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Clinicopathological study of encephalitis in greater Gwalior region: A hospital based study

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Abstract
Introduction: Encephalitis is inflammation of the brain parenchyma. Viral infection is the most common cause of the condition.
Aims And Objectives: To find out prevalence and encephalitis cases in hospital admitted patient at J.A Hospital, clinical spectrum of disease, laboratory parameter of routine CSF and Hematology and specialized molecular test.
Material and Methods: Prospective study to find the prevalence of encephalitis in the greater Gwalior region of patients admitted in Neurology and Paediatric ward, conducted by Department of pathology G.R.M.C in association with D.R.D.E, patients samples of CSF, blood and serum will be used for routine and molecular diagnosis.
Results and Observations: This evaluation and comparison of new molecular techniques RTPCR and Nucleotide Sequencing indicate that these test are highly specific in identifying etiological agent in viral encephalitis and has great potential value for use in epidemic situation. These molecular techniques can prove as a big asset to the society as they facilitate the early diagnosis of viral encephalitis and reduces the mortality and morbidity.
Conclusion: Incidence of viral encephalitis is very less (04%) in this region, clear male preponderance in overall encephalitis cases (M:F = 1.6:1). Pediatric age group is the most affected group of encephalitis patients (0-10 yrs), rise in the incidence of west nile virus encephalitis in this region which was rare for this region.

Keywords: encephalitis, brain parenchyma, viral infection

Introduction

Encephalitis is inflammation of the brain parenchyma. Viral infection is the most common cause of the condition. Acute encephalitis begins abruptly (hours to days) whereas chronic encephalitis is insidious in onset, occurring over weeks to months [1]. The common viral agent causing encephalitis in Asian Country is Japanese encephalitis [2] while in North America HSV-1 accounts for more of the cases. Globally Japanese encephalitis virus is the most important emerging viral encephalitis [3] Japanese encephalitis is a mosquito-borne arboviral infection which is the leading cause of viral encephalitis [4] Japanese encephalitis (JE) is the most important forms of epidemic and sporadic encephalitis in the tropical regions of Asia including Japan, China, Taiwan, Korea, Philippines all of the South-east Asia and India [5] JE is principally a disease of rural agricultural areas, wherever vector mosquitoes proliferate in close association with pigs, which are the principal vertebrate amplifying hosts [4] Age, season, geographical location, regional climate condition and the strength of the person immune system. Play role in development of the disease and severity of illness. Japanese encephalitis virus is the most common arbo virus in the world (virus transmitted by blood sucking mosquitoes or ticks. and is responsible for 50,000 cases and 15,000 death per year worldwide most of China, South East Asia and Indian Subcontinent are affected. In India epidemic of encephalitis in Lakhimpur Kheri a place near to Nepal Border where the most common cause to agent to be Japanese encephalitis.

There are three different group of causative agent that often are responsible for causing encephalitis. First group is the Herpes viruses - Herpes groups (HSV-1, HSV-2, VZV, Adenovirus, Chiken gunya virus, CMB, EBV, HHV6) [6]. The second is made of viruses and other causative agent that are spread by insects - West nile virus, St. Louies encephalitis virus. Third group include viruses that causes child hood infection. Some of these viruses causes measles and mumps [7]. And other Japanese encephalitis group, entero virus - A. Polio virus, B. Non poliovirus- Echo virus 18, Entero virus 71, Coxsackie virus.

Table 1: Causes of viral encephalitis [8]

1.	Herpes simplex virus (HSV-1, HSV-2)
2.	Other herpes viruses: varicella zoster virus (VZV), cytomegalovirus (CMV), Epstein-Barr virus (EBV), human herpes virus 6 (HHV6)
3.	Adenoviruses
4.	Influenza A
5.	Enteroviruses
6.	Poliovirus
7.	Measles, mumps and rubella viruses
8.	Rabies
9.	Arboviruses — for example, Japanese B encephalitis, St Louis encephalitis virus, West Nile encephalitis virus, Eastern, Western, and Venezuelan equine encephalitis virus, tick borne encephalitis viruses
10.	Bunyaviruses — for example, La Crosse strain of California virus
11.	Reoviruses — for example, Colorado tick fever virus
12.	Arenaviruses — for example, lymphocytic choriomeningitis virus

Symptoms of encephalitis vary from person to person encephalitis may cause no symptoms. If symptoms appear they

are often similar to symptoms of the flu and include aching muscles or joints, extreme tiredness fever headache. More severe cases are less common but can be life threatening - Double vision, Hallucination, impaired judgment, loss of consciousness, loss of sensation in some parts of the body. Memory loss, muscle weakness, partial paralysis in the arm and legs, personality changes, problem with speech or hearing, sudden severe dementia. Encephalitis in infants may causes different symptoms. Symptoms include - A full or bulging soft spot on top of an infant head, body stiffness, Constant crying, crying that gets worse when the child is picked up, vomiting.

