Chapter 4

Acute Viral Encephalitis/Encephalopathy in an Emergency Hospital in Japan: A Retrospective Study of 105 Cases in 2002 – 2011

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1. Introduction

Herpes simplex encephalitis (HSE) has come to be widely recognized as diagnosable and treatable at early stages of the disease. The incidence of encephalitis/encephalopathy resulting from other members of herpesvirus group such as varicella-zoster virus (VZV), Epstein-Barr virus (EBV), cytomegalovirus (CMV), and human herpes virus (HHV)-6 has also tended to increase in both healthy and immunocompromised patients (Shoji et al, 2002). In sharp contrast, the incidence of Japanese encephalitis (JE) in Japan has dramatically decreased to a few patients per year. However, JE remains a threat among the elderly and individuals with decreased or absent immunity to the JE virus (Ayukawa et al, 2002). Influenza-associated encephalopathy (FluE) is a threat for adults as well as children (Lee et al, 2010, Umemura et al, 2011, Watanabe et al, 2012). In the present study, we retrospectively analyzed the cases of 105 mainly adult patients with acute viral encephalitis/encephalopathy at our emergency hospital, St. Mary's Hospital, Kurume City during a recent 10-years period from 2002 to 2011.We present here our preliminary report of the changing patterns in HSE, JE and FluE during the past 10 years.

2. Objectives and methods

We extracted the clinical records of the 105 patients diagnosed with acute viral encephalitis/encephalopathy in 2002—2012 from the medical records of St. Mary's Hospital, Kurume

City. Our hospital is located in southwestern Japan and provides emergency medical care for approximately 500,000 local residents. The diagnostic criteria for each viral agent in the patients' clinical charts were, in principle, dependent on polymerase chain reaction (PCR) positivity in cerebrospinal fluid (CSF) or serologic four fold increases in pair sera or CSFs. HSE was diagnosed by clinical symptoms, CSF, magnetic resonance imaging (MRI), electroencephalogram (EEG), and virologic tests such as herpes simplex virus (HSV) PCR in CSF and enzyme immunoassay (EIA) IgG IgM antibodies. VZV-associated encephalitis was mainly diagnosed by characteristic skin eruptions. JE in Japan is seen from August to September. The diagnosis of JE is established by complement fixation (CF) or hemagglutination inhibition (HI) test in pair sera, or PCR for JE virus. FluE is defined as persistent consciousness impairment over 24 hours following an influenza infection; delirium or convulsive seizures due to high fever and metabolic disorders are excluded (Japanese guidlines for FluE, 2009).The clinical forms of FluE are divided into the status epilepticus type, thalamic type, acute necrotizing encephalopathy, hemorrhagic shock and encephalopathy, Reye syndrome, and others in which no CSF pleocytosis, high concentration of IL-6 and negative PCR in CSF for influenza virus are usually observed. Non-herpetic limbic encephalitis is identified by MRI findings in bilateral limbic systems and negative HSV PCR or EIA antibodies (Ichiyama T, 2008, Shoji et al, 2012). As for anti-N-methyl-D-aspartate receptor (anti-NMDAR) encephalitis or encephalopathy, ovarian teratoma is usually found, except for pedriatric cases (Dalmau et al, 2007, 2011). Patients with viral-related acute disseminated encephalomyelitis (ADEM) were diagnosed as having disseminated neurologic lesions following suspected viral infections.

3. Results

The following acute viral encephalitis/encephalopathy cases were identified among the 105 cases (Table 1): HSE, 14 cases; herpes zoster related encephalitis, 4; HHV-6 encephalopathy, 1; JE, 4; FluE, 20, mumps encephalitis, 3; and rotavirus encephalopathy, 1. As 'other' types, non-herpetic limbic encephalitis and anti-NMDAR encephalitis/encephalopathy numbered 7, and there were 12 viral-related ADEM cases.

The remaining 42 cases of viral encephalitis had unknown etiology. Thus, the incidence of HSE was 1.4 persons per year for 500,000 persons, JE was 0.4 per year, and FluE was 2.0 per year. With regard to seasonale occurrence, the HSE cases were sporadic and uncorrelated to the seasons, whereas the JE cases occurred in September and October, and FluE was observed during the winters.

