GOVERNMENT OF KERALA

Abstract

Health & Family Welfare Department - Technical Guidelines with regard to Management of Influenza Associated Encephalitis (IAE) - Orders issued.

HEALTH & FAMILY WELFARE (F) DEPARTMENT

G.O.(Rt)No.1653/2023/H&FWD Dated,Thiruvananthapuram, 10-07-2023

Read:- Letter No.DHS/12469/2023-PH1 dated 30.06.2023 from the Director of Health Services

ORDER

Influenza Associated Encephalitis [IAE] is a rare complication of influenza with high mortality rate. Influenza virus is endemic in Kerala and has been circulating in the state along with COVID 19 for the last 6 months. There has been a recent rise in H1N1 cases in the state.

In the above context, Government are pleased to issue the "*Technical Guidelines with regard to Management of Influenza Associated Encephalitis (IAE)"* incorporating the background, AES evaluation, AES treatment and practical approach to Encephalitis in the current scenario, as annexed to this order.

(By order of the Governor)
A P M MOHAMMED HANISH
PRINCIPAL SECRETARY

To:
The State Mission Director - National Health Mission, Thiruvananthapuram.
The Director of Health Services, Thiruvananthapuram.
The Director of Medical Education, Thiruvananthapuram.
The Director, Public Health Lab, Thiruvananthapuram.
All District Medical Officers.
Principal Accountant General (A&E/Audit) Kerala, Thiruvananthapuram.

Information & Public Relations (Web & New Media) Department.
Stock File/ Office Copy (to file F2/213/2023-HEALTH) .

Forwarded /By order

Signed by
Vilasini K V
Date: 10-07-2023 14:25:43

Section Officer

ANNEXURE

TECHNICAL GUIDELINES WITH REGARD TO MANAGEMENT OF INFLUENZA ASSOCIATED ENCEPHALITIS [IAE]

BACKGROUND

Influenza associated encephalitis [IAE] is a rare complication of influenza with high mortality rate. Most cases of IAE are due to Influenza A[H1N1, H3N2] infection where as Influenza B is responsible for 10 % of cases. A study on severe influenza-associated neurological disease [IAND] in Australian children [2008-2018] by Erin Donnelly et al showed that the annual incidence of IAND was 3.39 per million children ≤ 14 years. National surveillance data from Japan [2010-2015] indicate that the mean seasonal incidence of influenza-associated encephalopathy in Japanese children < 18 years was 2.83 per million.

Although the pathogenesis of IAE is not fully understood, the cytokine storm hypothesis is one of the postulated mechanisms which is widely accepted.According to this, influenza virus in certain individuals induces a dysregulated inflammatory response leading to increase in pro-inflammatory cytokines which crosses the blood-brain barrier and lead to encephalitis. In many case reports, in IAE time from onset of neurological symptoms to death was within 48 hours.The CSF profile of most patients with IAE lack significant abnormalities and only a small percentage of patients showed elevated protein and lymphocytes which shows that lack of CSF changes does not rule out IAE or other influenza associated neurological complications. Treatment options for IAE include oseltamivir and immunomodulatory strategies like high-dose corticosteroids, intravenous immunoglobulins and plasma exchange. None of these therapeutic modalities are supported by strong clinical evidence. In literature, role of steroid pulse therapy and immunoglobulin is still controversial. However, they are frequently used in IAE because an immune-mediated mechanism may be a major pathogenetic component All children with acute neurological symptoms during the influenza season should be evaluated for influenza-associated neurological complications, including IAE.

When suspected encephalitis occurs with influenza, CSF pleocytosis is often absent and the virus is typically not detected in the CSF, even with molecular assays (with the notable exception of a 1998 study from Japan, where virus was detected in 5 of 7 cases). Lack of CSF pleocytosis suggests that nervous system injury may be related to inflammatory or immune-mediated response.

Possible explanations for failure to detect virus in the CSF in a given case are that

1) The neurologic manifestations are due to encephalopathy rather than encephalitis.

2) The virus has already cleared in the CSF by the time encephalitis becomes apparent.

3) The encephalitis is an autoimmune, rather than an infectious, process.

