

Review Article

Understanding the Diagnosis of Viral Meningo-Encephalitis in India: A Systematic Review

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Abstract

Background and Objectives: Diagnosis of viral meningoencephalitis is very crucial for recognizing the occurrence of epidemics and for instituting appropriate treatment. The diagnostic capability of the country can be ascertained by studying the published reports of viral meningoencephalitis in our country from reputed scientific literature. Hence, we aimed to study the diagnostic methods used for viral meningo encephalitis from Indian studies indexed in PubMed database.

Methods: The data was gathered from human studies of actual cases of viral meningitis, encephalitis or meningoencephalitis in India up to 8th August 2016 [earliest study found was from the year 1988] indexed in PubMed database.

Results: A total of 186 articles were included from 1548 studies screened. Clinical diagnosis over arched all the methods of diagnosis of viral meningoencephalitis in all the studies. Only 23.1% studies reported definitive confirmation of the infectious agent by PCR. Only 34.3% studies reported any microbiological tests for viral etiology. SGPGI, NIV AND NIMHANS were the three major centers reporting molecular diagnosis. Over three decades PCR has superseded antibody testing for viral meningoencephalitis diagnosis.

Interpretation and Conclusion: Our analysis shows that the diagnosis of viral meningo encephalitis in India is mainly based on clinical diagnosis. Definitive diagnosis by molecular diagnostic methods can be achieved with the establishment of a greater number of molecular viral diagnostic and research labs.

Keywords: Viral Meningoencephalitis; Viral Encephalitis; Viral Meningitis; Viral Diagnostics; Molecular Diagnostics; Diagnostics India; Meta Analysis; Systematic Review

Introduction

Reports of deaths due to viral meningo encephalitis explode on the front pages of all newspapers, blogs and online news websites every year especially in the monsoon season in India [1]. In 2016 alone there have been 10,517 cases of viral meningoencephalitis and 1242 deaths. The NVBDCP published a report that these viral diseases have infected at least 60,823 Indians in just over the last five years and claimed 8548 lives [2]. In developing countries like India, the official estimates of cases and deaths are subject to gross under reporting [3,4]. Therefore, the true numbers might be still high.

Considering the magnitude of these endemic killer diseases, it is essential to understand our country's capability to identify these diseases as an initial measure towards their control. The identification of viral meningo encephalitis is done by a strong clinical

suspicion followed by serological diagnosis of antibodies to the pathogen and/or confirmation by molecular diagnostic methods such as PCR. The availability of these diagnostic methods across the country can be understood by reviewing the published reports of the diseases in reputed scientific literature. A portrait of the methods used in the diagnosis of viral meningo encephalitis in India can help in understanding our capabilities, identifying lacunae and planning well informed policies for diagnosis, treatment and prevention of rapidly exploding epidemics. Moreover, most of these infections are potential bio weapons. They can be deliberately used in terrorist attacks or in devastating weapons of war. Thus, a study to understand our present infrastructure to diagnose these diseases is all the more important.

We analyzed the diagnostic methods and availability of molecular diagnostic centers for viral meningo encephalitis from Indian studies published in authentic journals indexed in PUBMED website.

Methods

Literature Search

We searched PubMed website for all articles from India with viral meningo encephalitis up to 8th August 2016 [earliest study found was from the year 1988]. Specifically, the searches were:

1. Virus AND meningitis AND India
2. Virus AND meningoencephalitis AND India
3. Virus AND encephalitis AND India
4. Virus AND encephalopathy AND India
5. Viral AND meningitis AND India
6. Viral AND meningoencephalitis AND India
7. Viral AND encephalitis AND India
8. Viral AND encephalopathy AND India
9. Meningitis AND India
10. Meningoencephalitis AND India
11. Encephalitis AND India
12. Encephalopathy [tiab] AND India

Study Selection

The data was gathered from human studies of actual cases of viral meningitis, encephalitis or meningoencephalitis in India. In short case reports, case series and clinical trials of viral meningoencephalitis were included.

Data Extraction

Data from the included studies were extracted and summarized independently by two of the authors using a pre-standardized data extraction form. Any disagreement was resolved by the Senior Author (SA). The following data were extracted from each study: Name of study, year of publication, center of study, place of study, tests done for diagnosis of viral meningo encephalitis and viral agent studied. A total of 186 articles were included from 1548 studies screened (Fig 1).

