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Epidemiological Report

**EPIDEMICS OF ASEPTIC MENINGITIS DUE TO ECHOVIRUS 30
IN JAPAN**

*A report of the National Epidemiological Surveillance of Infectious Agents in Japan**

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SUMMARY: Two rages of epidemic of aseptic meningitis (AM) due to echovirus 30 (E30) in Japan were analyzed with respect to two sources of information, AM incidence and E30 isolation, both gathered through the National Epidemiological Surveillance of Infectious Diseases. The first E30 epidemic spread throughout Japan in 1983 and ceased within the year. The second epidemic, starting in 1989, continued for the three successive years, and in the last year, 1991, the total E30 reports numbered 4,061, the largest number of a single virus type ever reported. Although the epidemic showed temporal and geographical shift and lasted for one

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or two years in some areas, most laboratories reported the largest number of E30 isolation in 1991. Among E30-yielding cases with clinical information during 1982-1992, the associating frequency with AM was as high as 82.5%. Other central nervous system involvements such as encephalitis, myelitis, encephalomyelitis and/or paralysis were reported in 36 E30-yielding cases and their monthly and age distributions were different from those of AM cases. The proportion of such disease among E30-yielding cases (0.60%) was close to that of other enteroviruses (0.56%). During the epidemics, E30 was isolated more frequently from cerebrospinal fluid than was E4 or E9 which prevailed coincidentally. E30 was most frequently isolated from cases of 4-7 years of age, sharing the common characteristic pattern of age distribution with other enteroviral meningitis. E30-yielding cases, however, involved a large number of older age groups than those of other enterovirus infections, and this tendency was the most pronounced in the first epidemic year, 1983. The contribution of these E30 epidemics on the yearly trend of clinically reported AM incidence and on the shift of its age distribution was also analyzed.

INTRODUCTION

Echovirus (E) 30 is known to be the enterovirus most highly associated with aseptic meningitis (AM) in children (1). A sudden and nation-wide AM epidemic due to E30 broke out in Japan in 1983, and E30 again caused a large AM epidemic in three successive years from 1989 to 1991. AM is an officially reportable disease in Japan and these two rages of AM epidemics caused by E30 were recorded by two distinct information sources, the incidence of AM patients (2) and virus isolation reports (3), both gathered under the program of the National Epidemiological Surveillance of Infectious Diseases (NESID).

The information of virus isolation in relation to the enteroviral AM during 1981-1991 in Japan was analyzed in the previous report in which various types of enterovirus were characterized as the major cause of AM in Japan (4). AM cases increased in summer to various degrees with an incidence peak usually in July. These seasonal and yearly trends of enterovirus isolation of the relevant types as a whole paralleled those of AM case reports, but the types of the virus isolates and their number varied from year to year. During the past 11 years from 1981 through 1991, more than 8,500 reports of enterovirus isolation from AM cases were furnished by participating laboratories throughout Japan. Eight enterovirus types were associated with the AM epidemics. They were coxsackievirus (C) types B3 and B5, and echovirus (E) types 4, 6, 7, 9, 18 and 30. Thus most of the

major enterovirus types known to have caused AM epidemics in the world (1) were prevalent in Japan during these 11 years. Among them, the recent E30 epidemic showed an exceptional epidemic feature of enteroviruses; it was prevalent for the three successive years from 1989 to 1991, in contrast to the fact that a sudden and explosive nation-wide epidemic due to an enterovirus in this country used to last for one year or, at most, within two years. In addition, the reports of E30 isolation in the last epidemic year, 1991, numbered more than 4,000, which was the largest number of yearly reports of a single virus type ever since the reporting system started in 1979. Also, its AM-associating frequency recorded the highest in the previous enterovirus reports.

In this study, we further analyzed in detail the data on E30 isolation in Japan during 1982-1992 in comparison with other enteroviruses. In addition, we estimated the effect of the E30 epidemics on AM incidence reports collected through NESID, since the incidence involves the overall effects of various enteroviruses, which cause clinically indistinguishable AM prevailing at the time. The reports of E30 isolation in this manuscript were collected before September 30, 1993, whereas those in the previous report (4) were before January 22, 1992. Therefore, the number of isolation for each year increased in this manuscript, especially for 1991 by 2.3 times of the figure previously obtained.

