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Clinical Observation

Favorable Outcomes With Early Interleukin 6 Receptor Blockade in Severe Acute Necrotizing Encephalopathy of Childhood

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ABSTRACT

Background: Outcome in severe acute necrotizing encephalopathy of childhood is poor, with high mortality (30%) and moderate to severe disability in survivors despite the use of intravenous corticosteroids or immunoglobulins. Increased blood interleukin 6 level correlates with poor outcome.
Methods: We report the early use of tocilizumab, a monoclonal antibody against the interleukin 6 receptor, in three patients (aged five, eight, and 10 years) with severe acute necrotizing encephalopathy.
Results: All three patients experienced a rapid neurological deterioration associated with febrile viral illnesses and met criteria for severe acute necrotizing encephalopathy with a high risk for death or severe disability. Intravenous methylprednisolone and tocilizumab were administered at 18 to 32 hours of encephalopathy in addition to supportive medical therapy. No side effects were observed with this therapeutic strategy. The two patients with influenza A(H1N1)pdm09 virus-related acute necrotizing encephalopathy had a short illness with excellent clinical and radiological recovery. The patient with influenza B virus-related acute necrotizing encephalopathy and florid hemorrhagic brain lesions had a slow recovery with eventual mild disability despite focal encephalomalacia on follow-up neuroimaging.
Conclusions: The early use of interleukin 6 blockade in acute necrotizing encephalopathy is safe and may have a role in improving outcomes and preventing disability.

Introduction

Acute necrotizing encephalopathy (ANE) of childhood is a devastating parainfectious encephalopathy. Patients with ANE experience a rapid deterioration with encephalopathy, seizures, and motor deficits, occurring early in the course of a febrile viral illness.[1] Despite treatment with corticosteroids or intravenous immunoglobulins, death occurs in 30% and survivors have moderate to severe disability.[1-3] Cerebral atrophy occurs early in the illness,[1] whereas cavitation and gliosis characterize follow-up neuroimaging.[4] Brain injury is presumed to result from a cytokine storm, and increased blood interleukin 6 (IL-6) levels in the acute phase of neurological illness correlate strongly with poor outcome.[5] Tocilizumab, a monoclonal antibody that prevents binding of IL-6 to its receptor, has been shown to be useful in adults with severe autoimmune encephalitis.[6] We report the use of tocilizumab early in the disease course in three patients with severe ANE.

Patient Description

Patient 1

This five-year-old girl was increasingly somnolent and irritable on day three of an influenza A(H1N1)pdm09 virus-febrile coryzal

Ethics review and consent: All three patients were enrolled in the Paediatric Autoimmune Epilepsy, Demyelination and Encephalitis Study (PAEDES, CIRB Ref no 2015/2159), an ongoing observational clinical study of children with immune brain disease. Parents of the three children consented to the off-label use of intravenous tocilizumab for immune encephalopathy/encephalitis.

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illness. Physical examination was notable for hypotonia and extensor plantar responses. Magnetic resonance imaging (MRI) of the brain showed typical ANE lesions (Fig 1, Table) with a high-risk classification on the ANE severity score (ANE-SS).[7] She received intravenous methylprednisolone 30 mg/kg at 15 hours of encephalopathy followed by intravenous tocilizumab 12 mg/kg. Seizures with right-sided eye deviation and limb weakness occurred on day two. Arousal with limited speech was observed on day four and she improved rapidly thereafter. Sleep hypoventilation occurred on days three to five and mild left hemidystonia and right hemineglect was evident on days six to nine. Repeat MRI of the brain (on day five) showed improvement in lesion size and signal intensity, and normal language, behavior, and motor function were observed at discharge (day 11). At six months, she has preserved cognition and social functioning (modified Rankin Scale, mRS 0).

