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Laboratory diagnoses of patients with unknown fever and viral encephalitides in Fujian Province, China

WANG Huan-yu¹, HE Xiao-xia¹, LUO Jian², FU Shi-hong¹, HE Ying¹,
WENG Yu-wei³, LU Su-na¹, YAN Yan-sheng³, LIANG Guo-dong¹

(1. Department of Viral Encephalitis, Institute for Viral Disease Control and Prevention, Chinese Center for Disease Control and Prevention, Beijing 102206, China;

2. Medical Team of CAPF 8751 Unit, Gejiu 661017, China;

3. Fujian Center for Disease Control and Prevention, Fuzhou 350001, China)

ABSTRACT: Viral encephalitides (VE) are excluded in the list of notifiable infectious diseases for lack of systemic monitoring and specific laboratory test methods in China. In this study, the etiological profile of patients with unknown fever and viral encephalitides was investigated in three prefectures in Fujian Province between January and December, 2010. Among the 382 patients, serum specimens from 128 unknown fever cases and 176 viral encephalitis cases, and cerebrospinal fluid specimens from 78 viral encephalitis cases were collected. Five causative agents for viral encephalitides including Japanese encephalitis virus (JEV), echovirus (ECHOV), coxsackie virus (CoxV), herpes simplex virus (HSV), and mumps virus (MuV) were detected by virus-specific IgM antibody enzyme-linked immunosorbent assays (ELISA) and nucleic amplification tests (NAT). Eighty-one specimens were detected positive in either one test, with positive rates of 37/128 in unknown fever cases and 44/176 in viral encephalitis cases, respectively. It was revealed by NAT that 8 specimens were positive, including 7 infection cases of ECHOV and CoxV, and one HSV infection. Remarkably, the infection rate of enteroviruses (EVs) ranked (54/382) on top of the virus panel, accounting for 74.4% (29/39) in positive cases of the 0-10 year-old group. Apart from JE that had a single epidemic peak in July and August, no seasonal cluster was observed from March to December by epidemiological analysis. Therefore, four viruses, i. e., EVs, JEV, MuV and HSV, contributed to unknown fever and viral encephalitis cases in Fujian Province, 2010, while EV infections were predominant.

KEY WORDS: unknown fever; viral encephalitis; laboratory diagnosis; etiology

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Corresponding author: Liang Guo-dong, Email: gdliang@hotmail.com

More than 100 viruses can invade the central nervous system and cause viral encephalitis (VE) in human. It is estimated that the overall incidence rate of viral meningitis or VE ranged 3.5-7.5 per 100 K, therefore, millions of victims worldwide suffer from nervous system infections annually^[1]. Due to its high morbidity, mortality, and serious sequelae, VE has been a heavy burden to families and societies for decades and continues as a serious public health problem. In China, the predominant VE cases were caused by arboviruses and enteroviruses (EVs), while sporadic VE cases were attributed to Herpes and Rubella viruses^[1-2]. However, the nation-wide annual incidence data and relevant epidemiological information are currently incomplete in that VE is not a notifiable infectious disease, lacking systemic monitoring and virus-specific laboratory diagnostic tests in China^[3].

Infections of Japanese encephalitis virus (JEV) used to contribute considerable VE cases in China in the past decades, the predominant genotypes were G1 and G3. In recent years, less than 100 JE cases are reported annually in Fujian Province, G3 strains were the sole genotype identified thus far, although G1 strains have now been detected in mosquito pools^[4]. Moreover, several VE outbreaks associated with ECHO virus (ECHOV) 6 and 19 were documented in Fujian several years ago^[5-6]. In this study, in order to investigate the etiological profile of VE in Fujian, serum and cerebrospinal fluid (CSF) specimens were collected from patients with unknown fever or VE in three prefectures, i. e., Fuzhou, Longyan and Nanping, from January to December in 2010. Laboratory diagnostic tests for five viruses including JEV, ECHOV, coxsackie virus (CoxV), herpes simplex

virus (HSV) and mumps virus (MuV) were conducted. These results would reveal the etiological characterization of current VE cases, and facilitate the control, prevention, and clinical diagnosis of VE in Fujian as well as other regions in China.

