

ORIGINAL ARTICLE

Spinal cord hemangioblastomas in von Hippel–Lindau disease

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Study Design: Retrospective data analysis.

Objective: To clarify the clinical features and surgical management of spinal cord hemangioblastomas in patients with von Hippel–Lindau disease (VHL).

Setting: Clinical VHL Research Group in Japan, Japan.

Methods: Forty-eight out of 66 patients with associated spinal cord hemangioblastoma among 142 VHL patients were retrospectively examined with respect to clinical features, accompanying lesions and outcome of surgical treatment.

Results: Among these 48 patients, 46 of them (95.8%) also had a central nervous system (CNS) hemangioblastoma at another site: 42 (87.5%) with cerebellar hemangioblastoma and 11 (22.9%) with brain stem hemangioblastoma. Twenty-three patients (47.9%) had more than one spinal cord hemangioblastoma. The 48 patients with spinal cord hemangioblastomas collectively had a total of 74 tumors. The tumor was accompanied with a syrinx in 64 and without it in 10 patients. Forty of the 48 patients underwent surgical treatment for their spinal cord hemangioblastomas, and 7 of these 40 underwent surgical treatment twice. When functional changes in the patients after these 47 operations were examined by postoperative evaluation by McCormick's classification, 39 of these operations (83.0%) resulted in improvement/no change and 8 (17.0%) in aggravation of symptoms.

Conclusion: Von Hippel–Lindau disease patients bearing spinal cord hemangioblastomas mostly had a CNS hemangioblastoma at another site. These tumors can be removed in the majority of VHL patients without aggravation. In these patients, when the timing of treatment for spinal cord hemangioblastoma is determined, the probability of occurrence and treatment of other lesions should be considered.

Spinal Cord (2009) 47, 447–452; doi:10.1038/sc.2008.151; published online 25 November 2008

Keywords: spinal cord hemangioblastoma; von Hippel–Lindau disease; clinical features; surgical outcomes

Introduction

Von Hippel–Lindau disease (VHL) is an autosomal dominant hereditary disease in which central nervous system (CNS) and retinal hemangioblastomas; renal cell carcinomas; pheochromocytomas; abdominal cystic lesions such as those in the kidneys, liver, and pancreas; and epididymal cysts develop. VHL manifests itself by approximately 65 years of age and shows an annual incidence of one per 36 000 live births. Manifestations in the CNS include cerebellar, brain stem, spinal cord, and suprasellar hemangioblastomas and endolymphatic sac tumors.^{1–6} The causative gene, located in the chromosome 3p25–26 region,⁷ is also related to

the occurrence of sporadic CNS hemangioblastoma⁸ and renal cell carcinoma.⁹

Sixty to 80% of VHL patients manifest CNS hemangioblastomas in the cerebellum, brain stem and spinal cord.^{1,10–13} Spinal cord hemangioblastoma is the second most common among CNS hemangioblastomas, accounting for more than 40% of VHL-associated CNS lesions.¹⁴ Spinal cord hemangioblastomas have morphological features similar to CNS hemangioblastomas elsewhere. Histologically, CNS hemangioblastomas are highly vascular tumors composed of neoplastic stromal cells, pericytes and endothelial cells. The neoplastic cell of the origin for CNS hemangioblastomas is the mesoderm-derived, embryologically arrested hemangioblast.¹⁵ Although a small spinal cord hemangioblastoma is mostly asymptomatic, it becomes symptomatic after the syrinx associated with the tumor has enlarged. Among manifestations in patients with VHL, the earliest features

