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A clinical TRIAD for early suspicion of autoimmune encephalitis as a possibility in patients presenting with progressive cognitive decline

Chandra S.R.[a,*], Somdattaa Ray[b], Thomas Isaac[c], Anupama R.Pai[d], Haripriya Krishnareddy[b], Debjyoti Dhar[b], Mariamma Philip[e]

[a] NIMHANS, Neurology, Department of Neurology, Faculty block, Neurocentre, 560029, Bangalore, Karnataka, India
[b] Department of Neurology, National Institute of Mental Health and Neurosciences (NIMHANS), Bengaluru, 560029, Karnataka, India
[c] Department of Psychiatry, National Institute of Mental Health and Neurosciences (NIMHANS), Bengaluru, 560029, Karnataka, India
[d] Department of Neuromicrobiology, National Institute of Mental Health and Neurosciences (NIMHANS), Bengaluru, 560029, Karnataka, India
[e] Associate Professor of Biostatistics, National Institute of Mental Health and Neurosciences (NIMHANS), Bengaluru - 560029, Karnataka, India

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ABSTRACT

Patients with progressive cognitive decline mostly suffer from degenerative disease and carry a relatively poor prognosis. But small groups among these patients have a potentially treatable cause of illness and therefore every patient with dementia needs to be considered treatable unless proved otherwise. This group can be identified only by high degree of suspicion based on clinical clues. We have evaluated the validity of some simple clinical clues which we noticed in our patients with immune mediated dementias.

The Panic score, Epsworth sleepiness score, catatonic symptoms and history of seizures were compared between 23 and 11 patients with serologically confirmed anti-NMDA antibody and anti-VGKC antibody associated encephalitis respectively. They were compared with 20 patients with probable behavioral variant of Frontotemporal dementia (bvFTD) and 20 patients with probable Alzheimer's disease (AD). Chi-square test was used to compare across the groups and there was significant difference ($P < 0.05$) across the 4 groups comprising anti NMDA encephalitis, anti VGKC encephalitis, FTD and AD among the four variables (Panic scores, Catatonic symptoms, Epsworth sleepiness score and seizures) studied.

Our study revealed that panic and sleepiness is highly significant when tested across all groups and catatonia showed a trend towards NMDA and when compared with degenerative dementia versus immune mediated syndromes all the 4 parameters were highly significant This simple bedside TRIAD of panic, sleepiness with either of catatonia or seizures if found in patients it is appropriate to order antibody assessment before anything else is planned. This needs to be evaluated in a larger sample.

1. Introduction

Immune mediated dementias are a group of disorders where immune dysregulation is the cause for neuronal damage by inflammation followed by degeneration (Khadilkar et al., 2017). The symptoms can manifest at any age with a wide spectrum of features resulting in delay in diagnosis. First described in the year 2005 by the California Encephalitis project which identified NMDAR encephalitis as 4 times more frequent than Varicella Zoster virus (VZV), Herpes Simplex virus (HSV) and West Nile Virus (WNV) associated encephalitis. Multicentre encephalitis UK study revealed NMDAR encephalitis as 2nd most common immune mediated cause of encephalitis. (Florance et al., 2009; Miya et al., 2014; Campbell et al., Sept) Core symptoms resemble infectious encephalitis. The clue to diagnosis is often sub acute onset of memory complaint with at least one of the following like focal neurological deficits, unexplained seizures, mild Cerebrospinal fluid (CSF) pleocytosis, MRI suggestive of encephalitis and exclusion of other causes (Campbell et al., Sept; Chandra, 2018; Chandra et al., 2018). The common antibodies are N-methyl-D-aspartate receptor (NMDAR) antibodies, Glutamic acid decarboxylase (GAD) antibodies, Voltage gated potassium channel (VGKC) antibodies, leucine rich glioma inactivated 1 (LGI1) antibodies, Gamma aminobutyric acid receptor –B (GABA-B Receptor) antibodies and Contactin Associated Protein 2 (CASPR2) antibodies. Those associated with antibodies to intracellular antigens like anti-Hu are seen with malignancy, extracellular epitopes of ion channels, receptors associated proteins like NMDA, Intracellular

* Corresponding author.
E-mail addresses: drchandrasasi@yahoo.com (S.R. Chandra), somray227@gmail.com (S. Ray), thomasgregorissac@gmail.com (T. Isaac), anupama.rpai@yahoo.com (A. R.Pai), haripreya@gmail.com (H. Krishnareddy), deb.dhar.india@gmail.com (D. Dhar), dr.mariammaphilip@gmail.com (M. Philip).

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synaptic proteins like GAD65 in addition to syndromes with antigens like Systemic Lupus Erythematosis (SLE) and Rheumatologic disorders. Good number of patients are treated with several alternative diagnosis varying from psychiatric illness, SSPE (Sub Acute Sclerosing Pan Encephalitis) and Rabies. This results in gross delay in initiating the needed treatment (Chandra et al., 2018; Chandra et al., 2014; Chandra et al., 2015a). The antibodies against intracellular antigens are T-cell mediated with poor response to immunotherapy, antibodies to synaptic receptors are B-cell mediated which shows good response to immunotherapy. The common conditions are, NMDA receptor associated with ovarian teratoma, AMPA receptor with Thymoma, small cell lung cancer (SCLC), GABA B receptor associated with SCLC, GABA A receptor with Thymoma, mGluR5 with Hodgkin's Lymphoma, Dopamine 2 receptor and Ion channels and other cell-surface proteins like LGI1 with Thymoma, CASPR2 with Thymoma, Dipeptidyl-Peptidase-Like Protein 6 Antibody-Associated Encephalitis DPPX with Lymphoma, MOG, Aquaporin 4, GQ1b, Hu (ANNA1) with SCLC,Ma2 with Testicular Seminoma, GAD –with Thymoma, SCLC (Tobin et al., 2014).

