

Review Article

Prevalence of Varizella-Zoster Virus Infection among Encephalitis Study Groups World Wide

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Abstract

This review has gathered and summarized prevalence data of varicella zoster virus (VZV) infection among encephalitis patients reported in 20 studies conducted in different areas of the world. Varicella is considered as a less common disease in tropical areas compared to temperate areas. According to literature, VZV induced central nervous system (CNS) diseases such as encephalitis is common among adults compared to children, especially due to vaccination of children. Studies conducted in California, USA and Australia has concluded that the VZV induced encephalitis among children has reduced after the introduction of varicella vaccine. However, it was difficult to perform comparisons between VZV prevalence among encephalitis patients from tropical and temperate areas and between children and adults. The reasons were, the limited number of studies found from tropical area, lack of studies conducted exclusively with adults and the introductions of varicella vaccine since 1995. Different countries have different legislations regarding varicella immunization. In some countries, it is a part of national vaccination programmes. Studies included here were not categorized as from pre-vaccination or post-vaccination periods of reporting countries. However, among the indicated studies, the highest VZV prevalence was seen among children suffering with encephalitis in a temperate country (Finland – 25%) from 1973 to 1987. Lowest was reported in Eastern India (0.38%) from 2011 – 2012, a region extends across sub-tropical and tropical areas.

Keywords

- Varicella zoster virus
- Encephalitis
- Encephalopathy
- Meningoencephalitis
- Prevalence

ABBREVIATIONS

CNS: Central Nervous System; VZV: Varicella Zoster Virus; HSV: Herpes Simplex Virus; CSF: Cerebrospinal Fluid; VE: Viral Encephalitis; ELISA: Enzyme Linked Immunosorbent Assay

INTRODUCTION

Encephalitis is one of the major clinical outcomes of central nervous system (CNS) infections. It is defined as the acute inflammatory process affecting the brain. When the inflammation involves only meninges, the disease is called meningitis. The combined inflammation of brain and meninges (meningoencephalitis) may also occur. Although both viral and bacterial causes are involved in infective encephalitis, viral infection is the most common and important cause [1]. Infective encephalitis has been identified to cause high rates of illness with a high case fatality rate [2,3]. In some patients, encephalitis might occur due to an alteration of normal immune function in the context of a previous viral infection or following vaccination, which is called acute disseminated encephalomyelitis (ADEM) [1]. Encephalopathy is the general term used for any diffuse disease of the brain that alters brain function or structure and can be caused by infectious causes such as viruses [4].

Clinically, infective encephalitis is suspected when a patient is presented with an abrupt history of fever, headache progressive declining of mental status with development of focal neurological symptoms and focal seizures [5]. Viruses cause meningitis as well but in contrast to encephalitis, meningitis is usually mild and recovers even without treatment. However, some cases can be severe and lethal [6]. Meningitis has clinical features that are overlapping with encephalitis and presents with abrupt onset of fever, headache, irritability, nausea, vomiting, stiff neck, rash, or fatigue. However, encephalitis is clinically distinguished from meningitis, as meningitis patients may retain the command of their mental process, due to lack of brain involvement [7]. Encephalopathy can present with clinical features: progressive loss of memory and cognitive ability, subtle personality changes, inability to concentrate, lethargy, and progressive loss of consciousness, which are similar to acute encephalitis [4].

Viral encephalitis (VE) can be caused by several types of viruses i.e. Herpes simplex virus (HSV-1, HSV-2); Other herpes viruses like varicella zoster virus (VZV), cytomegalovirus (CMV), Epstein-Barr virus (EBV) and human herpes virus 6 (HHV6); Adenoviruses; Influenza A virus; Enteroviruses (EV) including poliovirus; Measles, mumps and rubella viruses; Rabies virus; Arboviruses like Japanese encephalitis (JE), St Louis encephalitis,

West Nile encephalitis, Eastern, Western, and Venezuelan equine encephalitis viruses and tick borne encephalitis virus; Bunyaviruses - for example La Crosse strain of California virus, Reoviruses such as Colorado tick fever virus; Arenaviruses such as lymphocytic choriomeningitis virus [1,5]. In industrialized countries, encephalitis has been identified with a case fatality rate of 6.5%–12%. But the situation in developing world is largely unknown. As a result, 60-80 % global incidence of encephalitis is reported with unknown etiology [2,3,8].