Materials and methods

Patients and specimens

A total of 382 patients with unknown fever or VE (age range, 13 days–84 years old) enrolled in this study between January and December 2010 in Fujian Province, from Tingzhou Hospital in Fuzhou, the First Hospital of Longyan in Longyan, and the First Hospital of Nanping in Nanping. Three hundred and four serum and 78 CSF specimens were collected within 0–30 days of illness onset.

Viral IgM antibody tests

All serum and CSF specimens were screened initially for JEV-specific IgM with a JEV IgM-capture enzyme-linked immunosorbent assay (ELISA) kit (Lot No. 1110-1, Shanghai B&C Biological Technology Co., Ltd., Shanghai, China). The JEV IgM-negative samples were tested for the other VE pathogens, including ECHOV, CoxV, HSV, and MuV using virus-specific IgM-ELISA kits (Virion/Serion Co., Wurzburg, Germany; Lot No. : LOT: SDB. DZ/SGB. CG, LOT: SCA. DE / SMA. CD, LOT: SFB. AV and LOT: SKA. DE., respectively). Any specimen that was positive in one assay was excluded in the following tests, although antibodies for ECHOV and CoxV were tested simultaneously. All assays were performed in accordance with the manufacturer's instructions.

Nucleic acid amplification tests

Total RNA and DNA were extracted from serum or CFS specimens using the QIAamp Viral RNA and DNA Simultaneous Extraction kit (QIAGEN, Valencia, CA, USA), in accordance with the manufacturer's protocol, and first-strand cDNA was prepared using Ready-To-Go You-Prime First-Strand beads (Amersham Pharmacia Biotech, Piscataway, NJ, USA), as described in the kit's manual. Virus-specific fragments were amplified by

polymerase chain reaction for JEV^[7], EVs^[8], HSV^[9], and MuV^[10], any positive specimen in one assay was excluded in the rest tests. PCR amplicons were recovered and sequenced at Biomed Biological Technology Company (Beijing, China).

Results

Evidence for viral infections

Virus infections were demonstrated in 81 specimens including 73 viral IgM-positive cases and 8 viral NAT-positive cases, and the positive rates were 28.9% (37/128) in unknown fever cases and 17.3% (44/254) in viral encephalitis cases, respectively (Table 1). Out of the 78 CSF specimens from VE patients, seven specimens were positive for EVs and one was HSV-positive. Subsequent sequencing revealed that viruses associated with these cases were ECHO6, ECHO9, ECHO16, CoxA9, CoxB5, and HSV5 (Tables 1 and 2, Figure 1). Particularly, the 73 IgM-positive serum samples were NAT-negative, ECHOV and/or CoxV was the most common pathogen which accounting for 66.7% (54/81) in this positive population, followed by MuV (13.6%, 11/81), JEV (11.1%, 9/81), and HSV (8.6%, 7/81).

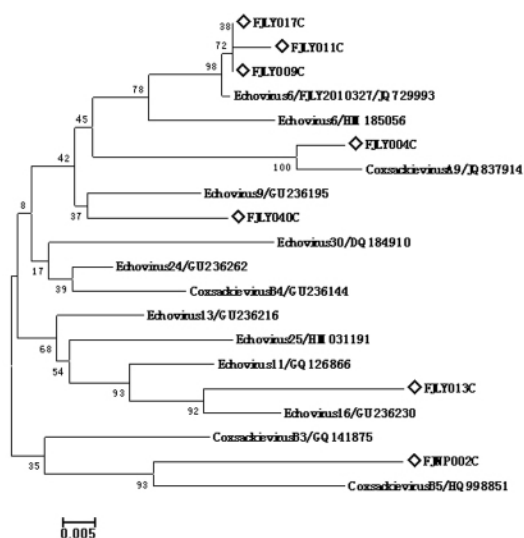


Fig. 1 Phylogenetic analysis of EVs strains in Fujian Province

Epidemiological characterization

The epidemiological characterization of this population was analyzed in the wake of laboratory tests. Among the 81 laboratory-confirmed patients, the male to female ratio was 1.38 : 1 (47 : 34).