2. Anti NMDA antibody syndrome

It is more common in children and young adults. Relapses are more when treatment delay is more than 40 days from symptom onset. Patients with HSV encephalitis might later develop NMDA encephalitis. Common situations which raise suspicion are as follows: rapidly progressive abnormal behaviour or cognitive dysfunction in a previously well preserved child. Speech and language impairment, altered sensorium, seizures, perioral or generalized dyskinesias, Autonomic dysfunction, hypoventilation with abnormality in one of the fallowing. EEG abnormalities, IgG anti-GluN1 antibodies, Systemic teratoma, CSF pleocytosis, oligoclonal bands and exclusion of other causes (Lancaster, 2016). Mechanism is believed to be due to binding of IgG1 and IgG3 to NR1 subunit of NMDA-R in the cortex and later subcortical structures Nagappa et al., 2016; Ahmad et al., 2017; Dalmau et al., 2008; Luca et al., 2012; Graus et al., 2016.

3. Anti VGKC antibody syndrome

Anti-voltage-gated potassium channel associated proteins antibodies (anti-VGKC-Ab) can cause a spectrum of peripheral and central nervous system disease. Isaac's syndrome and cramp-fasciculation syndrome, Morvan's syndrome manifesting as neuromyotonia and autonomic involvement, episodic memory impairment, psychosis and Faciobrachial dystonic seizures often mistaken as slow myoclonus. Morvan's syndrome is often associated with testicular and thymic tumors, lung masses and lymphoma Misawa and Mizusawa, 2010. The VGKC-positive subgroups include anti-LGI 1 causing limbic encephalitis and seizures, anti-CASPR2 syndrome with both CNS and PNS features (van Sonderen et al., 2016; Suleiman et al., 2011; Shin et al., 2013; Wong et al., 2010).

4. Patients and methods

The patients who were seen by the authors in the last 5 years with memory and cognition related symptoms were recruited. From the available data patients who had reversible dementias were segregated and then those with immune mediated disease belonging to NMDA and VGKC associated encephalitis were identified. The referral diagnosis, mean delay in diagnosis, the red herrings and the probable clues which could sensitize clinicians were evaluated. Hindi Mental Status Examination (HMSE), Every day Abilities scale of India (EASI), Panic Score, Epsworth Sleepiness Scores (ESS) and Bush Francis Criteria for catatonia were utilized.(Fig. 1a). No comparison was made between cognitive dysfunction in children and adults, instead irrespective of the age patients who deteriorated in cognitive and behavioral domains, which could point to the diagnosis of degenerative brain disease or psychiatric illness alone were taken into consideration.The data was analyzed. Only patients who had proper details were included. Those who had past history of head injury, epilepsy, cognitive disorders or any known central or peripheral nervous system disorders were excluded. Bar diagram showing distribution of patients who presented with memory complaints in the last five years (Fig. 1b).

5. Assessment of panic, catatonia and sleep

Panic was assessed using questionnaire which defines panic as sudden increase in anxiety with 4 or more of fallowing symptoms are experienced. Feeling short of breath, choking sweating, feeling unreal and detached, hot or cold flushes, numbness or tingling feeling, fear of doing something uncontrolled, palpitation and heart racing, associated chest discomfort, dizziness, stomach discomfort, trembling or shaking and fear of dying. The domains of frequency, severity and avoidance of the episodes was coded as maximum of 4 points, 8 points and 8 points respectively with minimum score 0 to maximum score 20. Malter et al., 2014

Catatonia was assessed using DSM-V criterion which includes the presence of three or more of the following:

1 Catalepsy (i.e., passive induction of a posture held against gravity),
2 Waxy flexibility (i.e., slight and even resistance to positioning by examiner),
3 Stupor (no psychomotor activity; not actively relating to environment),
4 Agitation, not influenced by external stimuli,
5 Mutism (i.e., no, or very little, verbal response [Note: Not applicable if there is an established aphasia]),
6 Negativism (i.e., opposing or not responding to instructions or external stimuli),
7 Posturing (i.e., spontaneous and active maintenance of a posture against gravity),
8 Mannerisms (i.e., odd caricature of normal actions)
9 Stereotypies (i.e., repetitive, abnormally frequent, non-goal directed movements),
10 Grimacing
11 Echolalia (i.e., mimicking another's speech),
12 Echopraxia (i.e., mimicking another's movements). (Chandra et al., 2015b)
13 Sleep assessed using Epworth sleepiness scale as normal if less than 10, excessive day time sleep if 10–16 and dangerously sleepy if more than 16. (Johns, 1991)

6. Results

Out of all patients with memory complaints seen by authors in last five years about 92 patients (12.2%) had reversible causes. Out of the 92 patients, 23 patients were having NMDA associated and 11 patients having VGKC associated and one case having a combination of HIV and VGKC associated disease was found. Though there were 29 patients who had NMDA-R antibody positive, we could include only 23 for this study due to lack of proper documentation of needed details in the 6 cases. (Table 1 shows the general differences between NMDA and VGKC encephalitis)

