"A Case of Acute Encephalitis Syndrome and Cranial Nerve Palsy secondary to Scrub Typhus: A Rare Presentation from Western Nepal".

SK Lamichhane[1], Eliz Achhami[2], Satyam Mahaju[2], Rabin Gautam[1], and Amrit Adhikari[1]

[1]Bir Hospital
[2]Sukraraj Tropical and Infectious Disease Hospital

March 7, 2023

Title Page:-

"A Case of Acute Encephalitis Syndrome and Cranial Nerve Palsy secondary to Scrub Typhus: A Rare Presentation from Western Nepal".

SK Lamichhane[1], Eliz Achhami[2], Satyam Mahaju[3], Rabin Gautam [4], Amrit Adhikari[5]

[1] Bir Hospital, Kathmandu, Nepal

(email:- lamichhaneak1312@gmail.com)

[2] Sukraraj Tropical & Infectious Disease Hospital, Kathmandu, Nepal

(email:- eliz0917@gmail.com)

[3] Sukraraj Tropical & Infectious Disease Hospital, Kathmandu, Nepal

(email:- mahaju.satyam1@gmail.com)

[4] Bir Hospital, Kathmandu, Nepal

(email:- rabingautam1@gmail.com)

[5] Bir Hospital, Kathmandu, Nepal

(email:- a1amrit12@gmail.com)

*Corresponding author.

Eliz Achhami, MBBS

Sukraraj Tropical & Infectious Disease Hospital, Kathmandu, Nepal

Mobile no. : - 977-9846710319

E-mail: eliz0917@gmail.com

ACKNOWLEDGMENT:-

We would like to acknowledge the patient herself and her relatives who allowed us to share their clinical report to the global platform, so that others will be benefitted.

CONFLICT OF INTEREST:-

The authors would like to declare that they have no competing interests.

A FUNDING STATEMENT:-

No funding was generated for this case report

AUTHORS CONTRIBUTION:-

1. SK lamichhane: involved in patient management, data collection, design of study, manuscript writing and revision.
2. Eliz Achhami : design of study, data collection, evidence collection, manuscript writing and revision, corresponding author.
3. Satyam Mahaju :- design of study, data collection, evidence collection, manuscript writing and revision
4. Rabin Gautam :- design of study, data collection, manuscript revision
5. Amrit Adhikari:- design of study, involved in patient management, manuscript revision.

ETHICAL APPROVAL:-

As case reports are exempt from ethical approval in our institution, our article which describes a case report does not require additional permissions from the Ethics committee.

CONSENT:-

Full written informed consent was obtained from the patient for publication of her case, clinical images, and radiographic images. A copy of written consent can be made available to the editor in chief of this journal upon request.

DATA AVAILABILITY S TATEMENT:-

All the data generated or analyzed during this study are included in the manuscript.

Introduction:-

Scrub typhus is a zoonotic rickettsiosis caused by the bacterium Orientia tsutsugamushi. It is transmitted by larvae of the Leptotrombidium mites and is endemic to a region called the tsutsugamushi triangle that extends from Southeast Asia to the Pacific Ocean [1]. Scrub typhus commonly infects farmers and field workers [1]. The central nervous system (CNS) can often be affected in scrub typhus, with neurological manifestations being present in approximately 20% of cases, either in the form of acute encephalitis, meningitis, or meningoencephalitis[2]. The clinical manifestations of scrub typhus are variable, with the involvement of nearly every system and organ, alone or in combination [3]. Recent epidemiological studies suggest that scrub typhus is a major cause of central nervous system infections in endemic areas [4–6]. The neurological manifestation of scrub typhus has become an emerging public health concern beyond current endemic areas, as ecological changes may increase the prevalence of arthropod-borne CNS-infected populations worldwide[7]. On the other hand, delayed treatment can lead to significant neurological creaks and even death [8].

Case presentation

A 17-year-old girl living in a village in western Nepal was taken to a tertiary hospital, Bir Hospital after being referred from another health center with chief complaints of fever for 17 days and altered sensorium of 4 days duration. She had a low-grade fever initially which got controlled partially with over-the-counter medication. The fever was insidious onset, gradually progressive but this time it was associated with headache, vomiting, and altered sensorium. She had no history of photophobia, ear discharge, convulsions, or focal neurological deficit. She was then taken to a nearby hospital from where she was referred to our hospital with a provisional diagnosis of meningitis. There was no similar history in the past and her family history was non-significant.