Regarding the outcomes and onset ages of the 14 HSE cases, one patient died of pneumonia, and two patients showed relapse. Five patients were more than 65 years old (Fig.1); the mean age at onset was 47.3 years, and the male to female ratio was 6:8. There were only two HSE patients under 20 years old; an infant and a 14-year-old boy. The oldest HSE patient, an 88-year-old man was admitted in late September in a delirious state with tonic seizures; his CSF showed 683 cells per mm^3 and protein at 186mg/dL. HSV PCR was negative in his CSF,

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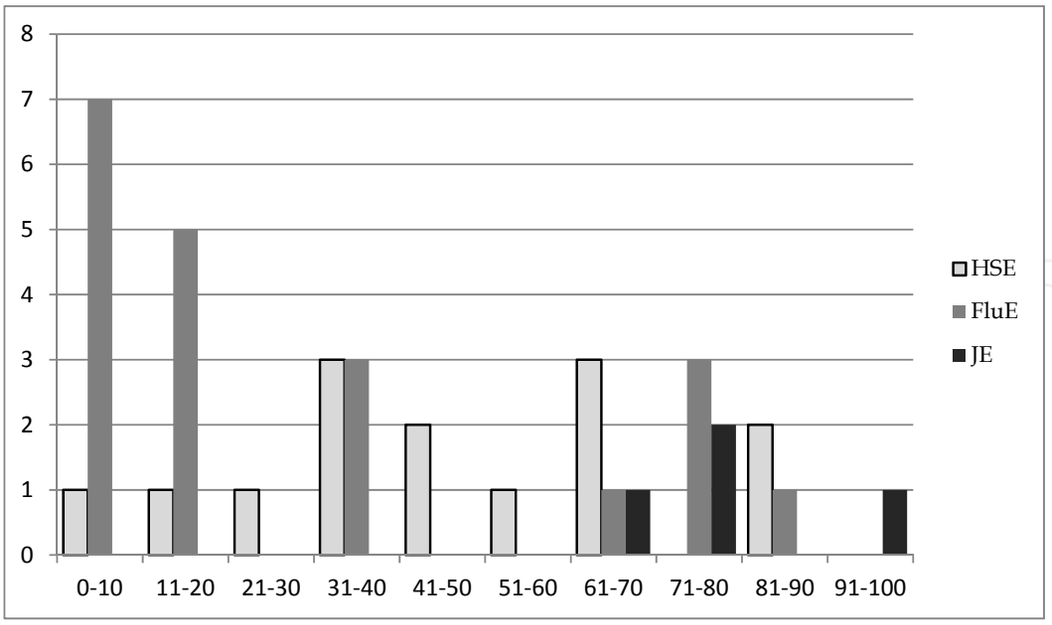
but the EIA IgG for HSV showed a significant increase, and his MRI DW revealed high intensities in the right limbic regions (Fig.2). Four patients with VZV-associated encephalitis were diagnosed by the characteristic skin eruptions. Of CMV, EBV, and HHV-6 associated with encephalitis or encephalopathy, the case of a one-year-old girl with probable HHV-6 encephalopathy was identified (Fig. 3). She was admitted to our hospital with a high fever, tonic seizures, and consciousness impairment. Although apparent clinical symptoms of exanthem subitum were not observed, her serum FA IgG titer in the recovery stage showed a high titer of 1280x for HHV-6.

	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	Total
HSE	2	1	1	2	2	1	0	0	3	2	14
H. zoster, HHV-6 encephalitis/encephalopathy	0	0	0	3	1	0	0	1	0	0	5
JE	0	0	1	0	0	1	0	0	0	2	4
FluE	3	0	1	4	2	3	0	7	0	0	20
Mumps encephalitis	0	1	0	0	0	1	0	0	0	1	3
Rotavirus encephalopathy	0	0	0	0	0	0	0	1	0	0	1
NHALE, Anti-NMDARE	1	1	1	0	0	0	1	4	0	2	10
Viral-related ADEM	1	1	0	1	2	2	1	0	2	2	12
Viral encephalitis	4	7	10	3	3	5	0	2	1	1	36
Total	11	11	14	13	10	13	2	15	6	10	105

