A Rare Cause of Acute Febrile Encephalopathy in a Four Year Old Boy–A Case Report with Review of Literature

A 4-year-old developmentally normal boy was brought with complaints of fever and vomiting of one day, with an onset of slurring of speech and facial asymmetry two hours before admission. There was no headache, altered sensorium, seizures, or weakness of limbs. There was no antecedent upper respiratory symptom or history of recent vaccination. There were no similar episodes in the past or significant family history. He had one episode of left focal seizure at admission and progressive deterioration of sensorium after that. Examination revealed normal vital signs with left upper motor neuron type of facial palsy, left hemiparesis, and signs of meningeal irritation. Fundus examination did not reveal any papilledema. A provisional diagnosis of acute meningoencephalitis was made and was started on empirical antibiotics, antiviral, antiedema, and antiepileptic medications. The complete blood count and blood biochemistry, including transaminases, were within normal limits. The cerebrospinal fluid (CSF) was acellular with mildly elevated protein (79 mg/dL) glucose (63 mg/dL, blood glucose- 96 mg/dL). A contrast-enhanced computed tomography (CECT) of the brain showed a right frontal hypodense lesion with no ring enhancement, suggestive of focal central nervous system (CNS) infection and possibly early cerebritis of brain abscess.

During the hospital stay, his sensorium worsened further, warranting mechanical ventilation. Magnetic Resonance Imaging (MRI) of the brain revealed a hyper-intense lesion in the right frontal and left parietal region, with foci of punctate hemorrhages [Figure 1], which was suggestive of acute hemorrhagic leukoencephalitis (AHLE). Since the possibility of infection was deemed less likely, he was pulsed with methylprednisolone for five days, followed by intravenous immunoglobulin (IVIG) (2 g/kg), as there was no improvement. After that, his condition remained static in terms of general well-being. The brain biopsy depicted acute hemorrhage and inflammatory infiltrates, confirming AHLE [Figure 2]. A detailed etiological workup for AHLE, including viral, bacterial, tubercular, and fungal organisms, was tested negative in appropriate CSF, blood, and nasopharyngeal specimens [Table 1]. Both CSF and serum tested negative for myelin oligodendrocyte glycoprotein (MOG) antibodies. Antinuclear antibodies were also tested negative. Hence, he was diagnosed with idiopathic AHLE.

Later in the course, he had severe neurological sequelae in the form of aphasia, dyskinetic movements, spastic quadriparesis, contractures, and autonomic instability. The child was managed with a multi-disciplinary approach with physiotherapy, nutritional rehabilitation, and occupational therapy. He was discharged on tube feeds after 75 days of hospital stay. On follow-up, his neurological status did not show any worsening, and there was a subtle improvement in non-verbal communication and spasticity. However, the lost milestones showed no trend towards improvement. The follow-up neuroimaging done six months after the second imaging depicted ill-defined FLAIR (fluid-attenuated inversion recovery) hyperintensity areas in bilateral cerebral hemispheres with associated volume loss in the right cerebral hemisphere—features suggestive of gliotic sequelae to the previous insult. In addition, multiple blooming foci were noted in susceptibility-weighted imaging (SWI) in the right frontoparietal region, suggestive of hemosiderin deposits due to the previous hemorrhage.