METHOD

The surveillance system: NESID in Japan gathers reports on infectious diseases through two distinct information sources; incidence reports from sentinel hospitals and clinics, and virus isolation reports from virus diagnostic laboratories including public health institutes (PHI). The Information Center for incidence is located in the Infectious Diseases Control Division, the Ministry of Health and Welfare. The virus isolation reports are collected by the Infectious Agents Surveillance Center in the National Institute of Health.

AM incidence: The information of incidence of AM was gathered from sentinel hospitals on a monthly basis (weekly until 1986) with information of the ages of cases. The designated hospitals were allocated in proportion to the population which each Health Center takes charge of. Their total number was 384 on average (284-466) until 1986, and thereafter 525 (511-546) in the whole country.

Laboratory information: Virus isolation reports gathered by this surveillance system collected exclusively the positive results of pathogen detection, without recording the number of specimens which failed to detect any pathogen.

An individual card (an optical mark record system) for one virus-positive case was provided. The reports were supplied by PHI in all 47 prefectures and 12 designated municipal areas. Certain national hospitals and commercial diagnostic laboratories collaborated by voluntarily reporting the information on isolation of viruses. They reported primarily the results of examinations conducted for diagnosis in the course of operating NESID, and also those on other diagnostic specimens, and, in addition, those derived from systematic studies at the institutions or from other surveillance project such as the National Epidemiological Surveillance of Vaccine Preventable Diseases.

Districts: Forty-seven prefectures in Japan were grouped into six geographical districts as defined in Fig. 1.

Fig. 1. Geographical districts for analysis. Forty-seven prefectures in Japan were grouped into six geographical districts.

RESULTS

Yearly Trend of E30 Isolation in Japan

The systematic records of enterovirus isolation in Japan have been available since 1963 (5). Although many enteroviruses were isolated every year from epidemics or sporadic cases, E30 had never appeared until 1978 when 11 isolates of E30 were reported for the first time in Japan. Of these, nine E30 were isolated during the period from June to August in Aichi PHI, located in District III; three were associated with AM, two with fever, one with diarrhea and the other three were from healthy children. The reports were followed by two reports of the isolation from nasopharyngeal specimens of cases with upper respiratory infection by Ishikawa PHI in the same district in September.

In the next year, 1979, when our reporting system started, three E30 were isolated in Ehime PHI, each one in May, July and August, followed by one in Hiroshima PHI in February, 1980 (both located in District V), but none was reported in 1981 (6). In 1982, however, nine E30 strains including four from cases of AM were reported from six PHI, followed by a nationwide epidemic of AM in 1983 (Table I). E30 isolation was reported from all six districts throughout Japan, total isolation numbering 615 in 1983. The epidemic ceased within the year, and E30 reports were only 66 in total from six PHIs from March to October in 1984. Afterwards until 1988, a few sporadic or local epidemic cases were reported from different areas.

The E30 reports suddenly increased in 1989 from laboratories of two districts in middle-west parts (Districts IV and V), came from many districts in 1990, and then dramatically increased in the whole country in 1991. Most laboratories except seven PHIs reported the most frequent E30 isolation per year in 1991; two in District II (Tochigi and Gunma) reported the largest number in 1990, three in Districts IV and V (Nara, Tottori and Tokushima) did so in 1989, one in District IV (Hiroshima City) did so in 1983, and another one in District IV (Ehime) did so in 1984. E30 disappeared from most prefectures in 1992. The reports of E30 isolation totaled 525 in 1989, 573 in 1990, 4,061 in 1991, and 63 in 1992. The annual E30 isolation in 1991 was the most frequent as that of a single virus type ever reported in this reporting system.

Monthly and Geographical Distribution of E30 Epidemic in Japan

E30 was most frequently isolated in the summer, that being the case in many other enteroviruses. From monthly reports in the national total of enterovirus isolation from AM cases, the peak of the E30 reports in 1983 was in July (data not shown) and that in 1989 in August (Fig. 2A). In 1990, however, the number of E30 isolation formed a broad peak from June to October. Then it kept relatively a high level during the winter and even after the next January, but increased abruptly in June, 1991, and formed a sharp peak in July, numbering 890 from AM cases (1,204 in total isolation) per month. More than 452 reports from AM cases (more than 600 in total) of E30 isolation per month continued through October.

