Japanese Journal of Ophthalmology (2019) 63:304–309
https://doi.org/10.1007/s10384-019-00668-5

THE OFFICIAL INTERNATIONAL JOURNAL OF THE JAPANESE OPHTHALMOLOGICAL SOCIETY

CLINICAL INVESTIGATION

Acute retinal necrosis following herpes simplex encephalitis: a nationwide survey in Japan

Daisuke Todokoro[1] · Satoshi Kamei[2] · Hiroshi Goto[3] · Yoshio Ikeda[4] · Hiroshi Koyama[5] · Hideo Akiyama[1]

Received: 4 October 2018 / Accepted: 9 April 2019 / Published online: 3 May 2019

Abstract

Purpose Acute retinal necrosis (ARN) is a severe necrotizing retinitis caused by varicella-zoster virus or herpes simplex virus (HSV) that often results in blindness. Occasionally, HSV-caused ARN develops after herpes simplex encephalitis (HSE). It remains unknown, however, when and how often ARN develops after HSE. To investigate the actual conditions of patients with ARN following HSE and the interval period between the prior HSE and the onset of ARN, a retrospective nationwide survey of the Japanese population was performed.

Study design Retrospective.

Methods Questionnaires were sent out to the neurology and ophthalmology departments of teaching hospitals in Japan. They inquired about HSE patients in neurology departments and ARN patients diagnosed with HSV in ophthalmology departments. The proportion of the HSV-ARN patients with a history of HSE and their interval periods were obtained from the questionnaires returned by the ophthalmology departments.

Results Neurology departments of 324 hospitals responded to the questionnaires (response proportion: 40.9%), and 53 HSE cases were reported. Ophthalmology departments of 535 hospitals responded the questionnaires (response proportion: 54.3%), and 67 HSV-ARN cases were reported. Among the 67 HSV-ARN cases, 16 (23.9%) had histories of prior HSE. Although the interval periods from the prior HSE to the onset of HSV-ARN varied among cases, nearly half developed HSV-ARN within 2 years.

Conclusions This nationwide survey of the Japanese population showed that HSV-ARN develops after HSE in higher frequency within 2 years. Neurologists and ophthalmologists should be aware that HSE survivors have a risk of contracting HSV-ARN.

Keywords: Acute retinal necrosis · Herpes simplex encephalitis · Herpes simplex virus

Introduction

Acute retinal necrosis (ARN) is a severe viral ocular infection that can rapidly develop and progress in immunocompetent patients and lead to panuveitis with necrotizing retinitis [1]. In spite of intensive therapies that include intravenous acyclovir and vitreoretinal surgery, visual outcomes for ARN are poor, as the devastated retina often contains multiple retinal breaks resulting in refractory retinal detachments. The most common causative viruses of ARN are varicella-zoster virus (VZV), followed by the herpes simplex virus (HSV) including types 1 and 2 [1].

Although there are many case reports of ARN caused by HSV (HSV-ARN) with a history of prior HSE [2–12], the incidence rate of HSV-ARN among HSE survivors remains unknown. Vandercam et al. state that HSE is a risk factor

Corresponding author: Daisuke Todokoro

✉ Daisuke Todokoro
dtodokor@gunma-u.ac.jp

1 Department of Ophthalmology, Gunma University Graduate School of Medicine, 3-39-15 Showa-machi, Maebashi, Gunma 371-8511, Japan

2 Division of Neurology, Department of Medicine, Nihon University School of Medicine, Itabashi, Japan

3 Department of Ophthalmology, Tokyo Medical University, Shinjuku, Japan

4 Department of Neurology, Gunma University Graduate School of Medicine, Maebashi, Japan

5 Department of Public Health, Gunma University Graduate School of Medicine, Maebashi, Japan

of ARN and report that 7 (13.5%) out of 52 ARN cases had histories of HSE. In their manuscript, they estimate the risk of ARN among HSE patients to be 3.7-11% [8]. However, this estimation was based on ARN cases reported at a single referral hospital in the Netherlands and on the prevalence of HSE in the United States [13]. Our current study conducted a nationwide survey of the Japanese population in order to investigate actual conditions of patients with HSV-ARN following HSE and interval periods between prior HSE and the onset of HSV-ARN.