The age group of patients with NMDA encephalitis varied from 3 years to 31 years and majority were females. Maximum number of patients in this group were children and in the 12 years to 18 years age group. Only two children in this group had ovarian teratoma. Their referral diagnosis varied from viral encephalitis, catatonia, attention deficit disorder, autism, Rheumatic chorea, autoimmune encephalitis, psychiatric illness unspecified, rabies in one and schizophrenia in one. Two thirds of these patients reported minor respiratory infection, there was history of dog bite in one patient who had also received anti-rabies vaccine 30 days before the symptom onset whereas others had new

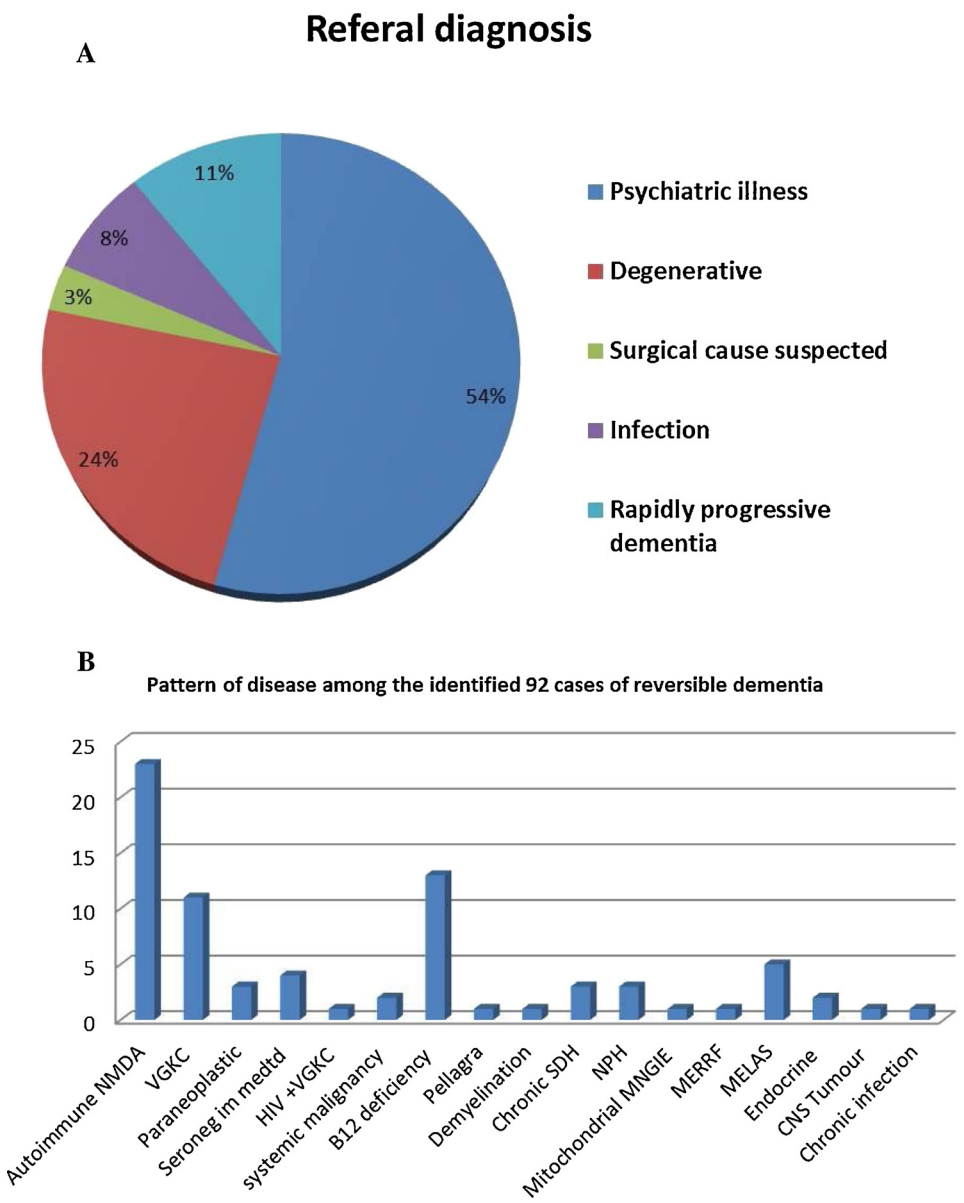

Fig. 1. a- Pie diagram showing referral diagnosis in the case of immune mediated dementias.b Bar diagram showing distribution of patients who presented with memory complaints in the last five years.

Table 1
shows the pattern in NMDA and VGKC antibody mediated encephalitis.

PARAMETERS	anti-NMDA receptor antibody associated encephalitis	anti-VGKC receptor antibody associated encephalitis
AGE	Young	Old
GENDER	Female	Male
TUMOURS	Present	Absent
PRECEDING INFECTION	Common	Less common
FASCIOBRACHIAL DYSTONIC SEIZURES	Not common	Common
FOCAL TWITCHING OF FACE	Present	Less common
PANIC	Common	Common
CATATONIA	Common	Not common
SLEPPINESS PROBLEMS	Common	Common

onset. Psychiatric symptoms consisting of severe panic was seen in 19 patients, anxiety symptoms in 7 patients, catatonic features in 6 patients, self- biting behaviour in one patient along with delusions and hallucinations in 7 patients respectively. Constitutional symptoms like fatigue and excessive sleepiness was observed in 14 patients. Neurological features were also observed which included hemiplegia and aphasia in one patient, mutism in one patient, seizures in twenty-one patients, cognitive decline in all the patients compared to the premorbid state, and chorea in three patients. Table 2 shows the details of assessment scores in various groups.

