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CASE REPORT

Unrelenting Hiccups as a Clue: Area Postrema Syndrome in Medullary Infarct – Two Case Reports

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ABSTRACT

Background: The area postrema, a medullary circumventricular organ lacking a blood-brain barrier, plays a key role in autonomic regulation. Ischemic area postrema syndrome (APS) is rare but presents with intractable nausea, vomiting, and hiccups.

Objectives: To highlight ischemic APS through two clinical cases and emphasize diagnostic and therapeutic considerations.

Methods: Two male patients presented with persistent hiccups, nausea, and vomiting. Imaging confirmed lateral medullary infarcts involving the area postrema. Etiological investigations included vascular imaging and thrombophilia workup.

Results: Case 1 had a vertebral artery thrombus and hyperhomocysteinemia. Case 2 showed a similar infarction with protein C and S deficiency. Both were treated conservatively with antiplatelets, vitamins, and symptomatic management, improving clinical outcomes.

Conclusion: Ischemic APS should be considered in stroke differentials with unexplained emetic symptoms. Early recognition and targeted therapy can improve outcomes, particularly in patients with underlying prothrombotic states.

Keywords: Ischemic area postrema syndrome (APS), hiccups, Medullary infarct

Introduction

Area postrema syndrome (APS) typically manifests as persistent nausea, vomiting, and hiccups. The area postrema, located in the medulla oblongata of the brain stem, is a circumventricular organ with permeable capillaries and sensory neurons that detect bloodborne chemical signals and transmit them as neural inputs.[1] Its proximity to the solitary tract nuclei facilitates autonomic functions like vomiting, thirst, hunger, and blood pressure regulation.[2] Located in the fourth ventricle, this vascular structure is rich in AQP4 receptors, and its lack of a blood-brain barrier permits AQP4-IgG entry, potentially signaling early neuromyelitis optica (NMO), a demyelinating disorder.[3,4]

Ischemic Area Postrema Syndrome (APS) is a rare neurological condition characterized by persistent nausea, vomiting, and hiccups resulting from an infarction in the area postrema, a highly vascularized, circumventricular structure in the dorsal medulla. Supplied by small perforating branches of the anterior spinal artery or vertebral artery, this chemoreceptor "vomiting center" lacks a typical blood–brain barrier, making it uniquely vulnerable to ischemic injury. Although ischemic stroke is an infrequent cause of APS, case reports—highlighting dorsal medullary infarcts confirmed on thin-slice diffusion-weighted MRI—demonstrate that small, localized ischemic events can disrupt the area's function and induce classic APS symptoms.[5,6]

We are hereby reporting two cases presenting with APS and ischemia as its aetiology in table 1.

Table 1- Clinical details of the case of ischemic APS

Parameter	Case 1	Case 2
Age / Sex	65-year-old male	53-year-old male
Clinical Presentation	Nausea, vomiting, hiccups, giddiness, tinnitus, and unstable gait for 4 days. BP: 200/100 mmHg, Pulse: 70/min. NIHSS score: 0 with equivocal plantar	Sudden-onset neck pain, radiating symptoms, hiccups, nausea, vomiting for 2 days. BP: 180/100 mmHg, Pulse: 90/min. NIHHS -0 with equivocal plantar
CT Findings	Lacunar infarcts in the right frontal and parietal lobes, corona radiata, and bilateral external capsules	Diffuse hypodensity in the periventricular region
MRI Findings	Acute lateral medullary infarct (right area postrema), loss of normal flow void in right vertebral artery and PICA → intraluminal thrombus	Infarct in lateral medullary area, thrombus in right vertebral artery, T2 hyperintensities in bilateral cerebral hemispheres perpendicular to corpus callosum
Other Investigations	Routine and viral marker:-Normal Carotid Doppler: Bilateral atherosclerosis Echocardiography: Mild LVH, mild AR, Grade I diastolic dysfunction, LVEF 60% Stroke panel-Hyperhomocysteinemia (20.7)	Routine and viral marker -Normal CSF: No abnormalities, oligoclonal bands absent Autoimmune workup (AQP4, ANA): Negative Stroke panel: Protein C and S deficiency -
Treatment	Antiplatelets, anticoagulants, Vitamin therapy Hiccups: Baclofen and chlorpromazine	Antiplatelet therapy, Vitamin supplementation, Hiccups: Baclofen and metoclopramide
Outcome	Symptomatic improvement; discharged	Improved with supportive care; discharged with follow-up

Discussion

The area postrema (AP) in the medulla oblongata triggers the emetic reflex and lacks blood-brain barrier protection, making it sensitive to circulating toxins.[7] Damage from aquaporin-4 antibodies (AQP4-IgG), as seen in neuromyelitis optica spectrum disorder (NMOSD), can cause nausea, vomiting, and hiccups, a triad known as area postrema syndrome (APS).[8] Similar symptoms can occur in autoimmune diseases like SLE.[9]