The diagnosis of viral cause can be achieved by several ways such as either by demonstrating viral nucleic acid, antibody in cerebrospinal fluid (CSF), by isolating the virus from CSF or brain tissue. Even with the best diagnostic tools and efforts, some cases of clinically suspected viral encephalitis remain with unknown etiology [9]. However, HSV and VZV are implicated as the major causes of viral encephalitis in most areas of the world [8]. According to a review by Herrmann et al. in 2016, HSV is the most frequent pathogen in 65% of studies, followed by VZV in other studies on viral etiology of encephalitis [10]. Hence, HSV type 1 (HSV-1) is considered as the most common cause of sporadic encephalitis [9,11-12]. However, reports from Scandinavia and central Europe, have indicated varicella zoster as the most common viral agent causing encephalitis [9,13-15].

VARIZELLA ZOSTER VIRUS

VZV is a wide spread human alpha herpes virus with a double stranded DNA genome. Mainly, it causes varicella (chicken pox) and herpes zoster (shingles) diseases. Close contact with varicella and herpes zoster cases transmits VZV to susceptible contacts. VZV can spread rapidly to other susceptible individuals. Especially, VZV transmission can occur by the respiratory route, which is a distinctive feature of VZV in contrast to other herpesviruses [16-18]. Approximately 90% susceptible household contacts who exposed to Varicella are more likely to get diseased. However, limited exposures occurring in places like school classrooms, can cause transmission rates of about 10 to 35% [18,19]. Getting a second episode of varicella is rare [18,20].

Chicken pox is a common childhood illness characterized with fever and a generalized pruritic vesicular rash as a result of primary VZV infection [18]. This virus can remain dormant in the nerves, including the cranial nerve ganglia, dorsal root ganglia, and autonomic ganglia after the primary infection [21]. The patient, even after recovered from chickenpox, the virus can reactivate to cause herpes zoster which is characterized by a painful, localized, vesicular rash in one or adjacent dermatomes. High incidence of herpes zoster involves with increasing age or immunosuppression [18]. Furthermore, the reactivation can cause a number of neurological disorders including encephalitis [21]. Hence VZV is among human neurotropic viruses that are responsible for significant neurological morbidity and mortality [22-24].

As many childhood infections can be commonly associated with central nervous system (CNS) diseases [25], some cases have been reported where the primary infection of VZV has manifested as encephalitis even in immune-competent pediatric patients

without any dermatological manifestations [26]. However, according to some literature, majority of CNS infections including encephalitis which are associated with VZV is seen among adults [25,27-30]. The successful control of many microbial diseases by vaccination of children is considered as the reason behind low incidence of VZV induced encephalitis among children nowadays [25, 31-35].

Epidemiology

VZV is a virus found worldwide. However, annual epidemics are more prevalent during late winter and spring in temperate climates [18,36-37]. Compared to temperate areas, Varicella is a less common disease among children in tropical areas. In temperate climates, the incidence of varicella infection almost equals to birth rate as almost all children are likely to acquire it during the first 5 to 10 years of their lives. The susceptibility rate among subjects over 18 years old is about 5% in temperate climates. However, in tropical regions, about 50% of young adults have not been exposed to primary VZV infection [18,38].

