]. Persistent and intractable singultus tends to be more closely associated with central etiology. A generalized summary of the pathological etiologies linked to singultus is found in Table 1 [5].

Treatment for singultus includes physical maneuvers and pharmacological options [7]. Acute singultus may be treated with physical maneuvers, including performing Valsalva maneuver, holding one’s breath, drinking cold fluids, palpating the eyes in order to stimulate a vagal response by means of the oculocardiac reflex [8]. Osteopathic manipulative treatment has also been shown in studies to successfully treat singultus [9]. Pharmacological treatments should be tailored to the etiology of the singultus. For singultus

caused by gastroesophageal reflux disease, proton pump inhibitors are very effective for singultus [10]. Furthermore, proton pump inhibitors can be considered as first line in treatment for singultus due to their safety profile even in the absence of acid reflux [10]. If initial, first line medications are not effective over 3-4 weeks, then changing to an alternative first line agent or multi-drug regimen should be considered depending on response and tolerance. Chosen agents should be based on the patient’s comorbidities and tolerance to treatments in addition to tailoring to the patient’s known or suspected etiology of singultus. For central etiologies, medications primarily target the dopaminergic or GABAergic pathways. First line therapy includes baclofen, gabapentin or metoclopramide. [11]. Pharmacological treatment can be continued until resolution of singultus, and in cases of recurrence then treatment should be restarted and implemented for longer duration as needed.

Baclofen, which is a Gamma-aminobutyric Acid (GABA) analog, may be considered a first-line agent for singultus for its action in blocking the hiccup stimulus, especially for central etiologies [12]. Baclofen can be started at 5 to 10 mg three times daily and increased thereafter up to 45mg daily total. Gabapentin, which is a GABA analog and anticonvulsant, may be used as a first-line agent for treatment of intractable hiccups [13]. Gabapentin can be started at 100mg three times daily and increased to 400mg three times daily thereafter. A first-generation antipsychotic, Chlorpromazine, has been approved by the FDA for treatment of intractable singultus. Chlorpromazine acts as a dopamine antagonist on the hypothalamus. It can be started at 25mg three times daily by mouth and increased thereafter to 50mg three times daily. [14]. Another option is metoclopramide which is a dopamine antagonist serving as a gastric motility agent. [15]. Beyond the above, there are additional medications for hiccups such as amantadine, other anticonvulsants including valproic acid, other antipsychotics including haloperidol, and even anesthetics including lidocaine.

Primary Central Nervous System Lymphoma (PCNSL) is a type of extranodal Non-Hodgkin Lymphoma (NHL) that can be associated with the brain, leptomeninges, eyes, or spinal cord. Majority of cases of PCNSL are attributed to aggressive lymphoma subtypes such as Diffuse Large B cell lymphoma (DLBCL) [16]. PCNSL, with an incidence of 4%, is heavily associated with immunocompromised states such as disease processes like HIV, though non-HIV related cases have been reported [17][18]. Limited literature is known for PCNSL associated singultus, as many cases involve tumors associated with gastrointestinal system or adrenal glands with predominance



Figure 1: Hiccup reflex arc pathway

Table 1: Etiologies for Singultus

CNS disorders							
Vascular	Ischemic/hemorrhagic stroke	AVMs	temporal arteritis				
Infections	Encephalitis	meningitis	brain abscess	neurosyphilis			
Structural	Head trauma	Intracranial neoplasms	MS	syringomyelia	hydrocephalus		
Peripheral (vagal and phrenic nerve)	laryngitis	pharyngitis	Goiter	neck cyst			
GI disorders	Gastric distention	gastritis	peptic ulcer disease	pancreatitis	hepatitis	esophagitis	aerophagia
Thoracic disorders	pneumonia	empyema	bronchitis	asthma	pleuritis	mediastinitis	pulmonary embolism
Toxic-metabolic	Alcohol	Diabetes mellitus	Hyponatremia	hypocalcemia	Hypocapnia	Tuberculosis	Uremia
Postoperative	Intubation	Traction on viscera	General anesthesia				
Drugs	Alpha methyl dopa	Dexamethasone	Chemotherapeutic agents	Diazepam	Short-acting barbiturates		
Psychogenic	Anorexia nervosa	Conversion	Malingering	Schizophrenia	Stress		

of diffuse large B-cell lymphoma reported. Clinical presentation of PCNSL varies according to localization of the lesion in the brain [19]. Focal neurological deficits are the most common associated feature of PCNSL. Other features include, neuropsychiatric symptoms, and elevated intracranial pressure symptoms. Diagnostic evaluation is mainly done by means of stereotactic brain biopsy followed by histopathologic evaluation of the tissue. Treatment of PCNSL is multifaceted. First line drug of choice to treat PCNSL is methotrexate, an anti-neoplastic agent. [20]. A multi-drug chemotherapeutic approach is often implemented with other agents such as rituximab, temozolomide being added in combination with methotrexate [21]. Additionally, PCNSL can be treated by radiation therapy; however there is known to be an associated risk of neurocognitive decline [22]. Focused Gamma knife radiation therapy has had a positive effect on reducing tumor burden without the associated neurocognitive risks [23].

