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(Deemed to be University)

TALES OF STORM IN THE BRAIN-A CASE SERIES

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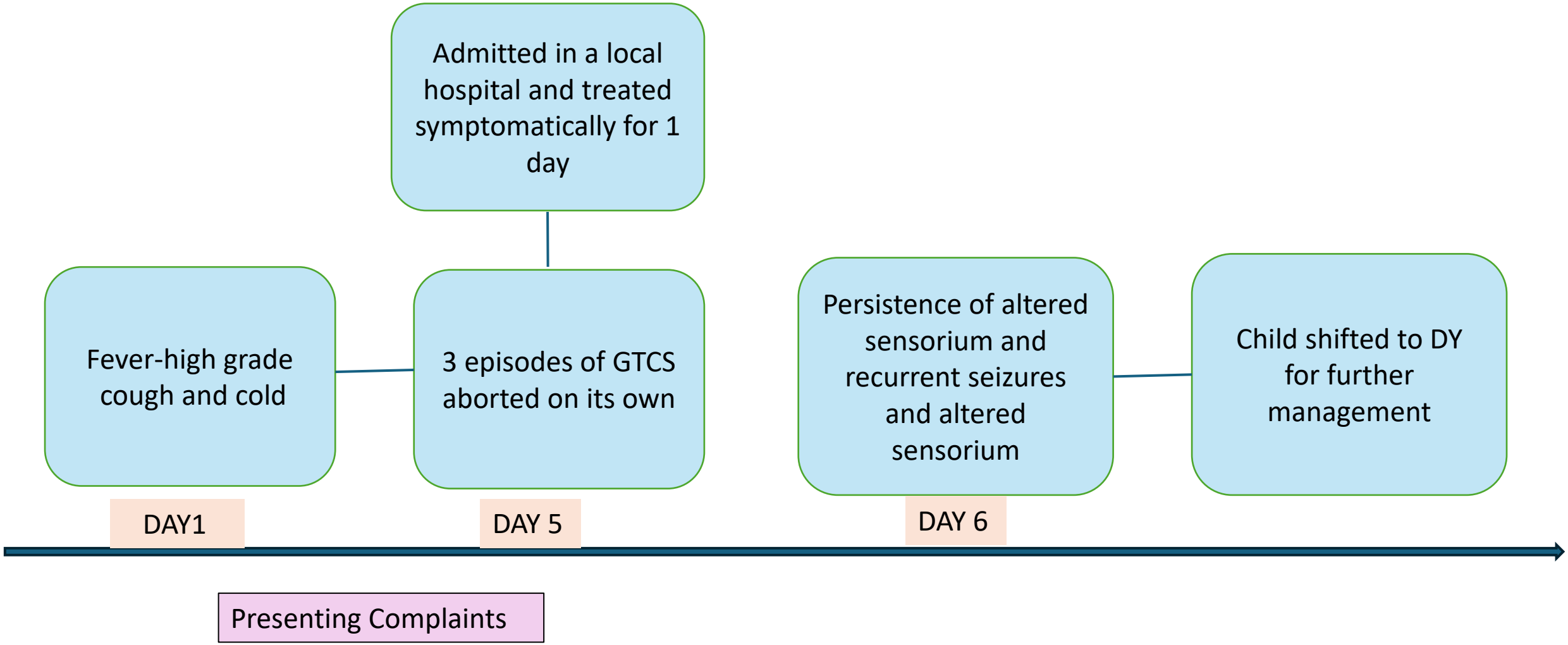
CLINICAL DETAILS

3 Years Old MCH With Normal Birth And Development 2nd Born Out Of NCM Presented With



EXAMINATION ON ADMISSION

Temp – 102°F(Febrile)

- HR – 140/min
- RR – 60/min
- BP – 91/52(65) mm HG (hypotensive)
- CRT – delayed
- Peripheral Pulse – Feeble
- SPO2 – 94% on room air

General Examination
Normal anthropometry
HC-53CM(1-2 SD)
No neurocutaneous markers

CNS Examination :
Higher Mental Functions :
GCS – 6/15 - E1V2M3

Child lethargic, poor orientation.
Not responding to verbal commands.

Sensory System Examination – (limited) Normal
Cerebellar Signs-No nystagmus
Meningeal signs :Absent
Skull &spine – Normal

Other Systemic Examinations

CVS – S1S2 heard, No murmur.

RS –Bilateral air entry present, Mild crepitations+

PA – Soft, non tender, no organomegaly.

Differentials Considered

Acute Encephalitis Syndrome

- Acute Meningoencephalitis
- Infection Triggered Encephalopathy Syndrome (ITES)
- Acute Demyelination Syndrome (ADS)

Management On Admission

Child was shifted to PICU ; Intubated due tachypnoea,falling saturations and poor sensorium.

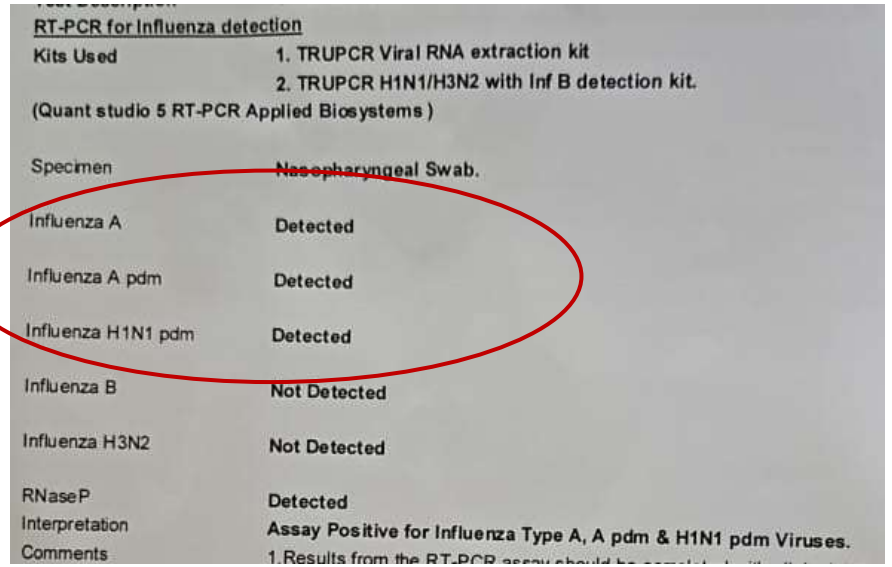
Started on

- ✓Ventilatory And Ionotropic Support
- ✓Relevant Investigations Sent
- ✓IV Ceftriaxone And Vancomycin
- ✓IV Acyclovir
- ✓IV Levetiracetam

INVESTIGATIONS

BLOOD	INVESTIGATIONS
Hb	12gm/dl
TLC(N/L)	8910(30/70)
platelets	118000
BSL	123 mg/dl
CRP	80
SGOT/PT	890/550
Na/k/cl	132/4/101
Ammonia	27
Lactate	7
Pt/inr ddimer	

SEROLOGY For Dengue And Chikungunya- Negative
Blood Cultures-Sterile



RT-PCR for Influenza detection

Kits Used	1. TRUPCR Viral RNA extraction kit 2. TRUPCR H1N1/H3N2 with Inf B detection kit.
(Quant studio 5 RT-PCR Applied Biosystems)	
Specimen	Nasopharyngeal Swab.
Influenza A	Detected
Influenza A pdm	Detected
Influenza H1N1 pdm	Detected
Influenza B	Not Detected
Influenza H3N2	Not Detected
RNaseP	Detected
Interpretation	Assay Positive for Influenza Type A, A pdm & H1N1 pdm Viruses.
Comments	1.Results from the RT-PCR assay