These monthly patterns of E30 isolation in the two epidemics were analyzed separately by district, together with the AM incidence data collected through NESID (Fig. 2B and Table I). For analysis, the district data of E30 isolation were expressed as the sum of prefectural reports and that of case incidence as the quotient of the number of case reports divided by the total number of sentinel hospitals in each district according to the grouping of Fig. 1.

The first isolation of E30 in Japan was five years before the 1983 epidemic, which appeared in the central part of the country, District III. In the following four years, a few reports of isolation scattering in other districts were sent in (Table I). The epidemic in 1983 showed a single peak in all districts in the summer (data not shown) and ceased within the year.

The second rage of E30 epidemic continued for three successive years in this country as shown in Fig. 2A. The spreading pattern of the epidemic during the three epidemic years, however, was not uniform among different districts. In the early months of 1989, the first year of the epidemic, E30 appeared in District V, and then spread within District V and to neighboring District VI in a small extent during the summer. No other district experienced the E30 infections in 1989, though AM cases due to other enteroviruses were reported. In the latter half of 1990, the second year of the rage, E30 further spread to Districts III and II and appeared in District I at the end of the year. This low-level but steady circulation continued to the early half of 1991, the third year of the epidemic, and was followed by an extraordinarily large epidemic throughout the country. Most of the AM incidence curves and peaks coincided with the frequency of E30 isolation. The virus isolation frequency reduced in the next year; most districts reported isolation from only 1-37 cases in 1992 (Table I).

Fig. 2. Monthly reports of aseptic meningitis cases and isolation of E30 and other enteroviruses from them collected through NESID, 1989-1991. The solid line shows aseptic meningitis cases per sentinel hospital. The black bar indicates E30 isolation from aseptic meningitis cases. The empty bar indicates other enterovirus isolation from aseptic meningitis cases. (A) The whole country. (B) By the district defined in Fig. 1.

Table I. Isolation of echovirus 30, by year and participating laboratory, 1982-1992

