Original Article

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A Common Agent: 2 Different Cases the Menace that is Opioid-Induced Leukoencephalopathy

Dr. Shaik Sulaiman Meeran A[1], Dr. Malathi S[2], Dr. Revathi A[3], Dr. Anish S Bharatwaj[4]

[1]Professor and HOD, [2]Associate Professor, [3]Senior Assistant Professor, [4]Junior Resident,
Department of Internal Medicine, Government Royapettah Hospital

Abstract

Leukoencephalopathy is a broad term used to refer to an affliction of White Matter Myelin arising from defects in either development or maintenance. There are multiple agents known to cause leukoencephalopathy, namely vascular insults, chronic inflammatory insults, infections, trauma and genetic mutations which can affect the myelin in many ways. In particular, one offending toxin with potentially lethal implications is the Opioid group of analgesics. Tapentadol is one such centrall acting Opioid Analgesic. In this article, we describe two cases of Tapentadol abuse with varied presentations and striking radiological features.

Keywords: *Tapentadol, Toxic Leukoencephalopathy*

Introduction

Simply put, Toxic leukoencephalopathy is a disorder of white matter due to exposure to a leuko toxin [1]. The mechanisms of toxins leading up to these disorders can vary from toxin to toxin, duration of exposure and concentration. Historically, the first reported case of Toxic leukoencephalopathy, or rather, spongiform encephalopathy as it was then called, was in 1982 from The Netherlands [2]. Back then, it was attributed to inhalation of Heroin. Although with the advent of MRI, clinicians were able to identify characteristic features, it is generally thought that Heroin induced Encephalopathy follows a fulminant course with an inevitable fatal outcome. While global literature shows cases of toxic leukoencephalopathies secondary to anaesthetic agents abuse (eg: Fentanyl and Nitrous Oxide), Recreational drugs, and Analgesics like Codeine, this is perhaps the first report of TLE secondary to Tapentadol, an oral opioid/NRI analgesic.

Case 1

A 22-year-old male, an AC servicing technician, came with chief complaints of fever for 4 weeks following an episode of seizure of unknown semiology one month prior, headache and lassitude. The fever was intermittent, occurring at least once every day, and was generally responsive to over-the-counter antipyretics. His headache was not localized, varying in severity, intermittent and was not associated with warning signs like "clap of thunder", blurry vision or focal deficit.

On probing further, he had admitted to using substances of abuse in varying capacities including Huffing of shoe polish, smoking Marijuana and occasionally consuming alcohol.

Clinical examination at that time was normal and the patient was started on Empirical Antibiotics with the possible diagnosis of Sub Acute Meningoencephalitis, probably Tuberculosis.

Initial CT brain and routine blood workup were normal. The patient was subject to a lumbar puncture after ruling out Papilledema by Fundus examination. The results of the first CSF analysis were as follows:

CSF Opening Pressure	22cm H2O
Color	Pale yellow
WBC count	75 (100% lymphocyte predominance)
Microbiology	Smear for AFB, organisms negative
Proteins	167 mg/dl
Chloride	122 meq
Glucose	29 mg/dl
CSF ADA	9.8

CSF CB NAAT was also sent for XPERT/MTB RIF and eventually turned out negative. Additionally, the patient's serology for HbsAg, HCV and HIV along with vasculitic and autoimmune profile were negative.

The patient was empirically started on ATT as per the Neurologist's advice, given the patient's clinical profile. He was also started on IV Corticosteroids (Dexamethasone 8 mg TDS) and Anti Epileptics.

The patient had an MRI Brain plain done. The following was the result.

