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Arterial spin labeling perfusion imaging demonstrates cerebral hyperperfusion in anti-NMDAR encephalitis

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ABSTRACT

Anti-N-methyl-D-aspartate receptor encephalitis is an increasingly recognized autoimmune disorder that results in substantial morbidity, prolonged hospital stays, and even death. The diagnosis is often delayed or unrecognized entirely as a result of absent or only subtle initial magnetic resonance imaging findings and a nonspecific clinical syndrome. The discovery of early imaging findings in this disease may help clinicians to more aggressively treat this autoimmune encephalitis and to potentially lessen morbidity and mortality. We report a novel case of anti-N-methyl-D-aspartate receptor encephalitis characterized by early evidence of increased cerebral perfusion on arterial spin labeling perfusion imaging, a finding that preceded laboratory diagnosis and conventional magnetic resonance imaging abnormalities. Further investigation is needed to firmly establish the pathologic basis of this finding.

Introduction

Anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis is an increasingly recognized entity that results in a wide variety of psychiatric and neurologic symptoms that include but are not limited to cognitive impairment, seizures (including status epilepticus), autonomic dysfunction, central hypoventilation, and coma [1]. This diagnosis may be frequently unrecognized partly in relation to young patient age and unusual early psychiatric manifestations, which may erroneously lead to a diagnosis of a psychiatric condition [1]. Additionally, conventional magnetic resonance imaging (MRI) findings are either subtle, nonspecific, or overlooked entirely, which limits efforts to diagnose early [1]. The diagnosis is confirmed by the detection of the anti-NMDAR antibody (typically in cerebrospinal fluid [CSF]), a test that may not be obtained until the patient becomes critically ill. We present a unique case where arterial spin labeling (ASL) perfusion imaging demonstrated marked abnormalities before the detection of any conventional MRI findings, an observation that may assist in suggesting this diagnosis with the goal of an earlier, potentially more effective therapeutic intervention.

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Case presentation

The patient is a 3-year-old African American male who initially presented with 2 possible seizures, characterized by staring spells, mouth twitching, and drooling. The initial head computed tomography imaging and electroencephalogram (EEG) were negative. Before the scheduled outpatient MRI, the patient returned to the emergency department with a new progressive left hemiparesis, spastic gait, lethargy, paucity of speech, and incontinence. Brain MRI, head magnetic resonance angiogram, and head magnetic resonance venography were essentially negative, although the initial ASL perfusion imaging demonstrated an asymmetric elevated cerebral blood flow to the right temporoparietal region and, to a lesser extent, to the right frontal lobe, findings that were thought to be attributed to a postictal state (Fig. 1). The EEG showed diffuse right-sided slowing and multifocal brief electrographic seizures without obvious motor activity. The patient continued to exhibit an aggressive behavior and labile moods. On hospital day 4, a lumbar puncture was performed and CSF analysis revealed a white blood cell count of 20,000 cells/μL (100% monocytes), a red blood cell count of 0 cell/μL, a protein level of 23 mg/dL, and a glucose level of 63 mg/dL. At this point, the clinical team initiated methylprednisolone for the treatment of a potential autoimmune syndrome. The patient remained clinically labile with intermittent periods of agitation and seizure activity while being minimally interactive. On hospital day 10, a repeat MRI of the brain was interpreted as essentially negative; however, the ASL imaging became more diffusely abnormal with a diffusely elevated cerebral blood flow (Fig. 2). Because of poor clinical response to steroids but persistent concern for an autoimmune encephalopathy, intravenous immunoglobulin (IVIG) therapy was instituted on hospital day 13. On hospital day 14, the anti-NMDAR antibody positive test result was received. The patient improved slightly clinically, but on hospital day 22, his agitation worsened and he was transferred to the pediatric intensive care unit for the management of sedation. On hospital day 23, plasmapheresis was initiated via a central venous catheter. The patient developed worsening of his orofacial dyskinesias, choreoathetoid movements, and worsening encephalopathy, requiring intubation for airway protection on hospital day 27. The patient exhibited intermittent tachycardia, bradycardia, and labile blood pressure. Follow-up MRI almost a month later (hospital day 38) demonstrated abnormal T2-weighted-fluid-attenuated inversion recovery hyperintensity within the bilateral basal ganglia and the posterior thalami (Fig. 3). The finding of a markedly increased cerebral blood flow remained evident on ASL imaging (Fig. 4), and the increased perfusion involved most of the supra- and infratentorial brain. The patient continued to suffer from severe agitation that slowly improved until his discharge to a rehabilitation facility on hospital day 116.

