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Perampanel in Non-Convulsive Status: Distinct Effects on Deeper Consciousness Structures, followed by a Gradual Effect on Neocortical Semiology Observed in a Case Study with Serial EEG Monitoring

Dr. Charchit Gupta

Consultant Neurologist and Physician, Department of General Medicine, Kalyan Singh Government Medical College Bulandshahr Uttar Pradesh

Abstract: ***A 16 year old girl, mentally challenged, with uncontrolled seizures for 10 years was hospitalized in an unconscious state, on ventilatory and inotropic support.***

Keywords: Perampanel therapy, status epilepticus, EEG monitoring, seizure management, ventilatory support

1. Methodology

She showed a repetitive ictal semiology, coinciding with respiratory and hemodynamic changes. A diagnosis of non-convulsive status was entertained. Seeing little change on sufficient intravenous drugs, Perampanel was added and gradually escalated. Serial EEGs were done.

2. Results

As PER dose was escalated, she continued to show the same semiology, but came off ventilatory support, and no inotropic supports were required, much before final doses were reached. Further escalation, made her semiology free, and restored her pre ictal state.

3. Summary

Perampanel in this case, as a last add-on, even at half the final dose seemed to show an initial propensity to ease depression of deeper and vital structures, (ventilation, vasomotor centers), allowing discontinuation of supports and shifting to step-down. Further neocortical suppression as semiology, came later with escalation of doses and expected awareness. EEG and semiology were part of corroboration.

4. Material and Methods

A sixteen year old mentally challenged girl, a known epileptic on anti -epileptic drugs (AEDS) was hospitalized on ventilator, and inotropic support, with a diagnosis of “aspiration”. No evidence of aspiration, systemic infection was found. During her stay in the ICU she remained unstable. Non-convulsive status was her diagnosis, based on semiology and EEG. Amongst her various bizarre movements, it was noted, that there was repetitive, stereotype array, that involved, ‘turning of head to the right, followed by flexion of left lower limb at the hip, flexion at the knee, that would cross towards the other side. This posturing would remain for a while, and ease out in 1-2 mins. It was during these episodes, that ventilator support would require upgradation, and adjustment of inotropes had to be done. Clinical assessment, and overall, 6 EEGs were done between Nov ’18 till discharge in April ’19. Her ICU stay, was for two weeks.

Perampenel, beginning with a dose of 2mg, escalated to six mg/day was started as a last add-on, and escalated as per response. Dose escalation of Perampanel showed a reduced need in adjustments of her support systems. At a dose of 16 mg/day, she no longer required the ventilator, or inotropic support. She was shifted out of the ICU. The noted semiology was about 20% less, but her vitals were stable, requiring no support. Finally, at a dose of 24mg/day, she was conscious, interactive, would waive out to the nurses, and interact with her sister. This was the best intellectual performance the family had seen in 10 years as even her pre-status refractory seizures, settled down.

5. Discussion

Control of complex partial status with PER as a last add-on has been reported.[1]. This 16 year old female, mentally challenged, having un-controlled seizures for 10 years, was hospitalized as a case of “aspiration pneumonia”, with fluctuating respiratory, and inotropic support. It was soon obvious, clinically, and through investigations, that there was minimal aspiration, and no systemic infection. Complex partial status was her defined clinical state.

The discussion of focal seizures spreading to in involve the neocortex, and later suppressing centers responsible for awareness and consciousness has been long and commented by various authorities in epileptology, from Penfield and Jasper [2], Luders [3,4], and Englot DJ et al [5]. Most of these try to define “unconsciousness”, its confirmation by clinical observation, EEG slowing, and hypoperfusion of the cortex. Nevertheless, to a lesser or greater point of analysis it comes to the level of defining various degrees of consciousness during a focal seizure. To emphasize, there is a caution that all disturbances of consciousness that begin with a focal onset

seizure are probably are not true “unconsciousness”. There is consensus that lowering of consciousness from focal onset seizures, is due to spread to the neo-cortex, and further to deeper structures that retain cognitive functions as lateral laminus, anterior hypothalamus. Luders has classified focal seizures with varying loss of awareness into five different types, from no effect in consciousness, to what may be termed to a state of coma, as defined by slow EEG rhythms, semiology, and cortical hypoperfusion [3,4]. Luders further states, that the final characterization of a seizure depends on the basic pathophysiology that is the cause of the seizure and that the actual form a seizure may take, including level of depressed consciousness [3,4].

