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(Deemed to be University)

Enduring an incurable illness

Dr. Aryan Gupta

Fellow in Pediatric Neurology

Dr. D.Y Patil Medical College, Hospital and Research Center, Pune

Under the guidance of –

Dr. Shailaja Mane – Professor and HOD Pediatrics

Dr. Shiji Chalipat - Professor, Pediatric neurologist

3-year-old male child presented with complaints of –

- ✓Fever since 7 days
- ✓On Day 5 – Altered sensorium in the form of drowsiness and Increased work of breathing
- ✓On Day 6 – Multiple episodes of Vomiting and Multiple episodes of generalized tonic-clonic seizures

- ✓No history suggestive of cranial nerve palsy
- ✓No history of tuberculosis contact
- ✓No history of weakness of limbs
- ✓No history of recent infection or vaccination
- ✓No history of visual impairment
- ✓No history of animal contact or bite
- ✓No history of recent travel

Outside hospital course

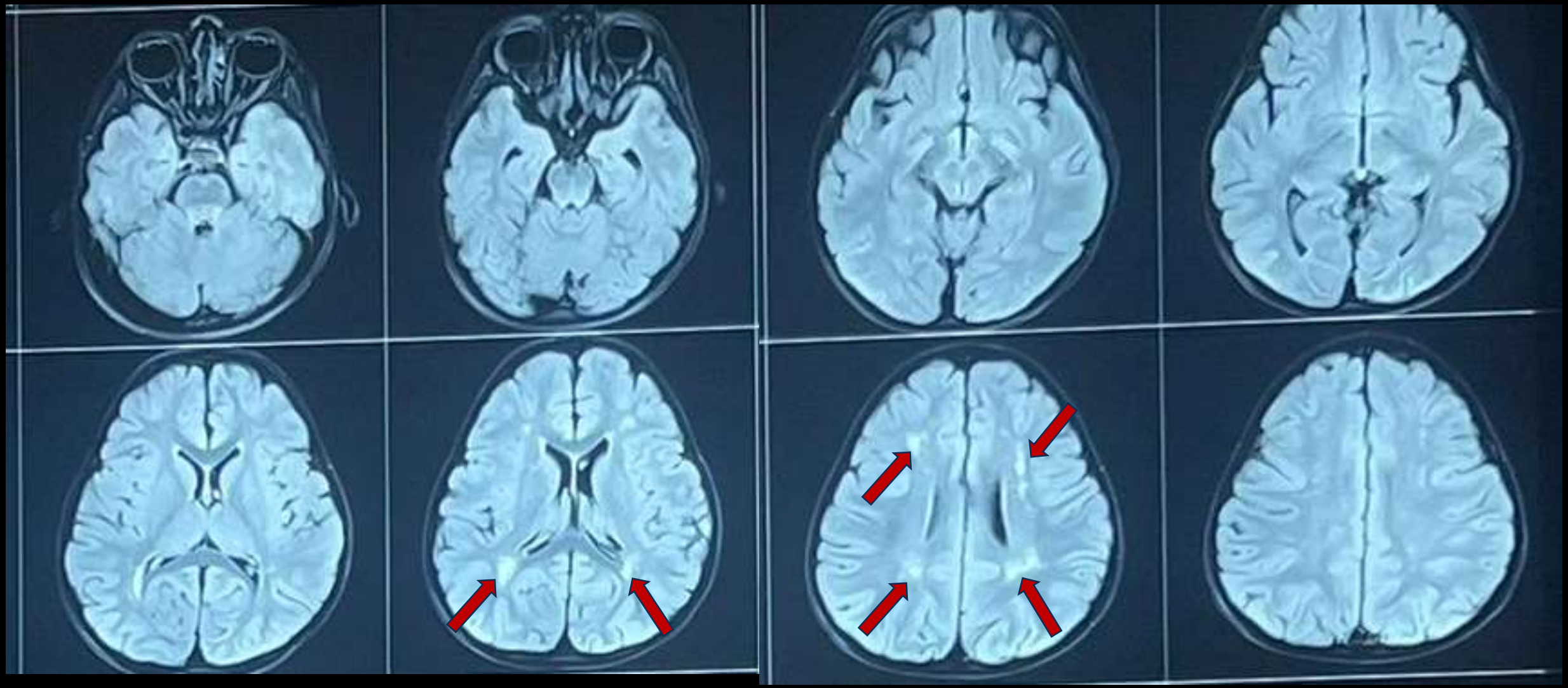
- ✓Patient was admitted in a hospital outside where he was stabilized and shifted to pediatric intensive care unit of the same hospital
- ✓He was started on Ceftriaxone, Oseltamivir, Acyclovir and Levetiracetam
- ✓Chest Xray was done findings of which were consistent with bronchopneumonia

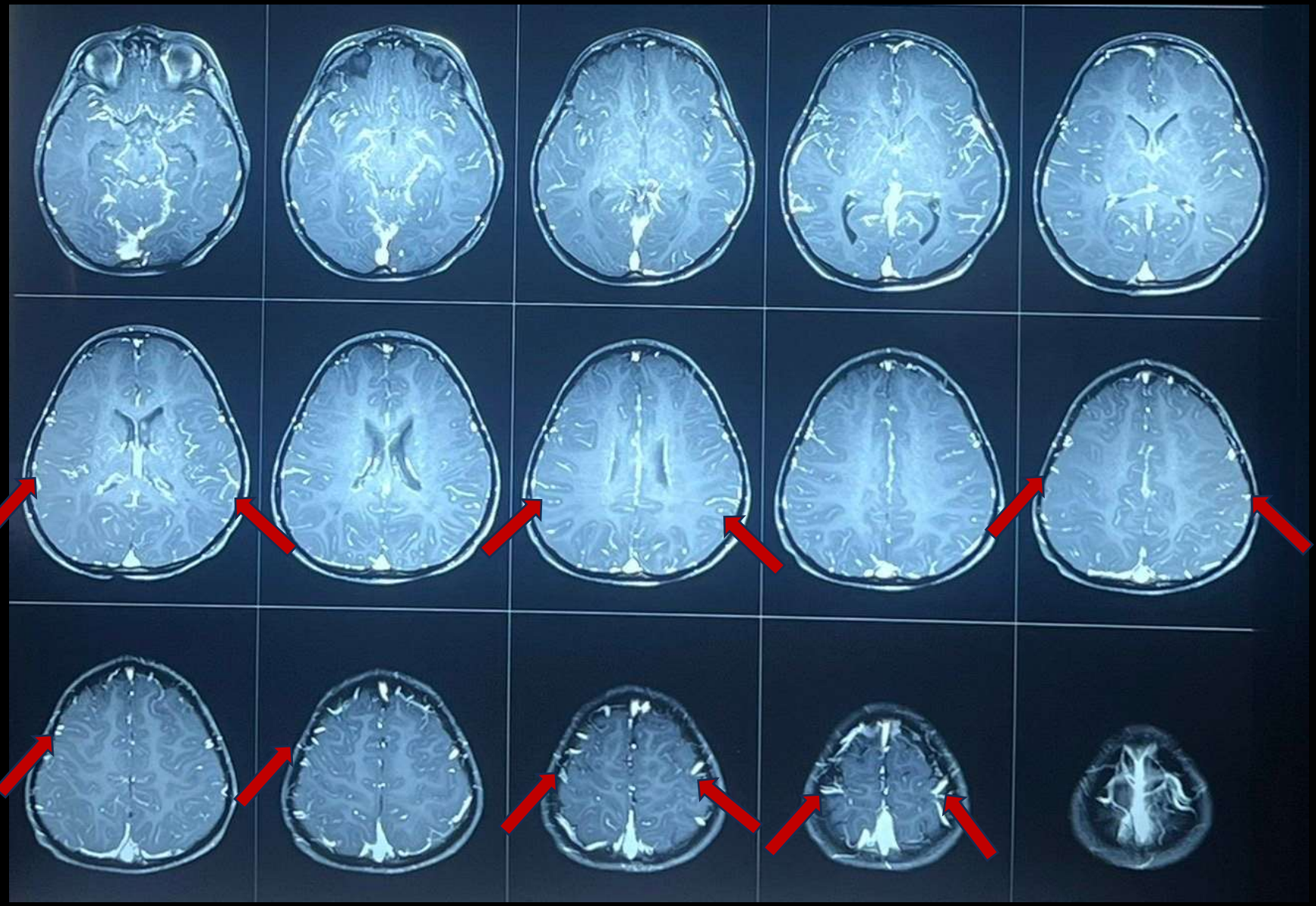
Investigations

- ✓*Hb – 12.5*
- ✓*TLC – 16,500 (N/L – 46/40)*
- ✓*Platelets – 246,000*
- ✓*CRP – 54*
- ✓*LFT – WNL*
- ✓*RFT – WNL*
- ✓*Serum electrolytes - WNL*

