Table 1
Baseline clinical characteristics of all subjects with and without endpoints

	Ischemic stroke			All-cause death		
	(−)	(+)	p	(−)	(+)	p
No. of subjects	7806	95		7740	161	
Age (years)	63.9 ± 9.7	69.6 ± 7.2	<0.001	63.9 ± 9.7	69.8 ± 7.8	<0.001
Body mass index (kg/m^2)	23.9 ± 2.9	23.6 ± 3.0	0.20	24.0 ± 2.9	22.9 ± 3.0	<0.001
Systolic blood pressure (mmHg)	131 ± 19	139 ± 20	<0.001	131 ± 19	132 ± 20	0.31
Diastolic blood pressure (mmHg)	79 ± 11	80 ± 11	0.31	79 ± 11	76 ± 10	0.006
Hemoglobin A1c (%)	5.15 ± 0.74	5.28 ± 0.83	0.09	5.15 ± 0.74	5.30 ± 0.98	0.052
Serum creatinine (mg/dL)	0.82 ± 0.20	0.85 ± 0.16	0.15	0.82 ± 0.19	0.88 ± 0.42	0.18
eGFR (mL/min/1.73 m^2)	73.4 ± 15.1	69.2 ± 13.5	0.006	73.4 ± 15.0	70.2 ± 18.0	0.004
Uric acid (mg/dL)	5.73 ± 1.35	5.45 ± 1.51	0.038	5.72 ± 1.35	5.95 ± 1.59	0.16
Total cholesterol (mg/dL)	191 ± 32	188 ± 35	0.15	192 ± 32	181 ± 35	0.001
Triglyceride (mg/dL)	126 ± 84	123 ± 85	0.41	126 ± 84	121 ± 81	0.39
LDL-cholesterol (mg/dL)	114 ± 29	112 ± 31	0.25	114 ± 29	107 ± 32	0.023
HDL-cholesterol (mg/dL)	56 ± 15	56 ± 16	0.90	56 ± 15	53 ± 17	0.002
hs-CRP (mg/L)	0.54	0.80	<0.001	0.55	1.07	<0.001
Hypertension (%)	45.6	67.4	<0.001	45.7	54.0	0.038
Diabetes mellitus (%)	7.7	11.6	0.17	7.6	14.3	0.004
Dyslipidemia (%)	21.6	18.9	0.61	21.4	26.1	0.17
Obesity (%)	33.3	33.7	0.91	33.5	26.1	0.052
Atrial fibrillation (%)	2.6	15.8	<0.001	2.7	6.2	0.013
Current/past smoking (%)	62.2	75.8	0.007	62.2	68.9	0.085

hs-CRP, high sensitivity C-reactive protein; HDL, high density lipoprotein; LDL, low density lipoprotein; eGFR: estimated glomerular filtration rate.
Log-transformed values were used for comparisons of CRP levels.
Data are shown as mean ± S.D. hs-CRP are shown as geometric mean.

2.5. Statistical analysis

The cumulative survival curves (free of ischemic stroke or free of all-cause death) by hs-CRP tertile levels were determined according to the age-adjusted Cox model (Fig. 1). The proportionality assumptions of the hazard by hs-CRP tertile were verified by log minus log curves. To determine the relative risks for each hs-CRP tertile level, multivariate Cox proportional hazard models were used. Age and known cardiovascular risk factors were used, and age (10-year increase), systolic blood pressure, total cholesterol, high density lipoprotein cholesterol, uric acid, estimated glomerular filtration rate, body mass index, smoking, and presence of diabetes were forced into the multivariate adjusted model. One rural community ($n = 728$) was excluded from multivariate analysis because of missing data for serum uric acid, and cases having other missing data as random phenomena were also excluded. This multivariate analysis was finally performed for 7127 subjects. The results are expressed as the hazard ratio (HR) and the corresponding 95% confidence interval (CI). The analyses were performed using the SPSS statistical package, version 11.0.