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Received 28 July 2008; accepted 24 October 2008; published online 25 November 2008

are mostly retinal and cerebellar hemangioblastomas, while it is relatively rare that spinal cord hemangioblastoma is the earliest manifestation. Although most of these hemangioblastomas are located in the intramedullary region accompanied with a syrinx, postoperative deterioration is not often encountered.^{14,16} Since the advent of the era of magnetic resonance imaging (MRI), small asymptomatic spinal cord hemangioblastomas can be easily detected on an MRI.¹ In VHL patients, spinal cord hemangioblastomas are frequently found. VHL patients harboring spinal cord hemangioblastomas face various treatment problems that are not encountered by patients harboring sporadic spinal cord hemangioblastomas, because VHL patients with spinal cord hemangioblastomas may also require treatment for other CNS hemangioblastomas or visceral tumors simultaneously or in the future. However, most of the previous studies have dealt with isolated sporadic spinal cord hemangioblastomas, and the clinical features and the management of spinal cord hemangioblastomas in VHL patients have not yet been fully clarified.¹⁴ Here, we describe clinical features and management for VHL patients with associated spinal cord hemangioblastomas.

Methods

Patients with VHL were collected by the Clinical VHL Research Group in Japan in 2000–2002. The members of the Clinical VHL Research Group in Japan consisted of neurosurgeons who belonged to 336 hospitals approved as training facilities for neurosurgery in Japan and joined this study. Diagnosis for VHL was based on the following the criteria³: (i) patients with a family history of developing hemangioblastoma in the CNS and retina, renal cell carcinoma, pheochromocytoma or pancreatic tumors or cysts, epididymal cystadenoma; (ii) patients without a family history of VHL disease, but who develop hemangioblastoma in combination with other tumors, such as renal cell carcinoma, pheochromocytoma, pancreatic tumors or cysts, or epididymal cystadenoma. All symptomatic and asymptomatic spinal cord hemangioblastomas were diagnosed based on clinical symptoms and neuroradiological findings by MRI (Figure 1), and all surgically removed spinal cord hemangioblastomas were histologically verified. Sixty-six patients having spinal cord hemangioblastomas among 142 VHL patients in 81 VHL families were retrospectively examined with respect to the following: gender, age, type of VHL, spinal tumor location, onset age of spinal cord hemangioblastoma and other lesions (cerebellar hemangioblastoma, brain stem hemangioblastoma, retinal hemangioblastoma or renal cell carcinoma), presence of a syrinx, number of spinal tumors, other CNS hemangioblastomas, other complicating lesions (endolymphatic tumor, renal cell carcinoma, pheochromocytoma, epididymal cyst, renal cyst, pancreas cyst and liver cyst), presence of VHL family history, manifestations in the family, follow-up period and outcome of surgical treatment. In addition, the age of the patient at the onset of spinal cord hemangioblastoma, the period between the onset of the earliest manifestation in VHL and the operation

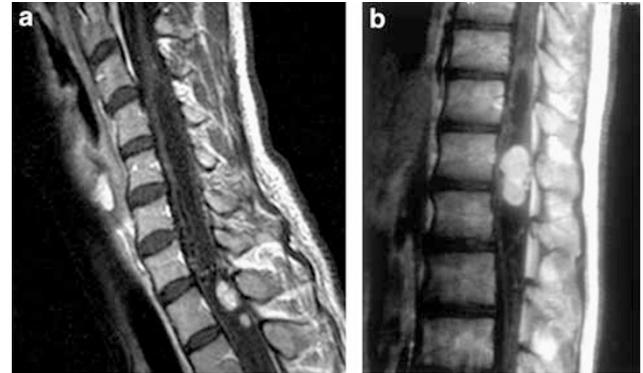


Figure 1 T1-weighted magnetic resonance imaging (MRI) of spinal cord hemangioblastomas in von Hippel–Lindau (VHL)-diseased patients. Spinal cord hemangioblastoma usually shows intramedullary homogeneously enhanced mass lesion frequently associated with syrinx on MRI. (a) Cervical cord hemangioblastoma in a VHL patient. (b) Lumbar cord hemangioblastoma in a VHL patient.

