Claustrum Hyperintensity in Autoimmune Encephalitis: Report of Two Patients

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Abstract

Autoimmune encephalitis (AE) is a well-recognized cause of encephalitis in the pediatric population, exhibiting a diverse array of symptoms including movement disorders, seizures, focal neurological deficits, altered mental status, neuroregression, and, to a lesser extent, psychiatric and behavioural symptoms, along with autonomic instability. Magnetic resonance imaging (MRI) usually reveals abnormalities, particularly in T2/FLAIR sequences. Notably, claustrum hyperintensities have recently emerged as a neuroimaging finding potentially linked to seronegative AE. This study aims to report the clinical profiles of two pediatric patients meeting diagnostic criteria for autoimmune encephalitis despite a negative antibody panel, and to describe their bilateral claustrum hyperintensities on neuroimaging. Two patients fulfilling diagnostic criteria for seronegative autoimmune encephalitis, with distinctive neuroimaging features including bilateral claustrum hyperintensities in T2/FLAIR sequences, were analysed. Clinical data, biochemical markers, response to immunotherapy, and long-term outcomes were comprehensively reviewed from patients' records. Both patients presented with intractable epilepsy unresponsive to anti- seizure medications, with negative anti-neural antibodies and electroencephalograms (EEGs) revealing frequent epileptic discharges. The first patient achieved seizure control following pulse steroid therapy, while the second patient required additional intravenous immunoglobulin alongside pulse therapy for seizure cessation. Both patients achieved complete seizure control with no recurrence on follow-up. The observed MRI pattern characterized by high T2- claustrum hyperintensities, particularly in patients fulfilling AE criteria, may signify an association with seronegative AE. This intriguing radiological phenomenon underscores the necessity for additional research to elucidate its underlying pathophysiology and significance in patient care.

Keywords: Claustrum hyperintensity; Autoimmune encephalitis; Status epilepticus

Introduction

Autoimmune encephalitis (AE) is a group of CNS inflammatory disorders characterized by neurological and neuropsychiatric symptoms and antibody production directed against surface or intracellular antigens.[1,2] This group of disorders can present with wide clinical symptoms in children, including movement disorders, seizures, focal neurological deficits, and, to a lesser extent, psychiatric and behavioral symptoms.[1]

Diagnosis of AE can be challenging due to its presentation with variable clinical syndromes, which makes diagnosis of these disorders challenging.[3] Therefore, this diagnosis can be supported by investigations including autoimmune panels in serum and cerebrospinal fluid, neuroimaging, and electroencephalography.

AE can be due to antibodies directed against neural surface antigens or antibodies against intracellular antigens. Neural surface antigens can be excitatory, inhibitory transmitter receptors, subunits of ion channels, adhesion molecules or soluble synaptic proteins. Examples of these antigens are NMDA, AMPA, GABAa, GABAb, CASPR2 and LGI1. Antibodies against intracellular antigens are more associated with paraneoplastic neurological syndromes. Examples of these antibodies are anti-Hu, Ri, Ma2. The neuronal damage in the later type is caused by cytotoxic T-cells with oligoclonal T-cell receptor expansion and autoreactivity against neuronal structures.[4]

MRI is the imaging modality of choice in patients with suspected autoimmune encephalitis. MRI can help in excluding other differentials and identifying findings supporting the diagnosis of AE. A recent study found that 39% of patients with AE have normal MRI.[5] MRI-positive cases typically show signal abnormalities in the limbic system with T2 and FLAIR hyperintensities and cortical swelling. Other areas that may be affected include the extralimbic cortex, deep gray matter, white matter, brainstem, cerebellum, and spinal cord.[5-7]

Claustrum hyperintensities have been described in patients presented with status epilepticus proceeded by febrile illnesses.[8] Moreover, it has been described as an imaging finding that could be seen in autoimmune encephalitis in association with or without refractory seizures.[9]

Given this association, herein, we describe in this report the case of two pediatric patients meeting the diagnostic criteria for autoimmune encephalitis with a negative antibody panel, and found to have bilateral claustrum hyperintensities.

Case Report

Case one

A 13-year-old girl with an uneventful perinatal history and normal development presented to our institute with focal seizures characterized by right eyelid twitching and deviation of the mouth towards the right, associated with automatism of the right hand followed by generalized body stiffening and impaired awareness. A week before her presentation, she had a fever and symptoms of an upper respiratory tract infection. She had no other focal neurological deficits, headache, photophobia, or myoclonic jerks. Additionally, there was no history of weight loss, recent travel, recent vaccinations, or any intoxication. There was also no history of hypertension, trauma, anticoagulant use, or a family history of epilepsy.