Subjects and methods

This retrospective nationwide survey study sent out questionnaires to the 792 neurology departments and 986 ophthalmology departments located in teaching hospitals in Japan. To improve the response rates, questionnaires were sent out using a two-step method. For the neurology departments, the first questionnaire asked about the presence of HSE patients during the 3-year period from 2011 to 2013. Departments that answered 'Yes' were then asked to provide detailed information that included age, gender, onset years and diagnostic criteria (such as the presence of either positive HSV-PCR of cerebrospinal fluid, intrathecal HSV antibody production, or positive brain imaging findings (CT/MRI) of inflammation in the fronto-temporal lobes suggesting HSE) (Fig. 1). For the ophthalmology departments, the first questionnaire asked about the presence of HSV-ARN patients during the 6-year period from 2011 to 2016. Departments that answered 'Yes' were then asked to provide detailed information that included age, gender, affected eyes, onset years, diagnostic criteria (the presence of both positive HSV-PCR of intraocular fluid and typical ocular findings and clinical courses), history of prior HSE and involvement of the fellow eyes (Fig. 2). All returned questionnaires were carefully reviewed, and all cases that did not meet the diagnostic criteria of HSE [14] and ARN [15] were excluded.

The number of HSE cases that visited the neurology departments from 2011 to 2013 was estimated by extrapolating the actual number of cases listed on the returned second questionnaires. The extrapolation was performed by assuming that both the responding and non-responding hospitals had the same incidence of the disease per hospital. HSE cases that visited the departments of internal medicine and pediatrics were also extrapolated, as a previous study reported that neurology, internal medicine and pediatrics covered 65.0%, 18.5% and 16.5% of HSE patients in Japan, respectively [16]. From these results, we assumed that very few patients were diagnosed at any other departments. Based on the above, we then estimated the total number of HSE cases in Japan during the 3-year period from 2011 to 2013. This number was used as a denominator when calculating the proportion of patients with HSV-ARN following HSE.

The actual number of HSV-ARN cases with histories of prior HSE from 2011 to 2016 was obtained from the second questionnaires returned from the ophthalmology departments. By extrapolating the actual number of HSV-ARN cases reported in these questionnaires, the total number of HSV-ARN cases with a history of prior HSE during