Nasal swab RTPCR-
INFLUENZA A

LAB INVESTIGATION REPORT

TEST	RESULT
	IMMUNOLOGY - CSF
Interleukin-6, CSF (FIA)	434.81

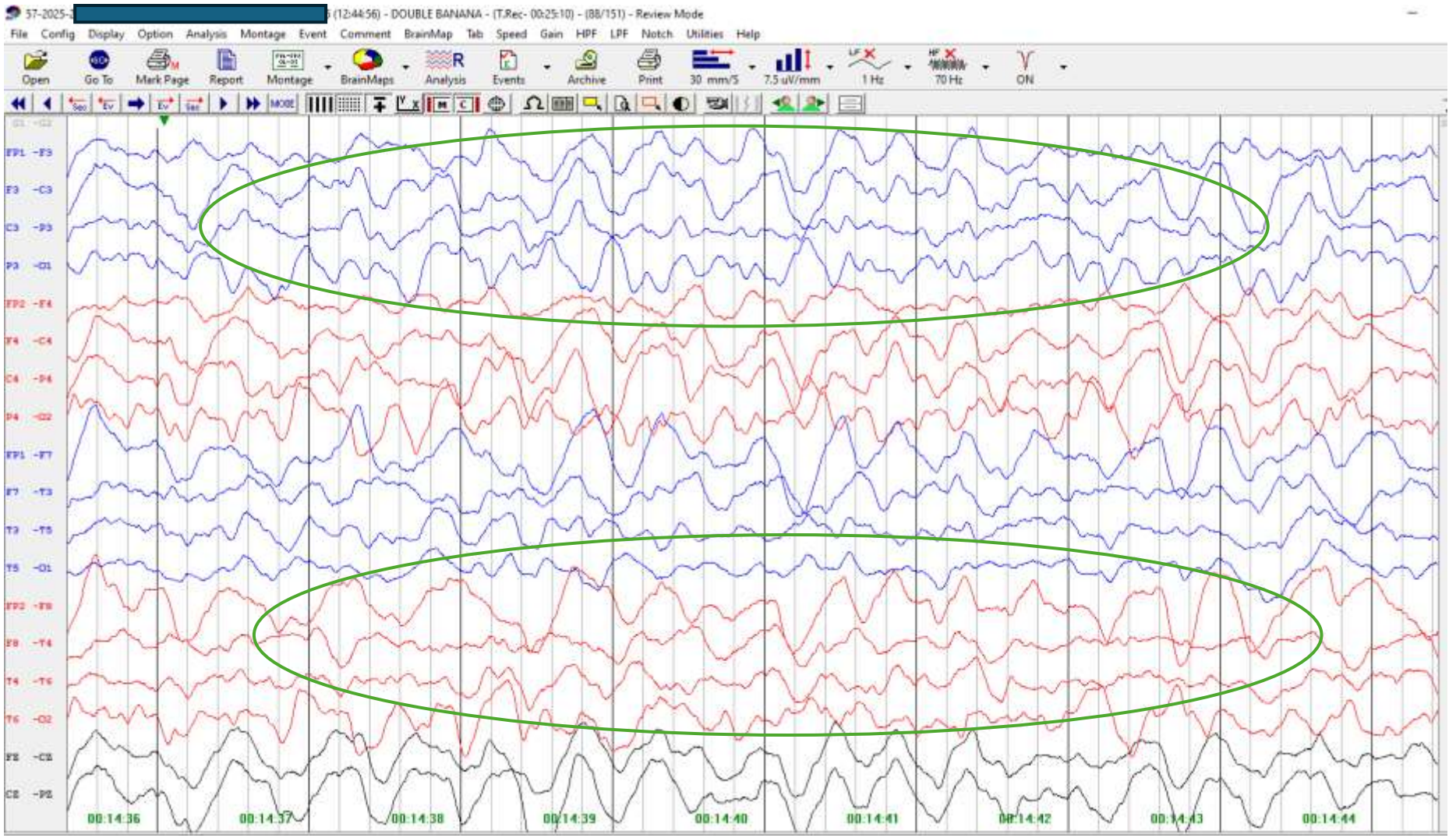
CSF	STUDY
GLUCOSE	170mg/dl
PROTEIN	72
CELLS	2(Lymphocytes)
RBC	NIL
ADA	12.6