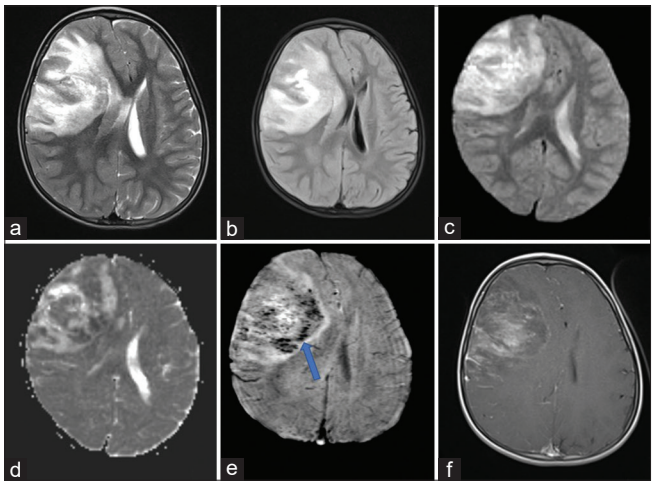

Figure 1: (a) Plain MRI T2 axial and (b) T2 FLAIR image showing hyperintensity in the right frontoparietal area with surrounding edema causing mass effect and midline shift with sub-falcine herniation; (c) and (d) Diffusion-weighted image showing high signal intensities in the right frontoparietal area with low ADC values suggestive of diffusion restriction; (e) susceptibility-weighted image (SWI) shows the area of blooming foci (blue arrow) suggestive of microhemorrhages; (f) Post-contrast T1 axial image showing moderate and heterogenous enhancement in the hyperintense area seen in T2 and FLAIR images

In children, acute febrile encephalopathy (AFE) encompasses both infectious and noninfectious causes of fever with altered sensorium with or without seizures. CNS infections, notably viral encephalitis, are the most common cause of acute febrile encephalopathy among children in India.[1] An etiology for AFE is not known in 40% of cases.[1] AHLE is a fulminant presentation of AFE, characterized by demyelination, focal neurological deficits, rapid progression, irreversible sequelae, or death.[2]

AHLE represents the severe form of acute disseminated encephalomyelitis (ADEM). AHLE, also called hyperacute ADEM, is more common in adults, whereas ADEM is more

Table 1: Investigations of the index case

Organism/Disease	Sample and method	Result
Streptococcus pneumonia	CSF PCR	Negative
Neisseria meningitidis	CSF PCR	Negative
Hemophilus species.	CSF PCR	Negative
Mycobacterium tuberculosis	CSF CBNAAT, BAL CBNAAT	Negative
Burkholderia pseudomallei	CSF and Blood culture	Negative
Herpes Simplex Virus	CSF and Blood PCR	Negative
Cytomegalovirus	CSF PCR	Negative
Ebstein-bar virus	CSF PCR	Negative
Cryptococcus	CSF PCR	Negative
Enterovirus	CSF PCR	Negative
Adenovirus	CSF, Nasopharyngeal swab	Negative
Respiratory syncytial virus	CSF, Nasopharyngeal swab	Negative
Human metapneumovirus	CSF, Nasopharyngeal swab	Negative
Coronavirus including SARS-CoV2	CSF, Nasopharyngeal swab, Serum antibodies	Negative
Acanthamoeba	CSF wet mount microscopy	Negative
Naegleria fowleri	CSF wet mount microscopy	Negative
Balamuthia mandralaris	CSF wet mount microscopy	Negative
Toxoplasma gondii	CSF PCR	Negative
Plasmodium species	CSF PCR	Negative
Scrub typhus	Serum and CSF PCR	Negative
Mycoplasma	Serum IgM ELISA	Negative
	Blood culture	Sterile
	CSF culture	Sterile
	Fungal culture	Sterile
	Urine culture	Sterile

CSF-Cerebrospinal fluid, BAL-Bronchoalveolar lavage, CBNAAT- cartridge-based nucleic acid amplification test, PCR- polymerase chain reaction