Laboratory Detection methods

Identifying the agent responsible for suspected cases of central nervous system (CNS) viral infection poses tremendous diagnostic challenges, and a specific organism is identified in only 30% of cases of suspected viral encephalitis [9].

These viral agents can be detected by conventional method of identification such as culture but it requires 1 to 30 days for culture and identification of virus. So now a day viral agents are detected by different molecular technique most commonly used are PCR and RTPCR. These molecular technique are more sensitive and more specific than conventional method of identification and it is less time consuming. Identification of viral agent by molecular methods can be done with in 24 hour or less. Identification of viral agent in CSF in more yielding and result are not influenced by any antiviral treatment.

Aims and Objectives

To find out prevalence and encephalitis cases in hospital admitted patient at J.A Hospital, clinical spectrum of disease, laboratory parameter of routine CSF and Hematology and specialized molecular test.

Material and Methods

It is a Prospective study, which is designed to find the prevalence of encephalitis in the grater Gwalior region of patients admitted in Neurology and Paediatric ward.

The study will be conducted by Department of pathology (Pathology Lab), G.R.M.C., Gwalior in association with D.R.D.E., (Defence Research and Development Establishment) Gwalior from May 1st 2015 to June 31st 2016. Around more than 100 samples of CSF and serum will be used in the study with respect to the patients admitted to the Neurology Department.

Material used for study is CSF, patient blood & serum suffering from encephalitis. Normally 2 ml. of CSF & 5 ml. of blood is used for study.

Following tests are planned for this study

Routine CSF Examination

Quantity of CSF, Colour of CSF, Transparency, Coagulum, Blood, Cell count & type of cell.

CSF sugar estimation will be done by auto analyzer & CSF protein will be determined by sulfosalicilic acid using spectrophotometer. These findings will be correlated with different viral etiological agent identified.

PCR/RTPCR examination for identification of viral agent. Blood

a) Haematology parameters including - Hemoglobin (Hb), TRBC, PCV, MCV, MCH, MCHC, RDW, TLC, DLC, Platelet count, MPV.
   With the help of 5 part hematology analyzer.
b) Serum Examination by PCR/RTPCR for viral agent in any.

Inclusion Criteria

All cases of encephalitis clinically diagnosed and preliminary verified by CSF examination.

Exclusion Criteria

All cases of tubercular, pyococcal and fungal meningitis are clinically diagnosed and verified by CSF examination are finally excluded for this study.

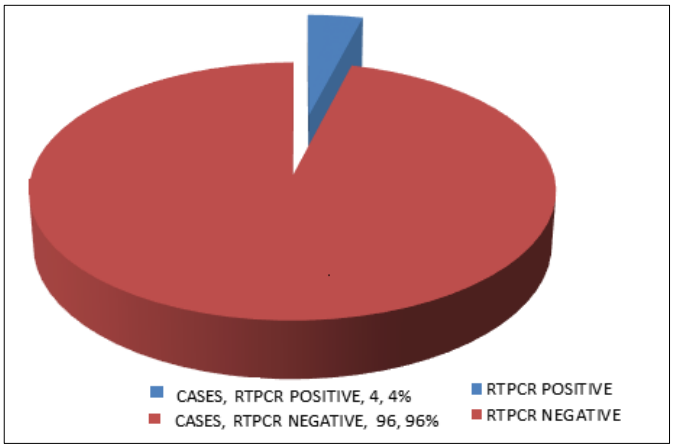
Results and Observations

The present study was conducted in Department of Pathology, G.R. Medical College. The present study consisted of screening of CSF samples and blood/serum samples for diagnosis of etiological agent in 100 clinically suspected cases of viral encephalitis by battery of diagnostic tests were performed to identify the presence of encephalitis causing viruses by direct and indirect techniques for diagnosis from J.A Group of Hospitals of G.R. Medical College from Jan 2015 to Feb 2016.

All the samples were stored at –20ºC before being transported for analysis and there after stored at –70ºC at Defence Research Development Establishment (DRDE), Gwalior, India.

After aseptic collection CSF and serum were taken to laboratory of J.A. Group of Hospitals, where routine CSF examination, protein estimation of CSF, sugar estimation of CSF and in blood haematological tests (Hb, PCV, TLC, DLC, platelet count) were performed.

Incidence of Viral Encephalitis



Age and Sex wise distribution of cases in study.

Fig 1: Shows out of 100 cases suspected of viral encephalitis, 04 cases (04%) were diagnosed as viral encephalitis by RTPCR. Pvalue for Incidence of viral encephalitis is 0.04 which is significant.

