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Clinical Observations

Focal Status Epilepticus-Related Unilateral Brain Edema: Magnetic Resonance Imaging Study of Children in Southwest China

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ABSTRACT

Background: Unilateral brain edema is a rare peri-ictal imaging abnormality related to focal status epilepticus. We present the largest series of these patients, describe their clinical features and magnetic resonance imaging (MRI) findings, and analyze the possible underlying pathophysiology.
Methods: We reviewed the medical records in Southwest China's largest tertiary's children's medical center from 2011 to 2017. Patients with focal status epilepticus were included if acute-phase cerebral MRI showed unilateral edematous swelling of the epileptic hemisphere.
Results: Eleven children were included. The age at which the patients presented with status epilepticus ranged from seven months to 10.8 years. All patients showed prolonged clonic seizures with marked unilateral predominance followed by hemiplegia of the ipsilateral limbs. The seizure duration ranged from one to 72 hours. All patients showed hyperintensities on T2-weighted images and diffusion-weighted images involving the whole pathologic hemisphere. Three patients showed involvement of the contralateral cerebellar hemisphere and one showed hippocampal herniation. Magnetic resonance angiography of the brain was performed in seven patients, among which three showed dilation of the affected hemispheric arteries. Three patients underwent follow-up MRI, and all the examinations revealed ipsilateral cerebral hemisphere atrophy.
Conclusions: Focal status epilepticus may cause unilateral brain edema, and cytotoxic edema probably plays an important role in the pathophysiology of brain injury.

Introduction

Status epilepticus is a common neurological emergency in children. Patients may experience a complete recovery or show differing degrees of sequelae. The increasing use of magnetic resonance imaging (MRI) in individuals with status epilepticus has allowed identification of the neuroanatomic changes related to status epilepticus.[1] Seizure-induced brain MRI abnormalities are widely variable, heterogeneous, and not necessarily anatomically correlated to the type of epilepsy. These abnormalities present in different locations with variable extents and show a wide range of signal and morphological characteristics.[2] Among the peri-ictal imaging abnormalities related to status epilepticus, unilateral panhemispheric changes have rarely been reported, with most reports being anecdotal or in small series.[3–5] We present a series of children who presented with status epilepticus-specific unilateral panhemispheric changes on MRI and attempt to analyze the possible underlying pathophysiology.

Methods

Patient selection

The medical data of patients with focal status epilepticus who were admitted to Children's Hospital of Chongqing Medical

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University from the year 2011 to 2017 were collected if the acute phase (within two weeks after the occurrence of status epilepticus) cerebral MRI showed unilateral edematous swelling of the epileptic hemisphere. This hospital is the largest tertiary children's medical center in Southwest China. Status epilepticus was defined as at least 30 minutes of continuous seizure activity or the occurrence of two or more series of seizures without recovery of consciousness in between the attacks. Some patients also underwent MRI examinations before this particular episode of status epilepticus or during their convalescence phase.

The study was approved by the ethics committee of the Children's Hospital of Chongqing Medical University.

Radiological characteristics

All of the MR images were obtained using a 1.5-Tesla MRI scanner (Signa Excite HD, GE Healthcare, Milwaukee, WI, USA) with routine sequencing and maximum slice thickness of 5 mm.

Results

Eleven patients met the selection criteria. The clinical features, history of seizures, and developmental history of these children are summarized in Table 1.

Etiologic evaluation

All patients underwent cerebral spinal fluid testing, and none exhibited pleocytosis or hyperproteinorrhachia. Plasma and cerebral spinal fluid screening for viral antibodies (herpes simplex virus, Epstein-Barr virus, enterovirus 71, and cytomegalovirus) was unremarkable. All patients exhibited normal serum ammonia and lactate assessments, tandem mass spectrometry screening, and urinary organic acid analysis with gas chromatography, making a diagnosis of metabolic encephalopathy less likely.