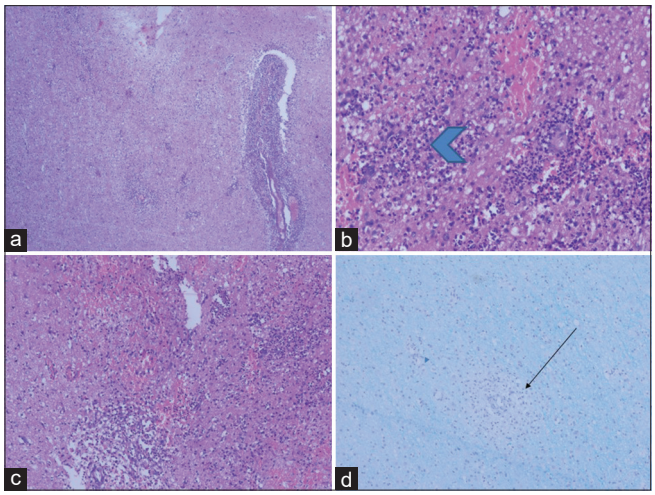

Figure 2: (a) Sections from the brain biopsy show multifocal dense perivascular inflammatory infiltrate in white matter (H&EX40): (b) high power reveals predominantly lymphocytes around blood vessels (H&EX200): (c) areas of hemorrhage (arrowhead) in between inflammatory foci (H&EX100): (d) Luxol fast blue stain show perivascular loss of myelin (line arrow) indicates demyelination (LFBX100)

common in children. The first pediatric AHLE was reported in 1945 by Shallard and Latham.[3] The characteristic features are acute onset, rapid neurological deterioration, multifocal brain lesions with necrosis, and hemorrhage. The pathogenesis of AHLE is believed to be autoimmune in nature following infectious triggers. However, half of the cases do not have a predisposing infection or vaccination, as with our index case. Infectious agents include HSV, EBV, Influenza A, JE, measles, mumps viruses, as well as mycoplasma and Plasmodium species.[4] Rosman *et al*.[5] reviewed nine cases of pediatric AHLE in 1997, where all of them had preceding infections before the onset of neurological symptoms.

The clinical presentation includes seizure, hemiparesis, cranial nerve palsies, aphasia, headache, and vomiting, of which the predominant symptoms were aphasia and hemiparesis in the reported pediatric patients.[5] Diagnosis is usually made by clinical, radiological, and histopathological means. The common mimics of AHLE include acute meningoencephalitis/pyogenic meningitis, brain abscess, intracerebral hemorrhage, CNS vasculitis, and MOG encephalitis. Kabakus *et al*.[6] reported a 3-year-old boy with acute hemorrhagic leukoencephalitis, manifesting as intracerebral hemorrhage, associated with herpes simplex virus type 1. In our case, the initial differentials were neuro-infection, MOG encephalitis, and CNS vasculitis, but CSF findings, negative autoimmune serology, and MRI evidence were pointers against the same, respectively.

Radiological diagnosis of AHLE by MRI brain is the gold standard and is characterized by large tumefactive lesions involving the white matter and sparing the cortex, associated punctate hemorrhages and extensive mass effect and surrounding edema, possibly involving of ganglia and thalami. Detection of cerebral microhemorrhages by gradient recalled echo (GRE) or the more sensitive susceptibility-weighted images (SWI) is an important finding.[7] Similar findings were observed in our case. The presence of punctate hemorrhages and sparing of subcortical U-fibres helps in differentiating it from ADEM. The histopathology is depicted by edema, congestion, punctate hemorrhages macroscopically, and hemorrhages around the necrotic venules resembling ring and ball, white matter ischemic changes adjacent necrotic postcapillary venules and hemorrhage more prominent than demyelination, as observed in our case.[8]

Treatment includes early diagnosis, aggressive supportive measures, such as managing cerebral edema, and immunomodulatory therapy like corticosteroids, IVIg, and plasmapheresis.[2] The cases that were not treated with immunosuppression succumbed within days of onset neurological symptoms, whereas the first survivor of pediatric AHLE was following pulsed steroids.[5] Panchal *et al*.[9] reported an 8-year-old boy with AHLE who responded dramatically to IVIg following plasmapheresis. Our case was pulsed with a course of steroids and IVIg, and repeat neuroimaging revealed a mild improvement in the lesion. A brief review of the pediatric AHLE cases, with their neuroimaging and outcome, is summarized in [Table 2].

