

# Persistent hiccups due to the use of intravenous methylprednisolone in a patient with relapsing remitting multiple sclerosis: a case report and literature review

Atak ve iyileşmelerle giden multipl skleroz hastasında intravenöz metilprednizolon kullanımına bağlı inatçı hıçkırık: bir olgu eşliğinde literatürün gözden geçirilmesi

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**Received/Accepted:** May 09, 2016 / June 09, 2016

**Conflict of interest:** There is not a conflict of interest.

## SUMMARY

Hiccups can be defined as the sudden, uncontrolled contractions of the diaphragm, followed by immediate inspiration and closure of the glottis over the trachea. Various etiologies are responsible for this reflex action such as instrumentations, gastrointestinal, cardiovascular, toxic-metabolic factors, and drugs. Most common drugs that may trigger hiccups are opioids, barbiturates, some antibiotics, chemotherapeutic agents, and steroids. Since steroids are one of the most common drugs in neurology practice, we here presented a patient with relapsing-remitting multiple sclerosis that experienced persistent hiccups after intravenous methyl- prednisolone treatment, to emphasize the side-effect of the drug.

**Keywords:** Hiccups, intravenous methyl-prednisolone, side effect

## ÖZET

Hıçkırık, trakenin üzerinden glottisin kapanması ve ani inspirasyon ile takip edilen, diyaframın ani ve kontrol edilemeyen kasılmaları olarak tanımlanabilir. Bu refleks eylemden enstrümantasyon, gastrointestinal, kardiyovasküler, toksik-metabolik faktörler ve ilaçlar gibi çeşitli etiyolojiler sorumludur. Hıçkırığı sıklıkla tetikleyen ilaçlar opiatlar, barbitüratlar, bazı antibiyotikler, kemoterapötik ajanlar ve steroidlerdir. Steroidler nöroloji pratiğinde en sık kullanılan ilaçlardan biri olduğundan, intravenöz metilprednizolon sonrası inatçı hıçkırık ortaya çıkan, atak ve iyileşmelerle giden bir multiple skleroz hastasını, ilacın yan etkisini vurgulamak amacıyla sunduk.

**Anahtar sözcükler:** Hıçkırık, intravenöz metilprednizolon, yan etki

## INTRODUCTION

Hiccups can be defined as the sudden, uncontrolled contractions of the diaphragm, followed by immediate inspiration and closure of the glottis over the trachea<sup>1</sup>.

It is a common problem in general population, and may occur equivalently in men and women. A retrospective review of consecutive patients attending a general hospital identified 55 of 100 000 patients that received a primary diagnosis of hiccups. However the exact frequency in general population is not clear, due to the lack of community – based studies<sup>2</sup>.

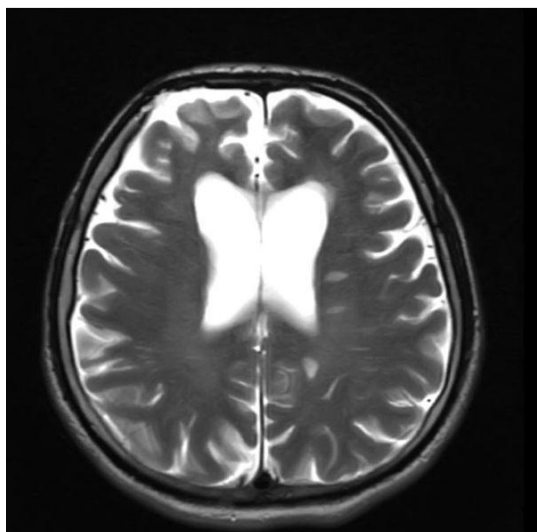
The pathological mechanisms underlying hiccups are considered as a reflex arc including an afferent part with phrenic nerve vagal nerve and sympathetic pathway from thoracic 6 to 12. The center of the arc is thought to be located between cervical 3 and 5, whereas the efferent part consisted of phrenic nerve, accessory respiratory muscles, the glottis, and autonomic processes with medullary reticular formation and hypothalamus. However the exact pathophysiology is unclear<sup>3,4</sup>.