When she arrived at the emergency department of Bir Hospital, her axillary temperature was 101.2°F, pulse was 86/min and blood pressure was 140/100 mm Hg. The respirations were regular with a rate of 18 per minute and oxygen saturation was 96%. She had no eschar, rashes, or lymphadenopathy, pupils were normally

responsive. The examination of respiratory system revealed normal vesicular sounds over both lungs without any added sounds. The cardiovascular examination was unremarkable.

On neurological examination, her Glasgow Coma Scale (GCS) was E3V4M6 (i.e. 13/15). She was drowsy and confused. Motor and sensory examination revealed normal findings, superficial and deep tendon reflexes were normal and bilateral planters were flexor. Cranial nerve examination revealed bilateral lateral rectus palsy (Figure 1 and 2), dysphagia, regurgitation of food on attempted feeding, dysarthria, and left sided upper motor neuron (UMN) type facial palsy (Figure 3).

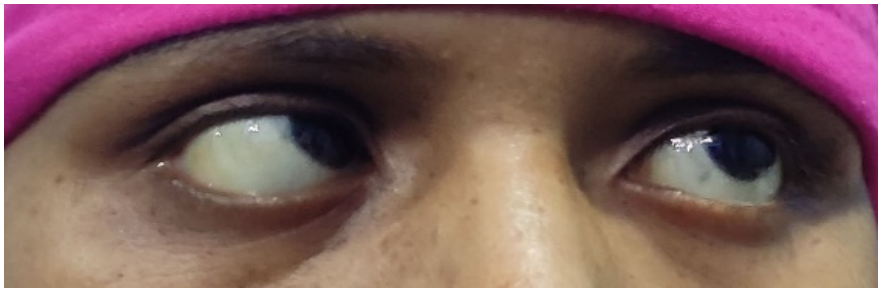


Figure 1: Left lateral rectus palsy in left gaze.

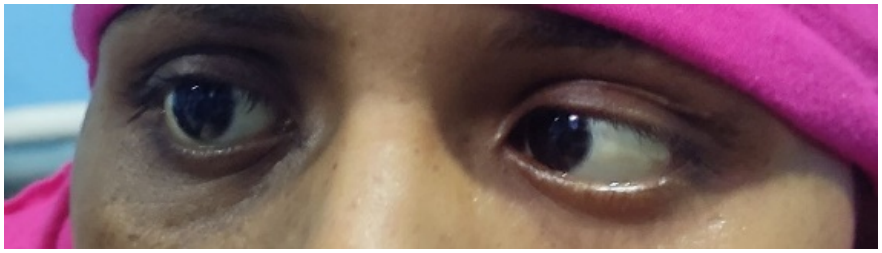


Figure 2 :Right lateral rectus palsy in right gaze.

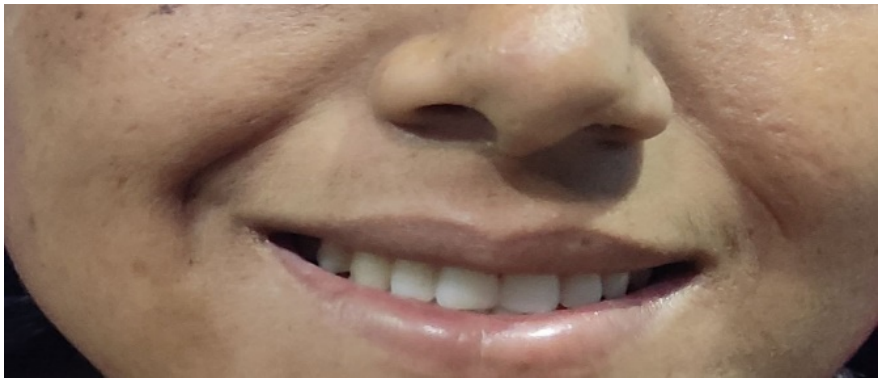


Figure 3: Decreased facial crease on left side.

