■ Clinical commentary

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Epileptic Disorders

Cortical unihemispheric brain edema (CUBE) due to a multi-system inflammatory syndrome in adults (MIS-A)

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ABSTRACT

Unilateral hemispheric edema may occur with or without seizures. It is a rare entity, found more often in children, than in adults. As many of these patients develop pronounced unilateral complete cortical hemispheric (uni-hemispheric) edema on MRI, we have used the term "cortical unihemispheric brain edema" (CUBE) to describe this entity. We describe a case of CUBE occurring along with a post COVID multi-system inflammatory syndrome in adults (MIS-A). A 30-year-old man was admitted with status epilepticus. He was found to have CUBE and features of MIS-A. He had a history of mild COVID-19 illness one month earlier. He was noted to have persistently elevated inflammatory markers and multi-organ dysfunction compatible with MIS-A. We review the cases of CUBE in the literature and describe the features and etiology of this uncommon syndrome. Furthermore, we discuss the differences between two types of CUBE; cytotoxic CUBE (CUBE-C) and vasogenic CUBE (CUBE-V).

Key words: unilateral hemispheric edema, cortical unihemispheric brain edema (CUBE), multi-system inflammatory syndrome in adults (MIS-A), cytotoxic CUBE (CUBE-C), vasogenic CUBE (CUBE-V)

Unilateral hemispheric cortical edema with status epilepticus is a rare entity. Most cases have been described in children, usually in the setting of infantile hemi-convulsion-hemiplegia-epilepsy (IHHE) syndrome or Rasmussen's encephalitis. Only a handful of adult cases have been described [1-3]. Two cases occurred in patients with pre-existing post traumatic epilepsy or cerebral palsy. The third case, which closely resembled our report, was described in the pre-COVID era. This patient presented with a febrile status epilepticus (FSE) and went on to develop multi-organ dysfunction syndrome (MODS) and disseminated intravascular coagulation (DIC). This patient was followed for 11 years and went on to develop hemispheric atrophy (hemiplegia, aphasia and hemispheric atrophy associated with febrile status epilepticus) [3].

As these patients, including our case, developed pronounced unilateral hemispheric (uni-hemispheric) cortical edema on magnetic resonance imaging (MRI), we have used the descriptive term "cortical unihemispheric brain edema" (CUBE) to describe this group. As the underlying pathophysiology could be either cytotoxic or vasogenic CUBE, we have further subclassified patients as CUBE-C (cytotoxic) or CUBE-V (vasogenic).

Status epilepticus (SE) is an uncommon neurological complication of COVID-19. Only around 50 cases of COVID-19-associated SE have been described [4].

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Seizures have been described in the post-COVID phase. Status epilepticus and CUBE with a multisystem inflammatory syndrome in adults (MIS-A) has not yet been reported [5, 6].

We report a patient with CUBE-C and SE as the presenting and prominent feature of a post-COVID MIS-A.

MIS-A is a well described entity in the post-COVID phase. The CDC criteria for MIS-A include the following five criteria [7]:

- it should occur in the context of a severe illness requiring hospitalization in an adult ≥21 years;
- a current or previous SARS-CoV-2 infection should be documented during admission or in the preceding three months with a positive RT-PCR, antigen, or SARS-CoV-2 antibody test;
- severe dysfunction of one or more extrapulmonary organ systems (*e.g.*, hypotension or shock, cardiac dysfunction, arterial or venous thrombosis or thromboembolism, or acute liver injury);
- accompanied by laboratory evidence of severe inflammation (*e.g.*, elevated CRP, ferritin, D-dimer, or interleukin-6);
- and absence of a severe respiratory illness or hypoxia that could explain the above findings. Mild respiratory illness is not inconsistent with diagnosis.