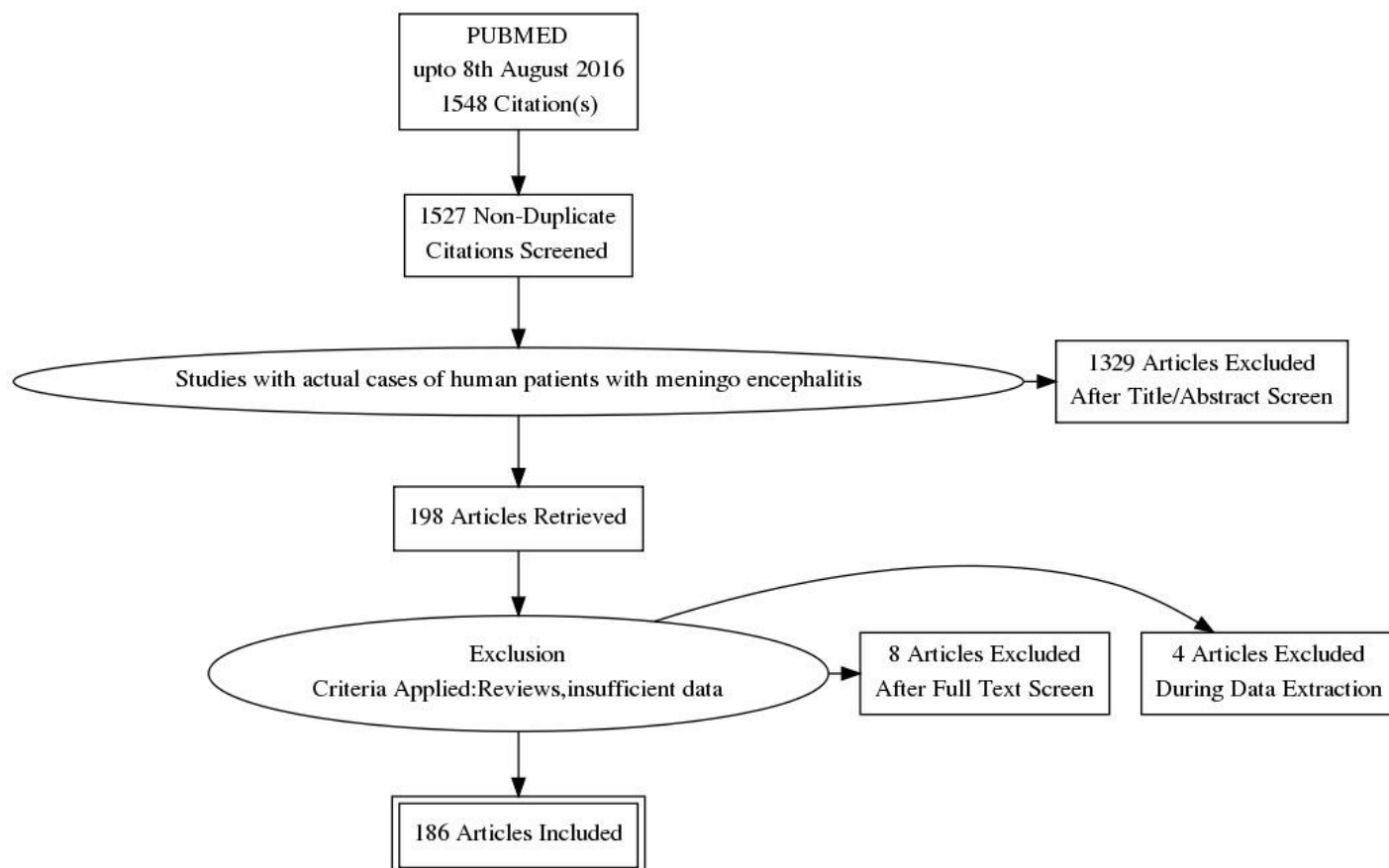


Figure 1: PRISMA diagram flow of the study.

Results

Majority of the studies were on Japanese Encephalitis virus and Herpes Simplex virus from Uttar Pradesh and Karnataka (Table 1 and 2). Only 23.1% studies report definitive confirmation of the infectious agent by PCR (Fig 2). Only 34.3% studies report microbiological tests for viral etiology. More than half [51.1%] of molecular diagnostics [PCR] studies are from just three centers - SGPGI, NIV AND NIMHANS (Fig. 3). Over three decades PCR has superseded viral meningoencephalitis diagnosis over antibody testing (Fig 4). Clinical diagnosis and treatment still take the major share of viral diagnostics.