The complete blood count revealed a total leucocyte count (TLC) of 6000/mm with 40% neutrophils, 50% lymphocytes, 8% monocytes, and 2% eosinophils. The hemoglobin was 9.4 g/L with a mean corpuscular volume of 79 fL and the platelet count was 320000/mcL. There was mild hepatic dysfunction with aspartate transaminase of 63 IU/L and alanine transaminase of 66 IU/L. Total serum bilirubin was 0.5 mg/dL and

albumin was 4 g/dL. Serum sodium, potassium, calcium, and phosphorus were within normal limit. The renal functions were normal with urea of 16 mg/dL and creatinine of 0.8 mg/dL.

Blood and urine cultures were sterile. Serological tests for dengue IgM antibodies and NS1 antigen, herpes simplex and Japanese B encephalitis IgM antibodies were negative. Simultaneous search for other tropical infections like malaria, and leptospirosis were negative, however, Scrub IgM was positive. A guarded lumbar puncture was performed and the CSF analysis yielded a cell count of 16 cells μ/L with 80% lymphocytes and 20% neutrophils. Total protein was elevated to 125 g/dL, glucose was 82 mg/dL and adenosine deaminase was 2.5 IU/L. No organism was seen on the Gram stain, Ziehl-Neelsen stain, and India ink stain. CSF cultures were sterile and PCR was negative for herpes simplex virus (HSV) and Mycobacterium tuberculosis. The Magnetic resonance imaging (MRI) of brain was done and MRI of brain reveled multiple mildly increased T2DM/FLAIR signal in midbrain, pons and in left middle cerebellar peduncle (Figures 4, 5 and 6).

Ceftriaxone, which was already started at the center where she was referred, was continued and the dose was doubled to 2gm two times per day. Acyclovir was added intravenously at a dose of 500 mg times per day and was discontinued after exclusion of herpes simplex encephalitis. Dexamethasone was started at a high dose (1gm) to ease cerebral edema. Ceftriaxone was substituted with doxycycline 100 mg two times per day intravenously after scrub typhus was diagnosed. Two days later, the fever subsided, and gradually she was able to communicate verbally and eat on her own. Objective improvement was documented on MRI. Doxycycline was administered for a total of 2 weeks.

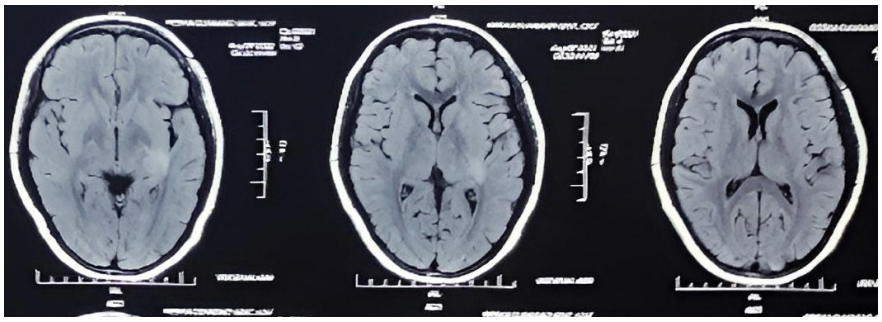


Figure 4. Hyperintense T2/FLAIR Axial images on left insular lobe and adjacent thalamus.

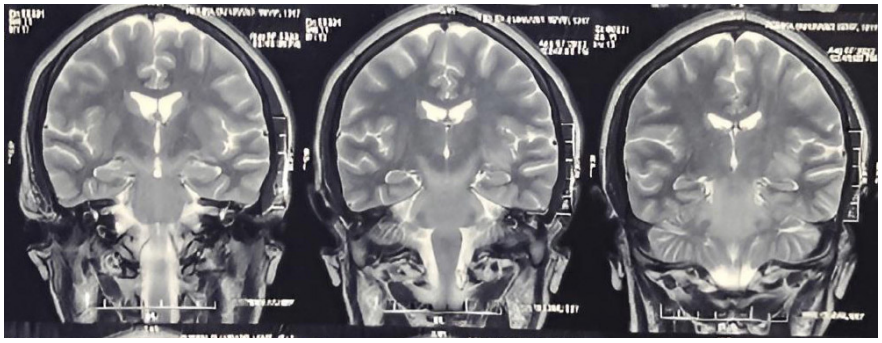


Figure 5. Hyperintense T2/FLAIR coronal images on left insular lobe and adjacent thalamus.

