INO and Nystagmus: A Case Report and Review of the Literature

Eric Pinkston, BS[1,2] Milan Sivakumar, BS[3] Jordan Farhat, DO[1,2] Thomas C. Varkey, MD, MBA, MEd [1,2,4] and Savdeep Singh, MD[1,2]

Abstract

The brachium pontis, also referred to as the middle cerebellar peduncle, serves as a connector between the cerebellum and cerebral cortex via the pons. As the largest of the three peduncles, it conveys the largest number of fibers and is utilized in the primary cortico-cerebellar-cortical loop, which helps facilitate motor planning. These fibers convey afferent information from the frontal and temporal lobes of the cortex to the posterior lobe of the contralateral cerebellum. Being composed primarily of white matter, brachium pontis lesions are most commonly seen in patients with multiple sclerosis and are rarely caused by stroke. Because of this, often these patients are initially not appropriately treated as their presentations do not match a classical presentation of cerebrovascular disease. Herein, we report a case of stroke located in the right brachium pontis resulting in nystagmus with a fast beating to the left and right lateral rectus palsy (also known as a reverse internuclear ophthalmoplegia), and we discuss key clinical pearls of treatment in these patients with rare hyperacute presentations.

Keywords: Ischemic stroke, internuclear ophthalmoplegia, brachium pontis, nystagmus, Lutz syndrome.

Introduction

The brachium pontis, also referred to as the middle cerebellar peduncle, is a paired structure that connects the cerebellum to the pons. This structure is made up of white matter fibers connecting the cerebral cortex to the cerebellum. The densely packed structure when damaged can cause any number of symptoms including discoordination, eye motion abnormalities, vertigo, double vision, or difficulty with coordination of complex movements such as walking since it contains a number of fibers that work to integrate the information coming from the balance system in the inner ear and the motion of the eyes with the cerebellum and basal ganglia. Brachium pontis lesions are classically described in multiple sclerosis or other demyelinating disease states as the structure is entirely made up of axons and myelin sheaths. Nevertheless, in very rare circumstances, brachium pontis lesions can appear in the hyperacute setting secondary to acute ischemic stroke (~0.15% of all strokes).[1,2] In addition, the brachium pontis fibers that carry information to the cerebellum receive information from both the medial and lateral vestibular nuclei of the pons which receive their information from the middle ear. Damage to these structures can cause nystagmus due to the loss of input from those ipsilateral brainstem nuclei. Secondary to the rarity of the lesion and the confusion that such a presentation can cause, these patients are often not initially

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appropriately treated for ischemic stroke. Herein, we report a case of stroke located in the right brachium pontis resulting in a posterior internuclear ophthalmoplegia of Lutz syndrome.

The Case

The patient was a 50-year-old man with a medical history of metabolic syndrome (hypertension, hyperlipidemia, and type 2 diabetes mellitus) who presented to his primary care physician's office complaining of new onset dizziness, nystagmus, and double vision. He reported that he awoke at 1:30 am that morning with new onset dizziness, diplopia, nausea, vertigo, and confusion. Around 3:30 am, he tried to walk and began to vomit. His wife stated that he appeared confused, but that this had resolved by the time he was seen by his primary care physician. His primary care physician sent him to the emergency department (ED) for further evaluation. The patient was seen by the stroke neurology team in the evening of the same day. By the time he was seen, he reported that the nausea was better but that he was still experiencing double vision when looking to the right side of the body past the midline.

On physical exam, his National Institutes of Health Stroke Scale score was 2 (2 points for horizontal gaze palsy). He was afebrile with stable vital signs. Neurologically, he was alert and oriented with right-sided lateral rectus palsy and right sided slow beating (fast beating to the left) nystagmus. Convergence was not impaired. No other motor or sensory deficits were noted. He was not confused on exam. Based on the symptoms and examination, his lesion appeared to localize to the pons and cerebellum.

Differential Diagnosis

Due to the hyperacute nature of the symptoms, the major differential diagnoses included acute ischemic stroke, acute hemorrhagic stroke, cerebral venous sinus thrombosis, demyelination such as from multiple sclerosis, adverse effect of medications, or illicit drug use. The patient's symptoms with right-sided lateral rectus palsy and left fast beating nystagmus is a clinical syndrome known as a posterior internuclear ophthalmoplegia of Lutz syndrome. While the differential diagnoses could explain the cause of the symptoms with localization to the white matter tracts within the pons, without a history of previous events and acute onset of symptoms, the classical cause of symptoms of this nature, namely multiple sclerosis, was considered to be less likely. He reported that he was not taking any medications that could cause these symptoms, and he reported that he was not taking any illicit drugs. However, due to the patient's risk factors including hypertension and type 2 diabetes mellitus, the specter of stroke rose in the differential as the most likely diagnosis.