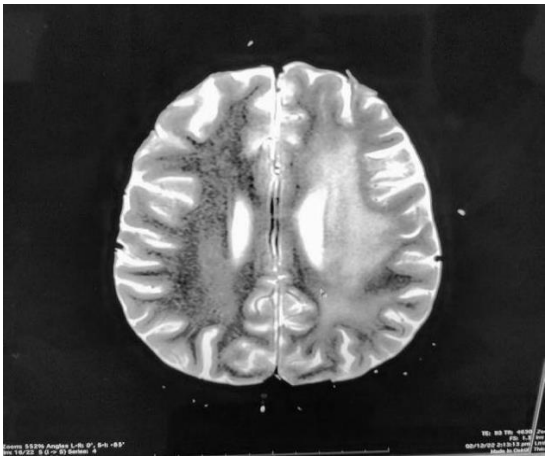

Fig 1: *Axial section of T2 W MRI showing bilateral White Matter edema in Frontal, Parietal and Occipital regions.*

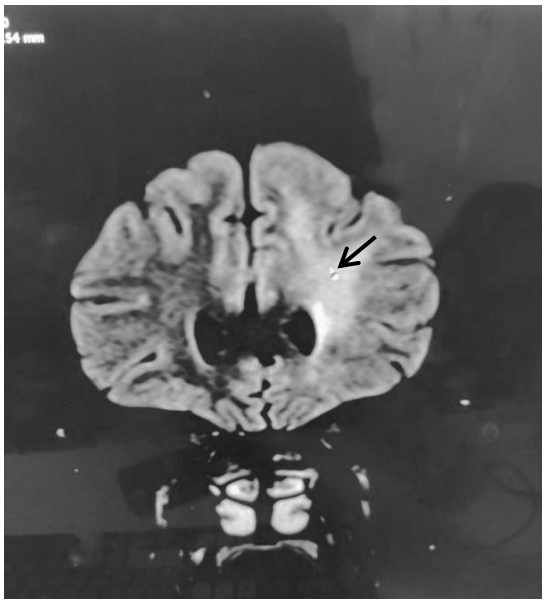

Fig 2: *MRI T2 FLAIR, coronal cuts showing increased signal intensity in right Parietal region and bilateral Cerebellum (white arrowhead).*

Given the CSF picture and MRI findings, the patient was presumed to have TB Cerebritis and therefore ATT was continued. However, the patient continued to deteriorate despite treatment. He continued to have high-grade fever spikes with one recorded episode of status epilepticus. The patient was subjected to a repeat MRI, this time with contrast.

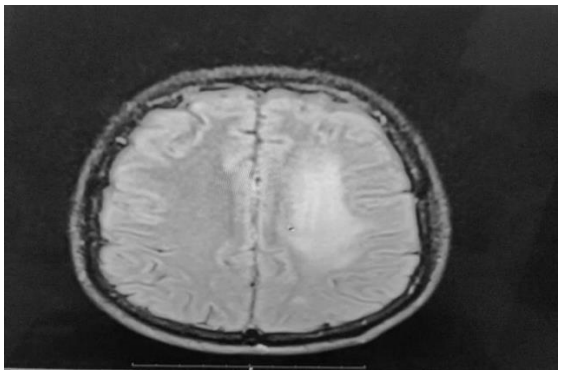

Fig 3: *MRI BRAIN T1 with Gadolinium enhancement showing predominant left sided white matter lesion in Parietal lobe. (Not shown here: Nil resolution of Cerebellar lesions)*

The patient also had a repeat Lumbar puncture done the results of which are as follows:

Appearance	Hazy
Color	Pale yellow
WBC count	395 (100% lymphocyte predominance)
Microbiology	Smear for AFB, organisms negative, India ink stain negative and yeast culture negative
Proteins	148 mg/dl
Chloride	122 meq
Glucose	29 mg/dl

At this point, the patient was again probed into the history for potential toxic agents which could have caused the neuronal insult. The patient then admitted to using Tapentadol which he crushed, reformulated with distilled water and injected IV. This happened about 2 months prior to admission and was the only time he ever used IV drugs.

With new evidence in light, the patient was started on Pulse Steroids (Inj. Methyl Prednisolone 1g IV OD for 5 days) followed by a gradual taper.

Despite all this, the patient continued to deteriorate, with a clinical course characterized by multiple episodes of seizures, high-grade fever spikes and development of meningismus. He finally succumbed to refractory Status Epilepticus after 2 weeks of hospital stay.

