Clinical Observation

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

Janine Cynthia Koh, MBBS a, Aaron Murugasu b, Janardhan Krishnappa, MBBS a, Terrence Thomas, MD a, *

a Paediatric Neurology Service, KK Women's and Children's Hospital, Singapore
b School of Medicine, Dentistry & Nursing, University of Glasgow, United Kingdom

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.

© 2019 Elsevier Inc. All rights reserved.

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. Despite treatment with corticosteroids or intravenous immunoglobulins, death occurs in 30% and survivors have moderate to severe disability. Cerebral atrophy occurs early in the illness, whereas cavitation and gliosis characterize follow-up neuroimaging. 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. 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. 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...
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). 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 enroute 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.
### TABLE
Clinical, Neuroimaging and Laboratory Features, With Severity Scoring and Outcome in the Three Patients With Severe ANE

<table>
<thead>
<tr>
<th>Feature</th>
<th>Patient 1</th>
<th>Patient 2</th>
<th>Patient 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>5.1 years</td>
<td>10.3 years</td>
<td>8.0 years</td>
</tr>
<tr>
<td>Gender</td>
<td>Female</td>
<td>Male</td>
<td>Female</td>
</tr>
<tr>
<td>Ethnicity</td>
<td>East Asian</td>
<td>East Asian</td>
<td>East Asian</td>
</tr>
<tr>
<td>Genetic susceptibility: RANBP2 and other genes</td>
<td>Negative</td>
<td>Negative</td>
<td>Negative</td>
</tr>
</tbody>
</table>

**Associated viral infection**
- Influenza A/H1N1/pdm09
- Influenza A/H1N1/pdm09
- Influenza B

**Neuromaging, timing from encephalopathy**
- MRI, at 13 hours
- CT (normal), at 3 hours from encephalopathy and MRI at 24 hours
- 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**
- Right thalamus
- Pontine tegmentum
- Bilateral thalamus

**Lesion distribution**
- Bilateral thalami
- Large, confluent lesions

**CSF analysis**
- Proteins 0.87 g/L
- Glucose 3.4 mmol/L
- Leukocytes 2/mm³
- Proteins 0.57 g/L
- Glucose 5.4 mmol/L
- Leukocytes 1/mm³
- Proteins 0.72 g/L
- Glucose 5.4 mmol/L
- Leukocytes 1/mm³

**Extra neurological involvement**
- Hemoglobin 12.0 g/dL
- White blood cells 4230/mm³
- Normal plasma lactate, acylcarnitines AST 65 U/L, ALT 36 U/L
- Hemoglobin 11.3 g/dL
- White blood cells 3820/mm³
- Normal plasma lactate, acylcarnitines AST 5152 U/L, ALT 2899 U/L
- Hemoglobin 12.6 g/dL
- White blood cells 6320/mm³
- 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 Immunglobulins 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<br>&lt;2.9 ng/mL, pretreatment
- 280 mg (8 mg/kg) at 32 hours<br>394 ng/mL, pretreatment
- 280 mg (8 mg/kg) at day 20 hours<br>12.8 ng/mL, 3 hours of treatment
- 280 mg (8 mg/kg) at day 20 hours<br>12.8 ng/mL, 24 hours
- 9.6 ng/mL, 48 hours
- 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
- Oral Ceftriaxone 1600 mg q12H, 2 days
- Oral 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.**)
- 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
- 2 at 3 months follow-up

**Outcome (mRS), timing**
- 0, at 1 month follow-up
- 0, at 2 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
- ANE-SS 5 – total score 5, High risk

1. Commercial gene panel of 180 epilepsy-related genes including ARX, CDKL5, CHD2, GABRA1, KCN2, POLG, SCN1A, SCN2A, SCN8A, STXB1P1, and STX1B.
2. CSF sampled on day 5 of illness as lumbar puncture was deferred because of thrombocytopenia.
3. Antibodies to neuronal cell surface antigens (NMDAR, CASPR2, LGI1, AMPAR 1 and 2, DPX, and GABAR) in blood and CSF.
4. 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. 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, 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 and as an adjunctive treatment in refractory autoimmune encephalitis. 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. 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. 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.

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. 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. 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. 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. Specific human leukocyte antigen alleles DRB1*09:01 and DQB1*03:03 may confer susceptibility to ANE in children of Japanese descent.

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.

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. Although no treatment side effects were apparent in our patients, hypersensitivity reactions and gastrointestinal perforation can occur with tocilizumab treatment.

Acknowledgments

We are grateful to the patient’s parents who kindly agreed for their children’s clinical details to be published.

References