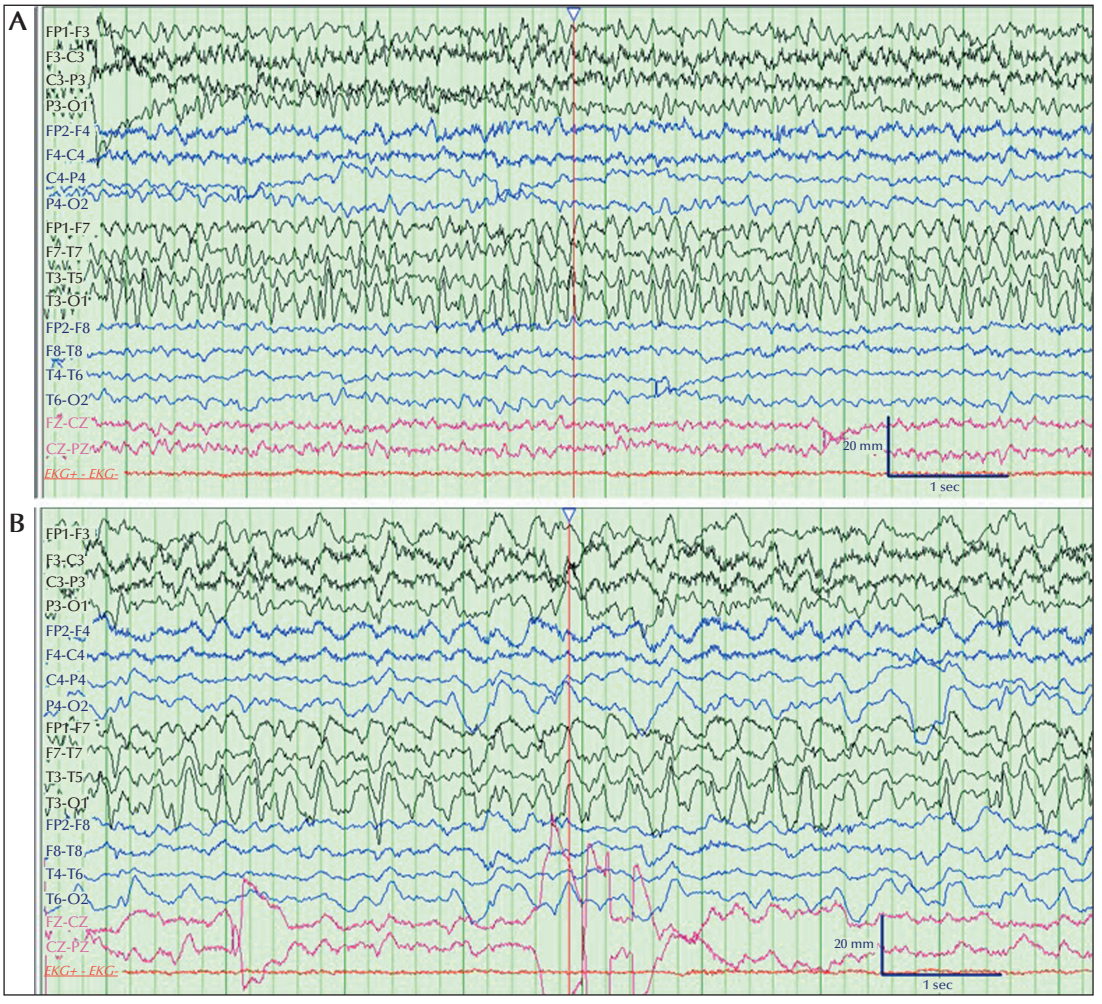
Case study

A 30-year-old man was admitted with status epilepticus. He was found seizing by the side of the road 10 days earlier. At an outside center, he was found to have dense right hemiplegia with accelerated hypertension (BP: 200/140 mm Hg). He was intubated and started on IV anticonvulsants (IV fosphenytoin 1,500 mg loading and 150 mg Q8 hourly, IV phenobarbitone 1,000 mg loading and 60 mg Q8H, IV levetiracetam 1,500 mg loading and 750 mg IV BD). Continuous EEG showed frequent left hemispheric rhythmic ictal discharges lasting for between 3 and 5 minutes (*figure 1*). He was noted to have elevated inflammatory markers, high CPK levels, acute kidney injury, acute myocarditis (ECHO showing global LV dysfunction and elevated troponin levels), acute liver injury and an upper gastrointestinal bleed. He was initiated on hemodialysis. The initial brain CT was normal. One week later, brain MRI showed left hemispheric cortical edema with diffusion restriction and crossed cerebellar diaschisis (*figure 2*). After transfer to our center, IV midazolam at 5 mg/hour and propofol (2 mg/kg IV bolus infusion), followed by a continuous infusion of 5 mg/kg/h for 24 hours and ketamine at 10 mg/kg/hour were initiated for super-refractory SE (SRSE). After 36 hours of burst suppression, his EEG showed only generalized slowing. A repeat MRI on Day 11 showed similar features with ipsilateral hyperperfusion. He had a remote history of post-traumatic resolved epilepsy 12 years earlier, which had remitted after two years (defined as seizure-free for 10 years and off medication for >five years) [8]. Brain CT at that time had shown a right temporal contusion.