A different study worldwide has produced information on the prevalence of VZV induced encephalitis among patients clinically suspected or clinically proven of having acute encephalitis. In this review, VZV prevalence among different study groups of encephalitis patients world-wide are gathered and summarized. Twenty studies on etiology and epidemiology of infectious encephalitis with prevalence data of VZV induced encephalitis are indicated below. These studies were listed in Google scholar and PubMed with keywords: Varicella-zoster, acute infectious encephalitis, prevalence, aetiology, epidemiology and surveillance. Only the prospective or retrospective studies with patients clinically suspected for acute encephalitis, acute encephalopathy or meningoencephalitis were included. Any study confined exclusively to viral encephalitis (VE) was excluded as very few studies available only with VE and because this review presents prevalence of VZV in study groups with acute encephalitis/encephalopathy/meningoencephalitis due to all probable causes. A brief summary of each study is provided, following an overall summarization illustrated in figure 1.

STUDIES CONDUCTED IN TEMPERATE REGIONS

Prospective studies with children

Finland: A study on acute encephalitis among Finnish children has conducted during a 2-year period: January 1993 to December 1994 in Southern Finland covering 85% of Finland's total child population. Children aged 15 years or younger were included except neonates (at 0 ± 4 weeks after birth). Neonates have been excluded because they may have generalized diseases in which encephalitis is only one aspect. Preliminary microbial diagnosis was done by detecting the rising antibody titer in paired serum and confirmation was done by detecting specific IgG antibodies for organisms in Cerebrospinal fluid (CSF). Out of 175 reported cases of acute encephalitis, 110 were proven or suggested due to microbial infections. VZV infection accounted for 22% of the children with known or suggested etiology. Around 19% out of all acute encephalitis cases are due to VZV [39].

