

ORIGINAL ARTICLE

Serotypes of human enteroviruses causing pediatric viral encephalitis and meningitis in Hebei province, China, from 2013 to 2015

Xiangpeng Chen¹ | Jiayun Guo¹ | Jingjie Li² | Qiuping Li¹ | Junhong Ai¹ | Suzhen Sun² | Zhengde Xie¹

¹Key Laboratory of Major Diseases in Children, Ministry of Education, Beijing Key Laboratory of Pediatric Respiratory Infection Diseases, Virology Laboratory, Beijing Pediatric Research Institute, Beijing Children's Hospital, Capital Medical University, National Center for Children's Health, Beijing, China

²Department of Neurology, Children's Hospital of Hebei Province, Shijiazhuang, China

Correspondence

Zhengde Xie, Key Laboratory of Major Diseases in Children, Ministry of Education, Beijing Key Laboratory of Pediatric Respiratory Infection Diseases, Virology Laboratory, Beijing Pediatric Research Institute, Beijing Children's Hospital, Capital Medical University, National Center for Children's Health, Beijing, China.

E-mail: xiezhengde@bch.com.cn;

Suzhen Sun, Department of Neurology, Children's Hospital of Hebei Province, Shijiazhuang, China, E-mail: sunsuzhen2004@126.com

Funding source

National Science and Technology Major Projects for the Control and Prevention of Major Infectious Diseases in China (grant numbers 2017ZX10104001-005-010, 2013ZX10004-202); Beijing Natural Science Foundation (grant number 7184208); Beijing Outstanding Young Talent Training Projects (grant number 2014000021469G237); Capital Clinical Feature Project of Beijing Technology Program (grant number Z151100004015046); Basic and Clinical Research Cooperation Project of Capital Medical University (grant number 17JL11); Research Training Fund of Capital Medical University (PYZ2017012)

Received: 3 April, 2018

Accepted: 5 June, 2018

ABSTRACT

Importance: Viral encephalitis and meningitis are severe infectious diseases responsible for substantial morbidity and mortality in children. Enteroviruses are typically the most common causative agents of viral encephalitis and meningitis.

Objective: This study aimed to investigate the etiology of viral encephalitis and meningitis among children in Hebei province, China.

Methods: Cerebrospinal fluid samples from children with viral encephalitis (n=309) and meningitis (n=133) were collected between Nov 2013 and Dec 2015 and viral pathogens were identified by real-time and multiplex PCR. Amplification and sequencing of partial VP1 genes was used to type enteroviruses.

Results: The causative pathogen was successfully detected in 176 (57%) patients with viral encephalitis and 82 (61.7%) patients with viral meningitis. The most common causative agents of both viral encephalitis and meningitis were enteroviruses (55.7% and 64.6% of cases, respectively). The most common enterovirus serotypes identified were echovirus 18, echovirus 6 and echovirus 30. Echovirus 18 accounted for 74.4% of all typed enteroviruses and caused a viral encephalitis and meningitis outbreak in Hebei province in 2015. By contrast, the major enterovirus serotypes circulating in 2014 were echovirus 6 and echovirus 30.

Interpretation: Enteroviruses were the main causative agents of viral encephalitis and meningitis in children in Hebei province from Nov 2013 to Dec 2015. Echovirus 18 became the leading cause of viral encephalitis and meningitis for the first time in Hebei province in 2015.

KEYWORDS

Viral encephalitis, Viral meningitis, Enterovirus, Children

DOI: 10.1002/ped4.12037

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

©2018 Chinese Medical Association. *Pediatric Investigation* published by John Wiley & Sons Australia, Ltd on behalf of Futang Research Center of Pediatric Development.

INTRODUCTION

Viral encephalitis (VE) and meningitis (VM) are severe infectious diseases responsible for substantial morbidity and mortality in children.^{1,2} More than 100 viruses are known to cause VE and VM. The main pathogens responsible for VE and VM vary by geographical region, season, and detection methodology. In England and Wales, the most common causative agents of VE and VM were enteroviruses (EVs), herpes simplex virus (HSV) and varicella zoster virus (VZV).³ In America, Leber et al. reported that the most common causative agents of VE and VM were EVs and human herpesvirus 6 (HHV6).² In Australia, the most common causative agents were HSV and VZV,⁴ while Japanese encephalitis virus (JEV) was the most common causative agent of VE among children in southern Vietnam.⁵

There is no national monitoring system for infectious encephalitis or meningitis in China, and the epidemiology of pediatric VE and VM in Hebei province is poorly understood. In previous work, we reported an outbreak of encephalitis and meningitis caused by the enterovirus, echovirus 18 (E18), in Hebei province in 2015.⁶ In the present study, we explored the etiology and epidemiology of pediatric VE and VM between November 2013 and December 2015 in Hebei province.