Table 1 Clinical/functional classification scheme^a

Grade	Definition
I	Neurologically normal; mild focal deficit not significantly affecting function of involved limb; mild spasticity or reflex abnormality; normal gait
II	Presence of sensorimotor deficit affecting function of involved limb; mild-to-moderate gait difficulty; severe pain or dysesthetic syndrome impairing patient's quality of life; still functions and ambulates independently
III	More severe neurological deficit; requires cane/brace for ambulation or significant bilateral upper extremity impairment; may or may not function independently
IV	Severe deficit; requires wheelchair or cane/brace with bilateral upper extremity impairment; usually not independent

^aCited from McCormick *et al.*¹⁷

for spinal cord hemangioblastoma and times of surgical treatment for spinal cord hemangioblastoma were examined. Data from the clinical charts and radiological records were used to obtain the above information. Evaluation of surgical treatment was assessed in terms of McCormick's functional grade (Table 1)¹⁷ before and 6 months after the operation. The change in the status of the patient after the operation was classified into three types: improved, no change and aggravated. The relationships between the postoperative McCormick's functional grade and age of patient at the time of the operation, number of simultaneously resected spinal cord hemangioblastomas during the operation, volume of the tumor preoperatively, spine level of the tumor, McCormick's functional grade before the operation and presence of a syrinx were assessed on MRI. Exclusion criteria were as follows: incomplete description in clinical charts and neuroradiological records about site of tumor, accompanying lesions, family history of VHL and surgical outcome evaluation. Then, among 66 patients bearing spinal cord hemangioblastomas associated with VHL, 48 of them, representing 45 VHL families, were examined. For statistical analysis, non-parametric test was applied by Mann–Whitney's *U*-test or Spearman's correlation coefficient by rank test. Statistical significance was set at $P < 0.05$.

Results

Forty-eight patients bearing spinal cord hemangioblastomas in 45 VHL families were collected from 27 hospitals including all districts in Japan, and consisted of 21 males and 27 females. The age of the patients ranged from 13 to 52 years, and the mean age was 33.5 ± 9.6 years. The follow-up period ranged from 1 to 20 years, with a mean of 6.5 ± 5.4 years. The 48 patients collectively had a total of 74 spinal cord hemangioblastomas. Among these 48 patients, 46 (95.8%) had more than one CNS hemangioblastoma at a site in addition to the spinal cord, and 12 of 46 had the spinal hemangioblastoma as the first manifestation associated with simultaneously recognized lesions. The remaining two patients without another CNS hemangioblastoma developed spinal cord hemangioblastomas at the ages of 12 and 16 years as the first manifestation of VHL. Twenty-three patients (47.9%) had more than one spinal cord hemangioblastoma, and the mean number of tumors in patients harboring spinal cord hemangioblastoma was 1.54. Forty-two patients (87.5%) also had cerebellar hemangioblastoma; and 11 (22.9%), a brain stem hemangioblastoma. Sixteen patients (33.3%) also presented with retinal hemangioblastoma, 16 (33.3%) with renal cell carcinoma, 11 (22.9%) with pancreas cyst, 5 (10.4%) with a renal cyst and 1 (2.1%) with a pheochromocytoma (Figure 2). The onset ages of spinal cord hemangioblastoma, cerebellar hemangioblastoma and brain stem hemangioblastoma ranged from 5 to 49 years, from 10 to 47 years and from 10 to 49 years (mean 27.5 ± 10.5 , 24.9 ± 8.2 and 27.5 ± 10.4 years), respectively. For other manifestations, the onset ages of retinal hemangioblastoma and renal cell carcinoma ranged from 11 to 49 years and from 19 to 49 years (mean 23.2 ± 11.5 and 32.9 ± 9.4 years), respectively (Figure 3). Spinal cord hemangioblastoma was the earliest manifestation in 23 patients, the second in 13, and the third in 12 patients. The mean period between the first manifestation of VHL except for spinal cord hemangioblastoma and the operation for spinal cord hemangioblastoma was 4.4 years (Figure 4).