Tab. 1 Virus screening of unknown fever or VE cases in Fujian Province, 2010

Location	Clinical cases				Laboratory detection									
	Unknown fever	Viral encephalitis		Unknown fever				Viral encephalitis				Total (positive/total)		
	Serum	Serum	CSF	Serum (IgM+)				Serum (IgM+)/CSF (PCR+)				IgM (+)	PCR (+)	
				JEV	EVs	MuV	HSV	JEV	EVs	MuV	HSV			
Fuzhou	46	54	2	3	11	4	1	1/0	5/0	0/0	1/1	26	1	
Longyan	6	92	50	0	0	0	0	1/0	19/6	5/0	2/0	27	6	
Nanping	76	30	26	4	11	2	1	0/0	1/1	0/0	1/0	20	1	
Total	128	176	78	7	22	6	2	2/0	25/7	5/0	4/1	73	8	
Positive rate (%)	28.9% (37/128)	17.3% (44/254)		28.9% (37/128)				20.5% (36/176) / 10.3% (8/78)				21.2% (81/382)		
Ratio				45.7% (37/81)				54.3% (44/81)				90.1% (73/81)	9.9% (8/81)	

Note: CSF (cerebrospinal fluid); JEV (Japanese encephalitis virus); EVs (Enterovirus); including ECHO and CoxV; MuV (Mumps virus); HSV (Herpes simplex Virus).

Tab. 2 Summary of the NAT positive cases

Case	Gender	Age	Onset/collection date	Interval	Clinical Diagnosis	Virus
1	Male	1-year	2010. 5. 28/2010. 6. 3	6 d	Central Nervous System Infections	CoxA9
2	Male	3-year	2010. 5. 24/2010. 6. 24	30 d	Central Nervous System Infections	ECHOV 6
3	Male	4-year	2010. 6. 1/2010. 6. 11	10 d	Central Nervous System, drowsiness	ECHOV 6
4	Male	12-year	2010. 6. 11/2010. 6. 24	13 d	Central Nervous System Infections	ECHOV 16
5	Male	3-year	2010. 6. 20/2010. 6. 23	3 d	Viral encephalitis	ECHOV 6
6	Female	6-year	2010. 6. 10/2010. 6. 13	3 d	Viral encephalitis	ECHOV 9
7	Male	7-year	2010. 9. 11/2010. 9. 13	2 d	Viral encephalitis	CoxB5
8	Male	1-year	2010. 10. 12/2010. 10. 16	4 d	Convulsion	HSV1

For age group distribution, two peaks were observed in two age groups, i. e., < 10 years-old group and 20-60 years-old group (Figure 2). Besides two pediatric JE cases, another seven adults over 20 years-old were detected positive for JEV-IgM. Although the 11 MuV cases were scattered in every age group, the four HSV-positive patients were solely aged between 1-10 years, while EV infection was predominant (74.4%, 29/39) in patients aged 0-10 years.

As for seasonal distribution of the 81 patients, which was either viral IgM-positive or NAT-positive, nine JEV IgM-positive cases occurred in July and August. The 54 ECHOV and/or CoxV IgM-positive or NAT-positive cases were distributed from March to December, although a peak between May to September was observed. On the other hand, the 11 MuV IgM-positive cases were distributed from April to November, the onset time of the seven HSV positive cases was irregular (Figure 3).