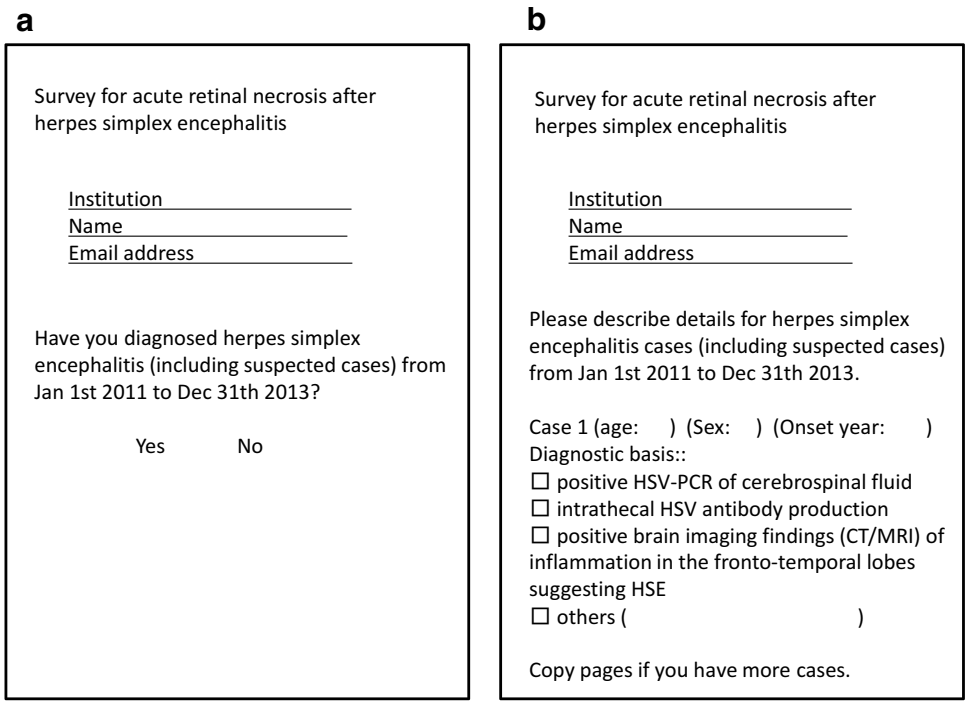

Fig. 1 Questionnaires for the neurology departments. Questionnaires were sent out using a two-step method. The first questionnaire asked about the presense of HSE patients during the 3-year period from 2011 to 2013 (a), and the second questionnaire asked to provide further detailed information of the HSE patients (b)

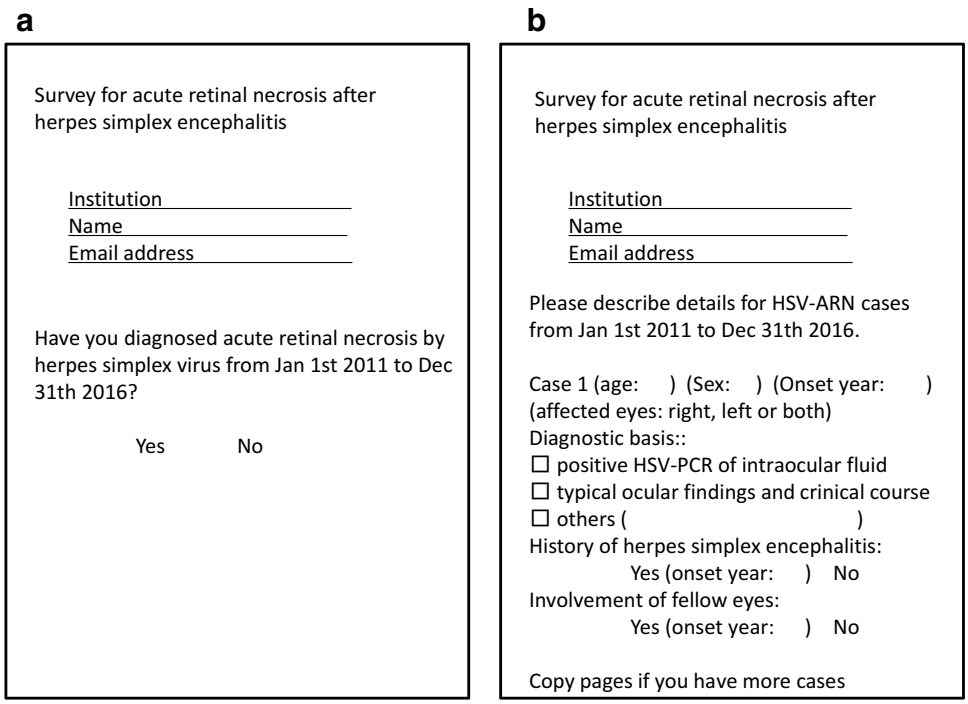

Fig. 2 Questionnaires for the ophthalmology departments. Questionnaires were sent out using a two-step method. The first questionnaire asked about the presense of HSV-ARN patients during the 6-year period from 2011 to 2016 (a), and the second questionnaire asked to provide further detailed information of the HSV-ARN patients (b)

the 6-year period from 2011 to 2016 was estimated. The extrapolation was also performed by assuming that both the responding and non-responding hospitals had the same incidence of the disease per hospital. It was assumed that there were only a few ARN patients diagnosed and treated as outpatients, as ARN is a severe disease that requires intensive therapy with hospitalization. The number of HSV-ARN cases with a history of HSE during 3 years was then calculated and used as a numerator when calculating the proportion of patients with HSV-ARN following HSE.