Initial Imaging and Labs

During his initial evaluation by the emergency medicine team, the patient underwent a computerized tomography (CT) scan of the head which was negative for subacute stroke, masses of any sort, or hemorrhage. He also underwent a CT angiogram of the head and neck which was negative for large vessel occlusion or cerebral venous sinus thrombosis. His hemoglobin A1c was elevated at 9.4% and his low density lipoproteins were elevated at 123 mg/dL. A magnetic resonance image (MRI) of the brain was ordered and the patient was monitored with neurological re-examinations by the nursing staff every four hours.

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Initial Management and Additional Imaging

While awaiting MRI, the patient was started on 81 mg of aspirin and 40 mg of atorvastatin. Initially, his systolic blood pressures were allowed to run high at a maximum of 200 mm Hg to allow for potential perfusion of other areas of tissue that might be at risk for stroke. This was brought down gradually with chlorthalidone 25 mg daily and losartan 100 mg daily. His transthoracic echocardiogram demonstrated a normal left ventricular ejection fraction. His MRI Brain demonstrated a small lesion on the right brachium pontis (Figure 1) which explained some of his symptoms. Further evaluation of T2 FLAIR and FIESTA MRI imaging demonstrated additional white matter damage throughout the brainstem worse on the right side than the left which provided explained his symptoms (Figures 2 and 3). Due to his young age, he underwent transesophageal echocardiography which demonstrated a small right to left interatrial shunt. This led to transcranial doppler studies which demonstrated that his shunt had a Spencer grade of 0/5 both at rest and with Valsalva making cardioembolic causes for his stroke unlikely.

Diagnosis and Treatment

Based on the history and the physical exam, it was determined that his stroke was caused by small vessel disease, and the patient was instructed to continue the 81 mg of aspirin and 40 mg of atorvastatin daily to decrease his risk. He was continued on chlorthalidone 25 mg daily and losartan 100 mg daily, was referred to his primary care physician for further management of his diabetes, and given instruction on a low glycemic diet. The patient underwent an outpatient sleep study which demonstrated 80.6 apneic events an hour per the American Academy of Sleep Medicine criteria, consistent with severe sleep apnea. This was treated with continuous positive airway pressure during sleep at 15 cm of water pressure and heated humidification to prevent further apneic events to decrease his risk of future stroke.

Discussion

The patient's physical exam findings were classic for a posterior internuclear ophthalmoplegia of Lutz which consists of a reverse internuclear ophthalmoplegia in which the eye ipsilateral to the lesion is unable to abduct laterally (i.e. a pseudo-abducens palsy) with a fast beating nystagmus to the side contralateral to the lesion. In the patient's disease state, the abducens nerve (cranial nerve VI) fascicle was damaged and the lateral vestibular nucleus of the pons was also damaged secondary to small vessel ischemia. Internuclear ophthalmoplegia (INO) consists of damage within the central nervous system, usually within the medial longitudinal fasciculus (MLF), that leads to an inability for one of the two eyes to appropriately adduct with lateral eye motions. There are a family of diseases that are also related to INOs (Table 1). Our patient suffered from symptoms that were consistent with a posterior INO of Lutz (also known as an INO of abduction) which has been described in the literature secondary to a lesion in the midbrain preventing relaxation of the medial rectus in the midbrain, a loss of internuclear neurons to the contralateral abducens nucleus via the MLF secondary to a lesion in the midbrain, or a posterior pontine lesion before the neuron's synapse within the abducens nerve nucleus as was seen in the case published by Bijvank and colleagues.[3] The patient's singular lesion in the middle cerebellar peduncle did not explain his level of disability; however, further evaluation of

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Figure 1. Diffusion weighted imaging and apparent diffusion coefficient images of the area of stroke in the brachium pontis.

