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Control Division,
Ministry of Health, Labour and Welfare

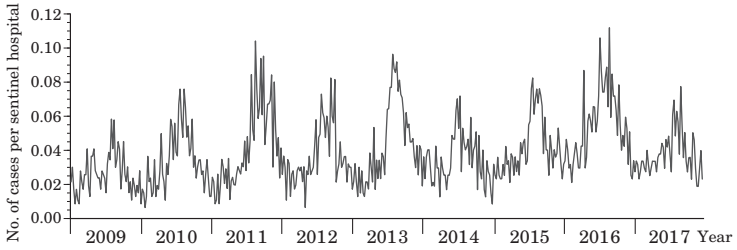
<THE TOPIC OF THIS MONTH>
Viruses detected from aseptic meningitis patients in Japan, through 2017

Aseptic meningitis is often characterized by symptoms of acute onset of fever, headache, and vomiting, but may also present with meningeal signs, such as a stiff neck and Kernig's sign. However, it is often the case that such manifestations may not be apparent in newborns or infants. The differentiation from bacterial meningitis is clinically very important, and, in addition to a negative result of bacterial detection from the cerebrospinal fluid (CSF), the following CSF tests are useful for the differentiation: first pressure, cell count and fractionation, CSF/serum glucose ratio, and protein quantity. Aseptic meningitis is caused by a variety of pathogens, and among viruses, enteroviruses are the most frequent, followed by the mumps virus. Enteroviruses detected in humans are classified into four species (*Enteroviruses A* to *D*), and *Enterovirus B* (echovirus, coxsackievirus group B) is the most frequently detected in patients with aseptic meningitis, followed by *Enterovirus A* [e.g., enterovirus A71 (EV-A71)].

According to the National Epidemiological Surveillance of Infectious Diseases (NESID) system based on the Infectious Diseases Control Law, aseptic meningitis is classified as a category V infectious disease. On a weekly basis, approximately 500 designated sentinel sites (hospitals with 300 or more beds; http://www.mhlw.go.jp/file/06-Seisakujouhou-10900000-Kenkoukyoku/0000203400.pdf) nationwide report patients that fulfill the notification criteria, based on clinical symptoms and laboratory findings (notification criteria: http://www.mhlw.go.jp/bunya/kenkou/kekkaku-kansenshou11/01-05-40.html). Based on specimens (e.g., CSF, feces, pharyngeal swabs) collected at the designated sentinel sites, prefectural and municipal public health institutes (PHIs) perform isolation/detection and identification of the etiologic agent of aseptic meningitis, and report those results with positive detections. This report describes the occurrence of patients with aseptic meningitis and recent trends in pathogens associated with aseptic meningitis, particularly enteroviruses.

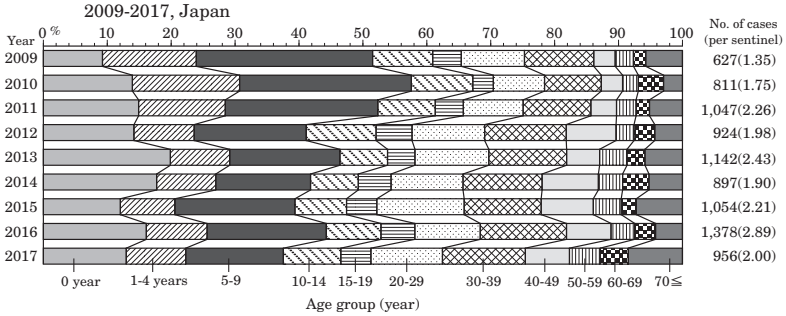
Cases notified under the NESID system: Figure 1 shows the reported number of aseptic meningitis cases per sentinel per week in 2009-2017. In Japan, an increase in aseptic meningitis is reported every year in the summer. The number of reported cases per sentinel site in each prefecture differed by region. With regards to the age distribution of aseptic meningitis patients, those under one year of age were the most frequent age group, and while those under 10 years of age made up more than half the cases in 2009-2011, the proportion of those 10 years or older increased since 2012 (Figure 2).