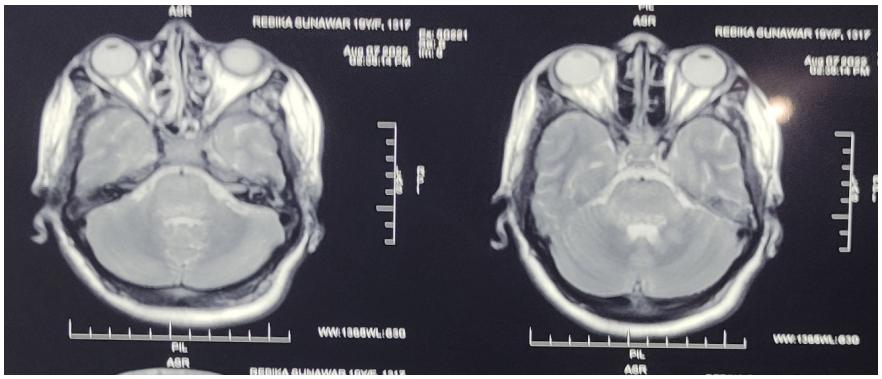


Figure 6: Hyperintense T2 Axial images with mildly incresed signal in pons.

Discussion:-

There have been few attempts to study scrub typhus in Nepal. In 1981, a high probability of scrub typhus was identified in Nepal by detecting high antibody titers (10%) in healthy adults. IgM antibodies to O. tsutsugamushi were positive in samples from various regions, including 30 districts in Nepal. Positive cases have been found in different ecological regions of Nepal [9].

Humans are infected by the bite of the larvae of the leptothrombidium mite. From the bite site, bacteria are distributed throughout the body via blood and lymph. It induces endothelial injury, leukocyte perivascular infiltration, increased vascular permeability, and an vasculitic response with severe microvascular thrombosis leading to organ damage [1,10]. Classically, scrub typhus presents with fever, headache, cough, myalgia, arthralgia, lymphadenopathy, and maculopapular rash that begins from the trunk and spreads to the limbs[11–13]. The 'eschar', which are thought to be the hallmark of the disease, are the bites of these chiggers that creates wound similar to 'cigarette burns' [1,10]. "Characteristic" symptoms of scrub typhus have been occasionally reported, with the characteristic crust occurring in only 20% of patients and lymphadenopathy in 24%. Nevertheless, the eschar occurs more frequently in adults, and conversely, and conversely organanomegaly can occur in children. However, the absence of these signs should not rule out scrub typhus infection, as these features are present in only 1 in 4-5 patients with confirmed CNS scrub typhus. Given its potential impact on long-term morbidity, clinicians should be alert to the possibility of acute convulsive activity in children with central nervous system scrub typhus [14]. The microbe has an increased propensity of infecting organs that are highly vascularized, like the liver, brain, heart, and lungs [11]. Hence, beginning from 2nd week, the infection, if untreated, progresses to complications like acute diffuse encephalomyelitis, encephalopathy, meningitis, cranial nerve palsies, congestive heart failure, vasculitis, myocarditis, pneumonia, acute respiratory distress syndrome, acute renal failure, gastrointestinal bleeding, alterations in liver functions and pancreatitis [11–13,15]. Among the complications, myocarditis and encephalitis are the most life-threatening ones[16]. Doxycycline is the drug of choice and azithromycin is the drug of choice for children and pregnant women[17].

Despite the growing number of clinical studies addressing the neurological complications of tsutsugamushi disease, there are surprisingly few studies to clarify the underlying mechanisms of neuroinvasion and neuroinflammation [8]. Spread of bacteria from the periphery to the central nervous system occurs by hematogenous spread [18,19].