Table 2: A brief review of literature of pediatric AHLE cases

Authors/Year of publication/Place	Age of presentation/ Gender	Clinical features/ Etiology (if any)	Neuroimaging	Treatment	Outcome
Shallard B, Latham O/1945/Australia	5 years/F	Siblings had measles Viral prodrome Right hemiparesis	Not available	Not specified	Death
Crawford T/1954/ London	2 years/M	Cough, vomiting, fever, focal seizures and left hemiplegia Pyramidal signs	Not available	Not specified	Death
Byers RK/1975/ USA	2 years/F	Viral prodrome, 3 weeks later-lethargy, seizures, coma	Not available	Not specified	Death
	15 years/M	Viral prodrome, 10 days later-lethargy, focal seizures, meningismus, coma	Not available	Not specified	Death
	15 years/F	Viral prodrome, 3 weeks later-headache, dysarthria, right hemiparesis, meningismus	Cerebral edema on CT	Steroids	Recovered
Rosman NP/1997/ USA	6 years/F	H/o rubella exposure Rash, diplopia, raised ICP features with rapid worsening Serum rubella titers high	MRI 1: numerous bilateral non-enhancing white-matter lesions in the right centrum semiovale, both cerebral peduncles, the tectum, internal capsules and Putamina MRI 2: the lesions in the brain stem and basal ganglia resolved completely, with lesions persistent in the right centrum semiovale	Dexamethasone, Prednisolone Isoniazid, Rifampicin (presumed TB)	Recovered and ambulatory
Takeda H/2002/ Japan	15 years/F	Viral prodrome Meningeal signs, fever Later right hemiparesis	MRI: diffuse high intensity signals in bilateral white matter with hemorrhages in various stages	High dose steroids and plasmapheresis	Death
Leake JA *et al.*/2002/USA	10 years/F	Fever, vomiting, headache, lethargy Hemiparesis Raised ICP requiring right decompressive hemicraniectomy Brain biopsy-Perivascular hemorrhagic necrosis with subacute inflammation in the subcortical white matter	MRI: extensive deep and subcortical white-matter changes in the right hemisphere and posterior left hemisphere	Anti-tubercular therapy, Acyclovir, Dexamethasone, IVIG	Discharged with residual weakness
Mader *et al.*/2004/ Germany	10 years/M	Upper respiratory infection followed by Recurrent vomiting, dystonia poor sensorium requiring mechanical ventilation Serum antibodies to H3N2 positive BAL positive for HHV6 PCR ; CSF negative for both organisms	MRI: Hyperintensities with hemorrhages on T2-images in thalami, right basal ganglia, left midbrain	Steroids, IVIG, Plasmapheresis	Recovered over 2 years but with sequelae of spasticity
Lann MA/2010/ USA	11 years/M	Gastroenteritis Followed by headache, dizziness, inability to walk, progressive worsening of sensorium	MRI: asymmetric, hyperintense T2-weighted lesions better visualized with FLAIR	High-dose corticosteroids	Death
Borlot *et al.*/2011/ Brazil	2 years/F	Irritability, difficulty walking, ataxia Improved initially after initial immunosuppression After 2 months, had recurrence with progressive refractory status epilepticus	First MRI: hyperintense FLAIR/T2 lesions in cerebellar white matter and also in central, periventricular and juxtacortical white matter Second MRI:	Methylprednisolone f/b oral prednisolone IVIG,	Death

Contd...