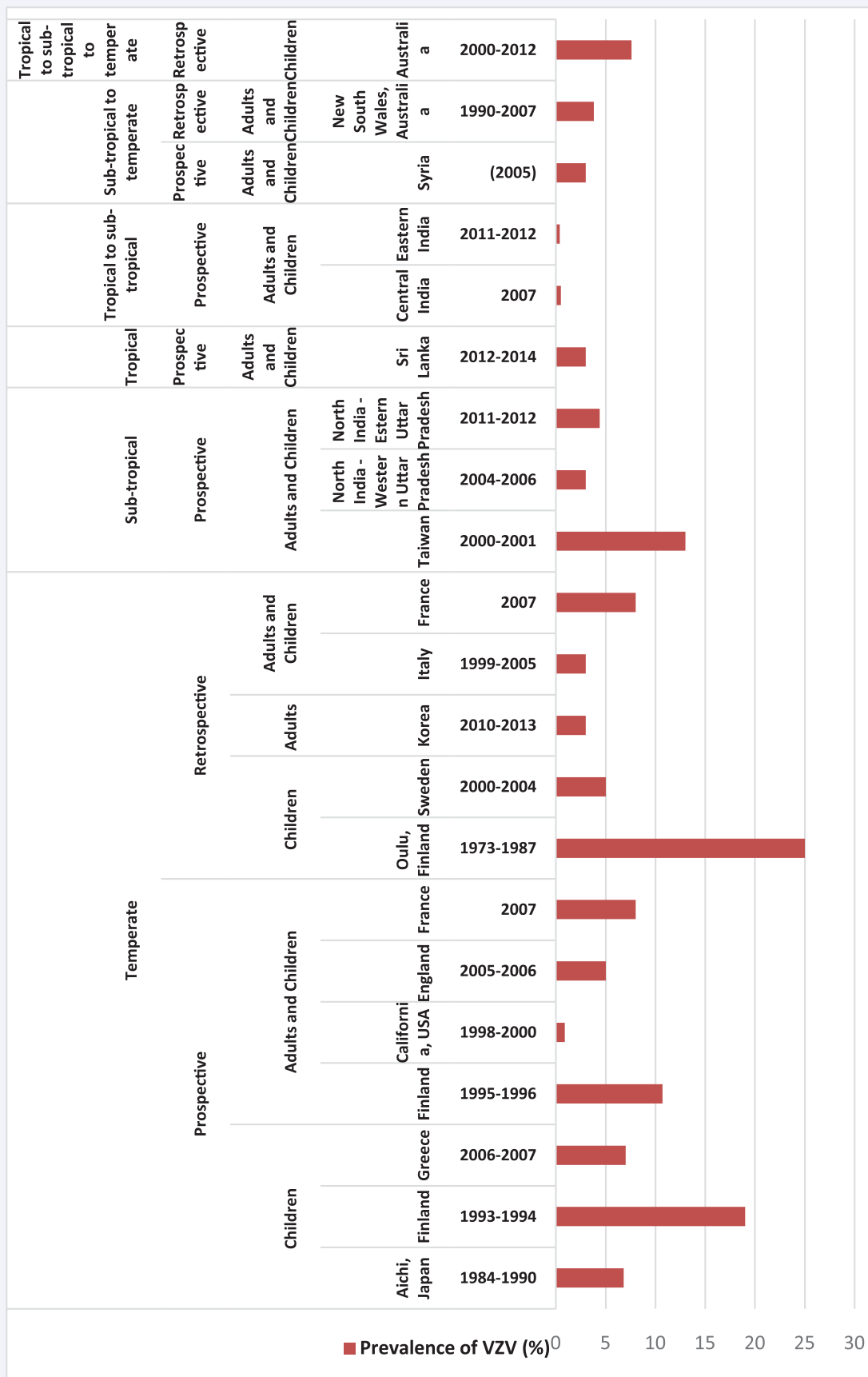


Figure 1 Prevalence of VZV among encephalitis patients in different study group.

Greece: A study conducted from January 2005 to December 2007 (3 years) at tertiary-care university-affiliated general hospitals in northern, north-western and southern regions of Greece. Children aged 1 month to 15 years with encephalitis were included. Pathogen detection was done by culturing or PCR with CSF samples taken from the patients. Forty-two patients were recruited and in 24 cases the microbial cause was confirmed. Among the patients with confirmed aetiology around 12.5% was caused by VZV. It is about 7% (3/42) of all cases [40].

Japan: Two hundred and fifty-six children aged 15 or less admitted to 36 hospitals of Aichi prefecture in Japan due to encephalitis during the period of 1984 to 1990 (7 years), were included in this study. These patients were presented with acute encephalitis including meningoencephalitis, acute encephalopathy as well as Reye syndrome; which are consisted of similar clinical features. The number of patients with acute encephalitis or meningoencephalitis was 190. Among them Varicella was detected in 13, indicating 6.8% prevalence of VZV among children with acute encephalitis or meningoencephalitis [41].

Prospective studies with children and adults

Finland: Patients of all ages with central nervous system diseases who presented at the Helsinki University Hospital from 1995 to 1996 have been studied for possible etiologies. CSF samples were tested with enzyme immune assays and PCR. Among 1014 patients presented with encephalitis, 565 were identified with confirmed, probable or possible viral causes. Ninety-six were detected with VZV while 13 had double infection with HSV and VZV. The overall prevalence of VZV in the study group with encephalitis was 10.7% (109/1014) [15].

England: Patients of all ages with symptoms suggestive of encephalitis were being recruited to this study from three different areas of England: London, the southwest, and the northwest of England; from 24 hospitals. The study period was 2 years: from October 2005, to November 2006 (1 year). Laboratory testing was carried out by PCR and antibody assays for all commonly recognised causes of infectious encephalitis. Ages of studied subjects ranged 0 to 87 years. Out of 203 patients studied, 86 had infectious causes. Varicella zoster virus was the responsible case of 5 % (10/203) of all encephalitis case [3].

France: In 2007, a total of 253 patients with acute onset of encephalitis from 106 medical units throughout France were included in the study. Their ages ranged from 1 month to 89 years. Microbial causes were determined by seroconversion in paired serum samples, or a high immunoglobulin IgM titer in the CSF. Cause of the encephalitis was determined in 131 patients. Among those 131 patients, 15% affected with Varicella-zoster virus. The VZV prevalence was 8% (20/253) among all encephalitis cases [42].

