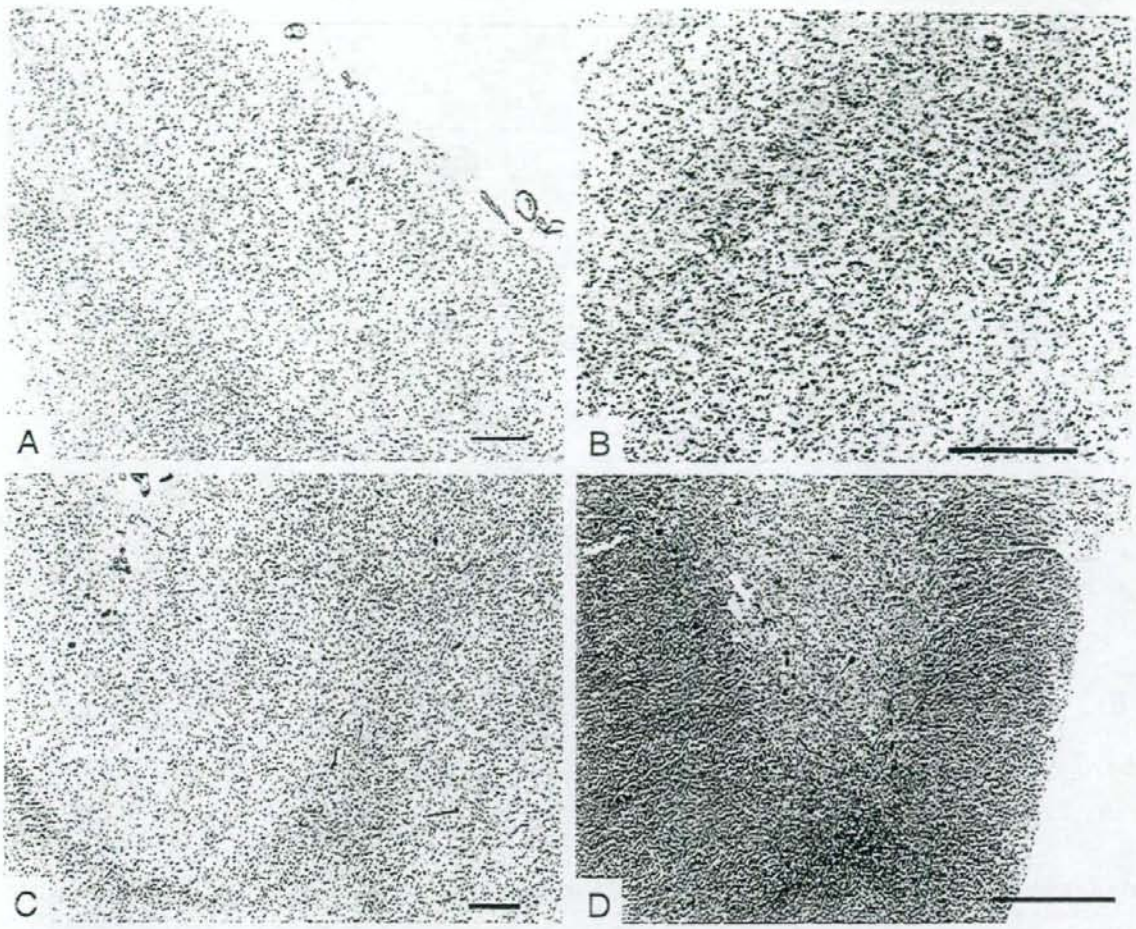

Fig. 4 Microscopic findings. (A–C) Severe neuronal loss, gliosis, and rarefaction of the neuropil can be seen. (A) Frontal lobe (HE; bar = 200 μm). (B) Precentral gyrus (HE; bar = 200 μm). (C) Temporal lobe (HE; bar = 400 μm). (D) Motor neurons in the anterior horn of the cervical cord are markedly reduced in number (HE; bar = 200 μm).

ever, there were no Bunina bodies or ubiquitin-positive intraneuronal inclusions.

DISCUSSION

The early decline in social interpersonal conduct, decline in personal hygiene and grooming, perseverative and stereotypical behaviors, and late mutism observed in the presented case are clinical features of FTD.[1,6] The bilateral pyramidal tract signs and neurogenic findings in EMG observed in the middle stage support the clinical diagnosis of MND. Therefore, with the rapid progression into akinetic mutism, this case is clinically compatible with FTD/MND.

The dysarthria observed in the initial stage was characterized by hoarseness, followed by the emergence of a nasal voice and volitional movement disorders of the speech organs, which ultimately evolved into AOS. MND signs, such as tongue atrophy and fasciculation, were not observed even in this stage; therefore, the severe dysarthria was thought to be attributable to AOS, not bulbar palsy. This is a unique clinical feature of our case because severe dysarthria is caused by bulbar palsy in FTD/MND.[1] Progressive AOS is a rare condition,[7] and to the best of our knowledge, no other case of progressive AOS with FTD has been reported in the literature. We propose that the combination of FTD and progressive AOS in our case was derived from severe and widespread lesions in the bilateral

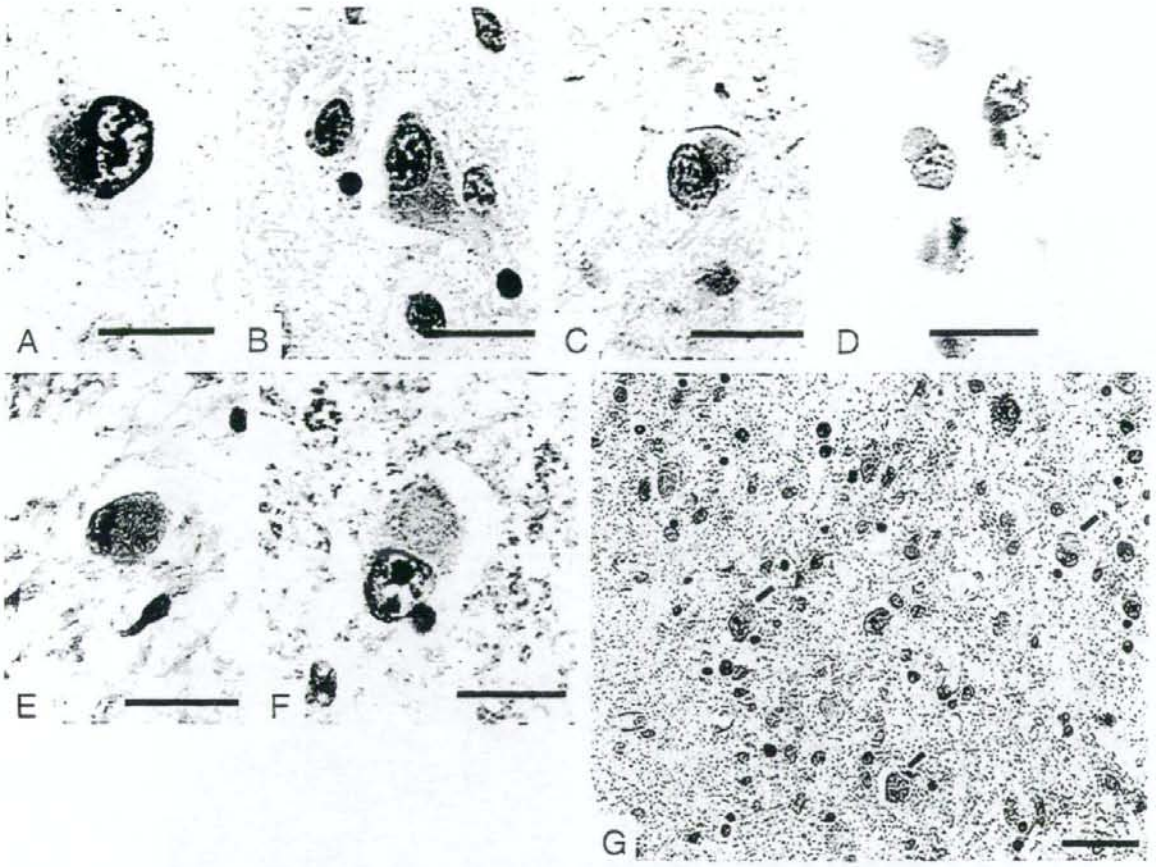

Fig. 5 Basophilic inclusion bodies observed in the brain. (A) Frontal lobe (HE; bar = 10 μm). (B) Temporal cortex (HE; bar = 20 μm). (C) Precentral gyrus (HE; bar = 20 μm). (D) Insular cortex (KB; bar = 20 μm. (E) Subthalamic nucleus (HE; bar = 20 μm). (F) Red nucleus (HE; bar = 10 μm). (G) Hippocampus, basophilic inclusions are indicated by arrows (HE; bar = 20 μm).

frontal lobes, including the anterior opercular area, which is supported by the SPECT and pathological findings.

Intraneuronal inclusions observed in the present case were basophilic with HE and KB stain, well stained with Nissl stain, weakly argyrophilic with Bodian's stain, and negative with AT8 and antiubiquitin immunostaining. Although electromicroscopic examination was not performed, these findings coincide well with a previous report of basophilic inclusions.[8] Basophilic inclusions have been described in cases of juvenile onset amyotrophic lateral sclerosis.[9-13] So far, adult-onset cases showing basophilic inclusions consist of two major subgroups:[14] one is a generalized variant of Pick's disease or relatively early onset FTD,[15] and the other is motor neuron disease with basophilic inclusions. Although only a few cases in each subgroup have been reported,[8,15-18] some of these cases show a widespread distribution of lesions as was observed in our case.

The present case showed clinicopathological features of both FTD and MND, which suggests that cases showing basophilic inclusions may constitute a clinicopathological spectrum of FTD/MND between a generalized variant of Pick's disease (FTD) and motor neuron disease with basophilic inclusions (MND). This condition clinically mimics FTD/MND with ubiquitin-positive inclusions, but differs pathologically.

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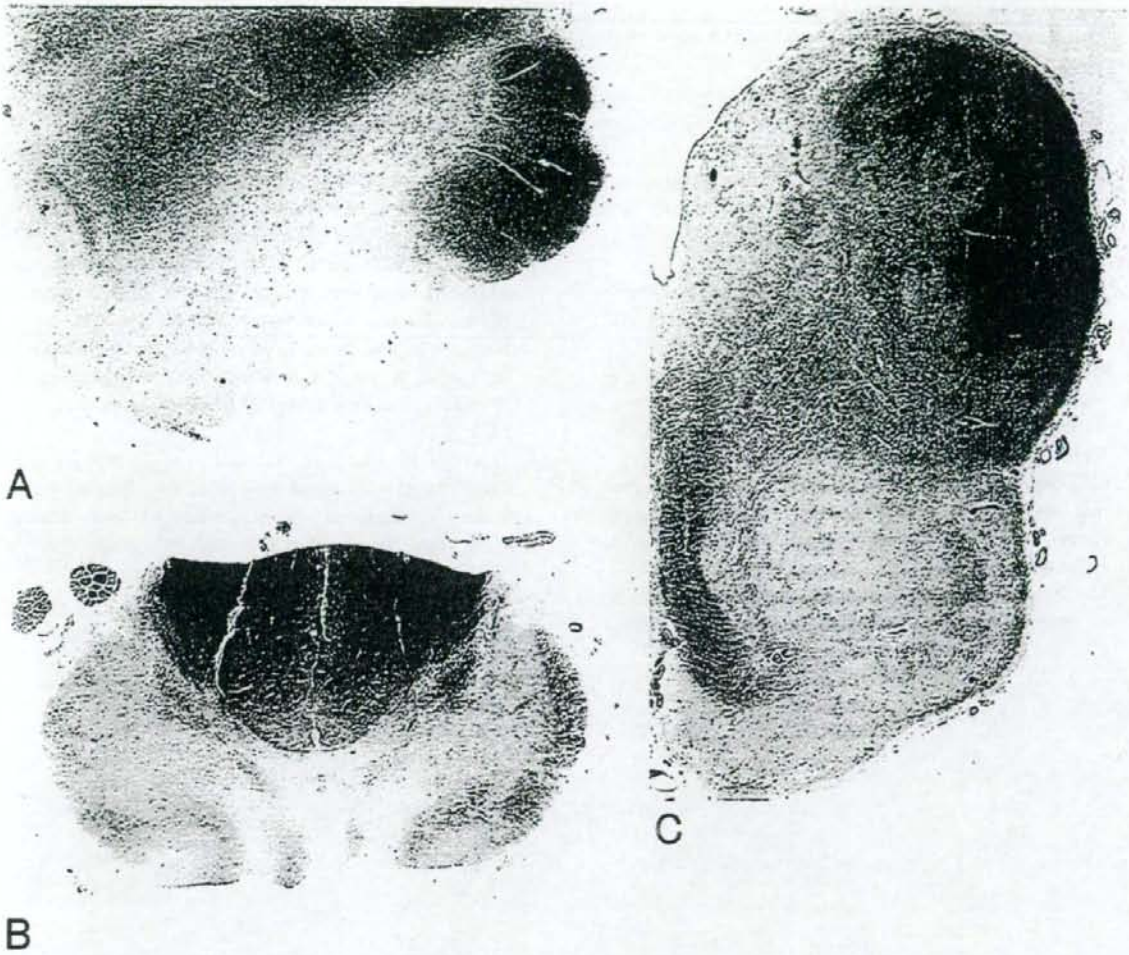