CSF CBNAAT - Negative
CSF Culture-Sterile

CSF viral PCR study along with influenza A -Negative

CSF IL6-HIGH

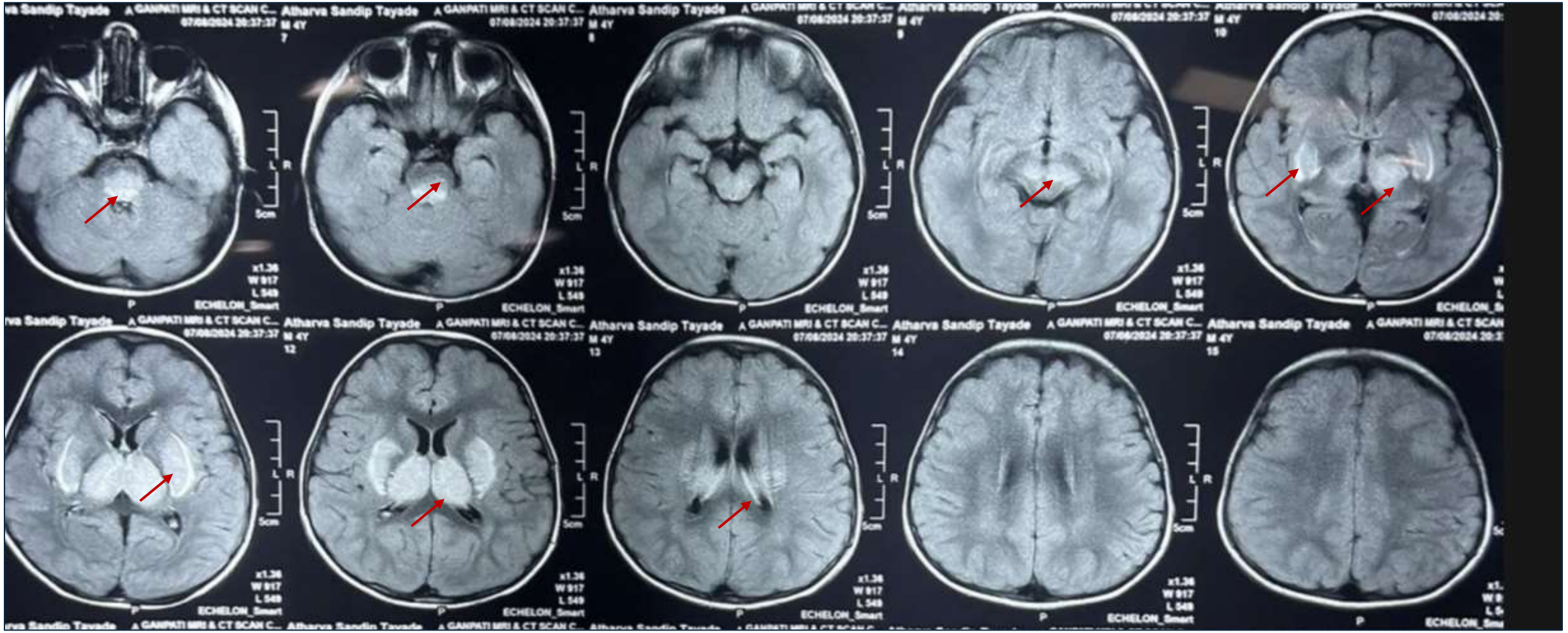
EEG



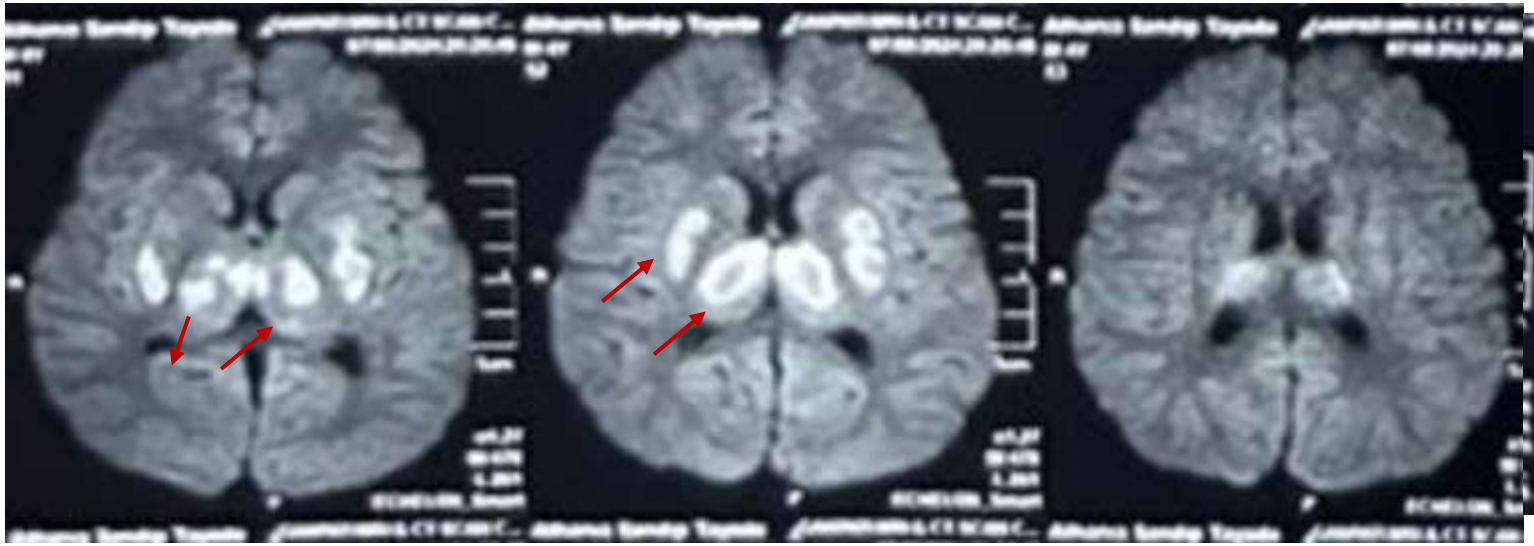
DIFFUSE BACKGROUND SLOWING WITH NO SLEEP ARCHITECTURE

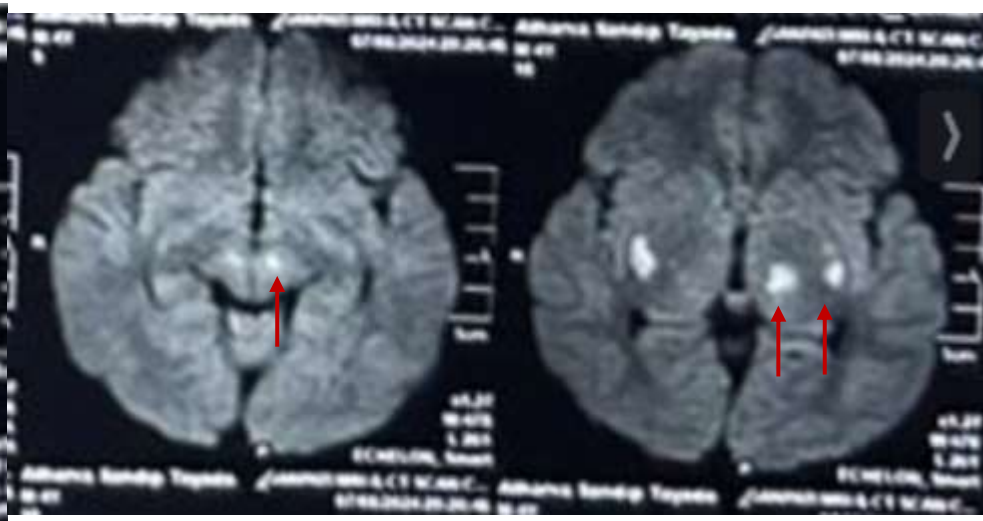
S/O MODERATE ENCEPHALOPATHY

MRI Brain

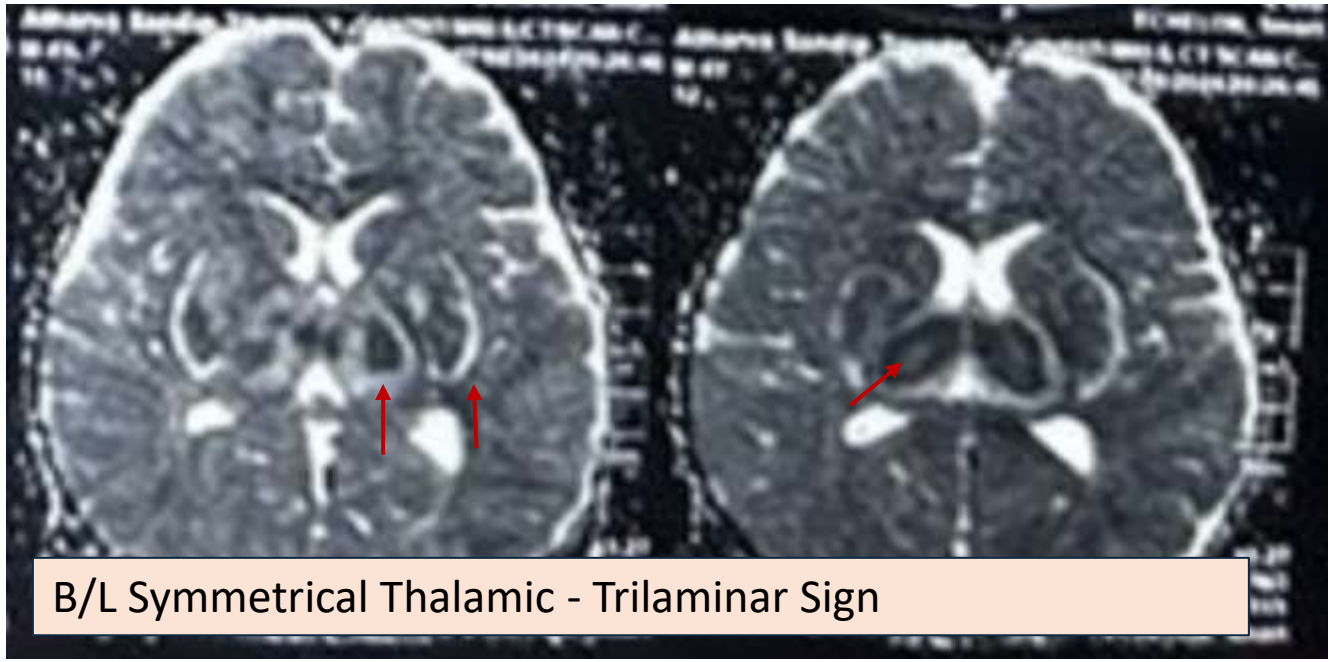


FLAIR Axial Section – Hyperintensity over Midbrain,Pons, bilateral thalamus and Putamen and External Capsule

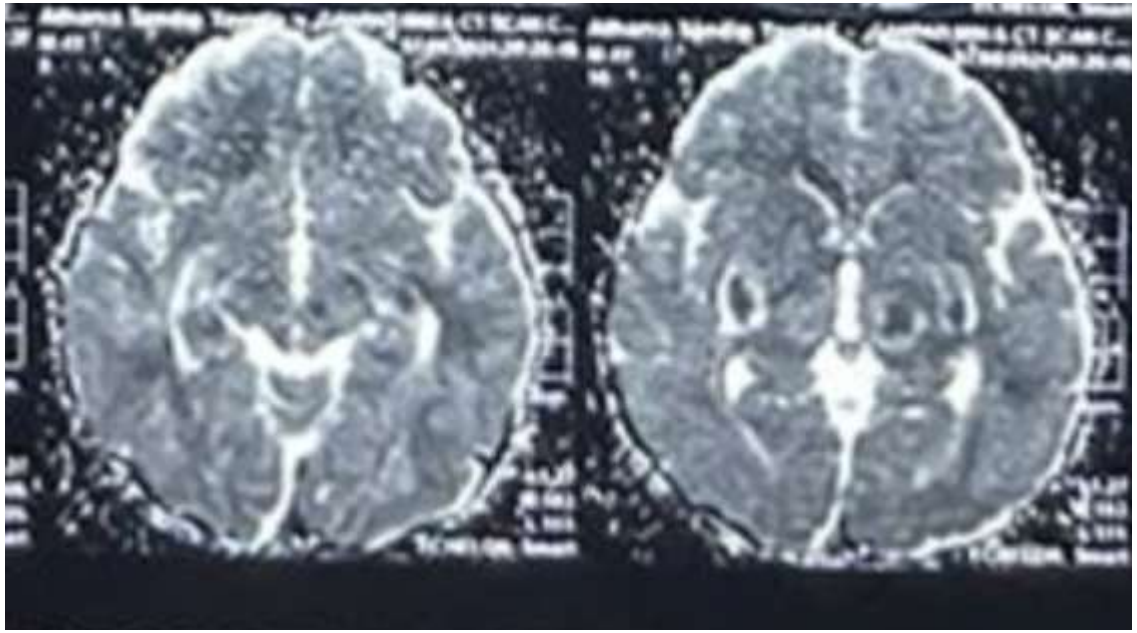




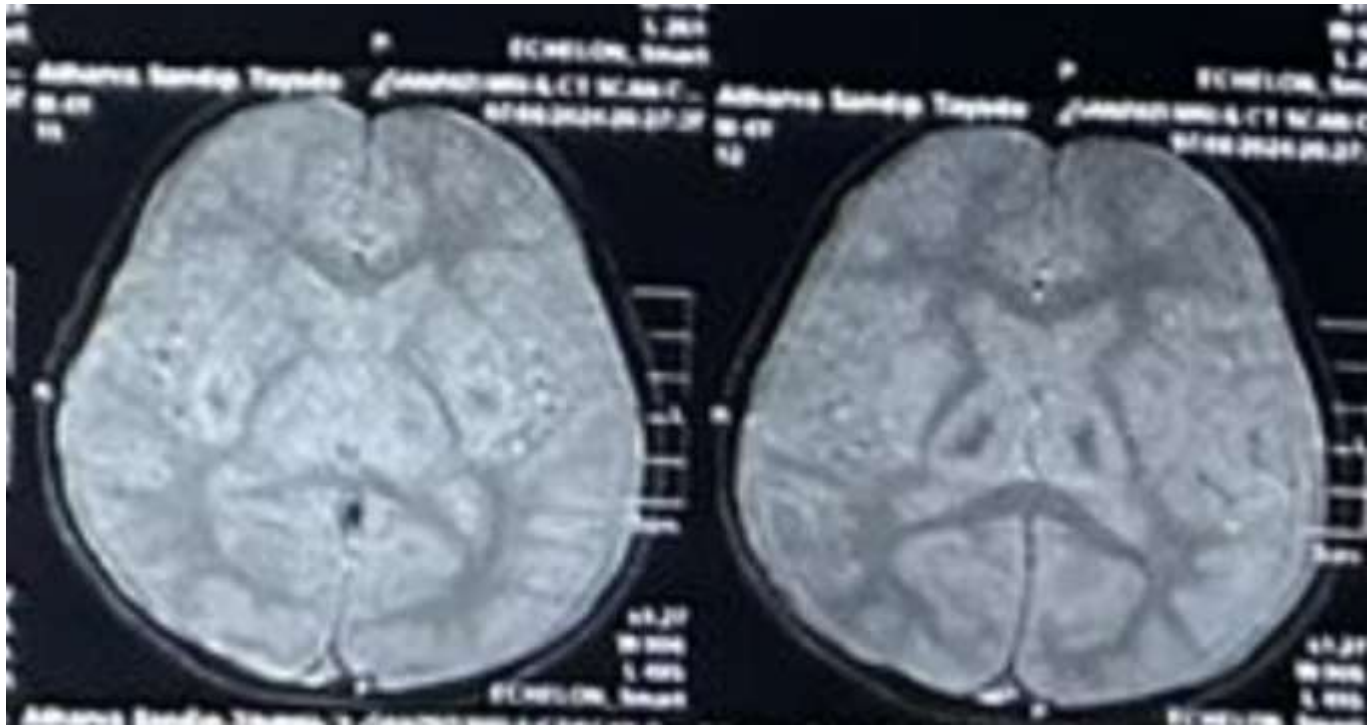
Diffusion Restriction Noted In Midbrain,thalamus,PLIC and Corresponding Low ADC