Thirty spinal cord hemangioblastomas (40.5%) were located at the cervical level, 40 (54.1%) at the thoracic and 4 (5.4%) at the lumbar. Although the thoracic site of spinal cord hemangioblastomas was the most dominant, tumors at the cervical level were relatively the most common on a per spine level (cervical, 4.3; thoracic, 3.3; lumbar, 0.8). This occurrence ratio of cervical commonness revealed that spinal cord hemangioblastoma in VHL usually occurred more rostrally than caudally. Sixty-four tumors (86.5%) were associated with a syrinx; and 10 (13.5%) without one. Among the 48 VHL patients harboring spinal cord hemangioblastomas, 40 of them (83.3%) underwent 47 surgical resections for spinal cord hemangioblastomas, whereas 8 patients were under observation because of no symptom with the tumor. Seven patients underwent two operations for spinal cord hemangioblastomas. The mean period between the first operation and the second operation for the latter group was 9.5 years. Among the 47 operations, 16 of them were for plural spinal lesions; and 31 for single lesion. Total removal was performed in 44 operations

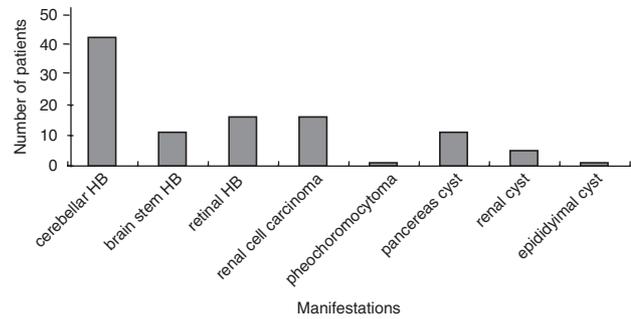


Figure 2 Accompanied manifestations in von Hippel–Lindau-diseased patients harboring spinal cord hemangioblastomas.

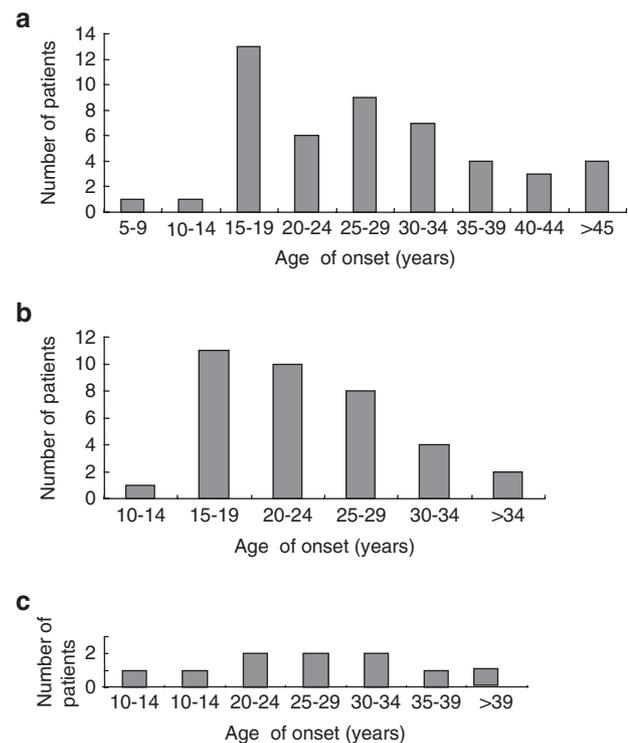


Figure 3 The onset ages of central nervous system hemangioblastomas in von Hippel–Lindau (VHL)-diseased patients harboring spinal cord hemangioblastomas. (a) Spinal cord hemangioblastomas. (b) Cerebellar hemangioblastomas. (c) Brain stem hemangioblastomas. The onset ages of spinal cord hemangioblastoma, cerebellar hemangioblastoma and brain stem hemangioblastoma were 27.5 ± 10.5 , 24.9 ± 8.2 and 27.7 ± 10.4 years, respectively.