Lumbar puncture –

- ✓Cells – 22 (80% - Lymphocytes, 20% - Neutrophils)
- ✓Proteins – 32.9
- ✓Glucose – 62
- ✓RBCs - 0
- ✓MRI Brain with Contrast





Outside hospital course

- ✓CSF Biofires was done which was negative
- ✓Nasopharyngeal swab Biofires was also done which was suggestive of parainfluenza virus infection

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- ✓In view of clinical presentation and neuroimaging findings possibility of demyelination/Auto-immune encephalitis was considered
- ✓Patient was started on Methylprednisolone and IVIG (single dose at 1g/kg)
- ✓During further course of stay progressive deterioration in sensorium, new onset squint of left eye, papilledema and hypertensive readings were noted

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- ✓Anti cerebral oedema measures were started

✓After 7 days of outside hospital stay (14th day of the onset of illness) patient got admitted at Dr. D.Y Patil Medical College and hospital, Pune

On admission –

✓GCS – 7/15 (E2V2M3)

✓Temperature – Febrile (101°F)

✓HR – 112/min

✓PP – Normal volume

✓RR – 56/min with intercostal and subcostal retractions

✓BP – 116/96 mm Hg (>99th centile)

✓Spo2 – 98% on O2 by nasal prongs

✓Normal anthropometric measures

✓No dysmorphism

✓No neurocutaneous markers

CNS examination

- ✓ HMF – Drowsy
- ✓ GCS – 7/15 (E2V2M3)
- ✓ Cranial nerve examination -
- ✓ Pupils - bilaterally equal and reactive
- ✓ Fundus – Changes of papilledema
- ✓ Left lateral rectus palsy s/o 6th nerve affection
- ✓ Rest of the cranial nerve examination - normal

- ✓ Motor examination –
- ✓ Tone – Spasticity present in both upper and lower limb (Grade - 1)
- ✓ Power – >3/5
- ✓ Brisk DTRs
- ✓ Extensor plantar

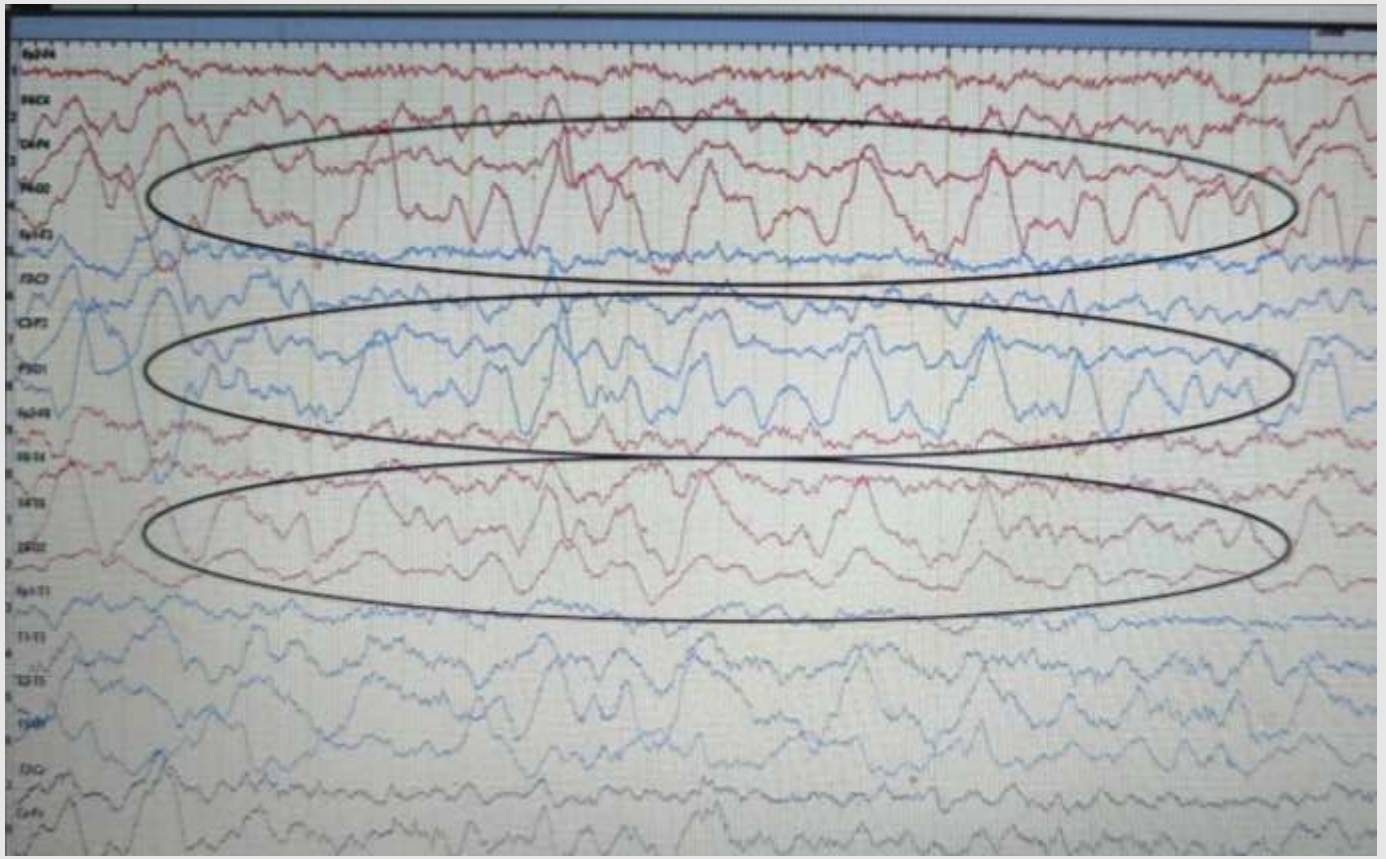
- ✓ Sensory system – withdrawal to pain present
- ✓ Cerebellar signs – Not present
- ✓ Meningeal signs – Neck rigidity and Kernig's sign present

- ✓ *Respiratory system* – Bilateral crepitations
- ✓ *Per Abdomen* - No organomegaly