District	Laboratory*	Year											Total
		1982	1983	1984	1985	1986	1987	1988	1989	1990	1991	1992	
I	Hokkaido P.	-	5	-	-	-	-	-	-	-	11	-	16
	Sapporo C.	-	-	-	-	-	-	-	-	-	6	-	6
	Aomori P.	-	1	-	-	-	-	-	-	7	25	-	33
	Sendai NHVRC	-	-	-	-	-	-	-	-	-	37	-	37
	Akita P.	-	7	-	-	-	-	-	-	1	70	-	78
	Yamagata P.	-	4	-	-	-	-	-	-	-	50	-	54
	Fukushima P.	-	-	-	-	100	-	-	-	-	117	-	217
II	Ibaraki P.	-	-	-	-	-	-	-	-	-	31	-	31
	Tochigi P.	-	-	-	-	-	-	-	-	18	11	-	29
	Gunma P.	-	2	-	-	-	-	-	-	110	25	2	139
	Saitama P.	-	6	-	-	-	-	-	-	22	63	-	91
	Chiba P.	-	12	-	-	-	-	-	-	-	52	-	64
	Tokyo M.	-	1	-	-	-	-	-	-	6	127	-	134
	Kanagawa P.	1	21	-	-	-	-	-	-	9	25	-	56
	Yokohama C.	-	5	-	-	-	-	-	-	-	16	-	21
	Kawasaki C.	-	-	-	-	-	-	-	-	6	113	-	119
	Yamanashi P.	-	-	-	-	-	-	-	-	-	22	-	22
	Nagano P.	-	1	-	-	-	-	-	-	14	74	14	103
III	Niigata P.	-	1	-	-	-	-	-	-	-	231	-	232
	Toyama P.	-	-	-	-	1	-	-	-	-	60	-	61
	Ishikawa P.	-	-	-	-	-	-	-	-	14	94	1	109
	Fukui P.	-	17	-	-	-	-	-	-	13	83	-	113
	Gifu P.	-	60	-	-	-	-	2	-	8	81	-	151
	Shizuoka P.	-	6	-	-	-	-	-	3	-	101	-	110
	Aichi P.	-	27	11	1	1	-	-	1	3	164	-	208
	Nagoya C.	-	46	-	-	-	-	-	-	22	135	-	203
IV	Mie P.	-	39	-	-	-	-	-	-	19	149	-	207
	Shiga P.	1	8	-	-	-	-	-	1	24	142	-	176
	Kyoto P.	-	-	-	-	-	-	-	1	-	30	-	31
	Kyoto C.	1	1	-	-	-	-	-	7	2	8	-	19
	Kyoto NHVRC	1	-	-	-	-	-	-	1	-	-	-	2
	Osaka P.	-	-	2	-	-	7	-	1	-	171	-	181
	Osaka C.	-	-	1	-	-	-	1	3	2	41	-	48
	Kobe C.	-	-	-	-	-	-	-	-	5	57	-	62
	Amagasaki C.	-	-	-	-	-	-	-	3	3	52	-	58
	Nara P.	-	5	-	-	-	-	-	62	-	39	1	107
	Wakayama P.	-	-	-	-	-	-	-	2	-	108	1	111
V	Tottori P.	3	24	5	-	-	-	-	277	9	118	17	453
	Shimane P.	-	30	-	-	-	-	-	14	4	74	-	122
	Okayama P.	-	5	-	-	-	3	-	1	21	61	-	91
	Hiroshima P.	-	38	-	-	-	-	-	18	40	87	-	183
	Hiroshima C.	-	178	1	-	-	-	-	17	49	52	-	297
	Yamaguchi P.	-	22	-	-	-	-	-	-	-	-	-	22
	Tokushima P.	-	1	-	-	-	-	7	36	-	13	-	57
	Kagawa P.	-	-	-	-	-	-	-	59	-	122	20	201
	Ehime P.	-	3	46	-	-	-	-	3	16	7	-	75
	Kochi P.	-	1	-	-	-	-	2	-	-	21	-	24
VI	Fukuoka P.	2	4	-	-	-	-	-	-	23	40	1	70
	Fukuoka C.	-	-	-	-	-	-	-	-	3	17	-	20
	Kitakyushu C.	-	-	-	-	-	-	-	-	8	3	-	11
	Saga P.	-	-	-	-	-	-	-	-	-	-	3	3
	Nagasaki P.	-	-	-	-	-	-	-	15	13	17	-	45
	Kumamoto P.	-	33	-	-	-	-	-	-	2	85	-	120
	Oita P.	-	-	-	-	-	-	-	-	23	128	-	151
	Miyazaki P.	-	1	-	-	-	-	-	-	-	21	-	22
	Kagoshima P.	-	-	-	-	-	-	-	-	1	26	-	27
CDL		-	-	-	-	-	-	-	-	53	548	3	604
Total		9	615	66	1	102	10	12	525	573	4,061	63	6,037

*P. : Prefecture; C. : City; and M. : Metropolitan Public Health Institute
 NHVRC: National Hospital Virus Research Center; CDL: Commercial diagnostic laboratory
 (Based on the data received before September 30, 1993)

The geographical analysis explained that the virus circulated throughout the country during the preceding two seasons, and then built up a nation-wide epidemic in 1991, or that the virus continued to spread to somewhere in this country during the three years, even though each district or prefecture had a two- or only one-year epidemic of E30. The AM incidence curves in the areas without circulation of E30 in the years showed the involvement of AM cases due to other enteroviruses (Fig. 2B); prevalence of AM due to E4 in 1989 and E9 in 1990-91 were reported (3). In addition, increasing number of mumps, caused by the virus highly associated with AM, was reported in 1983 (2), when the first E30 epidemic occurred.

Clinical Symptoms of E30-yielding Cases

E30 was the type of enterovirus most frequently associated with AM in Japan (4). Of the cases yielding E30 with reports of clinical symptoms during 1982-1992, 82.5% in total were associated with AM and the yearly highest ratio was 84.1% in 1991 (Table II). Other major symptoms reported were fever, gastrointestinal and upper respiratory disorders representing 70.1%, 25.5% and 18.6%, respectively, of the total of E30-yielding cases from 1982 to 1992. A total of 137 cases (2.5%) were among healthy children indicating the presence of inapparent infection among communities, even though the rate was no doubt an underestimate as it came from the results of tests done for only a small fraction of asymptomatic population.