Although the exact mechanism of entry into the central nervous system is unknown, there is evidence that direct entry may occur through damage to the microvascular endothelium or disruption of the blood-brain barrier through transcellular translocation of bacteria, which can occur independently or by way of macrophages that have engulfed the bacterium. After entering the central nervous system, it activates specific transcription factors, such as the nuclear factor kappa B, which causes inflammation [14]. Orientia tsutsugamushi has an endothelial cell tropism and invades dendritic cells, monocytes and tissue macrophages.

Endothelial invasion causes vascular injury with intestinal perivascular mononuclear infiltration leading to complications [20].

Several neurological syndromes have been reported in association with scrub typhus. Literature review reveals case reports of acute transverse myelitis, myoclonus, parkinsonism, and acute disseminated encephalomyelitis [21–23]. Solitary or multiple cranial neuropathy is a well-known neurological manifestation of scrub typhus infection [2]. Cranial nerve disorders such as facial paralysis, sensorineural hearing loss, trigeminal neuralgia, and diplopia due to abduction paralysis were observed[24–27]. Few authors suggest that scrub typhus should be considered as a differential diagnosis in all patients with aseptic meningitis with renal or hepatic impairment living in endemic areas[28]. They found that the CSF profile mimics tuberculous meningitis or viral meningitis. CSF had predominantly lymphocytic pleocytosis, elevated protein with low or normal glucose.

As per the definition, acute encephalitis syndrome presents with the fever in association with seizure, altered mental status and the focal neurological signs like ataxia, aphasia, cranial nerve palsy or hemiparesis [12]. Our patient presented with the symptoms of fever, headache, vomiting, and altered mental status associated with the signs of bilateral lateral rectus palsy, dysphagia, regurgitation of food, dysarthria, and left-sided UMN type facial palsy that is suggestive of acute encephalitis syndrome with cranial nerve palsy.

The Neuroimaging findings for meningoencephalitis due to scrub typhus are quite limited. There have been reports of radio imaging findings of lesions on a white matter involving the subcortical, periventricular deep white matter, corpus callosum, cerebellar peduncles, brain stem, and basal ganglia, as well as grey matter lesion and microhemorrhages[29]. Kar et. al(2014) have reported the presence of diffuse cerebral edema along with T2-weighted and FLAIR hyperintensities in the putamen and thalamus, suggesting brain parenchymal involvement[12]. The diagnosis of encephalitis in our case was further supported by the multiple mildly increased T2DM/FLAIR signal in the midbrain, pons, and left middle cerebellar peduncle.

Conclusion:-

In conclusion, we report a case of scrub typhus presenting as acute encephalitis and cranial nerve palsy treated successfully with high-dose dexamethasone and doxycycline. The unique feature in our case was the unusual involvement of cranial nerves due to scrub typhus. Therefore, while evaluating a case of AES with cranial nerve palsy with suspected infectious disease etiology, it is essential to consider scrub typhus among differential diagnoses, especially in the region of the tsutsugamushi triangle. A timely diagnosis and treatment can help prevent the development of various complications and can help with earlier recovery of patients.

REFERENCES:-

1. Xu G, Walker DH, Jupiter D, Melby PC, Arcari CM. A review of the global epidemiology of scrub typhus. *PLoS Negl Trop Dis* . 2017;11(11). doi:10.1371/JOURNAL.PNTD.0006062

2. Garg D, Manesh A. Neurological Facets of Scrub Typhus: A Comprehensive Narrative Review. *Ann Indian Acad Neurol* . 2021;24(6):849-864. doi:10.4103/AIAN.AIAN_739_21

3. Sharma N, Biswal M, Kumar A, Zaman K, Jain S, Bhalla A. Scrub Typhus in a Tertiary Care Hospital in North India. *Am J Trop Med Hyg* . 2016;95(2):447. doi:10.4269/AJTMH.16-0086

4. Dubot-Pérès A, Mayxay M, Phetsouvanh R, et al. Management of Central Nervous System Infections, Vientiane, Laos, 2003-2011. *Emerg Infect Dis* . 2019;25(5):898-910. doi:10.3201/EID2505.180914

5. Jain P, Prakash S, Tripathi PK, et al. Emergence of Orientia tsutsugamushi as an important cause of Acute Encephalitis Syndrome in India. *PLoS Negl Trop Dis* . 2018;12(3):e0006346. doi:10.1371/JOURNAL.PNTD.0006346