METHODS

Patients

Pediatric patients (ages 1 month–16 years) hospitalized with acute VE and VM between Nov 2013 and Dec 2015 were enrolled in this study. Patients with demyelinating, metabolic, toxic or neurological degenerative diseases or HIV infection were excluded. The Children's Hospital of Hebei Province is the largest comprehensive center for pediatric health care in the province. The hospital serves more than 1,000,000 outpatients and 40,000 inpatients each year.

Clinical definition

Diagnosis of acute VE was based on the following criteria: (i) acute symptom onset; (ii) alteration in mental state; (iii) documented fever $\geq 38^{\circ}\text{C}$ within 72 h (before or after) of clinical manifestations; (iv) generalized or partial seizures not fully explained by a preexisting seizure disorder; (v) brain parenchymal lesions on neuroimaging or abnormal electroencephalogram; (vi) no evidence of bacterial infection on microscopic examination or cerebrospinal fluid (CSF) culture.

Diagnosis of acute VM was based on the following criteria: (1) acute symptom onset; (2) fever plus symptoms such as headache, vomiting, and nuchal rigidity; (3) absence of parenchymal involvement; (4) no evidence of

bacterial meningitis on microscopic examination or CSF culture.

Clinical specimens and data collection

CSF was aseptically collected during the acute phase of infection based on clinical examination during hospitalization. All specimens were transported to the laboratory of virology at the Beijing children's hospital and stored at -80°C until further processing.

Data on demographic characteristics, clinical symptoms and signs, laboratory findings, neuroimaging and electroencephalography results, and patient outcomes were collected for all subjects.

PCR detection of viruses

Viral nucleic acid was extracted from CSF samples (0.2 mL) using the QIAamp MinElute Virus Spin Kit (QIAGEN, Germany, Cat. No. 57704), according to the manufacturer's instructions.

Screening for EVs, mumps virus (MuV) and JEV was performed using real-time PCR (PCR-fluorescent probe) (BioPerfectus Technologies, China, Cat. Nos. JC20101, JC60104, and JC70108, respectively).

Six herpes viruses, including HSV1, HSV2, VZV, Epstein-Barr virus (EBV), HHV6 and cytomegalovirus (CMV) were screened using a multiplex PCR method, the Seeplex® meningitis-V1 ACE Detection kit (Seegene, Korea, Cat. N. MG6611Y, V2.0).

Sequencing of the VP1 gene for EV typing

The genotypes of EVs were determined by sequencing of partial VP1 genes and BLAST analysis. All EV-positive samples were PCR-amplified with primer pairs 292–222.⁷ Samples that failed to amplify using primer pairs 292–222 were subjected to amplification with primer pairs 040–011 and 012–011.⁸

Ethics approval

The study protocol was approved by the Medical Ethics Committee of Beijing Children's Hospital, Capital Medical University. Written informed consent was obtained from legal guardians of all patients prior to the collection of CSF samples.

RESULTS

Case characteristics

A total of 442 patients (302 boys and 140 girls) qualified for inclusion in this study after excluding patients with bacterial meningitis (n=30), autoimmune encephalitis (n=8) and mitochondrial encephalomyopathy (n=2). Of these 442 patients, 309 were diagnosed with VE (age,

TABLE 1 Demographic characteristics of pediatric VE and VM patients.

Diseases	Sex			Age (years)				
	male	female	ratio	≤1	1–3	3–6	6–10	>10
Encephalitis (N=309)	216	93	2.32:1	15	40	146	98	10
Meningitis (N=133)	87	46	1.89:1	1	9	57	53	13
Total	303	139	2.18:1	16	49	203	151	23

mean \pm SD: 5.38 ± 2.60 years; age range: 1 month – 11.2 years), while 133 were diagnosed with VM (age, mean \pm SD: 6.38 ± 2.82 years; age range: 9 months – 13.9 years). The vast majority of patients were between 3 and 10 years old [78.96% (244/309) and 82.71% (110/133) of patients with acute VE and VM, respectively]. The proportions of patients with VE and VM who were younger than 3 years of age were 17.80% (55/309) and 7.52% (10/133), respectively. The demographic characteristics of patients are summarized in Table 1.