Fig. 6 Semimacroscopic findings of the brainstem and cervical cord. (A) Cerebral peduncle (KB). (B) Medulla oblongata (KB). (C) Upper cervical cord (KB). Prominent pallor of the myelin sheath of the corticospinal tract can be seen.

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REFERENCES

1. Snowden J, Neary D, Mann DMA. *Fronto-Temporal Lobar Degeneration: Frontotemporal Dementia, Progressive Aphasia, Semantic Dementia*. New York: Churchill Livingstone, 1996.
2. Bak TH, Hodges JR. Motor neurone disease, dementia and aphasia: coincidence, co-occurrence or continuum? *J Neurol* 2001; **248**: 260–270.
3. Jackson M, Lowe J. The new neuropathology of degenerative frontotemporal dementias. *Acta Neuropathol* 1996; **91**: 127–134.
4. Tolnay T, Probst A. Frontotemporal lobar degeneration. An update on clinical, pathological and genetic findings. *Gerontology* 2001; **47**: 1–8.
5. Nakano I. Frontotemporal dementia with motor neuron disease (amyotrophic lateral sclerosis with dementia). *Neuropathology* 2000; **20**: 68–75.
6. Neary D, Snowden JS, Gustafson L *et al.* Frontotemporal lobar degeneration. A consensus on clinical diagnostic criteria. *Neurology* 1998; **51**: 1546–1554.
7. Weller M. Anterior opercular cortex lesions cause dissociated lower cranial nerve palsies and anarthria but

no aphasia: Foix–Chavany–Marie syndrome and 'automatic voluntary dissociation' revisited. *J Neurol* 1993; **240**: 199–208.

8. Kusaka H, Matsumoto S, Imai T. Adult-onset motor neuron disease with basophilic intraneuronal inclusion bodies. *Clin Neuropathol* 1993; **12**: 215–218.
9. Wohlfart G, Swank RL. Pathology of amyotrophic lateral sclerosis. Fiber analysis of the ventral root and pyramidal tracts of the spinal cord. *Arch Neurol Psychiatry* 1941; **46**: 783–799.
10. Berry RG, Chambers RA, Duckett S *et al.* Clinicopathological study of juvenile amyotrophic lateral sclerosis. *Neurology* 1969; **19**: 312.
11. Nelson JS, Prensky AL. Sporadic juvenile amyotrophic lateral sclerosis. A clinicopathological study of a case with neuronal cytoplasmic inclusions containing RNA. *Arch Neurol* 1972; **27**: 300–306.
12. Oda M, Akagawa N, Tabuchi Y *et al.* A sporadic juvenile case of the amyotrophic lateral sclerosis with neuronal intracytoplasmic inclusions. *Acta Neuropathol* 1978; **44**: 211–216.
13. Matsumoto S, Kusaka H, Murakami N *et al.* Basophilic inclusions in sporadic juvenile amyotrophic lateral sclerosis: an immunocytochemical and ultrastructural study. *Acta Neuropathol* 1992; **83**: 579–583.
14. Munoz DG. The pathology of Pick complex. In: Kertesz A, Munoz DG (eds) *Pick's Disease and Pick Complex*. New York: Wiley-Liss, 1998; 211–241.
15. Munoz-Garcia D, Ludwin SK. Classic and generalized variants of Pick's disease: a clinicopathological, ultrastructural and immunocytochemical comparative study. *Ann Neurol* 1984; **16**: 467–480.
16. Kusaka H, Matsumoto S, Imai T. An adult-onset case of sporadic motor neuron disease with basophilic inclusions. *Acta Neuropathol* 1990; **80**: 660–665.
17. Hamada K, Fukazawa T, Yanagihara T *et al.* Dementia with ALS features and diffuse Pick body-like inclusions (atypical Pick's disease?). *Clin Neuropathol* 1995; **14**: 1–6.
18. Tsuchiya K, Ishizu H, Nakao I *et al.* Distribution of basal ganglia lesions in generalized variant of Pick's disease: a clinicopathological study of four autopsy cases. *Acta Neuropathol* 2001; **102**: 441–448.

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An unusual case of a spasticity-lacking phenotype with a novel *SACS* mutation

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Abstract

The authors describe an unusual case of autosomal recessive spastic ataxia of Charlevoix–Saguenay (ARSACS) without leg spasticity, which is a core clinical feature of ARSACS. This is the second family with a spasticity-lacking phenotype in ARSACS. A peripheral nerve conduction study disclosed decreases in motor and sensory nerve conduction velocities with the disease progression. Although the leg spasticity is reported to become progressively worse during the disease and is prevalent in older patients, we first observed that the symptom had disappeared, probably due to the progressive peripheral nerve degeneration in the disease course. Thus, we should analyze the *SACS* gene even in cases of early-onset cerebellar ataxia without spasticity. The patient had a novel homozygous 2-base pair deletion mutation (c.5988–9 del CT) of the *SACS* gene, but the genotype was different from that in our first family of this phenotype. A further genotype–phenotype correlation study is required to clarify the molecular mechanism underlying 'sacsinopathies'.

Keywords: ARSACS; Deletion mutation; Spasticity; SPECT with 3D-SSP analysis

1. Introduction

Autosomal recessive spastic ataxia of Charlevoix–Saguenay (ARSACS; OMIM 270550) was originally described in families from the Charlevoix–Saguenay region in Quebec, in the northeast of Canada. The clinical phenotype of ARSACS patients in Quebec is uniform, and characterized by early-onset ataxia of gait, progressive spasticity, peripheral neuropathy, normal mentality and retinal striation [1]. In 2000, the gene responsible for ARSACS, *SACS*, was discovered [2]. The open reading frame (ORF) of *SACS* was initially reported to comprise 11,487 bp and to be encoded by a single gigantic exon [2]. In the recent version of Genome Project Gene Predictions, however, eight exons upstream the original *SACS* ORF are indicated and thus the new ORF is 13,737 bp long (http://www.ncbi.nlm.nih.gov/entrez/viewer.fcgi?db=nucleotide&val=13620292). To date, more than 20 mutations have been reported worldwide [3–5].

Recent reports have revealed that ARSACS shows phenotypic variability, e.g., absence of retinal striation [6–9] and presence of mental impairment [9–12]. Furthermore, we previously reported two sibling cases without spasticity elsewhere [13], although we could not determine whether their spasticity had gradually decreased or not existed from the onset of disease. Here we report a case that exhibited a decrease in leg spasticity during the 29-year course of the disease, with a novel *SACS* gene mutation.

2. Methods

We report a patient in a Japanese family with early-onset ataxia. The unaffected elder sister underwent thorough neurological evaluation by H.S. The father and mother were not consanguineous, and had died at ages 82 and 34 years of pulmonary fibrosis and a sarcoma, respectively.

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We performed conventional nerve conduction studies on sensory and motor nerves. Sensory nerves were examined by means of the antidromic stimulation technique.

The patient was examined by means of *N*-isopropyl-*p* [^{123}I] iodoamphetamine (^{123}I-IMP) single photon emission computed tomography (SPECT), and the images obtained were analyzed by means of three-dimensional streotactic surface projection (3D-SSP) using image-analysis software, iSSP, ver. 3.5 (Nihon Medi-Physics).

Blood samples were obtained with informed consent from the patient and her elder sister. Genomic DNA was extracted from peripheral blood leukocytes. Using 38 appropriate primer pairs (all primer sequences are available on request), the coding exons of the *SACS* gene were amplified by PCR from 200 ng of genomic DNA, and then sequenced directly with an ABI PRISM 3100 genetic analyzer; the analysis was performed with Sequencing Analysis software, ver. 5.2 (Applied Biosystems).

This study was approved by the Medical Ethical Committee of Jichi Medical University.

3. Case report

A 57-year-old woman first walked at 3 years. Her gait was unsteady and she could not run in the first decade. She could walk with assistance until 25 years old. She was admitted to our hospital at age 27 years because of slowly progressive gait disturbance in October 1977. Neurological examination at age 27 years revealed mild distal muscle weakness and atrophy of the extremities. She exhibited spasticity in the lower extremities. Her tendon reflexes were exaggerated with the absence of ankle jerks. The Babinski sign was present bilaterally. She showed limb and truncal ataxia with scanning and slurred speech. Her gait was ataxic and spastic. Horizontal gaze-evoked nystagmus was noted. Vibratory sensation in the lower extremities was reduced. She showed claw-hand and hammer-toe deformities, and pes cavus. Myelinated retinal nerve fibers were observed in the retina. A nerve conduction study revealed that motor nerve conduction velocity was mildly reduced and sensory nerve conduction velocity was also reduced except for in the sural nerves, for which no sensory nerve action potential could be evoked (Table 1). Brain CT revealed cerebellar atrophy. A sural nerve biopsy revealed loss of large myelinated fibers (data not shown).

Table 1
Peripheral neurophysiologic study

	Nerve (left)	1977/11/04	2006/01/31	Normal
MCV	Ulnar	48.4	34.8	49–68 m/s
	Median	37.7	NE	47–60 m/s
	Common peroneal	26.8	NE	43–62 m/s
	Posterior tibial	27.0	NE	41–61 m/s
SCV	Ulnar (hand)	24.5	26.4	46–60 m/s
	Median (hand)	36.5	24.9	45–68 m/s
	Sural	NE	NE	34–49 m/s

MCV: motor nerve conduction velocity, SCV: sensory nerve conduction velocity, NE: not evoked.

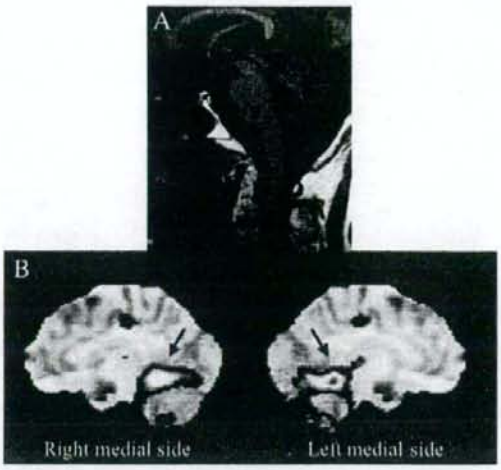

Fig. 1. (A) Brain MRI of the patient. Brain MRI revealed cerebellar superior vermian atrophy without brainstem atrophy. (B) ^{123}I-IMP SPECT with 3D-SSP analysis. The results showed decreased blood flow in the superior cerebellar vermis (arrow) and cerebellar hemisphere.