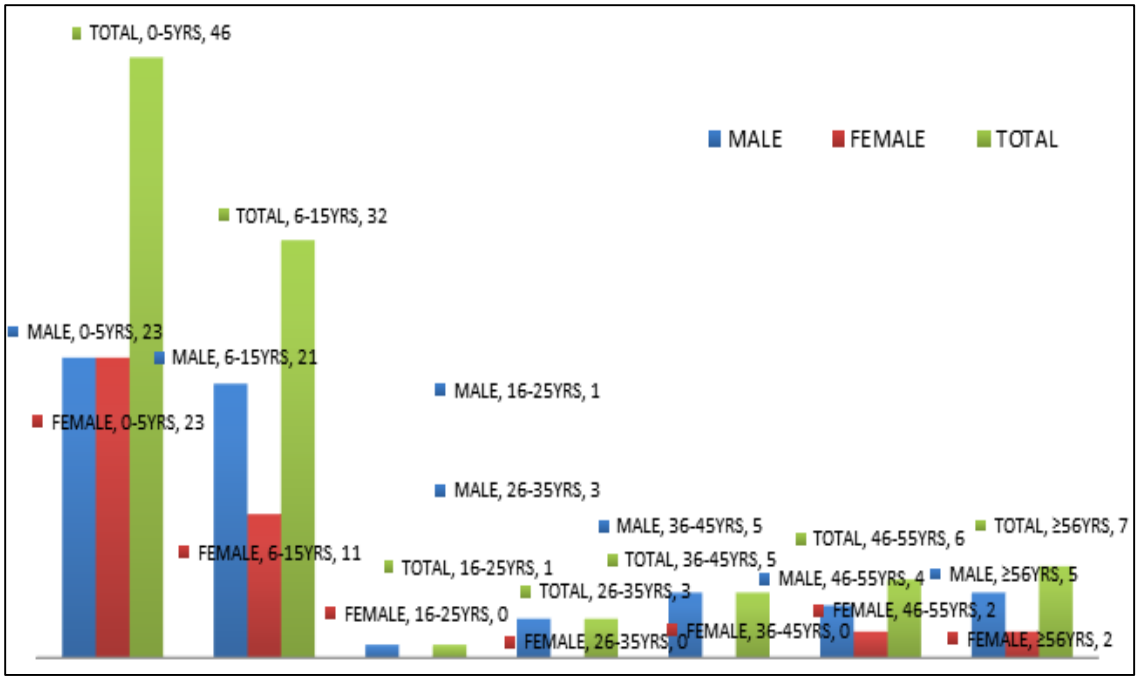


Fig 2: shows out of 100 cases, patients with age < 5yrs comprised of (46%), 6-15yrs comprised (32%), 36-45yrs comprised (5%) and >46 yrs age comprised (13%), Majority of cases of in our study are between 0-15yr (78%), Out of total 100 cases 62 male cases (62%) while 38 female cases (38%) with clear male preponderance, Male to female ratio – 1.6:1 P-value for Table No.13 is 0.184 which is insignificant.

