Review Article

Chandipura Virus: Another Exotic Tropical Disease?

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ABSTRACT

This review article discusses the current problem statement of the Chandipura Virus disease which is mainly neglected but an emerging as an exotic tropical disease in India. The epidemiology and clinical features are described along with geographical distribution where cases have been documented. Controversies around it have been stated. Along with treatment, preventive aspects, which is the mainstay management has been discussed in details. Disease preparedness & potential bioterrorism concern has been outlined.

KEY WORDS: Chandipura Virus, Encephalitis, Sand Fly.

INTRODUCTION

Till date, viral encephalitis remains an important public health problem worldwide in terms of contribution to mortality and morbidity. In India, most epidemics of acute encephalitis syndrome (AES) have been attributed to the Japanese encephalitis virus (JEV) [1,2].Much emphasis was thus put upon introduction of JE vaccine. Despite of widespread coverage of the vaccine, increasing numbers of AES cases continue to be reported from India. Thus the assertion that non-JEV aetiologies are important contributors to AES is gaining ground [3,4]. Many studies after 2000 have identified Chandipura Virus (CHPV) as being one of the common agents, in various outbreaks and surveillance studies [5, 6, 7].

PROBLEM STATEMENT

Bhatt and Rodrigues discovered the CHPV in 1966 as a novel agent causing febrile illness. The virus was named after the site of its first isolation from Chandipura region of Maharashtra [8]. But the virus remained largely neglected till 2003 when it shot back into prominence when it was first identified to be associated with an epidemic of AES in young children in Andhra Pradesh. There were 329 cases with 183 fatalities [6]. Subsequently another epidemic of AES was reported from Gujarat in 2004 with an alarming case fatality report of around 78% [9]. A retrospective analysis of another epidemic of AES in Andhra Pradesh revealed CHPV as the etiological agent [10].

Another epidemic was reported in 2007 in Nagpur with a high case fatality rate of more than 40% [7].CHPV had established itself as an important emerging deadly human pathogen in India. Gujarat is the fourth state in India to report CHPV along with Maharashtra, Madhya Pradesh, and Andhra Pradesh. Presence of CHPV has been reported from Sri Lanka and Africa including Nigeria and Senegal [11,12,13].In 2010, 31 deaths were registered, of which 15 had tested positive for CHPV. Rest had died of encephalitis. In 2011, the total number of death was 12, with 3 cases positive for CHPV [14].

EPIDEMIOLOGY

PATHOGEN

CHPV is classified under Rhabdoviridae family, genus Vesiculo virus. CHPV was earlier believed to be limited to Asia. But in recent years CHPV has been reported in western Africa. CHPV is a negative sense, single stranded enveloped RNA virus [15,16].

VECTOR

Phlebotomine sand flies are considered as one of the important vectors of the CHPV. Among the sand flies, Phlebetomus papatasi is one of the most common anthropophagic and domiciliary species prevalent in several parts of India. CHPV also infects mosquitoes

most commonly the Aedes aegypti. CHPV is disseminated to salivary gland within 4–5 days of infection and is then transmitted to other vertebrate hosts by crossing salivary gland barrier in the next 24 hours when an infected vector bites a human or other vertebrate [17,18].

PATHOGENESIS

CHPV epidemics have been largely limited to children below 15 years of age, while adults are largely refractory to natural infection. The retrospective analysis of data from Andhra Pradesh outbreak [10] suggests that death in children was due to brain stem encephalitis. The above study among various others suggests the strongly neurotropic character of CHPV. Like various other neurotropic viruses, neuronal maturation appears to provide resistance against viral replication induced apoptosis in adults [19].Other variables like maturity of the reticulo-endothelial system [15], maturation of defensive anatomic barriers may play an important role in the variable course of the disease as per age. CHPV-infected neurons undergo apoptosis through an extrinsic pathway mediated through the Fas-associated death domain [20].Findings from other studies indicate CHPV outbreaks to be due to vascular event rather than 'encephalitis'. The site of lesion was pinpointed to vascular territory of the middle cerebral artery. The nature of the arterial pathology was not investigated in details, but it was suggested to be spasm or transient obstruction due to vasculitis [21].