The case differed in the sense, that despite not much control over the seizures, with each typical semiology, she went into hypopnea, and hypotension, requiring the ventilator and inotrope regulation. An observation, that each bout of seizure had an additional penetration to deeper structures, including vital centers, respiratory, and vasomotor, gained credibility. As she had a congenital abnormal brain (Figure 1), it was possible, that the epileptic activity spread to deeper structures through abnormal tracts that passed the currents to the vital centers.

This case of seizures with a congenitally abnormal brain, showed additional respiratory dependency, and hemodynamic changes. The confirmation comes from the observation that vitals needed adjustment after each seizure semiology, the stabilization of vitals, and non- dependency of ICU, as doses increased and finally a near normal state expected under the circumstances Perampanel was added as a last resort [6,7], as it was obvious that repetitive ictal activity as described was the cause of the instability of respiratory and vaso-motor centres. That this indeed was the cause, was proved by adjusting doses of PER, where the patient showed clinically similar semiology, comparable EEGs, but was relieved of her ICU dependence, in 2 weeks. Perampanel was escalated, as per patient response, and at optimum doses she continued to level up to her pre-status normal state, along with other AEDs. In fact she was better with significant relief from pre-status state, with elimination of her, in fact improved, being free of her past state of refractory seizures duration, and finally cessation (Table 1). The question arises, that do some drugs act in a way, controlling seizures, in a sequential or combined manner, initially controlling epileptogenic activity in the medial structures, and later or simultaneously controlling cortical activity. This would at the most be a speculation, to be further corroborated, mostly by individual collective data. There persists a term as “drug of first choice, and with varying opinions, there are some guidelines on choice in primary generalized syndromes, and focal seizures [8].

Perampanel, is a new AMPA antagonist [9], found to be of use as a last add-on in status epilepticus [10]. Status epilepticus results from an imbalance between persistent cellular excitation mediated by excitatory neurotransmitters “glutamate” and failure of inhibitory synaptic transmission mediated by gamma-amino butyric acid “GABA”. As the epilepticus continues, it becomes more resistant to treatment secondary to the internalization of the postsynaptic GABA receptors to the cytoplasm, externalization of the NMDA and AMPA receptors to the surface, and change in chloride homeostasis in addition to an excess of the extracellular glutamate leading to perpetuation of the status via the AMPA receptors. This explains the resistance to those antiepileptic drugs having a GABAergic effect and explains the resistance to those antiepileptic drugs having a GABAergic effect and epilepticus [11]. The mode of action is based on non-competitive antagonism of AMPA a possible better response to those drugs acting on the excitatory receptors (NMDA and AMPA receptors) [9].

6. Summary

This study shows the benefits of higher doses of Parampanel in non- convulsive status. It further shows, that Perampanel, at a particular dose, creates a welcome dissociation of autonomic fluctuations, allowing a shift from ICU to step-down wards, even with persisting repetitive semiology, and EEG changes . A rough presumption in concluding, may be that its action may first prevent epileptic propagation to deeper structures, and finally, a beneficial control [4,5]. We cannot rule out whether this is specific to this case, or is a generalized property of the drug. Surely further data is required to assess its clinical mode of action, as well as a more definitive role in status epilepticus.