The most common clinical manifestations in patients with VE were headache (82.2%, 254/309), fever (75.0%, 232/309), vomiting (51.5%, 159/309), nausea (45.3%, 140/309) and lethargy (42.1%, 130/309). Other common clinical manifestations included abdominal pain

(6.5%, 20/309), convulsion (6.1%, 19/309), and loss of consciousness (4.2%, 13/309). The most common clinical manifestations in patients with VM were headache (96.2%, 128/133), fever (75.2%, 100/133), vomiting (60.7%, 88/133) and nausea (37.6%, 50/133). VE and VM both occurred year-round with a peak of cases observed during the month of July (Figure 1A).

Spectrum of viral pathogens in patients with VE and VM

In total, 176 VE cases were positive for viral pathogens for an overall virus-positive rate of 57.0% (176/309). The most commonly detected pathogens in patients with VE were EVs (55.7%, 98/176), HSV1 (19.9%, 35/176), EBV (6.8%, 12/176), and VZV (6.8%, 12/176). Viral pathogens were detected

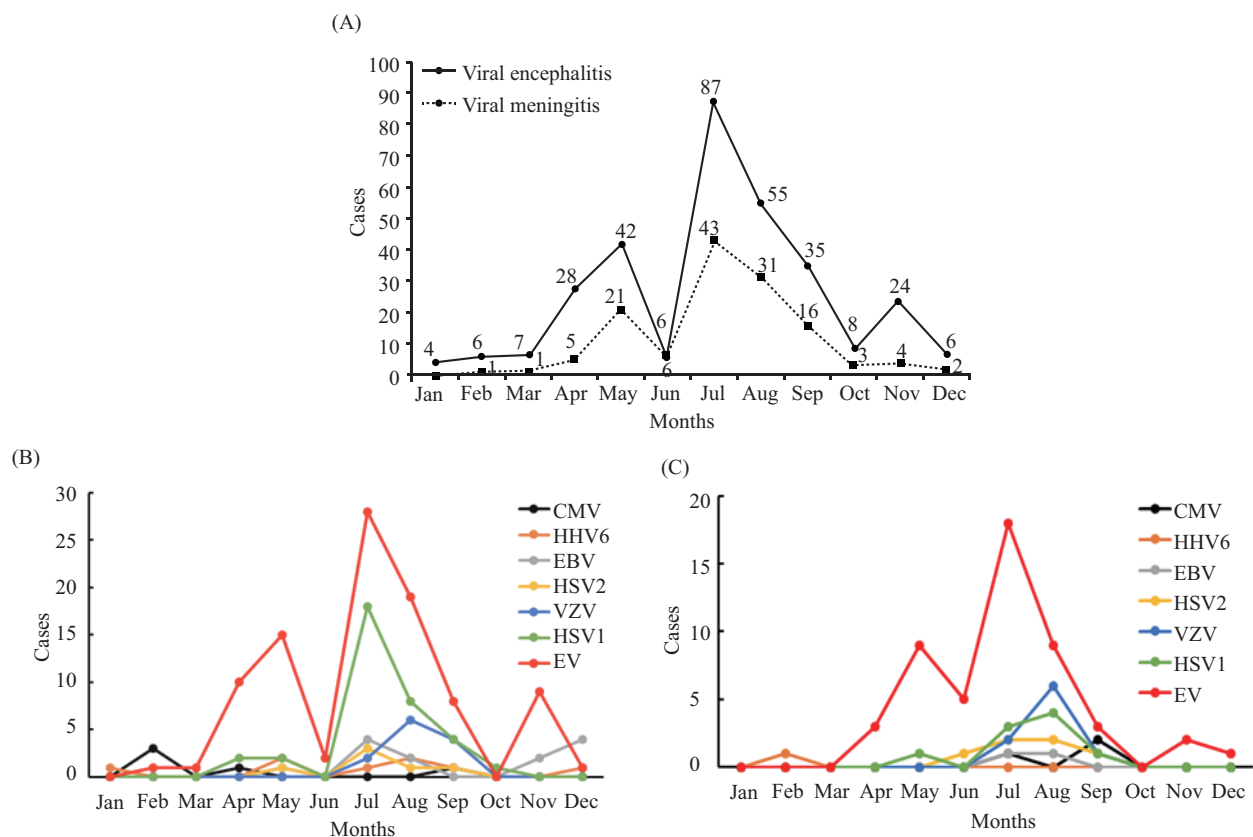


FIGURE 1 Monthly burden of viral encephalitis and meningitis cases during 2013–2015 in Hebei province, China (A). Monthly distribution of viral encephalitis (B) and viral meningitis (C) cases with confirmed etiology.