His past history was significant for COVID-19 illness one month prior to presentation with a partial history of COVID vaccination (1st Dose of ChAdOx1 vaccine) three months earlier. His laboratory reports showed elevated troponin levels, rapidly resolving ECG changes (initially V1-V3 ST segment elevation), abnormal liver enzymes (AST: 350 U/L, ALT: 375 U/L, total bilirubin: 3 mg/dL) and renal function tests (creatinine: 5 mg/dl), high CPK levels (33,000 U/L) and persistently elevated inflammatory markers over three weeks (ESR: 105 mm/hr, CRP: 98 m/dL, d-dimer: 9900 ng/mL, ferritin: 6,800 ng/mL). An extensive evaluation for sepsis, autoimmune and paraneoplastic antibodies, NMO and MOG antibodies was negative. CSF examination was within normal limits. He was started on antibiotics and IVIg at 2 mg/kg over five days. His inflammatory parameters slowly decreased and he was gradually rehabilitated. After two months, he started to ambulate with support and had mild word finding difficulty. A repeat MRI showed severe left hemispheric atrophy (*figure 2*).

Discussion

Peri-ictal and post-ictal neuroimaging findings are usually localized to the seizure onset zone or a single lobe; most often in the mesial temporal structures and neocortex and infrequently in the subcortical structures such as the thalamus or pulvinar [9]. Reduced ADC values with restricted diffusion are reflective of true cytotoxic edema (ruling out T2 shine through), although the reduction of these values is modest, compared to the normal side (<6-28%). They also depend on the timing of MRI with respect to the stage of SE. ADC values change during different stages of SE. In Stage 1, there is hyperperfusion without a detectable ADC change. In Stage 2, ADC increases as vasogenic extracellular oedema sets in. With Stage 3, further progression to cytotoxic oedema results in decreased ADC. Finally, in Stage 4, SE-related neuronal loss and gliosis increases the ADC values [10]. Crossed cerebellar diaschisis may be seen as a result of excitation of fronto-ponto-cerebellar circuits. In our patient, the MRI/ magnetic resonance angiogram (MRA) hyper-perfusion with cytotoxic edema suggested increased neuronal metabolic demand and



■ **Figure 1.** (A) EEG on Day 2 showing rhythmic left hemispheric ictal rhythm. (B) EEG on Day 3, showing a slower rhythmic left hemispheric ictal rhythm.

neurovascular coupling, which nevertheless was insufficient to meet the increased cortical metabolic demands, causing a supply-demand mismatch.

CUBE is rarely associated with SE. The differential diagnosis of CUBE varies based on the age at onset, association with fever or underlying neurological conditions. Most patients with CUBE present with a new-onset refractory status epilepticus (NORSE).

In children, the differential diagnosis includes:

• chronic autoimmune encephalitis such as Rasmussen's encephalitis. During the acute phase, MRI may show CUBE. Later on, gradual hemispheric atrophy sets in.

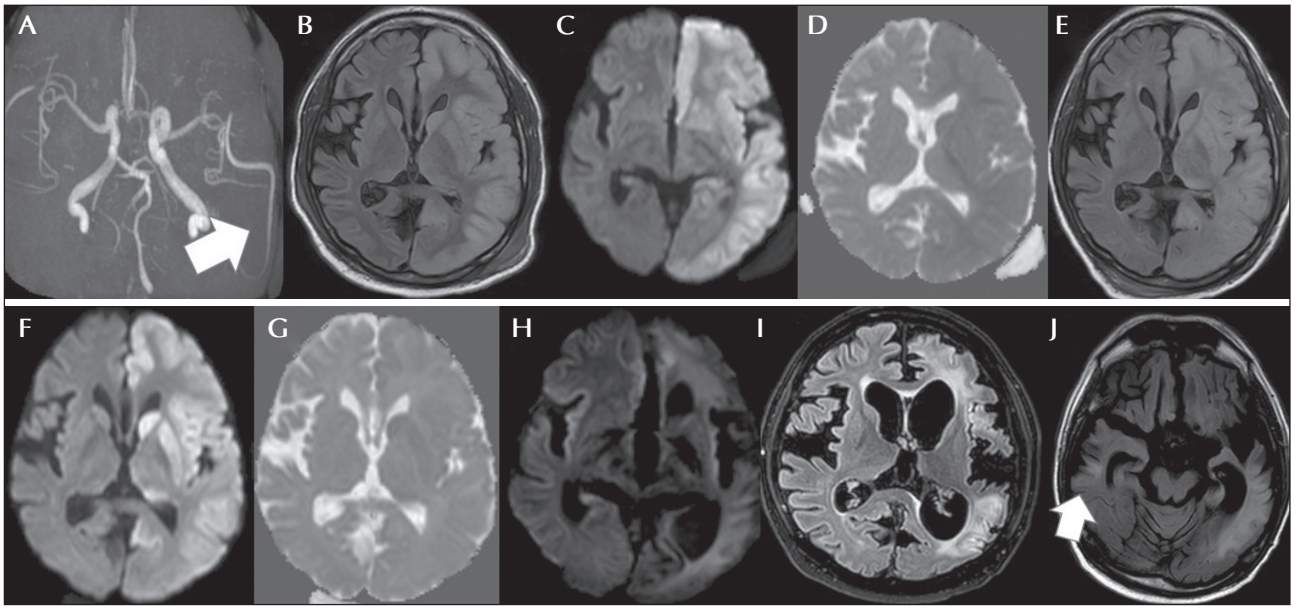
• infantile hemiconvulsion-hemiplegia-epilepsy (IHHE) syndrome. The International League Against Epilepsy defines IHHE as a syndrome with new-onset refractory status epilepticus in children aged less than two years. Patients with IHHE have unilateral (focal) seizures with fever, NORSE and may have CUBE with transient edema lasting at least 24 hours.