Vascular causes, including strokes in the posterior circulation (e.g., PICA, vertebral artery), can also lead to APS. These strokes may present with isolated vomiting or the full triad, even when lesions lie just outside the AP, suggesting broader neural involvement. While nausea and vomiting are common in posterior strokes due to vestibular nucleus involvement, hiccups are rarer and often overlooked.[10,11,12] Persistent hiccups due to the area postrema infarct is a recognized but poorly understood phenomenon. Several mechanisms have been proposed:[5,22,23]

1. **Neural Plasticity**: After injury, maladaptive rewiring in the brainstem, particularly between the AP, nucleus tractus solitarius (NTS), and reticular formation, may disrupt excitatory/inhibitory balance in the hiccup reflex arc.
2. **Reactive Gliosis**: Astrocyte and microglial proliferation form a glial scar that, while protective, may impair synaptic signaling and vagal modulation, contributing to hiccup persistence.
3. **Loss of Inhibitory Control**: Damage to GABA-regulated pathways reduces inhibitory tone over the hiccup central pattern generator. Reduced GABAergic activity post-stroke can enhance reflex excitability and prolong symptoms.

Early recognition of APS is crucial for timely diagnosis. In NMOSD, APS can precede MRI findings, warranting

early immunotherapy. In contrast to stroke, APS in NMOSD is driven by autoimmune astrocytopathy, where anti-AQP4 IgG binds to astrocytic water channels in the area postrema, triggering complement activation and resulting in **astrocyte loss**, immunoglobulin/complement deposition, and inflammatory infiltrates.[13,14,15,16,17] In a stroke, infarction leads to irreversible damage. Ischemic-stroke-induced Area Postrema Syndrome (APS) results from vascular occlusion—typically of perforating branches from the anterior spinal or vertebral arteries—leading to neuronal ischemia, necrosis, and microglial activation within the dorsal medulla, as demonstrated by diffusion-weighted MRI in case reports.[18,11,19] In NMOSD animal models, passive transfer of anti-AQP4 antibodies induces APS by targeting the same chemoreceptor zone , whereas ischemic APS develops in animal or human stroke models with documented dorsal medulla infarcts.[19,11] Clinically, NMOSD-related APS may precede other NMOSD signs, often followed by relapsing demyelinating events, while in stroke-related APS, symptoms are abrupt, typically self-limited, and improve once ischemia resolves or is managed.[5]
Further,

Table 2 highlights the rarity of ischemic causes of APS compared to its better-known autoimmune aetiology

Table 2- Reported Cases of Ischemic Area Postrema Syndrome in Literature[5,11,20,21,22,23]

Author (Year)	**Patient**	**Symptoms**	**Imaging**	**Outcome**
Cohen et al. (2020)	62M, DM, HTN	Abdominal pain, nausea, vomiting, gait issues	Right cerebellar infarct; small AP involvement	Good recovery with metoclopramide + ondansetron
Stancu et al. (2025)	63F, HTN, DM	Sudden nausea, vomiting, hiccups post neck manipulation	Small medullary infarct just above left AP	Resolved with ondansetron; hiccups resolved in 1 week
Schlaeger et al. (2010)	76F, HTN, DM	Acute vomiting	Infarct just above AP; vertebrobasilar stenosis	Not reported
Kim et al. (2003)	130 patients with lateral medullary stroke	Nausea/vomiting (67), hiccups (33)	Lateral medullary infarction	Not detailed