6. Lee HS, Sunwoo JS, Ahn SJ, et al. Central Nervous System Infection Associated with Orientia tsutsugamushi in South Korea. *Am J Trop Med Hyg* . 2017;97(4):1094. doi:10.4269/AJTMH.17-0077

7. Alam AM, Easton A, Nicholson TR, et al. Encephalitis: diagnosis, management and recent advances in the field of encephalitides.*Postgrad Med J* . Published online 2022. doi:10.1136/POSTGRADMEDJ-2022-141812

8. Fisher J, Card G, Soong L. Neuroinflammation associated with scrub typhus and spotted fever group rickettsioses. *PLoS Negl Trop Dis* . 2020;14(10):1-15. doi:10.1371/JOURNAL.PNTD.0008675

9. Upadhyaya BP, Shakya G, Adhikari S, et al. Scrub Typhus: An Emerging Neglected Tropical Disease in Nepal. *J Nepal Health Res Counc* . 2016;14(33):122-127. Accessed February 19, 2023. https://europepmc.org/article/med/27885295

10. Luce-Fedrow A, Lehman ML, Kelly DJ, et al. A Review of Scrub Typhus (Orientia tsutsugamushi and Related Organisms): Then, Now, and Tomorrow.*Trop Med Infect Dis* . 2018;3(1). doi:10.3390/TROPICALMED3010008

11. Upadhyaya A, Alam MR, Raeen AA, et al. Scrub Typhus Meningoencephalitis: An Overlooked Entity. *Cureus* . 2022;14(9). doi:10.7759/CUREUS.28989

12. Kar A, Dhanaraj M, Dedeepiya D, Harikrishna K. Acute encephalitis syndrome following scrub typhus infection. *Indian J Crit Care Med* . 2014;18(7):453-455. doi:10.4103/0972-5229.136074

13. Rajapakse S, Rodrigo C, Fernando D. Scrub typhus: pathophysiology, clinical manifestations and prognosis. *Asian Pac J Trop Med* . 2012;5(4):261-264. doi:10.1016/S1995-7645(12)60036-4

14. Khandaker G, Jung J, Britton PN, King C, Yin JK, Jones CA. Long-term outcomes of infective encephalitis in children: a systematic review and meta-analysis. *Dev Med Child Neurol* . 2016;58(11):1108-1115. doi:10.1111/DMCN.13197

15. Kumar ASP, Anupama MP. Scrub Typhus with Unusual Presentation.*Int J Prev Med* . 2014;5(8):1054. Accessed February 23, 2023. /pmc/articles/PMC4258667/

16. Pai H, Sohn S, Seong Y, Kee S, Chang WH, Choe KW. Central nervous system involvement in patients with scrub typhus. *Clin Infect Dis* . 1997;24(3):436-440. doi:10.1093/CLINIDS/24.3.436

17. Walker DH, Valbuena GA, Olano JP. Pathogenic mechanisms of diseases caused by Rickettsia. *Ann N Y Acad Sci* . 2003;990:1-11. doi:10.1111/J.1749-6632.2003.TB07331.X

18. Mahajan SK, Mahajan SK. Neuropsychiatric Manifestations of Scrub Typhus. *J Neurosci Rural Pract* . 2017;8(3):421-426. doi:10.4103/JNRP.JNRP_44_17

19. Drevets DA, Leenen PJM, Greenfield RA. Invasion of the Central Nervous System by Intracellular Bacteria. *Clin Microbiol Rev* . 2004;17(2):323. doi:10.1128/CMR.17.2.323-347.2004

20. Tantibhedhyangkul W, Matamnan S, Longkunan A, Boonwong C, Khowawisetsut L. Endothelial Activation in Orientia tsutsugamushi Infection Is Mediated by Cytokine Secretion From Infected Monocytes.*Front Cell Infect Microbiol* . 2021;11. doi:10.3389/FCIMB.2021.683017

21. Lee KL, Lee JK, Yim YM, Lim OK, Bae KH. Acute transverse myelitis associated with scrub typhus: case report and a review of literatures.*Diagn Microbiol Infect Dis* . 2008;60(2):237-239. doi:10.1016/J.DIAGMICROBIO.2007.09.015