Picture taken and displayed with due consent from the parents

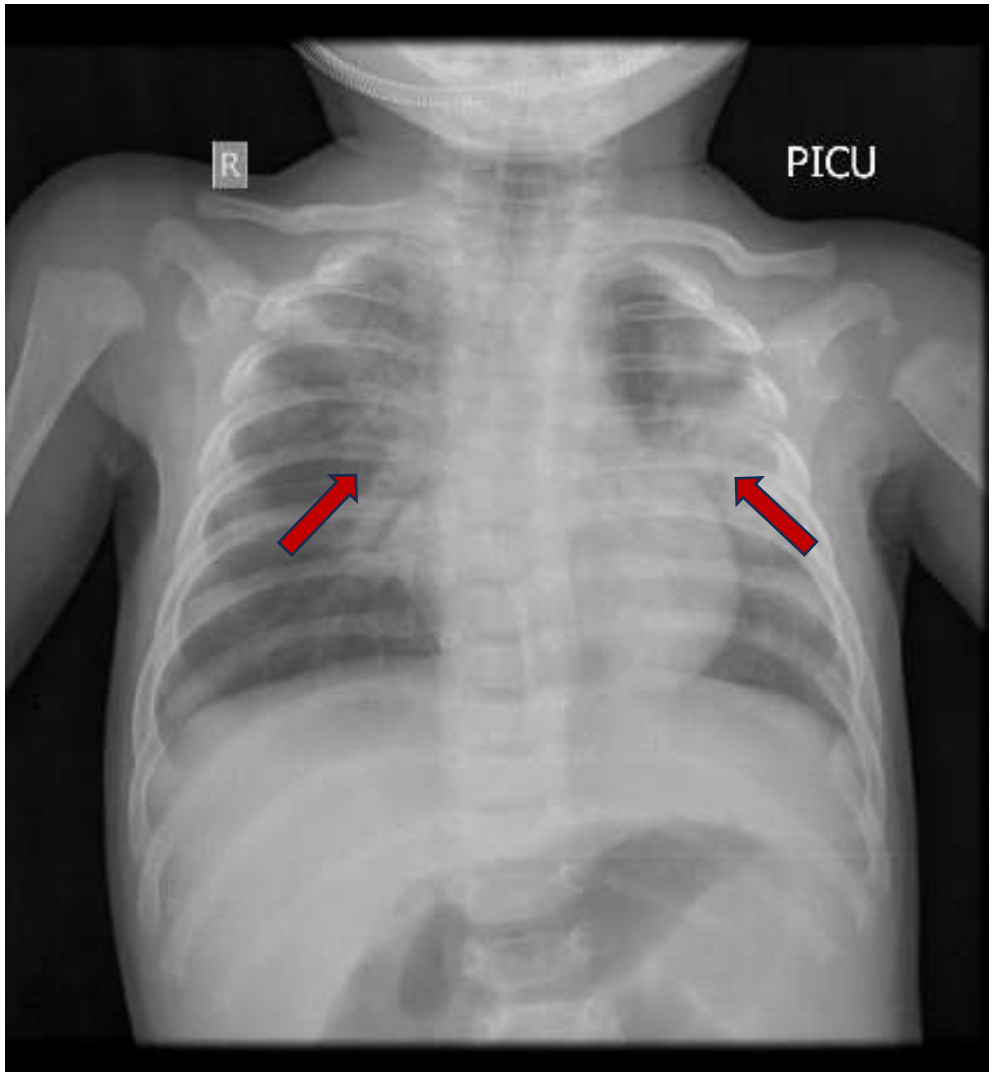
✓ Eye movements – suggestive of Oculogyric crisis

✓Bedside EEG – No ictal corelate - Diffuse delta slowing – Suggestive of Encephalopathy



✓ Autonomic fluctuation – Blood pressure, Heart rate and temperature were noticed

✓ Chest Xray – Fluffy interstitial infiltrates s/o atypical pneumonia



Summary

- ✓3-year-old male child with normal birth, development and family history presented with complaints of -
- ✓Fever, cough, cold, respiratory distress
- ✓Altered sensorium and
- ✓Multiple episodes of seizures
- ✓On examination the patient had a GCS of 7/15, signs of respiratory distress, autonomic fluctuations with positive pyramidal and extrapyramidal findings, signs of raised ICT and positive meningeal signs.

On the basis of history and examination following differential diagnoses were considered -

- ✓**Tubercular meningitis**
- ✓**Viral encephalitis (Possibility of Parainfluenza, Adenoviral, Enteroviral, Epstein bar virus)**
- ✓**Mycoplasma encephalitis**
- ✓**Autoimmune encephalitis**
- ✓**Acute Demyelination Syndrome**

Investigations

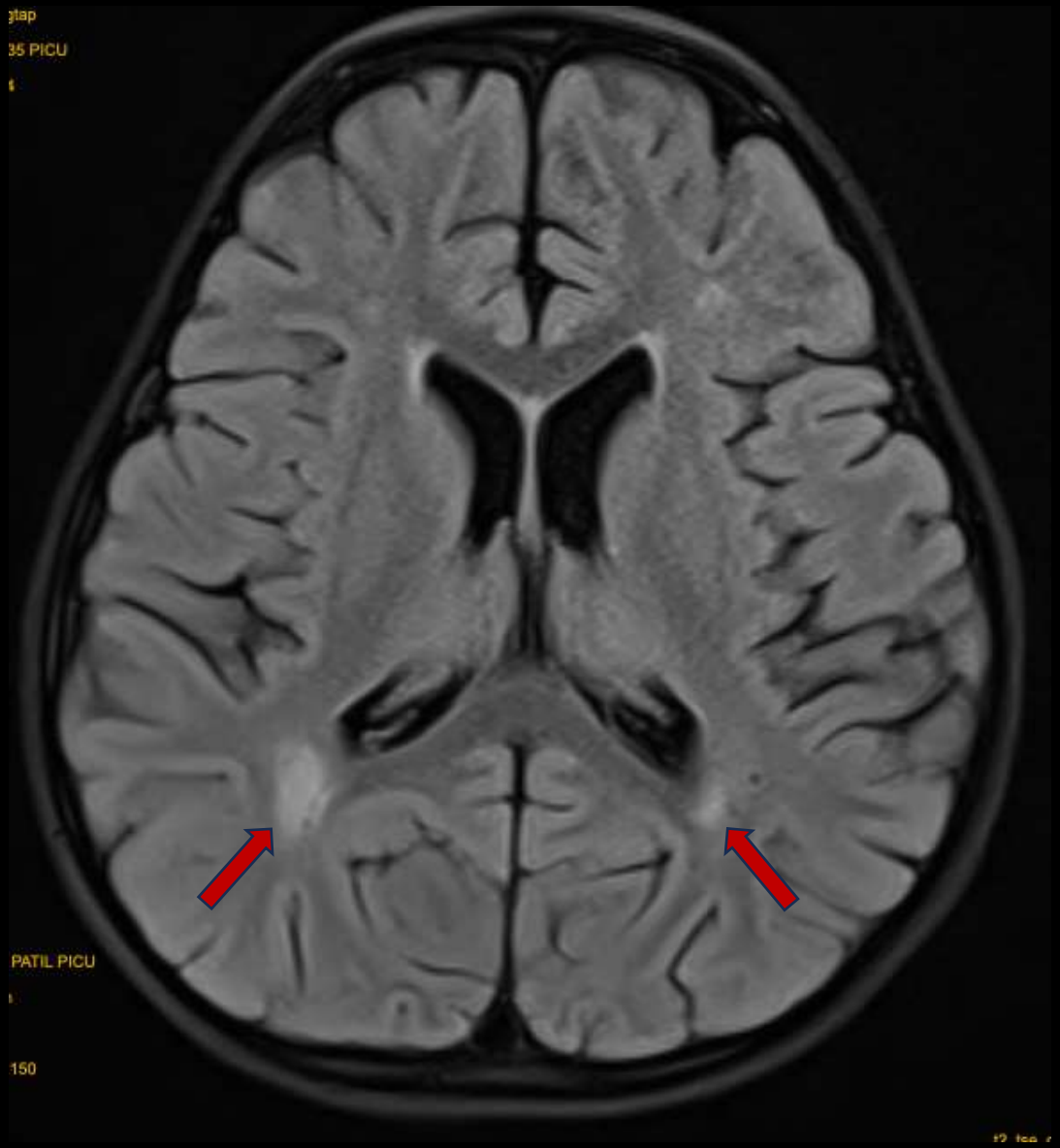
✓Complete blood count, C-Reactive Protein, Liver and Renal function test, Serum electrolytes

Investigations

- ✓*Hb – 12.5*
- ✓*TLC – 14,500 (N/L – 60/40)*
- ✓*Platelets – 212,000*
- ✓*CRP – 24*
- ✓*LFT – WNL*
- ✓*RFT – WNL*
- ✓*Serum electrolytes - WNL*