She was initially treated for meningoencephalitis and started on phenytoin for her seizures but showed no response. Carbamazepine was then added. Upon arrival at our institute, she received a loading dose of levetiracetam (40 mg/kg) and was placed on maintenance therapy. At this point, her seizures were controlled. The cerebrospinal fluid culture and viral panel came back negative, and antimicrobial therapy was discontinued.

MRI showed increase in signal intensity in T2 and FLAIR sequences in the right mesial temporal lobe and, to a lesser extent, in the left mesial temporal lobe. Bilateral symmetrical claustrum hyperintensities were present with mild diffusion restriction (**Figure 1**). There was no abnormal enhancement.

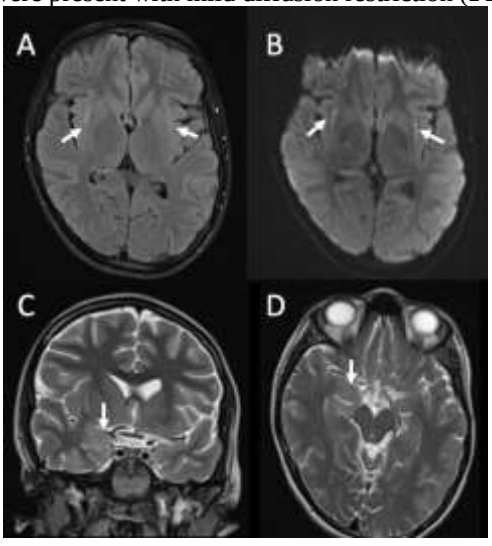

Figure 1. (A) Axial FLAIR image shows bilateral claustrum hyperintensities (arrows). (B) Diffusion-weighted image shows mild diffusion restriction in the claustrum (arrows) (ADC is not shown). (C, D) Coronal and axial T2-weighted images show abnormal T2 hyperintensities and mild swelling of the right mesial temporal lobe (arrows).

EEG was suggestive of encephalopathic process with one clinical event showing lateralization to left temporal region. Autoimmune antibodies were sent from serum and CSF for limbic encephalitis panel, and all came negative. Patient received intravenous methylprednisolone 30 mg/kg for 5 days followed by oral prednisolone over 6 weeks with a working diagnosis of seronegative autoimmune encephalitis. She significantly improved after second dose of steroids with complete seizure cessation. EEG after the second dose of methylprednisolone initiation showed complete resolution of epileptic discharges with diffuse slowing.

She was discharged on two anti-seizure medications with no neurological deficit and normal IQ assessment. At 8-month follow-up, she had no clinical seizures since her admission and her follow-up EEG was normal (at 3 and 8 months post-admission). She was weaned from one anti-seizure medication and kept on monotherapy. MRI repeat was planned at 1 year from her initial admission.

Case two

A 3-year- and-7-month-old female with uneventful perinatal history and normal development presented with encephalopathy and paroxysmal events consisting of staring, perioral cyanosis, tongue protrusion, frothing of saliva followed by generalized hypotonia of the body that proceeded with a one-week history of febrile illness. There was no documentation of dystonia or automatism. This presentation was preceded by emotional liability characterized by unexplained excessive crying four months prior to the presentation. She was initially treated for meningoencephalitis with no response to therapy. Apart from that, she had no other focal neurological symptoms, headache, photophobia, or myoclonic jerks. Furthermore, there was no history of weight loss, recent travel, recent vaccination, infectious symptoms, or any toxic exposure. In addition, there was no history of hypertension, history of trauma, use of anti-coagulation, and there was no family history of epilepsy. Subsequently, she was transferred to our institute for further management. She was initially started on phenytoin and later received a loading dose of levetiracetam, which was discontinued due to behavioral side effects. Valproic acid was then introduced, leading to a reduction in seizure frequency but not complete seizure freedom.

Consequently, she was placed on a midazolam infusion (2 mcg/kg/min) for one week, achieving seizure control. However, after tapering midazolam, she experienced frequent seizures, necessitating the addition of clobazam and topiramate. At this point, seizure control was achieved. MRI of the brain showed bilateral T2/FLAIR increased signal intensity in the mesial temporal lobes with involvement of the amygdala and hippocampi **(Figure 2A-B).**