B/L Symmetrical Thalamic - Trilaminar Sign

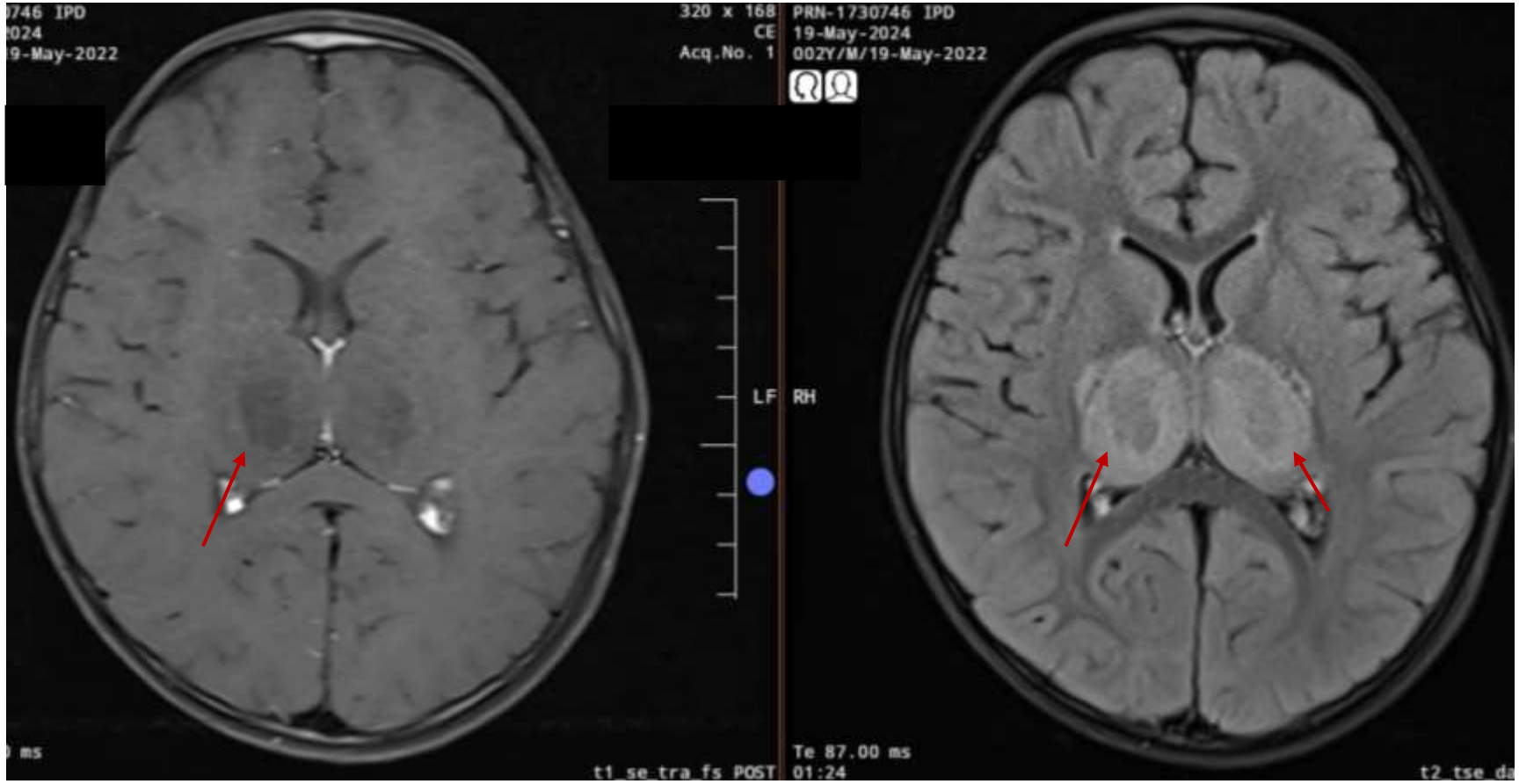


SWI



Showing Blooming In The Bilateral Thalamus And Putamen-S/o Necrosis

CONTRAST IMAGING



Showing subtle enhancement in the bilateral thalamic region

FINAL DIAGNOSIS

Clinical Presentation With Febrile Encephalopathy And Seizures

+

Characteristic Symmetrical Trilaminar Sign In Bilateral Thalamus

Acute Necrotising Encephalopathy Of Childhood (ANEC) with influenza A Positive On Nasal Swab

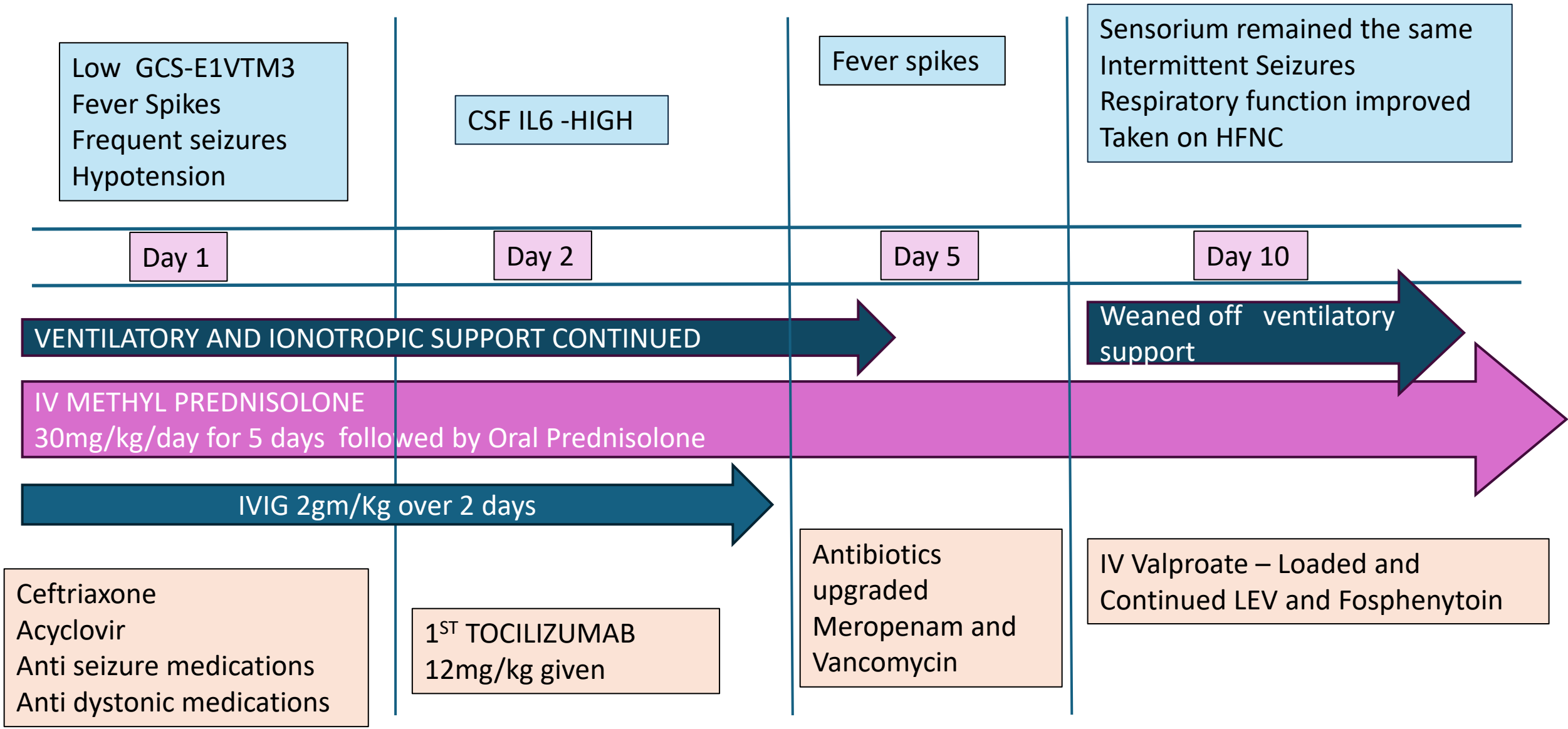
ANE-SS range from 0 to 9 points

- 2 Points - Age more than 2 years
- 3 Points - Existence of shock
- 1 Point – Low Platelet count (<100,000/µL)
- 1 Point - Elevated CSF protein (>60 mg/dl)
- 2 points - Brain stem lesions in MRI brain

