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National Institute of Infectious Diseases and
Tuberculosis and Infectious Diseases
Control Division,
Ministry of Health, Labour and Welfare

<THE TOPIC OF THIS MONTH>
Acute encephalitis in Japan, 2007-2018

The weekly number of acute encephalitis cases has been reported since April 1999 as a targeted disease monitored at designated sentinel sites according to the National Epidemiological Surveillance of Infectious Diseases (NESID) based on the Act on the Prevention of Infectious Diseases and Medical Care for Patients with Infectious Diseases (the Infectious Diseases Control Law). In November 2003, the law was revised, and acute encephalitis was included in notifiable disease surveillance due to the need for early detection of unknown diseases such as emerging diseases (IASR 28: 339-340, 2007). As of 2019, acute encephalitis, excluding West Nile encephalitis, Western equine encephalitis, tick-borne encephalitis, Eastern equine encephalitis, Japanese encephalitis, Venezuelan equine encephalitis, and Rift Valley fever, which are included in Category IV infectious diseases, all physicians are required to notify the local public health center within 7 days from diagnosis as a Category V infectious disease. The subjects of notification include acute encephalitis of unknown pathogen and cases presenting similar symptoms (hereinafter both referred to acute encephalitis). Cases that are obviously not infectious, such as febrile seizure, metabolic disease, cerebrovascular disorder, brain tumor, or trauma, are excluded. When notifiable disease surveillance of acute encephalitis began, if the original disease was a notification target, such as influenza encephalopathy or measles encephalitis, it was excluded from the report, but it became the subject of report from March 2004.

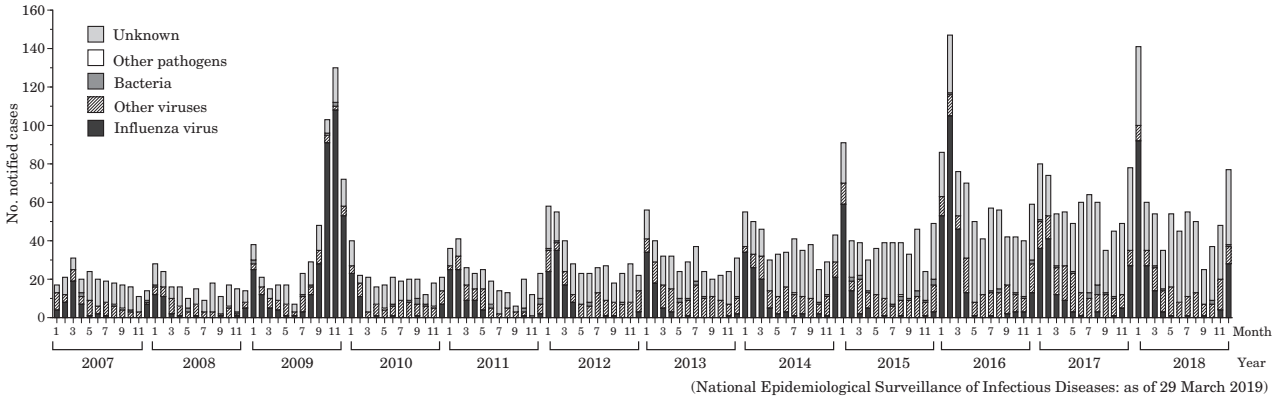
Annual and monthly incidence: In the 12 years from 2007 to 2018, 5,302 acute encephalitis cases were notified. Of those, 1,450 (27%) were influenza encephalopathy. The causative pathogens were: 1,127 (21%) virus other than influenza, 87 (2%) bacterial, 5 (0.1%) other pathogen than virus or bacterial, 2,633 (50%) unknown (Fig. 1). Many cases were notified in winter, being related to influenza encephalopathy. In 2009 during the pandemic of influenza A(H1N1)pdm09, more cases were notified than in the preceding and following years (520 cases, of which 343 were influenza encephalopathy). The notified number of acute encephalitis cases has increased each year since 2011, and approximately 700 cases have been notified each year for the last three years (766 in 2016, 703 in 2017, and 681 in 2018).

Gender and age distribution: The number of cases included slightly more males than females, 2,952 males and 2,350 females. One year olds were the most common (922 cases), and the median age was 5 years old (quartile range: age 1-13) (Fig. 2 in p. 94). Of these cases, 1,095 were in adults (20 years or older) and 400 (37%) were in their 60-70s.

Notifications by prefecture: Chiba prefecture had the most notifications, at 542 cases, followed by 513 in Tokyo, 405 in Osaka, 335 in Kanagawa, and 300 in Saitama. The fewest was 8 in Shimane prefecture, followed by 11 each in Tokushima and Kumamoto, 12 in Miyagi, and 14 in Tottori.

Investigation of pathogens: In November 2013, the Tuberculosis and Infectious Diseases Control Division of the Health Service Bureau in the Ministry of Health, Labour and Welfare requested prefectural and municipal public health institutes (PHIs) to carry out tests to detect pathogens as much as possible for cases of unknown pathogens among acute encephalitis cases notified by

Figure 1. Monthly number of notified acute encephalitis cases, 2007-2018, Japan



(National Epidemiological Surveillance of Infectious Diseases: as of 29 March 2019)

