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Review

Tick-borne encephalitis in China: A review of epidemiology and vaccines

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ABSTRACT

Tick-borne encephalitis (TBE) has been shown to be endemic in northern and western China, including the three mountain areas in Heilongjiang, Jilin, Inner Mongolia, and Xinjiang. In addition, serology evidence shows that there is human infection in south-west provinces of China, including Xizang (Tibet) and Yunnan. TBE in China is caused by the Far Eastern TBE virus subtype and there is no biphasic course for disease presentation. The majority of TBE cases in China have occurred in people who were living or working in forests. TBE vaccines became available in China soon after the virus was identified in the country and they have been used for more than 60 years to date, with different vaccine types used in different periods. Currently, an inactivated and purified whole-virus vaccine produced in a primary hamster kidney (PHK) cell line is used. Clinical trials have shown this vaccine to have higher immunogenicity and fewer adverse reactions than previous TBE vaccines. This paper provides a review on the epidemiology of TBE and the history of TBE vaccination in China.

Contents

1. Introduction . . . 1227
2. Diagnosis and clinical characteristics . . . 1228
3. Demographic features . . . 1228
4. Geographical distribution, incidence and seroprevalence . . . 1232
5. Seasonality . . . 1234
6. Secular trend . . . 1234
7. TBE vaccines in China . . . 1234
8. Conclusions . . . 1236
Conflict of interest . . . 1236
Acknowledgements . . . 1236
References . . . 1236

1. Introduction

Tick-borne encephalitis (TBE), named as "forest encephalitis" in Chinese, is an acute infectious disease of the central nervous system caused by the TBE virus (TBEV). In China, TBE patients were first reported in 1943 and TBEV was isolated in 1944 from the brain tissues of 2 patients and also from *Ixodes persulcatus* by Japanese military scientists [1,2]. TBEV was again isolated from patients and ticks (*I. persulcatus* and *Haemaphysalis concinna*) in 1952 by Chinese researchers [2]. Among the three subtypes of TBEV (European, Siberian, and Far Eastern) only the Far Eastern subtype is endemic in northeastern China and present in western and south-western China [3]. Due to the threat to forest workers, TBE vaccines have been developed and registered in China, including inactivated vaccines derived from mouse brain and chicken embryo tissue cultures (first manufactured in 1953), chicken embryo cell culture (first manufactured in 1960), and primary

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hamster kidney (PHK) cell culture (first manufactured in 1967); and purified inactivated vaccine derived from PHK cells (SenTaiBao®, approved in 2004) [4]. This paper provides a review on the epidemiology of TBE in China and the use of TBE vaccines.

2. Diagnosis and clinical characteristics

The national guideline, Diagnostic Criteria of Occupational Forest Encephalitis (GBZ 88-2002) that has been implemented since 1 June 2002 [5], states that diagnosis of TBE should be established following a comprehensive analysis of the following criteria: (1) patients having been to forest areas and having a history of tick bites in spring and summer seasons; (2) patients having a sudden fever and typical symptoms indicating acute impairment of the central nervous system; (3) positive findings for specific serological tests (i.e., anti-TBEV IgM antibodies or a fourfold rise of anti-TBEV IgG antibodies detected); (4) epidemiology survey indicating TBE endemic in the forest areas where the patients worked (or visited); and (5) excluding any diagnosis of diseases due to other causes [5]. The guideline also describes disease severity criteria as follows: (1) mild: sudden disease onset with fever, headache, nausea, vomiting, and other symptoms; fever for >1 week before returning to normal; and serum specific antibodies (IgM or IgG) positive. (2) Moderate: worsening of the above presentations, with neck stiffness and meningeal irritation, such as positive for Kernig's and/or Brudzinski's sign. (3) Severe: the above presentations aggravated with one of the following manifestations: (A) flaccid paralysis in the neck and shoulder or the limb(s); (B) difficulty swallowing; (C) speaking difficulties; (D) consciousness confusion or seizure; and (E) respiratory failure [5]. Infectious diseases that need to be differentiated from TBE in China include Crimean-Congo hemorrhagic fever, Rickettsial spotted fever, tick borne protozoan disease (such as human babesiosis), spirochetosis, Q fever, Japanese encephalitis, poliomyelitis, tuberculous meningitis, purulent meningitis, mumps, and viral encephalitis caused by echoviruses or coxsackieviruses [6,7].

An outbreak of TBE occurred in May to July of 1952 among forest workers in northeast China after the government decided to change lumbering from a seasonal (late autumn to mid-winter) to all-year practice in 1951. The patients had fever and symptoms involving the central nervous system with flaccid paralysis commonly seen in muscles of the neck, shoulder, and the upper limbs. Approximately one-third of the patients had sequelae and approximately one-third of the patients died. TBEV was isolated from brain tissues of the deceased patients as well as from local ticks (*I. persulcatus* and *H. concinna*) [2]. Since then, TBE has been recognized and reported in different regions in China.