Table 2 shows the scores of HMSE, EASI, PANIC SCALE, EPSWORTH scores, and catatonia in the patients evaluated.

The mean HMSE score in patients with dementia due to NMDA was 15, patients with VGKC it was 14, one patient with VGKC and HIV was nine, the probable AD it was 20 and Probable BvFTD it was 21. The other scores are seen in the table and the statistical evaluation is discussed.

EEG showed abnormality in all patients, background epileptiform discharges in nine, and extreme delta brush in eleven patients respectively. (Fig. 2)

MRI was normal in seven cases. Though reported normal subtle signal changes in limbic structures were observed in five cases. All

Table 2
shows the scores of HMSE, EASI, PANIC SCALE, EPSWORTH scores, and catatonia in the patients evaluated.

DIAGNOSIS	HMSE MEAN(31)	EASI MEAN(12)	PANIC MEAN(20)	SLEEP MEAN	CATATONIA	Seizures
NMDA	15/23	7/12	19/23 pts Range from 4 to 19. Mean -9.3	14/23 pts Score 10 to 16range.	6/23 patients	21/23 patients
VGKC	14	9/12	Range Range from 5 to 16. mean -9	7/11 pts Score 10 to 16 range	no	3/11 patients
VGKC &HIV	9	12/12	8	Less than 10	no	yes
Probable AD	20	8	0	Less than 10	no	no
Probable FTD	21	9	0	Less than 10	no	2/20

others showed clear-cut features of limbic encephalitis (Fig. 3).

CSF test showed moderate antibody titers with less than 10% of transfected cells showing two to three plus granular cytoplasmic florescence, and serum test showed very high titers of up to 40%–60% in seven cases, moderate in twelve cases, and mild positivity in 4 cases respectively. During follow-up at 6 months, only two patients remained positive in serum test. CSF was not tested during follow-up. Period of delay from onset to diagnosis was three weeks to 17 months with a mean delay of 9 ± 3 months.

There were VGKC antibody associated encephalitis in 11 patients and one patient had HIV and VGKC. Their age group varied from 49 to 70 years. There were 3 females and 9 males. Referral diagnosis varied from chronic schizophrenia, brain infection and Huntington's disease (Fig. 4 PET reported Huntington's disease) in one patient(genetic assessment done was negative), late onset agitated depression in 2 patients, behavioural variant of Frontotemporal dementia (bvFTD) in 2 patients, late onset SSPE in 2 patients, chronic encephalitis in one patient and as immune mediated diseases in 3 patients respectively.

Cognitive decline was seen in all the 12 patients. Faciobrachial dystonic seizures were seen in 3 patients, generalized seizures was seen in one case, agitation and restless was seen in 9 patients, catatonia was not seen in any of the patients but sleep disturbances and symptoms of panic were observed in all the patients. Duration onset of symptom to establishing diagnosis varied from 7 months to 3 years with a mean delay of 15.5 ± 6 months. MRI showed diffuse atrophy in 3 cases. Cingulum, insular and medial temporal lobe signal changes were seen in 7 patients. (Fig. 5). EEG showed frontal slowing, mid-positive triphasic waves, epileptiform discharges and non-specific slowing (Fig. 6) in nine patients but was normal in 2 patients.

7. Statistical evaluation

We have analyzed a total of 34 patients with immune mediated dementias, of which 23 were NMDA and 11 were VGKC. (Fig. 7).

The Panic score, Epsworth sleepiness score, catatonic symptoms and history of seizures were compared with the same in 20 patients with probable bvFTD and 20 probable AD. Chi square test was used to compare across the groups and there was significant difference ($P < 0.05$) across the 4 groups comprising anti NMDA encephalitis, anti VGKC encephalitis, FTD and AD among the four variables (Panic