After discharge, she could walk with a walker, but her gait disturbance gradually progressed and she became wheelchair-bound at age 45. She fell down and developed a subdural hematoma, and thus underwent burrhole irrigation at the same time. Dysphagia emerged at age 54. Neurological examination at age 57 years disclosed the absence of spasticity and moderate muscle weakness in the lower extremities. Her severe limb and truncal ataxia resulted in unsteadiness on sitting on the side of bed. Both superficial and deep sensations were disturbed, especially in the distal parts of the extremities. The tendon reflexes had almost completely disappeared in the upper and lower extremities. The Babinski sign was still present. The leg spasticity was no longer evident, apparently because of progressive motor and sensory neuropathies. A nerve conduction study revealed that motor nerve potentials were not evoked except for in the ulnar nerves and sensory nerve conduction velocity was reduced except for in the sural nerves, for which no sensory nerve action potential could be evoked (Table 1). Brain MRI revealed cerebellar atrophy, especially in the superior vermis (Fig. 1A). ^{123}I-IMP SPECT revealed decreased blood flow in the whole cerebellum (data not shown), whereas SPECT with 3D-SSP analysis showed decreased blood flow in the superior cerebellar vermis (Fig. 1B).

A homozygous 2-base pair deletion mutation, c.5988–9 del CT (GenBank Accession No. AL157766) in exon 9 of the *SACS* gene, was identified in the patient. The elder sister had a heterozygous state of this condition.

4. Discussion

The present patient showed characteristic features of ARSACS, as follows: cerebellar ataxia, peripheral neuropathy, retinal striation, and cerebellar atrophy, especially in the

superior vermis. However, it is noteworthy that our patient lacked leg spasticity, i.e., a core clinical feature of ARSACS. In Quebec and non-Quebec patients, the leg spasticity becomes progressively worse during the disease and is prevalent in older patients, and tendon reflexes remain preserved throughout the disease, except for ankle jerks [1,8]. Meanwhile, we previously reported two brothers with ARSACS without spasticity [13]. In those cases, we were not able to determine whether or not their spasticity had decreased during the disease course or had been absent from the onset, because we only observed them at one time [13]. In the present patient, we observed that leg spasticity and tendon reflexes decreased during the 29-year disease course. This is the second family with ARSACS without spasticity [13], and is the first observation that spasticity and tendon reflexes decreased during the disease course of ARSACS. There is a possibility that severe peripheral nerve degeneration, as indicated by the biopsied sural nerve and peripheral nerve conduction velocities, masked any spasticity. The present patient again indicates that progressive spasticity is not a constant feature of ARSACS [13], and that we should analyze the *SACS* gene even in cases of early-onset cerebellar ataxia without spasticity.

The characteristic MRI findings in ARSACS are cerebellar atrophy, especially in the upper vermis, as shown in our patient, and a small spinal cord in the cervical segment [3]. The MRI findings in 11 of 14 patients with early-onset cerebellar ataxia with retained tendon reflexes (EOCA) reflected marked cerebellar atrophy affecting the upper and lower vermis, and hemispheres to almost the same degree [15]. In Friedreich's ataxia (FA), the MRI findings in all 11 patients reflected upper cervical cord shrinkage, and only one of the 11 patients at an advanced stage showed moderate cerebellar atrophy [15]. Thus, there are some different MRI findings among EOCA, FA, and ARSACS. In the present study, we showed that 3D-SSP analysis on brain SPECT revealed decreased blood flow in the superior cerebellar vermis. This finding might reflect atrophy of the superior cerebellar vermis. To our knowledge, SPECT with 3D-SSP analysis in ARSACS has not been reported so far. Meanwhile, EOCA and FA often show a reduction in the parietotemporal cortex blood flow as well as cerebellar hypoperfusion [14], a different feature from ARSACS. Although we should perform further SPECT analyses in ARSACS, 3D-SSP analysis on brain SPECT could be a useful tool for the differential diagnosis of early-onset cerebellar ataxias in addition to brain and cervical MRI, and gene analysis.

Genetically, the present patient had a novel homozygous deletion mutation (c.5988–9 del CT) of the *SACS* gene, which resulted in a frameshift and a subsequent stop codon at amino acid residue 1999. This mutation leads to truncation of the predicted sacsin protein. However, our first ARSACS family without spasticity had a homozygous missense mutation of the *SACS* gene. Thus, it does not appear that the leg spasticity-lacking phenotype is affected by a certain genotype. Concerning the 2-base pair deletion mutation in the *SACS* gene like our case, there has been only one report with a compound heterozygous state in more than 20 mutations reported [9]. So far, a genotype–phenotype correlation has not been demonstrated in ARSACS. As more *SACS* mutations are identified, a finer genotype–phenotype correlation study will become possible.

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References

[1] Bouchard JP, Barbeau A, Bouchard R, Bouchard RW. Autosomal recessive spastic ataxia of Charlevoix–Saguenay. Can J Neurol Sci 1978;5:61–9.
[2] Engert JC, Berube P, Mercier J, Dore C, Lepage P, Ge B, et al. ARSACS, a spastic ataxia common in northeastern Quebec, is caused by mutations in a new gene encoding an 11.5-kb ORF. Nat Genet 2000;24:120–5.
[3] Takiyama Y. Autosomal recessive spastic ataxia of Charlevoix–Saguenay. Neuropathology 2006;26:368–75.
[4] Ouyang Y, Takiyama Y, Sakoe K, Shimazaki H, Ogawa T, Nagano S, et al. Sacsin-related ataxia (ARSACS): expanding the genotype upstream from the gigantic exon. Neurology 2006;66:1103–4.
[5] Criscuolo C, Sacca F, De Michele G, Mancini P, Combarros O, Infante J, et al. Novel mutation of *SACS* gene in a Spanish family with autosomal recessive spastic ataxia. Mov Disord 2005;20:1358–61.
[6] Hara K, Onodera O, Endo M, Kondo H, Shiota H, Miki K, et al. Sacsin-related autosomal recessive ataxia without prominent retinal myelinated fibers in Japan. Mov Disord 2005;20:380–2.
[7] Richter AM, Ozgul RK, Poisson VC, Topaloglu H. Private *SACS* mutations in autosomal recessive spastic ataxia of Charlevoix–Saguenay (ARSACS) families from Turkey. Neurogenetics 2004;5: 165–70.
[8] El Euch-Fayache G, Lalani I, Amouri R, Turki I, Ouahchi K, Hung WY, et al. Phenotypic features and genetic findings in sacsin-related autosomal recessive ataxia in Tunisia. Arch Neurol 2003;60:982–8.
[9] Yamamoto Y, Hiraoka K, Araki M, Nagano S, Shimazaki H, Takiyama Y, et al. Novel compound heterozygous mutations in sacsin-related ataxia. J Neurol Sci 2005;239:101–4.
[10] Criscuolo C, Banfi S, Orio M, Gasparini P, Monticelli A, Scarano V, et al. A novel mutation in *SACS* gene in a family from southern Italy. Neurology 2004;62:100–2.
[11] Ogawa T, Takiyama Y, Sakoe K, Mori K, Namekawa M, Shimazaki H, et al. Identification of a *SACS* gene missense mutation in ARSACS. Neurology 2004;62:107–9.
[12] Grieco GS, Malandrini A, Comanducci G, Leuzzi V, Valoppi M, Tessa A, et al. Novel *SACS* mutations in autosomal recessive spastic ataxia of Charlevoix–Saguenay type. Neurology 2004;62:103–6.
[13] Shimazaki H, Takiyama Y, Sakoe K, Ando Y, Nakano I. A phenotype without spasticity in sacsin-related ataxia. Neurology 2005;64: 2129–31.
[14] De Michele G, Mainenti PP, Soricelli A, Di Salle F, Salvatore E, Longobardi MR, et al. Cerebral blood flow in spinocerebellar degenerations: a single photon emission tomography study in 28 patients. J Neurol 1998;245:603–8.
[15] Klockgether T, Petersen D, Grodd W, Dichgans J. Early onset cerebellar ataxia with retained tendon reflexes. Clinical, electrophysiological and MRI observations in comparison with Friedreich's ataxia. Brain 1991;114:1559–73.

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Constant blood flow reduction in premotor frontal lobe regions in ALS with dementia – a SPECT study with 3D-SSP

Ishikawa T, Morita M, Nakano I. Constant blood flow reduction in premotor frontal lobe regions in ALS with dementia – a SPECT study with 3D-SSP.
Acta Neurol Scand 2007: 116: 340–344.

Objectives – We investigated the regional cerebral blood flow in amyotrophic lateral sclerosis with dementia (ALS-D) patients, using single photon emission computed tomography (SPECT). *Materials and methods* – The ^{123}I-IMP SPECT data for 5 ALS-D and 16 ALS patients were analyzed using three-dimensional stereotactic surface projection (3D-SSP). *Results* – 3D-SSP demonstrated marked prefrontal hypoperfusion in all the five ALS-D cases and significant bilateral prefrontal hypoperfusion in group comparisons. *Conclusions* – This study revealed prefrontal hypoperfusion in ALS-D cases to be an obvious abnormality with scientific objectivity.

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Key words: amyotrophic lateral sclerosis with dementia; premotor frontal lobe region; regional cerebral blood flow; single photon emission computed tomography; three-dimensional stereotactic surface projection

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Introduction

Amyotrophic lateral sclerosis (ALS) is a degenerative disorder that involves progressive muscle weakness, and the lesions are essentially restricted to upper and lower motor neurons. Traditionally, patients with ALS have been recognized to be free from cognitive impairment. Evidence is emerging, however, that the cognitive function is impaired in some ALS patients, and such cases have been repeatedly described, especially in Japan (1).

Single photon emission computed tomography (SPECT) studies have been performed for the evaluation of the regional cerebral blood flow (rCBF) in various neurodegenerative disorders, including ALS and ALS-D. Such studies revealed cortical hypoperfusion in the premotor frontal lobe cortex and/or motor cortex in ALS (2, 3) or ALS with dementia (ALS-D) (4, 5), leading the researchers to state that ALS-D is included in the spectrum of ALS (6). The reported hypoperfusion in these regions, however, lacked objectivity, because the SPECT data were not standardized. With recent advances in computer-assisted analysis of SPECT images using three-dimensional stereotactic surface projection (3D-SSP) (7, 8), we have become able to detect a slight change in rCBF with scientific objectivity. Nevertheless, there have been few studies to discriminate subjects with ALS-D from non-demented ALS cases using such statistical methods. The purpose of this study was to evaluate rCBF in ALS-D and ALS cases using an objective and accurate method for analysis such as 3D-SSP, and to discuss the relationship between ALS-D and classic ALS.

Material and methods

Cases

Forty-one ALS cases had been diagnosed in the Neurology Department of Jichi Medical University from 1997 to 2003, five of whom had dementia. Among them, 16 ALS patients and five ALS with dementia patients could be evaluated by SPECT. Five ALS-D (two men and three women, mean ± SD: 54.8 ± 3.4 years old) and 16 ALS cases (nine men and seven women, mean ± SD: 66.5 ± 11.8 years old) were selected for analysis. The diagnosis of ALS was established according to the El Escorial criteria (9). None of the patients had either symptoms of a cerebrovascular disease or infarcts detectable in CT or MR images.

