

## Two Incidences of Epidemic of Aseptic Meningitis and Summer Febrile Illness Occurred in Omura City, Nagasaki, Japan in 1974.

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**ABSTRACT:** It was noted that two epidemic incidences of aseptic meningitis among infants and summer febrile illness among babies were occurred in the same period in summer and in the limited area in Omura city, Nagasaki, in 1974. The outbreak of these incidences seemed to be considered the age dependency. In these incidences, the virus isolation was performed from 92 specimens in total of cerebrospinal fluids, throat washings and feces. Seventy-seven isolates were obtained from them and identified as Coxsackie virus B3. It was considered that the virus must have been disseminated all over the Japan islands since 1970.

It is well known that Coxsackie viruses are capable of manifestations as encephalitis, pericarditis, myocarditis in newborns and aseptic meningitis, herpangina, exanthema, respiratory illness in infants. Most common usually escapes clinical recognition or the mild infection.

There are numbers of reports, however, presenting epidemic or sporadic incidences of aseptic meningitis and febrile illness caused by Coxsackie viruses, particularly group B viruses in Japan since 1965. In Omura city, Nagasaki prefecture, these two types of epidemic caused by Coxsackie virus B 3 among children and babies occurred at the same period in summer, 1974. The outbreak of these incidences seems to be considered the age dependency. In this paper, the clinical and virological investigations on these incidences will be presented.

### MATERIALS AND METHODS

#### Virus isolation

Throat washings and feces were suspended with Hanks solution contained 1,000u per

ml of penicillin and 1,000 $\gamma$  per ml of streptomycine. These specimens and also cerebrospinal fluids were stored  $-75^{\circ}\text{C}$  before use. When the specimens were inoculated into monolayers of HeLa cell culture maintained with Eagle's medium contained 2 % calf serum, they were thawed and centrifuged at 9,000  $g$  for one hour at  $4^{\circ}\text{C}$ . The supernatant and cerebrospinal fluids themselves were used for the virus isolation. The cultures inoculated the specimens were observed daily for a week and all of them were reinoculated into fresh monolayers of HeLa cells without the consequence of cytopathic effect (CPE). After the reinoculation of three times, the specimens indicated no sign of CPE in the HeLa cell culture were excepted from the virus isolation. The isolates were identified with the neutralization test using the standard antiserum of rabbit given from the National Institute of Health, Japan, and the Institute for Poliovirus Research, Tokyo, Japan.

Serological examination

The complement fixation test on paired sera of patients and the neutralization test on the sera obtained from children in various ages before epidemic were carried out using a strain of isolates.

RESULTS

The incidences of aseptic meningitis and summer febrile illness distinguished from clinical signs were occurred in the same period in Omura city, Nagasaki prefecture, in summer, 1974.

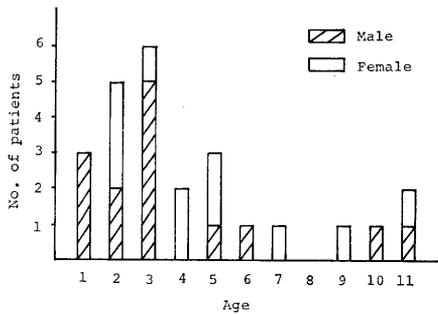


Fig. 1. Age and sex distribution in the epidemic of aseptic meningitis occurred in Omura city, 1974.

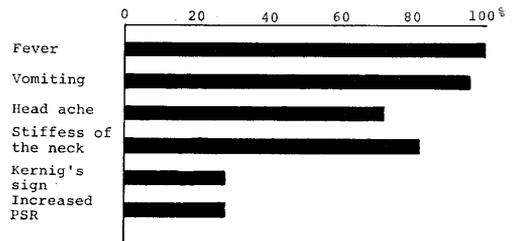


Fig. 2. Clinical findings of the patients in the epidemic of aseptic meningitis.