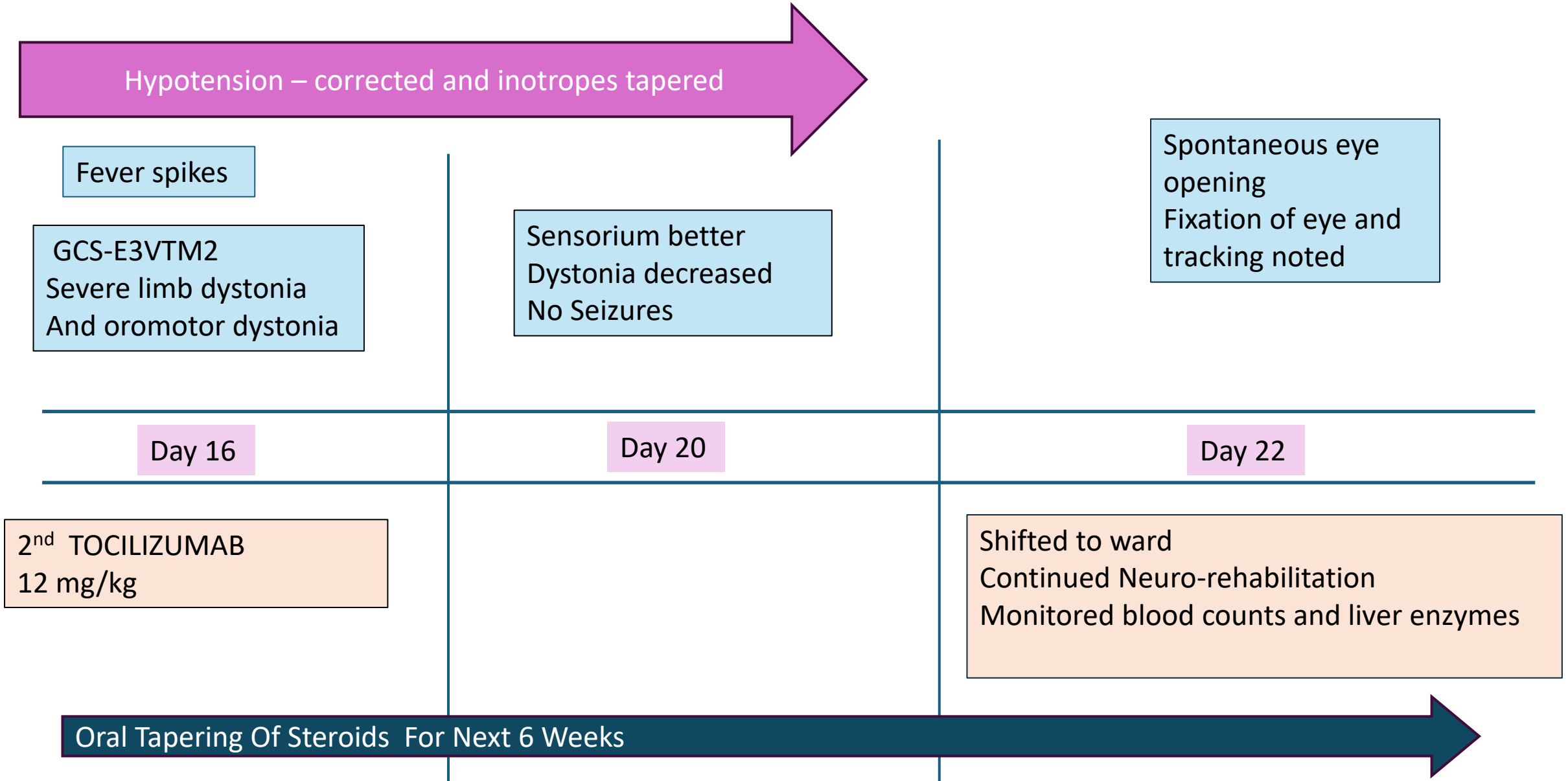
ANE - SS -7

Indicates high risk for poor neurological outcome

COURSE AND TREATMENT TIMELINE



COURSE AND TREATMENT TIMELINE



DISCHARGED ON DAY 30

Spontaneous eye opening and tracking of the objects
Started recognizing parents and vocalisation
Responding to verbal command and able to reach towards objects
Dystonia +
Poor oromotor coordination

On nasogastric tube feeding
Oral tapering dose of oral steroids tapered and stopped
Anti seizure medications tapered to minimal dosage.
Anti dystonic medications
Neurorehabilitation continued.