In acute necrotizing encephalitis CSF protein is high in the absence of CSF pleocytosis. Pre-mortem diagnosis requires magnetic resonance imaging (MRI). Bilateral symmetrical hyperintensities on T2 weighted MRI images typically involving the thalami but often with extensive involvement of other parts of the brain and even on occasion the spinal cord. Management remains controversial, but immune-modulatory agents are given.

GLOBAL SCENARIO

European Centre for Disease Prevention and Control (ECDC) in its weekly communicable disease update in March 2023 stated thatSwedish health officials are investigating a cluster of severe influenza B infections in children and adolescents, some of whom had complications, including myocarditis and meningoencephalitis.In similar lines, there are multiple reports of influenza associated encephalitis[IAE] from across the world in 2022 and 2023.There are reports of children developing seizures and progressing to coma in a relatively short period and eventually succumbing to death due to brainstem involvement [Shi-Guang-Li et al] in IAE. In a recently published study from China [Ruimu Zhang et al], on influenza associated neurologic complications [INC] in children from an H3N2 outbreak in Shenzhen, China, 97 [19%] out of 513 children with H3N2 developed INC of which 18 [4%] developed IAE.Three developed acute necrotizing encephalitis of which two expired. Both deaths occurred within 72 hours of onset of fever. In that study, patients with encephalopathy/encephalitis had a higher rate of elevated alanine aminotransferase (28% vs 3% ,=0.005). It was noted that H3N2-related neurologic complications in children mainly occur early in the disease course and most patients are previously healthy.

KERALA SCENARIO

A study by Sankar Hariharan et al on the clinical characteristics of neurological manifestations in influenza-A [H1N1] in SAT hospital Thiruvananthapuram during 2019 was published in Indian Journal of Child Health. The study analyzed the clinical features of 16 patients with INC including children with developmental delay and other comorbidities which constituted 50% of the patients. The conclusions from the study were thatneurological manifestations can occur in influenza A (HINI) and the symptoms develop in majority during the first 5 days of illness. The most common symptom in this cohort was altered sensorium. Intensive care for multi-organ dysfunction is required in most cases and the cause-specific mortality is 18.75%.

Influenza virus is endemic in Kerala and has been circulating in the state along with COVID 19 for the last 6 months. Reports of sporadic IAE and influenza associated necrotizing encephalitis in children have been reported from the state over last 6 months. There has been a recent surge in IAE in the State over last 3 weeks which is apparently more than the background rate. Majority of cases of IAE developed rapidly within 24 - 48 hr of symptom onset requiring pediatric intensive care support. There has been report of at least 4 cases of acute encephalitis which progressed to brain stem herniation within 12 hours of first seizure. Few of these children also had transaminitis.

CSF viral panel was negative in all these cases, while Influence A PCR was positive in nasopharyngeal swab of two fatal cases of encephalitis. In the background of catastrophic progression with negative CSF viral panel, an immunological insult causing severe brain edema also needs to be considered.

Surge of Autoimmune Encephalitis during COVID 19 Era

There are many published reports with regard to surge in autoimmune encephalitis during COVID 19 era. Autoimmune encephalitis is rare; the incidence rate from 2006 to 2015 was estimated to be 1.2 cases per 100,000 people. The prevalence of specific neural autoantibodies is as follows: myelin oligodendrocyte glycoprotein (MOG), 1.9/100,000; glutamic acid decarboxylase (GAD), 1.9/100,000; unclassified neural autoantibody, 1.4/100,000; leucine-rich glioma inactivated 1 (LGI1), 0.7/100,000; collapsin response mediator protein 5, 0.7/100,000; N-methyl-D-aspartate (NMDA) receptor, 0.6/100,000; antineuronal nuclear antibody type 2, 0.6/100,000; and glial fibrillary acidic protein α, 0.6/100,000. Voltage-gated potassium channel (VGKC) antibody incidence is not well established. In a case series highlighting the sharp rise in autoimmune encephalitis in COVID 19 era by Saffari et al , majority of patients with autoimmune encephalitis were mostly positive for glutamic acid decarboxylase (GAD) and/or voltage-gated potassium channel (VGKC) antibodies. In other study by Adina Stoian et al which is a systematic review on available literature on autoimmune encephalitis in COVID 19, the implicated auto-antibodies were anti NMDARantibodies [42.85%], anti-MOG antibodies [19.04%], anti-amphiphysin antibodies [9.5%] and one case with contactin-associated protein [Caspr2] anti-bodies.