The proportion of patients with HSV-ARN following HSE was calculated based on the estimated numbers of HSE and HSV-ARN after HSE cases during the 3-year period. The 95% confidence interval (95%CI) was calculated from the total number of samples and the number of events by using the statistical software EZR [17].

The interval periods from the prior HSE to the onset of HSV-ARN were extracted from the data obtained from the second questionnaires returned from the ophthalmology departments.

This study was approved by the Ethical Committee of Gunma University Hospital.

Results

Estimated number of HSE cases in Japan

The response proportion for the first questionnaire sent to the neurology departments was 324/792 departments (40.9%), while that for the second questionnaire was 33/63 (52.4%). There was a total of 53 HSE cases (33 men, 20 women) reported during the 3-year period from 2011 to 2013 by 33 hospitals. The diagnostic basis of the 53 HSE cases were as follows: positive HSV-PCR of cerebrospinal fluid (26 cases, 49.1%), intrathecal HSV antibody production (8 cases, 15.2%), and positive brain imaging finding (CT/MRI) of inflammation in the fronto-temporal lobes suggesting HSE (19 cases, 35.8%). The ages of the 53 patients ranged from 18 to 90 years (average: 64.5 years). Based on the extrapolation from these numbers, the total number of estimated HSE cases in Japan during the 3-year period was calculated to be 380 (Fig. 3). In addition, based on the 2011 Japanese population from the census information conducted by the Statistical Bureau of the Ministry of Internal Affairs, the annual incidence of HSE was calculated to be 1.0 per million.

The proportion of patients with HSV-ARN following HSE and interval periods between the prior HSE and the onset of HSV-ARN

The response proportion for the first questionnaire sent to the ophthalmology departments was 535/986 departments (54.3%), while that for the second questionnaire was 40/52 (76.9%). There were 67 HSV-ARN cases (38 men and 29 women) reported during the 6-year period from 2011 to 2016 by 40 hospitals. The ages of the 67 patients ranged from 0 to 87 years (average: 51.6 years). Among the 67 HSV-ARN cases, 16 (23.9%) had histories of prior HSE. The interval periods between the prior HSE and the onset