Table 1 Clinical features of the amyotrophic lateral sclerosis with dementia (ALS-D)

ALS-D cases	Age (years old) /Sex	The duration of illness at the time of SPECT (months)	Initial symptom	HDS-R	WAIS-R	Loss of memory	Insight into disease	Personality change /Emotional disorder	Autopsy
ALS-D 1	58/F	8	Memory loss	19	N/A	+	−	+	−
ALS-D 2	50/M	8	Memory loss	N/A	Verbal (57) Performance (51) Full (47)	+	−	+	+
ALS-D 3	59/F	19	Upper limb weakness	22	Verbal (100) Performance (75) Full (89)	−	−	+	+
ALS-D 4	52/F	27	Paranoia	18	N/A	+	−	+	+
ALS-D 5	55/M	45	Personality change	19	N/A	+	−	+	−
	54.8 ± 3.4 (mean ± SD)	21.4 ± 13.8 (mean ± SD)							
ALS cases Total 16 cases	66.5 ± 11.8 (mean ± SD)	21.4 ± 14.7 (mean ± SD)							

When individuals exhibited both ALS and an intellectual impairment constellation, such as loss of memory, personality change, emotional disorder and language impairment (the clinical features are summarized in Table 1), the diagnosis of ALS-D was made. For the evaluation of intellectual impairment, we used the Wechsler Adult Intelligence Scale-Revised (WAIS-R) and/or the revised Hasegawa Dementia Scale (HDS-R). The HDS-R is widely used as a brief cognitive screen instrument in Japan, and the result is known to be correlated well with the Mini-Mental State Examination (MMSE). The low-normal cut off is estimated to be 20, and the results are summarized in Table 1. Two ALS-D cases were also evaluated with the WAIS-R.

Assessment with the WAIS-R yielded a verbal IQ of 57, performance IQ of 51 and full IQ of 47 in case 2, a verbal IQ of 100, performance IQ of 75 and full IQ of 89 in case 3. Case 3 developed limb weakness as an initial symptom, and her intellectual impairment was negligible when she was diagnosed as having ALS, and SPECT study was carried out. Thereafter, she developed prominent dementia.

All the five ALS-D cases finally died of respiratory failure because of motor neuron involvement. Autopsy was performed in three cases (case 2, 3, and 4), and the diagnosis of ALS-D was confirmed according to the result of the autopsy. A total of 33 healthy volunteers (21 men and 12 women, mean ± SD: 58.6 ± 11.0 years old) was used as normal control subjects for 3D-SSP analysis.

SPECT and 3D-SSP

Single photon emission computed tomography with [^{123}I] isopropyl amphetamine (^{123}I-IMP SPECT) image sets was performed. The duration of illness at the time of SPECT was 21.4 ± 13.8 (mean ± SD) months in the ALS-D group and 21.4 ± 14.7 (mean ± SD) months in the ALS one, respectively. We performed 3D-SSP using the Neurological Statistical Image Analysis Software (NEUROSTAT) to evaluate the spatial distribution of an abnormal CBF, (8) and iSSP 35 for Windows to produce single subject *Z*-maps of decreased perfusion in patients. Following stereotactic anatomic standardization, the CBF in an individual's SPECT image set was extracted as a set of predefined surface pixels, which was used in the subsequent analysis. To quantify perfusion deficits, the normalized CBF in each patient was compared with that in 33 normal controls by pixel-by-pixel *Z*-score analysis ([normal mean]-[individual value])/(normal standard deviation; SD). We also compared the intergroup differences between the ALS-D group and normal controls, the ALS-D and ALS groups, and the ALS group and normal controls. A positive *Z*-score represents a reduced CBF in a patient relative to the control mean. In this study, we considered that a *Z*-score of > 3.0 was significant.

Results

The statistical *Z*-scores obtained with 3D-SSP in the ALS-D patients are presented in the Fig. 1.

The reduction of rCBF was consistently prominent and widespread in the middle to inferior areas of the premotor frontal lobe in all five ALS-D patients, while the rCBF decrease in such regions was only subtle and patchy in ALS patients. A mild decrease in the unilateral temporal lobe was also seen in all the five ALS-D patients.

A significant rCBF reduction in the bilateral frontal lobes, especially the premotor frontal lobes,

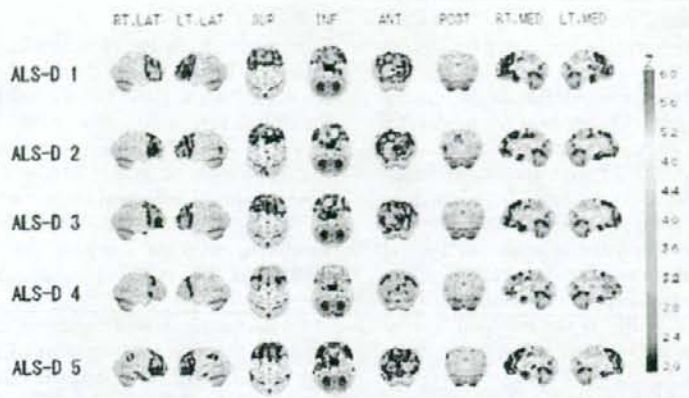

Figure 1. Three-dimensional stereotactic surface projection (3D-SSP) of the amyotrophic lateral sclerosis with dementia (ALS-D) cases compared with normal controls. The *Z*-score images obtained with 3D-SSP demonstrated marked regional cerebral blood flow reduction in the bilateral frontal lobes, especially the prefrontal lobes, in all five ALS-D patients. Images are constructed from eight views [in each line, from left to right, right lateral (RT. LAT), left lateral (LT. LAT), superior (SUP), inferior (INF), anterior (ANT), posterior (POST), right medial (RT. MED), and left medial (LT. MED)].

was evident in the ALS-D group compared with not only in normal controls but also in the ALS group (Fig. 2). One part of the left temporal lobe, the parahippocampal gyrus, also exhibited subtle hypoperfusion in the ALS-D group. On the contrary, in the ALS group, there were subtle rCBF decreases in the anterior part of the cingulate gyrus and the posterior part of the corpus callosum compared with in normal controls. Neither the ALS-D group nor the ALS one exhibited an obvious rCBF reduction in the regions corresponding to the precentral gyrus.

Discussion

Scintigraphical studies have been performed for the evaluation of rCBF in various neurodegenerative disorders, and some researchers have reported cortical hypoperfusion in the frontal cortex and motor cortex in ALS-D (4, 5). In the previous reports, however, as subjective approaches such as visual inspection were used, the reported hypoperfusion in these regions lacked objectivity. The 3D-SSP we used in this study is far superior to the visual inspection method in terms of objectivity. In addition, its sensitivity is reported to be high enough to be able to discriminate patients with a very early stage of the Alzheimer disease from healthy controls (7).

In our study, cortical hypoperfusion in the frontal lobe in the ALS-D group was consistently prominent compared to in the ALS cases, although the mean age of the ALS-D cases was lower than that of the controls or the ALS cases. CBF tends

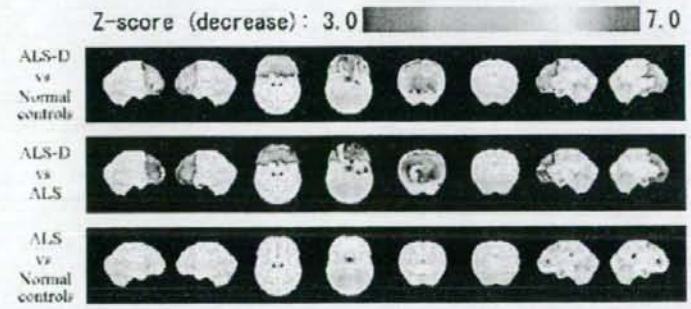

Figure 2. Decrease of regional cerebral blood flow (rCBF) adjusted to the global mean cerebral blood flow using three-dimensional stereotactic surface projection (3D-SSP) in group comparisons. 3D-SSP demonstrated a significant rCBF reduction in the bilateral frontal lobes, especially the prefrontal lobes, in the amyotrophic lateral sclerosis with dementia (ALS-D) group, when compared with either in normal controls or in the ALS group. On the contrary, subtle rCBF decreases in the anterior part of the cingulate gyrus and the posterior part of the corpus callosum were seen in the ALS group when compared with in normal controls. Images are constructed from 8 views in the same order as Fig. 1.

to be decreased in aged persons, so we might have underestimated the decrease in rCBF in the ALS-D group.

The change observed was notable in the inferolateral premotor frontal cortex in 4 of the 5 ALS cases, this being consistent with the previous results on ^{123}I-IMP SPECT and visual inspection (4, 5). This result is also supported by a previous neuropathological study on ALS-D that showed involvement of the inferomedial premotor frontal cortex, which is known to play important roles in emotional control and intellectual function (10). Thus, the decreased rCBF in the bilateral frontal lobe may play a role in the cognitive dysfunction in this condition.

In some of our ALS patients, a subtle reduction of rCBF in some parts of the frontal lobes, but strangely not in the precentral motor cortex, was observed, but the region was relatively restricted and variable. Our results are contrary to the findings in some previous studies (2, 3, 5) that revealed bilateral frontal hypoperfusion in ALS on visual inspection. In this study, no rCBF reduction was seen in the bilateral motor cortices not only in ALS-D but also in ALS. This result might indicate that there is actually no rCBF reduction in ALS, or we also need to consider the limit of sensitivity of this method.

What should we think about the relation between ALS and ALS-D? Most ALS-D cases reported previously shared characteristic neuropathological findings such as motor neuronal degeneration and Bunina bodies with classic/sporadic ALS. From the standpoint that ALS is a disease with widespread involvement of not only the pyramidal tract but also other systems, ALS-D belongs to the same clinical entity as ALS. However, the pattern of rCBF reduction in the ALS-D group in this study is apparently different from that of ALS, the pattern of ALS-D resembling that of fronto-temporal dementia (FTD). The hyporperfusion in the ALS-D group in this study could lead us to think that ALS-D is one form of FTD. However, most ALS-D cases reported previously had characteristic neuropathological findings consistent with sporadic ALS, such as Bunina bodies. It is essential that ALS-D is defined by supporting neuropathological investigation. If dementia is ultimately superimposed on ALS, the same decreasing rCBF pattern as in ALS-D should be observed in ALS cases, especially in ones with a long history. Actually, the most prominent rCBF reduction was observed in the case with the longest duration of the disease (45 months) among the ALS-D cases (case 5 of ALS-D). However, none of the 16 ALS cases showed the same pattern as that in ALS-D.

Furthermore, it is interesting that the cortical hypoperfusion in the frontal lobe was observed in one ALS-D case before the development of dementia. Case 3 with ALS-D developed limb weakness as an initial symptom, and at 19 months after the onset, ^{123}I-IMP SPECT was performed. Although the reduction of rCBF in the frontal lobe was obvious, her intellectual impairment was negligible at that time and became markedly worse after the examination. This suggests that a reduction of frontal rCBF could precede clinically evident dementia.

Based on our 3D-SSP analysis, it is reasonable to suppose that the pathogenesis of ALS-D is different from that of ALS, and 3D-SSP analysis might have a high predictive value for the diagnosis of ALS-D even at the stage of cryptic dementia.

There is the possibility that ALS-D may be overlooked, because ALS patients with severe bulbar symptoms tend to have trouble in verbal communication. We should always consider possible dementia hidden behind ALS, and recommend a SPECT study for ALS patients with any subtle signs and symptoms suggesting dementia.

Conclusion

Using 3D-SSP, we have demonstrated that ALS-D patients have a significantly reduced rCBF in the bilateral premotor frontal lobes compared with controls and ALS patients. The present study indicated that SPECT with 3D-SSP can clearly and objectively distinguish ALS-D from ALS. This finding seems to be useful for the diagnosis of ALS-D even at an early stage of dementia. A decreased rCBF in the bilateral premotor frontal lobes may be associated with dementia in ALS-D patients and help us to recognize the pathogenesis of the disease.

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References

1. Mitsuyama Y. Presenile dementia with motor neuron disease in Japan: clinico-pathological review of 26 cases. J Neurol Neurosurg Psychiatry 1984;**47**:953–9.
2. Abe K, Fujimura H. Single-photon emission computed tomographic investigation of patients with motor neuron disease. Neurology 1993;**43**:1569–73.
3. Waldemar G, Vorstrup S. Focal reductions of cerebral blood flow in amyotrophic lateral sclerosis: a [^{99m}Tc]-*d,l*-HMPAO SPECT study. J Neurol Sci 1992;**107**:19–28.