During this period, 35 cases yielding E30 were reported to have central nervous system (CNS) involvement other than AM; nine cases were myelitis, other eight encephalitis, and the other 18 not specified as encephalomyelitis, myelitis or encephalitis. Of these, three cases were reported to have paralysis. In addition, another one was reported to have meningitis and paralysis.

To compare the association with such CNS diseases between E30 and other enterovirus infections, the frequency of the CNS diseases other than AM, involving encephalitis, myelitis, encephalomyelitis and paralysis, are summarized in Table III. During 1982-1992, a total of 197 reports of isolation of enterovirus were from cases with these CNS diseases. The number accounted for 0.57% of the all enterovirus reports during the study period. These cases were sporadically reported every year in a range from 12 to 26 cases by 42 participating laboratories each having one to 25 cases. Twenty-nine enterovirus types were involved; nine

Table II. Symptoms of cases yielding echovirus 30, 1982-1992

	Number of cases (%)								Total
	1982	1983	1984-88	1989	1990	1991	1992		
Total reports	9	615	191	525	573	4,061	63	6,037	
Reports with clinical information	8 (100)	610 (100.0)	191 (100.0)	470 (100.0)	527 (100.0)	3,572 (100.0)	59 (100.0)	5,437 (100.0)	
No illness	1 (13)	32 (5.2)	3 (1.6)	-	33 (6.3)	68 (1.9)	-	137 (2.5)	
Reports of indicated symptom*									
Meningitis	4 (50)	478 (78.4)	154 (80.6)	388 (82.6)	416 (78.9)	3,005 (84.1)	38 (64.4)	4,483 (82.5)	
Encephalitis/myelitis/enchephalomyelitis	-	3 (0.5)	3 (1.6)	1 (0.2)	6 (1.1)	21 (0.6)	1 (1.7)	35 (0.6)	
Paralysis	-	2 (0.3)	1 (0.5)	-	-	1 (0.0)	-	4 (0.1)	
Fever	7 (88)	350 (57.4)	153 (80.1)	374 (79.6)	384 (72.9)	2,505 (70.1)	37 (62.7)	3,810 (70.1)	
Upper respiratory illness	5 (63)	108 (17.7)	55 (28.8)	179 (38.1)	86 (16.3)	570 (16.0)	11 (18.6)	1,014 (18.6)	
Lower respiratory illness/pneumonia	-	16 (2.6)	-	16 (3.4)	6 (1.1)	24 (0.7)	1 (1.7)	63 (1.2)	
Gastrointestinal disease	4 (50)	93 (15.2)	90 (47.1)	235 (50.0)	166 (31.5)	784 (21.9)	13 (22.0)	1,385 (25.5)	
Eruption/Vesicle	2 (25)	8 (1.3)	4 (2.1)	10 (2.1)	12 (2.3)	60 (1.7)	3 (5.1)	96 (1.8)	

*Multiple reports in some cases

Table III. Isolation of enteroviruses* from cases with encephalitis, myelitis, encephalomyelitis and/or paralysis, 1982-1992

