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【原著論文】

当院におけるposterior reversible encephalopathy syndrome（PRES）12症例の検討

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Retrospective Study of 12 PRES cases in Jichi Medical University Hospital

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Abstract

In 12 cases of PRES (five men and seven women with mean onset age of 38.5 years) that we encountered in Jichi Medical University Hospital from May, 2002 to December, 2009, We retrospectively analyzed the blood pressure at onset, symptoms, etiologies, radiological findings, and treatment for PRES.

Clinical presentations were mainly headache and seizure. Mean peak blood pressure was 206.0mmHg (minimum-maximum, 154 to 264mmHg) in the systole, and 122.7mmHg (minimum-maximum, 82 to 186mmHg) in diastole. Etiologies of PRES included obstetric disease, pheochromocytoma, chronic renal failure, medication, disseminated intravascular coagulation (DIC) and neuromyelitis optica (NMO). In brain MRIs, lesions were most often found in the occipital lobe (seven cases), followed by the parietal (five) and frontal lobe (four). As the therapy of PRES, antihypertensive agents were used in the most cases, anticonvulsants, and osmotic diuretic in some. One case was associated with cerebral hemorrhage, but the others recovered without significant sequelae.

In typical cases of PRES with prominent hypertension and severe headache, its diagnosis was easy to make from the symptoms and radiological findings. But, we have to be alert for some atypical cases of the condition with slight hypertension as seen in NMO cases or only mild headache as its onset symptom.

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Key words: Posterior Reversible Encephalopathy Syndrome (PRES), Neuromyelitis optica (NMO), Hypertension
PRES，視神経脊髄炎，高血圧

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はじめに

Posterior reversible encephalopathy syndrome（PRES）は，1996年にHincheyら[1]により高血圧性脳症や産褥子癇，免疫抑制剤の使用を背景にして可逆的で特徴的な臨床症候と画像所見を呈した15症例をもとに提唱された疾患概念である．当初はreversible posterior leukoencephalopathy syndrome（RPLS）と称されていたが，実際は大脳の白質のみならず皮質も障害されていることが少なくないこと等より，最近では皮質と白質病変の両者を包括するencephalopathyを用いた「PRES」が用いられることが多い[2]．PRESは異常な高血圧，妊娠分娩，免疫抑制剤使用等に伴い，頭痛や痙攣，意識障害等を引き起こし，頭部MRIで通常の血管支配領域には一致しない形で後方循環系白質を中心とする可逆性の浮腫性病変をきたすも，多くは後遺症を起こすことはない比較的予後良好な疾患である．

これまで国内ではPRESは症例報告が多く，まとまった検討は少ない．今回，我々は自験12例を通し，PRESの早期診断における注意点，海外の症例との違いなどを中心に考察した．

Table 1　Clinical findings in 12 PRES cases

Case No.	Age, Sex	Blood pressure at time of PRES, mmHg	Creatinine	Symptoms	Etiology	Lesions of brain MRIs	Treatment for PRES	Sequela
1	29years, Female	200/140	unavailable	Seizure, nausea	HELLP syndrome	Parietal, frontal, basal ganglia	Antihypertensive agents, osmotic diuretic	None
2	84years, Male	204/73	1.12	Dysarthria, movement loss	Shy-Drager syndrome, fludrocortisone	Brainstem	Antihypertensive agents	None
3	11years, Male	200/130	0.35	Headache, seizure	Pheochromocytoma	Occipital, parietal	Antihypertensive agents, anticonvulsants, extirpation of adrenal gland	None
4	47years, Female	154/82	0.4	Seizure	Neuromyelitis optica, methylprednisolone	Occipital, parietal, frontal	Antihypertensive agents, anticonvulsants, osmotic diuretic	None
5	27years, Female	190/140	0.58	Seizure, drowsiness	Post delivery, Traumatic subarachnoid hemorrhage	Occipital, frontal, , basal ganglia	Antihypertensive agents, anticonvulsants	None
6	53years, Female	214/124	0.81	Seizure	Hypertension	Occipital, parietal, frontal	Antihypertensive agents, anticonvulsants	None
7	16years, Male	unavailable	0.69	Headache, hyperthermia	Pheochromocytoma	Occipital, cerebellum	Extirpation of adrenal gland	None
8	32years, Male	220/120	1.88	Headache, nausea	Chronic renal failure	Brainstem, cerebellum, basal ganglia, thalamus	Antihypertensive agents, osmotic diuretic	None
9	33years, Male	264/186	4.98	Headache, nausea, lethargy	Chronic renal failure	Brainstem, cerebellum, basal ganglia	Antihypertensive agents, osmotic diuretic	None
10	32years, Female	unavailable	0.33	Headache, nausea, vomiting	Threatened premature delivery	Occipital, parietal	Analgesic	Cerebral hemorrhage, slightly visual disturbance
11	56years, Female	194/106	4.47	Headache, visual disturbance	Chronic renal failure, Post renal transplantation, tacrolimus, mycophenolate mofetil	Occipital	Antihypertensive agents, change of immunosuppressants	None
12	42years, Female	220/126	2.8	Coma	Acute renal failure, Disseminated intravascular coagulation	Occipital	Antihypertensive agents	None

対象と方法

当院で我々が2002年5月から2009年12月の間に経験したPRES 12症例を対象に発症時の血圧，症状，病因，画像所見，治療等について後方視的に検討した．なお，PRESの診断は，①臨床的に頭痛や痙攣や視野障害等の急性の神経症状を伴い，②頭部MRI所見が臨床症候と平行で部分的な血管原性浮腫を呈するものとした．

結　果

Table 1に12症例の臨床所見のまとめを示す．発症時年齢は11歳から84歳，平均38.5歳で女性7例，男性5例だった．男女間に明らかな年齢の差は認めなかった．病因は産科疾患が3例，褐色細胞腫が2例，慢性腎不全が2例，薬剤関連が2例でNMOも1例含まれていた（Fig. 1）．入院時に認められた症状は頭痛が6例と全体の半分を占めており，痙攣，嘔気，嘔吐，意識障害と

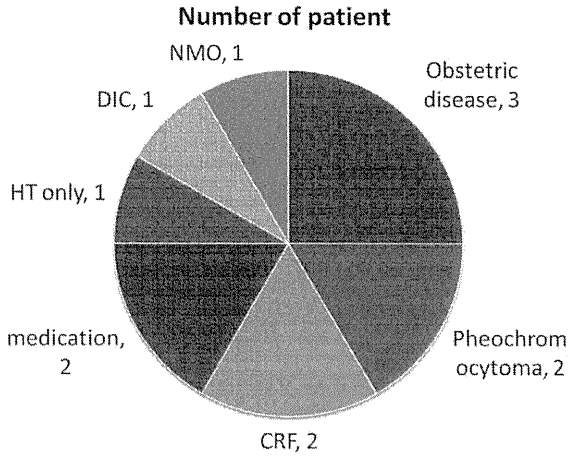

Fig. 1 Etiologies of PRES
Various diseases resulted in PRES, and obstetric diseases were the most frequent ones.
CRF: chronic renal failure, HT:hyper tension, DIC:disseminated intravascular coagulation, NMO: neuromyelitis optica.

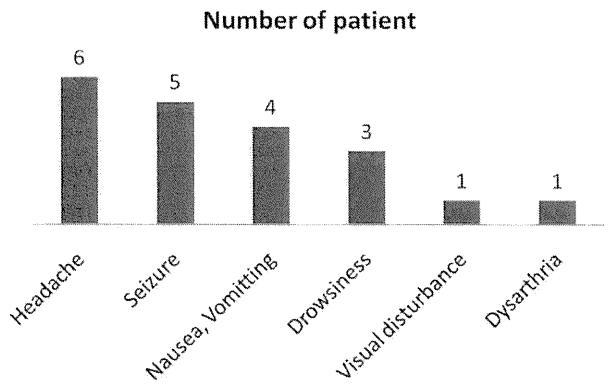

Fig. 2 Clinical manifestation
The most common clinical manifestation was headache, which was emerged in six out of the twelve cases.

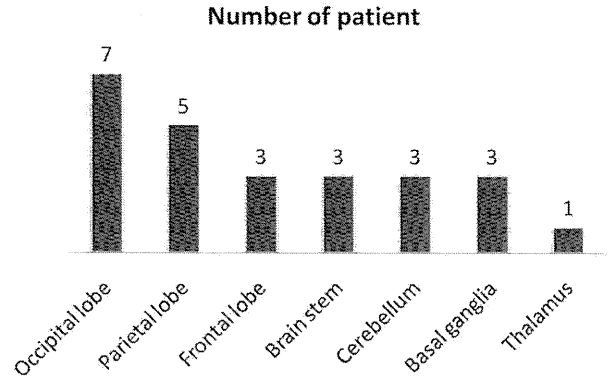

Fig. 3 Radiologic features in brain MRI
The most common, site of PRES lesion was in the occipital lobe, where we observed in seven out of the twelve cases.

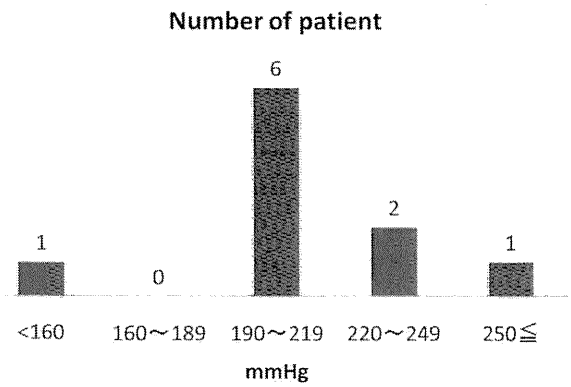

Fig. 4 Systolic blood pressure at the onset of PRES
We retrospectively analyzed ten cases of PRES. Systolic blood pressure was more than 190mmHg in nine cases of PRES. But in neuromyelitis optica case, systolic blood pressure was 154mmHg.