HSE=herpes simplex encephalitis, HHV-6=human herpesvirus-6, JE=Japanese encephalitis, FluE=influenza encephalopathy, NHALE=non-herpetic limbic encephalitis, anti-NMDARE=anti--N-methyl-D-aspartate receptor encephalitis, ADEM=acute disseminated encephalomyelitis

Table 1. Acute viral encephalitis/encephalopathy, St. Mary's Hospital, Kurume, Fukuoka, Japan, 2002 - 2011 (n=105)

Four cases of JE were recognized, with one case from September 2005, one from September 2007 and two from September and October 2011, respectively (Fig.4). The patients' ages and genders were 79 years/F, 93/F, 76/M, and 69/M, and the mean age was 79.3 years. One patient died one month after admission, and the other three patients suffered from severe sequelae. The 69-year-old man was found after having fallen in September 2011, and was admitted to our hospital. He was initially diagnosed as having had a stroke due to the onset of an acute right hemiparesis, but his CSF and MRI findings suggested JE, and the diagnosis was serologically confirmed by a significant increase in JE virus in the acute and convalescent sera. For all four JE cases, steroid pulse therapy was performed, but the effects were minimal.



Kurume, Fukuoka, Japan, 2002 - 2011
HSE=herpes simplex encephalitis, FluE =influenza encephalopathy, JE=Japanese encephalitis

Figure 1. Age distribution of HSE, FluE and JE patients (HSE n=14, FluE n=20, JE n=4) at St. Mary's Hospital,

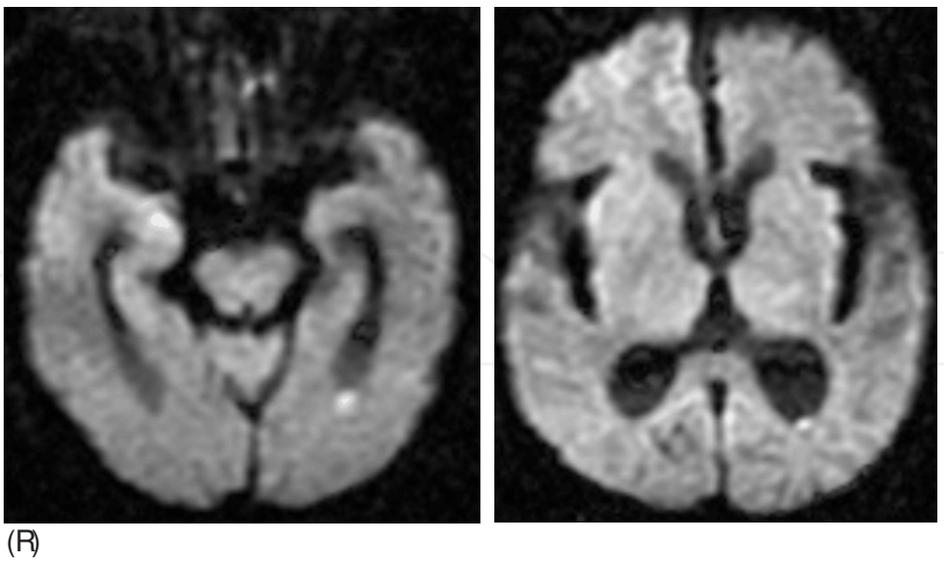


Figure 2. An 88-year-old man with herpes simplex encephalitis. MRI DW images on 4 days after onset revealed high intensities at the right amygdala, insula, and frontal lobe.