Patient 2

This 10-year-old boy developed confused speech and encephalopathy on day two of an influenza A (H1N1)pdm09 virus-febrile illness. A 20-minute generalized tonic-clonic seizure occurred en-route to hospital. MRI of the brain and laboratory parameters were consistent with severe ANE with a high-risk ANE-SS for disability (Table). He received intravenous methylprednisolone 30 mg/kg and intravenous tocilizumab 8 mg/kg at 30 and 32 hours of encephalopathy, respectively. Bilateral leg spasticity was observed on day two but there was a gradual recovery in sensorium and motor function from day three onward. By day seven, he was able to sit and stand, with fluent speech and articulation, but reported a burning sensation over the right foot. Normal cognition, language, and behavior with a residual right foot drop was present at discharge (day 14). At six months after illness, he has mild weakness in the right tibialis anterior muscle without dysesthesia, but has no activity limitation (mRS 0). Repeat MRI was normal.

Patient 3

On day two of an influenza B virus febrile illness with coryza, vomiting, and diarrhea, this eight-year-old girl awoke in the morning with confusion, altered behavior, and later experienced a brief generalized seizure with right-sided upward gaze. On arrival at our hospital, she was noted to be drowsy and combative, and had a left hemiparesis. MRI of the brain showed typical ANE lesions with restricted diffusion and widespread susceptibility blooming artifact in the cerebral hemispheres, thalami, and cerebellum (Table, Fig 2). Intravenous tocilizumab 8 mg/kg was administered at 20 hours of encephalopathy. She completed five days of intravenous methylprednisolone 30 mg/kg/day and received intravenous immunoglobulins 2 g/kg on day seven.

Left hemiplegia and right hemidystonia were present in the first week. She was extubated on day six, regained awareness soon after and was able to speak on day 13. Motor recovery was slow with prominent oromotor dyspraxia, truncal ataxia, and poor postural control. At discharge (nine weeks after illness), she had fluent language, independent feeding, stable gait, and a right homonymous hemianopia. At 3 months, she has independence in mobility and activities of daily living (mRS 2) despite a residual homonymous right upper quadrantanopia and mild truncal ataxia. Follow-up MRI scan shows focal cavitation and gliosis in the right cerebellar and cerebral parieto-occipital white matter (Fig 1). Full details are given in Table.