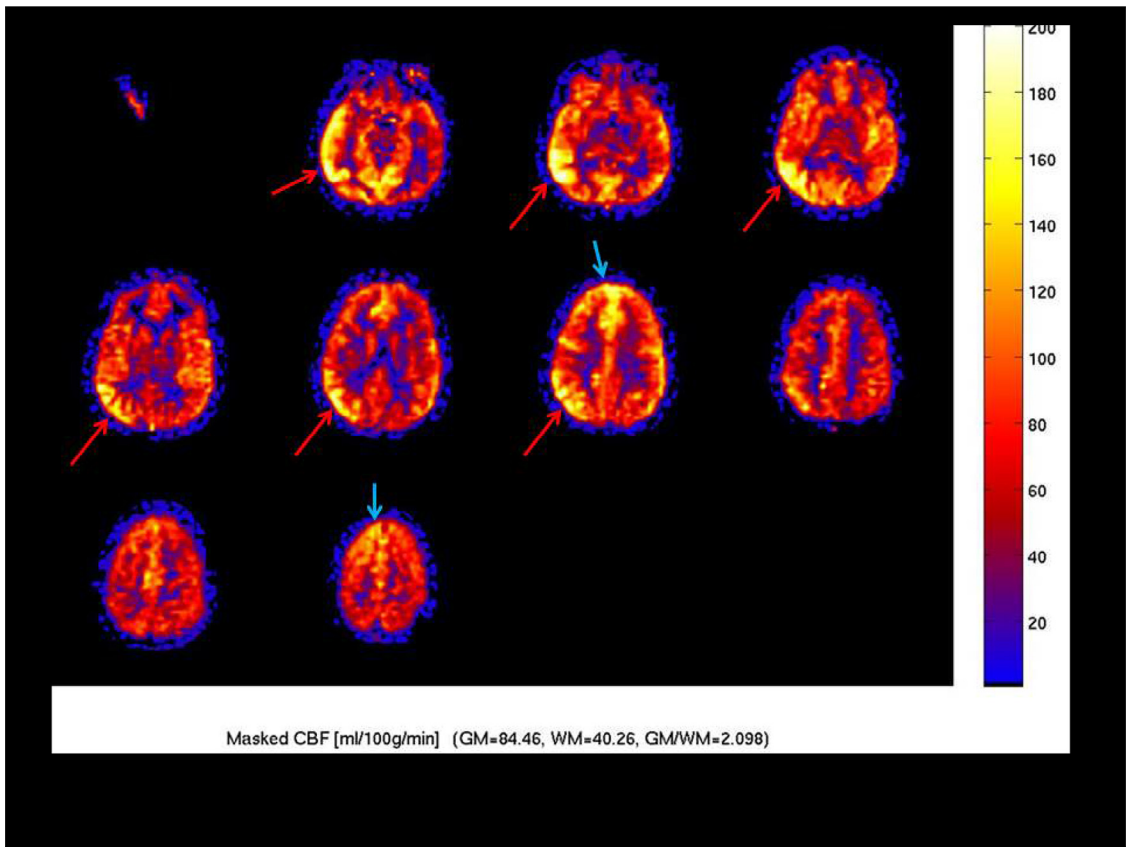

Fig. 1 – Initial brain magnetic resonance imaging arterial spin labeling perfusion images. Focally increased CBF is seen in the right temporoparietal region (red arrows). There is also apparent increased CBF in the paramedian right frontal lobe, but to a lesser extent (blue arrows). CBF, cerebral blood flow; GM, gray matter; WM, white matter.