Postictal electroencephalography

To rule out nonconvulsive status epilepticus, all patients underwent postictal electroencephalography (EEG). The EEG findings for seven patients showed unilateral diffuse slow waves and those for four patients (Patients 1, 7, 9, and 10) showed unilateral diffuse slow waves with sporadic focal spike-waves or spike-slow waves.

MRI features

MRI features before, during, and after the acute phase are summarized in Table 2. Typical MRI images are shown in Figures 1–4.

Discussion

Our patients illustrate that permanent brain injury can occur in one cerebral hemisphere following focal status epilepticus in children, and we believe that prolonged seizures were responsible for the unilateral brain edema and the consequent brain atrophy. Seizure-induced brain injury is a diagnosis of exclusion, and numerous causes of symptomatic seizures should be ruled out first. Some of the other causes of unilateral brain edema and the associated findings in this study are listed below.

Viral encephalitis

The findings of all cerebral spinal fluid tests were negative, and most importantly, viral encephalitis seldom causes strictly unilateral brain involvement.

Metabolic encephalopathy

All patients had unremarkable serum ammonia and lactate assessments, tandem mass spectrometry screening for blood spots, and urinary organic acid analysis with gas chromatography. Moreover, metabolic encephalopathy seldom causes strictly unilateral brain involvement.

Ischemic stroke

Since our patients had hemiplegia and MRI showed crossed cerebellar diaschisis, which is often observed in cortical infarction,[6] ischemic stroke was considered in the differential diagnosis. However, the brain lesions on MRI did not correspond to a vascular distribution and MR angiography showed no sign of cerebral artery occlusion.

Hemiconvulsion-hemiplegia syndrome

Our patients' clinical and MRI findings showed a striking resemblance to the core diagnostic criteria for hemiconvulsion-hemiplegia syndrome. According to the review by Nabbout,[7] hemiconvulsion-hemiplegia syndrome is characterized by the combination of unilateral convulsive status epilepticus, mainly clonic, followed by transient or permanent ipsilateral hemiplegia. The syndrome occurred during a febrile illness in a previously healthy child younger than four years of age. In our study, however, none of the patients met all the diagnostic criteria: nine children had a previous history of seizures with/without developmental delays, and the remaining two did not show fever. Thus, the diagnosis of hemiconvulsion-hemiplegia syndrome was excluded.

Autoimmune encephalitis

In recent years, several studies have highlighted the importance of autoimmunity in status epilepticus of unclear etiology.[8–12] Unfortunately, since this was a retrospective study, no relative neuroimmunology evaluation was performed for our patients. However, we think that the autoimmune origin should not be considered an etiologic factor for the status epilepticus in our patients because of the following reasons. (1) None of our patients experienced movement disorders or psychiatric symptoms at presentation, which are the typical manifestations of autoimmune encephalitis. (2) The classic antiepileptic drugs and new-generation antiepileptic drugs or their combinations usually fail to control seizures, and some patients show improvement with immunomodulatory treatment.[9] However, all patients in our study responded to antiepileptic drugs. (3) A prospective study revealed that neuronal antibodies are found in a sizeable portion of *de novo* status epilepticus patients,[8] while in our study, nine of 11 patients had a history of seizures. (4) Most importantly, individuals with antibody-mediated status epilepticus shown negative MRI results or only nonspecific abnormalities, and unilateral brain edema has not been reported.

Dravet syndrome

Some patients with Dravet syndrome, a well-recognized developmental and epileptic encephalopathy usually associated with

TABLE 1.
Summary of Clinical Features, Seizure History, and Developmental History