Investigations

✓Repeat MRI Brain with contrast and whole spine screening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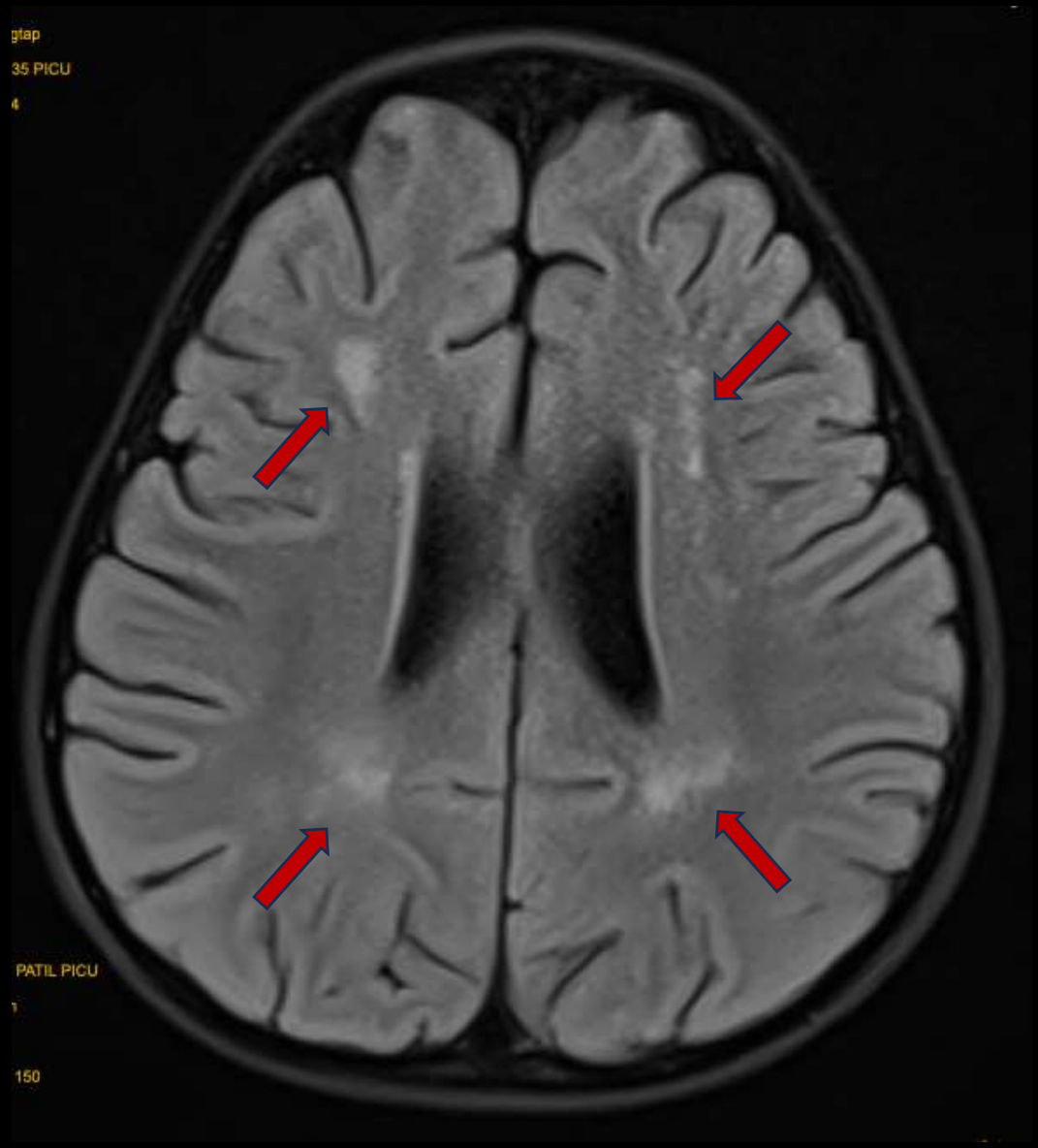
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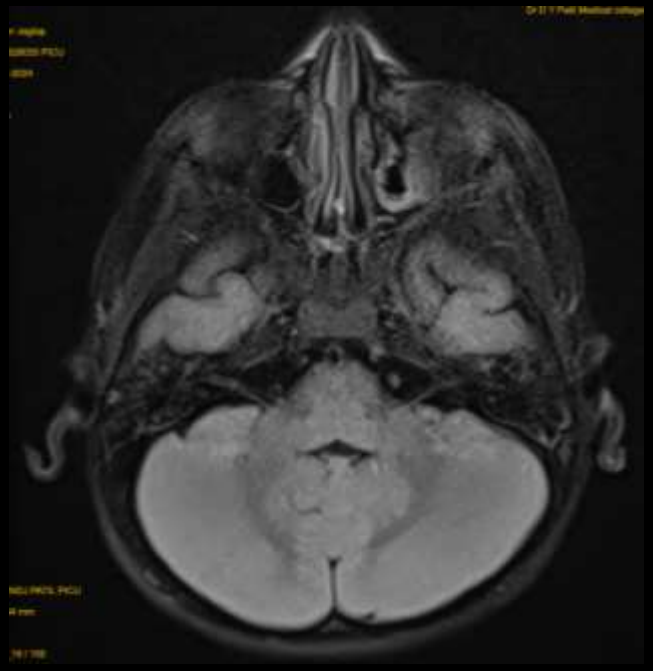

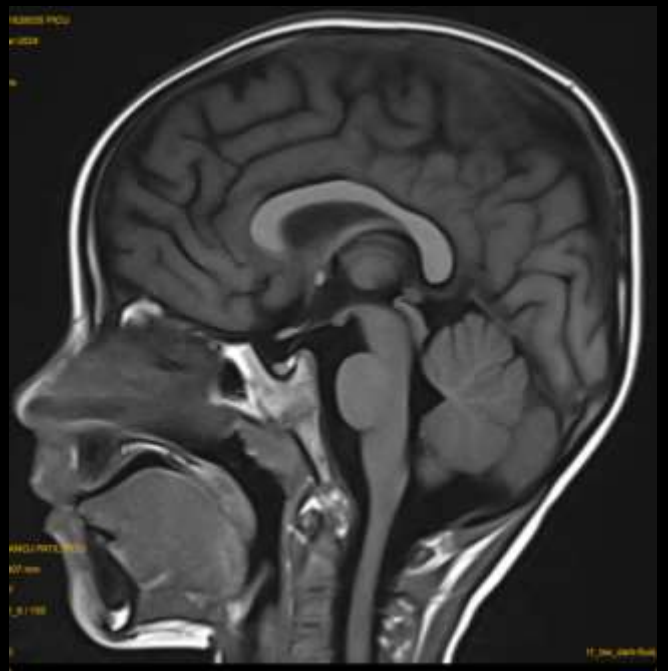


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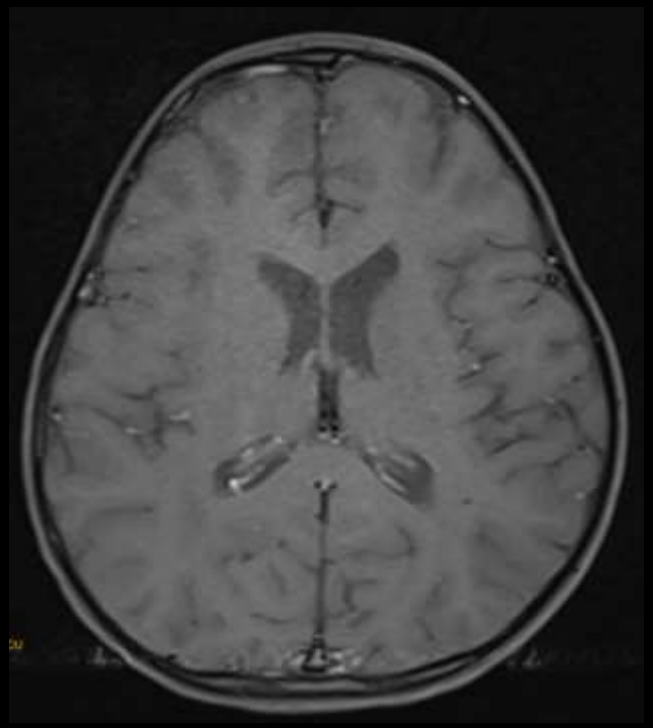