References

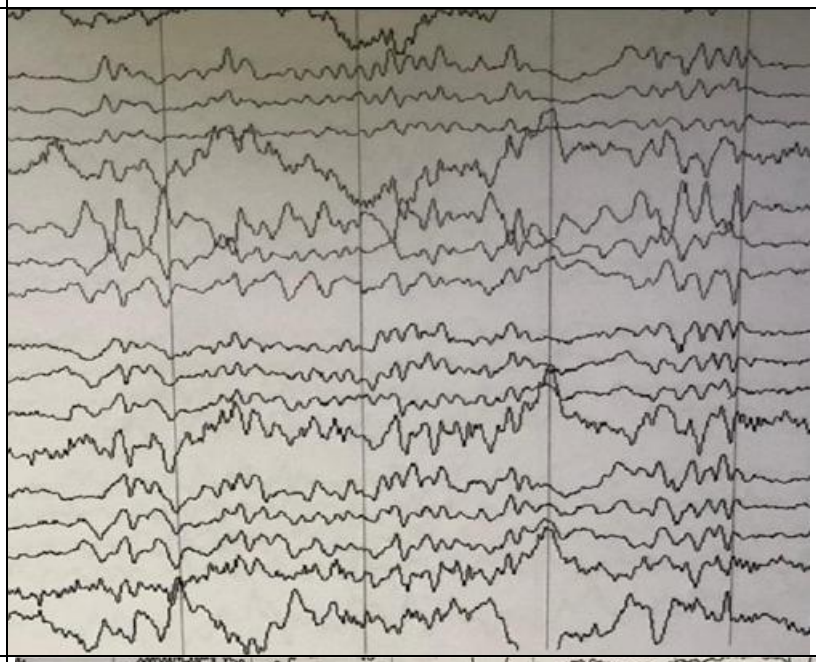
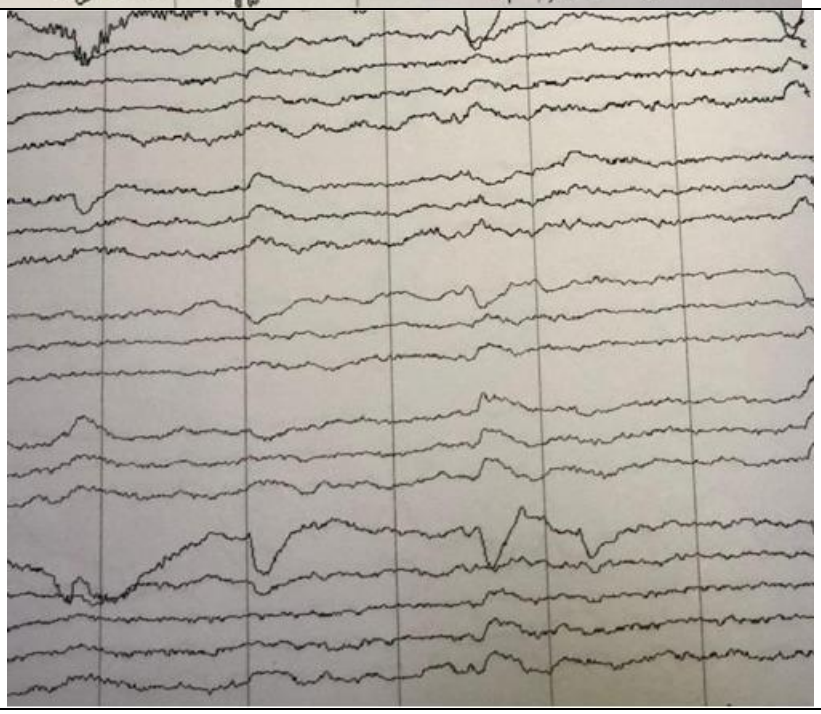
[1] French JA, Krauss GL, Biton V, et al. Adjunctive perampanel for refractory partial-onset seizures: randomized phase III study 304. Neurology 2012; 79:589–96.
[2] Wilder Penfield, Herbert Jasper. Epilepsy and the Functional Anatomy of the Human Brain. Science.07 May 1954; Vol. 119, Issue 3097: pp. 645-646 doi: 10.1126/science.119.3097.645-a.
[3] Hans Luders et al. Proposal: Different Types of Alteration and Loss of Consciousness in Epilepsy. Epilepsia.2014 Aug;55(8):1140-4. doi: 10.1111/epi.12595. Epub 2014 Jun 30.
[4] Hal Blumenfeld, Kimford J Meador. Consciousness as a Useful Concept in Epilepsy Classification. Epilepsia 2014 Aug;55(8):1145-50. doi: 10.1111/epi.12588. Epub 2014 Jun 30
[5] Englot DJ, Morgan VL, Chang C. Impaired vigilance networks in temporal lobe epilepsy: Mechanisms and clinical implications. Epilepsia. 2020 Feb;61(2):189-202. doi: 10.1111/epi.16423.
[6] M Hintz, S Nawratil , A Schulze-Bonhage. Perampanel as a Therapy Option in Patients with Epilepsy. Nervenarzt 2016 Aug;87(8):870-8. doi:10.1007/s00115-016-0131-z.
[7] Ivana Tyrlikova et al. Perampanel as monotherapy and adjunctive Therapy for focal Onset Seizures, focal to bilateral tonic-clonic seizures and as adjunctive therapy of generalized onset tonic-clonic seizures. Expert Rev Neurother. 2019 Jan;19(1):5-16. doi: 10.1080/14737175.2019.1555474.
[8] Marvin M. Goldenberg. Overview of Drugs Used For Epilepsy and Seizures-Etiology, Diagnosis, and Treatment. Pharmacy and Therapeutics. 2010 Jul; 35(7): 392–415
[9] Adam Strzelczyk et al. Perampanel Use in Established, Refractory, and Super-Refractory Status Epilepticus