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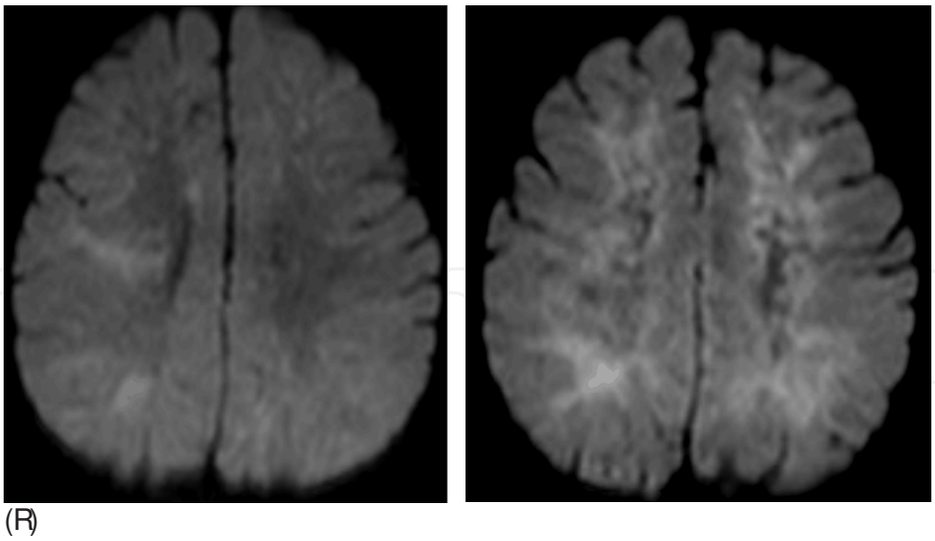

Figure 3. A 10-month-girl with HHV-6 encephalopathy; Lt, MRI DW on the 2nd day after onset showed high intensities at the right parietal and occipital lobes; Rt, 10 days later, the high intensities extended bilaterally into diffuse white matter.

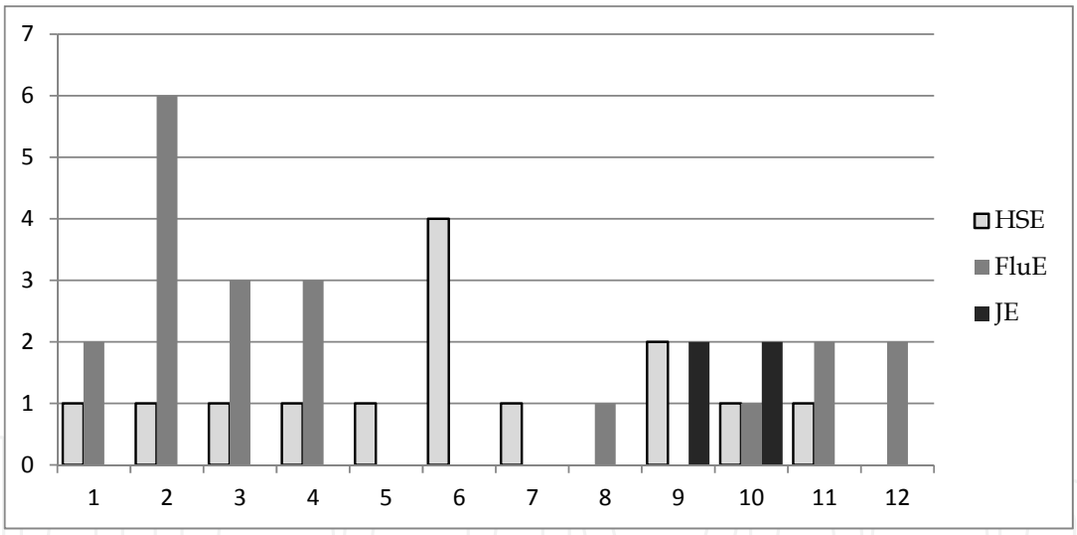

Figure 4. Monthly incidence of HSE, FluE and JE patients (HSE n=14, FluE n=20, JE n=4) at St. Mary's Hospital, Kurume, Fukuoka, Japan, 2002 – 2011

Ten pediatric and adult cases of FluE were identified, respectively. Seven FluE patients, including 4 adult cases, were seen consistent of the world epidemic of the new pig influenza H1N1 in 2009 (Fig.5).