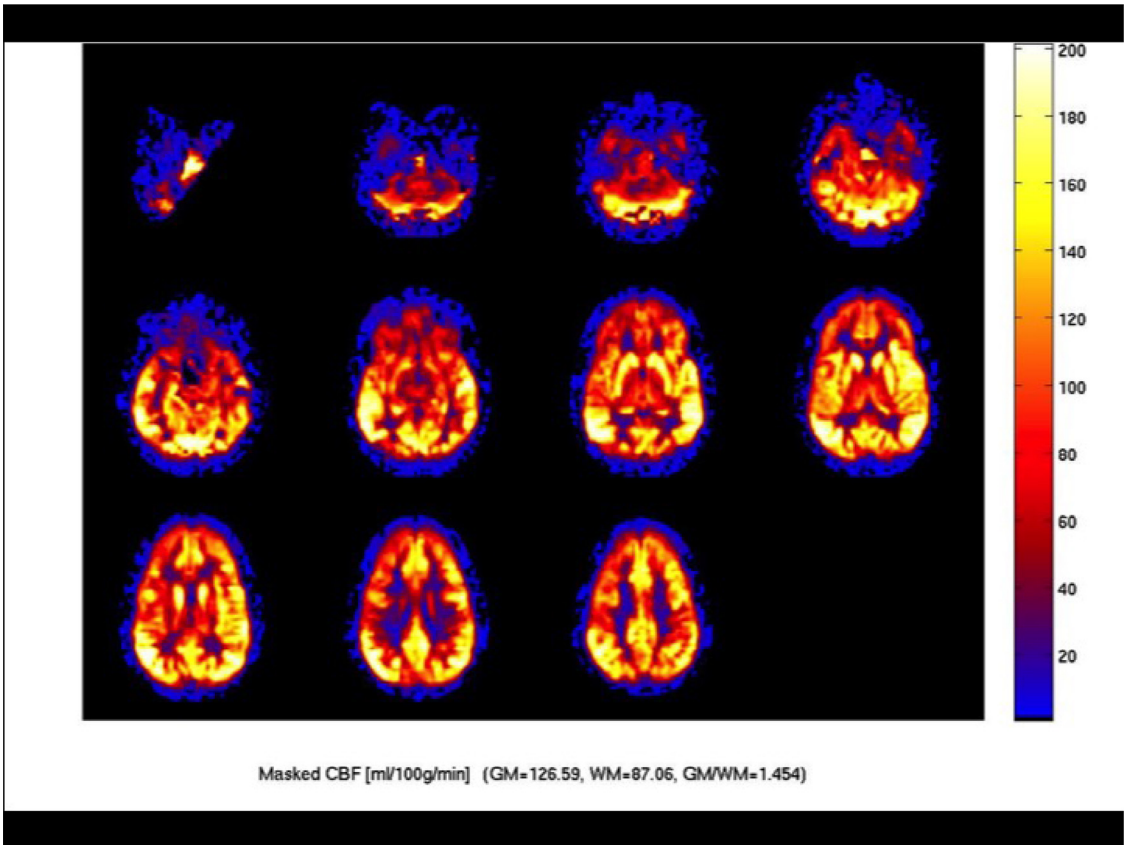

Fig. 2 – First follow-up brain magnetic resonance imaging arterial spin labeling perfusion study obtained on hospital day 10. Diffusely increased CBF is now present in both cerebral hemispheres and involves the bilateral basal ganglia. CBF, cerebral blood flow; GM, gray matter; WM, white matter.

