Letter to the Editor

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Response to "Before Diagnosing CHANTER Syndrome, All Possible Differential Diagnoses Must Be Carefully Excluded"

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We read with interest a letter titled "Before diagnosing CHANTER syndrome, all possible differential diagnoses must be carefully excluded" [1] regarding our recent publication [2]. We appreciate all the insights the readers have suggested and agree that, before making a diagnosis of cerebellar, hippocampal, and basal nuclei transient edema with restricted diffusion (CHANTER) syndrome, which is still relatively uncommon, other common metabolic encephalopathies and neurovascular insults should be excluded.

We attempted to diligently exclude all other conditions based on the clinical presentation, laboratory correlation, and imaging findings. Detailed explanations are provided below, structured as responses to each of the letters' comments, which are italicized and enclosed in quotes.

"First, research on the causes of the clinical presentation was inadequate for all three cases. Coma in patient-1, headache, arterial hypertension, and cerebral hypoxia in patient-2, and coma, seizures, and arterial hypertension in patient-3 require larger studies than previously reported. In this context, cerebrospinal fluid studies, electroencephalography recordings, information about cerebral perfusion MR angiography or CT angiography, MR venography, digital subtraction angiography, and MR spectroscopy are required in all three patients."

Response: Lumbar puncture was performed in all three patients, and there was no evidence of microbial growth suggestive of meningitis. Electroencephalography (EEG) and CT angiography were performed in all three patients and are detailed below. Digital subtraction angiography was not performed in any of our patients because it was an invasive procedure, and noninvasive vascular workup was negative and since suspicion of cerebral vasculitis remained very low. MR-spectroscopy was not performed as the MRI abnormalities suggested metabolic encephalopathy, and MRS would have limited aid in the further diagnosis and differential diagnosis of metabolic encephalopathy in our cases.

"In patients with headache at initial presentation (patient-2), it is imperative to rule out subarachnoid bleeding (SAB), reversible cerebral vasoconstriction syndrome, venous sinus thrombosis (VST), cerebral vasculitis, encephalitis, meningitis, seizures, and trauma."

Response: We agree that all of the conditions mentioned above could potentially cause headaches. Non-contrast head CT done at the time of admission did not reveal any subarachnoid bleeding (SAB). MRI of the brain performed on the same day did not reveal any abnormal leptomeningeal enhancement suggestive of meningitis. MRI revealed diffusion and fluid-attenuated inversion recovery signal changes in the globus pallidus and hippocampi, which were more suggestive of opioid-induced cerebral toxicity than encephalitis or reversible cerebral vasoconstriction, the latter typically affecting the cerebral cortex. The patient had a history of taking multiple narcotic medications. The patient had no history of trauma. CT angiography performed the following day did not reveal any arterial stenosis or venous thrombosis. The presence of normal CT angiogram could potentially exclude reversible cerebral vasoconstriction syndrome and a conventional angiogram was not performed due to the critical status of the patient. A lumbar puncture performed one day after admission was negative for meningitis. The neurology team felt that although the

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seizures were in the differential diagnosis, the patient's clinical presentation was more typical of encephalopathy. The EEG findings were described as follows: Findings are indicative of an improving generalized encephalopathy with superimposed diffuse cortical irritability. Although both findings are non-specific, a toxic or metabolic etiology should be considered. Epileptiform discharges or electrographic seizures were not observed.