続いた（Fig. 2）．頭部 MRI 上の病変部位は後頭葉が 7 例と最も多かったが，他に頭頂葉が 5 例，前頭葉 4 例，脳幹，小脳，基底核がそれぞれ 3 例，視床にも 1 例病変を認めた（Fig. 3）．また，apparent diffusion coefficient map（ADC map）が確認できたものは 9 例で 8 例が高信号で 1 例が等信号であった．細胞障害性浮腫を示すとされる ADC map の低信号は認めなかった．発症時の収縮期血圧は，発症時に血圧が確認できた 10 例で検討した．発症時の血圧の平均は 206.0/122.7mmHg で，収縮時血圧は 1 例が 160mmHg 未満と著明に低く，190mmHg ～ 219mmHg が 6 例，220mmHg ～ 249mmHg が 2 例，250mmHg 以上が 1 例だった（Fig. 4）．なお，160mmHg 未満の症例は背景疾患として NMO に罹患しており，血清抗 aquaporin4 抗体陽性であった．Fig. 5 に NMO 例の頭部 MRI を示す[3]．Fig. 5A は入院時の頭部 MRI で，両側後頭～頭頂葉にかけて fluid-attenuated inversion recovery（FLAIR），diffusion weighted image（DWI），ADC map で高信号，右延髄に FLAIR で高信号を認めた．Fig. 5B は 2 週後の頭部 MRI で，両側後頭～頭頂葉の FLAIR 高信号は消失し PRES と考えられた．右延髄の FLAIR 高信号は残存しており NMO の病変と考えられた．

考　察

我々の症例の大多数は，PRES 発症時の収縮期血圧

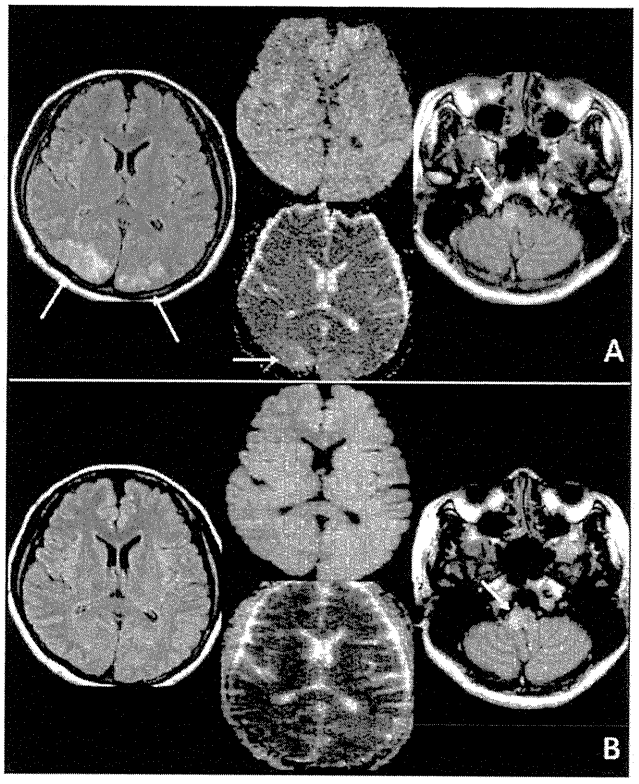

Fig. 5 Brain MRIs of the neuromyelitis optica case
A: Brain MRIs of the neuromyelitis optica case on admission. We could observed bilateral occipital and parietal high intensities in fluid-attenuated inversion recovery [FLAIR] (left), diffusion weighted image [DWI] (middle upper) and apparent diffusion coefficient map [ADC map] (middle lower). High intensity area in right medulla oblongata in FLAIR was also observed (right).
B: Brain MRIs on two weeks later. Bilateral occipital and parietal high intensity lesions were diminished, which could be considered the posterior reversible encephalopathy syndrome lesions. The medulla oblongata high intensity was still observed (right), indicating that was the lesion of neuromyelitis optica.
(From the reference 3, with the permission of the Japan Internal Medicine Society)

190mmHg 以上と著明高値を示したが，NMO 例では 154/84mmHg であった．また，同症例はステロイドパルス療法を行っており，ステロイドパルス療法前の血圧は 125/100mmHg で治療前後の血圧上昇も軽度であった．NMO は抗 aquaporin4 自己免疫により中枢神経系の水の流動が変化し PRES の素因となっていると推定される[4]．PRES をきたした NMO 例は今まで 6 例の報告があり[4,5]，発症時血圧が確認された 5 例のうち正常から軽度上昇までにとどまっていた 4 例はいずれも当院での NMO 例と同様に免疫改変療法が行われていた．一方，免疫改変療法を行わなかった 1 例は 220/140mmHg と著明な高血圧を示していた．

PRES は一般的に稀な疾患と考えられているが，Mayo Clinic では NMO-IgG 陽性 70 例の患者のうち実に 5 例（7%）が PRES と診断され，3 例（4%）で免疫改変療法が行われていた[4]．そのため NMO 例は PRES を起こしやすく，さらに免疫改変療法を施行されているものは，著明な高血圧がなくとも PRES に罹患しやすい可能性があるため，慎重な血圧管理を行い，頭痛や嘔吐等の症状発現時には必ず PRES を鑑別に入れ，対応が遅れないよう努めるべきと考えられた．

我々の症例では著明な高血圧を伴っているものが多く，治療も降圧剤を最も使用していた．過去の報告でも高血圧を伴うものが多く，そのような症例では治療は降圧剤が大きな柱と考えられる．PRES は対応が遅れると不可逆的な症状が残り致命的になりうることもあるため[6]，症状と画像所見から PRES の診断を行い，迅速な対応が必要と考えられる．

一方，過度の降圧から組織灌流が低下し不可逆的傷害をきたすこともありうる．Seventh report of the joint national committee on prevention, detection, evaluation, and treatment of high blood pressure（JNC7）のガイドラインでは最初の 1 時間以内では平均血圧で 25% 以上は降圧せず，次の 2 ～ 6 時間で 160/100 ～ 110mmHg を目標とし，さらに患者の状態が安定していれば次の 24 ～ 48 時間で徐々に正常域に低下させるとしている[7,8]．

今回の検討で PRES 発症時の症状は 12 例中頭痛が 6 例，痙攣が 5 例であったが，Hinchey らの論文では PRES 15 例中頭痛が 8 例，痙攣が 11 例であった[1]．また Fugate らの PRES 113 例を解析した論文でも頭痛が 29 例なのに対し痙攣は 84 例と何れも痙攣を多く認めており[9]，我々の検討ではやや頭痛が多く痙攣が少ない傾向があった．

PRES 発症時に血中クレアチニンが 1.0mg/dl を超えているのは確認できた 11 例中 5 例であったが，Hinchey らの論文では 15 例中 9 例であり[1]，Fugate らの論文でも 113 例中 64 例が血中クレアチニン 1.4mg/dl 以上であり[9]，我々の検討では腎機能障害も若干少ない傾向があった．以上より人種間等で症状や腎障害の頻度等に差がある可能性があり，今後さらに国内の症例を蓄積し検討が必要と考えられる．

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Clinical Study

High-Resolution Melting (HRM) Analysis of the Cu/Zn Superoxide Dismutase (SOD1) Gene in Japanese Sporadic Amyotrophic Lateral Sclerosis (SALS) Patients

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Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disorder, and the majority of ALS are sporadic (SALS). Recently, several causative genes for familial ALS (FALS) were identified, but the cause of the SALS is still unknown. This time, we aimed to identify the genetic background of SALS. First, we applied the new sensitive screening methods: high-resolution melting (HRM) analysis. HRM analysis detected 18 out of 19 known SOD1 gene mutations (94.7% sensitivity). Next, we screened *SOD1*, three novel mutations (C6Y, Q22H, and S134T) were identified in our own 184 SALS cases (1.63% prevalence), and four mutations in another 255 SALS cases (1.56% prevalence) registered from all over Japan. The patients with *SOD1* mutations suggested a relatively young onset and limb involvement at onset. The HRM analysis is a sensitive and easy screening method; we will use this method for screening other ALS causative genes and revealing the genetic background of SALS.

1. Introduction

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disorder primarily affecting motor neurons in the spinal cord, brain stem, and cerebral cortex. Five to ten percent of ALS cases are familial; the others are believed to be sporadic [1]. Mutations in the Cu/Zn superoxide dismutase gene (*SOD1*; OMIM 147450) are the most frequent genetic defects known to underlie ALS, accounting for 20% of familial cases (FALS) and one to seven percent of apparently sporadic cases (SALS) [1–7]. Recently, other mutations like the TARDBP gene (TDP-43) [8, 9], ANG gene [10], FUS/TLS gene [11], and OPTN gene [12] were identified as causative of ALS. Despite this genetic heterogeneity, *SOD1* mutations are the most frequent cause of adult onset ALS. Here, we report the results of screening for *SOD1* mutations in the 184 SALS cases in our hospital and 265 ALS cases all over Japan by high-resolution melting (HRM) analysis.

HRM analysis is a mutation scanning technique that monitors the progressive change in fluorescence caused by the release of an intercalating DNA dye from a DNA duplex as it is denatured with marginal increases in temperature [13]. The shifts and shapes of melting curves, there are obtained as fluorescence difference plots, are used to distinguish between mutations and controls. HRM analysis of PCR products amplified in the presence of LC Green Plus can detect all heterozygous and most homozygous sequence variations through differences in shape and position of a melting curve compared with a wild-type melting profile. Although single-strand conformation polymorphism (SSCP) [2, 3, 14–20] and denaturing high-performance liquid chromatography (DHPLC) [5, 6] seem to be the main screening strategies for *SOD1* mutations, HRM analysis has its own advantages. This is the first report of HRM analysis being applied to the *SOD1* screening. In this paper, we report the high sensitivity of HRM analysis for known *SOD1*

Table 1: Reported *SOD1* mutations to determine the sensitivity of HRM analysis.