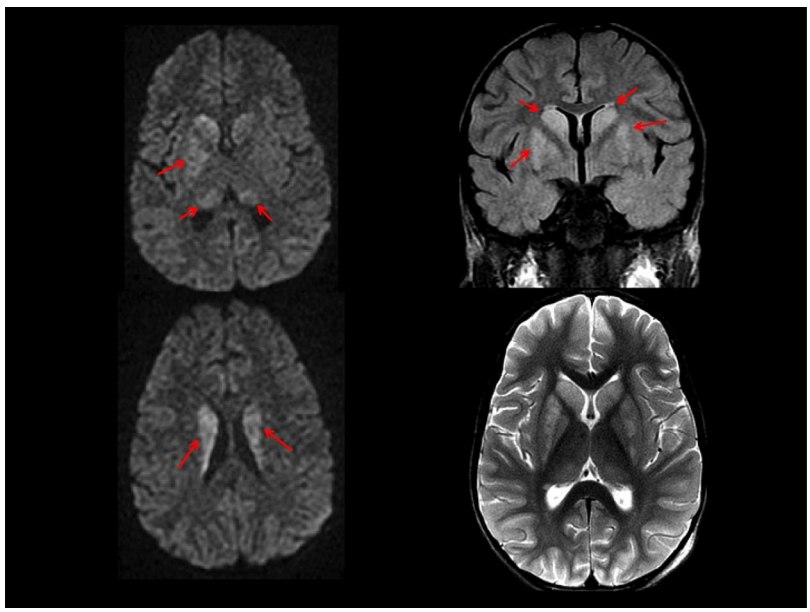

Fig. 3 – Magnetic resonance imaging findings on hospital day 38. Diffusion weighted imaging (left) demonstrates restricted diffusion (confirmed on apparent diffusion coefficient map—not shown) in the caudate nuclei, in the right putamen, and in the bilateral posterior thalami (the red arrows suggest cytotoxic edema). Coronal T2-weighted-fluid-attenuated inversion recovery (upper right) and axial T2-weighted imaging (bottom right) show high signal in the bilateral basal ganglia and in the thalami caused by edema.

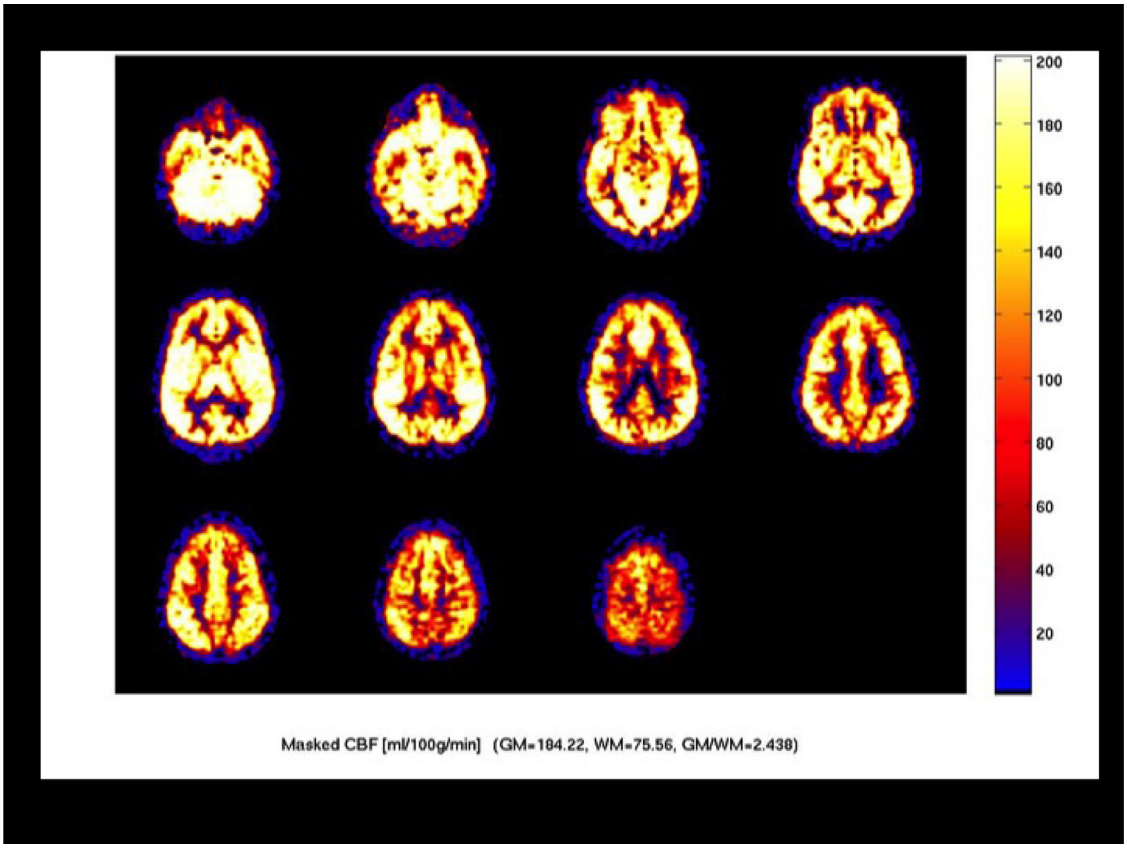

Fig. 4 – Arterial spin labeling perfusion imaging on hospital day 38. Persistent and diffuse markedly increased cerebral cortical blood flow is noted throughout the brain, worsened from the prior examination. CBF, cerebral blood flow; GM, gray matter; WM, white matter.