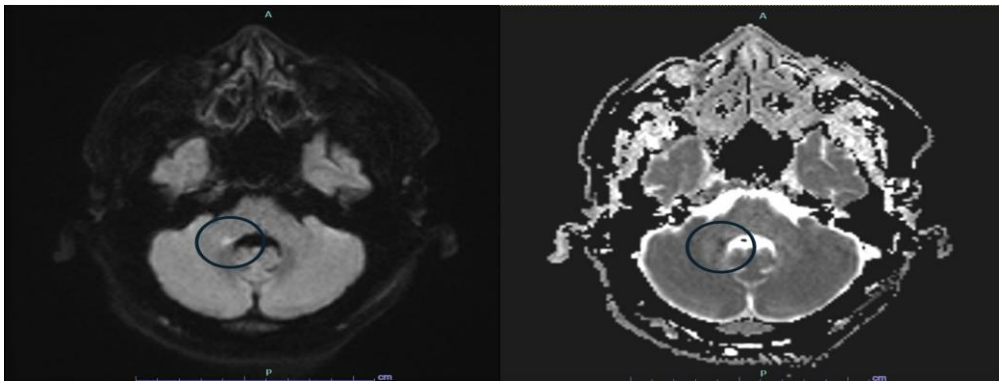

Figure 2. Images A-C: T2 FLAIR imaging with evidence of right- greater than left-sided periventricular hyperintensities consistent with microvascular injuries. Image D: T2 FIESTA imaging demonstrating T2 hyperintense lesions including the new stroke seen on DWI in key structures causing a posterior INO of Lutz syndrome.[3]

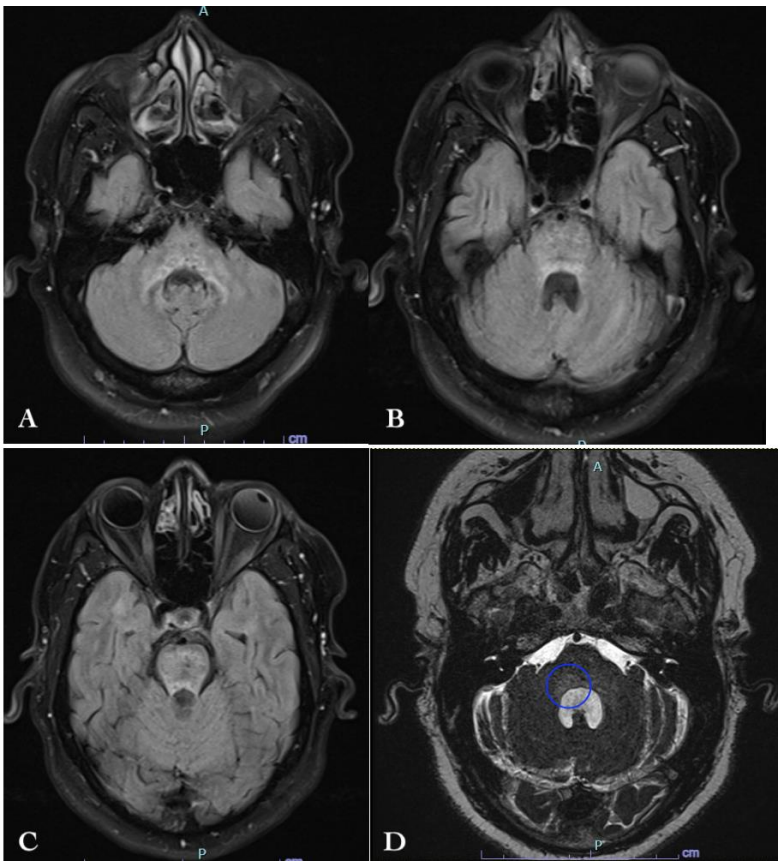

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Figure 3. Image of the pons and important nuclei caused by stroke affecting the fibers of the middle cerebral peduncle. Damage to lateral vestibular and medial vestibular nuclei likely explain the fast beating nystagmus to the side contralateral to the lesion.