Exon1	A4V, L8V, V14G
Exon2	H43R
Exon3	D76Y
Exon4	N86S, A89V, D90A (hetero), G93S, D101G, S105L, G114A, R115G
Exon5	L126delTT, G127X, A140A, L144F type2, L144FVX

Underlined mutation could not detect the mutation by HRM analysis.

mutations, and the prevalence and clinical features of *SOD1* mutations in Japanese SALS cases.

2. Patients and Methods

2.1. Patient Group 1. A total of consecutive 184 SALS cases (109 males and 75 females) visited our Neurology Division at the Jichi Medical University Hospital in Tochigi, Japan. Ethical approval was granted by the Bioethics Committee for Human Gene Analysis of our university and informed consent was obtained from all subjects according to the Declaration of Helsinki. Every patient fulfilled the diagnostic criteria for ALS as outlined by the *El Escorial Revisited* [21] classification; 177 definite, probable or possible ALS and 7 suspected ALS. None of the cases had a family history of a neuromuscular disorder. There was no significant difference in onset age between 109 males and 75 females (males: 60.4 years on average with a range of 27–80; females: 64.3 years with a range of 34–83).

2.2. Patient Group 2. In 2006, the Japanese Consortium for Amyotrophic Lateral Sclerosis Research (JaCALS) was organized with the aim of investigating the relationships of clinical and genetic aspects of ALS in Japan. The Ethics Committee of each institution granted ethical approval. The inclusion criteria for registration with the JaCALS are: (1) adult onset, steady progressive course, (2) definite, probable or possible ALS based on the *El Escorial Revisited* [21] criteria for diagnosis of ALS, and (3) informed consent for the genetic study and clinical checking every three months. From 2006 to 2008, 265 patients (10 FALS and 255 SALS) were registered, and blood samples and clinical data having been obtained by neurologists.

2.3. Reported SOD1 Mutations. We used 19 reported *SOD1* mutations in all five exons (Table 1) to determine the sensitivity of the HRM analysis. 19 reported *SOD1* mutations were obtained from our collaborators, Dr. Andersen P. (Umeå University, Sweden) and Dr. Watanabe Y. (Tottori University, Japan), and they were already direct sequenced and confirmed they had the mutations.

2.4. HRM Analysis and Sequencing. Genomic DNA was extracted from lymphocytes using a standard procedure. We designed PCR primers for HRM analysis to screen all five exons in *SOD1*. DNA samples were amplified with double-stranded DNA-binding dye LC Green Plus (Idaho Technology). PCR was performed with a Veriti 96-Well Thermal Cycler (Applied Biosystems) in 10 μL reaction mixtures comprising 10 ng DNA, 1XPCR buffer, LC Green Plus (Idaho Technology), and 1 U Taq polymerase, with 0.25 μM each forward and reverse primers. Initial denaturation was performed at 95°C for 2 min, followed by 45 cycles of 94°C for 30 sec and 62–68°C for 30 sec, with a final cycle of 94°C for 30 sec and 25°C for 30 sec.

We performed melting acquisition with a 96-well Light Scanner (Idaho Technology). The plate was heated from 80 to 98°C at 0.1°C/sec with a 300 ms frame interval, 15 ms exposure, and 100% LED power. Light Scanner Software was used for melting curve analysis. The Light Scanner analyses of 96 samples were performed in around 10 min. Sequencing of samples indicated to include mutations was then carried out using a BigDye Terminator v1.1 Cycle Sequencing Kit (Applied Biosystems) and an ABI 310 automated sequencer (PE Applied Biosystems).

First we examined 19 reported *SOD1* mutations to determine the sensitivity of HRM analysis. Next, we applied this method to Japanese ALS patients for mutation screening of *SOD1*.

3. Results

3.1. Sensitivity of HRM Analysis. HRM analysis clearly distinguished 18 of 19 previously identified *SOD1* mutations from normal controls. The mutation detection sensitivity was 94.7% for the reported mutations. The melting curves of control samples (wild-type) were tightly grouped for all fragments, and altered difference curves were easily identified for the 18 mutations (Figure 1). The mutation that could not be detected was Gly 114 Ala.

3.2. SOD1 Mutations and the Clinical Characteristics in Group 1. We found *SOD1* mutations in three out of the 184 SALS cases (1.63%) in the group 1. The mutations identified were all novel: Cys 6 Tyr (C6Y) and Gln 22 His (Q22H) in exon 1, and Ser 134 Thr (S134T) in exon 5 (Figure 2).

In case 1, a 34-year-old woman, there was a single-base pair substitution in exon 1 at codon 6 (TGC to TAC). This change created a cysteine 6 to tyrosine missense mutation (C6Y). She awoke with painful cramping and weakness in the right leg almost every morning at the age of 33 years. The cramping resolved, but her right leg weakness progressed and become accompanied by fasciculation. One year after the onset, neurological examination showed marked muscle atrophy and prominent fasciculation in her right leg. Tendon reflexes were normal, and plantar responses were flexor. Sensations in all four modalities were intact. Nerve conduction studies revealed mild reduction of motor nerve conduction velocity without conduction block. Needle electromyographic analysis showed repetitive discharges and hyperexcitability only in the right leg. Extensive screening for causes of the motor neuropathy was negative. The muscle weakness and atrophy progressed, and spread to the other parts of her body despite treatment with intravenous

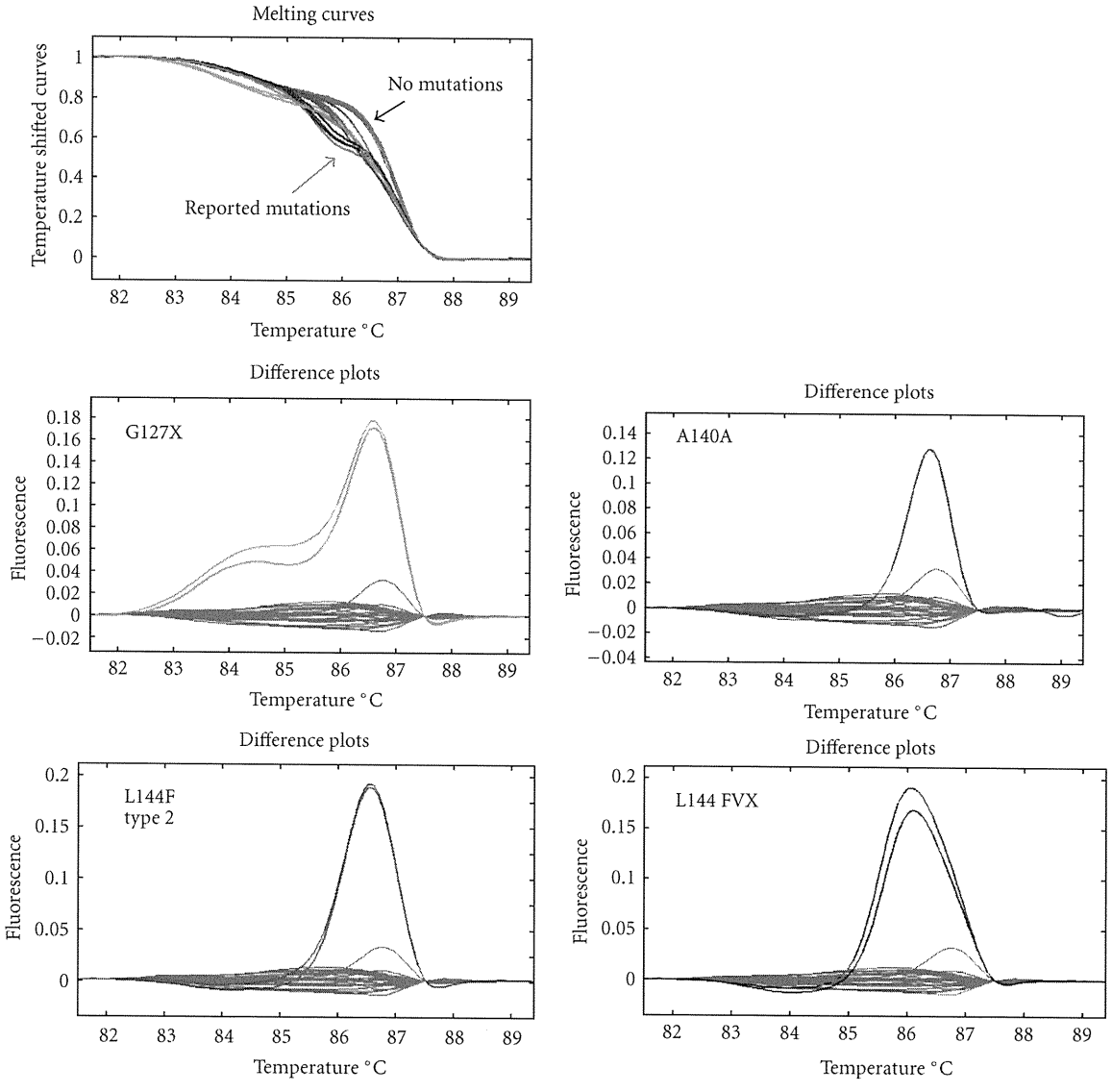
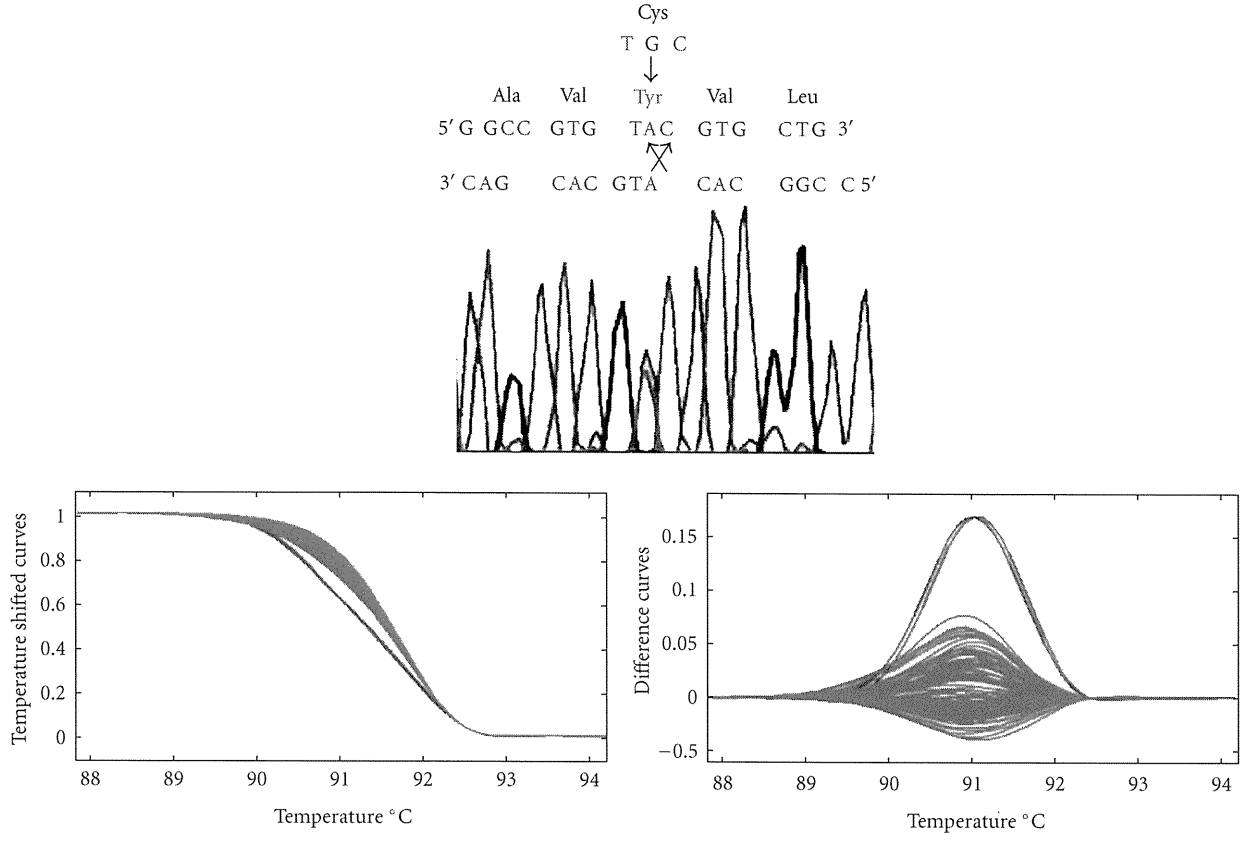