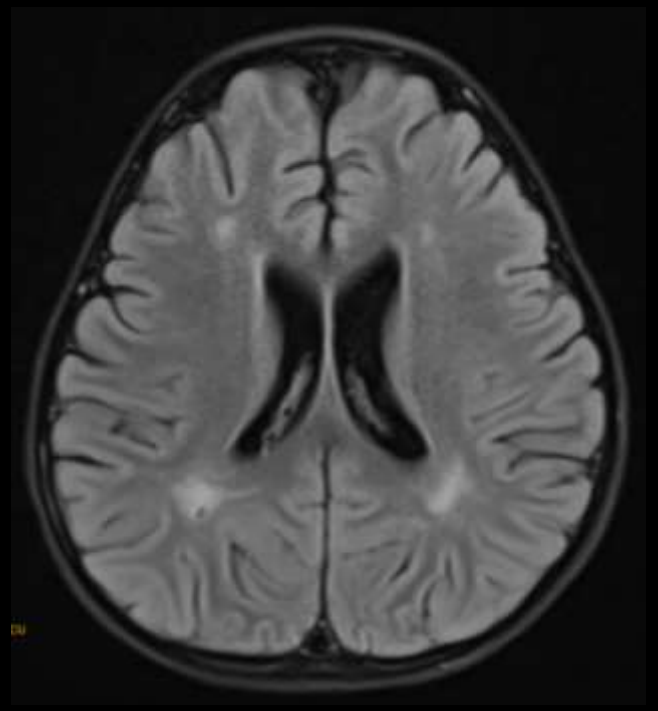

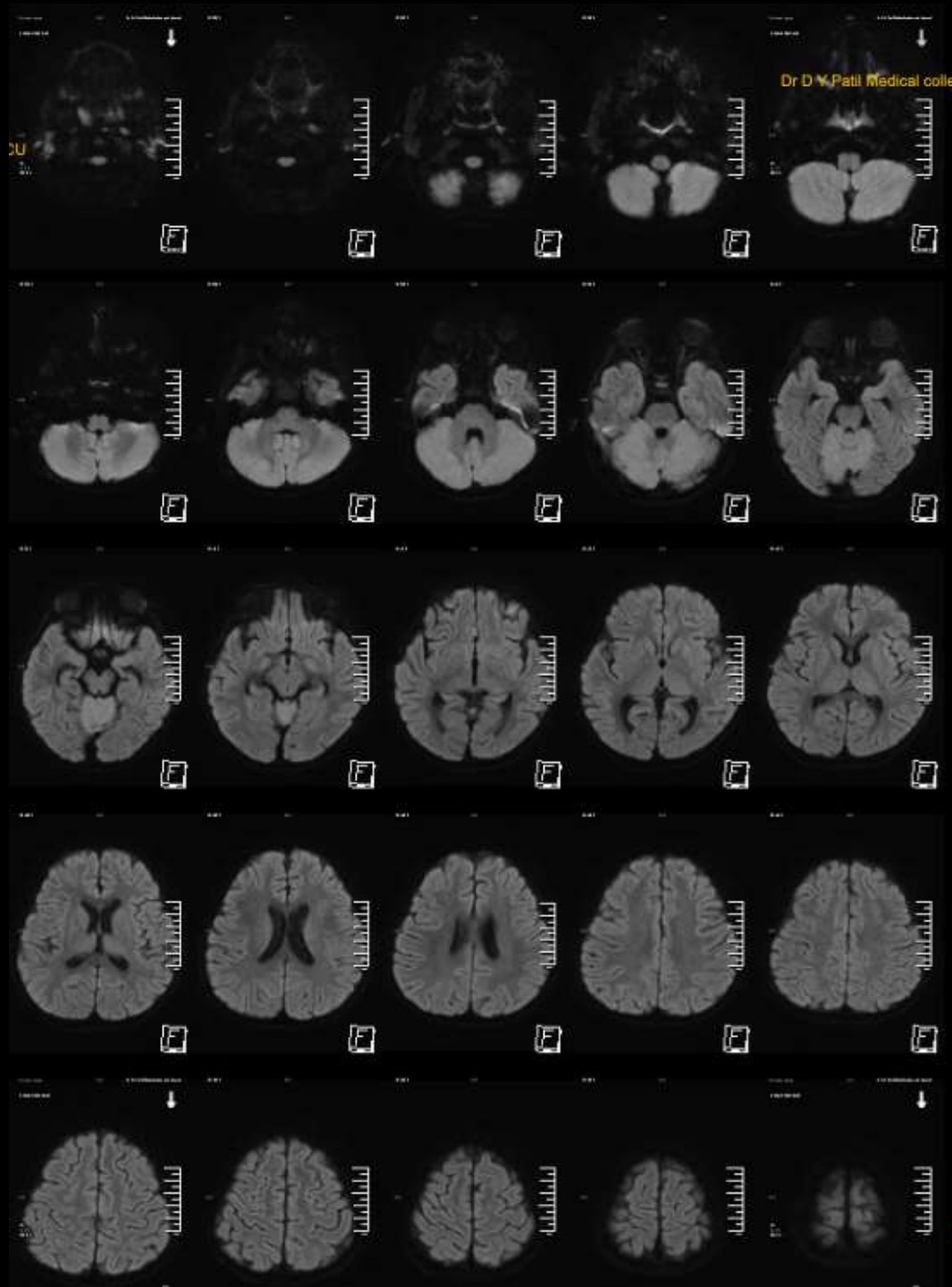
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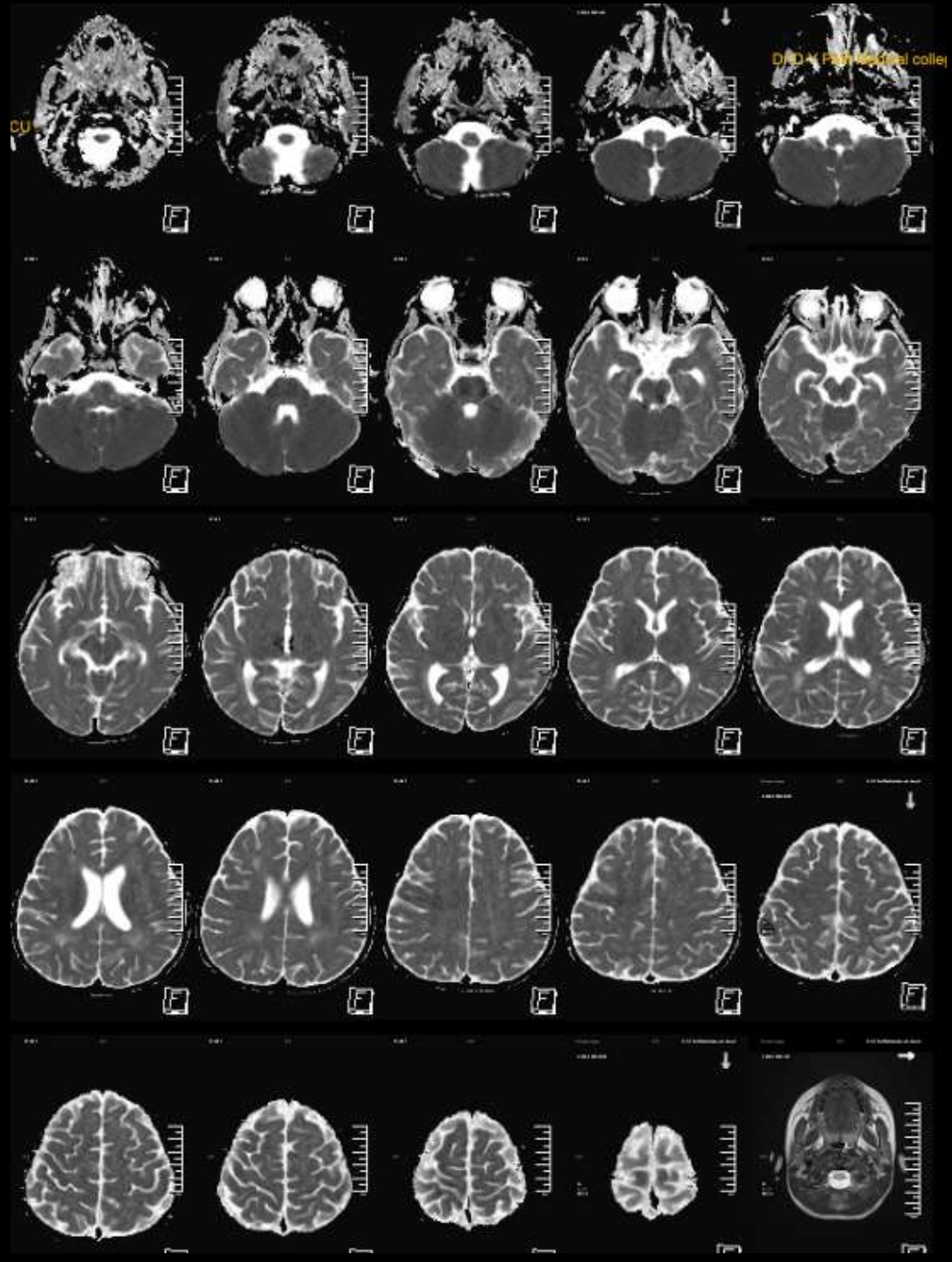
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Investigations