3. Results

The mean follow-up period was 2.7 years. During follow-up, 130 subjects (1.6%) had a first stroke. Of these, 95 (1.2%) had an ischemic stroke; 161 (2.0%) died due to any cause; and 34 (0.4%) had a new onset, non-fatal myocardial infarction (MI). All of the non-ischemic strokes were the result of intracerebral or subarachnoid hemorrhages.

Baseline characteristics of the participants with and without ischemic stroke or all-cause death are shown in Table 1. Age, systolic and diastolic blood pressures, serum creatinine level, the prevalence of hypertension, atrial fibrillation, and smoking were higher in those with ischemic stroke than in those without. On the other hand, eGFR was lower in those with ischemic stroke than in those without. Similar results were obtained with respect to all-cause death. Some paradoxical relationships were found with respect to the uric acid level in participants with ischemic stroke, and the total cholesterol level and LDL level in those with all-cause death (Table 1).

The median serum hs-CRP level was 0.5 mg/L (95 percentile range: 0.1–4.3 mg/L) in males. This median hs-CRP level was lower than the levels reported in other populations in which hs-CRP levels were measured using the same assay methodology [1–3]. A total of 917 participants showed CRP levels ≤0.1 mg/L. Overall tertile ranges for the hs-CRP levels were: 1st, 0.1–0.3; 2nd, 0.4–0.7; and 3rd, ≥0.8 mg/L. Participants showing CRP > 10.0 mg/L comprised 1.7% of the study population. However, presence of acute infectious condition cannot be judged by CRP level alone, so making a cut-off level for infection is not possible. We therefore ventured to perform analyses without any exclusion criteria for high CRP level.

Table 2
Hazard ratios for first ischemic stroke and all-cause death by hs-CRP tertile levels

	hs-CRP tertile	Incidence of events/no. of subjects, n (%)	Age adjusted hazard ratios (95% CI)	p	Multivariate adjusted hazard ratios (95% CI)[a]	p
Ischemic stroke	1	22/2922 (0.75)	1.00 (reference)		1.00 (reference)	
	2	28/2296 (1.22)	1.41 (0.80–2.48)	0.24	1.30 (0.72–2.33)	0.39
	3	45/2683 (1.68)	1.95 (1.17–3.25)	0.010	1.77 (1.04–3.03)	0.037
All-cause death	1	36/2922 (1.23)	1.00 (reference)		1.00 (reference)	
	2	37/2296 (1.61)	1.22 (0.77–1.93)	0.40	1.15 (0.71–1.88)	0.57
	3	88/2683 (3.28)	2.32 (1.57–3.42)	<0.001	2.26 (1.49–3.42)	<0.001

hs-CRP, high sensitivity C-reactive protein; CI, confidence interval.
[a] Age (10-year increase), systolic blood pressure, total cholesterol, high density lipoprotein cholesterol, uric acid, estimated glomerular filtration rate, body mass index, smoking (current and past), and the presence of diabetes were forced into the Cox regression analysis model.

As shown in Fig. 1, first ischemic stroke-free survival was lower in the higher hs-CRP tertile level when adjusted for age ($p = 0.034$). Similar results were observed for all-cause death-free survival rates ($p < 0.001$). The proportionality assumptions of the hazard by hs-CRP tertiles for these outcomes were satisfied.

In the multivariate Cox regression analysis model adjusted by age, a significantly increased hazard ratio of ischemic stroke was found in the 3rd hs-CRP tertile (HR = 1.95, $p = 0.010$) compared to the 1st hs-CRP tertile. After adjustment for age (10-year increase) and other classical cardiovascular risk factors, such as systolic and diastolic blood pressures, total cholesterol, high density lipoprotein cholesterol, uric acid, eGFR, BMI, smoking (current and past), and the presence of diabetes, the estimated HRs were maintained in the 3rd hs-CRP tertiles (HR = 1.77, $p = 0.037$). The results of the analysis of all-cause death were similar (Table 2). When the presence of atrial fibrillation was included in the multivariate adjusted model for ischemic stroke, the statistical significance of the hs-CRP tertiles declined (3rd hs-CRP tertile, HR = 1.56, $p = 0.10$).