FIGURE 1: Melting curves and subtractive fluorescent difference plots of a wild type (gray lines) and reported *SOD1* mutations (colour lines). Difference plots were easily identified for the mutations.

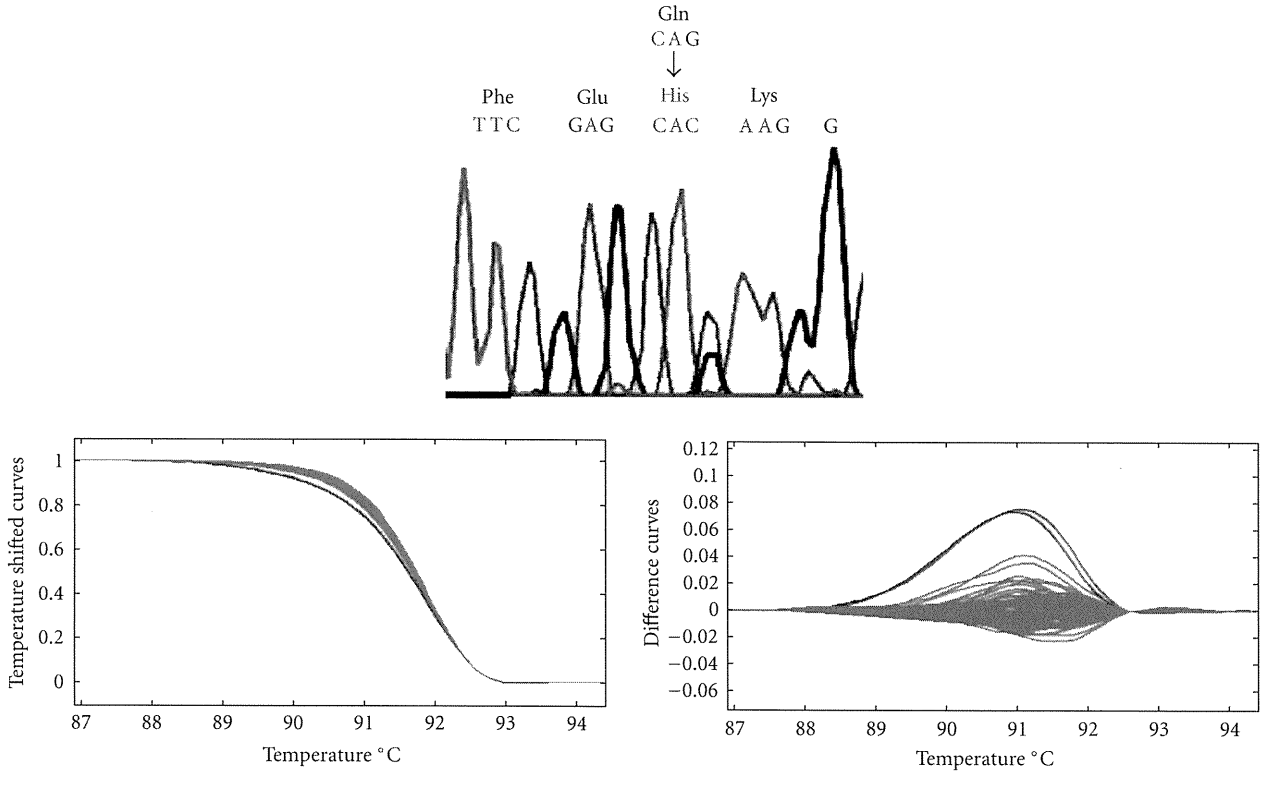
gamma globulin, cyclophosphamide, and plasmapheresis. The disease course was rapid and the bulbar symptom developed in the last stage. She expired 3 years after disease onset.

In case 2, a 48-year-old man, there was a single-base pair substitution in exon 1 at codon 22 (CAG to CAC). This change created a glutamine 22 to histidine missense mutation (Q22H). He developed left leg weakness and atrophy at the age of 46 years. Two years after the onset, neurological examination showed muscle weakness, atrophy and fasciculation were observed in the left leg. Tendon reflexes were brisk in the right leg and both arms. The weakness and atrophy spread to the right leg, confining him to a wheelchair at 51 years old and to bed at 52 years old. He underwent tracheotomy because of progressive respiratory failure, and artificial ventilation support was started eight years after disease onset. Five years after artificial ventilation support was started, he moved to another hospital and thus we could not follow him further.

In case 3, a 69-year-old man, there was a single-base pair substitution in exon 5 at codon 134 (AGT to ACT). This change created a serine 134 to threonine missense mutation (S134T). He noticed gait disturbance due to muscle weakness of the lower limbs at the age of 62 years. The weakness progressively worsened, and he could not walk by himself at 67 years old. Neurological examination showed muscle weakness, and fasciculation were evident in the upper and lower limbs. Tendon reflexes were diminished and plantar responses were flexor. No sensory abnormalities were noted. Nerve conduction studies demonstrated normal motor and sensory nerve conduction velocities. Electromyographic analysis revealed fasciculation and denervation in the upper and lower limbs. Although upper motor neuron impairment was not confirmed, ALS was considered as the most probable