Discussion

Early imaging diagnosis of anti-NMDA receptor encephalitis is complicated by normal or only subtle nonspecific findings [1]. Likewise, early clinical signs and symptoms are often nonspecific with an early prodromal phase of fever, headache, or malaise before the onset of psychiatric symptoms [2]. Initial conventional MRI is reported to be normal in 50% of patients, with subtle or nonspecific findings in the other 50%, including T2-weighted-fluid-attenuated inversion recovery hyperintensity within the basal ganglia, the cerebellum, the hippocampi, the cerebral cortex, the insula, or the brain stem [1]. There may be a subtle contrast enhancement affecting the parenchyma or the meninges, but the signs are typically subtle or easily overlooked. EEG findings are also not specific [3]. Follow-up MRI may remain normal or may show only minimal changes despite the critically ill nature of the patient. Ultimately, diagnosis is confirmed by the detection of anti-NMDA receptor antibodies in the CSF, usually a send-out test that may limit the expediency of results. With early diagnosis, it may be possible to decrease earlier the number of circulating anti-NMDA receptor antibodies in the blood with IVIG or plasmapheresis therapy, with the aim of decreasing the morbidity and mortality of this disease.

Although this entity may occur in the absence of a primary tumor, there is a known association of anti-NMDAR encephalitis with certain neoplasms, most commonly an ovarian teratoma [3,4]. The likelihood of a tumor being found is dependent on the patient's age, sex, and race. A tumor is less likely in those patients who are less than 18 years old, men, or non-black [5]. Eighty percent of patients with this disease have been women. One series of 400 patients found that nearly 50% of affected women had a coexisting tumor, and almost all of them had ovarian teratomas [3,5]. Other reported tumors included breast cancer, other ovarian tumors, pseudopapillary pancreatic neoplasm, testicular germ-cell tumor, and small-cell lung cancer.

Little has been published on the phenomenon of elevated cerebral blood flow in the setting of anti-NMDA receptor encephalitis, although 1 case report described a multifocal corticobasal hyperperfusion on Tc-99m hexamethylpropylene amine oxime single-photon emission computed tomography imaging [6]. Diffuse increased cerebral blood flow on ASL perfusion imaging is nonspecific and carries a broad differential diagnosis, including hypercarbia, global hypoxic-ischemic injury, and status epilepticus. Elevated cerebral perfusion is also seen as normal in young patients [7], although this is excluded as a possibility in this case as the initial ASL imaging was only focally elevated in the right temporoparietal region and the right frontal lobe.

The exact mechanism of diffusely elevated cerebral blood flow in the setting of anti-NMDA receptor encephalitis has not been elucidated. It is known that these patients will

experience central hypoventilation [1,8] that could result in hypercarbia accounting for a diffusely increased cerebral blood flow. However, the patchy nature of the hyperperfusion seen early in the clinical course of the reported case here would probably not be entirely due to hypercarbia, which would be a more global perfusion phenomenon. Autonomic instability, a characteristic clinical problem in anti-NMDAR encephalitis patients [3], may also contribute, possibly in relation to loss of cerebral vascular autoregulation. It is unclear whether these secondary factors account solely for the cerebral hyperperfusion or whether this increase in blood flow is a primary manifestation of the disease process. Further study is needed to firmly establish a pathologic mechanism.

To the authors' knowledge, this is the first example reported in the literature of how ASL perfusion imaging can demonstrate clear abnormality before the development of conventional MRI abnormalities in anti-NMDA receptor encephalitis. The ASL perfusion imaging findings in this case provide a striking visual corollary to the book *Brain on Fire, My Month of Madness*, in which Susannah Cahalan increases awareness of the disease by narrating her own experience. In our reported case, the patient was treated with high-dose steroids based upon high clinical suspicion of autoimmune encephalitis shortly after the diffuse ASL abnormality was detected, but before the diagnosis of anti-NMDAR encephalitis was confirmed by CSF antibody testing. If radiologists suggest this diagnosis based upon cerebral perfusion imaging in the appropriate clinical setting, clinicians could be afforded the opportunity to initiate earlier and more aggressive interventions (which may include IVIG or plasmapheresis) before laboratory confirmation of the diagnosis, which may give the patient a better chance at a quicker, more complete recovery. This case also highlights the role that ASL perfusion imaging may play in short-term follow-up imaging when initial MRI is normal or only shows a focal ASL abnormality. Perhaps this quick, noninvasive, easy-to-perform ASL magnetic resonance sequence could identify the figurative "fire" in the brain earlier, thereby allowing clinicians to treat earlier and more aggressively.

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