4. Neary D, Snowden JS. Frontal lobe dementia and motor neuron disease. J Neurol Neurosurg Psychiatry 1990;**53**: 23–32.
5. Vercelletto M, Ronin M. Frontal type dementia preceding amyotrophic lateral sclerosis: a neuropsychological and SPECT study of five clinical cases. Eur J Neurol 1999;**6**:295–9.
6. Talbot PR, Goulding PJ. Inter-relation between 'classic' motor neuron disease and frontotemporal dementia: neuropsychological and single photon emission computed tomography study. J Neurol Neurosurg Psychiatry 1995;**58**:541–7.
7. Imabayashi E, Matsuda H. Superiority of 3-dimensional stereotactic surface projection analysis over visual inspection in discrimination of patients with very early Alzheimer's disease from controls using brain perfusion SPECT. J Nucl Med 2004;**45**:1450–7.
8. Minoshima S, Frey KA. A diagnostic approach in Alzheimer's disease using three-dimensional stereotactic surface projections of fluorine-18-FDG PET. J Nucl Med 1995;**36**: 1238–48.
9. Brooks BR. El Escorial World Federation of Neurology criteria for the diagnosis of amyotrophic lateral sclerosis. Subcommittee on Motor Neuron Diseases/Amyotrophic Lateral Sclerosis of the World Federation of Neurology Research Group on Neuromuscular Diseases and the El Escorial 'Clinical limits of amyotrophic lateral sclerosis' workshop contributors. J Neurol Sci 1994;**124**:(Suppl.): 96–107.
10. Abe K, Fujimura H. Cognitive function in amyotrophic lateral sclerosis. J Neurol Sci 1997;**148**:95–100.

Reversible limbic encephalitis with antibodies against the membranes of neurones of the hippocampus

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PostScript

LETTERS

Reversible limbic encephalitis with antibodies against the membranes of neurones of the hippocampus

Paraneoplastic limbic encephalitis (PLE) is a rare neurological syndrome characterised by short-term memory impairment, seizures and various psychiatric disturbances. It is often associated with small-cell lung cancer, germ-cell tumours of the testis and breast cancer, but rarely with ovarian teratoma.[1] Several cases of PLE with ovarian teratoma have been reported, but the autoantigens of this disease remain unknown. Recently, an antibody to the membranes of neurones of the hippocampus (antigens colocalising with exchange factor for ADP-ribosylation factor 6 A (EFA6A)) was reported in association with PLE and ovarian teratoma.[2] Here, we report a case of a young Japanese woman who had PLE with ovarian teratoma, and whose serum and cerebrospinal fluid (CSF) contained an antibody against the membranes of neurones of the hippocampus. Immunosuppressive treatments resulted in a rapid improvement.

A 30-year-old woman was admitted to our hospital (Jichi Medical University, Tochigi, Japan) in April 2004 because of headache, fever and disorientation for 3 days. Figure 1A summarises the clinical course of the patient. She had no relevant family or medical history of interest. Her temperature was 37.8°C. Neurological examination on admission showed only recent memory disturbance. Examination of CSF showed increased protein concentration (670 mg/l), an increased number of mononuclear-dominant cells (40/mm^3) and 67 mg/dl glucose. CSF cytology was negative for malignant cells. Polymerase chain reaction for herpes simplex virus (HSV) was negative. No marked increase in anti-HSV, varicella zoster virus, human herpes virus type 6, cytomegalovirus or Epstein–Barr virus antibodies was detected in a paired CSF sample. Anti-toxoplasma and Japanese encephalitis virus antibodies were negative in the serum. The serum did not contain increased anti-nuclear, double-strand DNA, SS-A or thyroid antibodies. Anti-Yo, anti-Hu, anti-Ri, anti-CV2 (CRMP-5), anti-Tr, anti-Ma-2 and amphyphysin antibodies were negative in serum and CSF. Anti-voltage-gated potassium channel antibodies were not detected. Although axial plane and gadolinium-enhanced T1-weighted magnetic resonance images (MRI) were unremarkable, T2-weighted and fluid-attenuated inversion recovery images showed areas of mild hyperintensity in bilateral medial temporal lobes and hippocampus (fig 1B); these abnormalities had resolved by the time of the follow-up study in June 2004 (fig 1C).

Initial treatments included methylprednisolone (1000 mg/day for 3 days) and aciclovir (1500 mg/day). This treatment was associated with mild and transient decrease of fever, but tonic convulsions, disturbance of consciousness, restlessness and anxiety emerged and became worse. The electroencephalogram showed diffuse δ–θ waves. These symptoms and hypoventilation led to her being sedated and on a mechanical ventilator for 6 weeks with anticonvulsant treatment. Anisocoria, skew deviation and involuntary movement, such as epilepsia partialis continua, were observed for 2 weeks. Several attempts to wean the patient from the ventilator and decrease the sedation resulted in exacerbation of the involuntary movements and hypoventilation. Subsequently, the patient was treated with plasmapheresis (three exchanges) and intravenous immunoglobulin (400 mg/kg/day) for 5 days. The fever and convulsions began to subside about 4 weeks after her admission. She

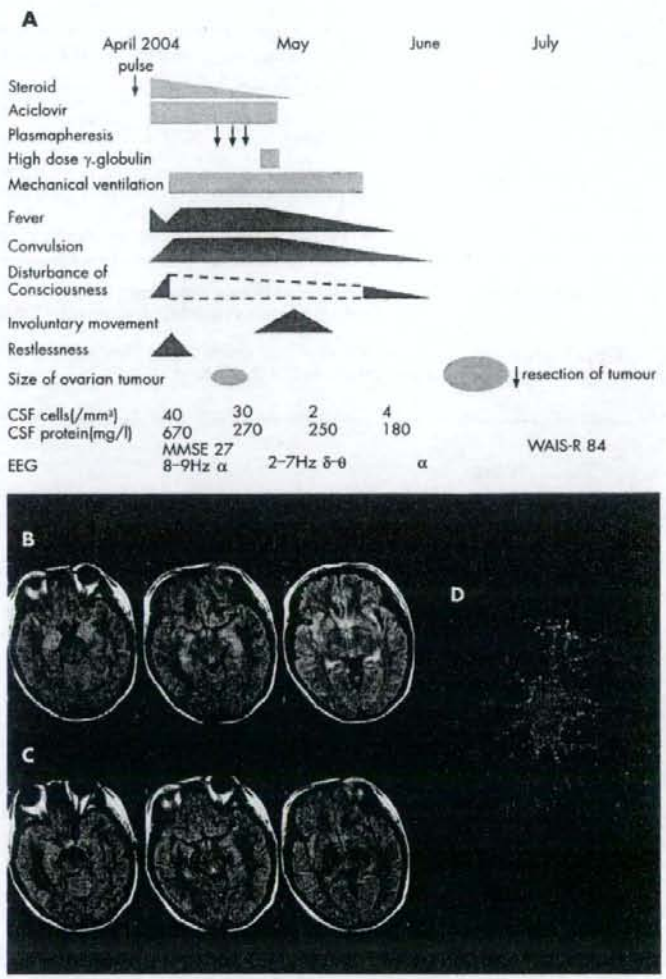

Figure 1 Clinical course of the patient, magnetic resonance image of the brain and immunolabelling of live rat hippocampal neurones with the patient's cerebrospinal fluid (CSF). (A) Clinical course of the patient. The symptoms and laboratory data were improved before the tumour resection. (B) MRI fluid-attenuated inversion recovery images of the brain in April 2004 showed areas of hyperintensity in the medial temporal lobes, cingulate gyrus, insular regions and hippocampus. (C) These abnormalities had resolved by June 2004. (D) The patient's antibodies, which colocalised with EFA6A, showed intense immunolabelling of the neuronal cell membranes and processes, using methods previously reported[2]. WAIS-R, Weschler Adult Intelligence Scale—Revised.

could breath spontaneously and all CSF studies became normal in May 2004.

In April 2004, an abdominal computed tomography had shown a 5 cm tumour in the right ovary, which was considered a benign cyst unrelated to the neurological disorder. In June 2004, the patient developed progressive constipation and a bulging appearance of the lower abdomen. Follow-up abdominal computed tomography and MRI showed an enlarged ovarian tumour, with a transverse diameter of 10 cm. On 28 June, resection of the tumour showed an immature teratoma that contained hair follicles, cartilage tissue, glandular structures and cerebral cortex-like tissue with normal appearing neurones. No inflammatory infiltrates were evident in the tumour.

Although her Wechsler Adult Intelligence Scale—Revised score was 84, she recovered and exhibited no limitations in activity of daily living in July 2004. After she was discharged from our hospital in July, she received ambulatory neurocognitive rehabilitation. She refused follow-up Wechsler Adult Intelligence Scale—Revised, but otherwise the cognitive functions and electroencephalogram appeared normal. She returned to her job as a medical resident in April 2005.

Analysis of the patient's serum and CSF showed antibodies, colocalised with EFA6A, which predominantly reacted with the neuropil of the hippocampus and cell membrane of rat hippocampal live neurones (fig 1D).

Discussion

We consider that this patient had definite paraneoplastic encephalitis, with predominant involvement of the limbic system. Accordingly, she developed subacute onset of short-term memory loss, seizures, psychiatric symptoms, CSF pleocytosis, MRI abnormalities in the limbic system and antineural antibodies.[3] Central nervous system tissue in the teratoma might be a trigger of the immune reaction. Central hypoventilation, skew deviation and anisocoria were observed during the most critical period. These symptoms suggest the involvement of her brain stem.

Previous reports of paraneoplastic encephalitis and ovarian teratoma showed MRI abnormalities in the frontal cortex, cerebellum and brain stem, but no case exhibited the characteristic medial temporal abnormalities observed in our patient.[2 4] This finding might have resulted from hippocampal inflammation related to the immune response predominantly reacting with hippocampal neurones.

Most patients with PLE and ovarian teratoma improved with resection of the teratomas.[2 4] We discovered the tumour in our patient 2 weeks after presentation of the encephalitis, but the benign appearance of the tumour and her poor physical status did not prompt for tumour resection. Instead, we started treatment with corticosteroids, plasmapheresis and intravenous immunoglobulin, and she began to improve before the tumour resection. This finding suggests that immunotherapy may provide the improvement needed to undergo the procedure for patients whose poor clinical condition prevents surgery. Furthermore, our patient began to recover faster (4 weeks after admission) than any other reported cases (7–16 weeks).[2] We presumed that this faster improvement resulted from the combination of immunotherapies. Immunocytochemistry with rat hippocampal live neurones showed the presence of antibodies to antigens present in the neuronal cell membranes and processes and colocalised with EFA6A, as previously reported.[1] The surface localisation of the autoantigen might be one reason for the effectiveness of these immunotherapies.[3]

PLE with ovarian teratoma has a better prognosis than that associated with other tumours.[2] Prompt detection of antibodies that colocalise with EFA6A is useful in predicting a clinical response to immunotherapy and tumour resection and a favourable outcome despite the severity of the disorder.

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Informed consent was obtained from the patient for publication of the features of the case.

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References

1 **Gultekin SH**, Rosenfeld MR, Voltz R, *et al.* Paraneoplastic limbic encephalitis: neurological symptoms, immunological findings and tumour association in 50 patients. *Brain* 2000;**123**:1481–94.
2 **Vitaliani R**, Mason W, Ances B, *et al.* Paraneoplastic encephalitis, psychiatric symptoms, and hypoventilation in ovarian teratoma. *Ann Neurol* 2005;**58**:594–604.
3 **Graus F**, Delattre JY, Antoine JC, *et al.* Recommended diagnostic criteria for paraneoplastic neurological syndromes. *J Neurol Neurosurg Psychiatry* 2004;**75**:1135–40.
4 **Kaide R**, Shimizu T, Kaike K, *et al.* EFA6A-like antibodies in paraneoplastic encephalitis associated with immature ovarian teratoma: a case report. *J Neuro-Oncol.* In press.
5 **Darnell RB**, Posner JB. A new cause of limbic encephalopathy. *Brain* 2005;**128**:1745–6.