(95.7%), subtotal in 1 (2.1%), and partial in 2 (4.2%) (Table 2). When functional grades before and after the operative stage were evaluated according to McCormick's classification, 6 of the 47 operations resulted 6 (12.8%) in improvement; 33 (70.2%) in no change; and 8 (17.0%) in aggravation. No change of more than 1 grade of McCormick's classification occurred after the operation (Figure 5). In addition, changes in McCormick's functional grade after the operation were not significantly correlated with the number of spinal cord hemangioblastomas surgically treated, presence of a syrinx, preoperative McCormick's

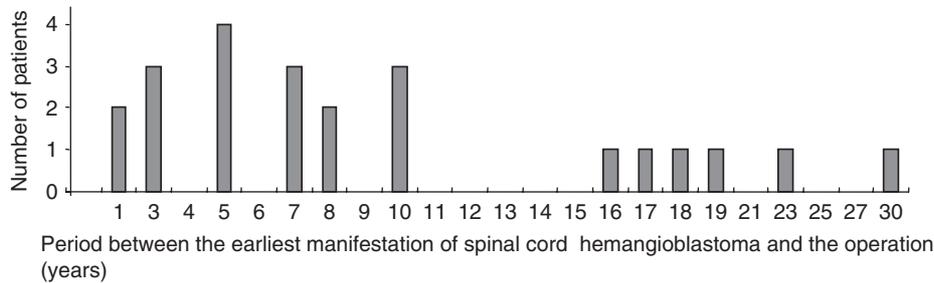


Figure 4 Period between the earliest manifestation of von Hippel–Lindau (VHL) disease preceding spinal cord hemangioblastoma and the operation for spinal cord hemangioblastoma with VHL. The mean period was 4.4 years.

Table 2 Summary of data on spinal hemangioblastomas (HBs) in von Hippel–Lindau (VHL)-diseased patients

Characteristics	
VHL families	45
VHL patients with spinal HB	48
Male/female	21/27
Age (mean years \pm s.d.)	33.5 \pm 9.6
Period of follow-up (mean years \pm s.d.)	6.5 \pm 5.4
Associated with >1 spinal HB	23
Associated with extra-spinal HB	46
Cerebellum	42
Brain stem	11
Number of VHL patients having undergone surgical treatment for spinal HB	40
Single operation	33
Multiple operations	7
Total number of surgical treatment	47
Extent of removal	
Total	44
Subtotal	1
Partial	2
Total number of spinal HB	74
With syrinx	64
Without syrinx	10
Volume of spinal HB (mm ³)	
>1000	28
500–1000	37
<500	28

functional grade or age of the patient at the time of the operation. However, the preoperative volume of the tumor was significantly correlated with postoperative changes in the grade ($P = 0.02$; Table 3).

Discussion

Spinal cord hemangioblastomas comprise 2–3% of primary intramedullary spinal cord tumors and are the third most common among them.^{15,18,19} Spinal cord hemangioblastomas may occur sporadically or in association with VHL, which is a multisystem familial cancer syndrome. Approximately two-thirds are sporadic in origin and the other third

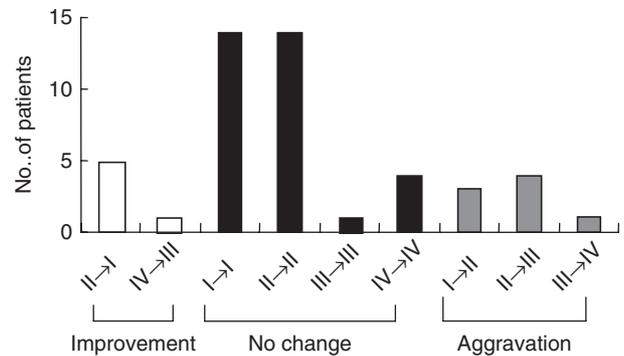


Figure 5 Functional neurological grades before and after the operative stage according to McCormick's classification. Six operations (12.8%) resulted in improvement (white columns); 33 (70.2%), no change (black columns); and 8 (17.0%), aggravation (grey columns). I, II, III and IV means McCormick's functional grades.