More research is needed to determine if COVID-19 infection and/or vaccination cause cytokine production of varying degrees that result in a heightened inflammatory and immune response; this heightened response may be a “catalyst” to many other neuropathological processes by activating autoimmunity. Molecular mimicry is another postulated mechanism. This idea is in line with growing data on the enhanced immune response in the pathophysiology of neurological disorders after COVID-19 .

Probable mechanism postulated to explain the apparent surge in IAE in Kerala over last 3 weeks

Almost all patients with IAE in Kerala during the current outbreak had high titres of SARS-CoV-2 IgG antibodies. Chance of patients primed with SARS-CoV-2 mounting a dysregulated immune response to a new viral trigger in the form of influenza has to be considered. Rapid neurological deterioration from symptom onset points to an inflammatory/autoimmune etiology rather than increased neurovirulence of the virus.

ROLE FOR EARLY ADMINISTRATION OF IMMUNOMODULATORS IN IAE

The mortality due to IAE in literature varies from 4% to 30%. In a study on IAE from Taiwan [Li-Wen Chen et al] from 2014-2017 involving 10 cases of IAE, the neurological symptoms developed rapidly within median 1 day after the first fever episode. All patients had altered consciousness. Seven patients (70%) had seizures at initial presentation, and six of them had status epilepticus. Anti-viral treatments were given in all patients, with median door-to-drug time 0.9 h for oseltamivir and 6.0 h for peramivir. Multi-modality treatments also included steroid pulse therapy, immunoglobulin treatment, and target temperature management, with 85.2% of the major treatments administered within 12 h after admission. Nine of the ten patients recovered without neurological sequelae. Only one patient had epilepsy requiring long-term anticonvulsants and concomitant cognitive decline. This is the only case series where case fatality due to IAE was nil. The Highlight of this study was the administration of antivirals and immunomodulators within 12 hours of admission. The case fatality rate in 2019 case series from SAT was 18.75% where patients were treated with only anti-viral drugs.

Diagnostic Criteria for Encephalitis and Encephalopathy of Presumed Infectious or Autoimmune Etiology

Major Criterion (required):
Patients presenting to medical attention with altered mental status (defined as decreased or altered level of consciousness, lethargy or personality change) lasting ≥24 h with no alternative cause identified.
Minor Criteria (2 required for possible encephalitis; ≥3 required for probable or confirmed[a] encephalitis):
Documented fever ≥38° C (100.4°F) within the 72 h before or after presentation[b]
Generalized or partial seizures not fully attributable to a preexisting seizure disorder[c]
New onset of focal neurologic findings
CSF WBC count ≥5/cubic mm[d]
Abnormality of brain parenchyma on neuroimaging suggestive of encephalitis that is either new from prior studies or appears acute in onset[e]
Abnormality on electroencephalography that is consistent with encephalitis and not attributable to another cause.[f]

AES evaluation and Treatment

Definition

Acute onset of **fever** and a change in **mental status** (including symptoms such as confusion, disorientation or coma,) AND/OR new onset of **seizures** (excluding simple febrile seizures).

Fever with in 72 hours of admission and any persistent altered sensorium lasting for more than 2 hours especially when associated with focal seizures or signs may be indicative of encephalitis.In patients presenting with febrile seizure specifically look for features of encephalitis specially when the child has personal history or history of contact with ILI.

History (important points to be noted)

- ILI symptoms (Influenza,mycoplasma, Nipah)
- GIT symptoms (Shigella, influenza, Dengue)
- Family member / contact with fever or ILI (influenza)
- Travel to endemic areas
- Rash, vesicles or past history of chicken pox
- Residence of child
- History of animal contact, dog bite, insect bite,tick bite.
- Recent vaccination (ADEM)
- Risk factor for immunodeficiency
- Markers of inborn errors of metabolism (past history of encephalopathy, consanguinity, SIDS in family etc)
- Premorbid neurological and developmental status
- H/O AES in neighborhood.