Devic's syndrome-like phenotype associated with thymoma and anti-CV2/CRMP5 antibodies

The case of a patient who presented with a necrotic myelopathy and bilateral optic neuritis in association with a thymoma and circulating anti-CV2/CRMP5 antibodies is reported. This case shows that in some rare instances, a clinical presentation suggestive of a neuromyelitis optica can be of paraneoplastic origin.

A 45-year-old woman with a history of Hashimoto thyroiditis presented with a 4-month history of asthenia and a weight loss of 10 kg. A computed tomography of the chest showed an anterior mediastinal mass suspicious for a thymoma. The mediastinal mass was completely removed by surgery. Histological examination showed a B2-type thymoma with pleural, pericardial and left phrenic local extension. There was no evidence of mediastinal adenopathy or metastasis on computed tomography of the abdomen and pelvis. Treatment with radiation therapy was planned, but 1 month later the patient developed difficulties in walking for over 2 weeks, paraesthesia of the four limbs and bladder dysfunction.

Neurological examination showed a left spastic motor paresis, brisk reflexes and a left Babinski response; proprioceptive sensation was predominantly affected on the left limbs, whereas pain and thermal sensation were affected on the right limbs, suggesting a left cervical Brown–Sequard syndrome. Visual acuity was initially normal. There was no sign of polyneuropathy, and electromyography was normal. The patient did not have fever, and had no signs of systemic disease and no sicca syndrome on general examination. Magnetic resonance imaging (MRI) of the spine showed an enlargement of the cervical cord consecutive to an extensive cervicodorsal (C1 to D7) intramedullary lesion with focal heterogenous gadolinium enhancement (fig 1A,B). MRI of the brain was normal. The cerebrospinal fluid (CSF) had only an increased protein concentration of 82 g/dl; there was no intrathecal synthesis of IgG, and isoelectric focusing was negative. Polymerase chain reaction of herpes simplex virus (HSV)1 and HSV2 was negative in the CSF on two occasions. The following microbiological tests were also negative: enterovirus, varicella zoster virus, cytomegalovirus, Epstein-Barr virus, Lyme disease, syphilis, HIV and *Mycoplasma pneumoniae*. Anti-double-stranded DNA antibodies and anti-Sjogren's syndrome A and B antibodies were negative.

As an intramedullary metastasis of the thymoma was suspected, a biopsy of the lesion was performed at level C7. On histological examination, the lesions were found to be localised in both white and and grey matter. These lesions consisted of a reactive gliosis, with foci of oedema and necrosis with numerous macrophages and some perivascular lymphocytes (fig 1C,D). Bodian luxol coloration showed demyelinisation. There were no features of vasculitis, nor of viral inclusion or tumour infiltration. This was consistent with a necrotic myelopathy. Serum screening for neuromyelitis optica (NMO) IgG antibodies was negative.[1] Serum screening for onconeural antibodies was negative for anti-Hu, anti-Ri, anti-Yo, and anti-amphyphysin antibodies, but was strongly positive for anti-CV2/CRMP5 antibodies. Immediately after the biopsy, the patient became quadripleglic; this deterioration was probably related to the biopsy. She developed an intestinal subocclusion complicated with aspiration pneumonia. She was treated with high-dose methylprednisolone, but her condition did not improve and she developed a respiratory insufficiency that necessitated artificial ventilation in an intensive care unit. Ten plasma exchanges were also ineffective. At 4 months after the onset of myelopathy, the patient presented a bilateral painless visual loss. Funduscopic examination was normal, and evoked visual potentials showed a bilateral optic neuropathy. The patient finally died of septicaemia 5 months after the onset of myelopathy. No necropsy was performed.

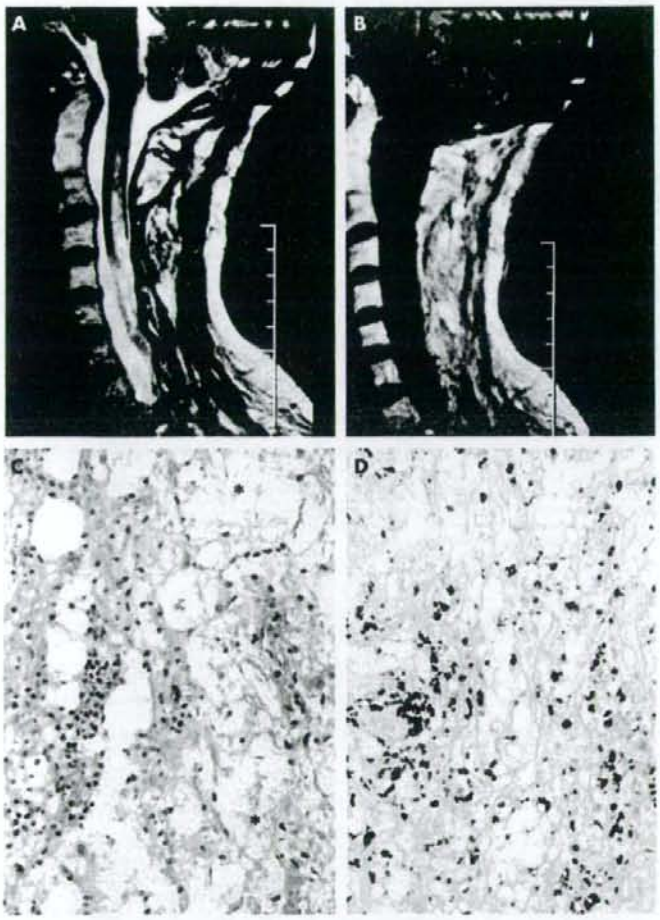

Figure 1 T2-weighted sequence of the spinal cord magnetic resonance imaging showing an extensive cervical intramedullary hypersignal (A). T1 sequence after gadolinium infusion showing focal heterogenous gadolinium enhancement (B). (C) Haematoxylin, ploxine and saffron staining of the biopsy showing reactive gliosis, oedema, necrosis (*) and microglial infiltration. (D) CD68 immunostaining showing microglial infiltration (brown colouration).

Discussion

Histological evaluation in our patient showed a necrotic myelopathy. It seems unlikely that occlusive vascular disease was implicated because the illness progressed over several weeks. Pathologically, there was no vascular occlusion, and the distribution of the lesions did not correspond to the territory of supply of any of the cord's vessels. There were neither clinical nor biological arguments for an infectious, postinfectious or vasculitic myelitis. In particular, HSV2, which has been reported in association with acute necrotic myelopathy in patients with cancer, was negative in the CSF (polymerase chain reaction). The patient did not receive radiotherapy, thus excluding a radiation myelopathy.

At 4 months after the onset of myelopathy, the patient presented a bilateral optic neuritis suggesting Devic's syndrome. As in our patient, the myelopathy in Devic's syndrome is usually necrotic. However, the subacute clinical onset, the context of a recently diagnosed malignant thymoma and the presence of anti-CV2/CRMP5 antibodies distinguish our case from that of patients with "classic" Devic's syndrome. These features rather suggest that in our patient this Devic's syndrome-like phenotype was paraneoplastic.[2] Furthermore, even if it does not exclude Devic's syndrome, we did not detect anti-NMO antibodies.[1] The clinical presentation and histological examination of the myelopathy could have been consistent with a paraneoplastic necrotising myelopathy, but a bilateral optic neuritis has never been described in this clinical entity.[3] A case of Devic's syndrome occurring after surgical resection of a thymoma was recently described by Antoine *et al*[4]. However, this patient was different because he had myasthenia gravis, developed necrotising myositis in addition to neuromyelitis optica, and had antibodies reacting with the central nervous system and thymic epithelial cells in the serum, but no anti-CV2/CRMP5 antibodies. In fact, the most likely hypothesis in our case is that the Devic's syndrome-like phenotype was related to the presence of anti-CV2/CRMP5 antibodies. Cross *et al*[5] recently reported three patients who had a myelopathy with optic neuritis, anti-CV2/CRMP5 antibodies and a cancer. Associated cancer was a thyroid papillary carcinoma, a small cell lung cancer and a renal cell cancer. Similar to our case, two patients had an extensive myelopathy and in one of them there was a gadolinium enhancement of the entire thoracic cord suggesting necrotic myelopathy. An autopsy was performed in a third patient (patient 15) with a less extensive myelopathy (spinal MRI abnormalities were limited to a patchy midthoracic T2 hypersignal). Spinal cord pathology showed microglial infiltration, important T cell infiltration but no necrosis. In contrast, the histological evaluation in our patient showed an important microglial infiltration with foci of oedema and necrosis. It shows that in patients with a Devic's syndrome-like phenotype and anti-CV2/CRMP5 antibodies, the myelopathy can be necrotic as in Devic's syndrome. Together with Cross *et al*'s[5] article, our report also suggests that the presence of anti-CV2/CRMP5 antibodies should be carefully studied in cases of myelopathy of unknown origin.

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References

1 **Lennon VA**, Wingerchuk DM, Kryzer TJ, *et al*. A serum autoantibody marker of neuromyelitis optica: distinction from multiple sclerosis. *Lancet* 2004;**364**:2106–12.
2 **Graus F**, Delattre JY, Antoine JC, *et al*. Recommended diagnostic criteria for paraneoplastic neurological syndromes. *J Neurol Neurosurg Psychiatry* 2004;**75**:1135–40.

3 **Ojeda VJ.** Necrotizing myelopathy associated with malignancy. A clinicopathologic study of two cases and literature review. *Cancer* 1984;**53**:1115–23.
4 **Antoine JC,** Camdessanché JP, Absi L, *et al.* Devic disease and thymoma with anti-central nervous system and antithymus antibodies. *Neurology* 2004;**62**:978–80.
5 **Cross SA,** Salomao DR, Parisi JE, *et al.* Paraneoplastic auto-immune optic neuritis with retinitis defined by CRMP-5-IgG. *Ann Neurol* 2003;**54**:38–50.

HFE H63D polymorphism is increased in patients with amyotrophic lateral sclerosis of Italian origin

A role for metal-mediated oxidative stress in the pathogenesis of amyotrophic lateral sclerosis (ALS) was proposed in 1994 in the first studies of familial ALS mutant superoxide dismutase 1, and interference with iron homoeostasis is now postulated.[1] The HFE gene on chromosome 6 is a mean corpuscular haemoglobin class I-like molecule related to iron regulation. Mutations in the coding region cause hereditary haemochromatosis, a common autosomal recessive disorder of iron metabolism that leads to iron overload in adulthood. Recent reports on HFE mutations in ALS showed contradictory results. Two studies described a higher prevalence of the HFE mutations in ALS than in the control group, and one study did not find any difference between the patients with ALS and the control group.[2–4] We analysed a series of Italian patients with ALS to investigate whether mutations in the HFE gene could represent a risk factor for ALS.