Biochemical findings of CSF

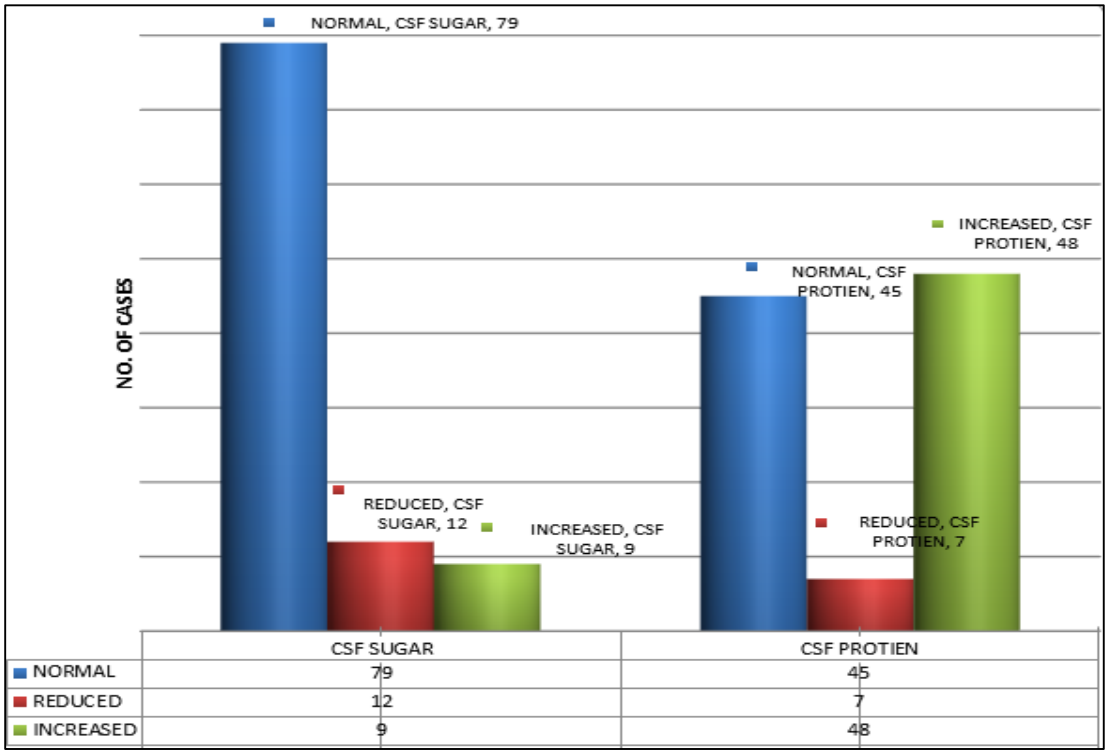


Fig 3: depicts biochemical findings of CSF examination. Out of 100 cases, 79 cases showed normal (40-70mg %) CSF sugar while 12 cases showed reduced (< 40mg %) CSF sugar and 09 cases showed increased CSF sugar (>70mg %).

Out of 100 cases, 45 cases showed normal (20-40 mg %) CSF protein while 48 cases showed increased (>40 mg %) CSF protein and 07 cases showed reduced CSF protein (<20mg %).

Microscopic findings of CSF

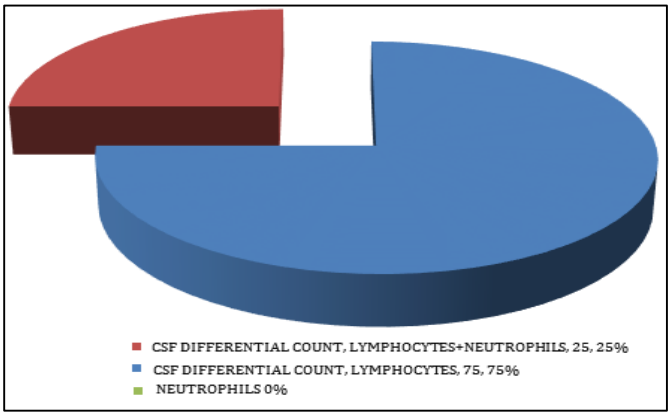


Fig 4: Shows Out of 100 CSF samples, 75 (75%) showed presence of lymphocytes only, 25 (25%) showed lymphocytes + neutrophils and none of the sample showed presence of neutrophils only.

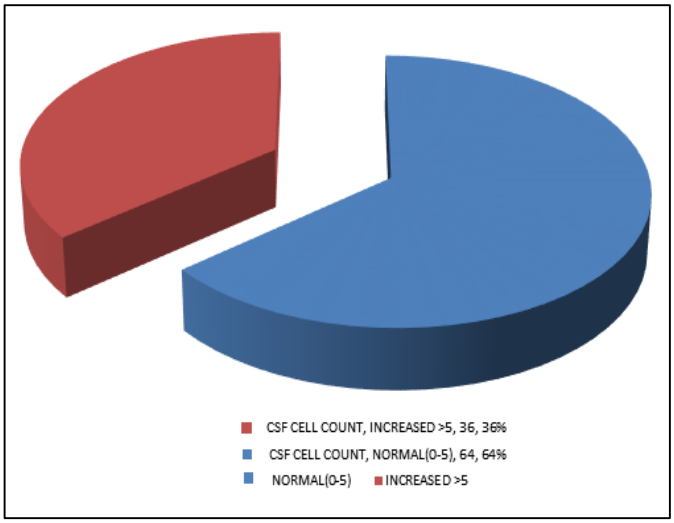
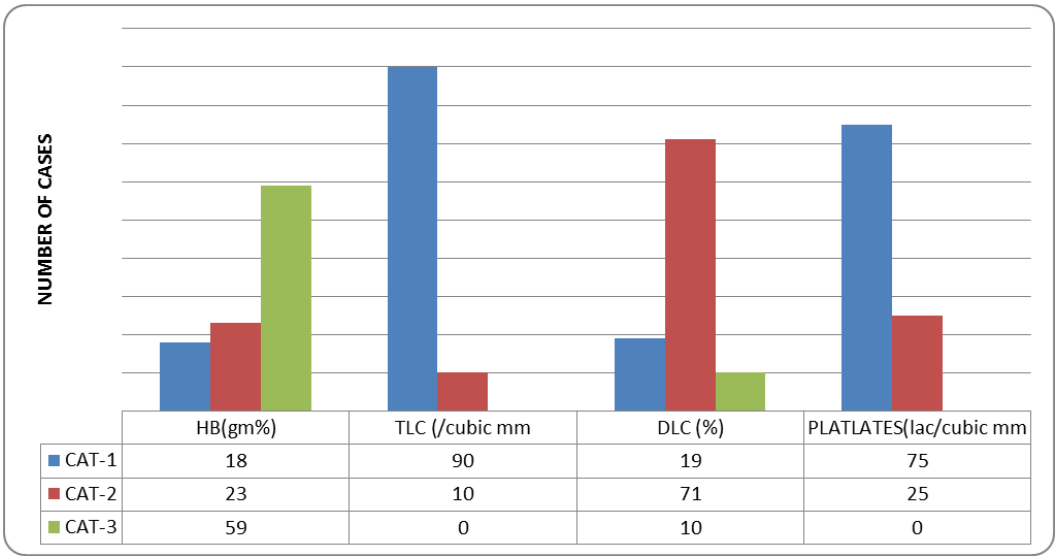