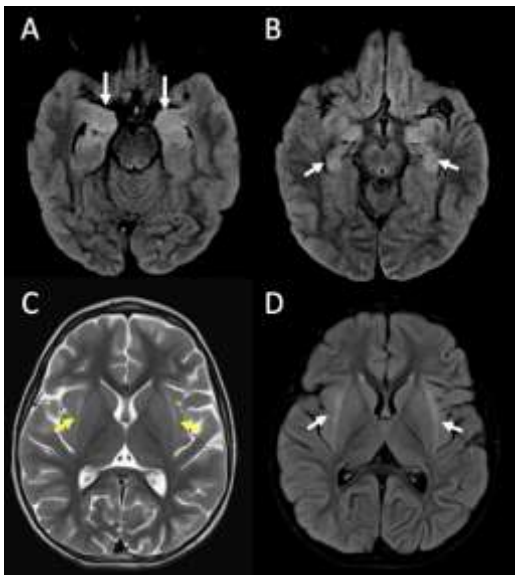

Figure 2. (A, B) Initial MRI: Bilateral FLAIR hyperintensities in the mesial temporal lobes with involvement of the amygdalae and hippocampi bilaterally (arrows). (C, D) Follow-up MRI after 2 weeks: Interval development of bilateral claustrum T2/FLAIR hyperintensities (arrows).

CSF examination revealed pleocytosis (WBC 13) with a normal glucose and protein levels. Serum and CSF neuronal antibodies were all negative. EEG showed diffuse delta activity with no evidence of focal or generalized epileptiform abnormalities.

Follow-up MRI after 3 weeks performed due to poor response to anti-seizure medication, revealed symmetrical T2/FLAIR hyperintensities in the claustrum without diffusion restriction or abnormal enhancement, with interval improvement of previously seen signal abnormalities in the mesial temporal lobes **(Figure 2C-D).**

Following that, she was started on immunotherapy, including pulse steroids and intravenous immunoglobulin (IVIG). She showed significant improvement after IVIG. At the 3-month follow-up, she was doing well with no seizure recurrence and no neurological deficit. Her repeated EEG demonstrated a normal background with no epileptic discharges. At 2.5 years follow-up, she was doing well on monotherapy with no seizure recurrence. The clinical features of both patients are summarized in Table 1.

Table 1: Summary of patients' Clinical Characteristics

Patient #	**1.**	**2.**
Age/ Sex	13 /F	3.7/ F
PC	Fatigue / Headache / Seizures	Encephalopathy Seizures
Fever*	Yes[7]	Yes[7]
Seizure Semiology	Eye deviation & Generalized tonic-clonic seizure	Staring, perioral cyanosis, tongue protruding & hypotonia
CSF Analysis	Unremarkable	Mildly elevated WBC 19 and RBC 29 otherwise, unremarkable
Autoimmune limbic encephalitis panel	Negative	Negative
EEG	Diffuse delta slow waves more noticeable over the temporal regions	Diffuse delta activity
Neuroimaging finding	Yes	Yes
ASMs used	CBZ, PHT, LEV	PHT, LEV, Mid, VPA, TPM, CLB
Immunotherapy	Steroids	Steroids, IVIG
Duration of admission	7 days	20 days
Discharge ASMs	CBZ / LEV	CLB / VPA / TPM
Clinical outcome	Seizure free on Monotherapy (9 months)	Seizure free off ASMs Achieved milestones (2.5 years)

** a Fever (number of days before neurologic symptoms onset).*
Abbreviations: PC: Presenting complaint, EEG: Electroencephalogram, CSF: cerebrospinal fluid, ASMs: anti-seizure medication, CBZ: carbamazepine; CLB: clobazam; LEV: levetiracetam; PHT: phenytoin; TPM: topiramate; VPA: valproate, IVIG: intravenous immunoglobulin.

Discussion

Neuroimaging is an important tool in investigating patients with encephalopathy and can provide supporting evidence for AE diagnostic criteria.[10] Neuroimaging findings in patients with AE can be variable and not very specific. These findings may include increased FLAIR signal intensities that involve limbic system structures.

Involvement of other structures including basal ganglia, striatum, diencephalon and rhombencephalon have been reported in patients with AE.[11,12]

In this study, we report two patients who met the diagnostic criteria for AE.[10] Both had a history of encephalopathy and an initial presentation with intractable seizures that responded to immune therapy. Our patients had bilateral symmetrical claustrum hyperintensities. Hyperintensities in the claustrum have been observed in cases linked to autoimmune encephalitis (AE), both in individuals experiencing refractory seizures and those without refractory seizure.[9] Additionally, such hyperintensities have been documented in patients who develop status epilepticus following febrile illness.[8]

Furthermore, claustrum sign has been reported in other disorders including acute necrotizing encephalopathy, COVID-19 associated encephalopathy, and immune effector cells associated neurotoxicity syndrome.[13] These disorders share cytokine storm as a possible underlying pathophysiology and, therefore, claustrum hyperintensity serves as a radiological marker of cytokine-mediated

neuroinflammation rather than being pathognomic of a particular condition.[13-15] The claustrum, situated amidst the insula and putamen, constitutes a subcortical gray matter region enveloped by white matter, bordered medially by the external capsule and laterally by the extreme capsule.[11] Despite its anatomical clarity, the precise function of this structure remains poorly elucidated.[10]

Several studies have documented claustral hyperintensities in individuals meeting the diagnostic criteria for autoimmune encephalitis, a majority of whom tested negative for autoimmune antibodies.[8,9] It has been described in patients who presented with status epilepticus proceeded by febrile illnesses.[8] Meletti et.al. screened 155 patients with refractory status epilepticus. Six out of 155 were found to have de novo status with no infectious etiology in the CSF and no previous history of febrile or afebrile seizures. All six patients were found to have bilateral claustral involvement during the acute phase of status epilepticus (3-10 days from SE onset). Interestingly, this MRI abnormality was not found before SE onset and after resolution of SE.