The clinical forms of the pediatric cases (age under 15 years) included the status epilepticus type, the thalamic type, and the acute hemorrhagic shock and encephalopathy type. The clinical forms of the adult cases included several cases of the status epilepticus type, and one adult presented Reye syndrome. Among the status epilepticus-type cases of

FluE, a 32-year-old-man was admitted to our hospital with a fever of 39℃ and tonic seizures in August, 2009. A rapid test for influenza virus using a throat swab showed influenza type A, and his CSF exhibited no cell increase. An MRI revealed abnormalities of the cingulate gyri and basal ganglia (Fig.6), and an EEG showed diffuse slowness. The four adult status epilepticus type cases improved markedly after control for status epilepiticus and steroid pulse therapy, and they were all discharged without sequelae. An 83-year-old-man presented with influenza B in March 2005, then developed Reye syndrome with symptoms of consciousness impairment, hyperammonemia, and hepatic and renal dysfunction; he died one month after admission. Reye syndrome is characterized by acute non-inflammatory encephalopathy and fatty degeneration of the liver, usually after viral infection. Because this disease mainly affects children and teenagers, our case of the advanced age of 83 years old is a quite rare example.

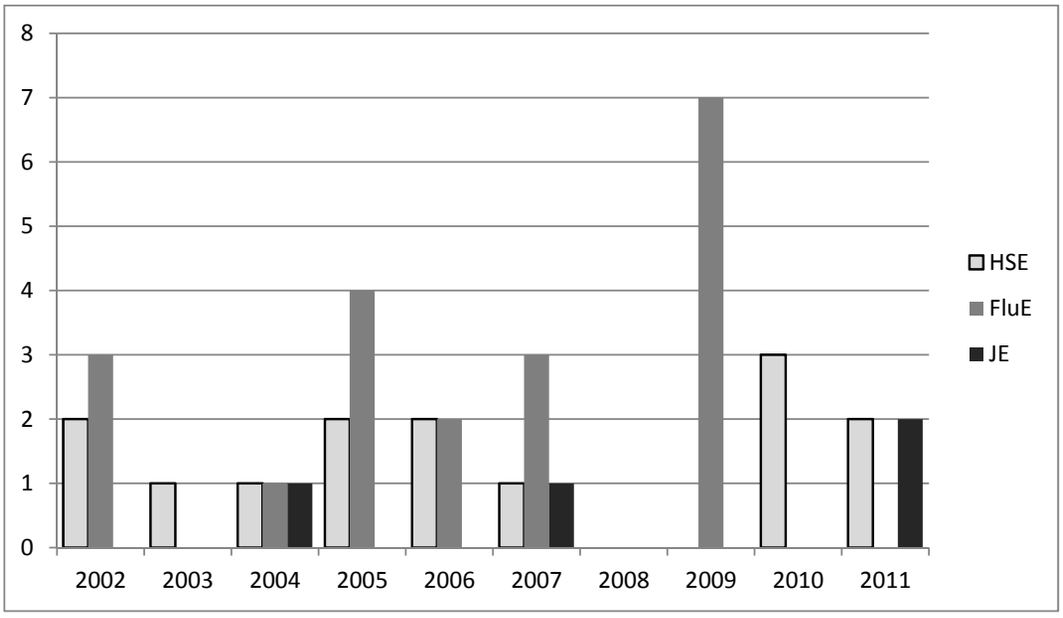

Figure 5. The occurrence by year of HSE, FluE and JE patients (HSE n=14, FluE n=20, JE n=4) at St. Mary's Hospital,Kurume, Fukuoka, Japan, 2002 – 2011

Next, a one-year-old boy with rotavirus encephalopathy was identified; he showed tonic seizures, consciousness impairment, hepatic and renal dysfunction, and disseminated intravascular coagulation following diarrhea and dehydration by rotavirus (acute hemorrhagic shock and encephalopathy type).

Low-temperature, steroid pulse and intravenous immunoglobulin therapies were performed, but he suffered from gait impairment and symptomatic epilepsy as sequelae.

Three cases of non-herpetic limbic encephalitis and four cases of anti-NMDAR encephalitis associated with ovarian teratoma were identified. The adult patient with anti-NMDAR encephalitis had a favorable outcome after resection of ovarian teratoma.