On the other hand, there was no significant association between the hs-CRP tertiles and strokes from any causes (trend $p = 0.19$) in the model adjusted by age and other classical cardiovascular risk factors.

4. Discussion

This prospective cohort study found that baseline serum hs-CRP level was an independent predictor for future ischemic stroke and all-cause mortality in an apparently healthy population. It is interesting that these results were obtained in the Japanese population, which has a lower median hs-CRP level than Western populations [4,5].

The major risk factors for stroke and cardiovascular disease, such as smoking, diabetes, and hypertension, are associated with higher hs-CRP levels [11,12]. These relationships could potentially explain the associations that have been found between hs-CRP level and stroke or mortality. However, since adjustment for such risk factors did not have a large effect on the associations, the traditional risk factors cannot completely explain the relationship between the hs-CRP level and ischemic stroke events.

Carotid plaque formation is a well-established predictor for future ischemic stroke in the general population [13,14]. Our previous data showed a close association between the hs-CRP level and the severity of carotid atherosclerosis as demonstrated by plaque formation in men [6]. The present prospective results show that future stroke events were related to elevated baseline hs-CRP levels; this finding appears to substantiate our previous cross-sectional data. Although a significant association between the hs-CRP level and carotid atherosclerosis was only seen in men in our previous data, the present study could not demonstrate a gender difference for the association between hs-CRP level and the study endpoint.

Atrial fibrillation has been known to be closely related with ischemic stroke due to cardiac thromboembolism. In the present study, the presence of atrial fibrillation was the strongest predictor for ischemic stroke in the same model of multivariate Cox regression analysis with various risk factors (HR = 5.13, 95% CI; 2.82–9.35, $p < 0.001$). It is considered natural that the significance of the hs-CRP tertiles declined when the presence of atrial fibrillation was included in the multivariate adjusted model for ischemic stroke.

In the present cohort, the association between elevated hs-CRP level and stroke was only present when the analysis was limited to the ischemic stroke subtype. In the present study's subjects, all non-ischemic strokes were intracranial hemorrhages, which are known to be caused by rupture of cerebral perforating arteries or an intracranial aneurysm. These pathological conditions develop primarily due to hypertension and small artery hyalinosis [15]. The relationship between cerebral aneurysm and atherosclerosis is not considered to be very strong [16]. Few large-scale prospective cohort studies have addressed stroke subtype.

The major results of our study are completely consistent with the findings of the Hisayama Study [7]. Although the novelty of our study may be lacking, we would raise some unique minor points of difference from the findings and design of the Hisayama Study. First, the presence of atrial fibrillation reduced the predictive power of CRP for ischemic stroke in our study. Second, hs-CRP measurement at baseline was planned a priori and the assay was performed immediately, without long-term cryopreservation. Third, registration of our study population was started in 2002. Compared with the survey in 1988 of the Hisayama study, many new anti-atherosclerotic agents such as strong statins, long-acting anti-hypertensive agents and angiotensin-receptor blockers were likely to be in more frequent use in our study population. Furthermore, our study population comprised older, more obese subjects compared with those in Hisayama Study. All of these characteristics are thought to represent a closer fit with modern Japanese society and community population.

It is possible that the hospital-based follow-up used in the present study was not completely reliable for detecting clinical events. However, an attempt was made to retrieve and view all medical charts from all hospitals and clinics located in the survey area, and the study included several remote teaching hospitals and tertiary referral medical centers. Furthermore, the population of the study district has been stable, with an annual variation rate of only 0.2%. Moreover, participants who developed cerebrovascular and cardiovascular diseases or fatal events had access to only a limited number of medical institutes. Therefore, most major clinical adverse events were likely to have been captured in the present study cohort.