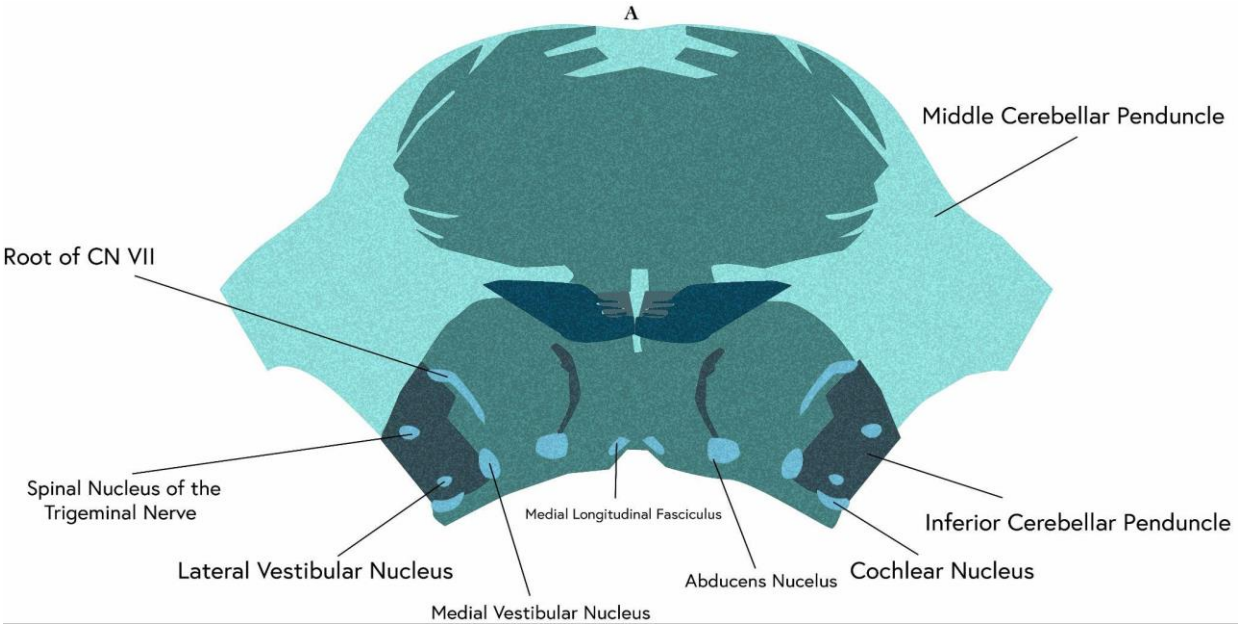

Figure 4. From the pontine nuclei, fibers travel through the contralateral brachium pontis to reach the cerebellar cortex as mossy fibers. The cerebellar cortex connects to the dentate nucleus, which then sends efferent fibers via the superior cerebellar peduncle.

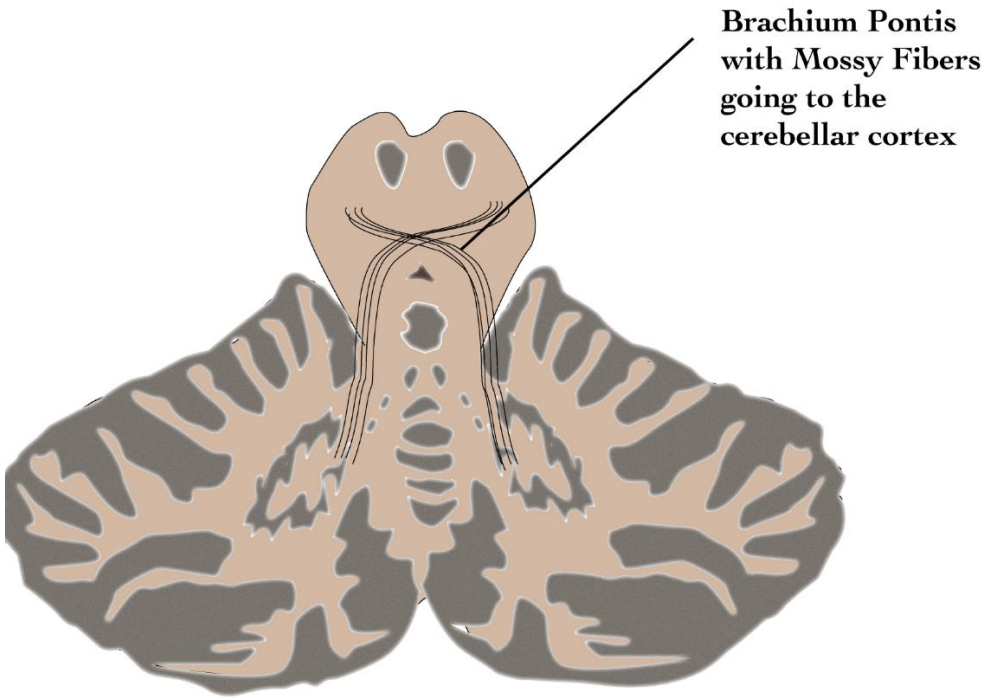

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Table 1. Internuclear Ophthalmoplegia (INO) and Associated Syndromes.