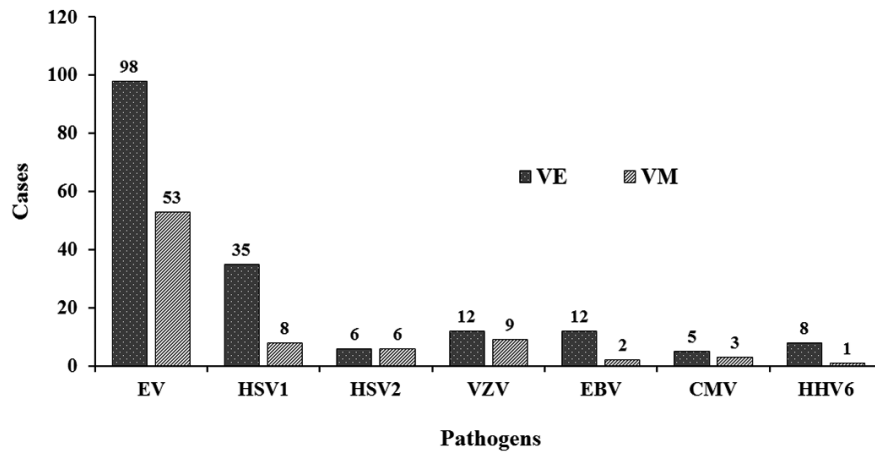


Figure 2 Distribution of viral pathogens responsible for pediatric VE and VM.

EVs, human enteroviruses; HSV1, herpes simplex virus 1; HSV2, herpes simplex virus 2; VZV, varicella zoster virus; EBV, Epstein-Barr virus; CMV, cytomegalovirus; HHV6, human herpes virus 6.

in 82 patients with VM for an overall virus-positive rate of 61.7% (82/133). The most commonly detected pathogens in patients with VM were EVs (64.6%, 53/82), VZV (11.0%, 9/82), HSV1 (9.8%, 8/82), and HSV2 (7.3%, 6/82) (Figure 2). Neither JEV nor MuV was detected in any patient in this study.

Cases of VE and VM occurred throughout the year. Cases of EV-related VE and VM occurred from April to September. The incidence of HSV1-associated VE was highest during July and August. No obvious seasonal trend was observed with respect to other viruses (Figure 1B, C).

Serotypes of enteroviruses in VE and VM

EV genotyping was conducted by sequencing partial VP1 genes and performing BLAST analyses. EVs derived

from 81 VE and 43 VM patients were typed. The EV serotypes of 17 VE samples and 10 VM samples could not be confirmed because of poor quality sequencing data. Seven EV serotypes were determined from patients with VE; these included E6 (15.3%, 15/98), E14 (1.0%, 1/98), E18 (39.8%, 39/98), E30 (15.3%, 15/98), E33 (5.1%, 5/98), Coxsackievirus B5 (CV-B5) (5.1%, 5/98), and CV-A9 (1.0%, 1/98). Five EV serotypes were determined from patients with VM; these included E6 (7.5%, 4/53), E18 (43.4%, 23/53), E30 (20.8%, 11/53), E33 (3.8%, 2/53), and CV-B5 (5.7%, 3/53). All of the typed EVs belonged to the EV-B group; the most common EVs were E18 (41.1%, 62/151), E30 (17.2%, 26/151) and E6 (12.6%, 19/151). Almost all E18 isolates were detected in 2015, with the exception of one case which was detected in 2014. E18 was the predominant EV serotype, accounting for 74.4% (61/82) of all typed EVs isolated from patients with VE/VM in 2015 (Table 2).