- ✓Repeat Lumbar puncture

Lumbar puncture –

- ✓Cells – 30 (100% Lymphocytes)
- ✓Proteins – 57.6 (Previous - 29)
- ✓Glucose – 75 (BSL - 92)
- ✓RBCs - 0

Investigations

✓TB work up and CSF CBNAAT - Negative

✓Serum Mycoplasma IgM antibody – Positive

✓CSF Auto-immune encephalitis panel – Negative

✓Serum EBV IgM antibody – Negative

✓Japanese encephalitis CSF IgM and PCR – Negative

✓Serum MOG and AqPo4 antibody - Negative

Treatment

- ✓Ceftriaxone (100 mg/kg/day), Acyclovir(60 mg/kg/day), Levetiracetam (40 mg/kg/day), Fosphenytoin (5 mg/kg/day), Oseltamivir (3 mg/kg/day), 3% NaCl (1 ml/kg/hour) were continued

- ✓At this stage, we considered 2 possibilities –
- ✓**1. Mycoplasma encephalitis and**
- ✓**2. Sero-negative Auto-immune encephalitis**

- ✓Azithromycin (10 mg/kg/day) was started in view of Mycoplasma encephalitis
- ✓IVIG (1 g/kg/day) and Methylprednisolone (30 mg/kg/day) was continued in view of possibility of Auto-immune encephalitis

- ✓On day 4 of admission (Day 18 of illness) – No improvement in sensorium was observed
- ✓Levofloxacin was also started which has been proven efficacious in cases of Azithromycin resistant Mycoplasma encephalitis

- ✓Day 8 of admission (Day 22 of illness) – IVIG, Methylprednisolone, Azithromycin, Levofloxacin - no improvement in the sensorium was seen
- ✓Progressive increase in dystonia and opisthotonic posturing was observed

- ✓Parents revealed a crucial history, which was concealed initially

- ✓A history of scratch below the right nostril resulting in a lacerated wound of 1 x 0.5 cm by a rabid dog which was later found to be deceased – WHO Category 3 rabies virus exposure 2 weeks before the onset of illness was revealed
- ✓By the time child was admitted, scratch was completely healed

- ✓Child received Anti-rabies vaccine on day 0, 3 and 7
- ✓Equine rabies Immunoglobulin on day 0 (dose of 40 IU/kg)
- ✓However, when the patient was scheduled for the 4^{th} dose of the vaccine, he began developing symptoms for which he was then admitted

- ✓In view of a category 3 rabies exposure, possibility of **Rabies Encephalitis** was now considered
- ✓We discussed the case with the National Institute of Virology, Pune as our patient did not exhibit classical signs such as hydrophobia or aerophobia or neuroparalysis and was administered both vaccine and immunoglobulin

✓We were then advised to send the following samples considering the rare possibility of the non-classical form of Rabies encephalitis–

- 3 serial saliva samples 4 hours apart
- CSF
- Serum
- Skin biopsy from the nape of the neck

Result of Molecular Testing for Rabies

Sample ID	Sample Type	Test performed	Result
2411764	Saliva	Real-time Reverse Transcription Polymerase Chain Reaction	No rabies virus RNA detected
2411765	Cerebrospinal fluid		
2411767	Neck skin biopsy		

Result of Serological Testing for Rabies

Sample ID	Sample Type	Test performed	Result
2411765	Cerebrospinal fluid	Rapid Fluorescent Focus Inhibition Test	Rabies virus neutralizing antibodies detected (Titre: 128)
2411766	Serum		Rabies virus neutralizing antibodies detected (Titre: Greater than 1024)

Diagnostic criteria for Rabies Encephalitis

- ✓ **Any detectable antibodies in a single CSF sample (irrespective of prior vaccination status)**

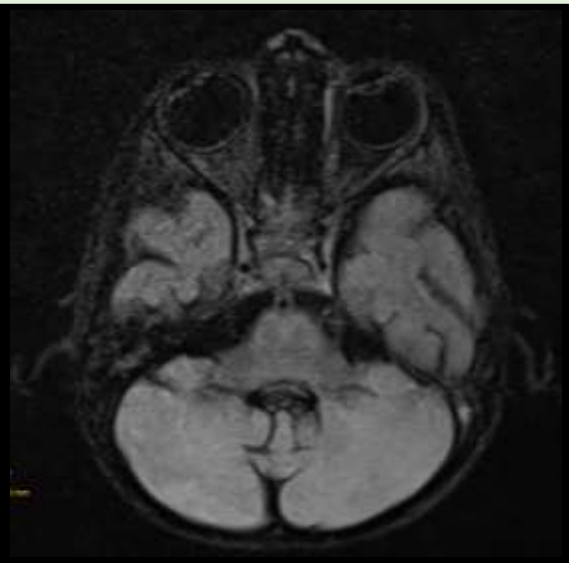
or

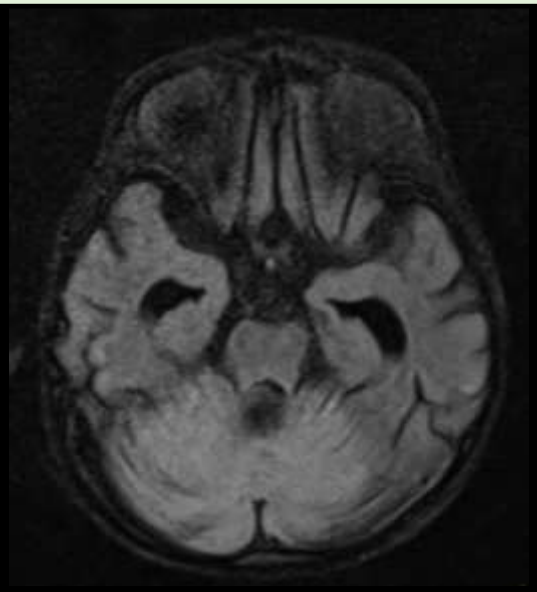
- ✓ **Detectable antibodies in serum sample of patients with no prior vaccination**

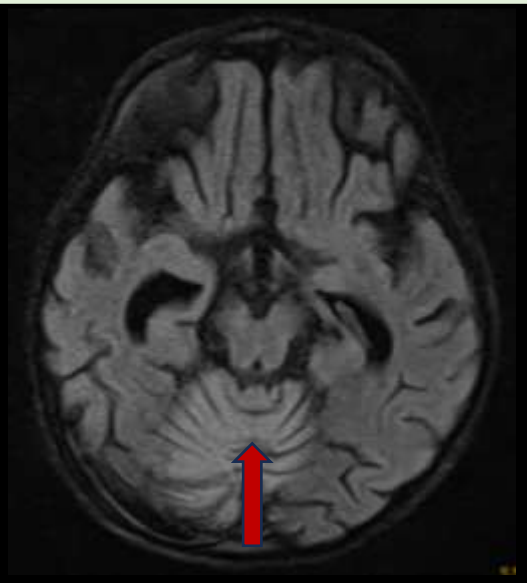
or

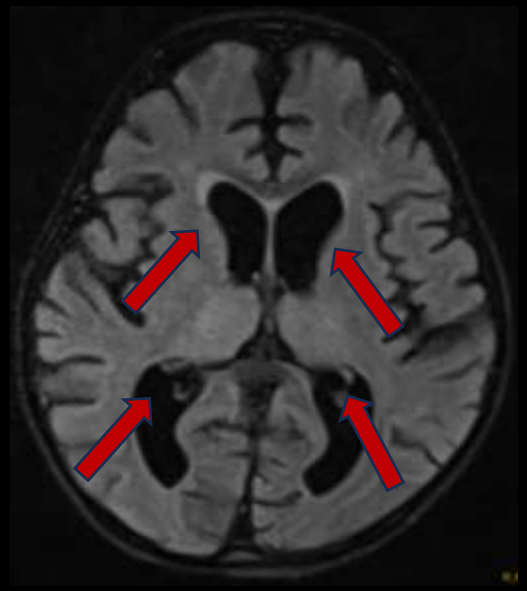
- ✓ In patients who have **received prior rabies vaccination** (partial or complete) - **Paired serum sample demonstrating a 4-fold or greater rise in antibody titres**