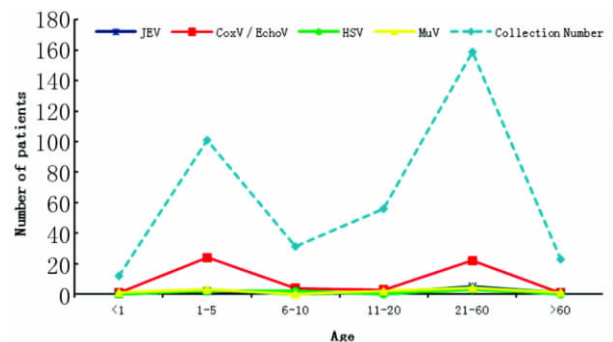


Fig. 2 Age distribution of cases positive for virus infection

Discussion

In this study, the etiological profile of 382 cases with unknown fever and VE in Fujian, 2010, was investigated by ELISA assays and NATs. It was indicated by laboratory tests that considerable viral infections were associated with unknown fever or VE patients, and that EVs (ECHOV and CoxV) were the predominant causative agents in this population, exceeding other viruses such as MuV, JEV, and HSV. MuV and JEV are vaccine

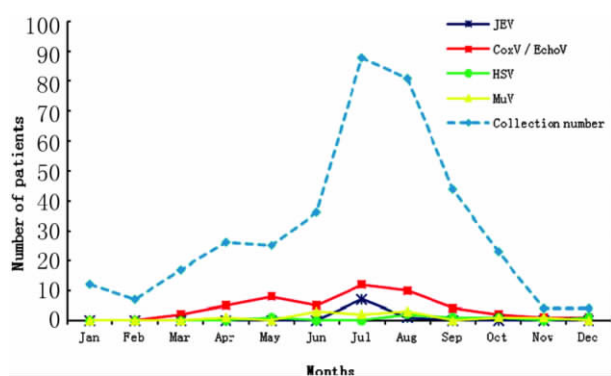


Fig. 3 Mouth distribution of positive cases with virus infection

preventable diseases; however, effective vaccines for EVs and HSV are not available yet.

The clinical manifestation of virus infection ranged from latency, mild febrile to systemic infection, hence, VE cases are largely underestimated unless acute fever and neck stiffness are presented. From our observation, the infection rate in patients with unknown fever was relatively high of 28.9% (37/128), accounting for 45.7% (37/81) of the positive cases, suggesting a large number of patients infected with common VE viruses were incorrectly classified as unknown fever cases. Therefore, it is critical to launch laboratory diagnosis of acute encephalitis syndrome in medical facilities^[12], especially for cases of idiopathic fever. Undoubtedly, timely identification of the etiological spectrum in sporadic or clustered unknown fever and VE cases would prevent large autochthonous VE outbreaks.

The etiological spectrum of VE differs among regions. It was reported in a domestic study in 2008 that VE pathogens in certain provinces in China were JEV, MuV, EVs, HSV, MV, Varicella-Zoster virus, Epstein-Barr virus, and cytomegalovirus^[13]. In this study, however, the order was EV, MuV, JEV, and HSV in Fujian Province. Similar to observations from other countries, EVs are predominant agents for VE^[14-15], indeed, several VE epidemics in Fujian in last decade were caused by EVs^[4-5,16]. MuV, which ranked the second, is also an important pathogen in Beijing children with increasing incidence rates^[17]. As for the other two viruses, the low positive rate of JEV is consistent with the low incidence rate of JE in Fujian Province^[18], while HSV is responsible for acute sporadic encephalitis cases in the United States^[11]. Thus, to certain extent, the etiological

spectrum of VE reflected the situation in Fujian at the post vaccine era, when national Expanded Program on Immunization (EPI) for Japanese encephalitis and measles launched in Fujian Province early in 2000s.

Infections of any EVs such as ECHOV 6, 9, 30, 33, 32, 4, 5, CoxB3, B5, and EV71 are common causes in VE cases, in particular, the predominant pathogenic EV types in Fujian Province are ECHOV 30, 25, 19, and 6^[19]. It was indicated by sequencing data that amplified viral fragments from CSF specimens belonging to ECHOV 6, 9, 16, and Cox A9 and B5, respectively. Both Cox A9 and B5 are rarely emerging types for VE in recent years^[20-21]. Cox B5 and ECHOV 9 were isolated from hand-foot-and-mouth disease cases in Fujian Province in 2010^[22]. In this study, the nucleotide sequence of an ECHOV 6 showed high homology with that of FJLY2010327 (GenBank Accession No: JQ729993), a representative isolate during an outbreak in Fujian Province in 2010^[5]. These findings indicated the emergence of rare EV types in VE patients in Fujian Province in recent years.