mRS-5

1ST Follow-up
1 Month After Discharge

2ND Follow-up
1 Month After Discharge

Child started feeding independently
Oromotor coordination improved

Started responding to verbal commands

Indicated needs non verbally and vocalisation

mRS-4

Good eye contact
Understanding 1-2 step command

Child started walking
Started Socializing with other kids

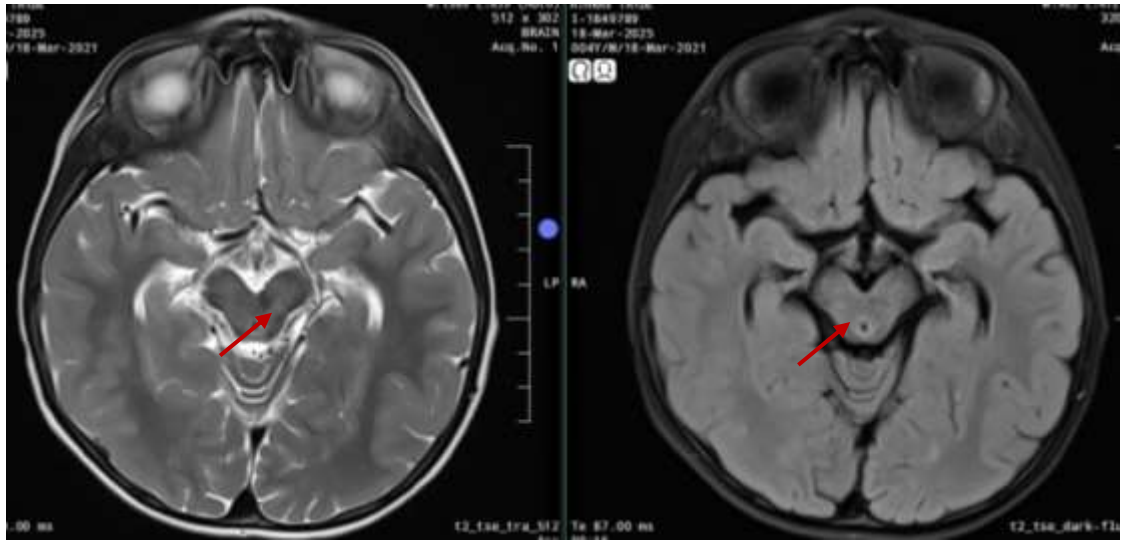
mRS-3

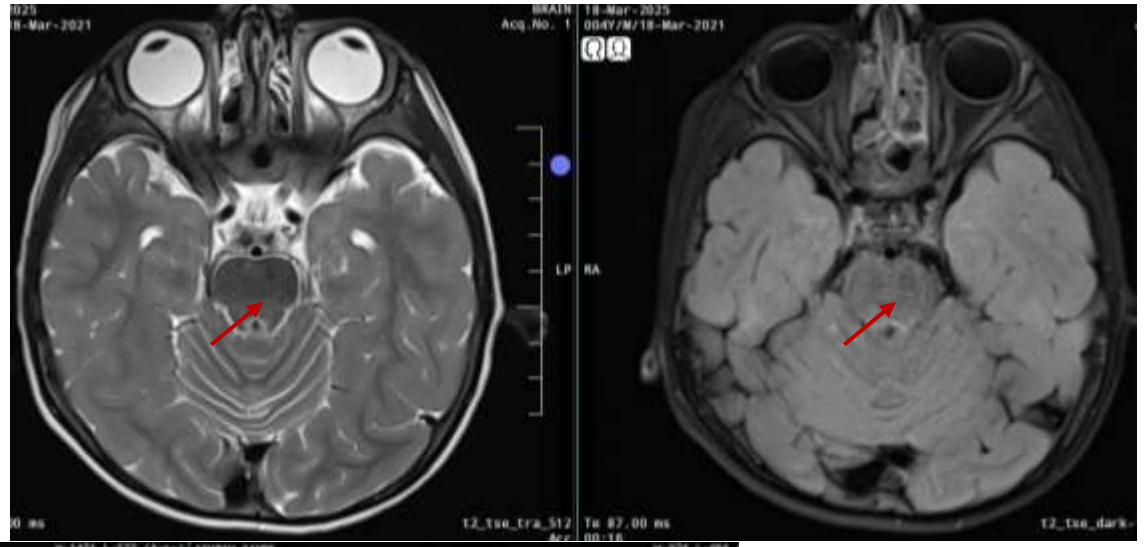
Follow-up After 6 Months

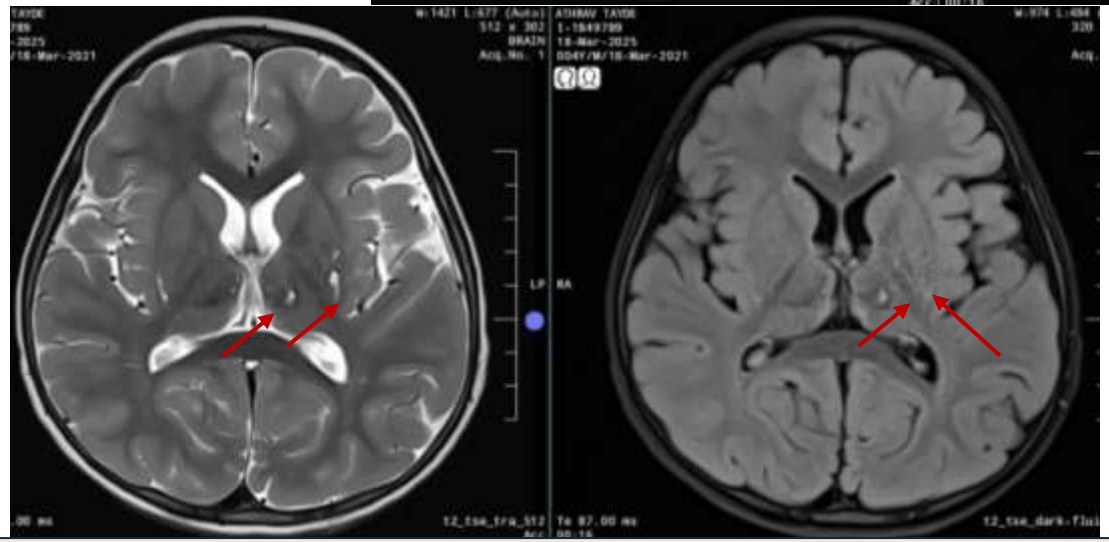
- No Further Seizures
- Mild Dysarthric Speech
- Mild Cognitive Deficits
- Disappearance of spasticity and dystonia

Antidystonic and Antispastic medications-tapered off
Levetiracetam tapered and stopped

REPEAT IMAGING DONE AFTER 6 MONTHS

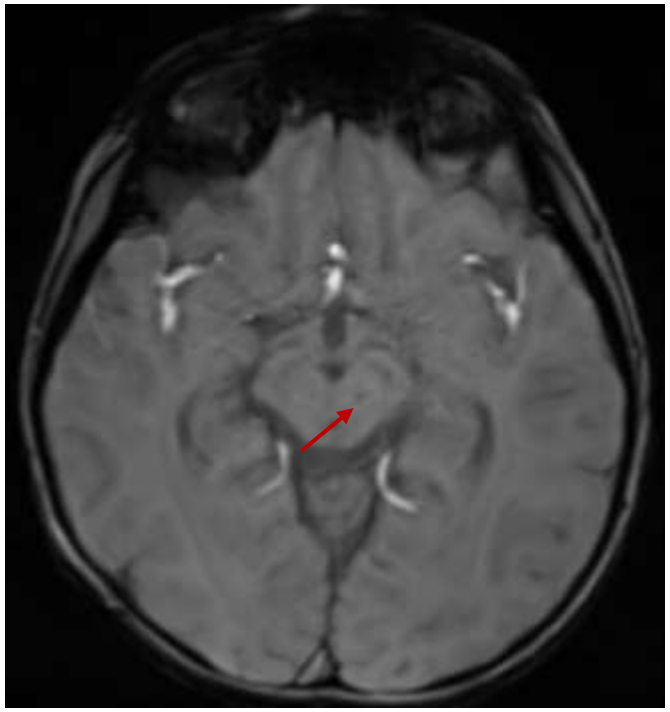


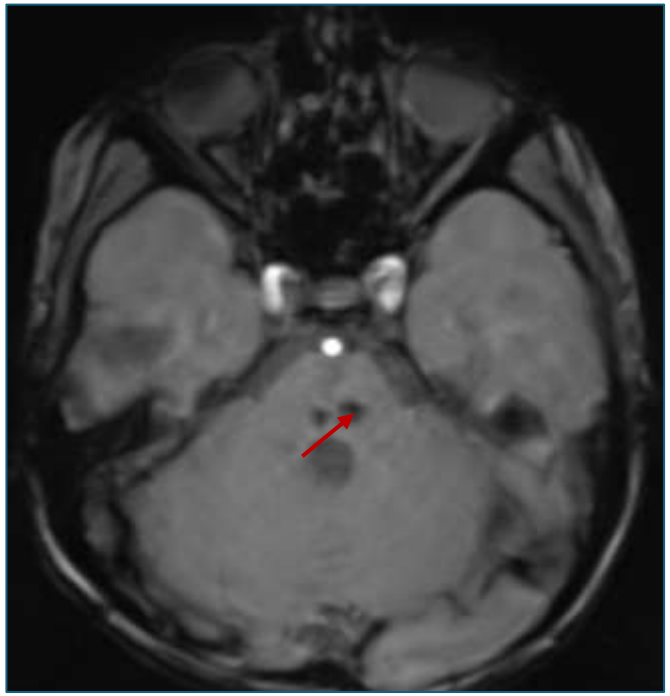


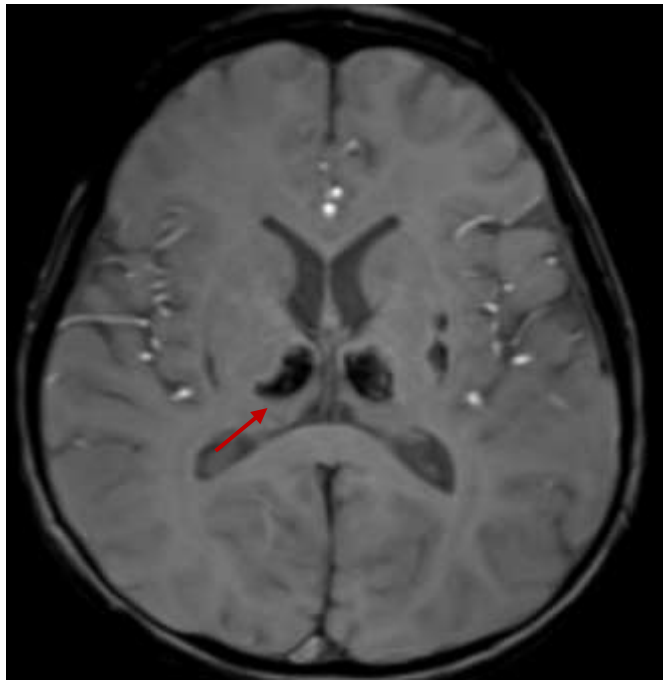


T2/FLAIR AXIAL SECTIONS SHOWING SHOWING DISCOID LESION IN LEFT CEREBELLAR HEMISPHERE PONS AND MIDBRAIN MIXED INTENSITIES ALONG WITH BILATERAL THALAMIC HYPERINTENSITY WITH BILATERAL EXTERNAL CAPSULE HYPERINTENSITIES-GLIOSIS

SWI







SWI showing blooming in the midbrain,pons and bilateral thalamus and external capsule

ANEC – Our Cohort Over 3 Years

- Total 17 children with ANEC (March 2022-March 2025 – 3 years)
- Mean age was 7.1 years ; Range 2yrs-13yrs
- M : F - 3.2:1

Clinical presentation

Fever and Encephalopathy – 17/ 17 (100%)

Seizures – 17/17 (100%)

Hypotension - 14/17 (82.3%)

Abnormal Neurological Examination - 17/17 (100%)

Recurrent Encephalopathy – 1 /17 (5.8%)

Investigations

INVESTIGATIONS	NUMBER OF CASES	PERCENTAGE
Leucocytosis	8/17	47 %
Leukopenia	6/17	35.2%
Thrombocytopenia	8/17	47 %
Transaminitis	12/17	70 %
Elevated CSF Protein	13/17	76.4%
Abnormal EEG	17/17	100%
Other system involvement	12/17	70 %