• focal status epilepticus-related unilateral brain edema (FSE-CUBE) is seen in children with pre-existing epilepsy or cerebral palsy [11]. These children behave like those with IHHE with an acute hemiparesis that often improves, and the child is left with residual focal epilepsy.

• acute encephalopathy with acute brain swelling with febrile illness (ABS) [12].

In children, the latter three features may represent a continuum of acute encephalopathies with brain swelling (AEBS).

• CUBE is rarer in adults, although the differential diagnosis encompasses the following conditions (*table 1*):



■ **Figure 2.** MRI and MRA. (A) MRA shows hypervascularity of left MCA branches (white arrow). (B) FLAIR. (C) Diffusion weighted. D) ADC map images on Day 11. (E) MRI images from Day 21 (FLAIR). (F) Diffusion image showing T2 shine through. G) Normal to increased ADC values on the left hemisphere. (H) MRI images after two months (diffusion-weighted). (I, J) FLAIR images showing severe left hemispheric atrophy; the white arrow shows the remote right temporal gliosis.

• CUBE-C related to focal or hemispheric status epilepticus in adults with or without crossed cerebellar diaschisis and hyper-perfusion on MRA [1-3, 13, 14]. CUBE-V has also been reported with better prognosis [15].

• unilateral hemispheric infective encephalitis.
• mitochondrial disorders such as MELAS (myopathy, encephalopathy, lactic acidosis and stroke-like episodes). However, the lesion is usually restricted to posterior head regions on MRI, although it may affect vascular territories.
• FIRES which may occur at any age.
• uni-hemispheric cerebral infarction.
• CUBE-V due to fulminant hepatic failure, resulting from unilateral hyper-perfusion syndrome [16].
• CUBE-V after cardiac surgery due to possible hyper-perfusion syndrome or reversible encephalopathy presenting with a stroke mimic without seizures [17].
• CUBE without diffusion restriction. FLAMES (FLAIR hyperintensities in Anti MOG associated encephalitis with seizures) is a unilateral cerebral cortical encephalitis. It is associated with myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD). Most FLAMES are focal lesions, although rarely CUBE is seen. These lesions show prominent FLAIR hyperintensities and post contrast T1 enhancement with ipsilateral hyper-perfusion [18].
• rarely, traumatic brain injury can present as CUBE [19].

Our patient with CUBE and SE had certain unusual features that differentiated it from the above conditions. The onset occurred in adulthood, without a history of recent fever within the past two weeks (ruling out FIRES or febrile SE), with no lesional epilepsy and MOG antibody negativity, and the patient had a multi-system inflammatory disorder with MODS. His MRI showed CUBE with diffusion restriction and ADC changes suggestive of CUBE-C. He also showed involvement of the subcortical structures- the basal ganglia and thalamus.
Although his MODS was initially thought to be due to prolonged SRSE itself, persistent elevation of systemic inflammatory markers and the time frame after COVID-19 were consistent with MIS-A. The presence of prominent multi-system involvement, fulfilment of diagnostic criteria for MIS-A, elevated systemic inflammatory markers (which is unusual in super-refractory SE unless intractable MODS sets in) and improvement with IVIg makes MIS-A the most likely etiology for his condition. Our patient had a history of

▼ **Table 1.** Literature on MRI of adults with unilateral brain edema.