Figure 1. Weekly number of reported aseptic meningitis cases, 2009-2017, Japan



(National Epidemiological Surveillance of Infectious Diseases: as of April 4, 2018)

Figure 2. Age distribution of aseptic meningitis cases reported from sentinel hospitals, 2009-2017, Japan



(National Epidemiological Surveillance of Infectious Diseases: as of April 4, 2018)

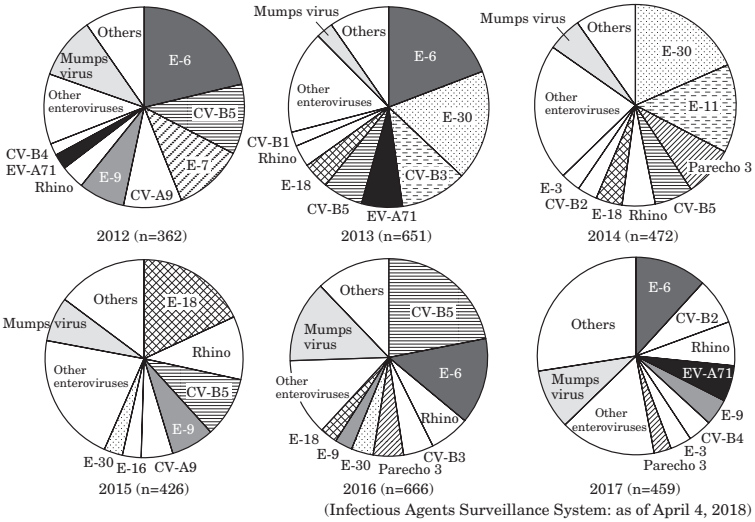
Isolation and detection of enteroviruses: During 2012-2017, enteroviruses, such as echovirus (E) and coxsackievirus group B (CV-B), accounted for 56-84% of the etiologic pathogens (Figure 3 in p. 90).

The annual number of viruses isolated or detected in patients with aseptic meningitis from 2009 to 2017 is shown in the Table in p. 91. Among these viruses, CV-B5 and E-6 were frequently reported, with a total of 344 and 548 cases detected during the 9-year period, respectively (see pp. 94, 96 & 97 of this issue). E-30 aseptic meningitis outbreaks occurred nationwide in 1983 [IASR 4(10): 1, 1983], 1989-1991 (IASR 12: 163, 1991 & 13: 155, 1992), and 1997-1998 (IASR 19: 174-175, 1998). In 2017, a regional outbreak of E-30-

(Continued on page 90′)

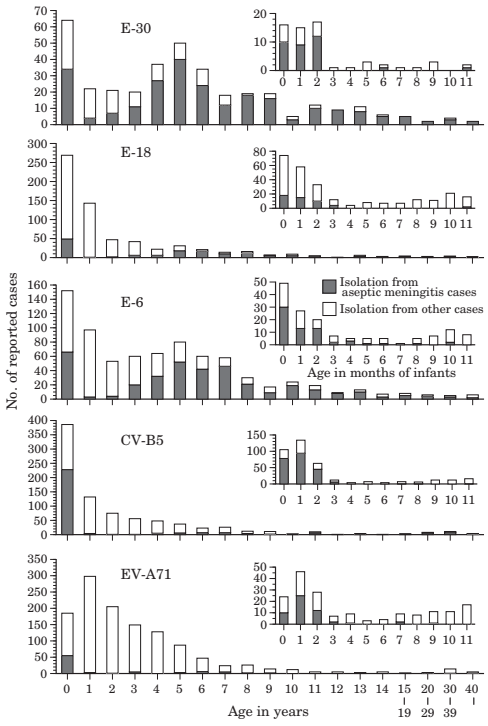
(THE TOPIC OF THIS MONTH-Continued)

Figure 3. Isolation/detection of viruses from aseptic meningitis cases, 2012-2017, Japan



(Infectious Agents Surveillance System: as of April 4, 2018)

Figure 4. Age distribution of cases with isolation/detevtion of E-30, E-18, E-6, CV-B5 or EV-A71, 2012-2017, Japan



(Infectious Agents Surveillance System: as of April 4, 2018)

associated aseptic meningitis was reported in Hokkaido, Japan (see p. 91 of this issue). High circulation of E-9 has also been reported from some localities (see p. 93 of this issue). As an etiologic agent of hand, foot, and mouth disease (HFMD), EV-A71 causes nationwide epidemics every 3-4 years, and is known to be frequently involved in central nervous system diseases; EV-A71 was detected in 43 and 30 patients with aseptic meningitis, respectively, in 2013 and 2017. If EV-A71 is detected when HFMD activity is high, attention should be paid to the occurrence of central nervous system diseases, including aseptic meningitis (see p. 94 of this issue).

In addition, the age distribution of cases with E-30, E-18, E-6, CV-B5, or EV-A71 detections reported through the Infectious Agents Surveillance System during 2012-2017, along with the proportion of these cases that were aseptic meningitis, are shown in Figure 4. These distributions differed by virus type. E-6 and E-30 were also detected in children and adults with meningitis, while CV-B5 and EV-A71 were detected mainly in young infants few months of age (IASR 38: 204-205, 2017).