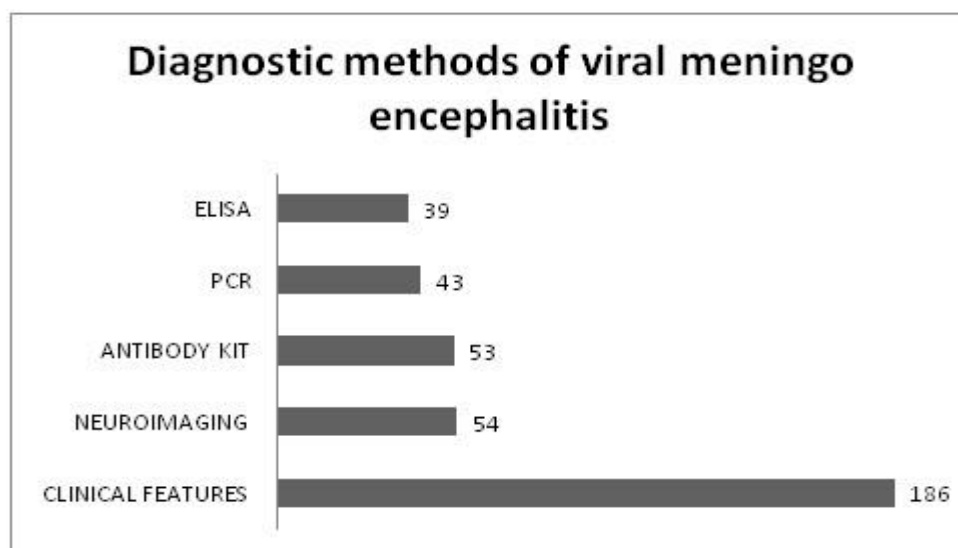


Figure 2: Various diagnostic modalities used for viral meningo encephalitis.



Figure 3: Various centers reporting molecular diagnostics. Numbers denote number of studies from each centre. PGIMER - Postgraduate Institute of Medical Education and Research, Chandigarh. LHMC - Lady Hardinge Medical College, New Delhi, ICMR - Indian Council of Medical Research, New Delhi. KGMU - King George's Medical University. SGPGI - Sanjay Gandhi Post graduate Institute. CSMMU - Chhatrapati Shahuji Maharaj Medical University. RMRC - Regional Medical Research Centre. ID and BG - Infectious Disease and BG Hospital, Kolkata. CIIMS - Central India Institute of Medical Sciences. NIV - National Institute of Virology. NIMHANS - National Institute of Mental Health and Neurosciences. CMC - Christian Medical College, Vellore. CRROR - Centre for Reference and Research on Rabies. KIPMR - King Institute of Preventive Medicine, Guindy. GOVT TD MCH - Government Tirumala Devaswom Medical College and Hospital.

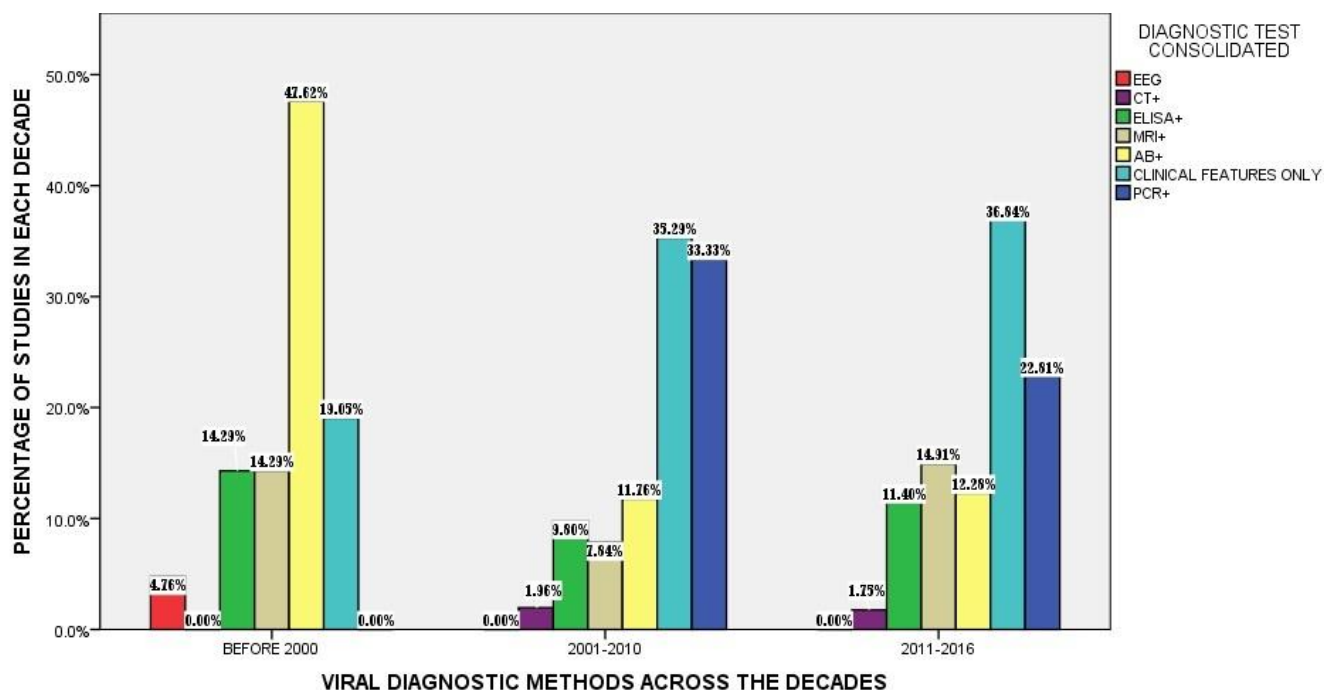


Figure 4: Diagnostic methods of viral meningo encephalitis over the years.