Patient	Age (Months)	Previous History of Seizures	Previous Seizure Pattern	Previous History of SE	Initial Development	Fever, Pre- or Post-SE	SE Semiology	SE Duration	Examination at Admission
1	28	Yes	Focal R hemiclonic	No	Normal	Prior	Focal R hemiclonic	2 h	R hemiplegia
2	43	Yes	GTCS	No	Delay	Post	Focal R hemiclonic	15 h	R hemiplegia
3	9	No	n/a	No	Normal	No fever	Focal L hemiclonic	6 h	L hemiplegia
4	30	Yes	Focal R hemiclonic GTCS	Yes	Normal	No fever	Focal R hemiclonic	10 h	R hemiplegia
5	54	Yes	Focal R hemiclonic	Yes	Delay	No fever	Focal R hemiclonic	15 h	R hemiplegia
6	63	No	n/a	No	Normal	No fever	Focal R hemiclonic	1 h	R hemiplegia
7	7	Yes	Focal R hemiclonic	Yes	Delay	Prior	Focal R hemiclonic	24 h	R hemiplegia
8	36	Yes	Focal L hemiclonic GTCS	Yes	Normal	Prior	Focal L hemiclonic	72 h	L hemiplegia
9	35	Yes	Epileptic spasm Focal R hemiclonic	Yes	Delay	Prior	Focal R hemiclonic	7 h	R hemiplegia
10	130	Yes	Focal L hemiclonic, Focal to bilateral tonic-clonic	Yes	Delay	Prior	Focal L hemiclonic	10 h	L hemiplegia
11	79	Yes	GTCS	No	Delay	No fever	Focal L hemiclonic	28 h	L hemiplegia

Abbreviations:
GTCS = generalized tonic-clonic seizure
L = left
n/a = not applicable
R = right
SE = status epilepticus

SCN1A mutation, can present with unilateral clonic seizures and MRI findings of unilateral brain edema.[13] In fact, Patient 7 might have Dravet syndrome. He had the first febrile seizure at age three months and then had several unilateral clonic seizures (often triggered by fever). He developed hemiplegia and unilateral brain edema after status epilepticus at age seven months. He experienced many afebrile seizures (focal seizures and myoclonic seizures) after the age of one year. He also had comprehensive developmental delay. However, the confirmation of Dravet syndrome due to *SCN1A* mutations is impossible without genetic testing.

A variety of neuroimaging changes related to status epilepticus have been described.[3,14,15] Cole concluded that these periictal

TABLE 2.
MRI Features Before, During, and After the Acute Phase of 11 Children

Patient	Periictal MRI Findings			Follow-up MRI (At least One Month Later)	Previous MRI
	Location	T2WI/FLAIR/DWI	MRA+MRV		
1	L whole hemisphere cortex, basal ganglia, and L thalamus	T2WI↑, FLAIR↑, DWI↑	dilation of L MCA and L PCA	None	None
2	L whole hemisphere cortex and basal ganglia; L hippocampal herniation	T2WI↑, FLAIR↑, DWI↑	dilation of L MCA and L PCA	None	Normal
3	R whole hemisphere cortex, basal ganglia, and R thalamus; crossed cerebellar diaschisis	T2WI↑, FLAIR↑, DWI↑	Normal	None	None
4	L whole hemisphere cortex, basal ganglia, and L thalamus; crossed cerebellar diaschisis	T2WI↑, FLAIR↑, DWI↑	Normal	None	Normal†
5	L whole hemisphere cortex and basal ganglia	T2WI↑, FLAIR↑, DWI↑	Normal	None	None
6	L whole hemisphere cortex	T2WI↑, FLAIR↑, DWI↑	None	L cerebral atrophy	None
7	L whole hemisphere cortex	T2WI↑, FLAIR↑, DWI↑	None	L cerebral atrophy	Normal*
8	R whole hemisphere cortex, basal ganglia, and R thalamus	T2WI↑, FLAIR↑, DWI↑	Normal	R cerebral atrophy	Normal*
9	L whole hemisphere cortex and basal ganglia; R cerebral atrophy	T2WI↑, FLAIR↑, DWI↑	dilation of L ACA, L MCA and L PCA	None	Bilateral cerebral atrophy†
10	R whole hemisphere cortex, basal ganglia and R thalamus; R corpus callosum; crossed cerebellar diaschisis	T2WI↑, FLAIR↑, DWI↑	None	None	None
11	R whole hemisphere cortex and R thalamus;	T2WI↑, FLAIR↑, DWI↑	None	None	None