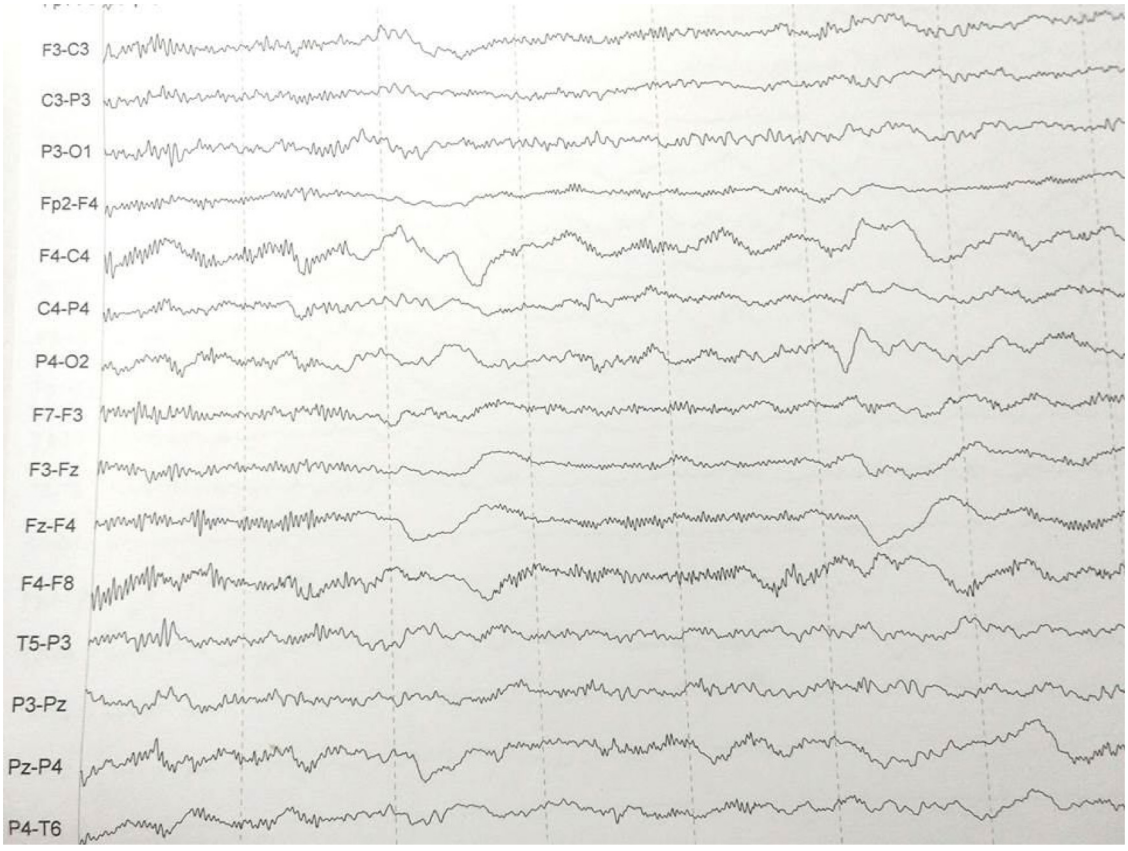

Fig. 2. EEG showing extreme delta brush and slowing.

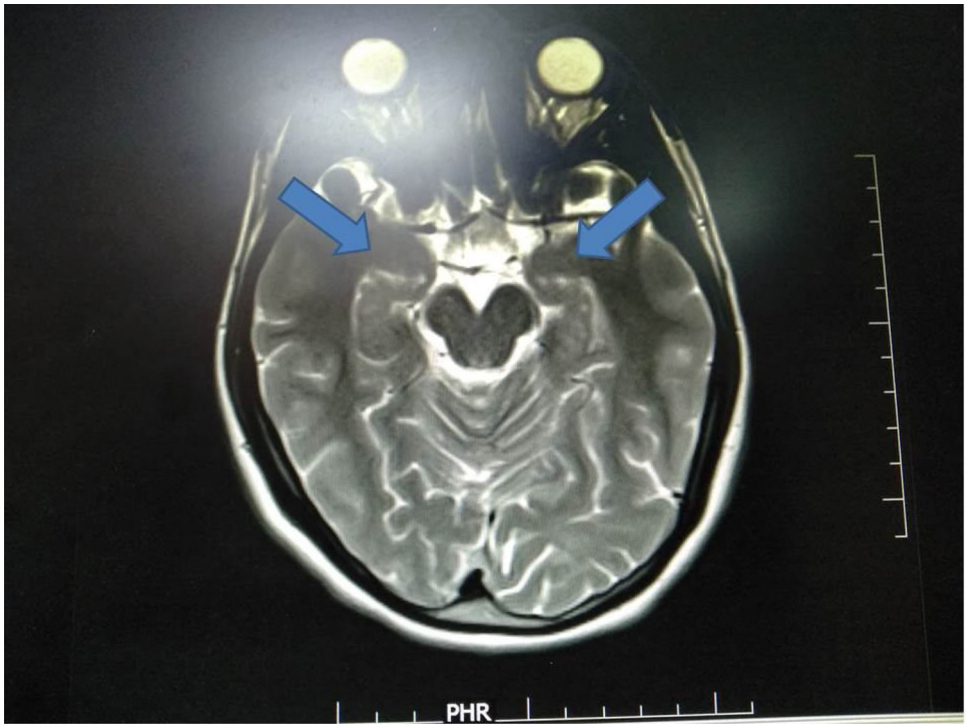

Fig. 3. MRI showing bilateral medial temporal lobe signal changes.

scores, Catatonic symptoms, Epsworth sleepiness score and seizures) studied. (Table 3)

The data between the NMDA and VGKC groups were also compared to look for any significant differences. It revealed a significant difference in the incidence of history of seizures among the NMDA group when compared with VGKC group as well as a trend for more prevalence of catatonic symptoms among the NMDA group than VGKC group though not statistically significant (Table 4).

However, when we compared the clinical features between Autoimmune encephalitis group (comprising of both NMDA and VGKC groups) and degenerative dementias, there was significant differences among both groups for all the symptom dimensions (Panic, Catatonia, sleep and seizures) which is enumerated in Table 5.

8. Treatment

Patients who had ovarian tumors underwent surgery as well as received intravenous methyl prednisone in a dose of 1 gm for 5 days (for