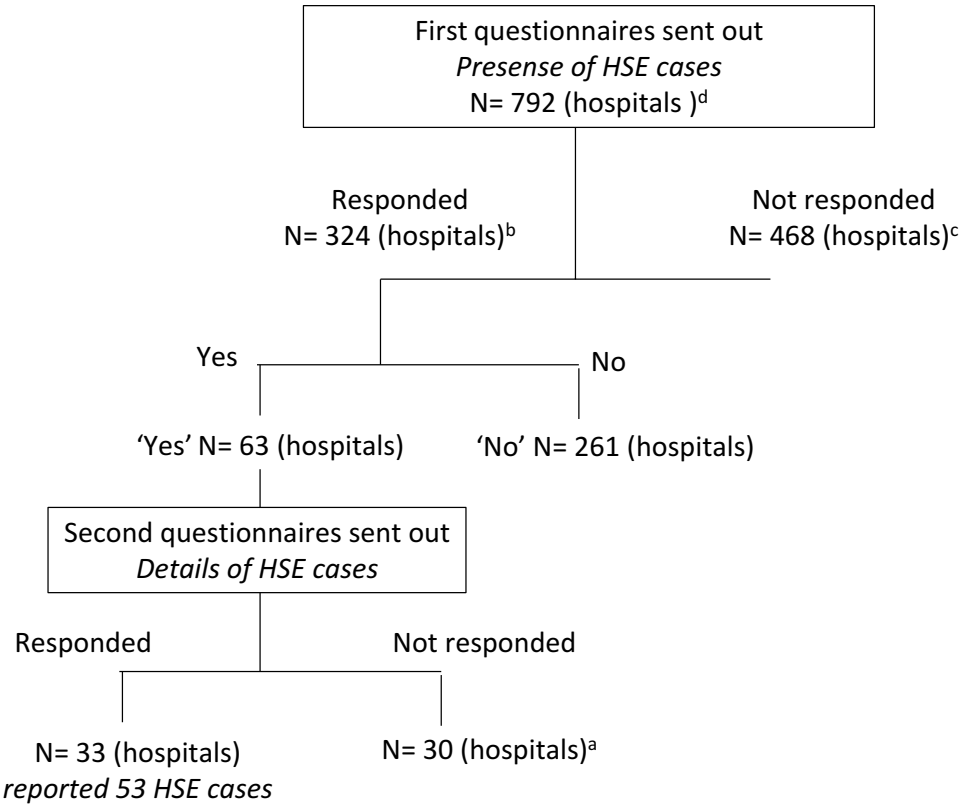

Fig. 3 Flowchart showing the result for questionnaires sent out to neurology departments about herpes simplex encephalitis. The first questionnaires asking about the presence of herpes simplex encephalitis (HSE) cases during 3 years (2011-2013) were sent out to neurology departments in 792 hospitals, and the response proportion was 40.9% (324/792 hospitals). The second questionnaires asking about the details of the HSE cases were sent out to 63 hospitals which answered 'Yes,' and the response proportion was 52.4% (33/63 hospitals). The extrapolation was performed as follows; (a) First, the 30 hospitals which did not respond the second questionnaires were assumed to include 48 HSE cases from the ratio of 53 cases among 33 hospitals. (b) Second, the 324 hospitals which responded the first questionnaires were assumed to include 101 HSE cases as a total of 53 and 48 cases. (c) Third, the 468 hospitals which did not respond the first questionnaires were assumed to include 146 HSE cases from the ratio of 101 cases among 324 hospitals. (d) Fourth, the 792 hospitals were assumed to include 247 HSE cases as a total of 101 and 146 cases. A previous study has reported that neurology, internal medicine and pediatric departments covered 65.0%, 18.5% and 16.5% of the HSE patients in Japan, respectively[16]. Therefore, 3-year HSE cases in Japan were finally calculated to be 380 from the assumption that neurology departments covered 65% of total HSE patients. HSE, herpes simplex encephalitis

of HSV-ARN reported in the 16 cases varied from a simultaneous onset to a period longer than 10 years. However, HSV-ARN developed within 2 years after HSE in nearly half of the cases (Table 1). In addition, bilateral eyes were involved in 5 (31.3%) out of the 16 cases with 2 showing simultaneous onset and the other 3 occurring within the following year.

Estimated incidence proportion of HSV-ARN following HSE

Using data extrapolation, the total number of estimated HSV-ARN cases with HSE history in Japan during the 6-year period from 2011 to 2016 was estimated to be 39 (Fig. 4). Therefore, the number of HSV-ARN cases with HSE in Japan during a 3-year period was calculated to be

Table 1 Interval periods between prior herpes simplex encephalitis and the onset of acute retinal necrosis

Interval period (year)	Cases (N)
<1	4
1-2	3
2-3	0
3-4	4
4-5	0
5-10	1
≥10	2
Unknown	2
Total	16