Type of INO	Symptoms	Localization
Typical INO (also called internuclear ophthalmoparasis)[14]	Ipsilateral adduction deficit on the side of the lesion and contralateral nystagmus when attempting gaze to the contralateral side to the lesion side	Lesional damage within the medial longitudinal fasciculus (MLF) within the pons or the midbrain
INO of abduction (Lutz posterior INO, or reverse INO and pseudo-abducens palsy)[3]	Ipsilateral abduction deficit on the side of the lesion and fast beating nystagmus to the side contralateral to the lesion	Midbrain lesion which prevents the relaxation of the medial rectus in the midbrain. a loss of internuclear neurons to the contralateral abducens nucleus via the MLF secondary to lesion in the midbrain, or a posterior pontine lesion before the neurons enter the VI nerve nucleus
Wall-eyed bilateral INO (WEBINO)[15]	Supranuclear vertical gaze palsy, dissociated abducting nystagmus, and impaired convergence	Bilateral lesional damage to the MLF within the midbrain, usually damaging the pretectum
Wall-eyed monocular INO (WEMINO)[16]	Typical INO symptoms (ipsilateral adduction deficit on the side of the lesion and contralateral nystagmus when attempting gaze to the contralateral side to the lesion side) + ipsilateral exotropia	Unilateral lesional damage to the MLF within the pons or midbrain
One and a half syndrome[17]	Typical INO symptoms (ipsilateral adduction deficit on the side of the lesion and contralateral nystagmus when attempting gaze to the contralateral side to the lesion side) + conjugate horizontal gaze palsy to the side contralateral to the lesion	Unilateral lesional damage to the paramedian pontine reticular formation or the abducens nucleus on one side, with interruption of internuclear fibers of the ipsilateral MLF after it crosses the midline
Eight-and-a-half syndrome[18]	Typical INO symptoms (ipsilateral adduction deficit on the side of the lesion and contralateral nystagmus when attempting gaze to the contralateral side to the lesion side) + conjugate horizontal gaze palsy to the contralateral side from the lesion + ipsilateral facial nerve palsy	Lesional damage within the pons to the MLF and the VI nerve fascicle and the VII nerve fascicle
Half-and-half syndrome[19]	Typical INO symptoms (ipsilateral adduction deficit on the side of the lesion and contralateral nystagmus when attempting gaze to the contralateral side to the lesion side) + ipsilateral VI nerve palsy	Pontine damage affecting the VI nerve fascicle and the MLF

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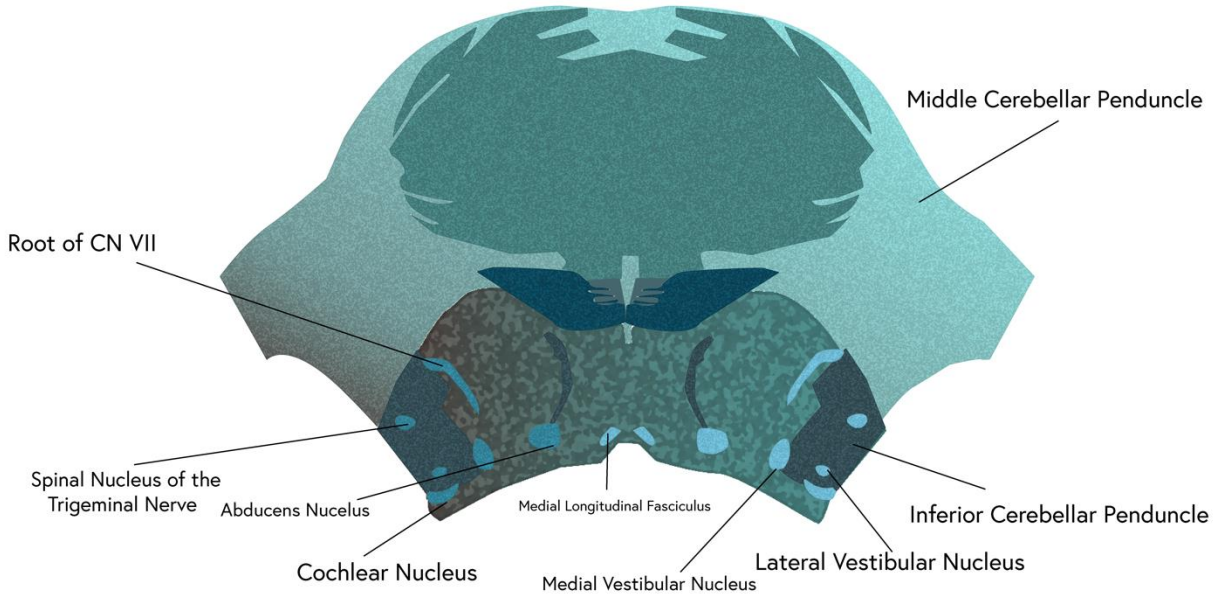
Figure 5. Area of darkened shading on the right-sided pons demonstrating the area that was affected by the long standing white matter disease, likely microvascular, and the resulting structures that would have been damaged leading to the patient's symptoms.