Virus	Total (A)	Age in years												Sex		Isolation from				Overall isolation (B)**	A/B (%)
		0	1	2	3	4	5	6	7	8	9	10-14	15≤	UK	M	F	CSF	FC	NS		
Total	197**	22	23	18	16	26	12	19	12	10	6	16	12	5	110	86	97	74	64	34,759	0.57
E30	36**	2	2	2	3	5	4	1	1	1	2	4	3	2	22	13	21	14	12	6,037	0.60
CA 9	8	3	-	-	1	1	-	-	1	1	-	1	1	-	7	1	3	3	4	967	0.82
Other CA	16	2	3	3	2	2	-	-	1	1	-	-	1	1	9	7	2	9	7	9,398	0.17
CB 2	15	3	1	-	-	3	-	1	-	-	2	3	2	-	12	3	9	4	7	1,121	1.34
CB 3	10	-	2	2	-	1	-	1	1	1	-	2	1	-	5	5	4	5	2	1,813	0.52
CB 5	14	1	1	1	-	2	1	1	2	-	2	1	2	-	3	11	7	4	4	1,876	0.75
Other CB	7	-	-	-	-	1	1	3	1	1	-	-	-	-	2	5	4	1	2	2,452	0.29
E6	8	1	2	-	-	1	1	2	-	1	-	-	-	-	6	2	4	1	3	1,334	0.60
E7	10	2	1	3	1	1	-	-	1	1	-	-	-	-	4	6	4	8	2	1,758	0.57
E9	16	2	2	2	1	3	-	2	2	2	-	-	-	-	7	9	12	8	5	1,813	0.88
E11	16	2	2	1	2	1	1	1	3	1	-	1	1	-	9	7	8	6	3	1,004	1.59
E18	7	1	-	-	-	1	1	2	-	-	-	-	1	1	3	4	4	3	-	1,228	0.57
E24	12	-	2	1	3	2	1	1	-	-	-	2	-	-	6	6	8	1	4	437	2.75
Other E	13	2	4	1	-	2	1	2	-	-	-	1	-	-	7	6	3	7	3	1,990	0.65
EV71	9	1	1	2	3	-	-	-	-	-	-	1	-	1	8	1	4	-	6	1,531	0.59

*Excluding poliovirus, **Including a case of unknown sex

***Number of overall isolation includes that from cases with no CNS symptoms.

UK: Unknown, CSF: Cerebrospinal fluid, FC: Feces, NS: Nasopharyngeal specimen

CA: coxsackievirus group A, CB: coxsackievirus group B, E: echovirus, EV: enterovirus

Other CA includes CA1 (1 case), CA2 (1), CA3 (1), CA4 (2), CA5 (1), CA6 (4), CA10 (4), and CA16 (2).

Other CB includes CB1 (3 cases) and CB4 (4).

Other E includes E3 (1 case), E5 (3), E14 (2), E16 (1), E21 (2), E22 (2), and E25 (2).

CA, five CB, and 14 echovirus types and enterovirus type 71. E30 was the most frequent type in number (36 cases) but its percentage to the total E30 reports (0.60%) was close to the average for other enteroviruses (0.56%).

Although the virus types rather frequently reported with these CNS diseases were those of the highly AM-associated enteroviruses, the age distribution of these CNS disease-related cases was not similar to that of AM cases; they scattered in a wide range of ages, contrasting to the peak age of 4-7 years in AM cases yielding E30 or most of other enteroviruses. In addition, no seasonal trend was seen in these CNS-related cases; CNS diseases occurred even in the winter (data not shown) when AM incidence due to enteroviruses became low.

During the study period, seven reports of enterovirus isolation were sent in from other CNS diseases than those mentioned above; four from encephalopathy (one each of E11, CA16, CB4 and A9) and the other three from ataxia (one each of E6, CA9 and E16), but no E30 was isolated in relation to these diseases.

Specimens for E30 Isolation

Table IV shows the results of isolation of E30, E9, and E4 from various specimens of AM cases. Among AM cases yielding E30, the virus was isolated from cerebrospinal fluid (CSF) in 58.2% in 1983 and in 65.2% in 1989-1991. These figures were extremely high as compared with two highly AM-associated enterovirus types, E9 (40.5%) and E4 (19.3%). Since these percentages for E4 and E9 were deduced from the data obtained during concurrent epidemics with E30 in 1989 and in 1990-1991, respectively, the results indicate that the virus isolation from CSF tended to be more frequent in E30-related AM cases than in those associated with such other viruses as E4 and E9 at least during the epidemic years under the study.

As the frequency of virus-positive specimens depends on the number of specimens tested, lower percentages of E30 isolation from other specimens than CSF probably resulted from preferential testing of CSF in some laboratories during epidemics; no other specimens may have been tested if CSF was positive in isolation, because virus isolation from CSF is considered to be the most reliable etiological diagnosis of AM. This seems to be suggested by the high percentage of singly CSF-positive cases shown in Table IV.