are associated with VHL. In VHL patients, spinal cord hemangioblastoma is a common feature, and spinal cord hemangioblastomas associated with VHL are often also accompanied by cerebellar and brain stem lesions; although sporadic spinal cord hemangioblastomas are almost always universally solitary. In addition, VHL patients with spinal cord hemangioblastomas usually also have tumors of other organs such as the eyes, the kidneys, the pancreas, the adrenal glands, paraganglia and the epididymus. This multiplicity accounts for the varied natural history of spinal cord hemangioblastomas associated with VHL, complexities in their management and uncertainties associated with long-term functional outcome.^{14,18,19}

Our study revealed that 66 (46.5%) out of 142 VHL patients examined had spinal cord hemangioblastomas. Although sporadic spinal cord hemangioblastomas are found in approximately 10–20% among all CNS hemangioblastomas, spinal cord hemangioblastoma with VHL is a more common manifestation. In addition, 95.8% of the 48 VHL patients with spinal cord hemangioblastoma examined also had CNS hemangioblastomas at another site. In particular, brain stem hemangioblastomas were associated with spinal cord hemangioblastomas. All 23 patients with more than one spinal cord hemangioblastoma also had CNS hemangioblastomas at sites in addition to the spinal region. From these results, when a spinal cord hemangioblastoma is found

Table 3 Change in McCormick's functional grade after the operation in patients with spinal hemangioblastomas (HBs)

Variables	Number of operation	Change of grade			P-value
		Improvement (n = 6)	No change (n = 33)	Aggravation (n = 8)	
<i>Age (years)</i>					
<21	17	4	10	3	0.54
21–40	23	1	18	4	
>40	7	1	5	1	
<i>Syrinx</i>					
Presence	42	6	29	7	0.51
No presence	5	0	4	1	
<i>Tumor volume (mm³)</i>					
<500	10	3	7	0	0.02
500–1000	26	3	18	5	
>1000	11	0	8	3	
<i>Operations for spinal HBs</i>					
Single	31	3	25	3	0.43
Multiple	16	3	8	5	
<i>Preoperative McCormick's grade</i>					
I	17	0	14	3	0.26
II	23	5	14	4	
III	2	0	1	1	
IV	5	1	4	0	

in a patient, VHL should be suspected and another manifestation associated with VHL should be explored, particularly a CNS hemangioblastoma. In contrast, when another manifestation of VHL aside from spinal cord hemangioblastoma is the earliest one in a VHL patient, spinal cord hemangioblastoma may be expected later. In our study, the interval between the onset of the initial manifestation and spinal cord hemangioblastoma was 4.4 years as a mean interval. When manifestation associated with VHL is detected and the patient is diagnosed as VHL, we can thus predict that a spinal cord hemangioblastoma will appear within 5 years.

Although previous reports on the spinal cord hemangioblastomas with VHL are limited, Lonser *et al.*¹⁴ examined 44 consecutive cases of patients who underwent 55 operations, and analyzed the relationship between clinical outcome and features. In their report, preoperative neurological function, the presence of a ventral or ventrolateral lesion and tumor size were correlated with postoperative neurological function and were useful as a predictor of outcome, but the presence of a syrinx was not a predictor of outcome. In our study, the preoperative neurological functions, age, number of simultaneously resected tumors and the presence of a syrinx were not correlated with the postoperative functions, but volume of the tumor was correlated with the functional change. The surgical outcome of the tumor volume <500 mm³ was better than >500 mm³. Before the tumor volume exceeds 500 mm³ during follow-up by MRI, surgical treatment should be considered.