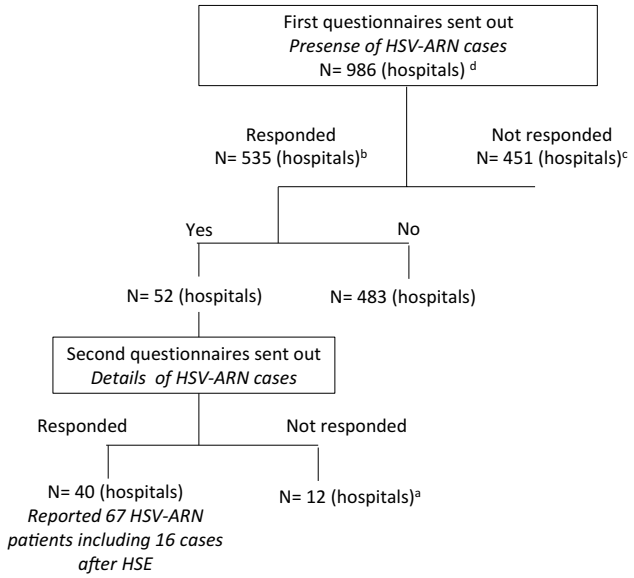

Fig. 4 Flowchart showing the result for questionnaires sent out to ophthalmology departments about acute retinal necrosis caused by herpes simplex virus with histories of herpes simplex encephalitis. The first questionnaires asking about the presence of acute retinal necrosis (ARN) cases caused by herpes simplex virus (HSV) during 6 years (2011-2016) were sent out to ophthalmology departments in 986 hospitals, and the response proportion was 54.3% (535/986 hospitals). The second questionnaires asking about the details of HSV-ARN cases sent out to 52 hospitals which answered 'Yes,' and the response proportion was 76.9% (40/53 hospitals). The 52 hospitals reported 16 HSV-ARN cases after HSE. The extrapolation was performed as follows; (a) First, the 12 hospitals which did not responded the second questionnaires were assumed to include 5 cases of HSV-ARN after HSE from the ratio of 16 cases among 40 hospitals. (b) Second, the 535 hospitals which responded to first questionnaires were assumed to include 21 HSV-ARN cases after HSE as a total of 16 and 5 cases. (c) Third, the 451 hospitals which did not respond the first questionnaires were assumed to include 18 cases of HSV-ARN cases after HSE from the ratio of 21 cases among 535 hospitals. (d) Finally, 6-year HSV-ARN cases with prior HSE in Japan were estimated to be 39 as a total of 21 and 18. ARN, acute retinal necrosis; HSE, herpes simplex encephalitis; HSV, herpes simplex virus

20 cases. Based on the number of cases estimated for HSE and for HSV-ARN with a history of HSE during the 3-year period, the incidence proportion of HSV-ARN following HSE was estimated to be 5.3% (95%CI: 3.2-8.0%). However, HSE has a high mortality rate, reported to be about 15% [18]. Thus, the incidence proportion among HSE survivors was estimated to be 6.2% (95%CI: 3.8-9.4%).

Discussion

ARN is a rare viral necrotizing retinitis caused by either VZV or HSV, with an annual population incidence estimated to be 0.5 to 0.63 per million [1]. In spite of the intensive medical and surgical therapies developed and used to treat this ocular disease, ARN continues to cause severe visual disturbances [1]. The prevention of ARN is difficult, as most ARN cases develop in immunocompetent patients as an acute onset without any precursory syndrome. However, there are multiple reports finding prior histories of HSE in HSV-ARN cases [2–12]. Based on these previous findings, it has been suggested that HSE is a risk factor of ARN [8]. However, it remains unknown as to how often ARN actually develops after HSE. Our current study performed a nationwide retrospective survey of the Japanese population and showed that 16 (23.9%) out of 67 HSV-ARN cases had histories of prior HSE. Additionally, it is estimated that the three-year incidence of HSV-ARN after HSE was 5.3% of the total HSE patients. If the mortality rate of HSE were to be taken into account, the proportion would be 6.2% of HSE survivors.