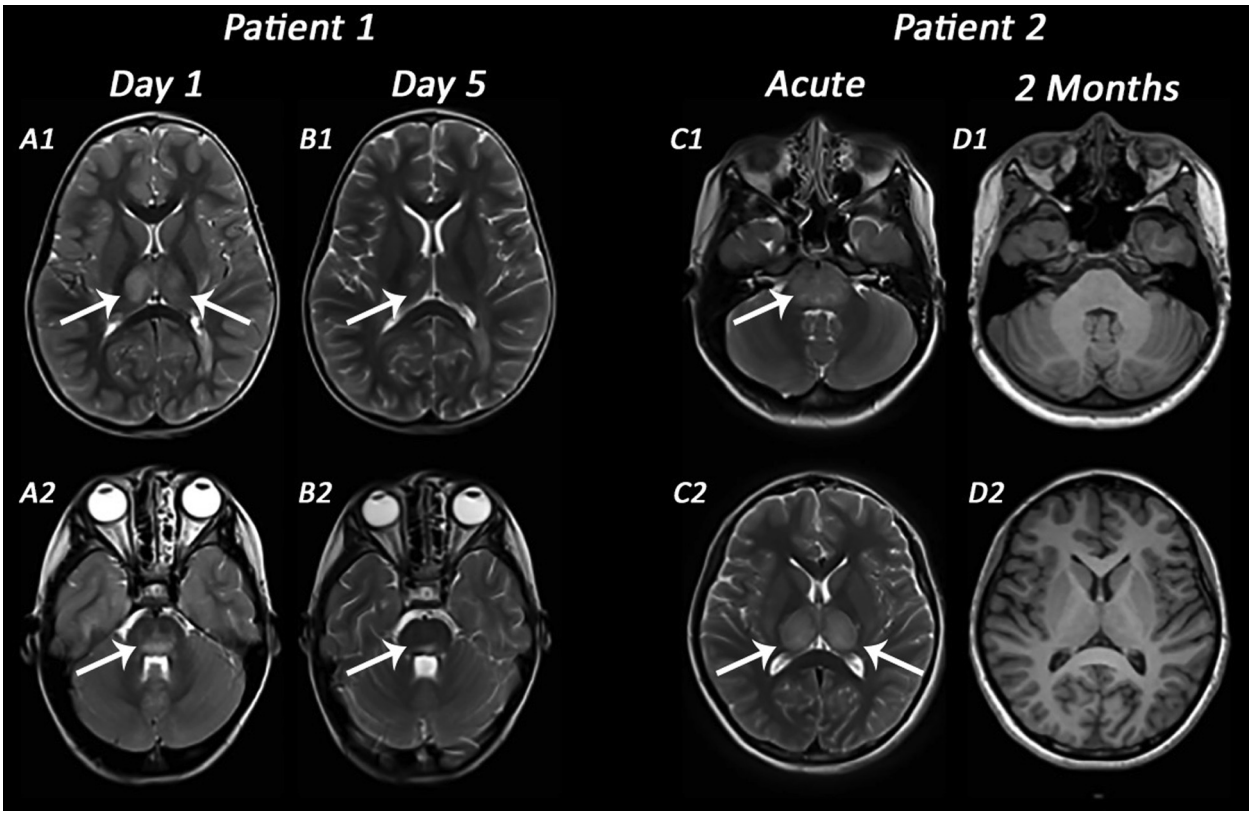

FIGURE 1. Magnetic resonance brain imaging for two patients with good clinical and radiological outcome. Patient 1: A and B, axial T2-weighted images. Hyperintense lesions in the pontine tegmentum and bilateral thalami (A1, A2, white arrows) on day one (16 hours of encephalopathy) with significant improvement in lesions on day five (B1, B2, white arrows). Patient 2: C, axial T2-weighted images and D, axial T1-weighted images. Hyperintense expansile lesions in the pons and bilateral thalami (C1, C2, white arrows) in the acute phase are completely resolved on the follow-up scan at two months after illness (D1, D2).

TABLE.
Clinical, Neuroimaging and Laboratory Features, With Severity Scoring and Outcome in the Three Patients With Severe ANE