"*In patients with impaired consciousness (patient-1, patient-3), it is essential to rule out nonconvulsive status epilepticus, acute disseminated encephalomyelitis, acute hemorrhagic, necrotizing encephalitis, stroke, hyperglycemia/hypoglycemia, cardiac arrest, liver or kidney failure, and acidosis, in addition to SAB, VST, vasculitis, encephalitis/meningitis, and epilepsy.*"

Response: The differential diagnosis for impaired consciousness is broad, and all the above conditions are likely differentials. Some conditions can potentially be explained using imaging. The MRI findings in both patients (1 and 3) suggested opioid-induced injury (supported by history and urine drug analysis). The MRI findings were not asymmetric or suggestive of acute disseminated encephalomyelitis or acute hemorrhagic, necrotizing encephalitis. The patterns of diffusion involvement in the bilateral deep gray matter and hippocampi suggest a metabolic insult rather than a stroke due to vascular causes. Although hypoglycemia could potentially cause the above imaging findings, involvement of the cerebellum and upstream hydrocephalus is atypical. The blood glucose levels were within the normal limits at the time of admission (89 mg/dL for patient 1). Blood glucose levels were elevated in patient 3 at admission (483 mg/dL); however, non-ketotic hyperglycemia presenting as T1 shortening in the basal ganglia was not observed. While there was a history of cardiac arrest in patient 1, and imaging findings of hypoxic injury and CHANTER could overlap, the spectrum of brain involvement (hippocampal involvement) was more typical of CHANTER.

The pattern of brain MRI findings was not typical of acute hepatic encephalopathy (no involvement of the insular cortex, thalamus, or internal capsules). There was also no biochemical evidence of renal dysfunction (creatinine 0.7 mg/dL in patient 1). Patient 1 had deranged alanine transferase and aspartate transferase levels (202 U/L and 272 U/L, respectively); however, the MRI findings did not suggest hepatic encephalopathy. The patient had no history of liver disease, and the clinical team attributed the deranged liver enzyme levels to drug-induced liver injury. Subsequently, biochemical normalization was performed.

None of the patients demonstrated SAB on non-contrast head CT. CT angiography of the head and neck revealed no vascular stenoses. While the MRI findings did not suggest vasculitis, these patients had no medical conditions suggestive of secondary central nervous system (CNS) vasculitis. Catheter angiography, which is the most sensitive method for excluding CNS vasculitis, was not performed because clinical suspicion was low and because of its invasive nature.

Both the patients had EEG findings that did not support the likelihood of seizures. The results of preoperative EEG of patient 1 were as follows: This is an abnormal video EEG due to the presence of diffuse delta slowing, indicative of severe encephalopathy. Generalized slowing is a non-specific finding that can be observed in processes that diffusely affect the cerebrum, including toxic, metabolic, post-hypoxic, multifocal, and degenerative conditions. No interictal epileptiform discharges or seizures were observed during the study. The EEG results of patient 3 were as follows: This is an abnormal video EEG due to the presence of: 1) diffuse theta with some delta activity noted, indicative of moderate encephalopathy, and 2) abundant beta activity. Generalized slowing is a non-specific finding that can be observed in processes that diffusely affect the cerebrum, including toxic, metabolic, post-hypoxic, multifocal, and degenerative conditions. Excessive beta activity is usually a medication effect. No interictal epileptiform discharges or seizures were observed during the study.

However, the postoperative course of patient 1 was complicated by a brief unresponsive episode, likely a seizure or syncope. Given the patient's recent surgery and some discharges (posterior poorly formed sharp waves) on postoperative EEG, the patient was started on Keppra per neurology department, with plans to follow up as an outpatient.

"*In patients with arterial hypertension (patient-2, patient-3), multifocal posterior reversible encephalopathy syndrome (PRES) must be excluded. In patients with seizures (patient-3), an epiphenomenon indicating a post-convulsive image abnormality must be excluded. Hypoxic brain injury must be excluded in patients with a history of cardiac arrest (patient-1) or respiratory failure (patient-2).*"

Response: Posterior reversible encephalopathy syndrome (PRES) presents as cortical and subcortical edema with

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no restricted diffusion; therefore, it was not included in the differential analysis. Status epilepticus MRI changes in patient 3 could be considered; however, the bilateral symmetrical changes in the cerebellum were atypical of status epilepticus. Patients with cardiac arrest and respiratory failure can present with similar findings and mimic CHANTER; our article [2] dives into the delicate delineation of hypoxic ischemic injury (HII) from CHANTER, which shares several similarities. The overwhelming involvement of the hippocampus and cerebellum, which can also be involved in HII, as mentioned in the discussion of our article [2]; however, the significant sparing of the cerebral cortex in our cases, which is a common feature of HII, suggested CHANTER. Several patients with drug overdoses have clinical respiratory and cardiac failure, and it is vital to distinguish the cerebral injury of these two overlapping entities in these patients.