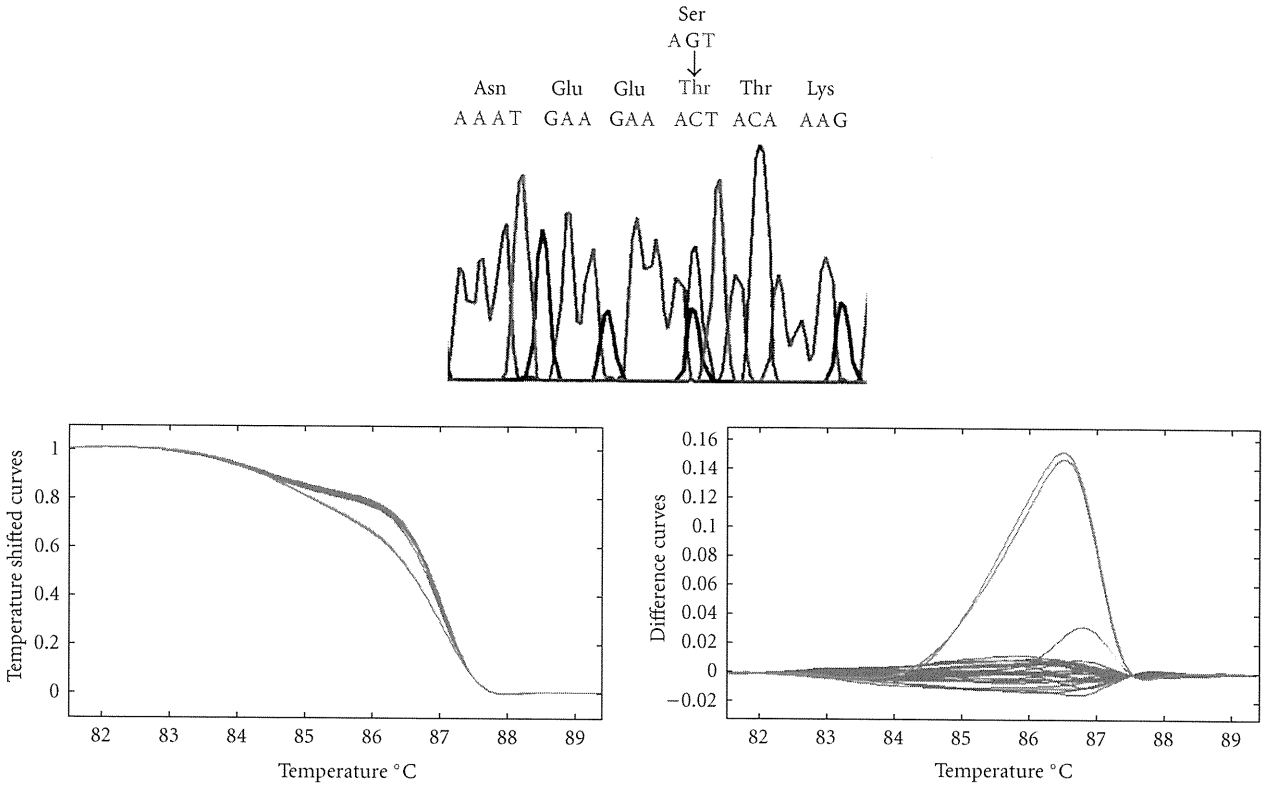


(a) Case 1 (20 G > A; C6Y)



(b) Case 2 (69 G > C; Q22H)

Figure 2: Continued.



(c) Case 3 (404 G > C; S134T)

FIGURE 2: Sequence (upper), melting curves (left lower) and subtractive fluorescent difference plots (right lower) of the three novel mutations.

diagnosis. The weakness progressed very slowly, and he died of respiratory insufficiency seven years after disease onset.

3.3. SOD1 Mutations in Group 2. We found *SOD1* mutations in eight out of 265 cases. Of these, four had family histories, mutations being Leu 38 Val (L38V) and His 46 Arg (H46R) in exon 2, Gly 93 Ser (G93S) in exon 3 and Gly 141 Ala (G141A) in exon 5. The G141A found in a woman whose brother probably died of ALS was a novel mutation. In this case, left hand weakness occurred at 57 years old. The clinical course was rapid that she died at 3 years and 11 months after the onset. The remaining four *SOD1* mutations were found in sporadic cases, mutations being Lys 3 Glu (K3E) in exon 1 and Gly 93 Ser (G93S) in exon 3. K3E was a novel mutation found in a woman who noticed right leg weakness at 52 years old, and artificial ventilation support was started 6 years after the onset. The G93S mutation was found in three unrelated patients. The prevalence of *SOD1* mutations in the SALS cases was 1.56% (4 of 255 SALS cases) in the group 2.

4. Discussion

4.1. HRM Analysis on SOD1. This is the first report of HRM analysis for *SOD1* mutation screening. HRM analysis could clearly distinguish 18 of 19 reported *SOD1* mutations from normal controls. We have demonstrated that HRM analysis is a rapid and sensitive (94.7% sensitivity) method for mutation scanning of *SOD1*. SSCP is a method that most laboratories use for the screening of gene mutations, but the sensitivity is not high (80% to 90%) [7]. DHPLC using WAVE system is also a screening method, but it cannot detect the D90A mutation [6], which is one of the worldwide detected *SOD1* mutations, and the most appropriate condition for analysis is difficult to determine. Using HRM analysis, we can analyze within 5 to 10 minutes on 96 samples and the running cost is not expensive.

The one mutation that HRM analysis could not detect was guanine to cytosine at nucleotide 341 substituting glycine (GGC) to alanine (GCC) at codon 114. On the other hand, guanine (TTG) to cytosine (TTC) mutations (L144F), and alanine (GCT) to alanine (GCA) mutations (A140A) in other samples were detected with this method, indicating the possibility that the G to C mutation detection failure may be a sequence-specific phenomenon.

4.2. SOD1 Mutations in SALS. We applied this method to our own 184 (group 1) and 255 (group 2) Japanese cases of SALS, finding three different novel *SOD1* mutations in three cases in the former (mutation prevalence, 1.63%), and one novel and three known mutations in four cases in the latter (mutation prevalence, 1.57%). We listed the prevalence and identified mutations of *SOD1* in SALS cases in other

Table 2: *SOD1* mutations in SALS patients of the different countries.

Country	Total SALS	No. of *SOD1*	*SOD1*/Total	Mutations identified	Screening method	Author, year
North England	46	1	2.1	D101N	SSCP	Jones et al. 1994 [14]
Scotland	57	4	7.0	E21K, I113T	SSCP	Jones et al. 1995 [2, 15]
Scandinavia	355	14	3.9	V14G, D90A (hetero & homo)	SSCP	Andersen et al. 1997 [16]
England	155	4	2.6	D90A, I113T, V118KTGPX	SSCP	Jackson et al. 1997 [17]
England	175	5	2.8	G72S	SSCP	Shaw et al. 1998 [18]
Belgium	69	3	4.3	D90A, N139N, IVS + 19A > G	SSCP	Aguirre et al. 1999 [3]
Italy	48	3	6.3	D90A (homo), I113T, A95T	DS	Gellera et al. 2001 [22]
Spain	87	1	1.2	N65S	SSCP	García-Redondo et al. 2002 [19]
Italy	225	0	0		SSCP	Batlistini et al. 2005 [20]
Spain (Catalonia)	94	4	4.2	D90A, N139H, A140A	DS	Gamez et al. 2006 [4]
Italy	66	3	4.5	K135X, N65S, A95T	DHPLC	Corrado et al. 2006 [5]
Italy	303	2	066	N19S, E133ΔE	DHPLC	Chiò et al. 2008 [6]
Japan	184	3	1.6	C6Y, Q22H, S134T	HRM	This article group1
Japan	255	4	1.5	K3E, G93S	HRM	This article group2
Total	2119	51	2.4			

DS: direct sequence (no screening method in the article).

countries (Table 2). The prevalence was high in the Scottish population (7%) and widely ranged in Italy (0%–6%), but in other countries, it was 2 to 4%, similar to our data. This time we found four novel mutations in SALS cases, and these mutations were not found in the Japanese control group.

In a sporadic ALS patient carrying an *SOD1* mutation, it is also difficult to ascertain whether it is a genuine sporadic case, a case due to a mutation, or a familial case with incomplete penetrance. To date, an SALS case with H80A is the only one with a proven de novo mutation [23]. In our analysis, the G93S mutation was found in three unrelated patients from the Tokai district of Japan (personal communication). There are at least 6 Japanese families with G93S, 4 of the 6 families being reported to be residents of the Tokai district [24–26]. The accumulation of G93S in Japanese SALS cases suggests the possibility of decreased penetrance or an incomplete family history rather than a de novo mutation.

4.3. Clinical Characteristics of SALS Involving SOD1 Mutations. Clinical characteristics such as onset age, onset symptoms, and clinical course of so far reported SALS patients having *SOD1* mutations are summarized in Table 3. Since A4V, D90A, and I113T have been observed worldwide and are considered to be the most common mutations in both familial and sporadic ALS cases [4, 7]. Because of the difficulty to define true sporadic, we did not include these three mutations in the table. Based on the results of analysis of these 20 *SOD1* mutations in 27 sporadic ALS patients (13 men, 10 women, and 4 unknown), the average age at onset was 43.8 (range 18–77) years, which is about 10 years younger that the mean age at onset reported for the sporadic ALS population [22]. The onset symptom was limb weakness in 21 cases and bulbar dysfunction only in one case. The clinical courses were under three years (rapid) in seven cases, over six years (slow) in nine cases, and three to six years (moderate) in five cases. The clinical characteristics of SALS involving *SOD1* mutations indicate a relatively young onset age and a high percentage of limb involvement at onset. These characteristics are similar to the features of ALSOD (ALS patients having *SOD1* mutations), not those of sporadic ALS [29].

The C6Y mutation in our case was difficult to diagnose because the main symptom was lower motor neuron dysfunction and the onset age was young (midthirties). But this clinical course was similar to that in the case of de novo mutation H80A [23]. There were nine (bold) patients whose onset ages were under forty, and eight of them had rapid or moderate clinical course (Table 3). On the other hand, there are four (underlined) patients whose onset ages were over 55, and three of them had slow clinical course (Table 3). Gamez and his colleagues reported [4] there were three types of sporadic ALS patients who were particular candidates for genetic testing for *SOD1*: (a) those with the typical Scandinavian phenotype, (b) those with clinical onset before 55 years of age, and (c) patients with slow progression/long survival. Compare with this theory (b) and (c), only one patient (N19S) is an exception for *SOD1* screening.

5. Conclusion

We have demonstrated that HRM analysis is a rapid and sensitive method for the mutation scanning of *SOD1*. With this method, four novel *SOD1* mutations were found in SALS cases, the prevalence of *SOD1* mutations in Japanese SALS cases being 1.6%. The clinical characteristics of SALS involving *SOD1* mutations are a young onset age and a high percentage of limb involvement at onset. We will screen other causative genes for ALS (*TDP-43, ANG, FUS/TLS, OPTN* and others) by HRM analysis and determine the cause of disease appearance.

Table 3: Clinical characteristics of the SALS patients having *SOD1* mutations.