Incidence of aseptic meningitis

Twenty-five cases as aseptic meningitis were investigated from 22th June to 26th August, 1974. Ages of the patients distributed from 1 to 11 years old and the most of them occurred in July and concentrated in 2 and 3 years old (Fig. 1 and Table 1 ). The clinical pictures in the most of cases showed fever, vomiting, head ache and stiffness of the neck associated with the sign of meningeal irritation. No cases showing the symptoms of cough, pharyngeal inflammation and diarrhae were observed in this epidemic (Fig.2). So far as the clinical examination of cerebrospinal fluids and electroencephalogram are

concerned, the cells in the fluids had increased in number from 101/3 cells to 500/3 cells per mm<sup>3</sup> at the proportion of 60% of all cases and 2 cases of them indicated more than 1000/3 cells per mm<sup>3</sup>. Three of 22 cases showed the abnormal S-P wave complex.

#### Virus isolation

Twelve isolates from 24 specimens of cerebrospinal fluids 14 isolates from 22 specimens of throat washings and 21 isolates from 23 specimens of feces were obtained. All of the isolates were identified as Coxsackie virus B 3 with neutralization test using the standard antiserum as presented in the methods. The antibodies rising more than 4 times against a strain of isolates were observed in 14 of 25 cases. However, the virus isolation from the specimens of 2 cases of them was not be able to make successfully (Table 1, Table 3).

Table 1. Outbreak of aseptic meningitis and virus isolation from patients and their clinical findings

No	Name	Age	Sex	Onset of illness	Virus isolation			CF titer		Max. temp.	Duration (days)	Signs			Symptoms
					CSF	T	F	Ac	Co			N	K	P	
1	N.M	1	M	22/Jun	+	NT	+	8	256	38.0	4	+	-	-	Fev Hea Vom
2	H.Y	3	M	24/Jun	+	NT	+	<4	16	39.1	8	+	-	-	Fev Vom
3	Y.H	3	M	25/Jun	-	NT	NT	16	32	39.2	3	+	+	-	Fev Hea Vom
4	A.H	6	M	27/Jun	-	+	+	32	128	38.2	4	+	+	+	Fev Hea Vom
5	I.M	11	F	28/Jun	-	-	+	4	64	37.8	2	+	+	-	Fev Hea Vom
6	H.M	2	F	28/Jun	+	+	+	<4	4	38.2	6	+	-	+	Fev Vom
7	N.H	3	M	29/Jul	+	+	+	NT	<4	38.4	8	-	-	-	Fev Hea
8	M.Y	3	M	1/Jul	-	+	+	16	4	39.0	5	-	-	-	Fev Hea Vom
9	M.K	5	F	1/Jul	+	+	+	<4	64	38.5	3	+	-	-	Fev Hea Vom
10	T.H	11	M	5/Jul	-	-	+	<4	128	39.5	5	+	+	-	Fev Hea Vom
11	M.A	4	F	17/Jul	-	+	+	4	64	37.5	3	+	-	-	Fev Hea Vom
12	O.A	4	F	17/Jul	-	+	+	<4	32	38.6	5	-	-	-	Fev Hea Vom
13	K.K	2	M	18/Jul	+	+	+	8	16	38.7	5	+	-	-	Fev Vom
14	Y.K	5	F	19/Jul	+	+	+	<4	64	39.2	5	+	-	+	Fev Hea Vom
15	S.K	5	M	26/Jul	+	+	+	<4	<4	39.6	3	+	+	+	Fev Hea Vom
16	D.M	7	F	27/Jul	+	+	+	16	128	39.4	2	-	-	-	Fev Hea Vom
17	A.T	3	F	28/Jul	NT	+	NT	16	32	39.5	6	+	-	-	Fev Hea Vom
18	Y.N	9	F	28/Jul	-	-	+	16	16	39.4	4	+	+	+	Fev Hea Vom
19	H.T	10	M	31/Jul	-	-	-	<4	16	37.4	2	+	+	-	Fev Hea Vom
20	O.M	2	F	1/Aug	-	-	+	<4	16	39.4	2	+	-	+	Fev Vom
21	S.K	1	M	6/Aug	-	-	-	32	128	38.9	5	+	-	-	Fev Hea Vom
22	N.T	2	F	6/Aug	+	-	+	64	32	38.4	4	+	-	+	Fev Vom
23	N.S	1	M	11/Aug	+	+	+	<4	16	39.8	4	+	-	-	Fev Vom
24	M.Y	3	M	18/Aug	+	+	+	4	4	39.0	5	+	-	-	Fev Hea Vom
25	K.Z	2	M	26/Aug	-	-	+	8	16	38.2	2	+	-	-	Fev Hea Vom