Authors of this paper speculated that claustrum hyperintensity may be associated with a very aggressive form of SE that requires ICU admission and the use of anesthetic agents. Furthermore, the time course may indicate the pathophysiological rule of claustrum dysfunction in SE and super-refractory SE. All patients tested negative for multiple neuronal antibodies. Outcomes were unfavorable with one fatality and five patients developing chronic epilepsy.[8] Moreover, it has been described as an

imaging finding that could be seen in autoimmune encephalitis in association with or without refractory seizures.[9]

Steriade et al. identified claustral hyperintensities in four out of 34 adult patients diagnosed with autoimmune limbic encephalitis and/or epilepsy. Explosive seizures followed by intractable epilepsy were the common presenting symptom among all patients. Among them, two patients tested negative for autoimmune antibodies, while the remaining two tested positive for anti-glutamic acid decarboxylase and anti-Ma2 antibodies, respectively. Despite undergoing immunomodulation therapy, all patients experienced intractable epilepsy with varying response rates.[9] Claustral hyperintensity appeared in a range between 10 days to 4 months from seizure onset. Full resolution of this finding was documented to be on average of 102 days after detection of MRI abnormality.[9] Moreover, in a study by Yang et al., five patients with seronegative autoimmune epilepsy were identified to exhibit claustrum hyperintensities, with four presenting in the acute phase and one in the chronic phase. Interestingly, these patients demonstrated a favorable outcome, characterized by controlled seizures and absence of cognitive impairment.[16]

A case of a 16-year-old female who initially experienced status epilepticus following fever and short-term memory impairment also had evidence of hyperintensities in the bilateral external capsule and claustrum. Subsequent MRI scans demonstrated the resolution of these abnormalities. Notably, autoimmune panel testing was not performed for this patient, and her outcome was not reported.[17]

The precise etiology and pathogenesis of claustral hyperintensities remain poorly understood. These lesions are speculated to arise from the activation of the epileptic network in autoimmune epilepsy, particularly within subcortical lesions linked to the epileptogenic cortex. However, substantiating this speculation requires additional basic science investigations. These neuroimaging findings have been observed in cases of limbic encephalitis devoid of seizure activity, casting doubt on the validity of this hypothesis.[9]

Moreover, it has been hypothesized that it is linked to dysregulated immune hyperactivation in genetically predisposed individuals following an infectious trigger. This was corroborated by the finding that children with febrile infection-related epilepsy syndrome (FIRES) may have higher CSF concentrations of cytokines and chemokines.[13] In addition, one study found that FIRES in children was linked to a mutation in IL-1 receptor antagonist gene (*IL1RN*).[18] Consequently, it appears that this explanation is more plausible than the first.

The favorable outcomes observed in our patients is similar to those documented in the study by Yang et al.[15] The diverse responses to immunomodulation and anti- seizure medications among the patients with claustral hyperintensities present an interesting phenomenon, likely stemming from various factors. primarily, a favorable outcome may be linked to younger age, while the extent of claustrum damage and its impact on the epileptogenic cortex represent potential additional risk factors.[9]

However, comprehensive large-scale studies are imperative to elucidate the potential risk factors associated with favorable outcomes.

In summary, claustrum hyperintensities represent a potential indicator of autoimmune encephalitis (AE), appearing in both seronegative and seropositive patients with outcomes that are variable. Moreover, rather than being disease-specific, it probably functions as a radiological marker for cytokine-mediated neuroinflammation. This intriguing radiological phenomenon underscores the necessity for additional research to elucidate its underlying pathophysiology and significance in patient care.

Conflict of interest

There is no conflict of interest. This manuscript has been contributed to, seen, and approved by all the authors. All the authors fulfill the authorship credit requirements. Alzahra'a Al-Saidi wrote the first draft of this manuscript. No honorarium grant or other form of payment was received for the preparation of this manuscript.

Ethics approval

Our institution does not require ethical approval for reporting individual cases or case series.

Informed consent

Written informed consent was obtained from a legally authorized representative(s) for anonymized patient information to be published in this article.

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