Examination (Cardinal points)

GCS score
Meningeal signs
Pupillary size, symmetry and reaction to light.
Dolls eye movement
Focal neurological deficit including cerebellar signs, limb weakness/involuntary movements
Rash,lymphadenopathy,Eschar.

Investigation

- **Basic Investigations**
  Blood RE, RFT, LFT, S Electrolytes, Blood Sugar
  Peripheral smear / RDT for malaria
  Chest Xray

- **Lumbar Puncture:** If patient hemodynamically stable and there are no features of raised ICP lumbar puncture should be performed. In those with persistent altered sensorium or if suspicion of raised ICP is there, do an imaging.
  - CSF study: Cytology, biochemistry, culture
  - CSF neuroviral panel + Influenza

- **Neuroimaging:** In emergency situation, only CT scan may be possible. It will help detect brain edema, CNS tumors, IC bleed, trauma, brain abscess, subdural empyema etc. MRI may give etiological clues in some conditions like ADEM, HSV encephalitis etc.

Etiology	MRI findings
HSV Encephalitis	Medial temporal lobe, cingulate gyrus, and orbital surface of frontal lobes.
Japanese B Encephalitis	Thalami , substantia nigra, and basal ganglia
Varicella	Cerebellitis, multifocal cortical abnormality, vasculitis
Nipah	Focal subcortical and deep white matter and grey matter lesions; small hyperintense lesions in the white matter, cortex, pons and cerebral peduncles.
ADEM	Multifocal abnormalities in subcortical white matter; involvement of thalami, basal ganglia, and brainstem also may be seen
West Nile virus	Deep grey matter involvement, brainstem, white matter lesions and meningeal enhancement
Chandipura	Normal
Dengue	Symmetrical lesion basal ganglia, thalamus, brainstem, cerebellum.
Influenza	Splenium of corpus callosum, bilateral thalamus,

- **EEG**
- **Coinfections / cause**
  Tropical Infection -Leptospirosis, scrub Typhus, Dengue IGM or PCR.
  PCR zika, chikungunya, Dengue in first week of illness.
- **Nasopharyngeal swab** for respiratory and neuroviral panel
- **Serology for** JE and West Nile [IgM JE/West Nile from serum and CSF]-consider JE in case of encephalitis with extrapyramidal symptoms and West Nile in case of encephalitis with flaccid quadriparesis due to anterior horn cell involvement.As JE and west Nile are flavi viruses like dengue there is chance of serological cross reactivity and hence results should be interpreted carefully.In JE and west Nile viremia is low and transient and hence aPCR does not have negative predictive value

- Stool PCR for Enterovirus and **Shigella.**
- **S**tool for culture in diarrhea.In children with diarrhea and encephalitis, consider shigella PCR from stool sample.

- Inflammatory Panel

    - If CRP / ESR is high send 2nd line inflammatory markers (D Dimer, Ferritin, NT Pro BNP) to rule out MIS-C.SARS-CoV-2 IgG may be sent.
    - Autoimmune encephalitis work up should be considered especially in cases with indolent presentation, behavioral abnormality,dysautonomia.
    - 5 ml serum, Urine, 1 ml CSF and nasopharyngeal swab should be collected in all cases of suspected encephalitis without a diagnosis.
    - In AES cases without diagnosis, Nipah PCR must be sought.
    - In case of viral hemorrhagic fever with encephalopathy send PCR forKFD, Hanta, Crimean Congo haemorrhagic fever and Dengue.

Sample collection, storage and transportation guidelines		
Blood	For viral isolation collect within 5days	
	For IgM collect blood after 5 days Take clotted blood. Separate serum after clot retraction.	If delay anticipated separate serum and store at -20C and transport on frozen Ice pack.
	Convalescent sample 10 -14days after 1st sample	
CSF Fluid	Cell count, bacteriology, biochemistry and virology -PCR,	If delay less than 24 hrs for PCR, viral culture store at 4C
	Serology IgM CSF for JE, Dengue, measles, Nipah, Chandipura	If greater delay store at -80C
Nasopharyngeal / throat/ vesicle swab	Dacron or nylon swab, put in viral transport medium	
Urine	10-20ml for culture, mumps PCR	Store at -20C
Stool	Clean container	Store at -20C
Brain Biopsy (post mortem , when feasible)	Sterile container.	
	Brain smear for viral antigen detection by immunofluorescent antibody staining, and for electron microscopy with negative staining.	