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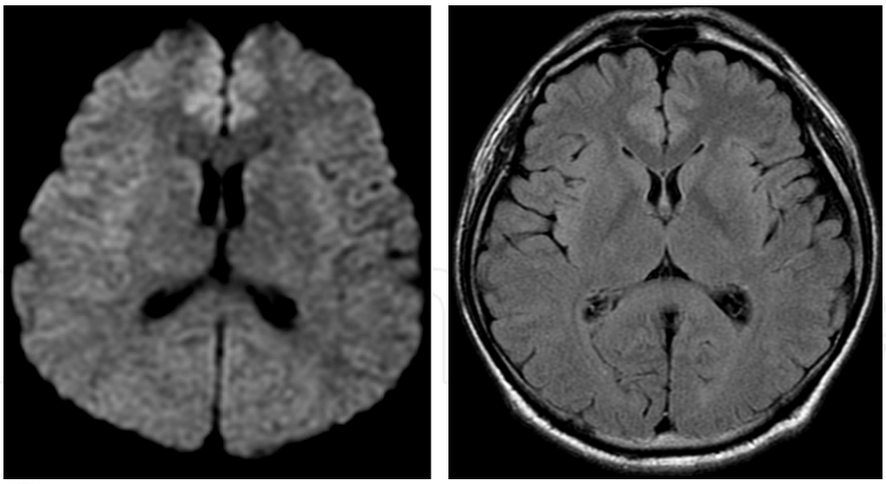

Figure 6. MRI DW & FLAIR images revealed high intensities at the cingulate gyri in a 32-year-old man with status epilepticus-type FluE (influenza-associated encephalopathy).

4. Discussion

The initial steps in emergency medicine for acute central nervous system (CNS) infections are to maintain a patent air-way, control convulsive seizures and protect the patient from brain edema, followed immediately by making a rapid etiological diagnosis and starting empiric therapy (Fitch et al, 2008, Solomon et al, 2010). Acute viral encephalitis/encephalopathy is non-invasively diagnosed by clinical symptoms, CSF, EEG, CT, MRI, and virologic tests such as PCR and EIA. The determination of the presence/absence of CSF pleocytosis is helpful for the differentiation of encephalitis and encephalopathy. Seasonable factors such as JE and FluE, and associated symptoms such as parotitis in mumps encephalitis should be considered for their diagnoses. Bacterial, fungal and tuberculous meningitis excluded on the basis of a decrease of glucose concentration in CSF and gram staining or bacterial latex tests.

The prevalence of viral and other types of encephalitis was estimated to be 17.7±3.2 per million person year, including 5.5±1.0 of viral, 1.2±0.07 of bacterial, and 8.9±0.7 of unknown etiology, in a nationwide questionnaire survey from 1989 to 1991(Kamei et al, 2000). HSE accounted for 63.9% of all identified cases of viral encephalitis, VZV for 8.0%, influenza virus for 1.3%, and Japanese B virus for 0.9% in this survey. The annual incidence with HSE was similar to that previously reported in the USA, 2.0 to 4.0 per million population (Whitley et al, 1998), while the incidence was 2.3 per million population in Sweden (Skoldenberg et al, 1984) and 1.0 per million population in the UK (Gulliford et al, 1984). According to this prevalence, the number of patients in our region over a 10-year period was estimated from 10 -18 for HSE, 0-2 for FluE, and 0-1 for JE, while we actually accumulated 14 HSE, 24 FluE, and 4 JE patients. The difference between the projected and actual numbers of adults with FluE in 2009 may have been caused by the new influenza A (H1N1) pandemic, in that year. Our hospital is located in southwestern Japan, and it is also likely that geographic factors

such as higher possessing JE virus antibody in pigs or mosquitoes led to an increase in the number of occurrences of JE.

On the other hand, acute encephalitis/encephalopathy in children under 15 years of age has occurred in approximately 1,000 cases per year, as indicated in a large-scale survey of Japan. The etiology in order from most prevalent to least prevalent is influenza (25%), HHV-6 (11%), and rotavirus (4%) (Morishima, 2009). The incidence of HHV-6 encephalopathy, 7.0 per 100,000 infants, was estimated from the infant population of Japan, and severe neurological complications remained in half of these infants (Ohashi, et al, 2006).

Regarding the onset age of the 14 HSE patients, the under-30-year-old cases included one infant, a 14-year-old boy, and a 24-year-old man; the mean age of all 14 patients was 47.3 years. The peak onset age was in the 60s, although our past study identified two peaks at 20 and the 50s. The oldest HSE patient, an 88-year-old man, died of complicated pneumonia one month after admission, and another 80-year-old man suffered from severe memory impairment as a sequela, despite early acyclovir treatment. The upward trend of elderly patients with HSE may reflect the 'graving' of the Japanese populations, and also suggests that the reactivation of HSV can occur even in elderly people (Suzuki et al, 2012). All four of present patients with VZV-associated encephalitis had favorable outcomes after high-dose of intravenous acyclovir therapy.