Fig 5: depicts microscopic findings of CSF samples examined in the present study. Out of 100 CSF samples, 64 (64%) had normal (0-5/mm^3) CSF count while 36 (36%) samples had increased (> 5/mm^3) CSF count.

Hematological Parameters of patients of the present study



*Various parameters for different categories

Fig 6: Depicts hematological parameters of patients of the present study. Out of 100 cases, 18 (18%) cases had hemoglobin < 10 gm%, 23 (23%) cases had hemoglobin in the range of 10-12 gm% and 59 (59%) cases had hemoglobin > 12 gm%.

Out of 100 cases, 90 (90%) cases had normal TLC, 10 (10%) cases had increased TLC and none of the case had decreased TLC. Out of 100 cases, 19 (19%) cases had lymphocytosis 71 (71%) cases had normal DLC while 10 (10%) of the case had neutrophilia. Out of 100 cases, 75 (75%) cases had normal platelet count, 25 (25%) cases had reduced platelet count and none of the case had increased platelet count.

Table 2

Category	Hb (gm %)	TLC (/cumm)	DL C (%)	Platelets (lac/ccmm)
CAT 1	<10	4000-11000	LYMPHOCYTES >45%	1.5 – 4.5
CAT 2	10-12	>11000	NORMAL DLC DISTRIBUTION	<1.5
CAT 3	>12	<4000	NUETROPHILLS>75%	>4.5

For molecular detection nucleic acid (RNA) were extracted using Qiagen Ultrasense kit. The nucleic acid from all the samples was initially processed by pan-Flavi, pan-Entero, and pan-Alpha RT-PCR. Results are as follows.

Results of RTPCR for PanFlavi virus

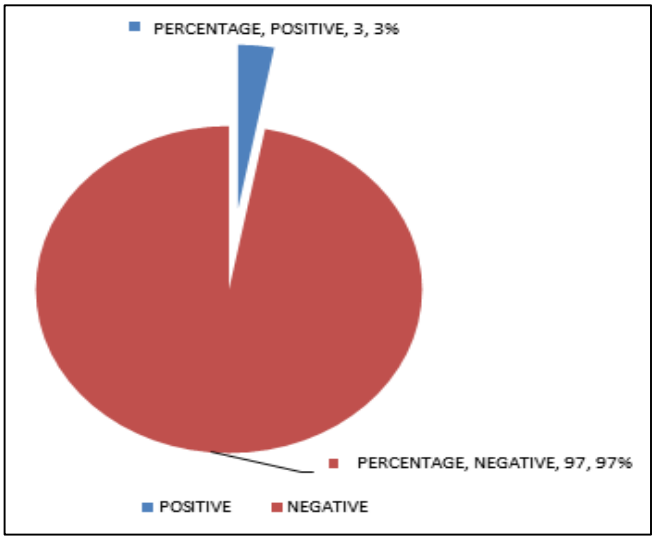
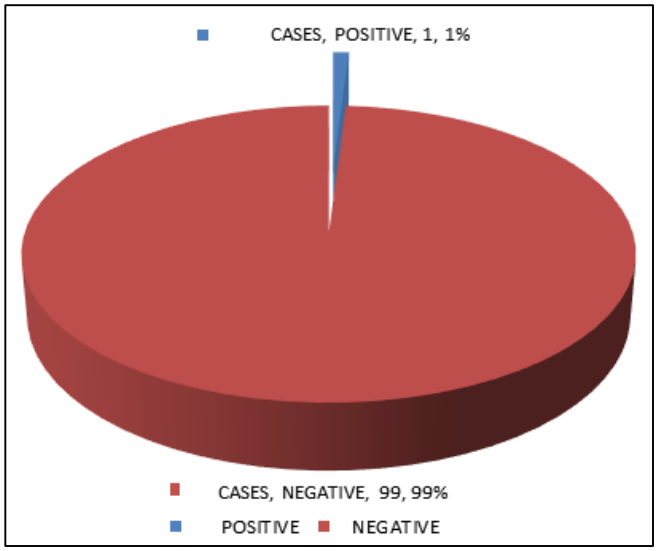
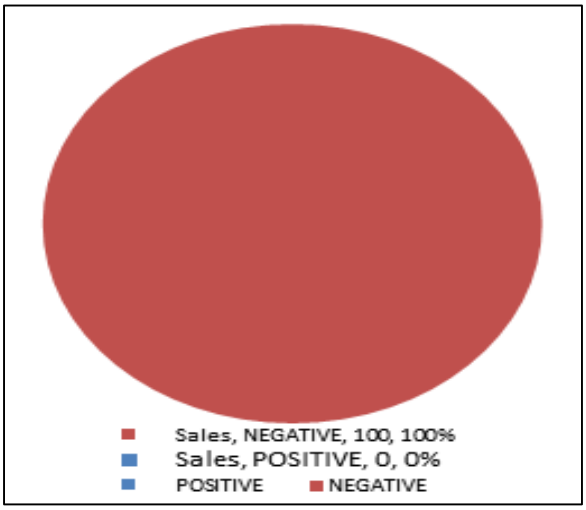