HSE is a form of sporadic encephalitis, the most common infectious encephalitis in industrialized countries [19]. The annual prevalence of HSE in the Japanese population is reported to be 3.5-3.9 per million [16, 20]. Even in the acyclovir era, HSE prognosis is still poor, with the 6-month outcome resulting in death (15%) and severe disabilities (20%) [18]. Furthermore, since HSE survivors suffer from neuropsychological dysfunction to some extent, there is often a delay before they consult an ophthalmologist during the early developmental stages of ARN. Therefore, neurologists need to be made aware of the fact that a percentage of HSE survivors may be affected by ARN at some point in the future.

The interval periods between the prior HSE and the onset of ARN varied among reported cases, ranging from a simultaneous onset to an onset longer than 10 years (Table). However, the onset periods of nearly half of the cases were within 2 years. It should be noted that 31.3% of HSV-ARN cases after HSE in this study involved both eyes. To protect the vision of HSE survivors, there are several options that should be considered. First, early consultations with ophthalmologists need to be undertaken when the visual symptoms initially develop. Second, patients need to be started on prophylactic oral antivirals to prevent ARN as a late-onset complication. However, although prophylactic oral antivirals are widely used for recurrent genital herpes there has yet to be any evidence that shows antivirals can prevent ARN after HSE. It is expected that successful vaccinations for the treatment or prevention of HSV infections will become available in the future.

It can be challenging to calculate an accurate incidence rate of HSV-ARN in HSE survivors, as these diseases are rare entities in different fields. In addition, performing a prospective study in order to determine the incidence is also difficult, because a large number of HSE patients need to be included and traced for many years. To overcome these difficulties, we conducted a retrospective nationwide survey.

However, there were several limitations in our current study. First, there is the possibility of an information bias, which includes a recall bias and an ascertainment bias. The recall bias could have resulted in a report of finding no cases when replying to the first questionnaires due to failures to review all the medical records. The ascertainment bias could have been caused with HSE cases whose causative viruses were not detected as being HSV because of false-negatives or due to not being examined, might have been dropped from our survey. Similarly, ARN cases in which the causative viruses were not confirmed could also have been potentially eliminated. It is also possible that there could have been a selection bias. In this study, questionnaires were sent to neurology and ophthalmology departments of teaching hospitals only. However, other departments, hospitals and clinics could have been involved. We also found that the response proportions were not all that high, especially for neurology departments. Thus, our extrapolation might have led to an over- or underestimation, as we supposed that the incidences were similar in both the neurology and ophthalmology departments of the responding as well as the non-responding hospitals and that each hospital has the same incidence rates of these diseases without considerating the size of the hospital. As mentioned above, we have many limitations to calculate the incidence proportion of HSV-ARN after HSE. However, we think it important to show the incidence proportion, because it can contribute to the early detection of HSV-ARN after HSE. To overcome the above limitation, a large-scale study based on insurance databases will need to be undertaken in the future.

In conclusion, this nationwide survey of the Japanese population showed that the proportion of patients with HSV-ARN following HSE was estimated to be 5.3% (95%CI: 3.2-8.0%). Although the interval periods between prior HSE and the onset of HSV-ARN varied, ranging from a simultaneous onset to longer than 10 years, nearly half of all cases are affected within 2 years. Neurologists and ophthalmologists need to be aware that HSE is a risk factor of HSV-ARN.

Acknowledgements We would like to thank all of the doctors who responded to our questionnaires, and Ms. Masumi Ishikawa for her assistance with this survey.

Conflicts of interest D.Todokoro, None; S.Kamei, None; H.Goto, None; Y.Ikeda, None; H.Koyama, None; H.Akiyama, None.