"*Second, patient-1 underwent a cerebral MRI after a suboccipital craniotomy [1]. The authors ruled out the possibility that the abnormalities observed on MRI were simply side effects of the operation and were independent of opiate intoxication.*"

Response: The Head CT scan selected from Case 1 was acquired preoperatively and demonstrated bilateral cerebellar hypodensity, which was unlikely to be a side effect of the operation.

"*Third, patient-3 did not undergo a cerebral MRI, making it difficult to verify the imaging abnormalities described in the case description.*"

Response: Patient 3 underwent cerebral MRI. However, we did not include the images of patient 3 images according to the journal's guidelines.

"*Fourth, central nervous system complications of SARS-CoV-2 infection were not ruled out [1]. Because the three cases appeared to have been diagnosed during the pandemic, it is imperative to document that RT-PCR for SARS-CoV-2 was negative upon admission and that a history of recent anti-SARS-CoV-2 vaccination was negative.*"

Response: COVID-19 testing was not performed on admission for patient 2; however, the patient tested two weeks later and was found to be negative. Both patients 1 and 3 were negative for SARS-CoV-2 infection upon admission.

"*Fifth, the indications for levetiracetam administration in patient-1 were not specified [1]. There was no evidence of seizures or a history of epilepsy. It is important to know why patient-1 received levetiracetam after surgery.*"

Response: The postoperative course was complicated by a brief unresponsive episode, likely a seizure or syncope. Given the patient's recent surgery and some discharges (posterior poorly formed sharp waves) on postoperative EEG, the patient was started on Keppra (levetiracetam) per the neurology department, with plans to follow up at the outpatient clinic.

"*Sixth, the treatment and outcomes of three patients were inadequately described. Of particular interest are the antiepileptic treatment in patient-3 and the long-term outcomes of all three patients.*"

Response: Patient 1 had uncharacteristic convulsive spells after an overdose of Midol, a formulation of acetaminophen, caffeine, and pyralamine maleate six months after discharge. She remained hospitalized due to a complex social situation, cognitive impairment, and severe depression. Patient 2 had a prolonged inpatient stay complicated by lung infection, acute-on-chronic osteomyelitis, pressure wounds, and a neurogenic bladder. The patient was discharged to a rehabilitation facility, and no follow-up documentation was available. Patient 3 was subsequently transferred to the inpatient rehabilitation department. She had periods of agitation that limited progress for a short period of time; however, this has since resolved, and the patient has progressed to a level that allows her to return home with the care of family. She was advised to closely follow the primary care physician and keep other appointments scheduled.

In summary, differential considerations, such as HII, PRES, opioid amnestic syndrome, and other metabolic encephalopathies have been meticulously excluded to the best of our ability through thorough imaging and biochemical assessments. However, it is important to note that several patients with CHANTER may exhibit imaging features overlapping with HII because these entities can coexist clinically. Nevertheless, the primary focus of our article was to shed light on the lesser-known CHANTER syndrome and ensure that it is not overshadowed by HII.

Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

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Author Contributions

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REFERENCES

1. Finsterer J, Mehri S. Before diagnosing CHANTER syndrome, all possible differential diagnoses must be carefully excluded. *Korean J Radiol* 2024;25:589-590
2. Pandit R, Hamki O, Gaddamanugu S. Cerebellar, hippocampal, and basal nuclei transient edema with restricted diffusion (CHANTER) syndrome: radiologic features and findings. *Korean J Radiol* 2024;25:314-318