Case 2

The patient a 26-year-old male, a chronic alcoholic with a history of multiple episodes of binge drinking, was apparently in his usual state of health a day prior to having been found in an unconscious state in his room. He was a Taxi driver who had recently taken on a long-distance inter-city tour and had reported no signs of illness. His mother mentioned that he had an episode of binge drinking prior to admission. Examination revealed a patient with neck rigidity, bilateral upper limb rigidity and mid-dilated pupils poorly responding to light. His GCS was E1V2M2. Vitals revealed a Pulse rate of 124 BPM, BP of 100/60, and SpO2 of 89% under room air.

In view of poor GCS, the patient was Intubated and put on a Mechanical Ventilator. An initial CT Brain was done but revealed no abnormal findings. A diagnosis of Severe Alcohol Intoxication with Wernicke's Encephalopathy was made and he was put on Thiamine at 500ug IV OD along with Multivitamins and Antibiotics. A trial of Naloxone was given but the patient did not show signs of recovery. His brother later showed up and provided a history of IV drug abuse. On probing further, it was found that he had used oral Tapentadol which was crushed and formulated with distilled water and then injected IV. Furthermore, his brother recounts multiple such episodes of IVID use, the exact number being unknown.

Routine blood work up revealed Leukocytosis with Transamnitis. There was no other marked derangement in Renal Function and Liver Function. Serology was sent and turned out to be negative for Hepatitis B, C and HIV.

A Lumbar Puncture was done and revealed the following:

Appearance	Clear
Color	Transparent
WBC count	Acellular
Microbiology	Smear for AFB, organisms negative
Proteins	76 mg/dl
Chloride	116 meq
Glucose	79 mg/dl
CSF ADA	0.9

An MRI was done. T2 FLAIR, Diffusion and SWI imaging revealed Diffusion restricting T2 FLAIR hyperintensities in the posterior aspect of bilateral Corpus Callosum with SWI showing Hemorrhage. This was suggestive of CLOCC (Cytotoxic Lesions of Corpus Callosum), a finding consistent with Toxic Leukoencephalopathy.

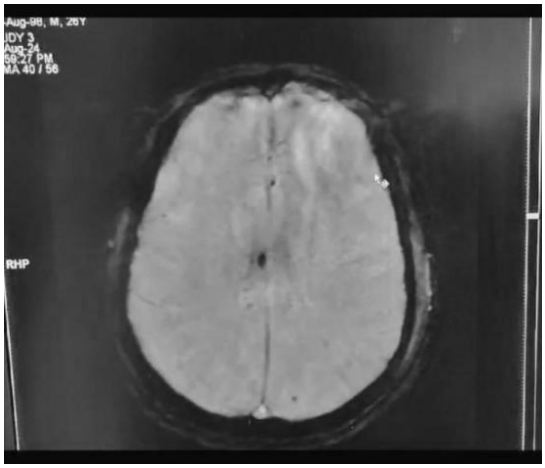

Fig 4: *SWI sequence showing blooming in the region of Corpus Callosum*

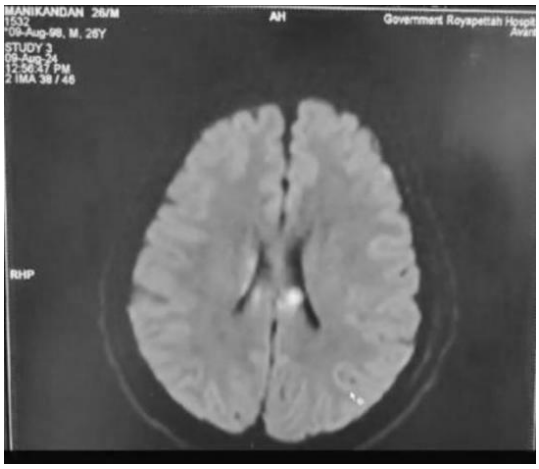

Fig 5: *T2 FLAIR sequence showing hyperintensity in the region of Corpus Callosum*

The patient was started on Pulse dose steroids. On day 3, he had an episode of Asystole which, after 2 cycles of CPR, was reverted to Sinus Rhythm. POCUS of the lung revealed no evidence of Pneumothorax. A repeat CT brain was done and showed no evidence of Hydrocephalus or Cerebral Edema. The patient continued to have worsened lab parameters characterized by persistently rising liver enzymes, probably as a consequence of post-cardiac arrest injury.