Elevated hs-CRP levels did not reflect the presence of imminent diseases from which stroke events or all-cause deaths had not yet occurred, since the interval between baseline hs-CRP measurement and the ischemic stroke event or death was relatively long: a mean of 1.8 years for ischemic stroke events and a mean of 1.9 years for all-cause death.

Some study limitations should be noted. The results of this study are based on one baseline hs-CRP measurement. Subjects who had recent acute inflammatory conditions, other than a mild "common cold", were not included in the study. However, the subjects were not examined to determine whether any chronic infections, including silent infections such as periodontitis, bladder cystitis, and chronic bronchitis, were present. Chronic infections have been known to have a relationship with carotid atherogenesis [17]. The present study did not assess the use of drugs that can lower hs-CRP levels, such as rennin–angiotensin system inhibitors [18,19], statins [20], and thiazolidinedione [21]. However, it was unlikely that the frequency of the use of these medications was higher in event-free participants. Although imaging was used to verify all stroke cases who visited the hospital with typical symptoms of neurological deficit, patients with events who were not hospitalized or those who were hospitalized at hospitals located outside the area could not be captured in this study design. However, this occurred very infrequently. Finally, this study tested several possible outcomes, including stroke and coronary heart disease in each gender, and then reported the significant findings. The possibility thus remains that chance findings were responsible for the present results.

In conclusion, CRP levels can predict future ischemic stroke and mortality in Japanese males from the general population, independently from traditional cardiovascular risk factors other than atrial fibrillation.

Conflict of interest

The authors report no conflicts of interest.

Acknowledgments

This study was supported by a Grant from the Ministry of Health and Welfare of Japan (No. 17120501 Director: Akira Ogawa, MD), and the Open Translational Research Center Project of our university.

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Symmetrical brainstem encephalitis caused by herpes simplex virus

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ARTICLE INFO

Article history:
Received 25 February 2008
Accepted 8 June 2008

Keywords:
Brainstem encephalitis
Herpes simplex virus
MRI

ABSTRACT

We describe a 53-year-old man with herpes simplex virus (HSV) brainstem encephalitis diagnosed based by positive HSV immunoglobulin M antibodies from cerebrospinal fluid. The MRI findings of this case had three unique features. First, the lesions were symmetrical. Second, the lesions may have been associated with reactivation of HSV infection in the region of the trigeminal nerve. Third, diffusion-weighted and apparent diffusion coefficient (ADC) imaging, conducted for the first time on an HSV brainstem encephalitis case, suggested that the lesions were associated with vasogenic edema.

1. Introduction

Herpes simplex virus (HSV) is one of the common pathogens causing encephalitis. On MRI, abnormalities associated with HSV encephalitis are frequently seen in the temporal lobe.[1] However, HSV encephalitis in the brainstem is uncommon. Here, we report the first case of HSV brainstem encephalitis with symmetrical brainstem lesions evident on MRI. We also review the clinical features of HSV brainstem encephalitis.

2. Case report

A 53-year-old man, previously healthy, felt febrile and noticed a headache and a single herpetic lesion on the upper lip. Six days later, he developed paresthesia of the upper lip. After another three days, he was admitted to our hospital due to the onset of diplopia, hiccups and dysphagia. His mental status was normal. His neck was stiff and the cranial nerve examination showed the following: equal-sized reactive pupils, full visual fields, normal visual acuity, mild limitation of left eye abduction, bilateral horizontal and vertical gaze-evoked nystagmus of high amplitude, bilateral facial hypesthesia, normal facial strength, dry eyes, dysphagia, paralysis of the bilateral soft palate, slurred speech, intraoral paresthesia, and a severely limited ability to protrude the tongue (although the tongue did not have atrophy). There was no abnormality in muscle tone, power, or deep tendon reflexes. There were no pathological reflexes. Mild ataxia of the trunk was noted. The Romberg test was negative. Bowel and bladder functions were normal.