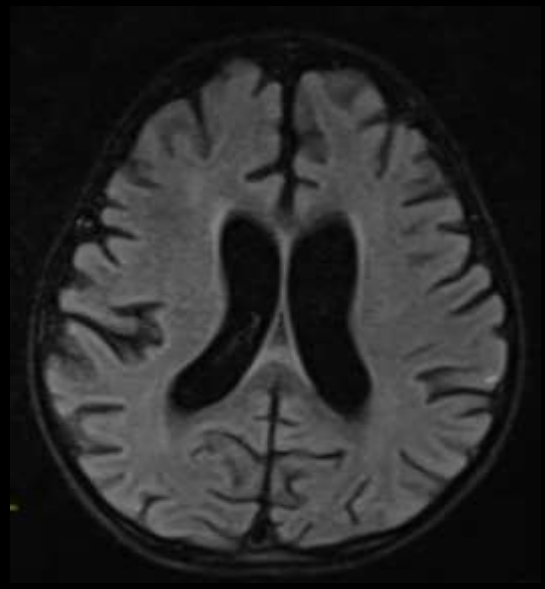
✓ A repeat MRI Brain was done at 36 days after the onset of illness in view of the progressive clinical deteoriation

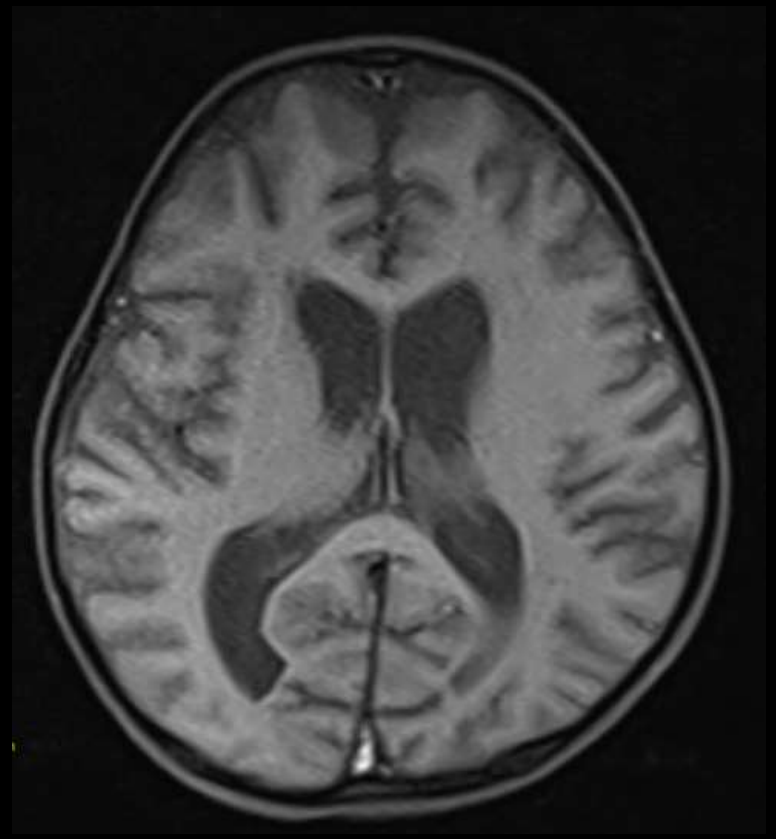










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1. Considering the history of **category 3 rabies exposure** (2 weeks before the onset of illness)
2. **Progressive clinical course**
3. **Progressive atrophy of cerebrum, cerebellum, caudate and thalamus**
4. **Presence of neutralizing rabies antibodies in the CSF**

✓A diagnosis of **atypical/Non-classical form of Rabies encephalitis** was confirmed

- ✓The patient was shifted to ward after 21 days of stay in PICU
- ✓Physiotherapy
- ✓Anti-dystonic/Anti-spasticity medicines
- ✓Ankle foot orthosis

  For dystonia, spasticity and contractures
- ✓Anti-seizure medication (Levetiracetam)
- ✓Frequent position change and water bed

  Prevention of bed sores
- ✓High calorie and protein diet via nasogastric tube
- ✓Anti-mycoplasma treatment was given for 14 days
- ✓Multi-vitamins and calcium supplements
- ✓The patient was started on Amantadine based on the evidence from case reports

- ✓62 days since the onset of illness
- ✓Currently in persistent vegetative state
- ✓mRS (Modified Rankin Score) of 5
- ✓Respiratory infection has settled
- ✓Intermittent autonomic fluctuation in blood pressure, heart rate and temperature
- ✓Severe dystonia
- ✓Ankle contractures

Picture taken and displayed with due consent from the parents

Rabies Infection

- ✓Rabies is one of the oldest known diseases in history with cases dating back to 4000 years ago
- ✓The origin of the word rabies is from the latin word "rabere" which translates to "to rage"
- ✓Rabies virus causes an acute progressive encephalomyelitis in humans and kills up to 70000 people/year worldwide and 20,000 people in India
- ✓Usually transmitted through the saliva of an infected animal, rabies encephalitis has the highest fatality rate (virtually 100%) among infectious diseases
- ✓Dogs, the main rabies reservoir species, usually infect by an unprovoked bite.
- ✓**Survival from rabies is rarely seen, with fewer than 20 adequately documented cases reported worldwide**

✓There are **5 stages** of rabies following inoculation:

Stage – 1 - Incubation;

Stage – 2 - Prodrome;

Stage – 3 - Acute neurologic illness;

Stage – 3 - ***Acute neurologic illness***;

3 types

1. **Encephalitic (Furious) form** – Most common (85%)

- ✓Hydrophobia
- ✓Aerophobia
- ✓Altered sensorium,
- ✓Autonomic dysfunction (tachycardia, tachypnoea, fever fluctuation in blood pressure)

2. Paralytic form – Less common (<20%)

- ✓Maybe confused with GBS
- ✓May have altered sensorium, fever and bladder dysfunction

3. Non-classic form or Atypical form – Rare

- ✓Seizures
- ✓Slowly progressive course
- ✓Autonomic dysfunction
- ✓Oculogyric crisis

- ✓Stage - 4 (Coma) – Usually begins within 10 days of stage - 3
- ✓Stage – 5 – Death
- ✓Following the onset of stage 4, without supportive care, most patients die within two to three days
- ✓Even with supportive therapy, virtually zero patients survive rabies

THE AMERICAN JOURNAL OF TROPICAL MEDICINE AND HYGIENE
official Journal of the American Society of Tropical Medicine and Hygiene

Am J Trop Med Hyg. 2019 Jan; 100(1): 165–169.
Published online 2018 Nov 5. doi: 10.4269/ajtmh.18-0711

PMCID: PMC6335910
PMID: 30398147

Case Reports: Survival from Rabies: Case Series from India

Reeta S. Mani,[1,*] Tina Damodar,[1] Divyashree S,[2] Srikanth Domala,[3] Birendra Gurung,[4] Vilas Jadhav,[5] Ramesh Konanki,[3] Lokesh Lingappa,[3] Sathish Kumar Loganathan,[6] Rajendra Salagare,[7] and Priyash Tambi[8]

- ✓ This is a case series from India describing the clinical and radiological findings of eight patients with laboratory confirmed rabies who survived the illness (ranging from up to 5 months to > 1 year post onset of symptoms)
- ✓ All of them had World Health Organization (WHO) category III rabies virus exposures through dog bites
- ✓ Wound management and anti-rabies vaccination (ARV) were initiated on the day of exposure in all patients, except in one case where ARV was initiated 12 days after the dog bite
- ✓ Only 3/8 (37.5%) received rabies immunoglobulin (RIG)

Details of patients with laboratory-confirmed rabies (n = 8)