CSF IL 6 levels - Done in 7 children – Elevated in all 7 cases

ANE - Severity Score – ANE - SS

ANE-SS range from 0 to 9 points

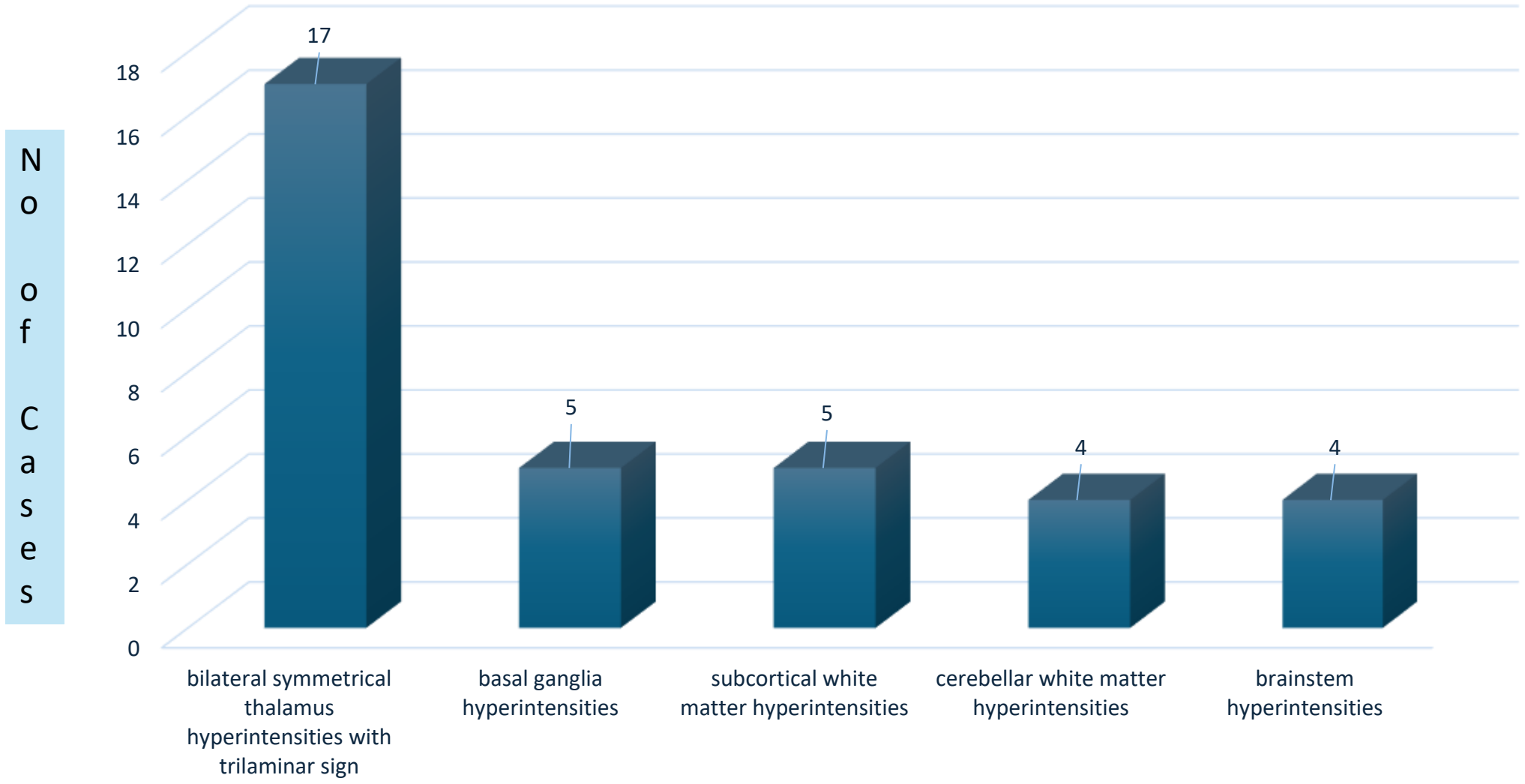
- 2 Points - Age more than 2 years
- 3 Points - Existence of shock
- 1 Point – Low Platelet count (<100,000/µL
- 1 Point - Elevated CSF protein (>60 mg/dl)
- 2 points - Brain stem lesions in MRI brain

Risk classification

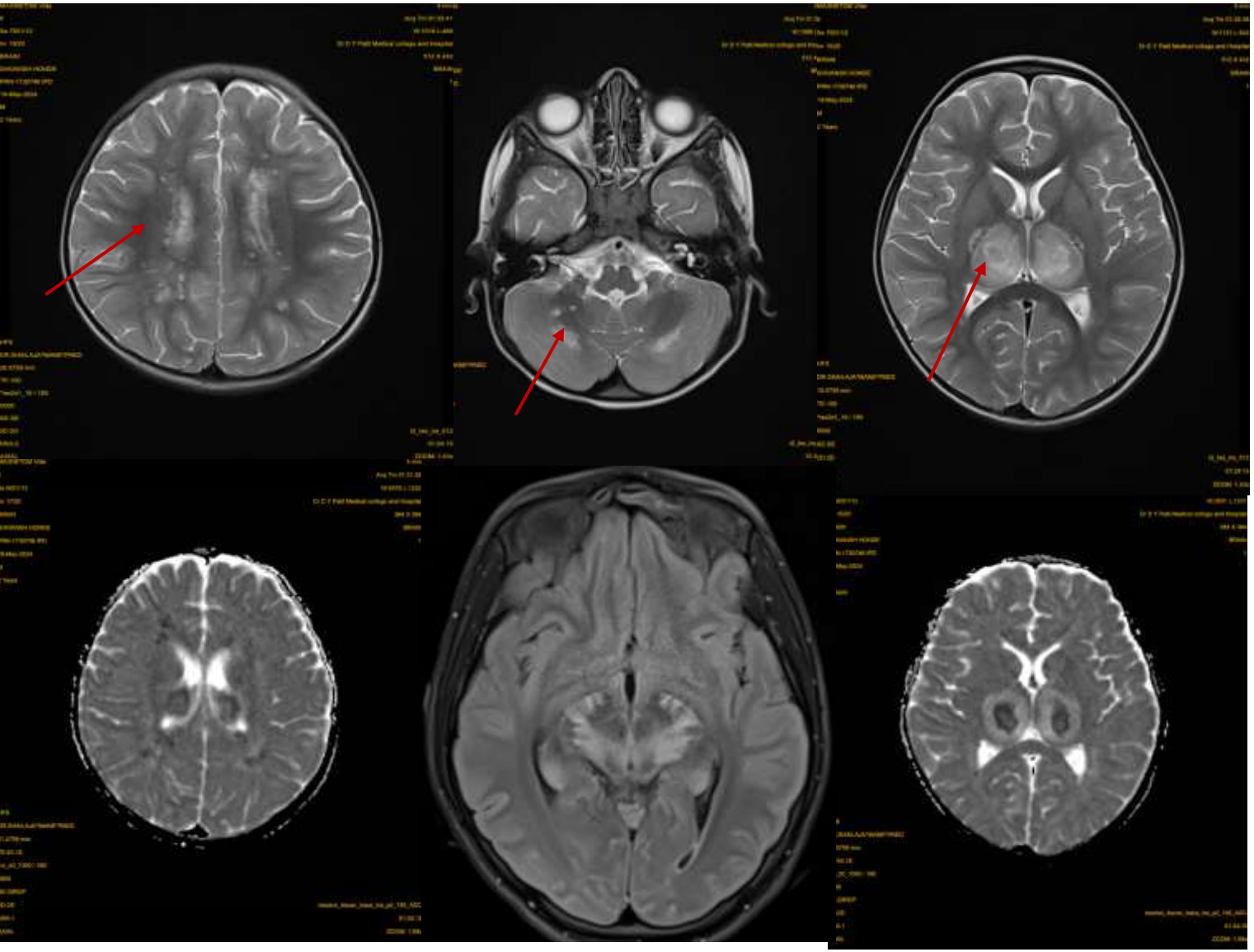
- Low risk (ANE-SS 0-1)
- Medium risk (ANE-SS 2-4)
- High risk (ANE-SS 5-9 points)

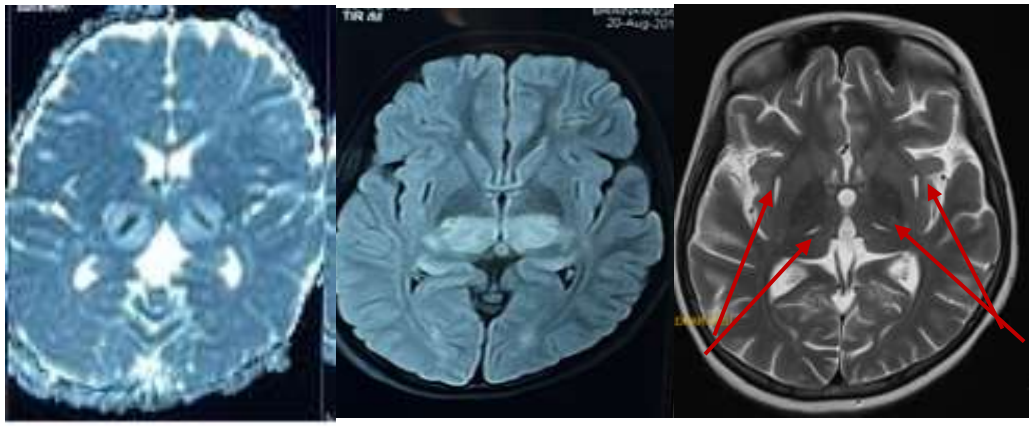
ANE-SS SCORING	NUMBER OF CASES	PERCENTAGE
LOW RISK (0-1)	0	0 %
MEDIUM RISK (2-4)	7	41.1 %
HIGH RISK (5-9)	10	58.8 %