Cerebrospinal fluid (CSF) analysis showed an opening pressure of 210 mmH_2O, 8 cells/μL (100% mononuclear), protein 27 mg/dL, glucose 90 mg/dL, and anti-HSV immunoglobulin M antibodies (evaluated using antibody capture enzyme immunoassay) had a 2.08 cutoff index. Polymerase chain reaction test of the CSF was negative for HSV. Immunoglobulin G index was 0.46. Serum immunoglobulin G level was mildly decreased (753 mg/dL; normal value: 918–1742 mg/dL). Serum antiglycolipid antibodies (GM1 ganglioside, asialo-GM1 ganglioside, GQ1b ganglioside, GD1b ganglioside) were negative.

MRI examination showed symmetrical high signal intensity of the bilateral brainstem tegmentum, middle and inferior cerebellar peduncle on the fluid-attenuated inversion recovery (FLAIR), T2-weighted, and diffusion-weighted MRI; slightly high signal intensity was shown with apparent diffusion coefficient (ADC) imaging; and low signal intensity on contrast-enhanced T1-weighted MRI (Fig. 1).

Upon treatment with acyclovir (1500 mg/day for 10 days) and methylprednisolone pulse therapy (1000 mg/day for 3 days), the symptoms improved except for mild impairment of facial sensations. Six months later, the abnormal signals disappeared in T2-weighted and FLAIR images on the MRI.

3. Discussion

There have been several reports describing HSV encephalitis limited to the brainstem as confirmed by MRI.[2–5] These previously described cases and the present case are listed in Table 1. The main lesions evident on MRI are not in the midbrain but in the pons/medulla and exist symmetrically in some cases. Routine CSF parameters vary among patients. Generally, the prognosis is good with acyclovir treatment. Only one patient with encephalitis caused by HSV2 had a recurrence; in general, patients with brainstem encephalitis caused by HSV2 are susceptible to relapse.

The MRI findings of our case are unique because of the symmetrical distribution of lesions and because of the high signal intensity area from the entry root of the trigeminal nerve through to the spinal tract of the trigeminal nerve of the medulla. Such a distribution may have increased the risk of reactivation of HSV infection in the region of the trigeminal nerve. There are a few reports of cases with clinical brainstem encephalitis caused by HSV whose brain MRIs revealed no abnormalities.[6,7] Therefore, the discordance between clinical illness and MRI changes in the present case is not without precedent. In this case, we performed diffusion-weighted and ADC imaging, which to our knowledge has not been previously conducted in similar cases. ADC imaging suggested the lesions might be associated with vasogenic edema, and the slightly high signal intensity on ADC imaging indicated a good prognosis. These findings suggest that an autoimmune mechanism might be involved in HSV brainstem encephalitis.