California, USA: Immunocompetent patients older than 6 months and presented with encephalitis or encephalopathy from California, USA, from June 1998-2000 (2.5 years) were enrolled in this study. Altogether, 334 patients were tested for

pathogen specific IgG antibody in serum, virus isolation from CSF/respiratory and stool samples and by PCR methods. Fifty-three patients had identified confirmed or probable infection. Among all patients VZV was responsible for only 0.9% (3/334) of encephalitis cases and none of these cases were due to primary varicella infection. Authors describe that the VZV was among the most common causes of encephalitis in studies conducted in the 1980s (22%–25% of cases)[39, 43-44] and the decrease in the prevalence of VZV encephalitis noted in this study can be due to the overall decrease in the prevalence of disease since the introduction of the varicella vaccine in USA in 1995 [44,45].

Retrospective studies with children

Sweden: A retrospective analysis of 93 children with acute encephalitis who were admitted to Karolinska University Hospital in Stockholm during January 2000 - December 2004 (5 years). Ages of the children ranged from 5 weeks to 17.7 years. Pathogen detection was done using several methods depending on the pathogen: direct immunofluorescent, enzyme immunoassay, PCR and pathogen specific IgG in CSF. A confirmed etiological agent was identified in eight cases and a probable in 37. Among the cases with confirmed or probable aetiology VZV indicated 11% (5/45) prevalence and among all encephalitis cases the VZV prevalence was 5% (5/93) [46].

Oulu, Finland: Medical data of department of pediatrics university of Oulu, Finland from January 1973 to 1987 December(14 years) has reviewed to identify patients with acute encephalitis and their etiology. Ninety-five children age range with 5 days to 14.7 years from Oulu were identified as acute encephalitis patients by clinical diagnosis criteria. Laboratory diagnoses were carried out by detecting the increase in serum antibodies, viral isolation from CSF, antigen detection in CSF or nasopharynx. VZV has turned out to be the most common cause among microbial causes (24 cases) accounting for 25% (24/95) among all encephalitis cases [43].

Retrospective studies with adults

Korea: A retrospective analysis of clinical data of adults (age > 16 years) including encephalitis and meningoencephalitis presented at Samsung medical centre in Seoul, Korea for 3 years (2010 – 2013). Pathogen identification has been done by PCR for CSF samples obtained from patients. Both immunocompetent and immunocompromised patients were included in the study. Sixty-five patients with involved in brain inflammation: 41 encephalitis patients and 24 meningoencephalitis patients have been studied. Among these 65 patients, 2 were detected with VZV. Hence the prevalence of VZV among the group of patients with encephalitis/meningoencephalitis was 3% (0 VZV infections among encephalitis patients and 2 among meningoencephalitis patients) [24].

Retrospective studies with children and adults

France: A retrospective study conducted with records on French national hospital discharge database (PMSI) in 2007. A total of 1694 non-HIV patients of all ages presenting with acute encephalitis were recorded in the PMSI, in mainland France and

VZV was responsible for 8% (146/1694) of all encephalitis cases [47].

Italy: A study conducted with hospital discharge data from the National Hospital Discharge Database of Italy for 7-year period. Encephalitis-associated hospitalization of patients of all ages, from 1999 to 2005 has accounted for 23,594 hospitalizations in North-East, North-West, Centre, South and Island areas of Italy. Only 4205 patients were detected with viruses causing encephalitis. Within this category VZV has shown a prevalence of 17.7% with 743 hospitalizations. Of all encephalitis associated hospitalizations VZV infection prevalence was 3% (743/23,594) [48].