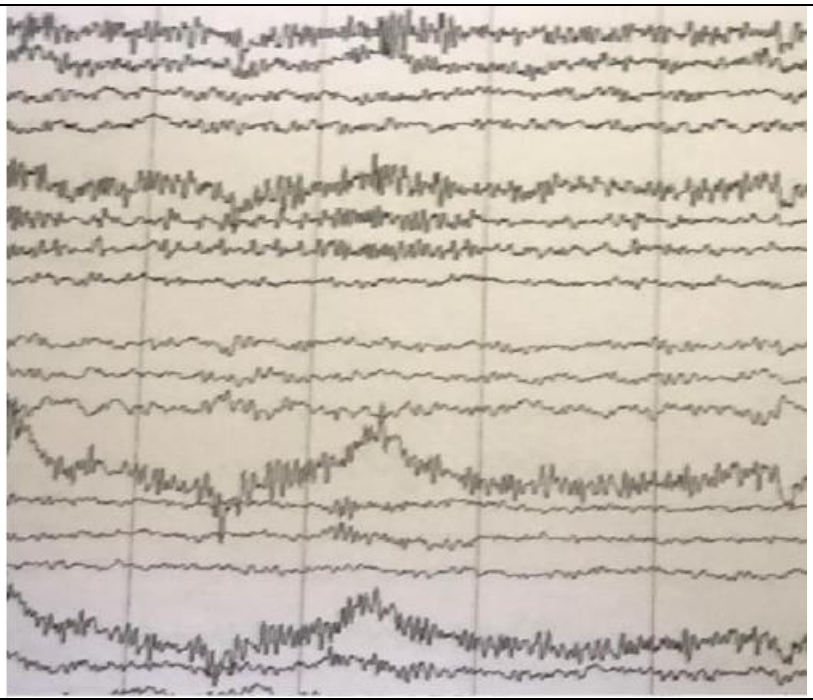
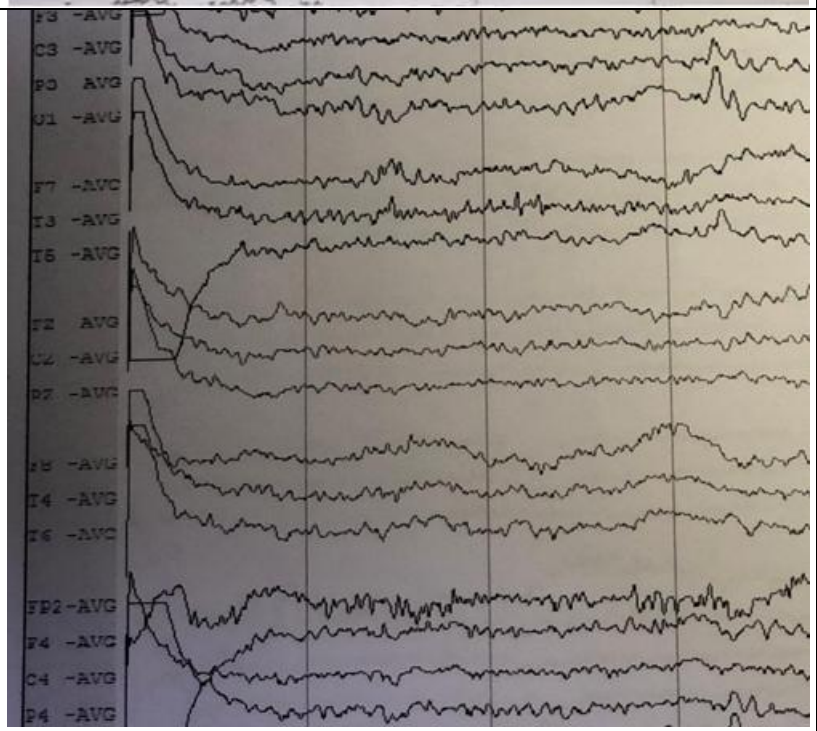
(SE): a Summary of Cases from Austria, Finland, Germany, and Spain. Neurology. April 2019; 92(15):3.5- 005.