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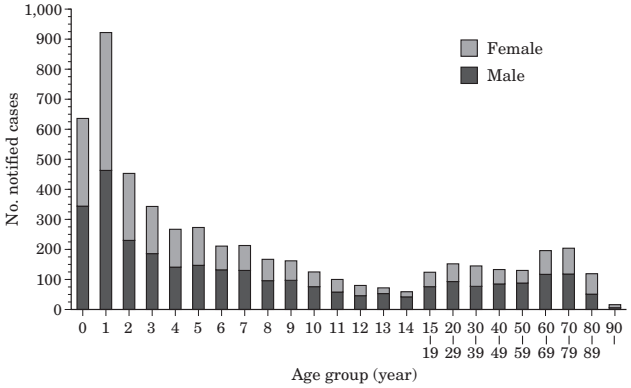
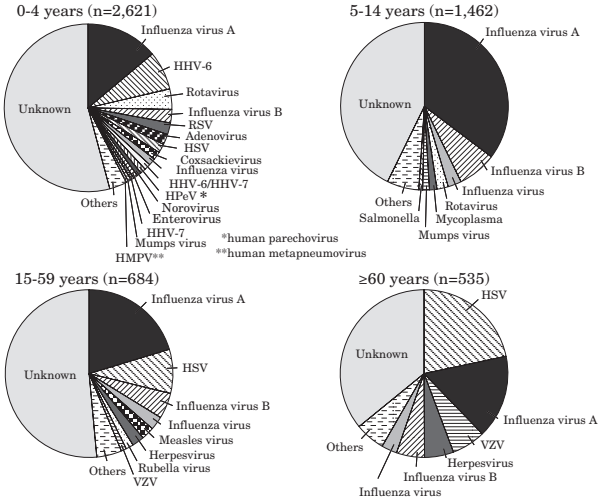
medical institutions based on the Infectious Diseases Control Law. Since then, active investigations by PHIs have been conducted (see pp. 95, 96, and 97 of this issue). If pathogens are not identified by testing or if testing at PHIs is judged as difficult, a research group funded by the Health and Labour Sciences Research Grant (represented by Dr. Keiko Tanaka-Taya), if requested, will conduct a comprehensive search for pathogens that may cause acute encephalitis, in addition to the tests for Japanese encephalitis and tick-borne encephalitis (see p. 100 of this issue). Spinal fluid, respiratory, stool, and blood samples in the early phases of onset (within a week) are of particular importance. If the investigation cannot be conducted immediately, the specimen should be subdivided and frozen in order to prevent freezing- thawing. Confirming a significant increase in antibody titers in acute and convalescent phase paired sera may be useful for estimation of the causative pathogen.

Figure 2. Age distribution of notified acute encephalitis cases by gender, 2007-2018, Japan



(National Epidemiological Surveillance of Infectious Diseases: as of 29 March 2019)

Figure 3. Detail of pathogens in acute encephalitis cases, 2007-2018, Japan



(National Epidemiological Surveillance of Infectious Diseases: as of 29 March 2019)

Notified pathogens: The suspected causative pathogens varied according to the age groups (Fig. 3). In all age groups, unknown pathogens were the most common. In the 0-4-year-old age group (2,621 cases), influenza A was the most common, followed by human herpesvirus 6 (HHV-6), rotavirus, influenza virus B, RS virus, adenovirus, herpes simplex virus (HSV), and coxsackie virus (CV). In the 5-14-year-old age group (1,462 cases), influenza virus A was the most common, followed by influenza virus B, influenza virus (not typed), rotavirus, mycoplasma, mumps virus, and *Salmonella species*. In the 15-59-year-old age group (684 cases), influenza virus A was the most common, followed by HSV, influenza virus B, influenza virus (not typed), measles virus, herpesvirus (not typed), rubella virus, and varicella-zoster virus (VZV). In the group over 60 years (535 cases), HSV was the most common, followed by influenza virus A, VZV, herpesvirus (not typed), influenza virus B, and influenza virus (not typed).

For details on each pathogen, refer to the special issue related articles: Influenza encephalopathy (see pp. 101 and 103 of this issue), HHV-6 encephalitis/encephalopathy (see p. 104 of this issue), HSV encephalitis (see p. 105 of this issue), enterovirus (EV) encephalitis (see p. 107 of this issue), and tick-borne encephalitis/Japanese encephalitis/Zika virus infection/West Nile fever, including West Nile encephalitis (see p. 100 of this issue).

Fatal cases: Of the 5,302 acute encephalitis cases notified during the 12 years from 2007 to 2018, the patients in 217 (10-31 cases/year) were dead at the time of notification, accounting for 4% of the total. Of these, 147 were in patients younger than 15 years old, and the pathogens were influenza virus A (51), influenza virus B (10), rotavirus (9), HHV-6 (4), influenza virus (not typed) (4), CV (CVA2, CVA6, CVB3, CV not typed) (4), RS virus (3), adenovirus (1), EV (1), mumps virus (1), coagulase negative *Staphylococci* (1), and unknown (58). Seventy fatal cases were in patients 15 years or older, and the pathogens were influenza virus A (24), influenza virus B (11), influenza virus (not typed) (6), HSV (3), VZV(1), Group A *Staphylococcus* (1), ESBL-producing *E. coli* (1), Enterohemorrhagic *E. coli* O157 (VT1&VT2) (1), *Rickettsia tsutsugamushi* (1), and unknown (21). Most deaths were reported at the time of notification, and it is estimated that there are more.

Conclusions: It has become well informed that notification of all cases of acute encephalitis is mandatory, and the number of notified cases is increasing year by year. However, approximately 1,600 to 1,700 cases are estimated to occur annually in Japan (see p. 96 of this issue), which suggests the existence of unrecognized cases. It is a severe disease with the possibility of death and sequelae, and early diagnosis and treatment are essential. Detection and identification of pathogens are important when considering treatment and prevention, and require sample collection in the acute phase. Furthermore, to evaluate the causative pathogens, it is necessary for the clinical and examination departments to share information (see pp. 95, 96, and 97 of this issue). The significance of acute encephalitis surveillance is further expected to increase by linking active pathogen surveillance with clinical and epidemiological information in collaboration with medical institutions, public health centers, PHIs, and NIID.

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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