Amino acid change	Sequence change	No. of pt.	Onset age	Onset symptom	Disease course/Disease duration	Author/Reference
K3E	AAG > GAG	1	52	Right leg weakness	Moderate, 6y	This article
C6Y	TGC > TAC	1	**34**	Right leg weakness	Moderate, 3y	This article
V14G	GTG > GGG	1	**39**	Both legs fatigue	ND, 16m~	Andersen et al. [16]
G16S	GGC > AGC	1	**18**	Hand paresis	Rapid, 1y	Kawamata et al. [27]
N19S	AAT > AGT	2	**32** 41	Both legs weakness Left arm weakness	Moderate, 36m ND	Mayeux et al. [28]
		1	77	Hand paresis	Rapid, 15m	Chiò et al. [6]
E21K	GAG > AAG	1	ND	ND	ND	Jones et al. [2]
Q22H	CAG > CAC	1	46	Left leg weakness	Slow, 8y	This article
N65S	AAT > AGT	1	44	Left leg weakness	Slow, 14y	García-Redondo et al. [19]
		1	40	Drop foot	Slow, 11y	Corrado et al. [5]
G72S	GGT > AGT	1	**29**	Left leg weakness	Rapid, 15m	Shaw et al. [18]
H80A	CAT > CGT	1	**24**	Left leg weakness	Rapid, 18m	Alexander et al. [23]
G93S	GGT > AGT	3	44 55 64	Both legs weakness Left leg weakness Right leg weakness	ND, 6y~ Slow, 8y~ Slow, 12y~	This article
A95T	GCC > ACC	1	**26**	Both legs weakness	Slow	Gellera et al. [22]
		1	45	Left drop foot	Slow, 20y	Corrado et al. [5]
D101N	GAT > AAT	1	53	ND	ND	Jones et al. [14]
V118 KTGPX	GTG > AAAACTG	1	**34**	ND	Rapid, 16m	Jackson et al. [17]
E133ΔE	GAA del GAA	1	54	Left leg weakness	Moderate, 4y	Chiò et al. [6]
S134T	AGT > ACT	1	62	Both legs weakness	Slow, 7y	This article
K136X	AAG > TAG	1	45	Left leg weakness	Rapid,12m	Corrado et al. [5]
N139H	AAG > CAC	1	53	ND	ND	Gamez et al. [4]
N139N	AAC > AAT	1	**33**	ND	Moderate, 3y	Aguirre et al. [3]
A140A	GCT > GCA	2	52 ND	Bulbar palsy Limb weakness	Rapid, 22m Slow	Gamez et al. [4]
Total/Average	20	27	43.8	21 Extremity 1 Bulbar 5 No data	7 Rapid 5 Moderate 9 Slow	

ND: no data, y: year or years, m: month or months, and y~ or m~: alive at the reported time.
Age: **under forty** (bold) and over fifty-five (underlined).
Disease course (until invasive ventilation support): ~2 years, rapid; 3–6 years, moderate; 7~ years, slow.

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Nationwide survey on the epidemiology of syringomyelia in Japan

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ABSTRACT

Background: Syringomyelia is a rare disease characterized by abnormal fluid-filled cavities within the spinal cord, and is associated with Chiari malformations, arachnoiditis, or spinal cord tumors. The widespread availability of magnetic resonance imaging (MRI) in Japan has allowed for easy identification of syrinxes. The aim of this study was to survey the clinicoepidemiological characteristics of syringomyelia in Japan.
Methods: A 2-stage postal survey was conducted in late 2009. The first survey aimed to estimate the number of patients with syringomyelia, and the second survey aimed to elucidate clinicoepidemiological characteristics. Diagnosis of syringomyelia was based on the findings of MRI or computed tomographic myelography.
Results: In the first survey, we received 2133 responses from 2937 randomly selected departments and collected data of 1215 syringomyelia patients (543 men and 672 women). The total response rate for the first survey was 73%. The estimated prevalence of ambulatory syringomyelia patients in Japan was 1.94 per 100000. In the second survey, the proportion of asymptomatic syringomyelia patients was 22.7%. Chiari type I malformations and idiopathic syringomyelia were the first and second most common etiologies.
Conclusions: Our nationwide survey indicated that widespread MRI availability has contributed to the diagnosis of both asymptomatic and idiopathic cases.

1. Introduction

Syringomyelia is a heterogeneous disorder characterized by abnormal fluid-filled cavities or cysts within the spinal cord. The etiologies of syringomyelia can include Chiari malformations, arachnoiditis, trauma, and spinal cord tumors [1–3], but the pathophysiology of syrinx development remains enigmatic. Some cases with Chiari Type I malformations manifested asymptomatic syringomyelia [4]. The reported prevalence was 8.2 to 8.4 per 100 000 in Western countries [5,6]. An epidemiologic survey that collected data from 1243 patients between 1982 and 1991 in Japan showed the predominance of Chiari Type I malformations in syringomyelia, and identified a few cases of spontaneous remission [7]. Surgical treatment for syringomyelia is essential to stop the progression of the disease and further cavity enlargement. However, the previous epidemiologic survey did not determine the prevalence of the disease in the Japanese population [7].

The diagnosis of syringomyelia has been greatly aided by the development and widespread availability of magnetic resonance imaging (MRI) scanners, which have allowed for the relatively easy identification of syrinxes. Japan has the highest number of magnetic resonance imaging (MRI) scanners per capita, with national healthcare insurance coverage allowing universal access to outpatient hospital care. Hence, both symptomatic and asymptomatic syringomyelia patients can be more adequately examined than was possible prior to MRI facilities becoming widely accessible.

The characteristics of asymptomatic syringomyelia have not been sufficiently investigated. The aim of this study, therefore, was to estimate the prevalence of syringomyelia in Japan and identify its clinicoepidemiological characteristics by taking advantage of the current widespread availability of MRI facilities.

2. Methods

We conducted a 2-stage postal survey according to methods described previously [8,9] in late 2009. The first survey aimed to estimate the number of individuals with syringomyelia, and the second survey aimed to elucidate the clinicoepidemiological characteristics

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of syringomyelia. We collected data from patients diagnosed with syringomyelia by neuroimaging from the departments of neurosurgery, neurology, orthopedics, and pediatrics. We requested the numbers of male and female ambulatory syringomyelia patients from each department in the past year (August 2008 to July 2009).

In the first survey, we adopted a definition of syringomyelia based on neuroimaging: a central or lateralized syrinx detected on MRI (including syrinxes with septums), or a syrinx detected with computed tomographic myelography in patients who could not undergo MRI because of metal in the body. The number of patients with syringomyelia in each institution was counted based on this definition. The departments surveyed were randomly selected by stratified sampling from a list of all hospitals with 20 or more beds; the list was obtained from the Ministry of Health and Welfare. Sampling rates were approximately 5%, 10%, 20%, 40%, 80%, and 100% for the stratum of general hospitals with 20 to 99 beds, 100 to 199 beds, 200 to 299 beds, 300 to 399 beds, 400 to 499 beds, and 500+ beds, respectively. Additionally, all university hospitals in Japan were surveyed.

In the second stage of the survey, we requested details of individual patients from each department that had 1 or more syringomyelia patients. The detailed information for each patient was reported based on a retrospective chart review. Epidemiological items included sex, date of birth, time of onset and diagnosis, family history, symptoms and signs, imaging findings, treatment, and clinical course. Symptoms included motor function, sensory disturbance, autonomic failure, cranial nerve disturbance, and skeletal deformity. Motor functions included weakness, muscle atrophy, spasticity, hypotonus, and planter reflex. Autonomic failure included Horner syndrome, anisocoria, dyshidrosis, abnormal nail development, limb hypertrophy, bladder and rectal disturbance, orthostatic hypotension, impotence, and neurogenic arthropathy.

This study was approved by the Institutional Review Board of Hokkaido University.

2.1. Estimation and statistical analysis

We estimated the prevalence of syringomyelia based on the results from the first stage of the survey. The estimation was based on the assumption that the responses of the departments were independent of the frequency of patients [8,10]. Formulas used to estimate the total number of patients, and the 95% confidence intervals are described below.

The point estimation of prevalence was calculated using the following equation, where SRT_k, RRT_k, NS_k, n_k, N_k, and N_{ki} denote the sampling rate, response rate, the number of sampling departments, the total number of departments, the number of responding departments, and the number of departments with i patients in stratum k, respectively.

$$\hat{\alpha}_k = \frac{1}{SRT_k RRT_k}\sum_i iN_{ki} = \frac{1}{\frac{NS_k}{n_k}\frac{N_k}{NS_k}}\sum_i iN_{ki} = \frac{n_k}{N_k}\sum_i iN_{ki}.$$

3. Results

In the first survey, we received 2133 responses from 2937 randomly selected departments, and collected data regarding 1215 syringomyelia patients (543 men and 672 women). The total response rate of the first survey was 73%.

Results from the first survey (Table 1) showed that the number of syringomyelia patients who were referred to a hospital between August 2008 and July 2009 was 2475 (95% CI: 2051–2899). The

Table 1
Summary of data collected in the first stage of the survey.