A total of 149 sporadic Italian patients with ALS (mean (standard deviation (SD)) age 59.4 (9.7) years) according to El Escorial criteria for clinically definite or probable ALS were consecutively recruited to this study. Control samples were obtained from 168 healthy people, matched by age (difference of 5 years), sex and ethnic origin (Italian region of birth) to patients with ALS. Patients and controls were informed about the objectives of the study, and informed consent was obtained. The study was approved by the institutional ethics committee. Blood samples were collected, and DNA was purified with a 6100 Nucleic acid Prep Station (ABI PRISM™). Rapid detection of H63D, C282Y and S65C, the three most common mutations in the HFE gene, was performed using the pyrosequencing technique (Pyrosequencing AB, Uppsala, Sweden). This assay is based on a duplex polymerase chain reaction (PCR) in which exons 2 and 4 are amplified together. The exon 2 PCR product is used for S65C and H63D polymorphisms, and the exon 4 PCR product for the C282Y mutation. The mutation analysis was subsequently carried out in a triplex assay by means of three pyrosequencing primers in one well. Forward PCR primers for each reaction were modified with biotin at the 5′ terminus to capture single-stranded templates from PCR products for pyrosequencing. The following PCR primers were used: for exon 2, ex2-F 5′-ggc tac gtg gat gac cag c-3′ and ex2-R 5′-gag ttc ggg gct cca cac-3′; for exon 4 ex4-F 5′-cct ggg gaa gag cag aga t-3′ and ex4-R 5′-cag atc aca atg agg ggc tg-3′. The primers used for sequencing were: 5′-gct gtt cgt gtt cta tg-3′ for exon 2 and 5′-ggg gaa gag cag aga t-3′ for exon 4. The PCRs were performed for 45 cycles, with initial denaturation at 95℃ for 10 min, followed by 95℃ for 30 s, annealing for 30 s and extension at 72℃ for 30 s. The final extension was at 72℃ for 5 min. Bound biotinylated single-stranded DNA was prepared following the protocols provided by the manufacturer (PSQ96 sample preparation kit; Pyrosequencing AB). SNP/AQ analysis was performed automatically on a PSQ™96 MA system using enzymes and reagents from an SNP Reagent kit (Pyrosequencing AB).

The group with ALS included 65 women and 84 men (mean (SD) age 61.1 (11.1) years), and the control group included 66 women and 102 men (mean (SD) age 60.7 (9.2) years). Table 1 shows the findings for the three SNPs H63D, C282Y and S65C. Analysis of HFE mutations showed a higher frequency of the mutated allele H63D in patients with ALS than in controls (28.8% *v* 14.8%; p = 0.004). The odds ratio conferred by the presence of the H63D allele was 2.25 (95% confidence interval 1.30 to 3.93). An increased frequency was also found in patients with ALS when all three mutations were combined (33.3% *v* 17.3%; p = 0.002). No significant differences were found between patients with the H63D allele and patients with wild-type HFE gene considering age of onset (63.4 (SD 9.3) *v* 60.2 (SD 11.9)), sex (22 men and 21 women *v* 62 men and 44 women), type of onset (33 spinal and 10 bulbar *v* 80 spinal and 26 bulbar) and disease duration (median survival time, 783 *v* 993 days).

Our data support the hypothesis that the change in iron metabolism may confer susceptibility to neurodegenerative diseases such as ALS. Our results are consistent with those found in the USA,[5] and in Ireland and Britain.[4] Interestingly, the second study reported an odds ratio of 1.85 (95% confidence interval 1.35 to 2.54) for the presence of the heterozygous H63D polymorphism, a value similar to that found in our population. In Europe, the C282Y allele has a north to west frequency-decreasing gradient, with higher frequencies reported in Ireland (28.4%) and Britain (17.4%) and lower frequencies in Italy (3.2%) and Greece (2.6%). Conversely, the H63D allele has a higher frequency in southern Europe (Spain, 32.3%) and a lower frequency in the Celtic populations (5%).[3] These marked ethnic differences may explain the negative findings of one study on patients with ALS in Texas, USA,[2] in which no matching for ethnic origin was performed.

The possible role of the H63D polymorphism in ALS is unclear. In a human neuronal cell line transfected with genes carrying the HFE mutations, the H63D polymorphism induced a decreased expression of SOD1, α-tubulin and β-actin;[5] these events can cause a disruption of axonal transport, a factor implicated in ALS pathogenesis. Alternatively, the H63D polymorphism may determine a subclinical increase in intracellular iron, possibly related to neurone oxidative damage. Further studies on the analysis of iron metabolism in patients with ALS are needed to elucidate the role of the H63D polymorphism as a genetic risk factor for sporadic ALS. An alternative possibility could be a linkage disequilibrium of ALS with an unknown gene located near the HFE locus.

Table 1 Frequency of HFE polymorphisms in patients with amyotrophic lateral sclerosis and controls

	Patients with ALS		Controls	
Polymorphisms	**No**	**%**	**No**	**%**
H63D/wild type	41	27.5	25	14.8
H63D/H63D	2	1.3	–	–
C282Y/wild type	5	3.3	3	1.8
S65C/wild type	2	1.3	1	0.6
Wild/wild type	99	66.4	139	82.7
Total	149	100	168	100

ALS, amyotrophic lateral sclerosis.

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References

1 **Carri MT,** Ferri A, Cozzolino M, *et al.* Neurodegeneration in amyotrophic lateral sclerosis: the role of oxidative stress and altered homeostasis of metals. *Brain Res Bull* 2003;**61**:365–74.
2 **Wang X-S,** Lee S, Simmons Z, *et al.* Increased incidence of the HFE mutation in amyotrophic lateral sclerosis and related cellular consequences. *J Neurol Sci* 2004;**227**:27–33.
3 **Yen AA,** Simpson EP, Henkel JS, *et al.* HFE mutations are not strongly associated with sporadic ALS. *Neurology* 2004;**62**:1611–12.
4 **Goodall EF,** Greenway MJ, van Marion I, *et al.* Association of the H63D polymorphism in the haemochromatosis gene with sporadic ALS. *Neurology* 2005;**65**:934–7.
5 **Le Gac G,** Ferec C. The molecular genetics of haemochromatosis. *Eur J Hum Genet* 2005;**13**:1172–85.

Causes of death in multiple system atrophy

Multiple system atrophy (MSA) is a heterogeneous neurodegenerative disorder, with a clinical presentation combining extrapyramidal,

cerebellar, autonomic or pyramidal symptoms. There are two major subtypes: MSA-P, with a clinical predominance of parkinsonism, and MSA-C, with a clinical predominance of cerebellar symptoms. Although various factors have been proposed to predict survival in MSA, including age at onset and several phenotypic features,[1] the terminal/end of life events have never been systematically studied. We present our results from a study on the causes of death in a series of pathologically confirmed, definite MSA cases.

All patients registered with the University of Miami/NPF Brain Endowment Bank (UM/BEB) donation programme with a diagnosis of neuropathologically confirmed, definite multiple system atrophy (MSA: n = 21) were included in this study. Pertinent information was gathered by two prospectively filled questionnaires used as part of the UM/BEB's recruitment process: (a) the UM/BEB Parkinson's disease registry form, a 128-item, self-administered questionnaire on demographics, environmental exposures, personal and family history, comorbid conditions, activities of daily living, clinical and treatment details; and (b) the "agonal state" form, a 25-item questionnaire on events covering the 48 h before death completed by the treating doctor/nurse. For comparisons, each MSA case was closely matched for age at disease onset (±2 years) and sex with a Parkinson's disease brain donor by an investigator blinded to the disease status and clinical information. Medical, hospital and hospice records of brain donors were also collected on an annual basis and all disease-related information was extracted by two independent clinical investigators (blinded to the aims of the study), and entered into separate databases that were checked for consistency. Brain removal, autopsy, fixation and sectioning were performed according to standard protocols. Postmortem diagnosis of MSA and Parkinson's disease were based on well-accepted criteria.[2 3] For statistical analysis, Mann–Whitney U test for two samples was used in non-parametric comparisons, and χ^2 tests with Yates' corrected p value and two-tailed Fisher exact p values in the comparison of proportions, as appropriate. The study was approved by the local institutional review board.

Table 1 shows the demographics and primary causes of death of all patients. Patients with MSA had significantly shorter disease duration ($p = 0.02$) than matched patients with Parkinson's disease, and most presented with parkinsonian-predominant symptoms. None of the patients had a predominantly autonomic presentation. In all, 15 of 21 (71.4%) patients with end-stage MSA had permanent in-dwelling balloon (Foley) catheters because of symptoms of urinary incontinence for at least 6 months before death; 13 (61.3%) had recurrent lower urinary tract infections (LUTIs). The recurrence of infections did not correlate with the presence of permanent Foley catheters; 4 of 13 (30.8%) patients with LUTIs did not have permanent Foley catheters. Two patients with MSA used clean intermittent self-urinary bladder catheterisation. Of the 13 patients with recurrent LUTIs, 5 (38.5%) died as a result of their infections. In addition, 7 (33.3%) patients had recurrent (≥2) episodes of aspiration and 8 (38.1%) had percutaneous gastrostomy (PEG) feeding tubes inserted because of swallowing/feeding difficulties and aspiration. The recurrence of aspirations was independent of PEG tubes, as 4 of 7 (57.1%) patients with PEG continued having episodes of aspiration after PEG. Of patients with recurrent aspirations, one died as a result of acute aspiration and two as a result of aspiration pneumonia.

Sudden death related to MSA was reported in 8 (38.1%) patients. In seven patients, sudden death was characterised as cardiopulmonary arrest of otherwise unknown aetiology, and in one as acute aspiration during sleep. In all, 5 of 6 (23.8%) patients with reported symptoms of laryngeal stridor as part of their disease died suddenly. Two of the patients with stridor had a permanent tracheostomy. Sudden death was reported in one of them. Skin infections in the form of complicated pressure ulcers were present in 6 (28.6%) patients. However, skin infections were not associated with death in any case. Marked weight loss (≥10% of premorbid weight) was reported in 16 (76.2%) patients. Weight loss was considerably less common in patients with PEG (5–31.2%) compared with those without PEG (11–68.8%). Three patients died as a result of weight loss and wasting. In contrast with Parkinson's disease, all patients with MSA died as a result of events related to their disease. One patient with MSA died from intestinal perforation after PEG tube misplacement.

Table 1 Characteristics and primary causes of death

	MSA (n = 21)	PD (n = 21)
Sex	10M/11F	10M/11F
Mean (SD) age at disease onset (years)	59.4 (10.1)	59.9 (8.9)
Mean (SD) disease duration (years)*	8.5 (4.7)	13.4 (8.2)
MSA type at presentation (%)		
MSA-P	16 (76.2)	
MSA-C	5 (23.8)	
Permanent balloon (Foley) catheters (%)†	15 (71.4)	7 (33.3)
Percutaneous gastrostomy (%)	8 (38.1)	3 (14.3)
Tracheostomy (%)	2 (9.5)	None
Sudden death (%)‡	8 (38.1)	3 (14.3)
Cause of death (%)		
Cardiopulmonary arrest	7 (33.3)	1 (4.8)
Urinary tract infection	5 (23.8)	None
Aspiration pneumonia	2 (9.5)	None
Infectious pneumonia	2 (9.5)	7 (33.3)
Acute aspiration	1 (4.8)	1 (4.8)
Wasting syndrome	3 (14.3)	1 (4.8)
Cerebrovascular accident	None	3 (14.3)
Myocardial infarction	None	2 (9.5)
Cancer	None	2 (9.5)
Other	1 (4.8)	1 (4.8)

F, female; M, male; MSA, multiple system atrophy; MSA-C, MSA with a clinical predominance of cerebellar symptoms; MSA-P; MSA with a clinical predominance of parkinsonism; PD, Parkinson's disease. Results in the comparisons between MSA and PD groups were significant for *p = 0.02, †p = 0.03 and ‡p = 0.02.