The patient was also started on ionotrope support. 2D echo revealed normal LV systolic function. Despite all efforts at treatment, the patient succumbed to his illness after 5 days of ICU stay.

Discussion

Opioid abuse is rampant the world over, yet the prevalence of TLE appears to be low due in part to the under-reporting of cases or the presence of multiple confounding factors possibly attributing to the aetiology. For instance, in our cases, the usage of both Marijuana and Tapentadol could have been the insult leading to TLE. However, the duration and frequency of cannabis use were not strong enough to support its role in the disease process. Korkman et all described a case of a 27-year-old male with TLE secondary to Marijuana use, which stretched to a duration of nearly 7-8 years and on a daily basis[4].

The clinical features of TLE have been broadly divided into three categories [3]:

Mild: characterized by subtle psychomotor disturbances, headache confusion and sometimes ataxia. Rarely, incontinence may be seen at this stage.

Moderate: Characterized by Corticospinal involvement with or without Extra Pyramidal Syndrome.

Severe: Generalized motor dysfunction with mutism/language deficit, varied degrees of inattention, apathy and altered mental status.

Despite the withdrawal of the offending agent, a coasting phenomenon appears to

contribute to continued disease evolution, sometimes up to even 6 months [5].

An MRI of the brain shows characteristic features that are by and large similar barring a few unique traits individual to each agent. The predominant picture is symmetrical White Matter hyperintensities on T2 and FLAIR in the region of Cerebellum, Posterior Cerebrum, Splenium of Corpus Callosum and the Pyramidal tracts [7]. Data regarding specific appearances of Tapentadol appears to be lacking if any are present at all.

The predominant biopsy findings are spongiform degeneration of White Matter with sparring of Sub Cortical U fibres. Additionally, vaccuole formation in the myelin sheaths may be visible under Electron Microscopy [8].

The mainstay of treatment is supportive care. Newer modalities of treatment include antioxidant use like CoQ, Vitamin E and Vitamin C, although success is varied [3].

The severity of the disease in general depends on duration, cumulative dose and history of consuming other substances of abuse. Death is more rampant among those who present with features suggestive of severity.

Our first case presented with mild symptoms. However, India still being endemic to Tuberculosis, the possibility of CNS TB outweighed that of TLE. We immediately started the patient on supportive care and Pulse dose Steroids upon MRI results. However, the patient's downhill course, characterized by multiple episodes of seizure, high-grade fever spikes, development of meningismus and rigidity eventually led to a final blow: refractory Status Epilepticus. The reason for his downhill course could perhaps be attributed to the presence of multiple substances of abuse including Toluene use and Marijuana and the formulation of Tapentadol that was used.

The second case presented with AMS and poor GCS warranting Mechanical Ventilation. The clinical picture was that of Acute Toxic Leukoencephalopathy given the very recent use of Tapentadol. Despite Pulse dose Steroids and supportive care, the Patient eventually succumbed to his illness and could not be revived. Most literature that we had gone through suggested that Acute Toxic Leukoencephalopathy has a poor prognosis similar to our patient.

We had attempted to treat both patients with Pulse dose Corticosteroids based on expert opinion. One case description reported the use of Naloxone. We also used Naloxone in our second patient given the acute presentation. However, no signs of recovery were demonstrated and mortality despite all supportive care appears to be high.

Conclusion

At the end of the case discussion, we wish to highlight that although medicine has taken leaps towards advanced investigations and standards of care, history-taking remains the quintessential tool for cracking a case. Early Prompt MRI and a CSF panel to rule out infections can help clinch the diagnosis provided there is antecedent history of exposure. It is important to anticipate worsening and involve a multi-disciplinary team in the management of TLE. We also wish to highlight the growing menace of Tapentadol abuse in our part of the city as we have seen many cases of Tapentadol abuse presenting with non-neurological complaints as well. A common difficulty encountered is that the first contact attenders, often their parents or family members, are not aware of substance use history and precious time is wasted in exploring other possibilities. In the future, we hope more

light is thrown on this ever-evolving disease entity and a community-wide effort is taken to spread awareness of the hazards of substance abuse.

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