TABLE 2 Enterovirus serotypes identified in this study

	2013		2014		2015		Total N(%)
	VE	VM	VE	VM	VE	VM	
CV-A9	0	0	0	0	1	0	1 (0.7)
CV-B5	1	1	3	2	1	0	8 (5.3)
E6	3	0	10	3	2	1	19 (12.6)
E14	0	0	0	0	1	0	1 (0.7)
E18	0	0	0	1	39	22	62 (41.1)
E30	2	1	6	3	7	7	26 (17.2)
E33	0	0	5	1	0	1	7 (4.6)
Untyped	1	1	12	6	3	4	27
Typed	8		34		82		124
Total	10		52		89		151

Prognosis of the patients

Outcome data were available for all but one patient with VE who was transferred to another hospital. About 97.7% (301/308) of patients with VE recovered completely, while six patients developed neurological sequelae and

one patient died. Neurological sequelae included epilepsy, coma, ataxia and visual impairment (Table 3). The patient who died was diagnosed with viral encephalitis caused by HSV1. All patients with VM recovered with no obvious neurologic sequelae.

TABLE 3 Details of VE patients who developed neurological sequelae or died

number	diseases	Age (years)	pathogens	hospitalization days (d)	Neurological sequelae
1	encephalitis	1.0	E6	27	Ataxia
2	encephalitis	5.4	HHV6	10	Coma
3	encephalitis	1.0	HHV6	28	Epilepsy
4	encephalitis	4.5	unknown	20	Ataxia
5	encephalitis	6.0	unknown	25	Visual impairment
6	encephalitis	1.0	unknown	27	Epilepsy
7	encephalitis	2.2	HSV1	2	Death

DISCUSSION

The etiology of VE shows geographical variation.⁹ EVs have been reported as the leading causes of VE in China.^{10,11} HSV was the most common causative agent of VE in the United States, England, France, Spain and eastern India,^{12–16} while JEV was reported as the primary viral pathogen responsible for VE among children in southern Vietnam and Thailand.^{5,17} Infection by EVs was the leading cause of VM in many parts of the world.^{16,18–20} Outbreaks of VM and VE associated with EV infection are usually caused by EV-B, most commonly by serotypes CV-B5, E6, and E30.^{21,22}

VE and VM surveillance data based on human specimens is very limited in China. In this study, we studied the etiology of VE and VM among children in Hebei province, China. During the study period, the most common causative pathogens of VE and VM were EVs, followed by HSV1 and VZV, which is consistent with results of previous studies conducted in China.^{11,23} EVs accounted for 55.7% (98/176) and 64.6% (53/82) of all cases of VE and VM with confirmed viral etiology, respectively. All EV serotypes belonged to the EV-B group, including E6, E14, E18, E30, E33, CV-A9 and CV-B5. No EVs of either the EV-A or EV-C group were detected.

The most common serotypes of EV causing VE and VM showed temporal variations. E30 was reported to be the predominant serotype responsible for EV-associated encephalitis in eastern China from 2002–2004 and 2010–2012, accounting for about 47.5% of VE cases from 2002 to 2012. E6 accounted for 32.0% of VE cases in eastern China in 2010.²⁴ An aseptic meningitis outbreak caused by EV serotype E6 was also reported.²⁵ In this study, the major EV serotypes observed were E6 and E30, which were detected in 25.0% and 17.3% of cases

in 2014, respectively. E18, which was detected at low prevalence in mainland China in previous studies,^{21,23} became the predominant EV serotype causing VE and VM in Hebei province in 2015.⁶ The E18 serotype of EV-B has caused many outbreaks of aseptic meningitis in the USA,^{26,27} Japan,²⁸ Germany,²⁹ and other regions.^{30,31} Prior to our study, E18 had been detected sporadically and was rarely reported in mainland China.²³ E18 has an epidemic pattern of circulation with increased levels of activity after prolonged quiescence. From 1970 to 2005 in the USA, two periods of increased E18 activity were observed (1986–1987 and 1995–2005). E18 activity reached its highest level in 2001. E18 appeared among the 15 most common enteroviruses in 18 of 36 years, from 1986 to 2005.³²

Knowledge of E18 molecular epidemiology has been very limited.⁶ High rates of nucleotide substitution and recombination are important mechanisms by which genetic diversity is propagated among EVs.³³ Little data regarding molecular evolution of the virus was gained during a single outbreak. Further study is urgently needed to gain better insights into the prevalence of E18 infection in mainland China.