	Emulsified brain tissue is suitable for tissue culture and after proteinase K treatment for PCR.

- **Treatment of AES**

Stabilisation

- Maintain adequate airway, breathing, and circulation (the 'ABCs'):
- Clear airway, and assist breathing were needed.
- If in circulatory failure give NS 20ml/kg bolus
- Measure GRBS if less than 60mg/dl give IV 10% Dextrose 2-5 ml per kg IV.

Treat Seizure: Terminate the seizure and prevent recurrence.

- 1st line AED: IV Lorazepam0.1mg per kg slow IV / IM Midazolam 0.2mg per kg / PR Diazepam 0.5mg/kg
- 2nd line AED: IV Phenytoin infusion 20mg/kg over 20 minutes(fosphenytoin if available can be given as 30mg/kg infusion over 10mts) or IV levetiracetam 60 mg per kg over 10mts
- Start maintenance dose 12 hours after loading dose.
- Take sample for investigations. Blood, serum, Urine, Np Swab, (CSF once stable).
- Diagnose and initiate therapy for life-threatening causes e.g. hypoglycaemia, Raised ICP, Meningitis.

Raised ICP (suspect in altered sensorium, anisocoria, lateral rectus palsy, decorticate or decerebrate posturing, abnormal breathing pattern, hypertension etc.)

- Keep head in mid position and head end elevation 15-30 ^{0} to facilitate venous drainage
- 3% saline 5ml/kg (especially if BP low) or mannitol 2.5 to 5 ml per kg
- IF GCS <8 Intubate with Rapid Sequence Intubation raised ICP protocol
- Maintain euthermia, euglycemia, normal Blood pressure.
- Avoid hypoxiaand Hypercarbia.
- Adequate sedo-analgesia

Empirical Treatment

- Inj. Ceftriaxone, Doxycycline, Inj. Acyclovir , Oseltamivir
- Child with ILI or AES to start oseltamivir early. 6mg per kg per dose(max. 150mg) BD.

A Practical Approach to Encephalitis in the current scenario

- All patients with suspected encephalitis should be subjected to influenza PCR from nasopharyngeal swab. As none of the commercially available CSF meningo-encephalitis panels include testing for influenza, nasopharyngeal swabs should be sent for influenza PCR.

- During influenza season IAE has occurred even in patients without symptoms of influenza and hence during influenza season influenza PCR should be done in all cases of suspected encephalitis.
- Till diagnosis is ascertained, empirical coverage for scrub typhus should be initiated as isolated encephalitic presentation for scrub typhus has been described.
- In diagnosed cases of IAE, encephalitis with ILI, or encephalitis in a child with contact with ILI early administration of immunomodulators [steroid pulse therapy/ immunoglobulins] must be considered in patients with features of raised ICT, GCS ≤8 or rapid neurological deterioration.
- As early use of immunomodulators in IAE is not supported by robust scientific evidence, the decision must be made based on opinion of institutional medical board comprising of pediatricians/physicians and neurologists.In such situations, the decision needs to be made on a case to case basis.

<table>
<tr><td colspan="3">Child with AES</td></tr>
<tr><td>Child with ILI</td><td>Contact with fever/ ILI</td><td>Only personal H/o fever</td></tr>
<tr><td>Oseltamivir</td><td>Oseltamivir</td><td>Oseltamivir</td></tr>
<tr><td colspan="3">Child deteriorates: GCS < 8, E/O raised ICP, Rapid fall in GCS, Intractable seizures</td></tr>
<tr><td colspan="3">To consider cytokine storm</td></tr>
<tr><td>May start pulse methylprednisolone 30mg/kg for 3 days*</td><td>May start pulse methylprednisolone 30mg/kg for 3 days *</td><td>To consider Immunomodulators [IVIG/Steroids]</td></tr>
<tr><td colspan="3">Ensure Double dose Oseltamivir for 14 -21 days when steroid given if Influenza positive.</td></tr>
<tr><td colspan="3">*Steroids/immunomodulators should be initiated after expert opinion from institutional medical board comprising of Paediatrician/Physician and Neurologist.</td></tr>
</table>

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