[10] F. Brigo, S. Lattanzi, A. Rohracher. Perampanel in the treatment of status epilepticus: a systematic review of the literature. Epilepsy and Behavior.2018 ; Vol. 86: 179–186.

[11] D. E. Naylor, H. Liu, C. G. Wasterlain. Trafficking of GABA(A) receptors, loss of inhibition, and a mechanism for pharmacoresistance in status epilepticus.The Journal of Neuroscience.2005;Vol. 25(34):7724–7733

Table 1

Serial. No.	PER Dose/day	EEG	Vital Support	Semiology
1. 8, Nov 2018	6 mg		Ventilator support + CMV Mode Ionotropic support ++ Noradrenalin e, Dopamine	+
2. 14, Nov 2018	8 mg		CMV mode but lesser support Ionotropic support ++ Noradrenalin e , Dopamine	+

3. 11, Jan 2019	10 mg		Ventilator support + SIMV Mode Ionotropic support + Dopamine	+
4. 25, Jan 2018	12 mg		Ventilator support- intermittent/ CPAP Ionotropic support + Dopamine	+

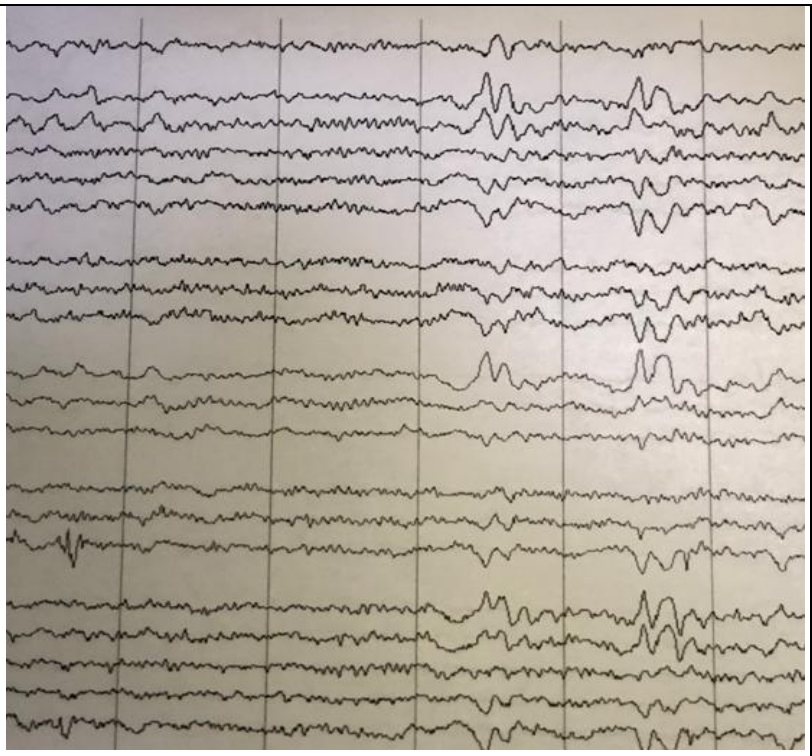
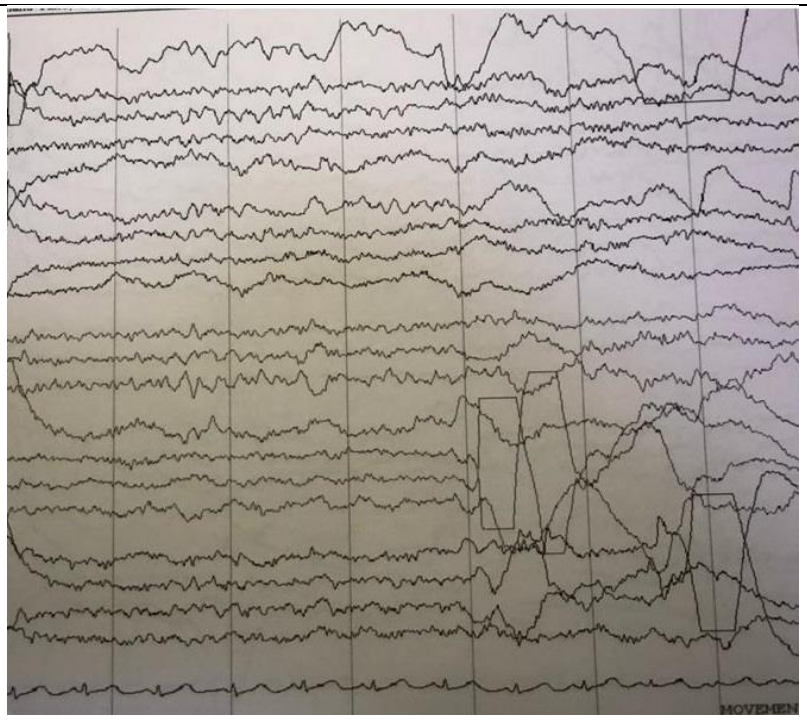
5. 2, Jan 2019	16 mg		**All supports stopped Shifted out from ICU** ? response to verbal commands	Less
6. 23, March 2019 10 days before discharge	24 mg		Supports – Nil **Intellectually patient recovered as in pre-ictal state**	Minimal for a few seconds

Table 1 Legends

a) All EEGs' were done in the average mode at 30 mm/second and sensitivity of 7.5 microvolt. Lead placements were anterior to posterior as follows- Fp1-Avg, F3-Avg -----F7,T3,T5------Pz, Cz, Oz F8-Avg , T4,T6,O2.
b) EEGs' were done on admission and serially followed at 10-15 days.
c) EEG serial no. 1 on admission shows, generalized activity, PER dosage-Nil.
d) EEG serial no. 2 shows post-ictal slowing, PER dosage-6mg.
e) EEG serial no. 3 shows background slowing with muscular artefacts, PER dosage-10mg.
f) EEG serial no. 4 shows slow background activity with epileptogenic spikes - left sided, PER dosage-12mg.
g) EEG serial no.5 shows suppressed alpha with paroxysm of spikes, PER dosage-16mg.
h) EEG serial no.6 shows theta activity and movement artefacts, PER dosage- 24mg.