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Authors/Year of publication/Place	Age of presentation/ Gender	Clinical features/ Etiology (if any)	Neuroimaging	Treatment	Outcome
		Required intubation with midazolam and thiopental infusion Succumbed to nosocomial pneumonia	Additionally showed hemorrhagic lesions in the corpus callosum and right centrum semiovale		
Khair AM *et al*/2015/Qatar	2.5 years/F	Fever and flu like symptoms, GTCS, Respiratory swab positive for H1N1 PCR using direct florescent assay	MRI: Micro-hemorrhages in thalamic, hippocampi, cerebellar hemispheres, pons, cortex	Methylprednisolone, plasma exchange, IVIG, therapeutic hypothermia	Recovered. ambulatory, seizure-free
Chellathurai A *et al*./2015/ Chennai	5 years/M	Fever, coryza and cough Seizures, headache, irritability CSF positive for Japanese encephalitis	MRI: asymmetric bilateral periventricular white matter T2/FLAIR hyperintensity particularly occipital lobes and cerebellar hemispheres with relative sparing of cerebral cortex with few hemorrhagic areas	Steroids (not specified)	Death
Kumar S *et al*/2015/ New Delhi	11 years/M	Fever, headache, vomiting Serum ELISA IgM positive antibodies to M. pneumoniae and positive M. pneumoniae gelatin particle agglutination test; CSF Mycoplasma PCR negative	MRI: hemorrhagic encephalitis – findings not specified	Immunosuppression not specified	Recovered
Khademi GR *et al*./2016/Iran	13 years/F	Right parotitis, fever and loss of consciousness Rapid worsening with decerebration	MRI 1: multifocal hemorrhages without edema in the right temporal white matter MRI 2 (20 days later) multiple hemorrhagic lesions in B/L pons and thalamus	Methylprednisolone, IVIG, acyclovir, plasmapheresis	Recovered
Waak M *et al*./2019/ Australia	15 years/M	Fever, headache, vomiting, right homonymous hemianopia Rapid worsening with raised ICP Mycoplasma IgM serology positive; PCR positive in pharyngeal aspirate and negative in CSF.	MRI: Focal left parieto-occipital lesion with mass effect, multiple hypodensities compatible with hemorrhages, associated with the white matter lesion	Dexamethasone, methylprednisolone	Death
	14 years/M	Fever, headache, myalgia Later neurological worsening with encephalopathy	MRI: extensive supratentorial, multifocal, symmetric white matter changes (bilateral thalamic, upper midbrain), restricted diffusion, and elevated lactate - hemorrhages on repeat MRI	IVIG, Methylprednisolone, Plasma Exchange cyclophosphamide, oral steroids	Recovered Near normal functions by week 10
Wellnitz K *et al*./2021/USA	14 years/M	Headache 3 weeks after 9-valent HPV vaccine Left hemiparesis, encephalopathy, incontinence Rapid worsening with severe cerebral edema Biopsy consistent with AHLE	MRI: diffuse hyperintensities on T2 and FLAIR sequences within the subcortical white matter, thalamus, and basal ganglia	Methylprednisolone, IVIG	Death
Sharma R *et al*./2022/ Chandigarh	8 years/F	Fever, headache, left focal seizures, encephalopathy Nasopharyngeal swab RT-PCR was positive for SARS-CoV-2	MRI: multifocal discrete coalescing lesions involving cerebral white matter and deep gray matter with diffusion restriction and interspersed microhemorrhages suggestive of AHLE	Immunosuppression not specified	Death

AHLE is rare in children, and hence any case of acute febrile encephalopathy, worsening within a matter of days, should prompt the treating pediatrician to evaluate for AHLE by MRI brain, which can pick up subtle findings, for the early start of treatment. Biopsy of the lesion is essential for confirmation of diagnosis due to the possibility of masqueraders with a similar picture.

Author contributions

KS, VS, and ACC managed the patient, reviewed the literature, and drafted the manuscript. VC, NP, and DG managed the patient, reviewed the manuscript, and critically revised the manuscript. BHS interpreted the histopathological image of the biopsy. All authors contributed to reviewing the literature, drafting the manuscript, and approving the final version of the manuscript. DG shall act as the guarantor of the paper.

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Conflicts of interest

There are no conflicts of interest.

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