All four of the JE patients we identified were elderly (including a 93-year-old), and their immunity to the JE virus was probably decreased or absent (Ayukawa et al 2002, Lee et al 2012). Presently, there is no specific therapy for JE, and thus JE vaccination might be advisable for elderly people in the epidemic area.

The incidence of FluE has increased in Japan since the 1997 winter influenza season. FluE affects mainly children under 10 years old (Okumura et al, 2012, Watanabe et al, 2012). In our hospital, 10 adult FluE cases were recognized in the 2002—2012 examination period, including four patients over 15 years old who were part of the epidemic of the new pig influenza variant in 2009 (Umemura et al, Lee N et al, 2010). For the pediatric patients, steroid pulse, intravenous immunoglobulin or low-temperature therapies were performed. The adult patients had favorable outcomes except for one case of Reye syndrome. Although hypercytokinemia has been contended to contribute to the pathogenesis, the IL-6 levels in our adult cases were in the normal range.

5. Conclusion

We analyzed the cases of 105 patients with acute viral encephalitis/encephalopathy who were treated at our emergency center, St. Mary's Hospital, Kurume City during the 10 years from 2002 to 2011. Fourteen HSE cases, 4 of herpes zoster-related encephalitis, 1 of HHV-6 white matter encephalopathy, 4 of JE, 20 of FluE, 3 of mumps encephalitis, and 1 of rotavirus encephalopathy were identified. As other types, 12 cases of viral-related ADEM and 7 cases of non-herpetic limbic encephalitis including anti-NMDAR encephalitis/encephalopathy were observed. The etiology of the remaining 42 cases of viral encephalitis was unknown.

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Our results show an upward trend in HSE and JE toward patients over 65 years of age and an increase in adult-onset FluE. Although mortality rates of HSE and JE cases were low, the JE patients remained severe sequelae. The adult FluE patients had more favorable outcomes compared to the pediatric patients. Specific anti-viral drugs are still limited, and acute viral encephalitis/encephalopathy such as FluE overlaps into immunological pathogenesis. Thus, the rapid diagnosis of etiology and pathophysiology and initiation of empiric therapy are required.

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References

[1] Ayukawa R; Fujimoto H, Ayabe M, Shoji H, Matsui R, Iwata Y, Fukuda H, Ochi K, Noda K, Ono Y, Sakai K, Takehisa Y, & Yasui K (2004). An unexpected outbreak of Japanese encephalitis in the Chugoku district of Japan, 2002. *Jpn J Infect Dis* 57. 63-66.

[2] Belay ED; Bresee JS, Holman RC, Khan AS, Shahriari A, & Schonberger LB. Reye's syndrome in the United States from 1981 through 1997 (1999). *N Engl J Med* 340. 1377-82.

[3] Costa PS; Ribeiro GM, Vale TC, Casali TG, Leite FJ (2011). Adult Reye-like syndrome associated with serologic evidence of acute parvovirus B19 infection. *Braz J Infect Dis* 15. 482-3.

[4] Dalmau J; Lancaster E, Martinez-Hernandez E, Rosenfeld MR, & Balice-Gordon R (2011). Clinical experience and laboratory investigations in patients with anti-NMDAR encephalitis. *Lancet Neurol* 10. 63-74.

[5] Dalmau, J.; Turzen. E., Wu, H.Y., Masjuan, J., Voloschin, A., Baehring,J.M.,Shimazaki, H., Koide, R., King, D., Mason, W., Sansing, L.H., Dichter,M.A., Rosenfeld, M.R. & , D.R. (2007). Paraneoplastic anti-N-methyl-D-asparate receptor encephalitis associated with ovarian teratoma. *Ann Neurol* 61.25-36.

[6] Fitch MT; Abrahamian FM, Moran GJ, & Talan DA.Emergency department management of meningitis and encephalitis (2008).*Infect Dis Clin North Am* 22:33-52.