Feature	Patient 1	Patient 2	Patient 3
Age	5.1 years	10.3 years	8.0 years
Gender	Female	Male	Female
Ethnicity	East Asian	East Asian	East Asian
Genetic susceptibility: RANBP2 and other genes*	Negative	Negative	Negative
Associated viral infection	Influenza A(H1N1)pdm09	Influenza A(H1N1)pdm09	Influenza B
Neuroimaging, timing from encephalopathy	MRI, at 13 hours	CT (normal), at 3 hours from encephalopathy and MRI at 24 hours	CT (abnormal), at 5 hours of awakening with encephalopathy MRI at 27 hours
Lesion distribution	Bilateral thalami, pontine tegmentum, periventricular white matter, left external capsule	Bilateral thalami, pons and right posterior lentiform nucleus	Bilateral thalami, pontine tegmentum, vermis, external capsules, and bilateral cerebral and cerebellar white matter
MRI Brain—susceptibility artifact (bleeding)	Right thalamus Pontine tegmentum	Bilateral thalami	Large, confluent lesions • Right thalamus • Cerebellar vermis cerebellar white matter • Right parieto-occipital white matter Punctate, disseminated lesions • Pontine tegmentum • Left thalamus • Frontal, temporal, and parietal white matter
CSF analysis	Proteins 0.87 g/L Glucose 3.4 mmol/L Leukocytes 2/mm^3	Proteins 0.57 g/L† Glucose 5.4 mmol/L† Leukocytes 1/mm^3	Proteins 0.72 g/L Glucose 5.4 mmol/L Leukocytes 1/mm^3
Extra neurological involvement	Hemoglobin 12.0 g/dL White blood cells 4230/mm^3 Platelets 195,000/mm^3 Normal plasma lactate, acylcarnitines AST 65 U/L ALT 36 U/L)	Hemoglobin 11.3 g/dL White blood cells 3820/mm^3 Platelets 42,000/mm^3 Normal plasma lactate, acylcarnitines AST 5152 U/L ALT 2899 U/L	Hemoglobin 12.6 g/dL White blood cells 6320/mm^3 Platelets 164,000/mm^3 Normal plasma lactate, acylcarnitines AST 57 U/L ALT 50 U/L
Evaluation for infectious and immune encephalitis	Negative antibody serology,‡ CSF viral studies,§ and sterile blood and CSF cultures	Negative antibody serology,‡ CSF viral studies,§ and sterile blood and CSF cultures	Negative antibody serology,‡ CSF viral studies,§ and sterile blood and CSF cultures
Immunotherapy, timing	IV Methylprednisolone 30 mg/kg, days 1-5 Taper of oral prednisolone over 6 weeks	IV Methylprednisolone 30 mg/kg, days 1-5 Taper of oral prednisolone over 6 weeks	IV Methylprednisolone 30 mg/kg, days 1-5 Taper of oral prednisolone over 3 months IV Immunoglobulins 2 g/kg on day 7 (as a single dose)
Tocilizumab, timing Pretreatment serum interleukin 6, timing	160 mg (12 mg/kg) at 18 hours <2.9 ng/mL, pretreatment	280 mg (8 mg/kg) at 32 hours 394 ng/mL, pretreatment	280 mg (8 mg/kg) at day 20 hours 12.8 ng/mL, 3 hours of treatment 14 ng/mL, 24 hours 9.6 ng/mL, 48 hours
Other treatments	IV Ceftriaxone 1400 mg q24H, 7 days IV Acyclovir 200 mg q8H, 2 days Oral Oseltamivir 30 mg q12H, 5 days	IV Ceftriaxone 200 mg q12H, 6 days IV Acyclovir 570 mg q8H, 2 days Oral Oseltamivir 60 mg q12H, 5 days. Oral Baclofen 5 mg BD	IV Ceftriaxone 1600 mg q12H, 2 days IV Acyclovir 480 mg q8H, 2 days Oral Oseltamivir 60 mg q12H, 5 days. Oral Baclofen 5 mg twice a day Oral L-dopa/carbidopa 30 mg (dopa base) thrice a day
ANE-SS (Yamamoto et al.[3])	ANE-SS 5 High risk	ANE-SS 5 High risk	ANE-SS 5 High risk
Follow-up MRI, timing	5 days, resolving regions without atrophy	2 months, normal study	3 months, focal encephalomalacia in the right cerebellar and parieto-occipital white matter
Outcome (mRS), timing	0, at 1 month follow-up	0, at 2 months follow-up	2, at 3 months follow-up

Abbreviations:
ALT = alanine aminotransferase
ANE = acute necrotizing encephalopathy
ANE-SS = ANE severity score
AST = aspartate aminotransferase
CSF = cerebrospinal fluid
CT = computed tomography
IV = intravenous
MRI = magnetic resonance imaging
mRS = modified Rankin Scale

* Commercial gene panel of 180 epilepsy-related genes including ARX, CDKL5, CHD2, GABRA1, KCNA2, POLG, SCN1A, SCN2A, SCN8A, STXBP1, and STX1B.
† CSF sampled on day 5 of illness as lumbar puncture was deferred because of thrombocytopenia.
‡ Antibodies to neuronal cell surface antigens (NMDAR, CASPR2, LGi1, AMPAR 1 and 2, DPPX, and GABAR) in blood and CSF.
§ Polymerase chain reaction for herpes simplex virus and enterovirus DNA.