Remarks. The abbreviation of signs in this table as follow: M: Male, F: Female, CSF: cerebrospinal fluid, T: throat washing, F: feces, Ac: acute, Co: convalescent, N: stiffness of the neck, K: Kernig's sign, P: increased PSR, Fev: fever, Hea: headache, Vom: vomiting, NT: not tested.

Incidence of summer febrile illness

Twenty-six cases as summer febrile illness occurred among babies in the institution for the nursing from 9th to 18th July (Table 2). The age distribution was fixed from 3 months to 2 years old in this epidemic. The clinical pictures in the most of cases were mainly fever and it was observed to manifest diarrhea, vomiting and cough in the proportion of 31%, 23% and 15% in cases respectively (Fig. 3, 4).

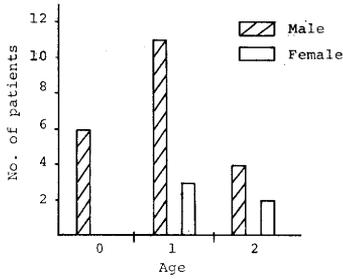


Fig. 3. Age and sex distribution in the epidemic of summer febrile illness occurred in Omura city, 1974.

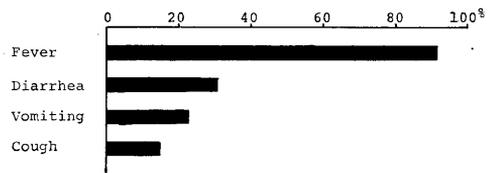
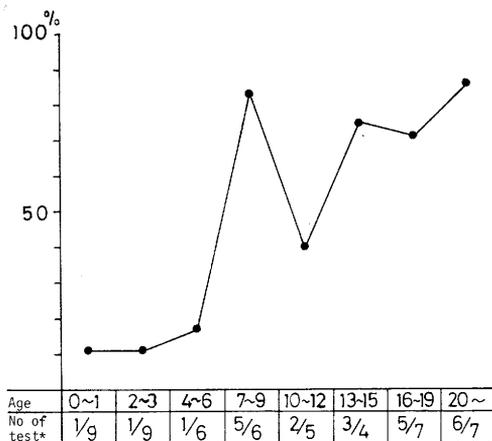


Fig. 4. Clinical findings of the patients in the epidemic of summer febrile illness.

Table 2. Outbreak of summer febrile illness and virus isolation from patients and their clinical findings