Abbreviations:
ACA = anterior cerebral artery
DWI = diffusion-weighted image
FLAIR = fluid-attenuated inversion recovery
L = left
R = right
MCA = middle cerebral artery
MRA = magnetic resonance angiography
MRV = magnetic resonance venography
PCA = posterior cerebral artery
T2WI = T2-weighted image
↑ = increased signal
* MRI after the previous status epilepticus attack.
† MRI after temporary hemiplegia following a status epilepticus attack

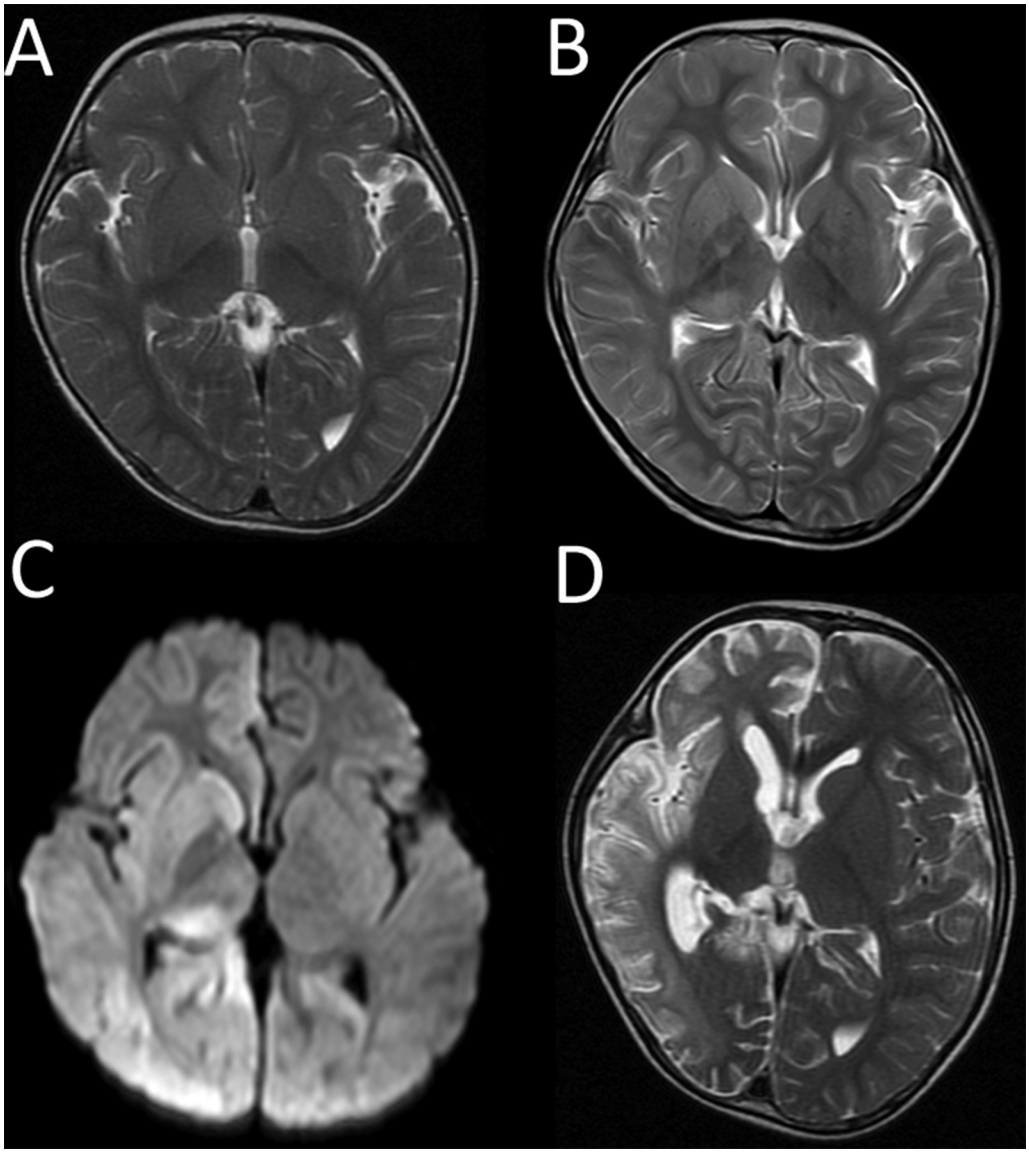

FIGURE 1. Normal MRI T2WI (A) (from Patient 8) after the first episode of SE 16 months prior to presentation. T2WI (B) and DWI (C) of the acute-phase MRI demonstrating restricted diffusion of the whole right cortex, basal ganglia, and thalamus. (D) T2WI obtained approximately two months later showing right-sided cerebral atrophy. DWI, diffusion-weighted image; MRI, magnetic resonance imaging; T2WI, T2-weighted image.

findings can be classified as either local or remote with respect to the site of maximal ictal EEG abnormality.[1] The local abnormalities are generally focal cortical lesions rather than the unilateral panhemispheric changes reported in our study. Cartagena et al. retrospectively reviewed 10 patients with status epilepticus whose cerebral MRI showed signal changes related to seizures. Only one patient showed changes affecting the whole cerebral hemisphere on MRI.[5]

An analysis of clinical and MRI data from our study and a previous case report revealed the cause-and-effect relationship between severe status epilepticus and unilateral cerebral edema, providing strong evidence of seizure-induced brain injury. Further, five of our patients had previous