Case no.	Age/gender; state; month and year of disease onset	Mode and site of exposure; World Health Organization category of exposure	Vaccine type, dose, and site	Type of rabies immunoglobulin; site (local and systemic)	Incubation period (days)	Presenting clinical features	Magnetic resonance imaging findings (day post onset of symptoms)	Neurological sequelae	Outcome/duration of survival (as of June 30, 2018)
1	13 years/M; Sikkim; June 2016	Dog bite; right leg; category III	PCEC; five doses; IM; site unknown (initiated 12 days after bite)	None	90	Fever of 2 weeks duration, breathlessness, paralysis, and aerophobia	Not carried out	Severe	Died after 5 months of survival
2	10 years/M; Andhra Pradesh; January 2015	Dog bite; right thigh and right loin; category III	PCEC; three doses; IM (site unknown)	None	17	Fever of 7 days duration, lethargy, and altered sensorium since 2 days	Bilateral bulky and long basal ganglia (right > left). Gyral swelling in the right posterior parietal cortex, showing mild diffusion restriction (day 8)	Severe	Died after 6 months of survival
3	5 years/F; Karnataka; December 2016	Dog bite; right leg; category III	PCEC; three doses; IM (site unknown)	None	20	Fever of 10 days duration, followed by vomiting and drowsiness, and altered sensorium of 1 week duration	Not carried out	Severe	Died after 8 months of survival
4	3 years/F; Maharashtra; October 2017	Dog bite; left hand (ring finger); category III	PCEC; five doses; IM (deltoid and gluteal regions)	None	25	Excessive sleep, lethargy, drowsiness, inability to walk, no spontaneous eye movement, no response to verbal commands	Lesions in the dorsal brainstem; thalamus and basal ganglia also involved (day 7)	Moderate	6 months (still surviving)
5	5 years/F; Maharashtra; November 2017	Dog bite; right side of shoulder, chest, and hip; category III	PCEC; four doses; IM (deltoid)	Human rabies immunoglobulin (local and IM)	19	Fever with chills of 6 days duration, drowsiness, and projectile vomiting of 2 days duration	T2/FLAIR hyperintensities seen in the bilateral parieto-occipital region (cortical), bilateral thalami, right putamen, and right insular cortex without any abnormal susceptibility on SWI or restriction on DWI (day 10)	Severe	7.5 months (still surviving)
6	4 years/M; Maharashtra; August 2017	Dog bite; right eyebrow; category III	PCEC; three doses; IM (triceps)	ERIG (local and IM)	20	Fever, altered sensorium, oculogyric crisis of 1-week duration	Midbrain and cervicomedullary T2 hyperintensities (day 4)	Severe	10 months (still surviving)
7	26 years/M; Maharashtra; April 2017	Dog bite; face; category III	PCEC; four doses; IM (deltoid)	None	16	Fever, body ache, ear discomfort, diplopia, difficulty walking, behavioral changes–restlessness, excessive and irrelevant talking	Abnormal T2 and flair hyperintensities over bilateral basal ganglia. Abnormal T2 hyperintensities involving pons and medulla (day 1)	Moderate	13 months (still surviving)
8	9 years/M; Telangana; April 2017	Dog bite; dorsal aspect of left mid-forearm; category III	PCEC; four doses; IM (site unknown)	ERIG–local (20 days after bite)	15	Fever, pain in the left upper limb, neck pain for 8 days, agitation and somnolence since 3 days	T2W and FLAIR hyperintensities in dorsal midbrain, dorsal pons, and cervical spinal cord upto C7 level suggestive of rhombencephalitis and myelitis (day 7) (Figure 1)	Mild	13 months (still surviving)

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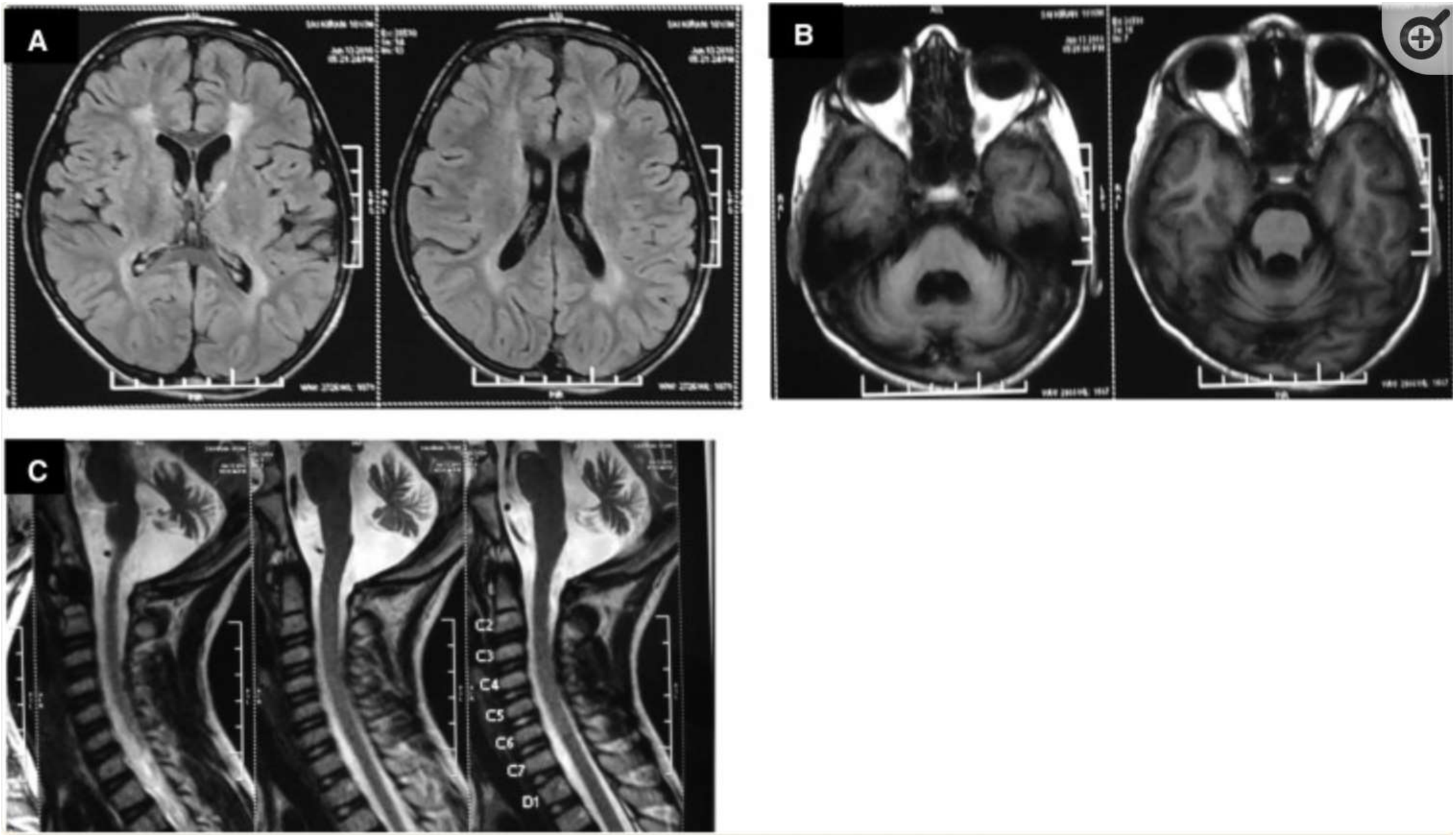
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✓Patients who have received **prior vaccination** but develop rabies

⬇

✓Rapidly **develop high concentrations of serum and CSF-neutralizing antibodies**

⬇

✓**Possibly leading to viral clearance**

⬇

✓Explains the **low sensitivity of PCR** which was seen in our case

✓Administration of vaccine and RIG

✓Alters the pathogenicity and natural progression of rabies virus infection

✓**Leading to atypical presentation of rabies encephalitis and survival**

- ✓Currently, there is no antiviral of proven efficacy in human rabies
- ✓A unique treatment, the "Milwaukee Protocol" which included induced coma and anti-excitotoxic therapy was credited with the survival of an unvaccinated teenager with bat rabies encephalitis in 2005
- ✓However, multiple efforts to replicate this protocol have not been largely successful
- ✓The Milwaukee Protocol, in its current version, is a supportive critical care

Conclusion

- ✓This is the 5th documented case from Maharashtra and 9th case from India who has survived rabies
- ✓It highlights the tragic occurrence of the disease despite vaccination and IG administration
- ✓It also emphasizes the importance of post exposure prophylaxis and post exposure prophylaxis protocols which should be strictly followed during administration of the vaccine and Immunoglobulin
- ✓The primary focus, therefore, should be on the "prevention" of rabies by preventing animal bite
- ✓Increasing awareness about the disease and PEP protocols among the public and health-care professionals in rabies endemic countries
- ✓ Providing pre exposure prophylaxis in high risk individuals

Acknowledgement

I would like to thank –

✓Department of Radiodiagnosis

✓Department of Microbiology

✓National Institute of Virology, Pune

Thank you!