STUDIES CONDUCTED IN SUB-TROPICAL REGIONS

Prospective studies with adults and children

Taiwan: To investigate encephalitis in Taiwan, a multicenter study has conducted in 30 major hospitals in North, Central, South and East regions of Taiwan. One-hundred and twenty-four patients with acute severe neurological dysfunction and suspected encephalitis were recruited from May 2000 to December 2001 (1.5 years). PCR analyses have performed for CSF/serum to determine the microbial etiology. Microbiological causes detected in 86 of 124 cases. The prevalence of VZV among all 124 patients was 13% (16/124) [49].

North India (Eastern Uttar Pradesh): A study conducted in Eastern Uttar Pradesh in North India for 2-year period from January 2011 to December 2012. Pathogen diagnosis has been carried out by detecting pathogen specific IgM antibodies in CSF. Age range of patients was 1-70 years. Depending on clinical and virological diagnosis, 921 patients were categorized as acute encephalitis patients. The prevalence of VZV among them was 4.4% (69/921) [50].

Prospective study with children

North India (Western Uttar Pradesh): A study conducted to detect the etiology of viral encephalitis (VE) among the children of western Uttar Pradesh in India. CSF and serum samples from pediatric patients suffering from encephalitis, hospitalized at Jawaharlal Nehru Medical College, Aligarh from July 2004 to November 2006 were tested using methods such as IgM ELISA (Enzyme linked immunosorbent assay), viral isolation. The prevalence of VZV encephalitis was 3% (3/87) among the total of 87 patients in the study group with an age range of 6 months to 12 years. The viral etiology was confirmed only among 19 patients among who the VZV was found among 16.8% (3/19) [51].

STUDIES FROM TROPICAL REGIONS

Prospective study involving adults and children

Sri Lanka: From November 2012 to August 2014, ninety-nine patients (adults and children), presented in two tertiary care hospitals in Colombo with encephalitis or meningoencephalitis were included in this study. Ages of the patients ranged from 1 month to 73 years. Pathogen detection was done with PCR

or antibody assays. Only 27.3% were having viral etiology. Three patients were detected with VZV, indicating 3% (3/99) prevalence of VZV in the study group [52].

STUDIES IN COUNTRIES SPANNING MORE THAN ONE CLIMATIC ZONE

Retrospective – Adult and children

Australia: A study conducted from 1990 to 2007 in New South Wales, Australia where both sub tropical and temperate climates present. Hospital discharge data of patients of all ages with acute encephalitis were gathered and analysed. Number of total hospitalizations was 5, 926 throughout the study period. The reported prevalence of VZV among these patients was 3.8% (226/5926) [2].

Retrospective – involving children

Australia: Another study has conducted in Australia by gathering data of encephalitis-related hospital admissions for encephalitis, acute disseminated encephalomyelitis (ADEM) and meningoencephalitis from 2000 to 2012, in national datasets among children ≤ 14 years. Australia is a country with diverse climates ranging from tropical to temperate. Majority of the Australian land lies in tropical and sub-tropical areas. Throughout the study period mentioned here, the number of total hospitalizations for encephalitis in Australia was 1847. The prevalence of VZV among all encephalitis related cases throughout the study period was 7.6% (141/1847). However, authors mention that the Varicella encephalitis hospitalisations decreased significantly after 2006 due to introduction of Varicella vaccine and elevated levels of vaccine coverage since 2006. Hence the prevalence of VZV among encephalitis related patients in the latter period of study: from 2009 to 2012 was only 2.1% (13/638) [53].

Prospective – Adults and children

Syria: A prospective study done in Syria (Middle Eastern country with both subtropical and temperate climatic regions) with CSF samples from 106 patients with encephalitis (the time frame of sample collection was not mentioned in the paper published in 2005). Pathogen detection has been done with pathogen specific PCR primers. Although the study group consisted of adults and children (1 month to 40 years), majority were children as the mean age was 4 years. However, the exact numbers of children and the adults were not mentioned. About 3% (3/106) prevalence of VZV has been detected in this study group [54].