22. Chiou YH, Yang CJ, Lai TH. Scrub typhus associated with transient parkinsonism and myoclonus. *J Clin Neurosci* . 2013;20(1):182-183. doi:10.1016/J.JOCN.2012.01.047

23. Chen PH, Hung KH, Cheng SJ, Hsu KN. Scrub typhus-associated acute disseminated encephalomyelitis. *Acta Neurol Taiwan* . 2006;15(4):251-254. Accessed February 21, 2023. https://pubmed.ncbi.nlm.nih.gov/17214088/

24. Lin WR, Chen TC, Lin CY, Lu PL, Chen YH. Bilateral simultaneous facial palsy following scrub typhus meningitis: a case report and literature review. *Kaohsiung J Med Sci* . 2011;27(12):573-576. doi:10.1016/J.KJMS.2011.10.003

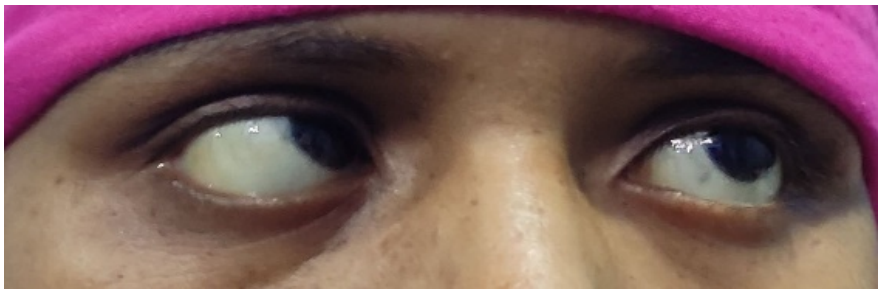
25. Kang JI, Kim DM, Lee J. Acute sensorineural hearing loss and severe otalgia due to scrub typhus. *BMC Infect Dis* . 2009;9:173. doi:10.1186/1471-2334-9-173

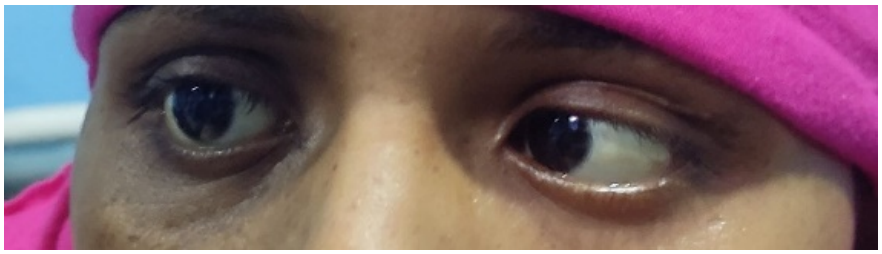
26. Viswanathan S, Muthu V, Iqbal N, Remalayam B, George T. Scrub Typhus Meningitis in South India — A Retrospective Study. *PLoS One* . 2013;8(6). doi:10.1371/JOURNAL.PONE.0066595

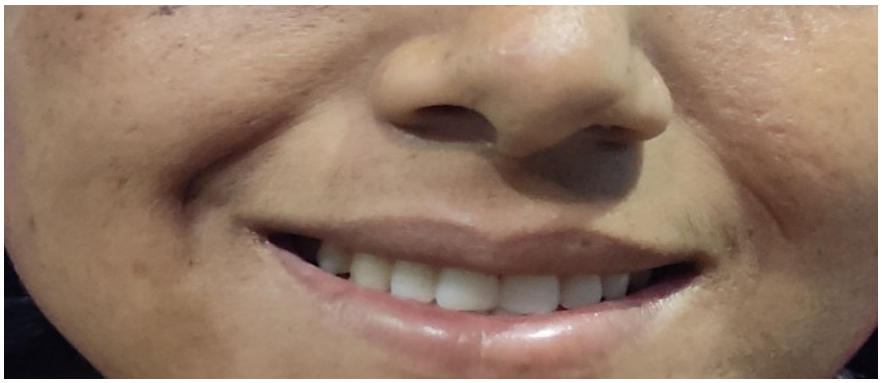
27. Arai M, Nakamura A, Shichi D. [Case of tsutsugamushi disease (scrub typhus) presenting with fever and pain indistinguishable from trigeminal neuralgia]. *Rinsho Shinkeigaku* . 2007;47(6):362-364. Accessed February 21, 2023. https://pubmed.ncbi.nlm.nih.gov/17633112/