CLINICAL FEATURES

During the outbreak in Gujarat, blood samples were taken from healthy individuals. Results showed that more than 10% of children had IgM antibodies to CHPV, indicating recent exposure to the virus and milder forms of the disease, sub-clinical or as self-resolving pyrexia [9]. Encephalitis cases caused by CHPV occur only among children. Suspected cases of CHPV infection occur usually in less than 15 year olds with the acute onset of fever and altered sensorium including coma or seizures in the absence of common aetiology like malaria, tuberculosis and other common bacterial causes [5]. Death usually ensues within a few hours to 48 hours of hospitalization. Manifestations may range from subclinical infection to high- grade fever to acute encephalitis. Rash has been reported with serous transudate and hyper pigmentation on healing.Hepatomegaly with deranged liver function tests has been reported. Neurological manifestations include abnormal plantar reflex, brisk deep tendon reflexes, pupillary abnormalities, tonal abnormalities and seizures. Other manifestations include respiratory distress, bleeding tendencies or anaemia. Routine haematological, biochemical and cerebrospinal fluid analysis in most cases were within normal limits. Anaemia, leucocytosis and disseminated intravascular coagulopathy have also been reported. Occasionally renal function tests or liver function tests may be deranged.

DIAGNOSIS

CHPV quantisation may be done in vivo (mice), in ova (Eggs) and in vitro (cell-lines) cultures for virus isolation. However, these methods are ore of academic interest. They are time consuming and labour intensive. The course of CHPV encephalitis is rapid with high mortality. Currently detection of viral RNA by nested RT-PCR represents the gold standard diagnostic method rather than IgM-anti-CHPV antibodies. Real-time one step RT-PCR assay offers an excellent alternative with several advantages such as high sensitivity, speed, accuracy and reproducibility [22].

MANAGEMENT

There is no specific antiviral therapy available to date against CHPV.Emergency treatment is aimed at protecting the neurons against further ischemia to minimize neurologic sequel. It includes good nursing care of the comatose patients at the earliest in the nearest hospital. Symptomatic treatment involves use of decongestants such as mannitol and furosemide to reduce cerebral oedema and raised intracranial pressure.

PROGNOSIS

Death or recovery occurs rapidly, within 2 to 3 days. Survivors have no sequel. Most of the deaths occur within 24 hours of onset of illness. . Case fatality rate was high with reports varying from 55% to 85% cases with majority of the deaths occurring within 24 hours of hospitalization [5-7].

DISEASE PREVENTION AND CONTROL

Prevention is the best method to suppress CHPV infection. Containment of disease transmitting vectors, maintaining good nutrition, health, hygiene and awareness in rural areas will help in curbing the menace of CHPV. Thus, to control virus transmission some immense preventive measures need to be attempted until a good anti-CHPV agent is developed.

CHPV: THE CONTROVERSIAL AGENT?

CHPV was believed mostly to be an orphan agent causing no illness in human beings or at the most benign febrile illness, with anecdotal instances of viral meningitis until epidemics of 'brain attack' was in 2003 when investigations at the National Institute of Virology (NIV) identified CHPV as the causative agent.

It is almost a decade now since the association was first reported but many experts have time and again raised serious doubts about the validity of evidences for Chandipura virus aetiologyof epidemic encephalopathy [21,23-25]. The 2003 epidemic of Andhra Pradesh had invited a lot of attention and was investigated by multiple experts. The detailed neurological findings including pathology were interpreted to show that the outbreak was not one of 'encephalitis', but of an acute vascular event or stroke with the site of lesion being that of territory of the middle cerebral artery. It was suggested that if CHPV was the causative agent, the disease was mediated by transient vasculitis or vascular spasm rather than encephalitis [21]. Doubts had been raised if the epidemic was a result of infection. Epidemic presentation, febrile illness, leukocytosis, neutrophilia, elevated C-Reactive protein and cytokines [29] have been cited as supportive evidence in support of an acute infectious aetiology. A study by Sriramachari et al suggests aetiology for the outbreak in form of heat pyrexia secondary to high environmental temperature, with or without secondary factors [26].