Neuroimaging Findings



NEUROIMAGING PATTERNS

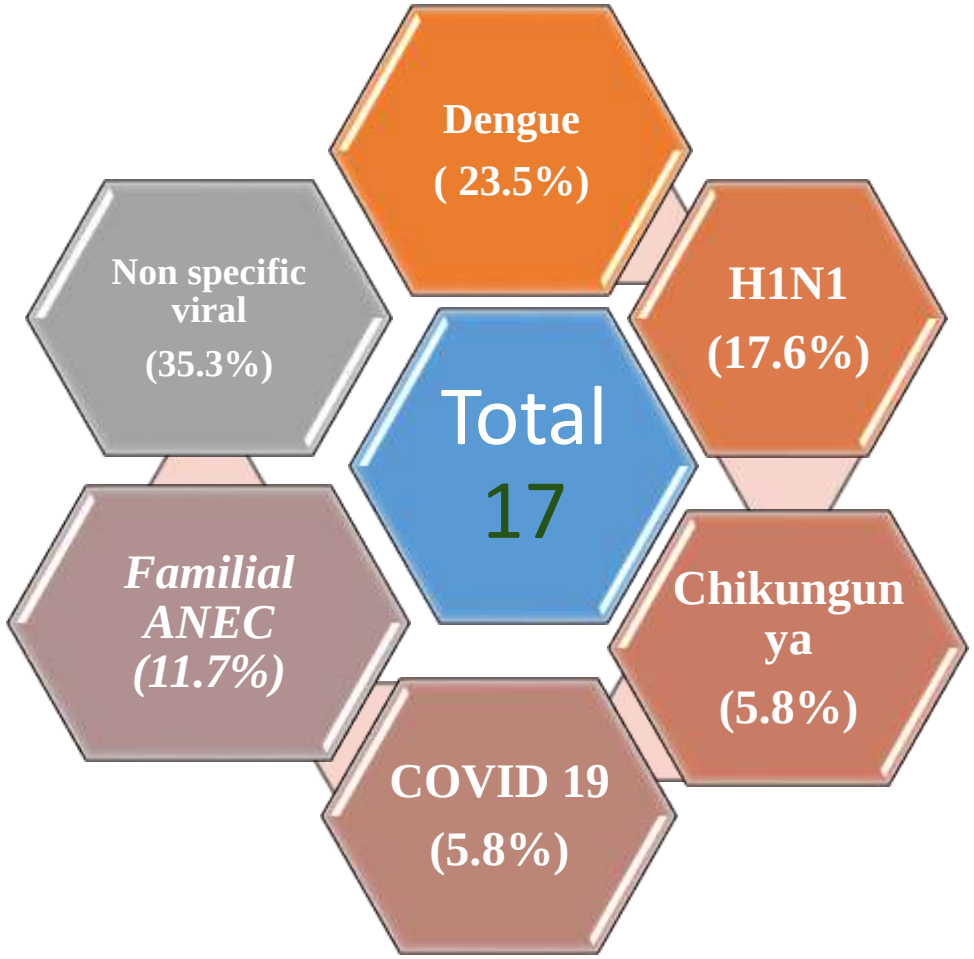




Children with Recurrent Encephalopathy - B/L Cysts in external capsule, foci of cystic encephalomalacia with surrounding gliosis in both thalami – Findings are typically described in Familial ANEC

ETIOLOGICAL SPECTRUM

- Dengue - 4 (23.5%)
- H1N1 – 3 (17.6%)
- Chikungunya - 1 (5.8%)
- Covid- 19 - 1 (5.8%)
- No definite cause - 6 (35.3%)
- Presumed Familial ANEC – 2 (11.7 %)



Treatment

- All children required Intensive care admission
- Mean duration of PICU stay - 10 ± 2.3 days
- Mechanical ventilation - 11/17
- Inotropic support -14/17
- Antiseizure medications ,anti-cerebral edema, anti-dystonic medications were given in all cases

Immunotherapy

- **IV Methylprednisolone -All Cases**

  @30mg/kg/day for 5 days
  followed by oral steroids for 6 weeks

IV – Immunoglobulin – 15 Cases

@2GM/KG over 2 days

Tocilizumab – 7 Cases

@8-12mg/kg one dose

Timeline for Initiation of Tocilizumab in 7 Cases

Initial 4 cases-on Day 5 or Day 6 — Persistent encephalopathy and raised CSF IL6

Based on the experience and good response noticed
Early tocilizumab----In the subsequent cases

Outcome in Non Tocilizumab group(10 Cases) – Modified Rankin Scale

		mRS	On Discharge	3 Month Follow-up	6 Month Follow-up
No symptoms		**0**			2
Non significant disability		**1**			1
Slight disability		**2**		2	2
Moderate disability		**3**		3	1
Moderately Severe disability		**4**	4		
Severe disability		**5**	2	1	
Dead		**6**	4		

Outcome in Tocilizumab group (6 Cases) – Modified Rankin Scale

		mRS	On Discharge	3 Month Follow-up	6 Month Follow-up
No symptoms		0		2	5
Non significant disability		1		2	1
Slight disability		2			
Moderate disability		3	1	2	
Moderately Severe disability		4	3		
Severe disability		5	2		
Dead		6			

Outcome In Non Tocilizumab Group With ANESS Score Comparison- At 3 &6 Months

MRS	0	1	2	3	4	5	6
• SCALE	• 0	• 0	• 2	• 3	• 0	• 1	4

ANESS scoring

LOW RISK (0-1)							
MEDIUM RISK (2-4)			**1**	**2**			**1**
HIGH RISK (5-9)			**1**	**1**		**1**	**3**

ANESS Scoring	No of cases
Low risk(0-1)	0
Medium risk(2-4)	4
High risk (5-9)	6

AT 6 MONTHS

LOW RISK (0-1)							
MEDIUM RISK (2-4)	**2**	**1**	**1**				
HIGH RISK (5-9)	**0**		**1**	**1**			

Outcome In Tocilizumab Group With ANESS Score Comparison- At 3 & 6 Months

MRS	0	1	2	3	4	5	6
• SCALE	• 0	• 0	• 2	• 3	• 0	• 1	4

ANESS scoring

LOW RISK (0-1)							
MEDIUM RISK (2-4)	2			1			
HIGH RISK (5-9)		1		1	1		

ANESS Scoring	No of cases
Low risk(0-1)	0
Medium risk(2-4)	3
High risk (5-9)	3

AT 6 MONTHS

LOW RISK (0-1)							
MEDIUM RISK (2-4)	2	1					
HIGH RISK (5-9)	2	1					

ANEC-ACUTE NECROTISING ENCEPHALOPATHY OF CHILDHOOD

- First described in the late 1900s by Mizuguchi et al.,
- Potentially devastating illness characterized by fever, acute encephalopathy, and bilateral thalamic lesions.
- Predominantly affects children in the toddler and preschool age group (1–6 years)
- Liver dysfunction is commonly seen.
- Cerebrospinal fluid (CSF) analysis reveals increased protein without pleocytosis.
- High mortality and poor neurological outcome.

WHY THERE IS THIS STORM??

WHERE IS THE STORM??

ETIO-PATHOGENESIS

- Nonspecific viral illness.
- Influenza A, influenza B, herpesvirus (HHV)-6, dengue, parainfluenza, varicella,covid-19, enterovirus, rotavirus, herpes simplex virus, rubella, and coxsackie A9
- Unclear exact etiopathogenesis
- Most believed hypothesis is infection triggered aberrant immune response

UNCONTROLLED CYTOKINE RESPONSE ⟹ CYTOKINE STORM IN THE BRAIN

Altered vessel wall permeability, contributing to brain injury

High concentrations of IL-6 ----neurotoxic effects

TNF-α --- damage the endothelium of the CNS.

HOW TO STOP THIS STORM??

TREATMENT

- Prompt immunomodulation-mainstay is high dose Methylprednisolone
- Robust intensive care

- ROLE OF TOCILIZUMAB
- Tocilizumab, a monoclonal antibody targeting the IL-6 receptor.
- Tocilizumab as an “adjunct” immunotherapy to steroids and immunoglobulin therapy
- Shown promising therapeutic effects.

Child Neurology: Acute Necrotizing Encephalopathy of Childhood Associated With Dengue Good Neurologic Outcome Despite a Fulminant Presentation

Juhi Gupta, MD, DM https://orcid.org/0000-0001-7019-315X, Richa Choudhary,

PROGNOSIS

- Outcome spans from complete recovery to severe neurologic sequelae and death.
- Mortality rates are as high as 40%.
- High-risk ANE-SS associated with increased mortality and severe morbidity
- At discharge--significant neurologic problems.
- The recovery is gradual
- Continued neurologic recovery at follow-up.

Acute necrotising encephalopathy of childhood – A narrative review. Karnataka Paediatr J 2023;38:103-9. doi: 10.25259/KPJ_30_2023 Banerjee B, Acharya UV

What This Study adds

- Dengue infection and H1N1 were the predominant etiologies.
- All the children received primary immunotherapy with in 24 hrs of admission
- Tocilizumab group of patients showed good recovery with zero mortality
- Early consideration of tocilizumab showed promising results and less sequalae
- Most of the children were bedridden at discharge (mRS scores 4–5) and their recovery continued at home
- Till date no case report has been published in regard to tocilizumab administration in ANEC from India

This will be the first ANEC case study from India

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7. Acute necrotising encephalopathy of childhood – A narrative review Bidisha Banerjee[1], Ullas V. Acharya[2]

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