FIGURE 1

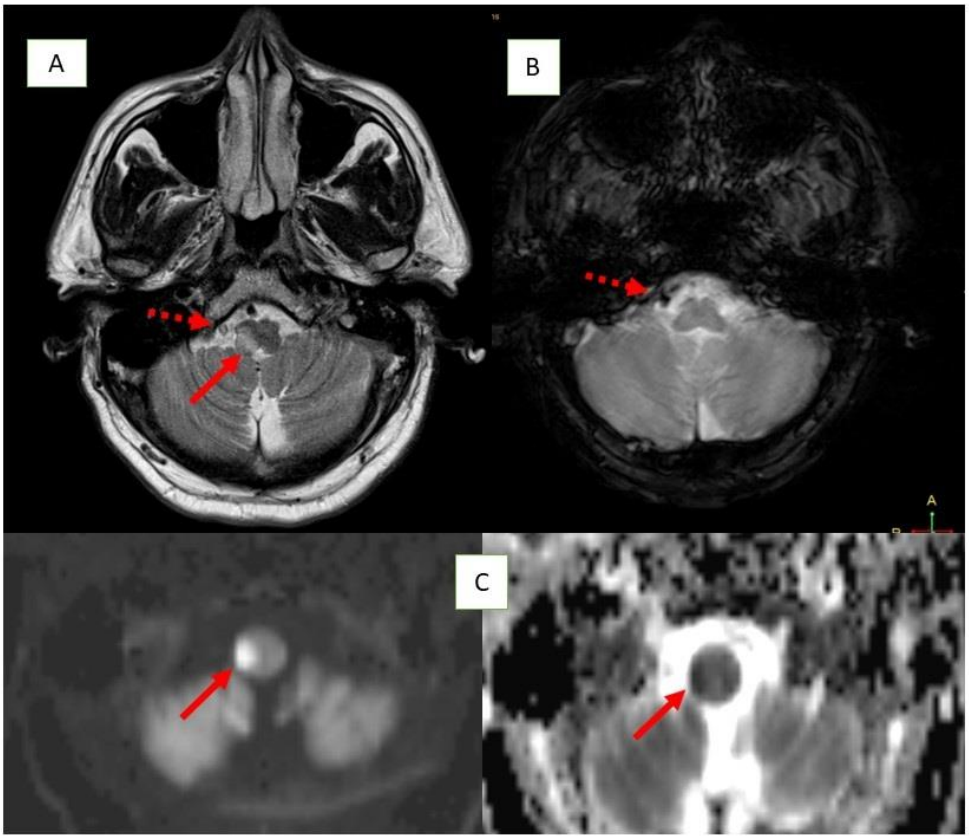

Figure 1-A: T2 Axial sequence→ Absent flow void within V4 right vertebral artery (red solid arrow): T2 hyperintensity in right dorsal medulla including area postrema
B: Axial GRE sequence→ Low signal with blooming on GRE suggestive of susceptibility sign in the right vertebral artery (red solid arrow)
C: FLAIR sequence→FLAIR hyperintensity in right dorsal medulla, including area postrema
D)Restricted diffusion in the form of high signal on DWI (red solid arrow) and low signal on ADC

FIGURE 2

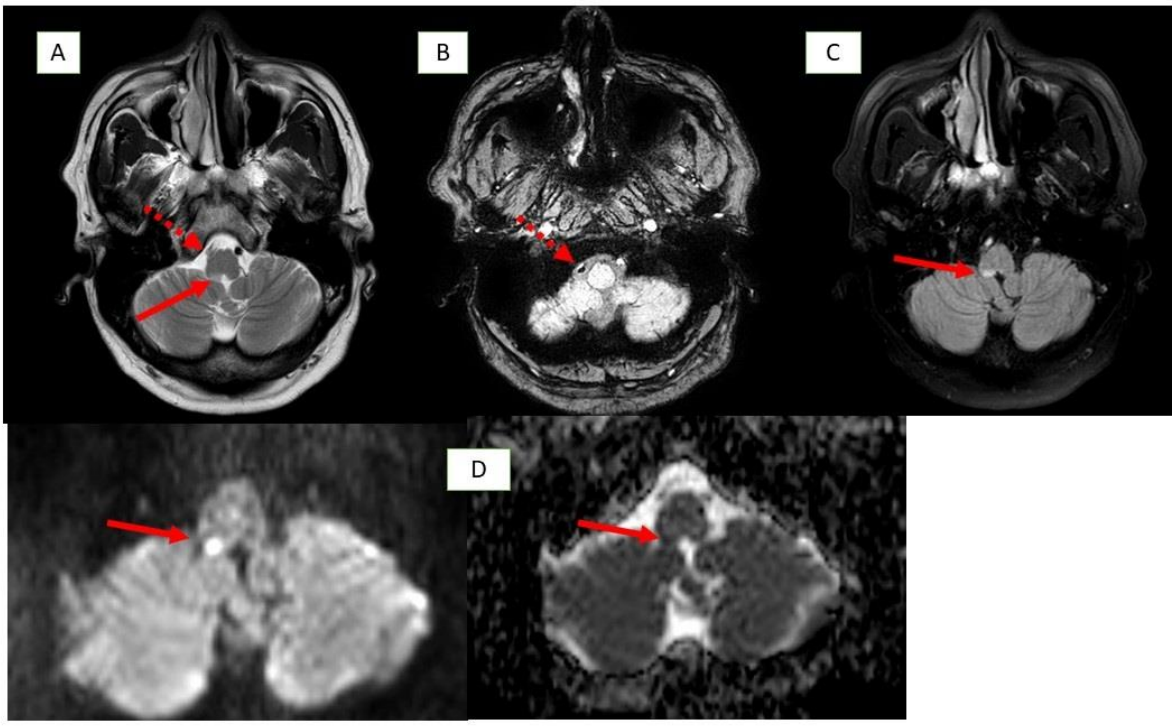

Figure 2-A: T2 Axial sequence- Absent flow void within V4 right vertebral artery (red solid arrow): T2 hyperintensity in right dorsal medulla, including area postrema
B: Axial GRE sequence, Low signal with blooming on GRE suggestive of susceptibility sign in the right vertebral artery (red solid arrow)
C: Restricted diffusion in the form of high signal on DWI (red solid arrow) and low signal on ADC (red dashed arrow)

Conclusion

These cases highlight the importance of recognizing APS as a clinical manifestation of medullary infarction. A high index of suspicion and prompt imaging studies are crucial for early diagnosis and management. Symptomatic relief of intractable hiccups can improve patient comfort and outcomes. Further research is warranted to explore the underlying mechanisms and optimize treatment strategies for APS in stroke patients.

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