[7] Gulliford MC; Chandrasekera CP, Cooper RA, & Murphy RP (1987). Acyclovir treatment of herpes simplex encephalitis: experience in a distinct hospital. *Postgrad Med J* 63. 1037-41.

[8] Ichiyama, T.; Shoji, H., Takahashi, Y., Matsushige, T., Kajimoto, M., Inuzuka, T. & Furukawa, S. (2008). Cerebrospinal fluid levels of cytokines in non-herpetic acute limbic encephalitis: comparison with herpes simplex encephalitis. *Cytokine* 44.149-153.

[9] Japanese committee for influenza encephalopathy (2009): Influenza encephalopathy guidelines.

[10] Kamei S; Takasu T (2000). Nationwide survey of the annual prevalence of viral and other neurological infections in Japanese inpatients. *Intern Med* 39: 894-900.

[11] Lee DW; Choe YJ, Kim JH, Song KM, Cho H, Bae GR, & Lee JK (2012). Epidemiology of Japanese encephalitis in South Korea, 2007-2010. *Int J Infect Dis* 16:e448-52.

[12] Lee N; Wong CK, Chan PK, Lindegardh N, White NJ, Hayden FG, Wong EH, Wong KS, Cockram CS, Sung JJ, & Hui DS (2010).Acute encephalopathy associated with influenza A infection in adults. *Emerg Infect Dis* 16: 139-42.

[13] Morishima T; (2009). Infantile viral encephalitis and encephalopathy in Japan.*Virus* 59. 59-66

[14] Ohashi M; Yoshikawa T, Miyake F, Sugata K, Suga S, & Asano Y (2006). Nationwide survey of exanthema subitum associated encephalitis/encephalopathy in Japan. *J Pediatric Infect Dis & Immun* 18. 385-92

[15] Okumura A; Tsuji T, Kubota T, Ando N, Kobayashi S, Kato T, Natsume J, Hayakawa F, & Shimizu T. (2012). Acute encephalopathy with 2009 pandemic flu: comparison with seasonal flu. *Brain Dev* 34:13-9

[16] Shoji H; Kimura N, Kumamoto T, Ichiyama T, & Takahash Y(2011). Non-herpetic acute limbic encephalitis: A new subgroup of limbic encephalitis? Ed by Hayasaka D. Pathogenesis of Encephaitis. *INTECH* p267-78.

[17] Shoji H; Wakasugi K, Miura Y, Imaizumi T, & Kazuyama Y. Herpesvirus infections of the central nervous system (2002). *Jpn J Infect Dis* 55:6-13.

[18] Skoldenberg B; Forsgren M, Alesting K, Bergström T, Burman L, Dahlqvist E, Forkman A, Frydén A, Lövgren K, & Norlin K (1984). Acyclovir versus vidarabine in herpes simplex encephalitis: randomized multicenter study in consecutive Swedish patients. *Lancet II* 707-11.

[19] Solomon T; Michael BD, Smith PE, Sanderson F, Davies NW, Hart IJ, Holland M, Easton A, Buckley C, Kneen R, & Beeching NJ (2012); National Encephalitis Guidelines Development and Stakeholder Groups.Management of suspected viral encephalitis in adults--Association of British Neurologists and British Infection Association National Guidelines. *J Infect* 64:347-73.

[20] Suzuki K; Shoji H, & Hondo R (2012). An 89-year-old female with elderly-onset herpes simplex encephalitis, who, recovering with acyclovir therapy, relapsed two months later and died. *Brain & Nerve* 64:1063-8.

[21] Umemura S, Yamasaki M, Takahashi Y, Matsumoto K, & Miyamura M (2011). An adult case of pandemic (H1N1) 2009 influenza associated encephalopathy (2011). *Rinsho Shinkeigaku* 51. 422-5.

[22] Watanabe Y; Tsuji M, Sameshima K, Wada T, Iai M, Yamashita S, Hayashi T, Aida N, & Osaka H (2012). Clinical characteristics of acute encephalopathies associated with influenza H1N1-2009 in children . *No To Hattatsu* 44:35-40.

[23] Whitley RJ; (1998). Herpes simplex virus infections of the central nerve system. A review. *Am J Med* 85 (supple 2A): 61-7.

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