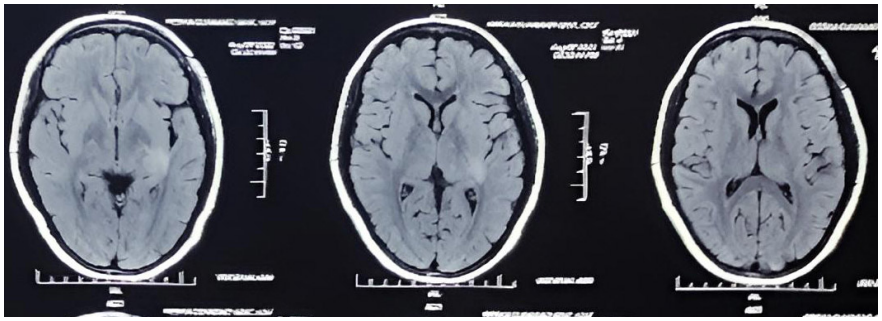
28. Silpapojakul K, Ukkachoke C, Krisanapan S, Silpapojakul K. Rickettsial Meningitis and Encephalitis. *Arch Intern Med* . 1991;151(9):1753-1757. doi:10.1001/ARCHINTE.1991.00400090051010

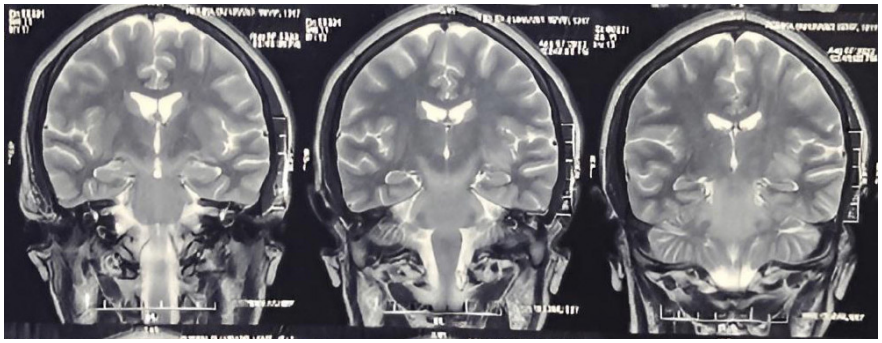
29. Biswas S, Ghosh R, Roy D, et al. Scrub Typhus Masquerading as Limbic Encephalitis. *The Neurohospitalist* . 2022;12(1):105-110. doi:10.1177/19418744211016107

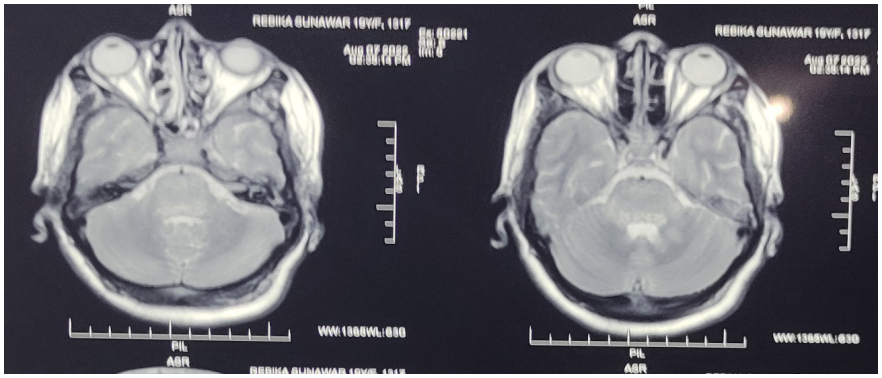












Hosted file

`figures.docx` available at https://authorea.com/users/593136/articles/628309--a-case-of-acute-encephalitis-syndrome-and-cranial-nerve-palsy-secondary-to-scrub-typhus-a-rare-presentation-from-western-nepal