the T2 FLAIR and the T2 FIESTA imaging demonstrated loss of the white matter tracts in the posterior pons causing his symptoms. This is similar in nature to the additive effects that can occur with other small vessel disease states, such as vascular dementia.

Review of Pertinent Anatomy

In this patient's case, there were several important structures affected. The brachium pontis primarily consists of afferent fibers to the cerebellum that are part of the cortico-ponto-cerebellar pathway. This pathway is a closed circuit between various parts of the cerebral cortex and cerebellum, which is involved in regulating motor tasks as well as the planning and initiation of those movements. From various parts of the motor, sensory, and prefrontal cortex, fibers travel down and converge in the pontine nuclei (Figure 3). From there, further fibers travel through the contralateral brachium pontis to reach the cerebellar cortex as mossy fibers. The cerebellar cortex connects to the dentate nucleus, which then sends efferent fibers via the superior cerebellar peduncle (Figure 4).[4,5] Classically, these fibers were thought to decussate to the contralateral red nucleus and then go to the ventrolateral nucleus of the thalamus, (with some fibers bypassing the red nucleus and going directly to the contralateral ventrolateral nucleus of thalamus), and then return to various regions of the cortex. However, more recent data have identified potential ipsilateral components of these tracts.[6,7] Figure 5 demonstrates the area that was affected by microvascular disease and the resulting structures that would have been damaged leading to the patient's symptoms.

Pathophysiologic Mechanisms

On exam, this patient was found to have left fast beating nystagmus and a right-sided lateral rectus palsy, but interestingly, no

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ataxia. Isolated vertigo and nystagmus has been reported in the past, as the cortico-ponto-cerebellar pathway contains white matter tracts that carry information about eye movements.[8] As discussed earlier, brachium pontis lesions are most commonly due to demyelinating diseases, and ischemic infarcts are possible as well in this area. This area is typically supplied by the anterior inferior cerebellar artery, although potentially some components of the superior cerebellar artery may also supply this region. Thromboembolic events or severe atherosclerotic disease can produce ischemic stroke, however, ischemic infarcts are much less common of an etiology for these lesions.[9-11] The literature contains few reports of unilateral middle cerebral peduncle (MCP) infarcts, often in patients with other complex medical conditions such as Fragile-X associated tremor/ataxia syndrome,[12] with most articles describing bilateral MCP infarcts associated with a variety of etiologies.[13,14]

With these facts in mind, one might naturally first suspect that our patient had an underlying demyelinating disease contributing to his presentation and imaging. However, his medical history and demographics seem to argue against this and support our conclusions that this lesion resulted from an ischemic infarction. Demyelinating diseases are less likely to present in middle aged male patients. In addition, our patient has several risk factors for ischemic infarcts, including uncontrolled hypertension, hyperlipidemia (LDL 123), and uncontrolled diabetes, in addition to severe obstructive sleep apnea.

Conclusions

This case demonstrates the importance of a focused differential and consideration of disease states that might not fit classical illness scripts during the hyperacute phase of a disease. This patient's presentation fits well with a multiple sclerosis flair due to white matter tract involvement within the brainstem and cerebellar fibers. However, in consideration of the patient's risk factors and history, appropriate steps were taken to work up potential stroke, reduce his risk factors, and prevent further harm. In addition, consideration of the root causes of sleep apnea and treatment of his insulin resistance were key to ensuring his long term health.

Author Affiliations

Department of Neurology, University of Arizona, Phoenix USA[1]

Banner University Medical Center, Phoenix, Arizona USA[2]

University of Texas Southwestern, Dallas, TX USA[3]

Grand Canyon University, Phoenix, Arizona USA[4]

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Corresponding Author

Thomas C. Varkey, MD, MBA, MEd
Department of Neurology
University of Arizona, Phoenix, Arizona USA
thmsvrk7@gmail.com

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