Type s of departments	Type s of hospitals and beds	Total no. of departments	Sampling rate (%)	No. of surveyed departments	No. of departments that responded	Response rate (%)	No. of reported patients	No. of estimated patients
Neurosurgery	General hospitals with ≤99 beds	710	5%	35	22	63%	0	0
	General hospitals with 100–199 beds	528	10%	52	27	52%	7	137
	General hospitals with 200–299 beds	298	20%	59	37	63%	26	209
	General hospitals with 300–399 beds	296	40%	119	73	61%	23	93
	General hospitals with 400–499 beds	167	80%	133	94	71%	40	71
	General hospitals with ≥500 beds	216	100%	216	147	68%	133	195
	University hospitals	113	100%	113	94	83%	267	321
	Subtotal	2328		727	494	68%	496	1027
Neurology	General hospitals with ≤99 beds	506	5%	25	13	52%	0	0
	General hospitals with 100–199 beds	335	10%	34	18	53%	3	56
	General hospitals with 200–299 beds	170	20%	34	27	79%	6	38
	General hospitals with 300–399 beds	170	40%	68	38	56%	7	31
	General hospitals with 400–499 beds	91	100%	91	59	65%	21	32
	General hospitals with ≥500 beds	93	100%	93	60	65%	25	39
	University hospitals	118	100%	118	103	87%	53	61
	Subtotal	1483		463	318	69%	115	257
Orthopedics	General hospitals with ≤99 beds	2278	5%	114	66	58%	4	138
	General hospitals with 100–199 beds	1047	10%	105	70	67%	10	150
	General hospitals with 200–299 beds	436	20%	87	63	72%	10	69
	General hospitals with 300–399 beds	362	40%	145	110	76%	48	158
	General hospitals with 400–499 beds	190	80%	152	107	70%	20	36
	General hospitals with ≥500 beds	228	100%	228	178	78%	120	154
	University hospitals	118	100%	118	98	83%	300	361
	Subtotal	4659		949	692	73%	512	1065
Pediatrics	General hospitals with ≤99 beds	1069	5%	54	32	59%	0	0
	General hospitals with 100–199 beds	613	10%	62	41	66%	0	0
	General hospitals with 200–299 beds	356	20%	71	49	69%	0	0
	General hospitals with 300–399 beds	339	40%	136	105	77%	7	23
	General hospitals with 400–499 beds	184	80%	147	120	82%	11	17
	General hospitals with ≥500 beds	214	100%	214	183	86%	58	68
	University hospitals	114	100%	114	99	87%	16	18
	Subtotal	2889		798	629	79%	92	126
	Total	11359	26%	2937	2133	73%	1215	2475

estimated prevalence of ambulatory syringomyelia patients in Japan was 1.94 per 100 000. In the second survey, we collected reports from 720 of the 1215 patients from the first survey. The response rate for the second survey was 59%. There were 12 duplicated reports, and thus, we integrated the data reported in them.

Results of the second survey (Table 2) described the characteristics of both symptomatic and asymptomatic syringomyelia. The proportion of patients with asymptomatic syringomyelia was 22.7% (161 cases). The mean ages at survey and diagnosis of asymptomatic syringomyelia (28.9 ± 23.3 and 24.4 ± 24.1 years, respectively) were lower than those of patients with symptomatic syringomyelia (40.8 ± 22.8 and 35.3 ± 22.5 years, respectively). Asymptomatic syringomyelia tended to be primarily associated with localized cavities. The proportion of syringomyelia cases with a Chiari type I malformation etiology was higher among symptomatic than asymptomatic syringomyelia patients. Conversely, the proportion of cases with idiopathic etiologies was higher in asymptomatic than in symptomatic syringomyelia.

A subset of patients with symptomatic syringomyelia (Table 3) included both those who had, and those who had not undergone surgical treatment. The mean age at onset and diagnosis of patients who had undergone surgical treatment (29.4 ± 21.0 and 31.6 ± 21.5 years, respectively) was lesser than that of patients who had not received surgical treatment (40.1 ± 22.6 and 44.8 ± 22.3 years, respectively). There were only 2 cases with a family history of the disease. Approximately 11% of patients in each group experienced an improvement in their symptoms. The most common symptom was sensory disturbance, which was reported in 75.3% of patients with surgical treatment and 68.8% of those without surgical treatment. Motor disturbance was the second most common symptom in each group (59.8% and 51.0%, respectively). Patient histories showed that approximately one-tenth of the patients in each group had previous injuries of the head or spine.

The characteristics of patients in each age group (Table 4) showed that the prevalence of idiopathic syringomyelia was higher in adults, particularly in the elderly, than in children.

Fig. 1 shows the distributions of patient's ages at the time of survey (Fig. 1A), age at diagnosis (Fig. 1B), age at surgical treatment (Fig. 1C), and year of diagnosis (Fig. 1D). The distribution of ages at survey consisted of 2 peaks, at 10 to 20 years of age, and at 60 to 70 years of age. The distribution of age at diagnosis showed a higher proportion of 0- to 20-year-olds. Finally, the distribution of diagnosis year showed an acute increment in the number of cases diagnosed in more recent years.

Table 2
Demographics of patients in the second stage of the survey.

	Symptomatic (N = 543)	Asymptomatic (N = 161)	Total (N = 708[a])	Missing
Age at survey (Mean ± SD)	40.8 ± 22.8	28.9 ± 23.3	38.0 ± 23.5	35
Age at diagnosis (mean ± SD)	35.3 ± 22.5	24.4 ± 24.1	32.7 ± 23.4	66
Sex (%)				
Male	41.6	44.1	42.1	1
Female	57.3	53.4	56.5	3
Missing	1.1	2.5	1.4	0
Morphology (%)				
Asymmetry	31.3	8.1	25.8	0
Symmetry	58.9	83.2	64.4	2
Missing	9.8	8.7	9.7	2
Distribution (%)				
Syringobulbia				
Bulbus only	1.5	0.6	1.3	0
Bulbus and spinal cord	5.7	1.2	4.8	1
Syringomyelia				
Cervical cord only	18.6	32.9	21.8	0
Thoracic cord only	7.9	8.7	8.2	1
Lumbosacral cord only	0.9	9.9	3.1	1
Cervical–thoracic	49.4	27.3	44.1	0
Thoracic–lumbosacral	2.6	4.3	3.0	0
Cervical–lumbosacral	4.6	4.3	4.5	0
Missing	8.8	10.6	9.3	1
Etiology (%)				
Chiari type I	53.6	30.4	48.0	0
Chiari type II	4.4	20.5	8.1	0
Bone anomaly	1.1	0.6	1.0	0
Arachnoiditis	5.7	2.5	4.9	0
Trauma	9.6	0.6	7.5	0
Spinal cord tumor	5.2	5.6	5.2	0
Idiopathic	12.9	24.8	15.7	1
Other	6.1	13.0	7.9	2
Suspected two or more	1.1	1.2	1.1	0
Missing	0.4	0.6	0.6	1

[a] Four patients who did not report on the existence of symptoms were excluded.

Table 3
Demographics, clinical history, and manifestations of symptomatic patients.

		Surgical treatment			
		Yes	No	Total	Missing
Number of cases		376	157	543	10
Age at onset (mean ± SD)		29.4 ± 21.0	40.1 ± 22.6	32.3 ± 22.0	
Age at diagnosis (mean ± SD)		31.6 ± 21.5	44.8 ± 22.3	35.3 ± 22.5	
Age at surgery (mean ± SD)		32.6 ± 21.0			
Family history (%)	Yes	0.3	0.6	0.4	0
	No	64.4	59.9	62.2	2
	Unknown/ missing	31.1	35.0	32.4	
Course of symptoms after initial diagnosis (%)					
Worsen		51.1	22.3	42.2	2
Unchanged		26.3	56.7	35.5	5
Improved		11.2	10.8	10.9	0
Stop after progression		4.8	5.7	5.0	0
Missing		6.6	4.5	6.4	
Symptoms (%)					
Motor	Yes	59.8	51.0	57.5	7
	No	37.8	45.9	39.4	0
	Unknown/ missing	2.4	3.2	3.1	
Sensory	Yes	75.3	68.8	72.7	4
	No	19.9	21.0	19.9	0
	Unknown/ missing	4.8	10.2	7.4	
Autonomic	Yes	20.7	19.1	19.9	0
	No	65.2	65.6	64.6	3
	Unknown/ Missing	14.1	15.3	15.5	
Cranial nerves	Yes	10.1	7.0	9.2	1
	No	83.2	80.9	81.4	2
	Unknown/ missing	6.6	12.1	9.4	
Skeletal deformity	Yes	31.4	22.9	29.3	5
	No	64.9	75.2	67.4	4
	Missing	3.7	1.9	3.3	
Past history (%)					
CNS infections	Yes	3.5	3.8	3.7	1
	No	80.6	74.5	78.3	5
	Unknown/ missing	16.0	21.7	18.0	4
Injuries of head or spine	Yes	11.4	10.2	10.9	0
	No	76.3	75.8	75.7	5
		12.2	14.0	13.4	

(continued on next page)

4. Discussion

This study revealed the prevalence (1.94 per 100 000) and characteristics of ambulatory syringomyelia patients in Japan. Among these patients, the prevalence of asymptomatic syringomyelia was 22.6%,

Table 4
Summary of characteristics of patients according to age group.

Age	Female (%)	Asymptomatic (%)	Etiology 1st / 2nd / 3rd	%	Localized cavity (%)
<10	51.11	40.9	Chiari type I	40.6	36.9
			Chiari type II	34.8	
			Other	14.5	
10–19	66.07	23.9	Chiari type I	78.8	36.2
			Idiopathic	6.2	
			Other	5.3	
20–29	52.63	14.0	Chiari type I	47.4	47.1
			Idiopathic	22.8	
			Trauma	14.0	
30–39	46.34	20.5	Chiari type I	49.4	39.0
			Idiopathic	17.3	
			Trauma	14.8	
40–49	55.17	15.3	Chiari type I	55.9	27.8
			Idiopathic	18.6	
			Spinal cord tumor	10.2	
50–59	69.74	14.5	Chiari type I	42.1	40.6
			Idiopathic	23.7	
			Spinal cord tumor	10.5	
60–69	54.55	11.5	Chiari type I	28.2	42.9
			Idiopathic	24.4	
			Trauma	16.7	
>70	66.67	24.3	Idiopathic	37.8	40.0
			Chiari type I	27.0	
			Arachnoiditis	13.5	

and that of idiopathic syringomyelia was 15.8% according to the second survey.