VE is common in Chinese children^[1-2]. Although no children's hospital was investigated in the present study, two peaks were observed in the 1-10 years-old group and the >20 years-old group, accounting for 47.0% (38/81) and 45.7% (37/81) of the positive cases. Nation-wide EPI for JE immunization has protected the majority of children, however, the number of adult JE cases has been increasing in China^[23-24], and it is not surprising that five adults aged between 21 to 60 years old were JEV-IgM positive among the nine confirmed JE cases. These results suggested that the JE epidemic trend is shifting from children to adults in Fujian, which has not been demonstrated yet by statistical data available, and that extensive surveillance of JE cases is required.

The seasonal distribution of JEV and EVs infections mainly occur during summer and autumn, while MuV is actively circulating in winter and spring, and HSV is sporadic throughout the year^[2]. In this study, the onset of viral infections other than JEV was documented between March to December, whereas EVs infections were mainly in July-August, and most MuV infections occurred in June-August, therefore, no significant seasonal cluster was observed in VE cases. Despite limited

time span, geographic coverage, and case numbers in this study, the observation highlighted the etiological characterization of patients with unknown fever or VE in Fujian will contribute to laboratory diagnosis, control and prevention of VE cases in the future.

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福建省不明原因发热和病毒性脑炎患者病毒感染的实验室检测

王环宇¹, 赫晓霞¹, 罗建², 付士红¹, 何英¹, 翁育伟³, 鲁苏娜¹, 严延生³, 梁国栋¹

摘要:目的 了解福建省不明原因发热、病毒性脑炎患者中病毒感染类型与流行特征。方法 于 2010 年 1—12 月采集医院中就诊的不明原因发热和病毒性脑炎患者血清和脑脊液标本。使用免疫学和分子生物学方法检测患者标本中 5 种常见病毒(乙型脑炎病毒、埃可病毒、柯萨奇病毒、单纯疱疹病毒和腮腺炎病毒)特异性 IgM 抗体和病毒基因。结果 共采集到 382 例发热和病毒性脑炎患者标本,其中发热患者 128 例(128 份急性期血清),病毒性脑炎患者 254 例(176 份急性期血清,78 份脑脊液)。检测结果显示,共 81 例患者标本检测到病毒感染阳性,其中不明原因发热患者血清的病毒 IgM 抗体阳性率为 28.9%(37/128),病毒性脑炎患者血清的病毒 IgM 抗体或脑脊液的 PCR 阳性率为 17.3%(44/254)。肠道病毒感染在所有病例中所占比例最高为 66.7%(54/81),在 1—10 岁病毒感染阳性患者中肠道病毒感染占 74.4%(29/39)。8 份脑脊液标本检测病毒核酸阳性中,7 份为肠道病毒阳性,1 份为单纯疱疹病毒阳性。流行病学分析显示,病毒感染阳性标本分布在 3—12 月,除了乙型脑炎病例全部集中在 7—8 月以外,其他病毒感染未见明显季节聚集性。结论 实验室检测发现,2010 年全年在福建省部分医院采集的发热和病毒性脑炎患者标本中存在肠道病毒、乙型脑炎病毒、腮腺炎病毒和单纯疱疹病毒感染,以肠道病毒感染为主。

关键词:病毒性脑炎;不明原因发热;实验室诊断;病原学

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通讯作者:梁国栋, Email:gdliang@hotmail.com

作者单位:1. 中国疾病预防控制中心病毒病预防控制所,北京 102206;

2. 武警 8751 部队卫生队,个旧 661017;

3. 福建省疾病预防控制中心,福州 350001

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