The epidemic in Andhra Pradesh in 2005-2006 revealed some more interesting information.25 out of the 90 cases showed serologic evidence of CHPVinfection; however, no virus could be isolated in any of these cases. But around 70% of the asymptomatic cases in the less than 15 years age group and around 95% of those more than 15 years were found to be IgG antibody positive for CHPV. Thus CHPV infection seems to be endemic in the region with high rate of subclinical infection causing sero-conversion. It is possible that acute encephalopathy represents only the tip of the iceberg. The entire clinical spectrum of CHPV infection can be elucidated only after further detailed studies [5]. But intriguingly epidemic encephalopathy by CHPV has been rare. Recent genetic studies have not revealed major mutations in CHPV to account for recent acquisition of virulence to cause encephalopathy [27].

An earlier epidemic in 2002 in Warangal district in Andhra Pradesh had patients with very similar clinical profile acute encephalopathy. The same was investigated by experts from NIV who reported the isolation of measles virus directly from CSF of a few patients. Similarly another epidemic of acute encephalopathy syndrome was reported in Haryana, also was attributed to measles virus [28]. Is it purely coincidental that very similar clinical syndrome of acute encephalopathy is caused by two different viruses, as measles and CHPV?

Subsequent analysis proposed the above epidemic to have been attributed to measles virus secondary to a laboratory contamination with measles vaccine virus [30]. Similar possibilities cannot be ruled out in case of CHPV. Evidence from multiple studies from multiple laboratories is necessary to establish CHPV as a causative pathogen for encephalopathy syndromes.

DISEASE PREPAREDNESS IN INDIA: THE WAY AHEAD

The outbreaks of CHPV have become a regular phenomenon in India over the years. Till date; fortunately the epidemics have been limited to very few states in India. But given the widespread presence of sand fly as well as mosquitoes as vectors, the emergence of disease in virgin territories always remains a possibility. India being the country where both CHPV and its vectors are present, there is need for better preparation and surveillance mechanism for CHPV.Perhaps currently there are more questions rather than answers as regards to CHPV. The debate is there to remain as more outbreaks probably occur and more data is available for analysis. But that should not occur as a hindrance to disease preparedness and prevention.

- To detect and monitor emerging disease threats disease surveillance system must be strengthened. It is often a "bottom up" approach with the initial reporting and response to epidemics occurs at the local/municipal level.
- Investigation of an epidemic requires a rapid action team of experienced specialists, provision of finances for rapid and sensitive investigations.Accredited Laboratory facilities need strengthening for timely diagnosis of CHPV.
- Efficient and rapid communication among public health authorities is key to increase awareness once an epidemic occurs so that timely critical measures can be implemented to mitigate the impact and prevent further spread.

- Effective case management is limited to reduction of cerebral oedema. Mannitol must be administered at the earliest to optimize recovery.
- Research must be directed towards development of safe and effective vaccines against CHPV.
- Efforts must be directed towards vector control activities through integrated vector management
- Basic studies on CHPV must continue to elucidate the natural history as it is a common agent of infection India. Moreover, it is a vesiculo virus and much can be learned about the host-virus interactions of the genus, to which belongs rabies virus also.

POTENTIAL BIOTERRORISM CONCERNS

Breeding of sand fly species and their artificial infection difficulties are limiting factors for the use of sand fly borne viruses as efficient biological weapons. Moreover, CHPV is most commonly associated with sub-clinical or mild self-resolving infections. Direct inter-human transmission has never been demonstrated. These criteria make CHPV unlikely candidates for the use as potential weapons for bioterrorism [31].

CONCLUSION

The ubiquitous presence of CHPV in many regions along with suitable vectors with multiple vertebrate hosts combines to aid CHPV as a potential threat. This combined with rapid movement of people and animals on a global scale with increased interactions lead to favourable conditions in which new and more virulent viral pathogens are regularly emerging and spreading to hitherto virgin areas. Disease preparedness is the key to address the emerging and re-emerging diseases. The real challenge is to device measures for control of emerging diseases in developing countries like India that are often plagued with limited resources.

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