More than one third of patients with MSA in this study died suddenly. Several mechanisms for sudden death have been proposed in MSA. The combination of passive glottic narrowing by selective paralysis of the vocal cord abductors and active narrowing by adductor activation during inspiration[4] have been associated with stridor and acute airway obstruction. Furthermore, patients with MSA show minimal to no chemosensitivity to hypoxia (especially during sleep) possibly owing to the degeneration of brain stem respiratory centres. These may explain sudden death in patients with MSA even after tracheostomy.[5]

Dysphagia caused by delays in the oral and pharyngeal phases of swallowing, in combination with laryngeal (airway and sensory) and oesophageal sphincter disturbances may lead to both aspiration pneumonia and acute aspiration.[6] PEG tube feeding prevented considerable weight loss and wasting, but not the recurrence of aspirations and aspiration pneumonia. Additional measures, such as improvement of oral/dental hygiene and proper patient postprandial and sleep positioning,[7] may be considered to decrease mortality from aspiration. An additional finding of this study is the high prevalence of weight loss among patients with end-stage MSA. Weight loss is a risk factor for mortality in chronically ill patients.[8] Dietary adjustments, early swallowing studies and PEG tube feeding may reduce mortality in patients with MSA.

Neurogenic lower urinary tract dysfunction is considered a valuable diagnostic tool for MSA.[9] Urinary urgency or incontinence (storage disorder) and incomplete emptying or urinary retention (voiding disorder) may occur simultaneously and lead to intractable LUTIs, which are major causes of morbidity in this disorder.[10] More than half of our patients reported recurrent LUTIs and a large number died from complications related to LUTIs. Frequent urological monitoring and treatment of complications, in addition to the use of clean intermittent self-urinary bladder catheterization, may reduce the risk of LUTI-associated mortality.

In summary, all patients with MSA died from disease-related events, with sudden death and infections being the most common. We propose that careful screening for laryngeal stridor, neurogenic bladder dysfunction and dysphagia with aggressive treatment may increase total survival time in patients with MSA. More studies on the patient are warranted. Research efforts should be directed towards the development of more efficient identification and prevention strategies for the major complications of MSA.

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References

1 **Watanabe H**, Saito Y, Terao S, *et al*. Progression and prognosis in multiple system atrophy: an analysis of 230 Japanese patients. *Brain* 2002;**125**(Pt 5):1070–83.
2 **Gilman S**, Low PA, Quinn N, *et al*. Consensus statement on the diagnosis of multiple system atrophy. *J Neurol Sci* 1999;**163**:94–8.
3 **Hughes AJ**, Daniel SE, Kilford L, *et al*. Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinico-pathological study of 100 cases. *J Neurol Neurosurg Psychiatry* 1992;**55**:181–4.
4 **Isozaki E**, Osanai R, Horiguchi S, *et al*. Laryngeal electromyography with separated surface electrodes in patients with multiple system atrophy presenting with vocal cord paralysis. *J Neurol* 1994;**241**:551–6.
5 **Silber MH**, Levine S. Stridor and death in multiple system atrophy. *Mov Disord* 2000;**15**:699–704.
6 **Higo R**, Nito T, Tayama N. Swallowing function in patients with multiple-system atrophy with a clinical predominance of cerebellar symptoms (MSA-C). *Eur Arch Otorhinolaryngol* 2005;**262**:646–50.
7 **Matsui T**, Yamaya M, Ohrui T, *et al*. Sitting position to prevent aspiration in bed-bound patients. *Gerontology* 2002;**48**:194–5.
8 **Sauerwein HP**, Romijn JA. More consideration to dietary protein in the nutrition of chronically ill adults with tendency to weight loss. *Ned Tijdschr Geneeskd* 1999;**143**:886–9.
9 **Gilman S**, Low PA, Quinn N, *et al*. Consensus statement on the diagnosis of multiple system atrophy. *J Auton Nerv Syst* 1998;**74**:189–92.
10 **Ito T**, Sakakibara R, Yasuda K, *et al*. Incomplete emptying and urinary retention in multiple-system atrophy: when does it occur and how do we manage it? *Mov Disord* 2006;**21**:816–23.

Pisa syndrome after unilateral pallidotomy in Parkinson's disease: an unrecognised, delayed adverse event?

Dystonic lateroflexion of the trunk, also referred to as Pisa syndrome, pleurothotonus or a lean to the side, was originally described in association with prior exposure to neuroleptics. However, axial deformities (Pisa syndrome, camptocormia and antecollis) are also well recognised but poorly understood features of multiple system atrophy or late-stage Parkinson's disease. Here, we report on three patients with longstanding Parkinson's disease who, 4–9 years after a left pallidotomy, developed a Pisa syndrome to the right.

Case histories

The first patient, now 72 years old, was diagnosed with Parkinson's disease at age 44 years, after initially presenting with pain in his right arm and leg. The right side always remained the more affected and the dyskinesias that developed after 4 years of levodopa treatment were also more pronounced on the right side. Because of progressive motor fluctuations, a left-sided pallidotomy was performed after 17 years of disease, which resulted in abolition of the right-sided dyskinesias and an improvement in the tremor and rigidity on the right. Eight years after the pallidotomy, 25 years after disease onset, he gradually developed a lean to the right, which showed some diurnal fluctuation and responded modestly to dopaminergic treatment. When "on", he still remains independent for most daily activities. Parkinson's disease dementia has recently been diagnosed.

In the second patient, now 63 years old, Parkinson's disease was diagnosed at the age of 47 years when he first noticed decreased dexterity and a tremor of his right hand. He developed limb dyskinesias (more on the right side than on the left) after only 1 year of levodopa treatment. After unsuccessful alternative drug regimens, a left-sided pallidotomy was performed after 6 years of disease. The dyskinesias on the right completely disappeared and a beneficial effect on tremor and walking were documented. Fifteen years after his first symptoms, and about 9 years after surgery, a lean to the right evolved that was unresponsive to dopaminergic drugs. Over the past year, he has developed features of early Parkinson's disease dementia. He uses a wheelchair for outdoor activities only.

The third patient, now 69 years old, noticed a tremor of his right hand when he was 43 years old. Dyskinesias, mainly on the right, became apparent 3 years after levodopa treatment. Seventeen years after onset, he underwent a left-sided pallidotomy. The dyskinesias on the right side subsided, and he also experienced "off"-period improvement and better balance. In his 21st year of disease, 4 years after the pallidotomy, he developed a mild torticollis to the right. Around the same time, he started to gradually develop a lean to the right (fig 1), sometimes causing him to fall out of a chair. Mild Parkinson's disease dementia was established recently. He is still able to walk unsupported.

Comment

The outcome and follow-up after a median 14 months of 26 patients with Parkinson's disease who underwent a unilateral medial pallidotomy in our hospital in 1995–96 have been reported previously.[1] Here, we describe the further follow-up of three of these patients, because they developed a marked lean (Pisa syndrome) to the right side 4–9 years after a left pallidotomy, at disease durations of 15–25 years. The truncal lateroflexion came on gradually, and showed some diurnal fluctuation and dopamine responsiveness in only one patient. In all patients, signs and symptoms started and remained more pronounced on the right side, which was also the more dyskinetic side, hence the choice of a left-sided pallidotomy. Despite the long disease duration, mobility was still relatively well preserved, particularly in patients 1 and 3, and the dyskinesias continued to be less severe on the side contralateral to the pallidotomy.

Figure 1 A 69-year-old man with a 26-year history of Parkinson's disease underwent a left pallidotomy 9 years ago. Four years after this procedure, he gradually developed a lean to the right. These photographs show the marked lean to the right, which is present during both sitting and walking, as well as a mild head tilt to the left. Informed consent was obtained for publication of this figure.

Importantly, postoperative imaging in these three patients confirmed that the lesions were confined to the medial pallidum (without extension to the internal capsule or lateral pallidum as observed in four others).[1]

Although we did not perform magnetic resonance imaging or electromyography studies of the paraspinal muscles, we believe that this truncal lateroflexion results from dystonia or asymmetric rigidity and not from a unilateral paraspinal myopathy.

The main question is whether this leaning towards one side is merely a phenomenon of an advanced stage Parkinson's disease or a hitherto unrecognised delayed-onset consequence of unilateral pallidotomy in Parkinson's disease.

Unilateral pallidal lesions in rats result in curling and head turning towards the side contralateral to the lesion.[2] The rarely reported acquired unilateral pallidal lesions in humans seem to particularly give rise to contralateral limb dystonia, hemidystonia or hemiparkinsonism rather than to axial abnormalities.[3] If the leaning in our patients is directly related to the pallidum lesion, the delay of 4–9 years after pallidotomy is rather difficult to explain, although delayed-onset progressive dystonia has been reported in bilateral anoxic pallidal lesions.

Previous observations noted the common presence of scoliosis in Parkinson's disease and postencephalitic parkinsonism, which was usually concave to the clinically less affected side—that is, directed towards the side with more severe nigrostriatal pathology.[4 5] This is corroborated by animal studies, as rodents with unilateral lesions of the substantia nigra display a deviated spinal curvature and/or abnormal turning behaviour directed towards the lesioned side; however, when these animals are given dopaminergic agents, their body asymmetry reverses from ipsiversive to contraversive.[6] In a 6-hydroxydopamine rat model of Parkinson's disease, with a unilateral substantia nigra lesion causing ipsiversive body axis deviation without and contraversive turning with dopamine agonists, a unilateral pallidotomy (ipsilateral to the substantia nigra lesion) alleviated both body axis asymmetry and abnormal turning.[2] The human correlate seems to be the notion that the scoliosis to the right in patients with postencephalitic parkinsonism with clinically more left-side than right-side involvement was corrected after a right pallidotomy.[5]

Further extrapolation to our patients is impossible because animal models or human data that predict the net effect of a unilateral pallidal lesion in a system of bilateral but asymmetrical nigrostriatal dopamine deficiency and chronic exposure to dopaminergic agents on truncal posture are not available. Consequently, we do not know whether the Pisa syndrome in our patients parallels advanced Parkinson's disease or actually represents an unrecognised delayed effect of unilateral pallidotomies in patients with Parkinson's disease.

We would like this letter to serve as an invitation to continue reporting on the follow-up of pallidotomy in patients, including less obvious clinical and easily overlooked features such as a lean to one side.

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References

1 **Schrag A**, Samuel M, Caputo E, *et al*. Unilateral pallidotomy for Parkinson's disease: results after more than 1 year. *J Neurol Neurosurg Psychiatry* 1999;**67**:511–17.

2 **Henderson J**, Doherty K, Allbutt H, *et al*. Effects of pallidotomy on motor symptoms in an animal model of Parkinson's disease. *Behav Brain Res* 2006;**169**:29–38.

3 **Bhatia KP**, Marsden CD. The behavioural and motor consequences of focal lesions of the basal ganglia in man. *Brain* 1994;**117**(Pt 4):859–76.

4 **Duvoisin RC**, Marsden CD. Note on the scoliosis of parkinsonism. *J Neurol Neurosurg Psychiatry* 1975;**38**:787–93.

5 **Martin JP**. Curvature of the spine in post-encephalitic parkinsonism. *J Neurol Neurosurg Psychiatry* 1965;**28**:395–400.

6 **Schwarting RK**, Huston JP. The unilateral 6-hydroxydopamine lesion model in behavioral brain research. Analysis of functional deficits, recovery and treatments. *Prog Neurobiol* 1996;**50**:275–331.

CORRECTIONS

K Talbot. Amyotrophic lateral sclerosis, 2nd edn (*J Neurol Neurosurg Psychiatry* 2007;**78**:109). In this book review the acronym TMS was incorrectly expanded to "traumatic masturbatory syndrome"; it should actually be "transcranial magnetic stimulation". In addition, the first sentence should read:

Amyotrophic lateral sclerosis, through its first edition, has become the standard text for clinicians and researchers in the field of ALS/MND.

The online version has been corrected. We sincerely apologise for these errors introduced on copyediting.

A Larner. How to examine the nervous system, 4th edn (*J Neurol Neurosurg Psychiatry* 2007;**78**:110). In this book review the book details were incorrectly published. The correct book review details are:

Edited by R T Ross. Published by Humana Press, New Jersey, 2006, £36.00 (hardback), pp 242. ISBN 1-58829-811-6.

The online version has been corrected. We sincerely apologise for this error introduced on copyediting.