Age Distribution of AM Cases Yielding E30

Figure 3 shows the age distribution of E30--yielding cases with AM, together with that of AM cases yielding E4 or E9, the highly AM-associated entero-

Table IV. Isolation of echovirus 30, 9, and 4 from aseptic meningitis cases by source of specimens

Source	Number of cases (%)				
	E30			E9	E4
	1983	1984-88	1989-91	1989-91	1989
Cerebrospinal fluid (C)	278 (58.2)	47 (30.5)	2,485 (65.2)	157 (40.5)	34 (19.3)
Feces (F)	169 (35.4)	96 (62.3)	1,465 (38.5)	180 (46.4)	63 (35.8)
Nasopharynx (N)	143 (29.9)	78 (50.6)	1,511 (39.7)	201 (51.8)	102 (58.0)
Others	-	-	6	1	-
Total	478 (100.0)	154 (100.0)	3,809 (100.0)	388 (100.0)	176 (100.0)
A single or multiple specimens					
C only	211 (44.1)	27 (17.5)	1,575 (41.3)	93 (24.0)	32 (18.2)
C + F	17 (3.6)	4 (2.6)	204 (5.4)	18 (4.6)	1 (0.6)
C + N	40 (8.4)	2 (1.3)	324 (8.5)	19 (4.9)	-
C + F + N	10 (2.1)	14 (9.1)	382 (10.0)	27 (7.0)	1 (0.6)
F only	107 (22.4)	45 (29.2)	519 (13.6)	75 (19.3)	41 (23.3)
N only	58 (12.1)	29 (18.8)	445 (11.7)	95 (24.5)	81 (46.0)
F + N	35 (7.3)	33 (21.4)	360 (9.5)	60 (15.5)	20 (11.4)

viruses (4) coincidentally prevailed with E30 in 1989 and 1990/1991, respectively. Although the proportions in age distribution slightly changed when the total isolation reports including other than AM were count, the same tendency and patterns are seen in both data.

In every epidemic year, E30 was most frequently isolated from children aged from 4 to 7 years accounting for from 42.7% to 62.8% of all the E30-yielding cases with AM. The highest proportion of this age group among AM cases was commonly shown for E4 (50.8%) and E9 (52.1-56.4%), and also reported in other enterovirus infections (4,7).

The proportion of elder children and adults was higher in 1983 than the later E30 epidemic years; E30 isolation from cases of 8 years or more of age accounted for 34.4% in 1983, as compared with 19.1-23.0% in 1989-1991 ($p < 0.05$). The latter percentages of 8-year-old or older cases were almost comparable to that of E4 (22.3%) in 1989 and much higher than that of E9 (14.6-17.3%) in 1990-1992.

In contrast to the fact that a high frequency of isolation from infants was shown in some enteroviral epidemics, E30 was the type infrequently reported from infants (4), sharing the same pattern with E4 and E9 in Fig. 3. In 1991, however, analysis of E30 reports from infants showed increased isolation from neonates as compared with the preceding epidemic seasons; the reports in 1991

Fig. 3. Age distribution of AM cases yielding E30, E4 or E9, 1983-1992.

from infants less than 12 months of age numbered 286 (7.3% of the total E30 isolation), of which those from the cases aged under 3 months were 203, including 105 from newborns, 71 from one-month old and 27 from two-months old. The proportion of cases of less than 3 months of age (5.2% of the total E30 isolation) was significantly higher than 3.1% in 1983, 1.1% in 1989, and 2.7% in 1990 ($p < 0.05$). Increased E30 infection in neonates in 1991 seemed to be an effect of the large epidemic of E30, which widely spread among the community involving child-bearing ages and also nosocomially infected cases (8,9).

The Explanation of the Effect of E30 Epidemic on the Age Distribution of AM Incidence

The AM incidence report of NESID consists of the sum of AM cases caused by many types of enterovirus, for which the frequency of association with AM is different depending upon the type and the prevalent types and their proportions vary from year to year.

Fig. 4. Age distribution of clinically diagnosed aseptic meningitis cases, 1982-1992.

