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Clinical presentation, etiology, and survival in adult acute encephalitis syndrome in rural Central India

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ABSTRACT

Background: Acute encephalitis syndrome (AES) is a constellation of symptoms that includes fever and altered mental status. Most cases are attributed to viral encephalitis (VE), occurring either in outbreaks or sporadically. We conducted hospital-based surveillance for sporadic adult-AES in rural Central India in order to describe its incidence, spatial and temporal distribution, clinical profile, etiology and predictors of mortality.

Methods: All consecutive hospital admissions during the study period were screened to identify adult-AES cases and were followed until 30-days of hospitalization. We estimated incidence by administrative sub-division of residence and described the temporal distribution of cases. We performed viral diagnostic studies on cerebrospinal fluid (CSF) samples to determine the etiology of AES. The diagnostic tests included RT-PCR (for enteroviruses, HSV 1 and 2), conventional PCR (for flaviviruses), CSF IgM capture ELISA (for Japanese encephalitis virus, dengue, West Nile virus, Varicella zoster virus, measles, and mumps). We compared demographic and clinical variables across etiologic subtypes and estimated predictors of 30-day mortality.

Results: A total of 183 AES cases were identified between January and October 2007, representing 2.38% of all admissions. The incidence of adult AES in the administrative subdivisions closest to the hospital was 16 per 100,000. Of the 183 cases, a non-viral etiology was confirmed in 31 (16.9%) and the remaining 152 were considered as VE suspects. Of the VE suspects, we could confirm a viral etiology in 31 cases: 17 (11.2%) enterovirus; 8 (5.2%) flavivirus; 3 (1.9%) Varicella zoster; 1 (0.6%) herpesvirus; and 2 (1.3%) mixed etiology); the etiology remained unknown in remaining 121 (79.6%) cases. 53 (36%) of the AES patients died; the case fatality proportion was similar in patients with a confirmed and unknown viral etiology (45.1 and 33.6% respectively). A requirement for assisted ventilation significantly increased mortality (HR 2.14 (95% CI 1.0–4.77)), while a high Glasgow coma score (HR 0.76 (95% CI 0.69–0.83)), and longer duration of hospitalization (HR 0.88 (95% CI 0.83–0.94)) were protective.

Conclusion: This study is the first description of the etiology of adult-AES in India, and provides a framework for future surveillance programs in India.

1. Introduction

Acute encephalitis syndrome (AES) is defined as the acute onset of fever and a change in mental status (including symptoms such as confusion, disorientation, coma, or inability to talk) and/or new onset of seizures (excluding simple febrile seizures) in a person of any age at any time of year [1]. This broad syndromic definition is mainly used for disease surveillance because the clinical

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presentation of AES caused by different etiologic agents is similar. AES occurs in explosive epidemics or in a non-epidemic (sporadic) form. A systematic review of non-epidemic studies in children, all-age groups, and adults reported incidences of at least 10, 6, and 2 per 100,000 in children, all-age groups and adults respectively; these results have been suggested as levels for effective AES surveillance [2].

A large number of neurotropic viruses and non-viral etiologies can produce AES, making specific diagnosis difficult. Epidemics in India have been attributed to Japanese encephalitis virus (JEV) infection and have predominantly affected children [3–6]. Various novel agents have been reported more recently as causes of AES including enteroviruses [7], Chandipura virus [8,9] and Nipah virus [10]. Only a few surveillance studies have been performed on sporadic AES, all of them in children [11–13]. JEV, enteroviruses, and Chandipura virus were the primary etiologic agents in these studies. There are no previous surveillance studies on adult AES from India. In a previous study by our group, 16% of adults hospitalized with acute fever had AES, and 21% of them died during hospitalization [14].

While epidemics have a singular etiology, sporadic cases are more likely to be due to multiple etiologies, which require testing for multiple pathogens for effective surveillance. Despite advances made in virology in recent decades, the technology to detect these agents is expensive and often not available outside a select group of reference laboratories. This makes periodic hospital-based epidemiological investigations essential to determine the spectrum of agents that cause AES. This information can be used to develop preventive measures against specific etiologic agents. We designed this prospective study to answer three specific research questions (a) what is the incidence and distribution (spatial and temporal) of AES cases in Central India?; (b) what is the spectrum of etiological agents causing viral encephalitis in Central India?; and (c) what are the predictors of mortality in patients with AES?