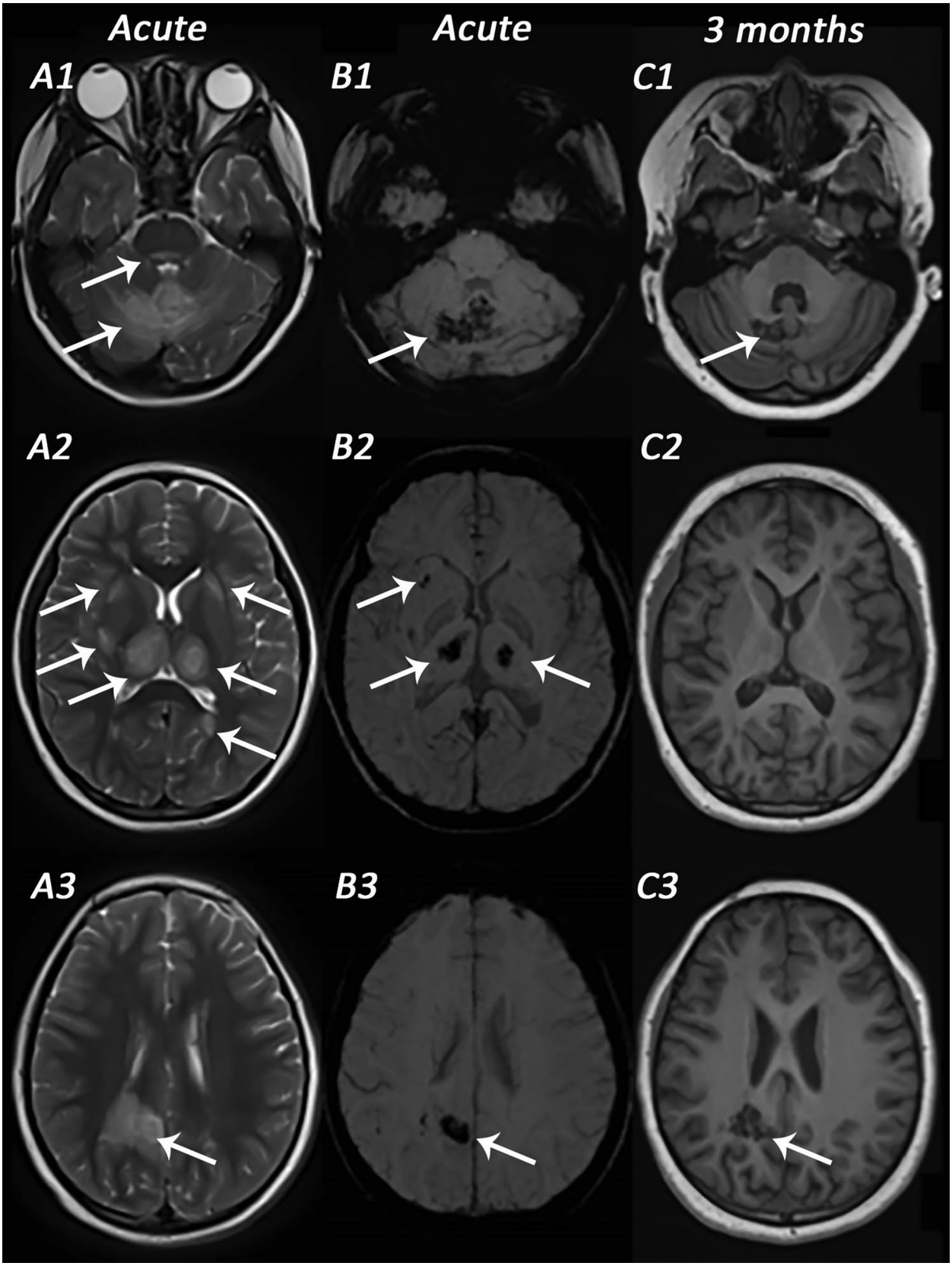

FIGURE 2. Magnetic resonance brain imaging for Patient 3 with a mild disability outcome. A, B images at acute illness: A1-A3, axial T2-weighted images. Hyperintense lesions in the pontine tegmentum, cerebellar white matter and vermis, bilateral thalami, external and internal capsule, and cerebral white matter (white arrows). B1-B3, axial susceptibility weighted images. Blooming artifact indicating hemorrhage in the cerebellar white matter, vermis, bilateral thalami, external capsule, and cerebral white matter (white arrows). Multifocal punctate microhemorrhages were also observed in the cerebral hemispheres bilaterally. C1-C3 images, at three months follow-up. Axial T1-weighted imaging (angle of slices differs slightly from A and B images). Focal encephalomalacia in the right parieto-occipital and cerebellar white matter (white arrows). Both thalami appear normal.

Discussion

We have shown that early IL-6 blockade in severe ANE is safe and may help modify outcomes. Our patients were older (more than four years) and had brainstem lesions, key factors predicting a high risk (88%) for death or severe disability on the ANE severity score.[3] Two patients made an excellent clinical (mRS 0) and radiological recovery and the third who had extensive hemorrhagic lesions recovered with mild disability (mRS 2) despite residual focal encephalomalacia.