Author	Clinical features (most abnormal laboratory parameters)	Pre-existing neurological conditions	MRI findings	Etiology and outcome
Inamasu *et al.* 2001 [16]	49-year-old man Generalized seizure	None	Diffuse cortical edema with ipsilateral hyperperfusion. DW MRI not available	Fulminant hepatic failure with hyperperfusion syndrome Residual sensory aphasia at discharge
Heo *et al.* 2007 [14]	49-year-old man Non-convulsive status epilepticus	None	CUBE with diffusion restriction	Possible autoimmune/ infective encephalitis. Complete recovery
Wijdicks *et al.* 2008 [17]	34-year-old man Postoperative left flaccid hemiplegia and anosognosia No seizures	None	CUBE-V on MRI T2 shine through without diffusion restriction Complete MRI resolution by Day 25 No residual atrophy or gliosis.	After cardiac surgery Hyperperfusion syndrome or reversible encephalopathy Good outcome
Carroll *et al.* 2010 [15]	37-year-old man Gradual recovery to baseline over 2 months	Prior craniopharyngioma and seizures	Reversible T2 shine through without diffusion restriction (vasogenic edema)	Symptomatic seizures Complete resolution on follow-up MRI at 5 months. Good improvement. Residual focal seizures.
Ali *et al.* 2013 [1]	30-year-old woman Unihemispheric status epilepticus. Normal CSF, blood parameters Viral workup negative.	Prior traumatic brain injury, vegetative state	CUBE with ipsilateral hyperperfusion and crossed cerebellar diaschisis	Symptomatic seizures Improved to baseline status
Dubin *et al.* 2017 [13]	67-year-old woman Single seizure Normal CSF, blood parameters Viral workup negative	None	MRI- left hemispheric cerebral edema DW imaging- focal diffusion restriction No vascular occlusion	Possible influenza A infection Good outcome
Ogawa *et al.* 2017 [18]	38-year-old man Focal-generalized seizures Right hemiparesis, aphasia CSF- pleocytosis (>300 cells) Serum MOG antibody positive	None	MRI- unilateral hemispheric cortical hyperintense lesions on fluid-attenuated recovery (FLAIR) imaging No diffusion restriction Ipsilateral hyperperfusion on brain SPECT	MOG antibody associated encephalitis Full recovery after IV methylprednisolone Follow up MRI after 6 years was normal
Ferilli *et al.* 2018 [2]	68-year-old woman Unihemispheric status epilepticus Normal CSF, blood parameters	Cerebral palsy	CUBE with ipsilateral hypoperfusion	Symptomatic seizures. Recovery with residual hemiparesis

▼ **Table 1.** Literature on MRI of adults with unilateral brain edema (*continued*).

Author	Clinical features (most abnormal laboratory parameters)	Pre-existing neurological conditions	MRI findings	Etiology and outcome
Naoi *et al.* 2021 [3]	43-year-old man Status epilepticus Focal to secondary generalized epilepsy Normal CSF MODS, DIC Progressive cerebral atrophy on follow-up.	None	CUBE with persistent ipsilateral cerebral hypoperfusion on MRA at Day 20	Acute febrile SE Residual hemiplegia and aphasia
Our case, 2021	CSF normal MODS Increased systemic inflammatory markers (ESR:105 mm/hr, CRP: 98m/dL, d-dimer: 9900 ng/mL, ferritin: 6800 ng/mL)	COVID-19, 8 weeks earlier.	CUBE with persistent ipsilateral hypervascularity on Day 21.	MIS-A Unresponsive state during wakefulness

remote post traumatic epilepsy with right temporal gliosis. However, he developed CUBE on the contralateral side. It is unclear as to why the cytokine storm associated with MIS-A triggered a status epilepticus from the contralateral side.

Most of the conditions associated with CUBE and seizures share a common underlying pathophysiology; a triggering febrile illness, autoimmune encephalitis, cytokine storm, unilateral hyperperfusion, trauma or other mechanisms [20]. Our case depicts the rare onset of CUBE with post-COVID MIS-A and suggests the influence of a dysregulated host immune response in the post-viral phase. Why these factors should produce a strictly unilateral involvement is still unclear. ■

Supplementary material.
Summary slides accompanying the manuscript are available at www.epilepticdisorders.com.

Disclosures.
The authors declare no conflicts of interest.

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TEST YOURSELF

(1) What is multi-system inflammatory syndrome in adults (MIS-A)?

(2) What is the mechanism of status epilepticus in MIS-A?

(3) How is MIS-A with CNS involvement treated?

Note: Reading the manuscript provides an answer to all questions. Correct answers may be accessed on the website, www.epilepticdisorders.com.