References

1. Schoenberger SD, Kim SJ, Thorne JE, Mruthyunjaya P, Yeh S, Bakri SJ, et al. Diagnosis and treatment of acute retinal necrosis: a report by the American Academy of Ophthalmology. Ophthalmology. 2017;124:382–92.
2. Shahi SK. Acute retinal necrosis results in low vision in a young patient with a history of herpes simplex virus encephalitis. Clin Exp Optom. 2017;100:208–13.
3. Zhou C, Zhu L, Fang S. Fulminant bilateral acute retinal necrosis syndrome associated with viral encephalitis: a case report. Exp Ther Med. 2016;12:2227–9.
4. Arruti M, Aldazabal M, Blanco A, Pineiro L, Zapico MS, Gonzalez F, et al. [Acute herpes simplex virus type 1 retinal necrosis three years after herpes simplex encephalitis]. Rev Neurol. 2014;58:45–6.
5. Sugitani K, Hirano Y, Yasukawa T, Yoshida M, Ogura Y. Unilateral acute retinal necrosis 2 months after herpes simplex encephalitis. Ophthalmic Surg Lasers Imaging. 2010;9:1–5.
6. Patel P, Ahmed E, Subramanian ML. Intravitreal foscarnet therapy for acyclovir-resistant acute retinal necrosis after herpes simplex encephalitis. Ophthalmic Surg Lasers Imaging. 2010;9:1–3.
7. Kianersi F, Masjedi A, Ghanbari H. Acute retinal necrosis after herpetic encephalitis. Case Rep Ophthalmol. 2010;1:85–9.
8. Vandercam T, Hintzen RQ, de Boer JH, Van der Lelij A. Herpetic encephalitis is a risk factor for acute retinal necrosis. Neurology. 2008;71:1268–74.
9. Yamamoto S, Nakao T, Kajiyama K. Acute retinal necrosis following herpes simplex encephalitis. Arch Neurol. 2007;64:283.
10. Klein A, Lefebvre P. Three consecutive episodes of acute retinal necrosis due to herpes simplex-1 over twelve years following herpetic encephalitis. Ocul Immunol Inflamm. 2007;15:411–3.
11. Curtis TH, Mandava N. Acute retinal necrosis as a late sequela of herpes simplex type 1 encephalitis in a child. J AAPOS. 2007;11:509–10.
12. Bristow EA, Cottrell DG, Pandit RJ. Bilateral acute retinal necrosis syndrome following herpes simplex type 1 encephalitis. Eye (Lond). 2006;20:1327–30.
13. Whitley RJ. Herpes simplex encephalitis: adolescents and adults. Antiviral Res. 2006;71:141–8.
14. Solomon T, Michael BD, Smith PE, Sanderson F, Davies NW, Hart IJ, et al. Management of suspected viral encephalitis in adults–Association of British Neurologists and British Infection Association National Guidelines. J Infect. 2012;64:347–73.
15. Takase H, Okada AA, Goto H, Mizuki N, Namba K, Ohguro N, et al. Development and validation of new diagnostic criteria for acute retinal necrosis. Jpn J Ophthalmol. 2015;59:14–20.
16. Kamei S, Takasu T. Nationwide survey of the annual prevalence of viral and other neurological infections in Japanese inpatients. Intern Med. 2000;39:894–900.
17. Kanda Y. Investigation of the freely available easy-to-use software 'EZR' for medical statistics. Bone Marrow Transplant. 2013;48:452–8.
18. Raschilas F, Wolff M, Delatour F, Chaffaut C, De Broucker T, Chevret S, et al. Outcome of and prognostic factors for herpes simplex encephalitis in adult patients: results of a multicenter study. Clin Infect Dis. 2002;35:254–60.
19. Boucher A, Herrmann JL, Morand P, Buzele R, Crabol Y, Stahl JP, et al. Epidemiology of infectious encephalitis causes in 2016. Med Mal Infect. 2017;47:221–35.
20. Wada-Isoe K, Kusumi M, Kai T, Awaki E, Shimoda M, Yano H, et al. Epidemiological study of acute encephalitis in Tottori Prefecture. Japan. Eur J Neurol. 2008;15:1075–9.