The clinical manifestations of TBE in China are described by some studies (Table 1) [8–11]. In general, after an incubation of 4–28 days (average 8 days), TBE starts with an acute onset characterized by high fever (39–49 °C) that may persist for 5–7 days (can be 12–14 days). Meningism is the characteristic manifestation, with nausea, vomiting, severe headache, and neck stiffness. Paralysis may follow. These clinical presentations are typical of the Far Eastern subtype TBEV infection, and are in contrast to those caused by the European or the Siberian subtypes of TBEV. The latter two subtypes usually cause a characteristic biphasic course of disease with influenza-like illness followed by neurological symptoms, with approximately 25% of the patients having only the influenza-like illness [12]. The disease presentations among patients with TBE in China are neurological—similar to that of the second phase of TBE caused by the European or the Siberian subtypes of TBEV. Among TBE infections, the majority are asymptomatic and patients are self-resolved. In addition, patients with mild infection do not show signs of damage of the nervous system [9–11,13]. Among studies, the rate of severe TBE cases varied between 29.9% (113/378) [11] and 67.6% of all TBE cases (257/380) [10], while the proportion of patients with mild infection was 33.0% (125/378) [11] and 11.8% (45/380) [10], respectively. No indication of a biphasic course of TBE in China was found from the literature provided in this review.

One study [10] systematically investigated the symptoms of 380 TBE patients who were diagnosed according to the following criteria: history of living or working in endemic areas, history of tick bites, onset in epidemic seasons, clinical signs and symptoms, and positive serological results in indirect immunofluorescence assay (IFA) for TBE-specific IgM or IgG antibodies. Two hundred and seventy-five of the patients from Jilin (Yanbian region) and Heilongjiang were diagnosed in 1987–1990, and 105 patients were diagnosed at the DaXingAnLing Forestry Central Hospital of Inner Mongolia in 1995–1999. Among the 380 patients, the most common symptoms included fever (100%), nausea (96.8%), fatigue (96.6%), loss of appetite (95.8%), dizziness (94.7%), headache (90.3%), and myalgia (90.0%). Stiff neck (76.3%), disturbance of consciousness (57.9%), Kernig's sign (57.1%), vomiting (51.3%), muscle paralysis (33.4%), difficulties with verbal communication (16.3%), and difficulties with swallowing (14.7%) were also observed. Noticeably, the symptoms were different among patients with different disease severities. The occurrence rates of nausea and vomiting were significantly higher among patients with severe TBE than among those with mild infection (i.e., patients who did not show signs of meningeal irritation) and moderate TBE. Neurological symptoms were rare among patients with mild infection, and those with moderate TBE showed only neck stiffness and Kernig's sign, while muscle paralysis, disturbance of consciousness, and difficulties in swallowing and verbal communication were only seen in patients with severe TBE. It was also found that at disease onset, patients with the longest incubation period had less severe disease, and those with the mild infection had the longest incubation period [10]. Another study reported a different clinical profile in a TBE patient in Yunnan with high fever, cough, chest pain, and rashes as the main symptoms [14].

Few studies have reported the case fatality rate (CFR) of TBE. In the early 1950s, CFR of TBE in the northeastern forest areas was over 25%, but since the 1980s it has decreased to around 8% due to improvements in disease awareness, diagnostic methods, and the quality of medical care [1,2,15]. Some studies reported that using oral Mongolian medicine (herbal medicine for the treatment of fever and headache) combined with western medicine (antiviral medicine, such as ribavirin, plus antibiotics) to treat TBE had a better effect in reducing the disease duration, severity of headache, and fever [16,17]. Another study summarized data from 1963 to 2002 and reported a CFR of 2.4% (31/1303), with a higher rate before 1994 compared with later periods (9.3% [8/86] vs 1.9% [23/1217]) in the northern forest areas of Inner Mongolia [18].

Long-lasting sequelae of TBE are common, almost one-third of the patients in the 1952 outbreak had paralysis in the neck muscles or the shoulder muscles [2]. A more recent study analyzed the complications of TBE over a ten-year period [19], and found that 16.6% (90/542) of the patients developed long-term disabilities. The sequelae included neurasthenia-like symptoms (28%), tremor (17%), mental disorder (16%), epilepsy (13%), unilateral extremity flaccid paralysis (12%), drooping head or weakness in the neck (8%), and dementia (7%); 36% of those with sequelae (32 cases) lost the ability to work [19].

3. Demographic features

The majority of TBE patients in China were male—70–84% of the patient population in different studies—and most patients were