JEV is the main causative agent of serious VE worldwide; China, in particular, has a long history of high JEV prevalence.³⁴ Since the JEV vaccine became available, the morbidity of JEV infection has declined sharply. It was also reported that JEV is much more prevalent in southern China as compared with northern China.³⁵ All cases in this study were from northern China, which is consistent with the absence of JEV in this study population. EVs were the main causative agents responsible for VE and VM in children of Hebei province from Nov 2013 to Dec 2015. The majority of the EVs detected from the cases were from the EV-B group, such as E18, E30, and E6. However, in this study, these viral investigations were confined to a

relatively short time and to a limited area, limiting trend analyses of VE and VM pathogens. The surveillance data reflects only part of the reality of VE and VM prevalence in China. Further study is needed to understand the true situation. Ongoing national monitoring of the clinical and molecular epidemiology of EVs causing VE and VM is a key imperative.

ACKNOWLEDGEMENTS

This study was supported by the Beijing Children's Hospital Affiliated to Capital Medical University, Children's Hospital of Hebei Province. We would like to acknowledge all the physicians and participants for collecting clinical specimens from the patients in this study.

CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

REFERENCES

- Vora NM, Holman RC, Mehal JM, Steiner CA, Blanton J, Sejvar J. Burden of encephalitis-associated hospitalizations in the United States, 1998-2010. *Neurology*. 2014;82:443-451.
- Leber AL, Everhart K, Balada-Llasat JM, et al. Multicenter Evaluation of the BioFire FilmArray Meningitis Encephalitis Panel for the Detection of Bacteria, Viruses and Yeast in Cerebrospinal Fluid Specimens. *J Clin Microbiol*. 2016;54:2251-2261.
- Kadambari S, Okike I, Ribeiro S, et al. Seven-fold increase in viral meningo-encephalitis reports in England and Wales during 2004-2013. *J Infect*. 2014;69:326-332.
- Huppertz C, Durrheim DN, Levi C, et al. Etiology of encephalitis in Australia, 1990-2007. *Emerg Infect Dis*. 2009;15:1359-1365.
- Le VT, Phan TQ, Do QH, et al. Viral etiology of encephalitis in children in southern Vietnam: results of a one-year prospective descriptive study. *PLoS Negl Trop Dis*. 2010;4:e854.
- Chen X, Li J, Guo J, Xu W, Sun S, Xie Z. An outbreak of echovirus 18 encephalitis/meningitis in children in Hebei Province, China, 2015. *Emerg Microbes Infect*. 2017;6:e54.
- Oberste MS, Nix WA, Maher K, Pallansch MA. Improved molecular identification of enteroviruses by RT-PCR and amplicon sequencing. *J Clin Virol*. 2003;26:375-377.
- Oberste MS, Maher K, Kilpatrick DR, Flemister MR, Brown BA, Pallansch MA. Typing of human enteroviruses by partial sequencing of VP1. *J Clin Microbiol*. 1999;37:1288-1293.
- Johnson RT. Acute encephalitis. *Clin Infect Dis*. 1996;23:219-224; quiz 25-26.
- Kong X, Zhang L, Liu K, et al. Epidemiological features of viral encephalitis in Cangzhou of China with use of multiplex RT-PCR for five RNA viruses. *J Virol Methods*. 2015;222:178-181.
- Zhang XS, Wang XX, Yu DS, et al. Analysis of pathogen spectrum of Encephalitis/Meningitis in northwestern area of China. *Chinese Journal of Preventive Medicine*. 2013;47:924-927.(in Chinese)
- Ramakrishna C, Openshaw H, Cantin EM. The case for immunomodulatory approaches in treating HSV encephalitis. *Future Virol*. 2013;8:259-272.
- Granerod J, Ambrose HE, Davies NW, et al. Causes of encephalitis and differences in their clinical presentations in England: a multicentre, population-based prospective study. *Lancet Infect Dis*. 2010;10:835-844.
- Mailles A, Stahl JP, Brouard C, Vaillant V. Epidemiology, improvement of etiological diagnosis, and outcome of infectious encephalitis in France in 2007: preliminary results of a national prospective study. *Med Mal Infect*. 2008;38 Suppl 2:S37-38.
- Rathore SK, Dwibedi B, Kar SK, Dixit S, Sabat J, Panda M. Viral aetiology and clinico-epidemiological features of acute encephalitis syndrome in eastern India. *Epidemiol Infect*. 2014;142:2514-2521.
- de Ory F, Avellon A, Echevarria JE, et al. Viral infections of the central nervous system in Spain: a prospective study. *J Med Virol*. 2013;85:554-562.
- Olsen SJ, Campbell AP, Supawat K, et al. Infectious causes of encephalitis and meningoencephalitis in Thailand, 2003-2005. *Emerg Infect Dis*. 2015;21:280-289.
- Nougairde A, Bessaud M, Thiberville SD, et al. Widespread circulation of a new echovirus 30 variant causing aseptic meningitis and non-specific viral illness, South-East France, 2013. *J Clin Virol*. 2014;61:118-124.
- Milia MG, Cerutti F, Gregori G, et al. Recent outbreak of aseptic meningitis in Italy due to Echovirus 30 and phylogenetic relationship with other European circulating strains. *J Clin Virol*. 2013;58:579-583.
- Hosseinasab A, Alborzi A, Ziyaeyan M, et al. Viral etiology of aseptic meningitis among children in southern Iran. *J Med Virol*. 2011;83:884-888.
- Li W, Qiong Z, Xiao-Ting S, et al. Molecular epidemiological study of enteroviruses associated with encephalitis in children from Hangzhou, China. *Medicine (Baltimore)* 2016;95:e4870.
- Yan J, Miao Z, Lyu H, et al. Etiology and molecular-epidemiological characteristics of viral meningoencephalitis of Zhejiang province in 2013. *Chinese Journal of Epidemiology*. 2015;36:280-284.(In Chinese)
- Zhu Y, Zhou X, Liu J, et al. Molecular identification of human enteroviruses associated with aseptic meningitis in Yunnan province, Southwest China. *Springerplus*. 2016;5:1515.
- Zhang L, Yan J, Ojcius DM, et al. Novel and predominant pathogen responsible for the enterovirus-associated encephalitis in eastern China. *PLoS One*. 2013;8:e85023.
- Mao N, Zhao L, Zhu Z, et al. An aseptic meningitis outbreak caused by echovirus 6 in Anhui province, China. *J Med Virol*. 2010;82:441-445.
- Wilfert CM, Lauer BA, Cohen M, Costenbader ML, Myers E. An epidemic of echovirus 18 meningitis. *J Infect Dis*. 1975;131:75-78.
- Turabelidze G, Lin M, Butler C, Fick F, Russo T. Outbreak of echovirus 18 meningitis in a rural Missouri community. *Missouri medicine*. 2009;106:420-424.
- Miyamura K, Yamashita K, Yamadera S, Kato N, Akatsuka M, Yamazaki S. An epidemic of echovirus 18 in 1988 in Japan-high association with clinical manifestation of exanthem. A report of the National Epidemiological Surveillance of Infectious Agents in Japan. *Jpn J Med Sci Biol*. 1990;43:51-