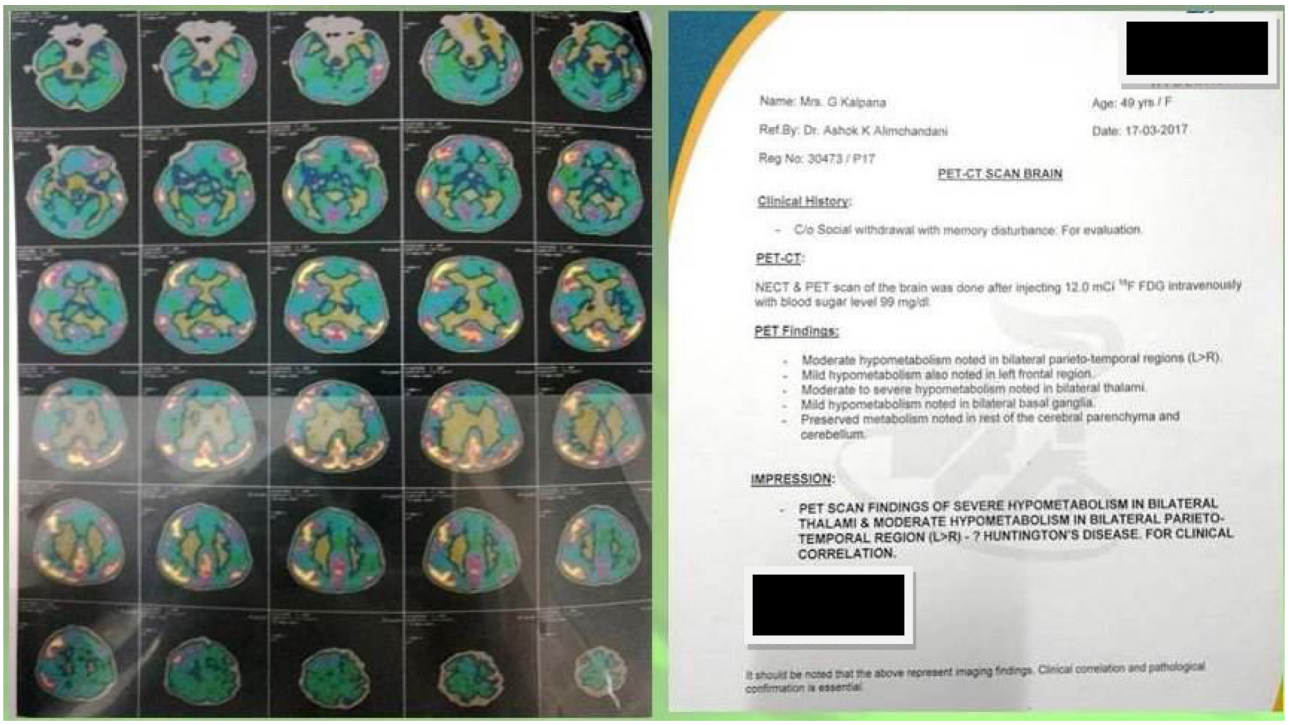

Fig. 4. PET scan reported Huntington's disease in a patient with anti VGKC antibody positivity.

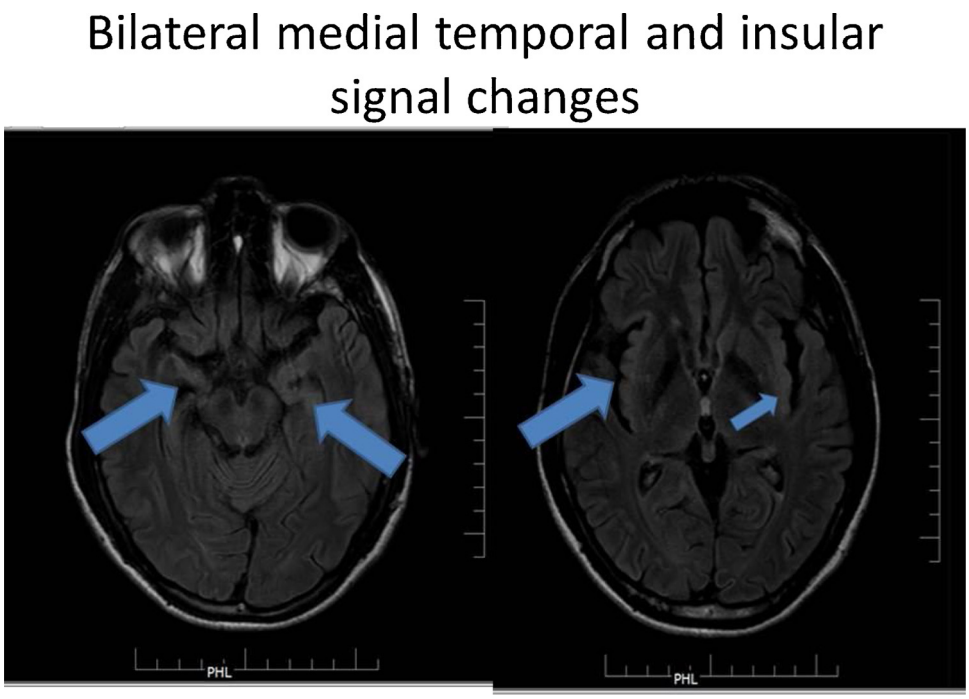

Fig. 5. Medial temporal lobe signal changes in MRI.