No	Name	Age (Y.M)	Sex	Onset of illness	Virus isolation		CF titer		Max. temp.	Duration (days)	Symptoms
					T	F	Ac	Co			
1	M.T	2.3	M	9/Jul	NT	NT	NT	32	38.8	2	Fev
2	U.N	2.5	F	12/Jul	-	NT	4	32	39.4	4	Fev
3	T.T	2.5	F	13/Jul	+	+	<4	16	37.8	1	Fev
4	K.T	1.11	M	13/Jul	+	+	<4	128	39.4	4	Fev
5	K.M	1.10	M	13/Jul	+	+	<4	128	37.9	2	Fev
6	Y.M	1.10	M	13/Jul	+	+	<4	16	39.4	5	Fev
7	H.T	1.8	F	13/Jul	+	+	<4	16	38.2	2	Fev Dia
8	T.Y	1.7	M	13/Jul	+	+	<4	64	38.3	2	Fev Cou Vom
9	H.N	1.7	M	13/Jul	+	+	<4	8	39.2	4	Fev Cou Vom
10	T.H	1.5	M	13/Jul	+	+	<4	64	38.2	4	Fev
11	K.K	1.10	M	13/Jul	+	+	<4	4	38.0	3	Fev Dia
12	K.M	1.10	M	13/Jul	+	+	<4	16	38.5	2	Fev Dia
13	S.S	0.9	M	13/Jul	+	+	<4	64	37.2	1	Fev
14	T.K	1.4	M	13/Jul	+	-	<4	16	38.0	3	Fev
15	H.T	0.11	M	13/Jul	NT	+	<4	32	38.2	4	Fev
16	K.K	1.10	F	14/Jul	NT	+	<4	64	38.1	3	Fev Dia Vom
17	Y.K	2.2	M	14/Jul	+	+	<4	32	38.1	2	Fev Dia
18	W.H	1.3	M	14/Jul	NT	NT	NT	NT	38.7	4	Fev Dia
19	K.A	1.1	M	14/Jul	NT	NT	NT	8	37.7	2	Fev
20	H.T	2.3	M	15/Jul	NT	NT	NT	16	38.3	2	Fev Cou
21	M.M	0.3	M	15/Jul	+	+	<4	4	38.2	2	Fev Dia Vom
22	N.Y	2.2	M	16/Jul	+	+	<4	16	37.8	3	Fev Cou Vom
23	K.M	0.7	M	18/Jul	NT	NT	NT	4	37.8	2	Fev
24	M.H	0.6	M	18/Jul	NT	NT	NT	4	37.7	2	Fev Dia Vom
25	K.H	1.2	F		NT	NT	NT	32	36.6		
26	M.H	0.7	M		NT	NT	NT	32	37.0		

Remarks. The abbreviation of signs in this table as follow: M:Male, F:Female, T: throat washing, F: feces, Ac: acute, Co: convalescent, Fev:Fever, Cou: cough, Dia: diarrhea, Vom: vomiting, NT: not tested.



\* Numerator shows number of seropositive and denominator number of cases.

Fig. 5. The possessing rate of neutrization antibody against Coxsackie B3 virus among infants and adolescence in 1973.

possession of neutralization antibody against Coxsackie virus B 3

The low proportion of the antibody possession in infants under 6 years old was observed and, in proportion as ages more than 7 years old increased, the rate of the antibody possession reached over 80% as seen in Fig. 5.

### Virus isolation

Fifteen isolates from 16 specimens of throat washings and 16 isolates from 17 specimens of feces collected from 26 cases were obtained respectively. These isolates were identified as Coxsackie virus B 3 with the neutralization test as described in the methods. Fifteen of 26 cases had responded in the antibody rising against a strain of isolates identified as Coxsackie virus B 3. Even though the virus isolation from the specimens obtained from 1 of 18 cases could not performed, the antibodies rising against Coxsackie virus B 3 were confirmed successfully (Table 2, Table 3).

The relation between ages and the

Table 3. Virus isolation from aseptic meningitis and summer febrile illness

Specimens	No of patients (%)	
	Aseptic meningitis	Summer febrile illness
C S F**	12/24 (50)	NT*
Feces	21/23 (91)	16/17 (94)
Throat washing	14/22 (64)	15/16 (94)

\*NT not tested

\*\*C S F cerebrospinal fluid

### COMMENTS

So far as group A of Coxsackie viruses is concerned, in Nagasaki area, the epidemic of exanthem with febrile illness caused by Coxsackie virus A9 in 1968, the epidemic of hand foot and mouth disease caused by Coxsackie virus A5 and A16 in 1968 and 1970, furthermore, the epidemic of herpangina caused by Coxsackie virus A4