In addition, when function before and after the operation was evaluated according to McCormick's classification, 83% of the surgical cases remained unchanged or showed improvement. With respect to the functional outcome, this

result indicates that spinal cord hemangioblastomas can be removed in the majority of patients without aggravation.

Central nervous system hemangioblastomas in VHL often have multiple periods of tumor growth separated by periods of arrested growth and exhibit stuttering growth patterns. Therefore, many untreated hemangioblastomas frequently remain asymptomatic, and do not require treatment for long intervals.^{5,20} These natural history of CNS hemangioblastomas in VHL should be considered when determining the optimal timing of screening for individual patients and for evaluating the timing and results of treatment.

The VHL patients often have opportunities to undergo plural operations for spinal cord hemangioblastomas. In our study, seven patients underwent operations twice, with a mean interval of 9.5 years. However, the preoperative functional grade at the second operation for spinal cord hemangioblastomas decreased in comparison with the postoperative grade after the first operation. As VHL patients frequently develop multiple spinal cord hemangioblastomas and have opportunities for multiple operations, neurological aggravation should be avoided at the first operation for spinal cord hemangioblastoma with VHL, if possible.

In conclusions, most VHL patients bearing spinal hemangioblastoma also have a hemangioblastoma at some other site. Although most spinal hemangioblastomas are located in the intramedullary region and have a syrinx, the aggravation rate after surgical resection for spinal hemangioblastomas is low. Generally, spinal cord hemangioblastomas can be safely removed in the majority of patients in VHL. The prognosis of spinal cord hemangioblastomas in VHL disease is good as long as consequent yearly surveillance is performed. The probability of the multiple occurrence and treatments of

other VHL-related lesions should be taken into account when the timing of the surgery is determined.

Acknowledgements

This study was supported by a grant-in-aid for scientific research from the Ministry of Health and Labor of Japan (No. 15-1). The present investigators involved in the co-authorship of this article, that is, the Clinical VHL Research Group in Japan, and their affiliations are as follows: Dr Yukihiko Ibayashi, Dr Toshihiko Yamaki, Sapporo Medical University; Dr Yoshihiro Numagami, Dr Eiji Jokura, Tohoku University; Dr Yoshimasa Kayama, Yamagata University; Dr Yuji Yamada, Tokyo Medical University; Dr Yoshiaki Shiokawa, Kyorin University; Dr Junko Yamashita, Dr Mitsuhiro Hasegawa, Kanazawa University; Dr Hisashi Hatano, Nagoya University; Dr Jun Shinoda, Dr Noboru Sakai, Gifu University; Dr Waro Taki, Satoshi Matsushima, Kenichi Murao, Toshio Matsubara, Mie University; Dr Jun A Takahashi, Kyoto University; Dr Kengo Matsumoto, Dr Hiroyuki Nakajima, Okayama University; Dr Masanori Hashimoto, University of Occupational and Environmental Health; Dr Shigeo Matsumoto, Kobe Municipal Central Hospital; Dr Kiyoshi Ichigizaki, National Tokyo Medical Center; Dr Ikuro Murase, Saiseikai Utsunomiya Hospital; Dr Kengo Kashiwabara, Fukui Prefectural Hospital; Dr Yuzo Yamakawa, Miyazaki Prefectural Hospital; Dr Hiromichi Yamazaki, Yamanashi Prefectural Central Hospital; Dr Satoshi Kubo, Kyoto Second Red Cross Hospital; Dr Koichi Tokuda, Kashiwaba Neurosurgery Hospital; Dr Seisho Abiko, Ubekosan Central Hospital; Dr Hiromichi Miyazaki, Hiratsuka Municipal Hospital; Dr Anda T, Dr Shibata S, Nagasaki University; Dr Tsunehiko Miyamoto, Seirei Mikatagahara Hospital; Dr Naosumi Okawa, Hoshigaoka Koseinenkin Hospital; Dr Shigebumi Morimoto, Dr Michio Inoue; and Dr Mitsuhiro Miyagami, Nippon University Surugadai Hospital.

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