MRI; none of these individuals exhibited a lesion in the affected hemisphere before having status epilepticus, and one patient showed bilateral cerebral atrophy. Then, after the latest prolonged seizure, edema was noted in the affected hemisphere. Ali et al. described a woman in her late 30s with a baseline vegetative state and bilateral cerebral atrophy following a traumatic brain injury. She developed right-sided pancortical edema after prolonged right-sided status epilepticus, along with left-crossed cerebellar diaschisis and dilation of the arteries of the right hemisphere.[3] This interesting and noteworthy phenomenon suggests that the hemispheric edema is attributable to the severe status epilepticus even though the hemisphere had previously been atrophic.

In our study, the seizure duration and intensity seem to be important in determining whether status epilepticus will result in permanent brain injury. Six of our patients had a history of status epilepticus, and two of them experienced transient hemiplegia in the absence of unilateral edema on the acute phase MRI after less prolonged seizures. However, we know that later irreversible brain injury developed following longer episodes of status epilepticus.

From the evidence and analysis above, we believe that the brain injury in our patients was caused by status epilepticus, which raised questions about the underlying pathophysiologic mechanism. The typical pattern of hyperintense signals on T2WIs with restricted diffusion (indicating limited diffusion of water molecules *in vivo*) shown in previous studies[1,3] and in our series suggests cytotoxic edema rather than vasogenic edema.