Table 4. Distribution of Coxsackie viruses in Japan

Cox. virus type	Clinical symptoms	Outbreak of patients	Places
type B3	Meningitis	<i>epidemic</i>	Toyama, Hokkaido (1965) Shimane (1966) (1969), Ehime (1969) Iwate(1971), Aichi (1974), <u>Nagasaki (1974)</u>
		sporadic	Ehime(1966)(1967), Aichi, Tokyo (1966) Osaka(1967),Mie (1968), Tokyo, Kanagawa, Aichi (1970) Tokyo, Aichi (1973)
	U R I	sporadic	Chiba(1969), Aichi(1970), Ehime (1972) Aichi, Fukushima (1973), Ishikawa, Tottori, Shizuoka, Nagoya (1974)
		<i>epidemic</i>	Shizuoka (1970) (1971)
	Fever	sporadic	Shimane, Aichi (1970), Aichi (1971) (1973)
		<i>epidemic</i>	Tochigi, Kobe (1970)
	L R I	sporadic	Tokyo, Kanagawa (1970), Fukushima (1971)
		sporadic	Tokyo (1970), Fukushima (1973) Shizuoka (1974)
	P C F	sporadic	Tokyo (1971)
	Exanthem	sporadic	Yamanashi (1971), Aichi, Kanagawa (1973)
	Stomatitis	sporadic	Tokyo (1972)
	Acute cerebral ataxia	sporadic	Tokyo (1973)
	H F M D	sporadic	Kanagawa (1973)
No illness	special survey	Tottori, Ibaraki, Kochi, Gifu, Toyama (1970), Kochi(1971), Iwate(1972)Aichi(1973)	

in 1970 and A2 in 1972 had been investigated respectively.

On the other hand, it had been reported by Hayashi and Taguchi (1961) that the latent infection of Coxsackie virus B1, B3 and B5 among children at the survey of the epidemic of poliomyelitis had been confirmed from the results of virus isolation and serological investigations in Nagasaki area in 1960. Though only an epidemic incidence caused by Coxsackie viruses group B has not been observed till quite recently, it is considered, however, that the possibility of an outbreak of epidemic or sporadic cases caused by them might be always latent among infants and adolescence in Nagasaki area as seen in Fig. 5. So far as epidemic or sporadic incidences of aseptic meningitis and respiratory illness caused by Coxsackie virus B3 are concerned, it was reported that the virus isolation had been made in Toyama districts and Hokkaido area, north parts of Japan islands, in 1965. It will be considered that the virus must have been disseminated all over the main islands of Japan particularly since 1970 as shown in Table 4. It was noted, however, that two epidemic incidences caused by Coxsackie virus B3 distinguished from the clinical signs occurred in the same period in summer, 1974, in Omura city, Nagasaki. It might

be depended upon the condition of cases with ages to manifest the clinical pictures as aseptic meningitis among infants and the other as summer febrile illness among babies.

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1974年夏、大村市に発生した無菌性髄膜炎及び夏かぜ症の流行例

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大村市において1974年6月22日から8月26日まで特に7月に集中して小児の無菌性髄膜炎の流行があった。患者は1才から11才までの年齢層に亘っていたが、2才ないし3才が最も多かった。本流行例では髄膜刺激症状が強く上気道感染の症状はほとんどみられなかった。髄液24検体から12株、うがい液22検体から14株、便23検体から21株のウイルスを分離し、すべて *Coxsackie virus B3* と同定された。同市に同じ時期に7月に集中して、上気道感染の症状のみを呈した夏かぜ症状の流行が乳児の間に起った。うがい液16検体から15株、便17検体から16株のウイルスを分離し、すべて *Coxsackie virus B3* と同定された。1960年、林等によって、長崎地方のポリオ流行の調査の時に、*Coxsackie virus B1*, *B3* 及び *B5* の潜在感染を警告したが、今日まで *Coxsackie virus B3* による流行例は経験されなかった。全国的にみて、*Coxsackie B3* ウイルスは1970年以後急速に広く分布したことが WHO Reference Center の報告から推定された。低年齢層間の流行は今後も注意されねばならない。

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