Enteroviruses isolated or detected in patients diagnosed with aseptic meningitis between 2009 and 2017 were predominantly from CSF, feces, or throat swabs. For those with particularly high isolations/detections, namely E-6, E-18, E-30, and CV-B5 of the *Enterovirus B* family, CSF comprised 74-80% and feces 20-43% of the samples. In contrast, for aseptic meningitis patients from whom EV-A71 (belonging to the *Enterovirus A* family) was isolated/detected, 21% were from CSF and 63% from fecal samples. For aseptic meningitis, it is important to examine multiple samples, not only CSF, but also those such as feces and throat swabs. Recently, many enteroviruses have been identified from clinical samples by direct PCR detection and sequencing (see p. 98 of this issue).

Non-enterovirus aseptic meningitis-associated viruses (Figure 3, see pp. 94, 96, 97 & 99 of this issue): Non-enterovirus viruses detected in patients with aseptic meningitis included the mumps virus (12%), rhinovirus (5.8%), and parechovirus type 3 (2.4%) (% values indicated in parentheses for each virus represent the respective proportions among the total number of reported aseptic meningitis cases with isolations/detections of enteroviruses or the aforementioned viruses in 2009-2017, Table in p. 91). Rhinovirus was detected mostly from throat swabs, and the association with aseptic meningitis was unclear in many cases. Mumps meningitis occurred frequently during mumps epidemic years [IASR 37: 185-186, 2016; median age of 6 years (range, 2-36 years) for 35 verified mumps meningitis cases in 2016 reported from the designated sentinel sites]. Although mumps is a disease that can be prevented by vaccination, the mumps vaccination is voluntary in Japan, and the vaccination coverage is around 30% (according to the National Epidemiological Surveillance of Vaccine-preventable Diseases: https://www.niid.go.jp/niid/ja/y-graphs/7457-mumps-yosoku-vaccine2016.html), a level inadequate for the control of mumps.

Conclusions: Aseptic meningitis is an outbreak-prone disease, and identification of the pathogen is important because measures and precautions differ by pathogen. It is important to strengthen both patient-based surveillance and laboratory-based (pathogen) surveillance on a routine basis. Under the NESID system, all the designated sentinel sites are to conduct laboratory-based surveillance for aseptic meningitis. When an outbreak of meningitis is detected in a medical facility, active epidemiological investigation is warranted, based on the Infectious Diseases Control Law. It should be emphasized that CSF, feces and throat swab samples should be collected at an early stage of aseptic meningitis, in order to enable direct detection of pathogens (e.g. by PCR, isolation), and for neonates, blood samples should also be collected.

The statistics in this report are based on 1) the data concerning patients and laboratory findings obtained by the National Epidemiological Surveillance of Infectious Diseases undertaken in compliance with the Act on the Prevention of Infectious Diseases and Medical Care for Patients with Infectious Diseases, and 2) other data covering various aspects of infectious diseases. The prefectural and municipal health centers and public health institutes (PHIs), the Department of Environmental Health and Food Safety, the Ministry of Health, Labour and Welfare, and quarantine stations, have provided the above data.

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＜特集関連情報＞

北海道釧路保健所管内で発生したエコーウイルス30型による無菌性髄膜炎の多発事例について

2017年８～12月にかけて，北海道釧路保健所管内の定点医療機関から無菌性髄膜炎患者の報告が相次いだ。管内の小児科医から情報提供を受けた同保健所が主な医療機関の協力を得て調査した結果，95人の無菌性髄膜炎による入院患者を把握した。患者の性別は男性53人，女性42人であり，年齢中央値は16歳（範囲：0～61歳）で，世代の内訳は乳幼児が18人，小学生が25人，中学生・高校生が５人，19～29歳が15人，30～39歳が29人，40歳以上が３人であった（図１）。症状は発熱が63人，頭痛が56人，嘔吐・嘔気が43人，項部硬直などの髄膜刺激徴候が41人にみられた。小児の症例

