

TEACHING FILES (GRAND ROUNDS)

ACUTE ENCEPHALOPATHY: WHAT TO SUSPECT AND HOW TO PREVENT?

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Clinical Problem:

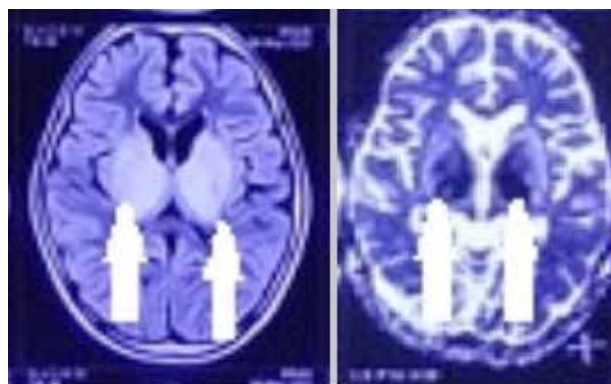
A 9-year-old girl presented with convulsions followed by unconsciousness. She had fever and cough for one week. On examination, Glasgow coma score (GCS) was 8/15. There were no meningeal signs or focal weakness. Fundus examination was normal. Other systemic examination was normal. Investigations showed hemoglobin 11 g/dl, total leucocyte count 4200/cumm with 52% polymorphs and 39% lymphocytes, serum bilirubin 0.5 mg/dL with normal transaminases and INR of 1.9. Arterial blood gas showed pH of 7.38 and bicarbonate 23 mEq/L. Lumbar puncture showed clear cerebrospinal fluid (CSF) with normal pressure, 71.4 mg/dL glucose, 16.2 mg/dL protein, 4 cells/cumm (mostly polymorphs and few degenerated cells) and no bacteria. Nasopharyngeal swab was negative for Covid-19 RT-PCR. Blood and CSF was negative for Japanese Encephalitis IgM. Testing for influenza virus was unavailable at our centre. MRI brain showed symmetrical hyper-intense signal intensity on T2W/FLAIR, restricted diffusion on DWI and signal drop (apparent diffusion coefficient) involving bilateral ganglio-thalamic complexes, brain stem and cerebral peduncles (Figure 1). Injection ceftriaxone (100 mg/kg/day in 2 divided doses), vancomycin (60 mg/kg/day in 4 divided doses) and acyclovir (45 mg/kg/day in 3 divided doses) were started intravenously (IV). Oseltamivir was unavailable. Convulsions were controlled with levetiracetam (40 mg/kg/day in 2 divided doses). Intravenous Immunoglobulin (IVIG) (30 mg/kg/day for 3 days) followed by oral prednisolone (2 mg/kg/day in 2 divided doses) were also given. On 3rd day, patient showed improved sensorium and no further convulsions. On follow-up at three months, distal athetoid movements remained but repeat MRI brain showed resolution.

What is the diagnosis?

Discussion:

Acute necrotizing encephalopathy of childhood (ANEC). Mizuguchi et al described ANEC in Japan in 1995.¹ Most cases are from East Asia but not limited to any particular race.² ANEC follows infection with

Figure 1. MRI brain shows thalamic hyperintensity on T2W and restricted diffusion in bilateral thalamus on DWI.



influenza, Herpes Simplex Virus, Human Herpes Virus-6, Parainfluenza virus, Varicella Zoster Virus, reovirus, rotavirus, enterovirus, measles, coxsackie-A9 and mycoplasma.³ ANEC occurs within days of fever and presents with convulsions and coma.¹ Acute manifestations are febrile seizures, movement disorder, frontal lobe encephalopathy and multiorgan failure.^{2,3} Subacute manifestations are Guillain-Barre syndrome, transverse myelitis, acute disseminated encephalomyelitis, cerebellitis and myositis. Late manifestations are parkinsonism and encephalitis lethargica.³ Patients of 2009 H1N1 influenza pandemic showed heightened neurological complications and ANEC compared to 2004–2008 seasonal influenza.³ Cytokine storm following viral infection leads to systemic immune response causing multiorgan injury, brain cell apoptosis and cerebral edema from disruption of blood-brain barrier in ANEC.^{2,3} RANBP2 genetic polymorphism is associated with recurrent episodes of ANEC with viral respiratory infections.⁴ Central necrosis, surrounding cytotoxic oedema and peripheral vasogenic oedema forms pathological basis for MRI appearance.³ T1W show hypointense lesions, T2W/FLAIR display corresponding mixed hyperintense signals with restricted diffusion on DWI and circular enhancement on contrast MRI.² Normal CSF and characteristic bilateral thalamic involvement with diffusion restriction help in making diagnosis.⁵ Acute disseminated encephalomyelitis, neurovascular accidents, Reye's syndrome, mitochondrial dysfunction and fulminant hepatitis are other differentials.^{3,6} Outcomes range

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from full recovery (<10%), neurologic sequelae in survivors to fulminant progression in majority.³ Li et al observed positive correlation between MRI findings and clinical outcome.² Observation of hemorrhage and local tissue loss on MRI predicts a poor prognosis.² Selective vulnerability of thalami seems to be determining factor.⁶ Antivirals, immunoglobulin, plasmapheresis, antithrombin-III, and therapeutic hypothermia has been tried.³ High dose steroids used in earlier stages determines the prognosis.⁶ Follow-up imaging shows regression of lesions with residual cortical atrophy, cystic changes and haemosiderin deposition. Functional recovery following rehabilitation has been reported.³ Given the potential for ANEC recurrence, monitoring of children with history of neurological complications following respiratory illness is indicated during influenza season with prompt testing and antiviral therapy.⁴ Annual influenza vaccination is important for ANEC survivors and their household contacts.⁴

Compliance with ethical standards

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Conflict of Interest: None

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