As ANE is primarily a cytokine-driven process,[1,5] we looked to an anti–IL-6 treatment strategy as a potential disease modifying therapy. In our patients, tocilizumab was administered early in the illness (18 to 32 hours of encephalopathy) and when serum IL-6 was not significantly increased (less than 2.9 to 394 ng/mL; Table). Serial measurements were only performed in Patient 3, and remained low at 24 and 48 hours after tocilizumab therapy. There are recent reports of IL-6 receptor blockade showing efficacy in the acute stage of new onset refractory status epilepticus[8] and as an adjunctive treatment in refractory autoimmune encephalitis.[6,9] Notably, only a single dose of tocilizumab was required in three patients in our series and seven adults in the new onset refractory status epilepticus series, inferring an alternate effect of IL-6 blockade in early disease from those with chronic encephalitis in whom a clinical response was observed only with repeat doses over a number of weeks.

An anticytokine action is one of the many advantages of therapeutic hypothermia in acute brain injury, and a reduction in serum IL-6 and cytokine levels after therapeutic hypothermia in neonatal hypoxic-ischemic encephalopathy and childhood traumatic brain injury is associated with a good outcome.[10,11] There are small case series and anecdotal reports of benefit from therapeutic hypothermia in combination with immunotherapy (intravenous methylprednisolone or immunoglobulins) in children with ANE and virus associated encephalopathy.[7,12] This anticytokine effect may ameliorate a secondary process of excitotoxic brain injury in virus associated encephalopathy as is observed with therapeutic hypothermia in hypoxic-ischemic encephalopathy. Excitotoxic brain injury is evident in children with acute encephalopathy with biphasic seizures and late restricted diffusion, a more common but equally devastating form of virus associated encephalopathy in which a biphasic clinical course and clinical deterioration ensues from a secondary process of excitotoxic injury.[13]

Brain lesions with hemorrhage on MRI were already present in our patients within 16 to 27 hours of encephalopathy implying that these lesions evolved early in the process of encephalopathy and occur independently of an increase in serum IL-6 (Table). The exact role of IL-6 in brain immune disease and brain injury is unclear. IL-6 performs critical roles in neuronal and glial biology, and regulation of innate and adaptive immunity but has pathologic actions in the induction and maintenance of brain-directed immune disease.[14] it is extremely difficult to establish a myelin oligodendrocyte glycoprotein–induced experimental autoimmune encephalomyelitis disease process, the main experimental murine model of multiple sclerosis, in IL-6 knockout mice.[15] The positive effect of B cell depletion therapy on inflammation in myelin oligodendrocyte glycoprotein–induced experimental autoimmune encephalomyelitis is primarily because of a reduction in pathogenic IL-6 producing B cells.[16]

Genetic mutations for susceptibility to febrile encephalopathy were absent in our three patients, similar to ANE patients of East Asian ancestry who are also typically negative for RANBP2 mutations.[1] Specific human leukocyte antigen alleles DRB1*09:01 and DQB1*03:03 may confer susceptibility to ANE in children of Japanese descent.[17]

Given the short time window for intervention in ANE, treatment protocols should target an urgent diagnostic brain MRI before treatment with intravenous methylprednisolone (30 mg/kg for three to five days) and anticytokine interventions with intravenous tocilizumab (12 mg/kg for children less than 30 kg and 8 mg/kg for children greater than 30 kg) and/or therapeutic hypothermia. Antimicrobials are started empirically and may be discontinued once pathogen studies are negative. We used oral oseltamivir in accordance with Centers for Disease Control and Prevention guidelines for children (30 to 60 mg q12H (weight based) for five days) although the use of neuraminidase inhibitors in influenza infections have only been shown to reduce the length of respiratory symptoms with no effect in limiting brain or lung complications.[18] This approach may be considered in all ANE patients, as risk of severe sequelae and death is significant even in low-risk (27%) and medium-risk (67%) ANE-SSs.[2] Although no treatment side effects were apparent in our patients, hypersensitivity reactions and gastrointestinal perforation can occur with tocilizumab treatment.

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