As shown in Fig. 4, the proportion of AM cases aged 5 years or more was higher in 1983 and 1991 than other years ($p < 0.05$). Since these years were of E30-epidemics when the proportion of the elder age groups was higher in E30 isolation reports than isolation of other enteroviruses as shown in Fig. 3, E30 infection must have been the most likely reason for the increased AM cases among elder children. The proportion of E30 to causative agents isolated from AM cases was 89% in 1991 and 66% in 1983 (Fig. 4). In 1989 and 1990, however, the proportions were 39% and 42%, respectively; the higher association of E30 in elder ages may have been diluted with concurrent AM cases due to other virus infection.

DISCUSSION

E30 was one of the most frequently reported types of enteroviruses through the WHO virus-reporting system during the 8-year period from 1967 to 1974 (10). Our findings in Japan on the behavior and pattern of E30 epidemics coincided with the data of WHO (1,10) in the high frequency of association with AM cases,

recurrent epidemic at a longer time intervals causing a larger epidemic than endemically circulating enteroviruses, and an increased proportion of infection in older age groups. The evidence seems to indicate a possible inherent characteristic of E30 infection.

The analysis of the data collected by NESID shows two rages of E30 epidemic in Japan; the first rage spread throughout the country in 1983 and ceased within the year, and the second rage, starting after an interval of six years from the first one spread more slowly but obviously for three summer seasons reaching an extra large epidemic in the last year, 1991, when the reports of E30 isolation became the largest number in all districts. On the local basis, however, the epidemic shifted temporarily and geographically and E30 isolation was limited to one or two seasons in some prefectures and areas as reported by others (11,12). These patterns, evidenced by information from each prefecture, indicate a critical role of the local surveillance activity for analysis of viruses actually prevailing in the community.

It has remained to be explained why the rage of E30 first introduced ceased within one year, whereas the second rage lasted for three successive years reaching an extra large epidemic throughout the country. No E30 prevalence was demonstrated for more than 20 years before its first rage in 1983 by virus isolation reports (5); further, seroepidemiological study indicated accumulation of susceptible population to E30 infection (13).

It is interesting that E30 infection and AM epidemics due to the virus coincidentally increased also in the WHO reports and in USA. E30 reports have been increasing since 1977 in virus-report system (1), and elevated frequency of E30 isolation was reported in USA in 1981 and 1982, when E30 was the most or the second most frequently reported nonpolio enterovirus accounting for 19.9% and 16.9% of the yearly isolation (14). In USA, an increased activity of E30 was again reported in 1990 and 1991 (15). It remains to find whether the simultaneous prevalence of E30 both in Japan and in USA reflects any link between the two countries.

It should be noted that our reporting system collects only the virus-positive results and that the most common form of enterovirus infection is asymptomatic or only no more than minor malaise. Although E30 was most frequently isolated from children of 4-7 years of age, the data no doubt reflect selectively high association of these ages with AM as seen in other enteroviruses. A similarly high frequency of E30 infection among younger ages was shown by seroepidemiological studies (16-18).

Isolation of E30 from CSF was more frequently reported than that of other enteroviruses, when compared with E4- and E9-associated AM cases. Manifestation of severe meningitis in CSF (increased leukocytes and protein concentration) was indicated (19). On the other hand, more frequent reports of E30 isolation from CSF than other specimens seem most likely to have been due to biased testings; it is conceivable that under the circumstances of a large epidemic, CSF is the first choice of specimen, making other specimens tested less frequently in some laboratories because of their limited capacity. More frequent E30 isolation from feces or throat swabs than CSF of AM cases was reported in parallel testings of all specimens of patients (12,19).

In general, the number of laboratory reports is influenced by the activity and priority of the laboratory. It seems, however, that enterovirus surveillance is being steadily made in most laboratories in Japan in recent years, as recent introduction (after the 1983 epidemic) of RD-18S cells (20), which are highly susceptible to E30 growth (21), may have improved the efficiency of E30 isolation in some laboratories.

During the study period from 1982 to 1992, E30 infection was most frequently associated with not only AM but also other CNS involvement, numbering 36 cases. The proportion of CNS diseases-related isolation among the total E30 isolation, however, was close to the average value of other enteroviruses. Therefore, it seems to reflect the extra large prevalence of the virus causing remarkably large involvement of infection among the community. The seasonal prevalence of these CNS diseases or the age distribution of the cases were not similar to those of AM.

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