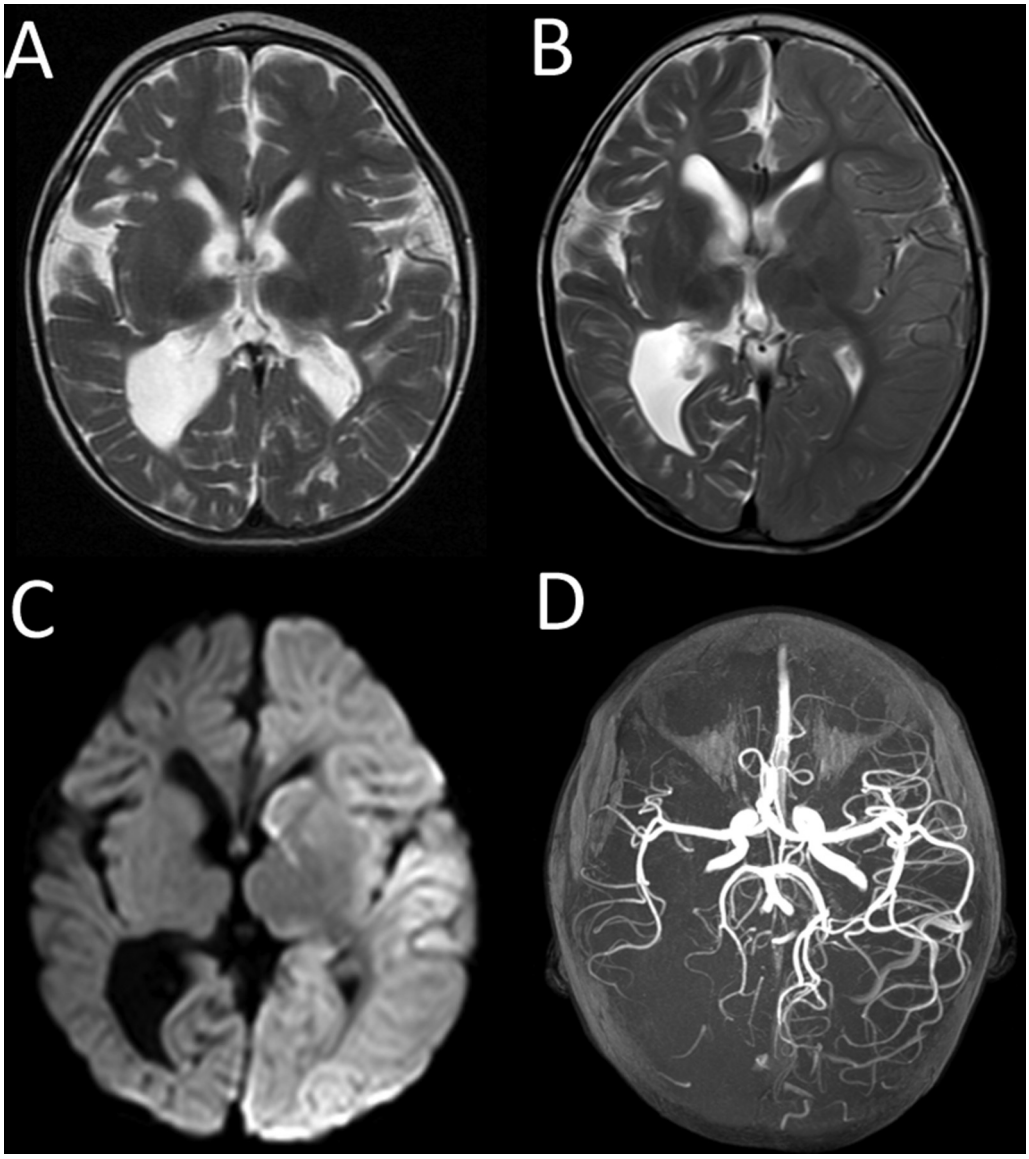

FIGURE 2. T2WI (A) from Patient 9 done eight months prior to presentation showing generalized atrophy of both cerebral hemispheres. T2WI (B) and DWI (C) of the acute-phase MRI demonstrating narrowing of the left lateral ventricle and restricted diffusion of the whole left cortex and basal ganglia. As before, the right lateral ventricle enlarged and right cerebral hemisphere atrophied. MR angiogram (D) showed dilation of the left anterior, middle, and posterior cerebral arteries. DWIs, diffusion-weighted image; MRI, magnetic resonance imaging; T2WI, T2-weighted image.

The cytotoxic edema theory is supported by findings from animal studies, gross anatomic studies, and radiological studies. Animal models have demonstrated that if seizure activity is prolonged, large increases in the cerebral metabolic rate of glucose and oxygen consumption occur and continue throughout status epilepticus. Over time, an energy failure of the Na^+/K^+-ATPase pump may occur causing an influx of water and Na^+ into the cell, and finally leading to hypermetabolic neuronal necrosis.[16] In addition, status epilepticus represents persistent neuronal firing with the release of excess glutamate, which activates postsynaptic *N*-methyl-D-aspartate receptors and triggers receptor-mediated calcium influx. The calcium influx causes a cascade of biochemical changes, mitochondrial dysfunction, oxidative stress, gene expression, and initiation of cell death.[4]