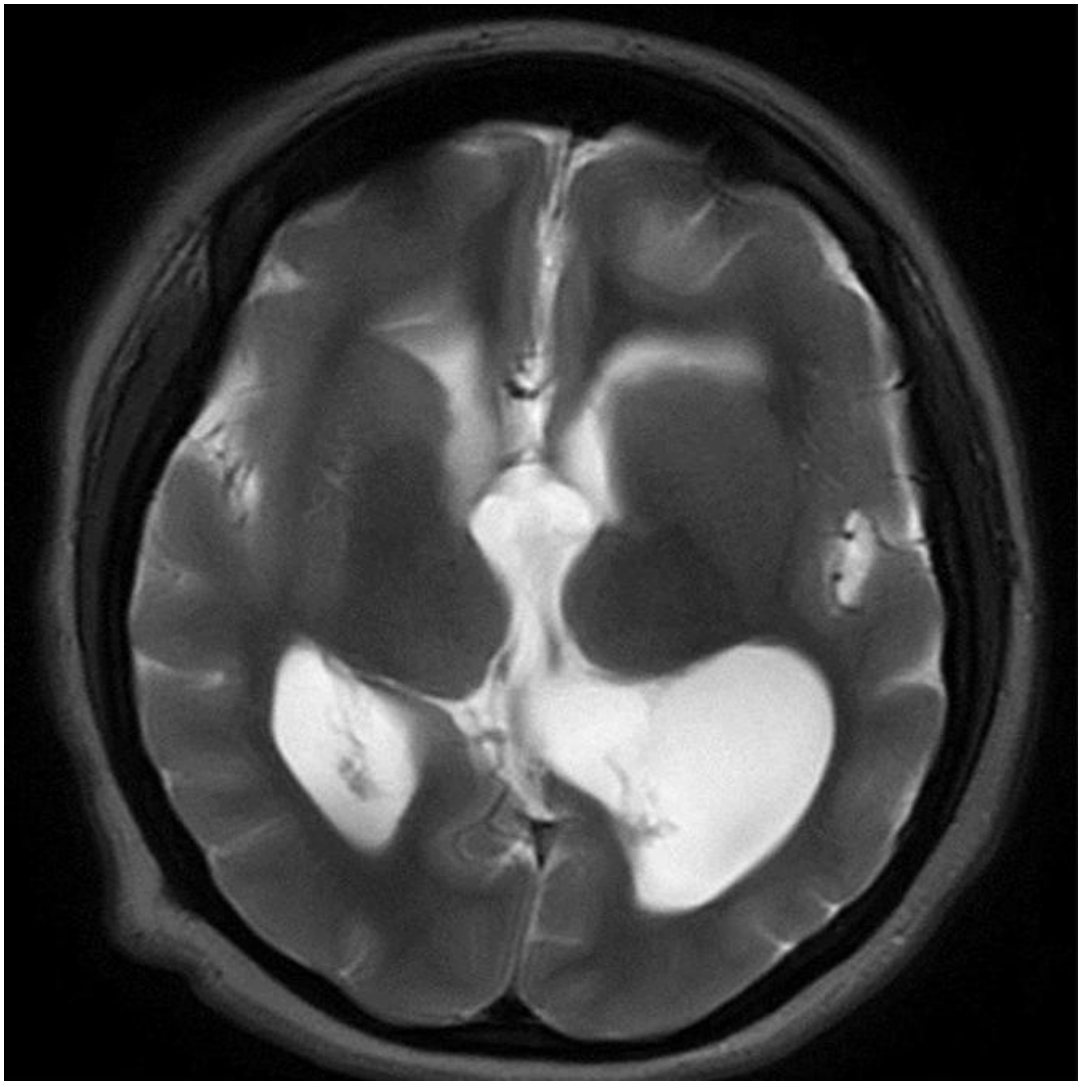


Figure 1

Figure Legends
Figure-1- shows T2 weighted MRI brain shows ill-defined gyri with hydrocephalus left more than the right.