CASE PRESENTATION

A 46-year-old Hispanic male with a past medical history significant for right axillary Methicillin-resistant *Staphylococcus aureus* abscess that had been drained 2 months prior presented to the hospital's emergency department. The patient arrived with main complaints of persistent daily hiccups and fever. The hiccups started since he finished his 10-day course of doxycycline for the right axillary abscess 4 days ago. The hiccups had been constantly occurring at a rate of 8-13 every minute. The patient found them to be a significant impairment in his breathing, preventing him from taking large deep breaths. In addition, the hiccups were described to impede on the quality of his sleep as well as occasionally disrupting his capability to eat or drink normally. The fever was reported to have reached 103.8F. He reported to be a non-smoker and non-drinker. No significant allergies or home medications were endorsed by the patient. His initial vitals at the time of presentation were significant for low grade fever with temperature of 100.4F. He appeared in mild discomfort while breathing in between hiccups. He was alert and oriented to person, place and time. An anterior-posterior chest radiograph demonstrated bilateral interstitial prominence without evidence of focal consolidations, pleural effusions or pneumothoraces.

On physical examination, aside from the axillary drainage site, the patient was found to have significant oral thrush. For this, the patient was started on nystatin, fluconazole, pantoprazole 40 mg once daily, and Gabapentin 100 mg three times per day. Hiccups improved but continued to persist and be disruptive. Initial neurological examination found left sided hemiparesis with lower extremity worse than upper extremity. Patient had pronator drift in his left upper extremity against gravity and was unable to completely lift his left leg off the bed. He had an impaired gait, best described as hemiplegic gait. Neuroimaging was obtained due to lateralizing weakness concerning for a CNS lesion. Both a CT brain with and without contrast and an MRI brain with/without GAD (Figure 2) were performed which showed a 3.1 x 3.7 cm right periventricular frontal lobe lesion with ipsilateral extension to the basal ganglia and to the cerebral peduncle.

An Electroencephalogram (EEG) was performed in the awake state and found to be a grossly normal study without ictal or interictal epileptiform activity. A lumbar puncture was performed, and the CSF was sent for cytology and infectious studies. CSF glucose was found to be 48 mg/dL (ref 45-80 mg/dL) and CSF protein was found to be 37 mg/dL (ref 15-45 mg/dL). Opening pressure was 9.5 mm CSF on the manometer. The studies returned positive for EBV, CMV, Herpes simplex virus-2 and West Nile Virus IgG antibody. The patient was promptly started on intravenous acyclovir 600mg every 8 hours. HIV and Hepatitis antibody testing were ordered early on in course and resulted reactive to HIV p24 antigen. CD4 of 46 later resulted. Viral load was 874,000. Infectious disease started on prophylaxis for opportunistic infections and placed on highly active antiretroviral therapy (HAART). Stereotactic biopsy was performed for pathology evaluation of brain lesion and patient was found to have PCNSL, specifically high-grade B cell lymphoma. Neurosurgery performed

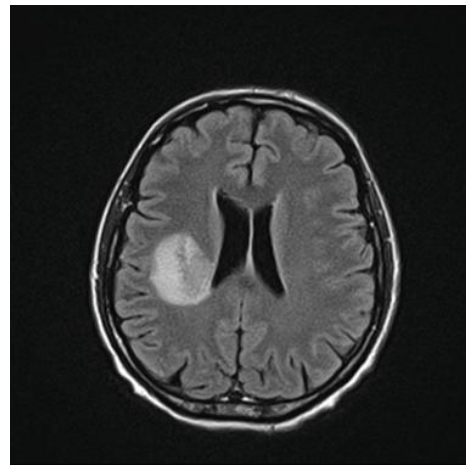


Figure 2: MRI brain W/WO GAD axial FLAIR

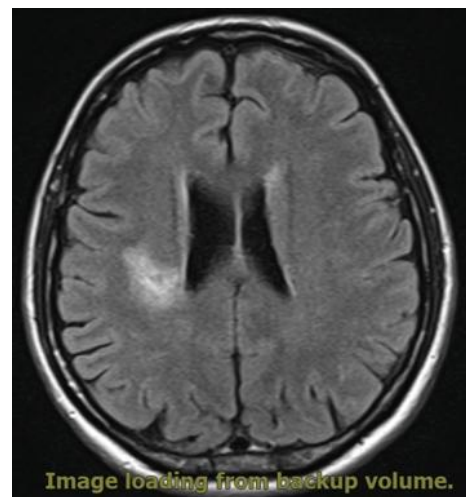


Figure 3: MRI Brain W/WO GAD axial FLAIR

gamma knife radiosurgery on the brain lesion at approximately day 30 of admission. Repeat surveillance brain MRI (Figure 3) performed several weeks later showed stable lesion with no new lesions, further extension, or increase in tumor burden. The patient's course was further complicated with positive findings of disseminated histoplasmosis and CMV pneumonia. Oncology followed the case closely and advised withholding methotrexate therapy until the patient's considerable infectious disease processes were treated. The patient over the course of his hospital stay showed improvement in left hemiparesis. No new lateralizing or focal deficits and no worsening neurocognitive deficits were observed on subsequent neurological examinations following the gamma knife therapy. The patient was eventually transferred to another facility and was lost to follow up after a prolonged multiple month hospital stay.