Some of our patients' MR angiograms demonstrated increased arterial circulation in the affected hemisphere, which is likely a compensatory response to the hypermetabolism associated with seizure activity. Multimodal studies—single-photon emission computed tomography, positron emission tomography, intracranial Doppler, and MR angiography studies—suggest that a focal seizure is associated with high metabolic demands and a marked increase in blood flow to the seizure focus.[17,18] When the increased blood flow fails to compensate for the local glucose hypermetabolism, anaerobic metabolism occurs and decompensation begins.[19]

The crossed cerebellar diaschisis phenomenon may represent another compensatory sequence. Because each cerebral hemisphere is connected with the contralateral cerebellar hemisphere through cortico-ponto-cerebellar projecting fibers, hypermetabolism in a cerebral hemisphere during status epilepticus may cause blood flow redistribution, resulting in ischemia of the contralateral cerebellar hemisphere. According to Ali et al., the crossed cerebellar diaschisis phenomenon results from reduced metabolism and blood flow in the cerebellar hemisphere contralateral to a cerebral pathology.[3]

This study is limited by the lack of immunologic and genetic evaluation to establish the underlying etiology of status epilepticus. However, on the basis of the current findings and analysis, we

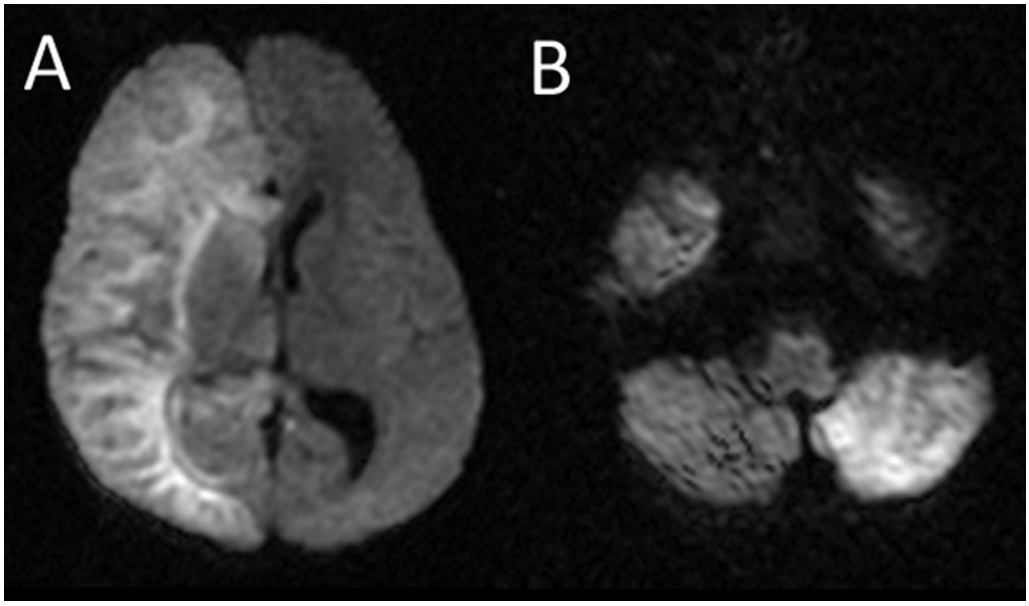

FIGURE 3. (A and B): DWIs (from Patient 10) depict hyperintense signals of the right cortex, right basal ganglia, right thalamus, right corpus callosum, and left cerebellum (consistent with crossed cerebellar diaschisis). DWIs, diffusion-weighted images.