2. Methods

2.1. Design

We performed a prospective hospital based surveillance of adult-AES patients with a 30-day follow up from date of hospital admission.

2.2. Setting

Mahatma Gandhi Institute of Medical Sciences (MGIMS) is a 760 bed teaching hospital located at Sevagram, in Wardha district of Maharashtra state in India. About 40,000 patients are admitted to the in-patient services of the hospital annually and 10,000 of these are cared for in the medicine wards. Most adult patients with AES are referred to the hospital from primary and secondary care facilities in and around the district, and are admitted in the medicine wards. As part of the standard treatment protocol of AES in the hospital, treating physicians perform a lumbar puncture and send cerebrospinal fluid (CSF) sample for microscopy, biochemistry (CSF sugar and proteins), and bacterial cultures. The hospital has an electronic patient medical record system, where clinical summary, investigation results, and diagnoses on discharge or death were available to study investigators for purpose of surveillance.

The hospital has a catchment area of about 72,000 square kilometers (between latitudes19 and 22 N, and longitudes 77 and 80 E), with an adult population of about 14 million (2001 census). This catchment area consists of about 70 administrative subdivisions in districts of Wardha, Yeotmal, Chandrapur, Amravati, Nagpur, Gadchiroli, Nanded, Washim, and Adilabad. MGIMS hospital is one of two teaching hospitals in the Wardha district, the only locations where mechanical ventilation is available. MGIMS hospital is a state-funded hospital, in contrast to the other teaching hospital, which is privately funded.

2.3. Patients: initial screening

At the onset of the study, emergency medical officers and house-residents were sensitized about the study, to ensure that all adults with AES are admitted to the hospital, standard management protocols are followed, and a member of the study team is contacted when any patient with AES is admitted, and lumbar puncture is planned. A member of the surveillance team (usually a trained laboratory technician or a social worker) attended to all lumbar puncture procedures, to confirm eligibility of participants, obtain consent, and to ensure proper collection of additional CSF sample required for the study. Treating physicians and house-residents screened all consecutive hospital admissions to identify adult patients with (a) fever of 14 or fewer days and (b) a change in mental status (including symptoms such as irritability, somnolence or abnormal behavior, confusion, disorientation, coma, or inability to talk), with fever having preceded the onset of the change in mental status. Patients were excluded if (a) a peripheral blood-smear and/or serology for malaria was positive, (b) an alternate explanation for fever (such as a definite localized infection such as abnormal chest X-ray suggestive of pneumonia or tuberculosis, positive acid fast bacilli in respiratory secretions, urinary tract infection, soft-tissue infection with sepsis etc.) was plausible (c) there was biochemical or clinical evidence of a metabolic encephalopathy (including but not limited to hyponatremia, hepatic dysfunction, hypoglycemia, or alcohol intoxication). All patients who satisfied the above eligibility criteria were classified as having AES and were approached for participation in the study. Similar case definitions have been used in previous studies [9,13]. In addition a study investigator (RJ) with access to electronic hospital information system maintained a log of all consecutive admissions and their discharge diagnosis from the medical wards.

2.4. Informed consent process

Because patients with AES are cognitively compromised, surrogate written informed-consent was sought from an available closest caregiver of the patient (the order of closeness being spouse, parent, offspring, sibling, friend, and other relation or friend) for administration of the questionnaire, to obtain additional serum and CSF samples, and follow up. We sought a second consent from patients, as and if they became cognitively competent. All informed consent materials were available in the local language *Marathi.* The study design was approved by the institutional review boards of participating institutes (MGIMS Sevagram, Bhopal Memorial hospital and research center, Bhopal and University of California, Berkeley).

2.5. Additional exclusion criteria

Patients were excluded from the study, after obtaining the informed consent, if there was definite evidence of a non-viral etiology for encephalitis. The additional exclusion criteria were: (a) CSF suggestive of bacterial meningitis, based on either a positive culture for pathogenic bacteria, five or more polymorphonuclear cells in CSF, CSF glucose <40 mg/dL, or a CSF/blood glucose ratio <0.25; (b) positive mycobacterial cultures for tubercular meningitis (mycobacterial cultures were done with 1 mL of the freshly collected CSF, which was inoculated in BACTEC), (c) positive cryptococcal antigen test in CSF sample suggestive of cryptococcal meningitis. This test was done in patients who were HIV