- 58.
29. Krumbholz A, Egerer R, Braun H, et al. Analysis of an echovirus 18 outbreak in Thuringia, Germany: insights into the molecular epidemiology and evolution of several enterovirus species B members. *Med Microbiol Immunol*. 2016;205:471-473.
30. Baek K, Park K, Jung E, et al. Molecular and epidemiological characterization of enteroviruses isolated in Chungnam, Korea from 2005 to 2006. *J Microbiol Biotechnol*. 2009;19:1055-1064.
31. Wang SM, Ho TS, Shen CF, Wang JR, Liu CC. Echovirus 18 meningitis in southern Taiwan. *Pediatr Infect Dis J*. 2011;30:259-260.
32. Khetsuriani N, Lamonte-Fowlkes A, Oberst S, Pallansch MA, Centers for Disease C, Prevention. Enterovirus surveillance--United States, 1970-2005. *MMWR Surveill Summ*. 2006;55:1-20.
33. Garcia J, Espejo V, Nelson M, et al. Human rhinoviruses and enteroviruses in influenza-like illness in Latin America. *Virology*. 2013;10:305.
34. Gao X, Li X, Li M, et al. Vaccine strategies for the control and prevention of Japanese encephalitis in Mainland China, 1951-2011. *PLoS Negl Trop Dis*. 2014;8: e3015.
35. Yin Z, Wang H, Yang J, et al. Japanese encephalitis disease burden and clinical features of Japanese encephalitis in four cities in the People's Republic of China. *Am J Trop Med Hyg*. 2010;83:766-773.

How to cite this article: Chen X, Guo J, Li Q, et al. Serotypes of human enteroviruses causing pediatric viral encephalitis and meningitis in Hebei province, China, from 2013 to 2015. *Pediatr Invest*. 2018;2:98-104. <https://doi.org/10.1002/ped4.12037>.



Painted by hospitalized children.

Provided by and reprinted with permission from Beijing Children's Hospital.