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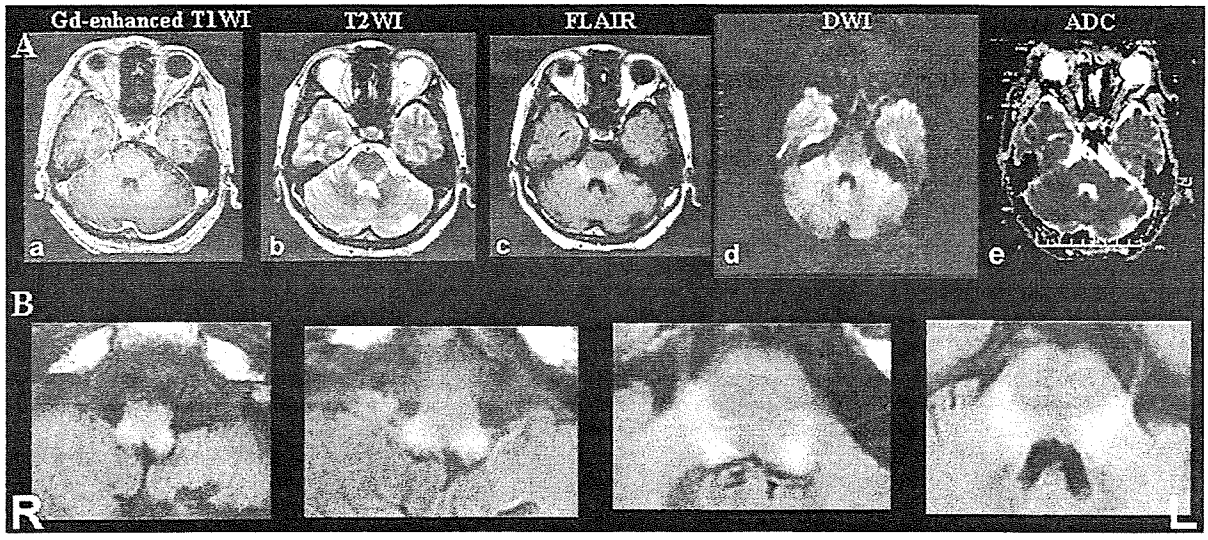

Fig. 1. Brain MRI. (A) Panels from left to right: (a) Gd-enhanced T1-weighted (Gadollinium-enhanced T1-W1) MRI showed symmetrical low signal intensity in the bilateral pontine tegmentum and middle cerebellar peduncle, (b) T2-weighted (T2-W1), (c) fluid-attenuated inversion recovery (FLAIR) and (d) diffusion-weighted (DW1) MRI demonstrated symmetrical high signal intensity in the bilateral pontine tegmentum and middle cerebellar peduncle. In the same area, (e) apparent diffusion coefficient (ADC) imaging showed slightly high signal intensity. (B) FLAIR MRI demonstrated a high signal intensity area from the entry root of the trigeminal nerve through to the spinal tract of the trigeminal nerve in the medulla.

Table 1
Case reports describing HSV encephalitis limited to the brainstem as confirmed by MRI

Year Author	1993 Mertens et al.	1994 Shoji et al.	1998 Sakakibara et al.	2003 Tang et al.	Present case
Age (years)	21	35	45	27	53
Sex	Female	Male	Male	Female	Male
HSV type	HSV1	HSV1	HSV1	HSV2	Not determined
Initial symptoms	Influenza like symptoms	ND	Headache	Painful vesicular genital rash	Headache, single herpetic lesion on the upper lip
Other neurological features	Photophobia, diplopia, bilateral abducens nerve palsy, facial palsy	ND	Coma, dysrhythmic breathing	Headache, gait unsteadiness, diplopia, photophobia, upper limb intention tremor, truncal ataxia, oscillopsia, ophthalmoplegia, nystugmus,respiratory failure,	Left abducens nerve palsy, nystagmus, bilateral facial hypesthesia, dry eyes, dysphagia, paralysis of the bilateral soft palate, slurred speech, intraoral paresthesia, limited ability to protrude the tongue, mild trunk ataxia
Areas of abnormal intensity on brain MRI	Upper pons, medulla	Pons, medulla	Right-side dominant, bilateral pontine extending slightly to the midbrain and medulla	Central medulla, ventral pons	Bilateral pontine tegmentum and lateral medulla, middle and inferior cerebellar peduncle
CSF cell count (No. cells/μL)	386 (lymphocytes 76%)	ND	10	220	8 (mononuclear 100%)
Protein levels of CSF (mg/dL)	27	ND	93	200	27
Treatment	Acyclovir	Acyclovir	Acyclovir, vidarabine, steroid, mannitol	Acyclovir	Acyclovir, steroid
Sequelae	None	Mild	Mild	Relapse	Mild

CSF = cerebrospinal fluid, HSV = herpes simplex virus, ND = not described.

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doi:10.1016/j.jocn.2008.06.005