The prevalence of syringomyelia in this survey is lower than that in previous studies that used different methods for estimation [5,6]. Estimation of prevalence in this survey was based on patients who were referred to a hospital for evaluation or treatment. Therefore, the data from patients whose syringomyelia was stable and who had discontinued their ambulatory care were not collected in this study. It is noteworthy that the early detection of syringomyelia by MRI can allow for early interventions, including surgery. Early diagnosis and intervention are more likely to lead to a positive outcome, and may therefore reduce the number of patients requiring ambulatory care. The lower number of patients diagnosed in the years preceding 2005 (Fig. 1-D) is consistent with our speculation. However, these results show the characteristics of ambulatory care among syringomyelia patients.

The etiology of syringomyelia can include Chiari malformation, trauma, arachnoiditis, and idiopathic origin, among other causes. In our study, Chiari malformations, including both types I and II, were the most common cause in both children and adults, and this finding is consistent with those of previous studies [7,11]. In particular, Chiari malformation is more frequent in children than in adults. These results may be associated with the widespread availability of MRI, which contributes to early diagnoses in cases of syringomyelia caused by Chiari malformation. Interestingly, idiopathic syringomyelia was the second most common cause according to our survey. Bogdanov et al. suggested that idiopathic syringomyelia is associated with a small posterior fossa with a narrow cerebrospinal fluid (CSF) space as well as with Chiari I malformation [12]. It is possible that some of the cases of idiopathic syringomyelia in our survey may be attributable to a small posterior

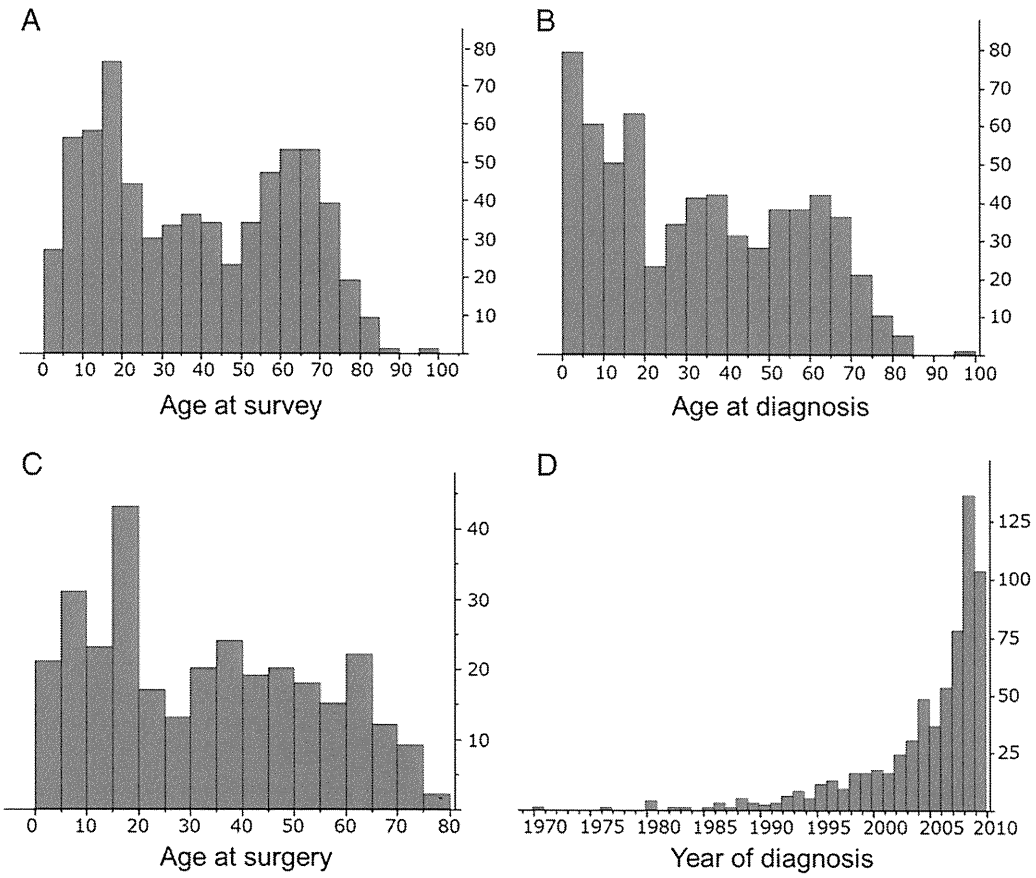

Fig. 1. (A) Histogram showing age distribution of patients at time of survey. (B) Histogram showing age distribution of patients at diagnosis. (C) Histogram showing age distribution at time of surgery. (D) Histogram showing the diagnosis by year.

fossa. Holly et al. described slit-like syrinx cavities characterized by remnants of the central canal and an asymptomatic clinical course [13]. Therefore, idiopathic syringomyelia has several potential causes, including congenital remnants of the central canal and acquired dilations by a small posterior fossa. Hida et al. reported an association between syringomyelia with Chiari I malformation and birth injuries [14]. In this study, patients with problem at delivery accounted for 2.0% of symptomatic syringomyelia cases, but it had a higher unknown/missing proportion in the past history. Nakamura et al. discuss 2 types of idiopathic syringomyelia: localized and extended. Localized syringomyelia is associated with congenital enlargement of the central canal of the spinal cord and can be managed conservatively [15]. Actually, most of the patients with idiopathic cases in our study did not undergo surgical treatment. Idiopathic syringomyelia might be less progressive than syringomyelia with other causes.

Asymptomatic syringomyelia comprised 22.7% of all syringomyelia cases in our second survey. Prior to this survey, the proportion of asymptomatic syringomyelia cases was unknown. Cases of a few patients with asymptomatic syringomyelia caused by a brain tumor of the posterior fossa have been previously reported [16–18]. The infrequency of asymptomatic syringomyelia seems inconsistent with our survey results. There are 2 possible explanations for the relatively high proportion of asymptomatic syringomyelia in our survey. Firstly, the symptoms of patients who did not complain because of their age were underestimated. Secondly, the availability of MRI in Japan has resulted in an increase in the number of incidental diagnoses of asymptomatic syringomyelia including slit-like syrinx cavities.

Resolution of syringomyelia without surgical treatment was observed in 17 patients (3.2% of symptomatic patients) in our second survey. Spontaneous resolution of syringomyelia has recently been found to be more common than previously thought [19]. The mechanisms involved in the development and spontaneous resolution of syringomyelia are unclear despite multiple hypotheses [20]. The number of patients with spontaneous resolution may be underestimated because cases of asymptomatic syringomyelia patients who had not sought consultation were not evaluated in our survey.

Symptoms of syringomyelia include pain, sensory disturbance, and amyotrophy. Bogdanov et al. reported that 90% of patients had unilateral or bilateral sensory disturbances, while 79% of patients experienced weakness or wasting of the upper limbs [21].

Familial syringomyelia cases with autosomal dominant or recessive inheritance have been reported [22,23]. Chatel et al. suggested that the incidence of familial syringomyelia is approximately 2% [24]. However, a large-scale survey has not yet been conducted to determine the proportion of familial cases. In our study, familial syringomyelia comprised only 2 cases (0.6%) of patients with a reported family history. Although a potentially large number of patients who have been lost to follow-up affect the accuracy of the proportion of syringomyelia, familial syringomyelia cases are extremely rare.

This study has several limitations. Firstly, the prevalence of syringomyelia reported in this study was calculated using the estimated number of ambulatory patients. Cases of patients who did not receive ambulatory care in the past year were not evaluated. Therefore, the potential number of syringomyelia patients may be larger than that reported in this study. Secondly, this cross-sectional survey could not evaluate the entire clinical course of syringomyelia. The disease progression from asymptomatic to symptomatic is particularly unclear. The clinical course of idiopathic cases is also unclear. Further investigation is required to determine the most appropriate evaluations and treatments for these patients. Thirdly, the response rates in this study were 73% and 59% in the first and second stage surveys, respectively. Characteristics of patients whose cases were not reported in the second survey are unknown. The effect of this selection bias on our results is also unknown.

Finally, the definition of syringomyelia associated with spinal cord tumor has been changing, and peritumoral cysts have been differentiated from other distinct forms of syringomyelia. In this study, syringomyelia associated with spinal cord tumor was regarded as merely 1 type of syringomyelia.

Taken together, the findings of our survey can contribute to the development of healthcare services for syringomyelia patients. Knowledge of the characteristics of asymptomatic and symptomatic syringomyelia patients without surgical treatment can be useful for the optimization of those services. Further evaluations of the potential number of non-ambulatory syringomyelia patients should be performed to estimate the precise prevalence of syringomyelia.

In conclusion, we have investigated the epidemiology of syringomyelia in Japan. Asymptomatic and idiopathic syringomyelia cases are more common than was previously believed. The widespread availability of MRI scanners has potentially contributed to the early diagnosis of these cases.

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A functional variant in *ZNF512B* is associated with susceptibility to amyotrophic lateral sclerosis in Japanese

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Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease characterized by the selective loss of motor neurons. Several susceptibility genes for ALS have been reported; however, ALS etiology and pathogenesis remain largely unknown. To identify further ALS-susceptibility genes, we conducted a large-scale case–control association study using gene-based tag single-nucleotide polymorphisms (SNPs). A functional SNP (rs2275294) was found to be significantly associated with ALS through a stepwise screening approach (combined $P = 9.3 \times 10^{-10}$, odds ratio = 1.32). The SNP was located in an enhancer region of *ZNF512B*, a transcription factor of unknown biological function, and the susceptibility allele showed decreased activity and decreased binding to nuclear proteins. ZNF512B over-expression increased transforming growth factor-β (TGF-β) signaling, while knockdown had the opposite effect. ZNF512B expression was increased in the anterior horn motor neurons of the spinal cord of ALS patients when compared with controls. Our results strongly suggest that ZNF512B is an important positive regulator of TGF-β signaling and that decreased *ZNF512B* expression increases susceptibility to ALS.

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