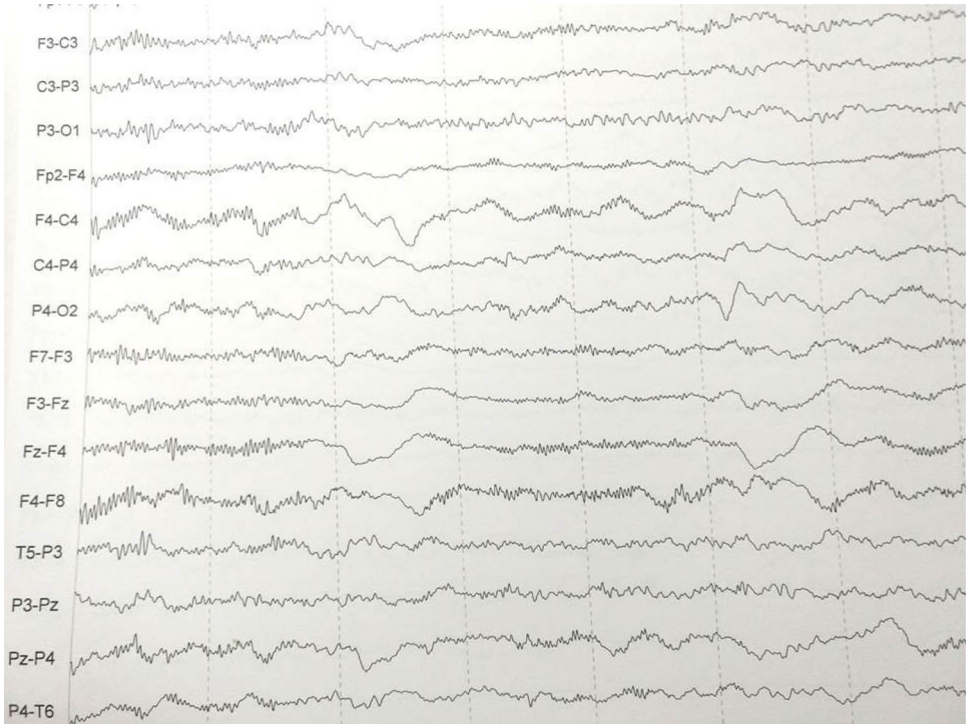

Fig. 6. EEG showing epileptic discharges and slowing).

patients more than 40 Kg) and those with weight < 40 kg received intravenous methyl prednisone 30 mg/Kg monthly 5 doses for 6 months. Those who showed inadequate response received additional plasmapharesis and or intravenous immunoglobulin (IVIG) based on response. Interval therapy consisted of providing Azathioprine or Mycophenolate mofetil in addition to anticonvulsants and supportive measures. Other co- morbidities were also addressed. The patients who were older and had delayed initiation of treatment showed poor response to treatment. One patient who had very good remission and could return to his job relapsed 3 years later following surgery for hip fracture and went in for super refractory status epilepticus from which he could not be saved.

9. Discussion

Disorders resulting in cognitive dysfunction are of great concern as the quality of life of the patient as well as that of carers becomes seriously affected. It is important to always look for potentially treatable condition which mimics degenerative dementia. Immune mediated cognitive decline affects all age groups and presents with a wide spectrum of clinical manifestations making diagnosis difficult (Antoine,

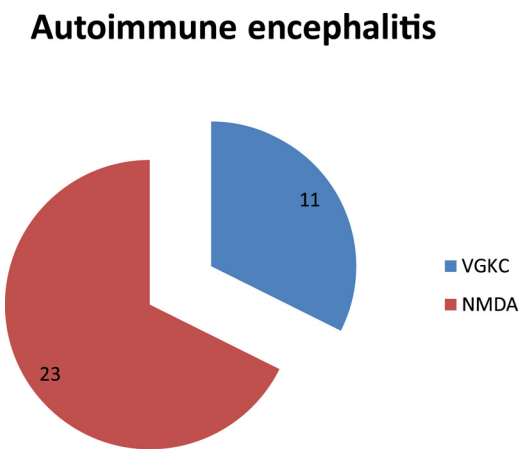

Fig. 7. Pie diagram showing the distribution of NMDA and VGKC antibodies among the patients with autoimmune encephalitis.

2016; Zand, 2017). In this study we have tried to find out the efficacy of a clinical triad to improve suspicion of immune mediated encephalitis based on bedside observations. When patients present with Core symptoms of cognitive and psychiatric dysfunctions, degenerative brain disease AD which presents as Cognitve decline and BvFTD which presents with psychiatric features are considered as possibilities. Some of them get labelled as primary mental illness or as degenerative dementias. Can they be differentiated from treatable disorders when a group of symptoms come together for simple bedside easily assessable clues so that early diagnosis can be suspected was our aim. They receive neuroleptics with the associated side effects and loss of the benefits of immunotherapy. Therefore we tested the observed clinical triad with confirmed cases of immune mediated and degenerative dementias. We have not included pure psychiatric patients as we are unable to get drug naïve patients. The combination of the triad appears more relevant than their appearance in isolation as a clinical clue for raising suspicion. There are some studies which have reported that psychosis is not unique in this group. We have applied panic score, Epsworth sleepiness score and Bush Francis criteria based diagnosis of catatonia and history of seizures in Antibody positive cases of VGKC and NMDA associated encephalitis patients who presented with cognitive decline as the symptom. Sleep disorders of all types are common in autoimmune encephalitis like insomnia continuous or recurrent, narcolepsy, parasomnias, sleep apneas and hypersomnias. Insomnias are more often reported with anti VGKC syndromes and hypersomnias with NMO,Ma1 and Ma2 antibodies. When hypersomnia is seen in a child or adult presenting with a neuropsychiatric syndrome our small observational study serves as a key point to differentiate from neurodegenerative or purely psychiatric cause of the symptoms and investigate the patient further. None of the symptoms are useful as a stand-alone pointer. Our aim is to sensitize the clinicians when this triad is present to investigate further (Silber, 2016; Warren et al., 2018; Najjar et al., 2018; Zandi et al., 2011). The data revealed that panic score, sleepiness score and seizures were highly significant when compared across all groups. When compared in between groups significant difference in seizures among the NMDA group when compared with VGKC group as well as a trend for more prevalence of catatonic symptoms among the NMDA group than VGKC group was also seen though not statistically significant. However, when we compared the clinical features between Autoimmune encephalitis group (comprising of both NMDA and VGKC groups) and degenerative dementias, there was significant differences among both groups for all the symptom dimensions (Panic, Catatonia, sleep and seizures). There are several postulates regarding the neural basis of various emotions. The main structure involved is limbic system. There are two systems for emotions based on the theory of dual system. The first is jungle alarm system which is fast, default and bypasses the cortex. The second is planned, slow and involves the cortical decision making system. One such pathway runs from the eye or ear via the thalamus to the amygdala, the emotional control center. This shortcut enables a quick, precognitive emotional response before the intellect intervenes. The cortex can also override the decision of the amygdala to react. Role of Amygdaloid fear memory depends on the integrity of the amygdala. Amygdaloid lesions disrupt wide range of emotional behaviors and physiological responses. Papez fear circuit was postulated in 1937. Cannon Bard theory talks about a separate fear center in the thalamo cortical route. Pavlovian fear conditioning describes it as conditioned reflex. Lesions of the central nucleus and the lateral nucleus of amygdala abolish conditioned fear. The central nuclei causes freezing (immobility), tachycardia (rapid heartbeat), increased respiration, and stress-hormone release. Amygdala lesions cause Taming effects and Psychic blindness. Amygdala stimulation results in defensive and flight reactions in cats, feelings of fear and anxiety in humans and increased autonomic activity. In 1940's Walter Hess demonstrated that Lateral hypothalamic stimulation in unanaesthetised cats produced autonomic & somatic responses of anger. Lateral hypothalamic lesion produced placid animal. Medial hypothalamic lesion causes aggressive animal Hypothalamus integrates & produces well organized autonomic & somatic responses. In Panic disorder sudden fear attack occurs