Eastern India: A study conducted with acute encephalitis patients in the eastern Indian region (spanning in sub-tropical and tropical areas in India) through hospital-based case enrolment during April 2011 to July 2012. Age ranged from 1 month to 60 years. Blood and CSF samples of 526 acute encephalitis cases were investigated by serology and/or PCR. Viral aetiology identified in 91 cases. The prevalence of VZV among all acute encephalitis cases was 0-38% (3/526) and 3.3% (3/91) among VE [55].

Central India: Total of 183 acute encephalitis cases

identified between January and October 2007 in rural central India (spanning in sub-tropical and tropical areas in India). All consecutive hospital admissions during the study period screened to identify adult-acute encephalitis cases and pathogen screening was done by IgM capture ELISA for CSF. Among the study group of 183, viral encephalitis (VE) was suspected among 152. Of the VE suspects, viral etiology was confirmed in 31 cases. Only one patient was detected with VZV indicating a prevalence of 0.5% (1/183) among all acute encephalitis cases [56].

DISCUSSION & CONCLUSION

A summary of VZV prevalence among encephalitis patients from different countries/areas are illustrated in figure 1. Majority of a fore mentioned studies were done in temperate areas. Only a few studies found conducted in sub-tropical or tropical areas (from various parts of India, Taiwan and Sri Lanka). In most of the studies, adults and children were studied together. Only one study was found conducted exclusively with adults (from Korea). Hence more advanced meta analyses are required in order to separately analyse the situation among children and adults. However, the studies conducted in California, USA and Australia, have concluded that the prevalence of VZV encephalitis among children have reduced with the reduction of overall prevalence of varicella disease after the introduction of varicella vaccine [44, 53]. The varicella vaccine was licenced and introduced in USA in 1995 for the first time in the world [57].

Among the data summarized in figure 1, there are three studies started and completed before 1995, which were conducted among children with encephalitis in Southern Finland, Oulu in Finland and Aichi in Japan. Both studies conducted in Finland before 1995 have shown prevalence of VZV (19% and 25%) higher than any other study. Another study conducted in Finland from 1995-1996 showed a lesser prevalence (10.7%). However, this study included both adults and children and the varicella vaccination is not routinely prescribed in Finland except for susceptible or high-risk individuals [58]. Hence, it is not known whether the vaccination has played any roll in the decrease of VZV prevalence in latter study (1995-1996) in Finland. Even in the pre-vaccination era, the VZV prevalence among children with encephalitis reported in Aichi, Japan (6.8%) seems comparatively lesser than the Finland studies. Rest of the studies except the study conducted in Taiwan, shows prevalence values less than 10%. The 13% prevalence reported in Taiwan is from a study conducted with both children and adults before the country introduced a free vaccination programme for VZV in 2004 [59]. However, the current status in Taiwan is not known.

Although, the number of relevant studies found in tropical areas is considerably less to perform any comparison with temperate areas and to draw any conclusions, lowest prevalence data were from Eastern and Central Indian lands (0.38% and 0.5%; adults and children) which extend from sub-tropical to tropical areas. It can be because varicella is a less common infection in tropical areas compared to temperate areas [18] or we may speculate it is partly due to the availability of varicella vaccine in India since 1999 [60]. Sri Lanka, reports only 3% prevalence of VZV among encephalitis related cases (adults and children) from Colombo. A country has no routine vaccination

programme for VZV [52]. However, the vaccine is available from private healthcare facilities and the authors of this study had mentioned that all patients who were positive for VZV were adults.

With exception of six studies: from Finland, England, France, Italy, Taiwan and Australia which have covered the whole or most parts of the country, other studies were confined to certain areas of the respective countries. Hence, the prevalence data produced from those studies represent only a particular area in a country rather than the whole country. Therefore, more studies and metadata are required in order to further analyse patterns of VZV prevalence among encephalitis related cases from world-wide.

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