Regarding the patient's singultus treatment, chlorpromazine was added to the regimen early in his course around day 4 of admission but later discontinued due to side effects including worsening sleep disturbance and increased risk for agranulocytosis as the patient was later confirmed to have HIV. Later, gabapentin was increased to 300mg three times per day and baclofen increased to 10mg daily, and Pantoprazole 40mg daily was continued. Patient was on this combination for approximately 2 weeks when metoclopramide was added and with this multidrug regimen, the patient had resolution of singultus by day 23 of admission. Non-pharmacological therapy included osteopathic manipulative therapy (OMT) which was started around day 10 of admission.

DISCUSSION

The patient in this case report presented with persistent singultus based on defined time interval guidelines, though this could be arguably a case of intractable singultus. Patient had multiple causative factors for his singultus, including thrush and centrally with an identified brain lesion. The persistent nature of his singultus despite successful resolution of the thrush provide strong evidence for the primary etiology being his central brain lesion which was found to be impinging on the brainstem structure of the cerebral peduncle as well as the basal ganglia with subthalamic nucleus involvement. Brainstem lesions and subthalamic nucleus lesions have been documented to be involved in mediation of hiccup reflex arc, which is supported by our study.

A multi-regimen approach involving combination of pharmacological first line agents along with physical maneuvers with OMT ultimately proved to be effective in treating singultus by day 23. Chlorpromazine was discontinued due to the side effect of worsening sleep disturbance and upon final confirmation of AIDS, the risk of development of agranulocytosis outweighed potential benefits. The first line regimen of baclofen, gabapentin and metoclopramide proved to be the best tailored regimen for effectively treating the singultus while minimizing side effects and sustaining drug tolerability.

CONCLUSION

We present a unique case of persistent, near intractable singultus in a patient who was subsequently found to be in immunocompromised state and found to have central brain lesion with a newly diagnosed primary central nervous system lymphoma. Singultus is a usually benign process that when persists should strongly indicate need for further neurological workup and evaluation for central nervous system lesion. Neuroimaging is vital in assessing central etiologies contributing to persistent singultus, especially in the setting of neurological deficits. This patient had additional non-central factors likely contributing to his singultus with significant thrush on examination. This study elucidates need for comprehensive workup of central etiologies despite the presence of an otherwise obvious cause. Our study emphasizes a need for comprehensive neurological assessment in patients with persistent singultus due to the importance in evaluating for focal, lateralizing, and cranial nerve deficits which may point to an underlying central lesion.

This case further illustrates the benefit of having a multi-regimen approach involving a tailored pharmacological plan in addition to physical manipulative therapy. Baclofen, gabapentin, and metoclopramide proved to be an effective, and tolerable combination for the treatment of persistent singultus. Additionally, this regimen proved to have a gradual reduction to eventual resolution of the singultus over a 3-4-week interval. An expected gradual not immediate improvement of singultus in central etiologies is further supported by this case study.

Furthermore, gamma knife radiosurgery was shown to be an effective and tolerable therapy option for this patient with a newly diagnosed PCNSL. The patient had stable MRI brain scans without new or worsening tumor burden. The patient had slow, gradual improvement of left sided hemiparesis without any new focal, lateralizing deficits or bulbar and cranial nerve deficits over the treatment course. The patient also did not exhibit any neurocognitive decline with the gamma knife procedure, which is often seen in whole body brain radiation. Thus, our study supports the consideration of gamma knife radiation as a viable therapeutic option in conjunction with chemotherapy in the treatment of PCNSL.

ABBREVIATIONS

PCNSL – Primary Central Nervous System Lymphoma

CNS – central Nervous System

MRI – Magnetic Resonance Imaging

CT – Computed Tomography

GAD – Gadolinium

IgG – Immunoglobulin G

CNS – Central Nervous System

AVMs – Arteriovenous Malformations

MS – Multiple Sclerosis

GI – Gastrointestinal

OMT – Osteopathic Manipulative Treatment

IBD – Inflammatory Bowel Disease

ACKNOWLEDGEMENTS

Dr. Mohan Deochand & Dr. Hector Lalama for their role as attending physicians on the Neurology consult service. Marcos A. Sanchez-Gonzalez, MD, PhD, for his role in the supervision of this case report.

CONFLICT OF INTEREST: The authors declare no conflicts of interest

AUTHORS CONTRIBUTIONS: All authors read approved the final manuscript.

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