Virus	Number of Studies
Japanese Encephalitis	42
Herpes simplex	18
Dengue	18
Entero	8
Chikungunya	8
Chandipura	8
West Nile	7
Varicella zoster	4
Mumps	3
Measles	3
Influenza	3
Ebstein Barr	3
Rabies	2
HIV	2
Coxsackie	2
Nipah	1
Echo	1

Table 1: List of viruses published in the studies.

State	Number of Studies
Uttar Pradesh	48
Karnataka	22
Maharashtra	17
Delhi	16

West Bengal	11
Assam	11
Chandigarh	10
Tamil Nadu	8
Kerala	6
Rajasthan	5
Odisha	3
Punjab	3
Andhra Pradesh	3
Madhya Pradesh	2
Kashmir	2
Goa	1
Himachal Pradesh	1
Uttaranchal	1

Table 2: Geographical distribution of the studies.

Discussion

A Meta analysis of the methods used in viral meningo encephalitis in India from PubMed literature revealed that molecular methods of diagnosis are under used in comparison to clinical assessment. While all the studies show a clinical diagnosis, only 23.1% report molecular diagnosis and 39.5% report serological testing. This indicates that many centers lack the most important confirmatory equipment for viral diagnosis. There is thus a gross unmet need for viral diagnostics and then the analysis also shows clearly that only three centers have reported > 50% studies with molecular testing. In a country with 1.2 billion people with six hundred and eighty-seven districts, they do not even constitute a micro drop in an ocean [5]. Many more localized centers are needed. This can identify local infections, detect new threats, decrease crippling morbidity and prevent dreadful deaths due to viral encephalitis.

Our analysis of viral encephalitis diagnostics shows that, over three decades, there is a shift from the usage of antibody testing to PCR, but clinical diagnosis alone is still the basis for management in most of the studies. Even though these viral infections kill thousands of youths and children, they are still orphan diseases. Except for certain viruses like Herpes simplex encephalitis and CMV infection, there is no specific treatment at present for viral meningoencephalitis, hence policy makers do not consider the diagnosis of viral etiology as a priority [6]. But a brief look back at the history of medicine easily demonstrates the short sightedness of this thinking. If our ancestors had continued to designate syphilis as a punishment to sin, had left epileptics to treatment by shamans and malaria to the influence of air from marsh lands, millions of deaths and eons of suffering would not have been avoided [7-9]. This was possible only because of in-depth study of these diseases at a time when they were deep mysteries. Even in the modern day, only by years of research on enigmatic viruses, we are now able to control deadly diseases like HIV and prevent fatal Japanese Encephalitis and yellow fever by vaccination. Hence the study of viral encephalitis that are killing our people is very important.

Molecular diagnostic methods confirm the presence of viruses which may not be detected by less sensitive clinical, radiological and antibody-based techniques. These are important where there is a need for thorough, precise diagnosis of the etiological agent. This includes identification of the agent, quantification of the viral load and also to understand the pathogenetic mechanisms. These tests can differentiate potentially treatable conditions in deceptively similar presentations of different diseases. Our study is a portrait of the molecular testing being done in our country and it shows that much improvement is needed, with establishment of regional centers being the priority.

There are certain limitations to our study. Studies indexed in PubMed alone may not completely capture the entire work being done in India. Many Indian journals are not indexed in PubMed. PubMed being an international standard archive, indexes only high-quality journals. These journals might be biased in accepting molecular diagnostic based studies only as these are the world standard for viral disease diagnoses at present.

Another problem is the lack of a precision for delineating viral encephalitis under the umbrella of the acute encephalitic syndrome [10]. This confounds the results with the heterogeneity of the cases recorded in the studies. In our study the majority of cases are reported from Uttar Pradesh with JE being the chief etiological agent studied. This might result in our findings being skewed towards the data from these areas. And then again most of the regional areas have no infrastructure for microbiological diagnosis and the investigations are channeled to the few available centers mentioned above Fig. 3 and therefore the disease distribution is difficult to ascertain from the location of the reports. Many private hospitals in the peripheries do not publish their cases and these may be missed by our study.

Conclusion

Notwithstanding above constraints, our analysis shows that the diagnosis of viral meningo encephalitis in India is mainly based on clinical diagnosis. Definitive diagnosis by molecular diagnostic methods can be achieved with the establishment of fully functioning molecular viral diagnostic and research labs distributed evenly across the country.

Conflict of Interest

The authors have no conflict of interest to declare.

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