The clinical manifestation may be transient and can be defined as hiccups lasting 48 hours or less, or persistent in cases of hiccups lasting longer than 48 hours, or intractable when it lasts more than a month.<sup>3</sup> Since the etiology of hiccups is broad, it can be a result of psychogenic, metabolic, gastrointestinal, neurological, pulmonary, cardiovascular diseases or drugs including some antiparkinsonian drugs, morphine, opioids, some antibiotics, or steroids<sup>1,5</sup>.

Thus we here presented a patient who suffered from persistent hiccups after intravenous metilprednisolone (IVMP) treatment for RRMS, to emphasize this relatively infrequent side-effect of corticosteroids.

## CASE REPORT

A- 38 years old male patient presented to our neurology outpatient clinic with gait difficulty, which had begun 4 years ago. He stated that he was diagnosed as RRMS 3 month ago regarding to his relapsing and remitting complaints and neuroimaging, and laboratory investigations. His medical reports revealed no per oral medication or illness other than RRMS. There was a slight decrease in his lower limbs with muscle strength of 4/5 in his motor examination. He had brisk deep tendon reflexes bilaterally and he had an achill clonus. His plantar reflexes were flexor bilaterally. Cerebellar system and sensory examinations were also normal. Following his hospitalization, the patient underwent cranial magnetic resonance imaging (MRI) investigation, and there were pericallosal, and periventricular lesions touching the ventricles with subcortical, juxtacortical lesions in the axial T2-weighted cranial MRI (Figure-1). The cerebrospinal fluid analysis was unremarkable. As acute attack treatment, 1 gram/ day IVMP treatment for 5 days was administered to the patient. On the second day of pulse steroid treatment, hiccups occurred which was lasting whole day, and disappearing while the patient was asleep. Since this hiccups persisted during the IVMP treatment, and did not recover with conventional techniques such as valsalva maneuver, or holding breath, but disappeared approximately 12 hours following the discontinuation of IVMP at the end of 5<sup>th</sup> day, it was considered as persistent hiccups. While the hiccups were found to be related with IVMP treatment, it was considered as a side effect of corticosteroid treatment.



**Figure 1. Axial T2-weighted cranial MRI: Periventricular T2 hyperintense lesions.**

## DISCUSSION

Hiccups are reflex actions due to the sudden contraction of diaphragm by the stimulation of nervus phrenicus, which is generally self-limiting, and benign<sup>1</sup>. The medical term for this condition is ‘Singultus’, which can be defined as ‘to be caught in the act of sobbing’<sup>6</sup>.

Since it is a reflex action, any disease or pathology affecting brain, diaphragm or abdominal viscera can trigger the brainstem, and proximal cord via vagal or phrenic efferents, leading repetitive myoclonic contractions of the diaphragm, which is followed by the activation of recurrent laryngeal nerve and closes the glottis with the “hic” sound of hiccups<sup>7</sup>.

The etiology that may trigger and activate the reflex arc of hiccups is summarized in Table-1. The most causative drugs in the etiology of hiccups are barbiturates, opioids, antibiotics like macrolides, and steroids<sup>4</sup>. Our literature review demonstrated that corticosteroids which are used for several conditions may trigger transient, persistent, or intractable hiccups<sup>8-10</sup>.

Since corticosteroid are the most common drugs in neurology practice, in the acute treatment of RRMS, in particular, it is important to be aware and keep in mind the hiccups as a side-effect of corticosteroids.

**Table-1. Hiccups etiology**

<b>Etiology of hiccups</b>	
Gastrointestinal diseases	Gastro-oesophageal reflux Hiatus hernia Peptic ulceration Abdominal tumors, or abcess
Cardiovascular diseases	Myocardial infarction Thoracic aneurism Pericarditis
Infections	Otitis Rhinitis Pharyngitis Meningitis, encephalitis
Central nervous system disease	Ischemic or hemorrhagic brainstem disease Intracranial tumor Parkinson' s disease Epilepsy
Toxic-metabolic diseases	Hyponatremia Hypocalcemia Hyponatremia Blood sugar regulation problems, diabetes mellitus Alcohol consumption
Instrumentations	Endoscopy Intubation Central venous catheter
Drugs	Dopamine agonists Opioids Barbiturates Some antibiotics Chemotherapy Steroids
Psychosomatic	Stres Anxiety Fear

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