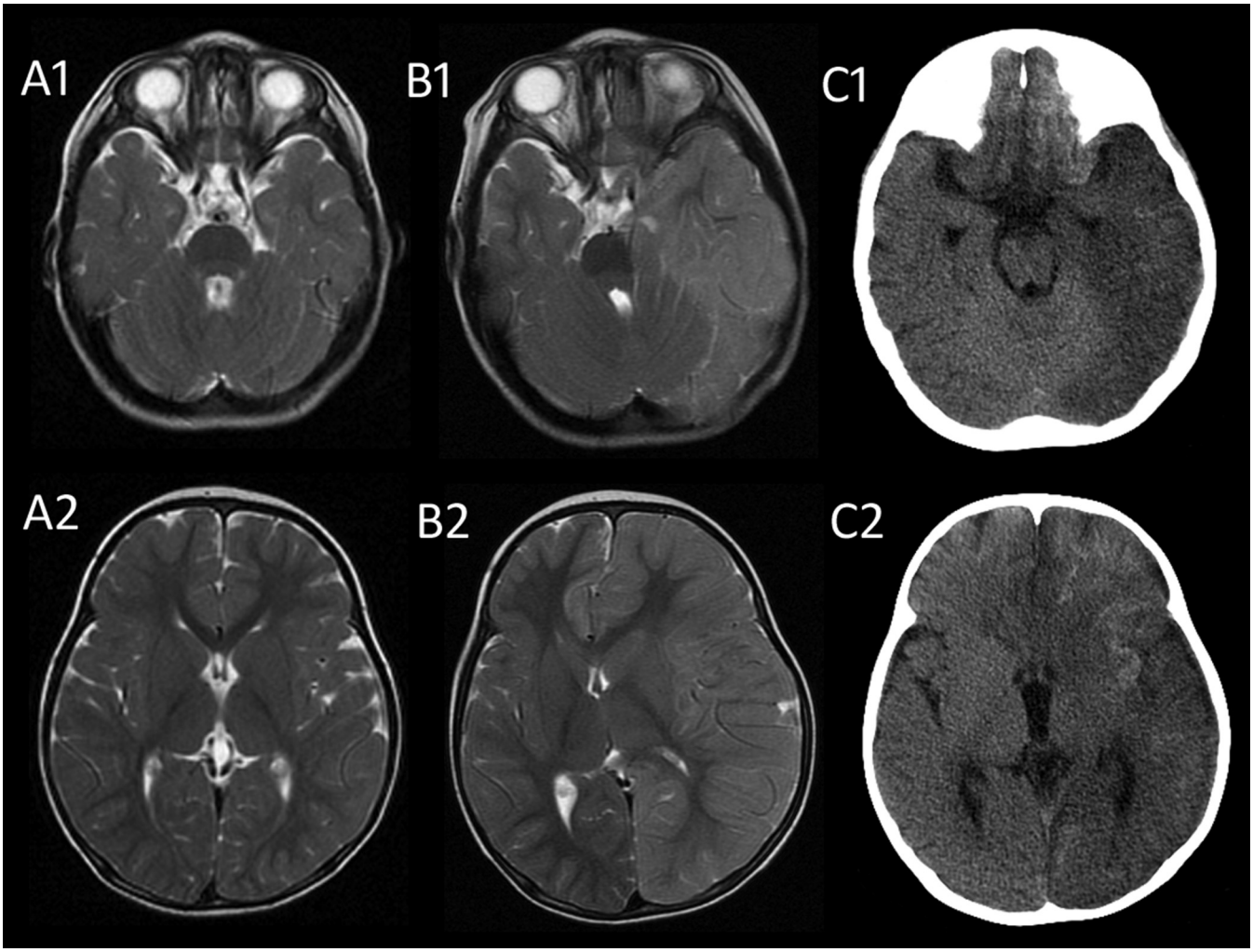

FIGURE 4. Normal T2WIs (A1 and A2) obtained six months prior to presentation of Patient 2. T2WI (B1) of the acute-phase MRI demonstrates hippocampal herniation, and T2WI (B2) shows obvious swelling of the left cerebral hemisphere with a midline shift. CT scans (C1 and C2) obtained 12 days after the acute-phase MRI showing resolution of swelling. CT, computed tomography; DWI, diffusion-weighted image; MRI, magnetic resonance imaging; T2WI, T2-weighted image.

conclude that focal status epilepticus may cause unilateral brain edema, and cytotoxic edema probably plays a major role in the pathophysiology of brain injury.

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Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.pediatrneurol.2018.08.028.

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