Table 4
Comparison between anti NMDA and anti VGKC groups.

	NMDA(n = 23)	VGKC(n = 11)	χ^2 value	p-value
Panic(+)	19 (82.6%)	7 (63.6%)	1.49	0.222
panic (−)	4	4		
Catatonia(+)	6 (26.1%)	0	3.48	0.062
Catatonia(−)	17	11		
day time sleepiness(+)	14 (60.9%)	7 (63.6%)	0.024	0.877
day time sleepiness(−)	9	4		
Seizures(+)	21(91.3%)	3 (27.2%)	14.7	< 0.001
Seizure(−)	**2**	**8**		

Table 5
Comparison between Autoimmune encephalitis and degenerative dementias (FTD and AD).

Clinical Features	Autoimmune encephalitis (NMDA and VGKC)(n = 34)	Dementias (FTD and AD) (n = 40)	χ^2 value	p-value
Panic	26 (76.4%)	0	47.2	< 0.01
Catatonia	6 (17.65)	0	7.68	0.006
Sleep score	21 (61.8%)	1 (2.5%)	30.9	< 0.001
Seizures	24 (70.6%)	2 (5%)	34.7	< 0.001

Table 3
Comparison across the groups with respect to the symptoms studied.

CLINICAL FEATURES	anti NMDA encephalitis n = 23	anti VGKC encephalitis n = 11	Frontotemporal dementia n = 20	Alzheimer's dementia n = 20	χ^2 value	p-value
PANIC	19	7	0	0	48.3	< 0.001
CATATONIA	6	0	0	0	14.5	0.002
SLEEPINESS SCORE	14	7	1	0	31.0	< 0.001
SEIZURES	21	3	0	2	48.5	< 0.001

without provocation. Common symptoms during a panic attack are palpitations, breathlessness, chest tightness, diarrhoea, paresthesia, sweating, fear of death, and agoraphobia.

Anxiety and fear can have similar features but unlike fear which appears episodically, anxiety is generally more prolonged and the bed nucleus of Stria terminalis is supposed to be the neural structure. Catatonia is known to be produced by lesions of Ventral Tegmental Area (VTA). Excitation of the ascending reticular activating system and there is a role of dopaminergic/GABAnergic modulation. Activation of anterior cingulate and medial prefrontal cortex is observed. This results in a heightened activity of the affective division of the anterior cingulate and complete down-regulation of the motor portion of the anterior cingulate causing mutism. Imbalance between medial and lateral orbitofrontal cortex causes affective symptoms. Globus Pallidus internum dysfunction causes rigidity (Daniels, 2009). These are the structures commonly affected in all kinds of limbic encephalitis.

Therefore, this study demonstrates that this simple bed side clue is very valuable to improve the clinical suspicion of immune mediated dementia and reduce delay in initiating appropriate treatment.

10. Conclusion

Immune mediated cognitive decline is a spectrum of treatable dementias which carry excellent prognosis if diagnosed early. However, due to the general nihilistic approach to patients presenting with cognitive decline and also the possibility of laboratory clues with imaging and EEG finding being nonspecific or very subtle, there is very large delay in clinical suspicion and therefore diagnosis. This simple bedside TRIAD of panic, sleepiness with either of catatonia or seizures if found in patients is an indicator to order antibody assessment before anything else is planned. This needs to be evaluated in a larger sample. We have not included children with various neuropsychiatric disorders and pure psychosis in adults as controls. That work is being planned for future.

11. Limitation

Ours being a government institution, all patients suspected to have autoimmune encephalitis could not undergo full panel of investigations due to economic constraints. Therefore, those patients who were suspected to have autoimmune encephalitis clinically but not proved serologically have been missed. The numbers of patients evaluated are small and needs to be repeated in a larger sample.

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Conflict of interest

None.

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