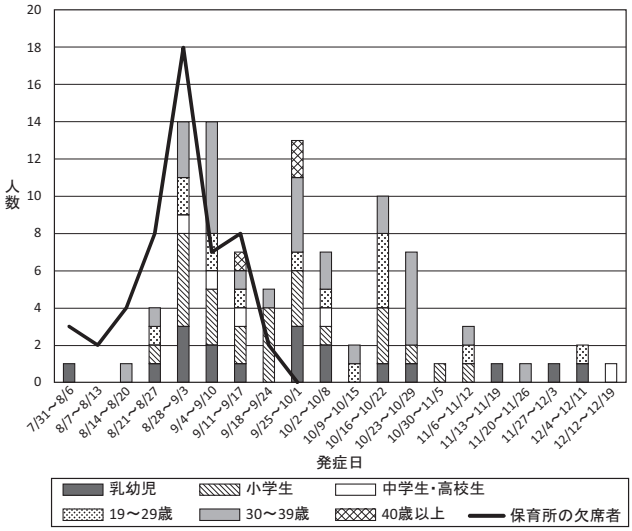

図1. 無菌性髄膜炎による入院患者の発症状況

（特集つづき）（THE TOPIC OF THIS MONTH-Continued）

表. 無菌性髄膜炎患者からのエンテロウイルス、ムンプスウイルスなど検出報告数，2009～2017年
Table. Number of enterovirus and mumps virus isolations/detections from aseptic meningitis cases, 2009-2017, Japan

型 Type	検体採取年 Year of specimen collection									合計 Total
	2009	2010	2011	2012	2013	2014	2015	2016	2017	
Enterovirus NT	17	11	33	20	23	18	9	7	2	140
Coxsackievirus A2	−	2	−	1	−	1	2	1	3	10
Coxsackievirus A4	−	2	1	2	−	4	−	3	−	12
Coxsackievirus A5	−	−	−	−	−	3	−	1	−	4
Coxsackievirus A6	1	2	7	−	12	1	4	3	11	41
Coxsackievirus A8	−	−	−	−	4	−	−	−	−	4
Coxsackievirus A9	13	3	6	34	4	5	42	3	9	119
Coxsackievirus A10	−	−	3	−	−	1	1	2	2	9
Coxsackievirus A14	−	−	−	−	2	−	−	1	−	3
Coxsackievirus A16	−	3	−	−	1	1	9	1	−	15
Coxsackievirus B1	5	18	82	2	15	5	1	11	2	141
Coxsackievirus B2	8	25	7	1	12	15	7	15	38	128
Coxsackievirus B3	19	3	3	2	70	12	9	33	1	152
Coxsackievirus B4	13	23	21	7	13	9	6	7	18	117
Coxsackievirus B5	2	2	50	41	42	29	30	146	2	344
Coxsackievirus B6	−	1	−	−	−	−	−	−	−	1
Echovirus 3	1	3	5	1	2	15	9	8	17	61
Echovirus 4	−	−	−	−	−	−	−	2	−	2
Echovirus 5	−	−	−	−	−	−	−	1	−	1
Echovirus 6	17	39	128	77	125	7	6	94	55	548
Echovirus 7	4	−	17	41	2	4	1	−	8	77
Echovirus 9	4	1	51	27	11	8	22	22	20	166
Echovirus 11	12	−	4	−	8	67	3	1	2	97
Echovirus 12	1	−	−	−	−	−	−	−	−	1
Echovirus 14	−	1	2	−	−	1	−	−	−	4
Echovirus 16	−	1	1	−	−	3	13	1	−	19
Echovirus 17	−	−	−	1	1	−	−	−	−	2
Echovirus 18	2	−	−	3	28	20	77	19	3	152
Echovirus 19	−	−	−	2	3	−	−	−	−	5
Echovirus 20	−	−	−	1	−	−	−	−	−	1
Echovirus 21	−	−	1	−	−	−	−	−	−	1
Echovirus 25	−	25	2	1	6	1	5	4	7	51
Echovirus 30	13	6	1	1	116	87	13	24	3	264
Echovirus 33	−	−	−	−	−	−	1	−	−	1
Poliovirus 1	1	−	−	−	−	−	−	−	−	1
Poliovirus 2	1	−	−	−	−	−	−	−	−	1
Poliovirus 3	1	−	−	−	−	−	−	−	−	1
Enterovirus D68	−	−	−	−	2	−	5	−	1	8
Enterovirus A71	4	61	−	9	43	5	−	1	30	153
Parechovirus NT	2	−	−	−	−	10	7	5	7	31
Parechovirus 1	2	1	1	3	1	5	6	3	3	25
Parechovirus 2	−	−	−	−	−	−	−	−	1	1
Parechovirus 3	−	1	3	−	1	38	−	33	13	89
Rhinovirus	3	12	14	14	23	25	44	44	33	212
Mumps virus	45	82	57	36	18	26	31	89	45	429
合計	191	328	500	327	588	426	363	585	336	3,644

NT: 未型別　　NT: Not typed
（病原微生物検出情報：2018年4月4日現在報告数）
[Infectious Agents Surveillance System: as of April 4, 2018 from prefectural and municipal public health institutes (PHIs)]