Fig 7: depicts results of RTPCR for Flavivirus. Out of 100 cases 3 cases are positive for Flavivirus, and rest of 97 cases were negative.



Results of rtpcr for Pan Enterovirus

Fig 8: depicts results of RTPCR for Panentero virus. Out of 100 cases, 1(1%) case positive for pan Enterovirus, and rest of 99(99%) cases were negative.



Results of rtpcr for PanAlphavirus

Fig 9: Depicts results of RTPCR for Alphavirus. Out of 100 cases, all 100 (100%) cases were negative.

Result of RTPCR for PanAlpha virus

The nucleic acid was then processed by RT PCR for HSV-1,2, HHV-3,4,5; Enterovirus, west-nile virus, Measles and Metapneumovirus using primer design kits as mentioned in material and methods. Results are as follows

Table 3: Etiological agents identified in positive samples

Virus identified	No. of cases	Percentage (%)
Enterovirus	1	25%
Flavi-Group (west-nile virus)	3	75%
HSV-1	0	0
HSV-2	0	0
VZV(HHV-3)	0	0
CMV(HHV-4)	0	0
HHV-5	0	0
Metapneumo Virus	0	0
Total	4	100

Table No. 3 depicts etiological agents identified in positive samples. Out of 4 positive cases, 3 (71.4%) cases showed presence of Flavi group (west-nile virus) and 1 (28.6%) showed presence of Enterovirus. None of the other viruses were identified.

Table 4: Comparative table of clinical features among positive cases

Feature	No. (%) of EV (+ve patient)	No. (%) of FLAVI-VIRUS (+ve patient)
Fever	1(100%)	3(100%)
Altered sensorium	1(100%)	3(100%)
convulsion	1 (100%)	1 (33.33%)
Spleenomegaly	0 (0%)	1 (33.33%)
Brisk DTR	1 (100%)	1 (33.33%)
Meningeal sign	1 (100%)	2 (66.66%)
Total no. of patients	1(100%)	3(100%)

Table No. 4 shows that fever and altered sensorium (100%) is statistically significant in all the positive cases in our study. All the positive cases shows fever and altered sensorium.
Convulsion is statistically significant in all positive Enterovirus case 1 (100%)
Out of 3 positive Flavivirus cases convulsion was present in 1(33.33%) cases.
Out of 3 positive Flavivirus cases spleenomegaly was present in 1(33.33%) case each.
Brisk Deep Tendon Reflex was present in 1 cases (100) of EV, while 1 (33.33%) case of Flavivirus showed brisk Deep Tendon Reflex. Meningeal sign was present in 1 case (100%) of EV, and in 2 cases (66.66%) of Flavivirus. P-value for Table No.04 is 0.939 which is insignificant.

Table 5: Age and Sex distribution of our study in positive cases

SAMPLE ID	Agent	Age	Sex
SAMPLE NO 16	Flavi-virus	36 months	F
SAMPLE NO 36	Entero-virus	< 1month (25 days)	F
SAMPLE NO 38	Flavi-virus	24 months	M
SAMPLE NO 59	Flavi-virus	1 month (32 days)	F

Table No. 5 shows that out of 4 positive cases, 1 case was male (25%) and 3 cases were female (75%).
Among positive cases there was single Enterovirus case which was female (100%) and in Flavivirus 2 (66.66%) cases were female and 1 (33.33%) case was male. Among these patients majority of patients belong to age group less than 10 yr (4 cases out of 4). This show that incidence of viral encephalitis is more common in children.

Table 6: Comparison of positivity in CSF and Serum samples in all cases

Total	CSF		Serum	
	Positive	Negative	Positive	Negative
Cases (100)	4	96	1	99
	4%	96%	1%	99%

Table No. 6 shows that out of 100 CSF sample, 4 sample are positive i.e. (4%) while out of 100 serum sample 1 samples was positive i.e. (1%).
Above table showed that virus were diagnosed more in CSF than in serum. P-value for Table No. 6 is 0.174 which is insignificant. Sensitivity is 80% and specificity is 57%.

Table 7: Comparison of CSF and Serum sample in positive cases

Viruses identified	CSF		Serum	
	No.	%	No.	%
1	100	100		
Flavivirus Total 3 (100%)	3	100	0	00

Table No. 7 shows that out of 100 samples in CSF 4 samples are positive, out of which 3 Flavivirus (75%) and 1 Enterovirus (25%) while in serum 1 Enterovirus identified and no Flavivirus detected in serum. serum sample is from same patient with CSF positivity. Hence, should not be presented as separate case.
This table also shows that viruses were diagnosed more in CSF than in serum.

Discussion

The viral encephalitis spectrum consist of patients with confirm non-viral, viral and unknown etiology. We found some clinical differences across these subtypes. Cases with confirm non-viral etiologies had a longer duration of fever before they develop altered sensorium, were more likely to have a stiff neck, and had a higher CSF protein levels. Typically in tubercular and cryptococcal meningitis, the clinical course is long and indolent before neurological detoriation. In contrast, as compared to patients in with an unknown etiology patient with a confirm viral etiology were more likely to have a stiff neck, CSF pleocytosis suggestive of meningeal inflammation.
Clinical and survival characteristics of patients with known viral and unknown etiologies were similar. It is a plaucible that patient with known viral encephalitis, had higher viral loads and consequently more meningeal inflammation, and those classified as unknown etiology were due to an unidentified viral agent with lower viral loads.
Overall incidence of encephalitis in tropical countries including India is 6.34/100000. It occurs in sporadic as well as epidemic forms. Encephalitis is an inflammation of the brain parenchyma, most commonly caused by viruses and associated with substantial morbidity and mortality. Increasing evidences of viral encephalitis are now reported from several parts of India at regular intervals indicating a serious threat to the health of people in India. Major virus implicated in causing viral encephalitis are Herpes viruses, Enterovirus, Arboviruses including Japanese Encephalitis virus, West Nile virus, EEEV, WEEV, Measles, Mumps, Rabies virus etc. Recent incidence of encephalitis outbreaks in many parts of UP and Bihar (www.promedmail.com, Archieve no. 201110123054) highlights the urgent need to tackle viral encephalitis threats to public health. Since encephalitis is a dangerous condition with a high mortality emphasis should be given for early diagnosis of patient and also early diagnosis can play crucial role to forecast an early warning of epidemic and help in better patient's management. Confirmatory diagnosis can only be achieved with laboratory support.
The current trends of viral encephalitis diagnosis include virus isolation, serodiagnosis and/or molecular detection by demonstration of viral genome by RT-PCR, QRT-PCR and PCR. In addition there is a need to characterize the viruses into different genotypes in order to identify the emergence of newer viral genotypes. Keeping, this in view the present study was undertaken to identify the incriminating viral genotypes from

suspected encephalitis samples.

Our study illustrate the challenge of identifying the causative agent in patient with acute encephalitis. A confirmed or probable etiology was identified only in 4% of enrolled patients, which is with same range as reported by Beghi *et al* (1982), Pederson (1954), Ponka *et al* (1980), Henrich *et al* (2003) and Treveja (2004).

In our present study (2016) the incidence of Viral Encephalitis was found to be very low (4%). It might be due to low genomic copy number or patients admitted late in the course of disease or viruses may be lost during transportation or as we have not used the brain biopsy for identification of viral agent, which is a gold standard method.

In present study, male to female ratio was 1.63:1 which is similar to study done by Karmarkar *et al* (2008) in Delhi where it was 1.71:1, Farzana K Beig *et al* (2009), Y.R. Khinchi *et al* (2010) Nepal, Baswati *et al* (2013) and Abhishek Roy *et al* (2015) 1.8:1 which was also similar. In most of the studies male were predominant which is also similar in present study male (62%) and female (38%).

Majority of patients in our study (2016) are belongs to age group 0-15 yrs. It comprises about 78% of total cases and all positive cases were from 0-10yrs of age group.

Similarly various studies from India and abroad also shown almost same most common affecting age group which is found to be 0 to 15 yrs, Gajanan *et al* (2006) UP, Farzana K Beig *et al* (2009). Y.R. Khichni *et al* (2010), Girishchandra *et al* (2012), Hiroshi shoji *et al* (2013) and Abhishek Roy *et al* (2015).

Comparing the various viral etiological agents in our present study (2016) it was found that Flavivirus (75%) was the most common etiological agent sequenced out of four positive cases where as only one case of Entrovirus (25%) was found which was the most common etiological agent in most of the studies done in India and around the world. This may be due to the less numbers of cases in our study and may be due to there were very less studies done in Gwalior (Central India) region on encephalitis as it is not a common problem in this area. However in present study it was clearly shown the rising incidence of Flavivirus Encephelitis.

Comparison of clinical features and viral etiology was done in the study. Convulsions, altered sensorium and fever appears to be significantly associated with viral Encephalitis. No other clinical finding was significantly associated with VE. Splenomegaly, Brisk DTR, meningeal sign is present in 25%, 50% and 75% in positive cases respectively.

In our study out of 100 cases four cases were detected in CSF(4%) while one case were detected in serum (1%) this finding on comparison with study done by Jain Reena *et al* (2015) Gwalior showed almost similar results with our study [CSF (4.1%) & SERUM (1.6%)]. While Gajanan et at (2006) UP found 27.7% positive cases in CSF & 5.9% cases positive in Serum.

Similarly Farzana K Beig *et al* (2009) also sequenced in both CSF(12.6%) and SERUM (21.7%) which showed contradictory result with other studies and with our study as in most of studies CSF positivity of cases is more than serum positivity.

Out of 100 cases in our study 64 cases showed CSF cell count < 5 cells per cu mm while 36 cases showed csf cell counts to be more > 5 cells per cu mm i.e. CSF pleocytosis. In positive cases all cases showed lymphocytosis. Similar results were shown in studies done by Rashmi Kumar *et al* (2005) CSF cell count < 10 cells/mm (50.6%), Karmarkar *et al* (2008) CSF cell count < 5cells/mm in 26% cases, while csf pleocytosis in found in majority of cases in study done by Jain Reena *et al* (2015) >5 cells/mm in 94% cases. In our study csf lym phocytosis was found in most of cases (75%) similar results shown in Jain Reena *et al* (2015) in 86.6% cases.

our study 18 cases showed haemoglobin < 10 gm% (18%) while 82 cases had haemoglobin > 10 gm% (82%). Total count and differential count on 100 blood sample showed that only 10 cases (10%) show lecocytosis, which out of 19 cases showed Relative lymphocytosis while 10 cases showed Relative Neutrophilia. Thrombocytopenia was found in 25 cases (25%).

In our study children mostly affected were from rural areas (90%) and belong to low socioeconomic group (63%). This correlated well with the earlier studies where the patients were children of farmers or farm laborers of low socioeconomic group residing in rural areas (R. Potula *et al* 2003, R.Kumar *et al* 2005).This may be due to favorable epidemiological factors like presence of water logged paddy field supporting profuse breeding of vector mosquitoes, piggeries in close proximity to residence, nonuse of bed nets and outdoor playing habits of children.

In our study, none of the WNV patients had neurological sequelae at the time of discharge, and no one died in hospital. Neurological sequelae in JE are the common observation (K.S. Avabratha et at 2012, Y.C.Wu *et al* 1999). In a study of certain prognostic features in 49 patients of JE in Thailand only deep coma was found to correlate with mortality which is in conformity to the present study. Similar association was also noted in other different studies (D. S. Burke *et al* 1985, S. K. Klein *et al* 1994, K.S. Avabratha *et al* 2012). We could not establish any association of mortality with various signs and symptoms (like the meningeal signs and elevated level of CSF cell count and CSF protein) as there was no death reported among the 03 WNV positive cases. In contrary to this, the study conducted by Avabratha *et al*. in Bellary, Karnataka, revealed association between mortality and meningeal signs (K.S. Avabratha *et al* 2012). This may be mentioned here that our observation is only from a small number of patients who were admitted in the hospital and it is an ongoing study. In future, with more number of patients, we may be able to shed some more light on mortality and its association with meningeal signs.

In conclusion, WNV is a major cause of VE in children in this part of India. The most common clinical presentations were fever, altered sensorium, seizure, headache, vomiting and signs of meningeal irritation. The case fatality was not recorded, and all the three positive cases walked out of the hospital with relief of all the symptoms. First time report of WNV VE from this part of India will definitely lead to more screening of cases to look for the actual incidence of this virus disease. This will help in understanding the local factors leading to the problem and the will help in the control of this viral disease.

Conclusion

This hospital based prospective study on viral encephalitis done in greater Gwalior region shows that incidence of viral encephalitis is very less (04%) in this region. There is a clear male preponderance in overall encephalitis cases (MF = 1.6:1). Pediatric age group is the most affected group of encephalitis

patients (0-10 yrs).Study also showed that there was rise in the incidence of west nile virus encephalitis in this region which was rare for this region.

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