Table 1 Profiles and follow-up information of the patients who received IFNβ-1b therapy

	No. of patients	Age, y/M:F	Optic neuritis	Brain lesions[a]	Anti-AQP4 antibody, +/−/ND	OCB, +/−/ND	CSF cell >50/mm^3	Spinal lesions <3 VS	LESCLs	Patients who suspended IFNβ-1b/duration of injection, mo, mean ± SD	Patients with severe exacerbations	Patients who could not be followed
Total	56	39.3 ± 12.2/17:39	33	37	14/12/30	11/26/19	4	41	20	19/14.2 ± 23.8	7	8
NMO definite	14	43.2 ± 13.6/2:12	14	5	14/0/0	0/8/6	4	14	14	13/12.5 ± 22.5	7	0
NMO high risk	6	50.5 ± 13.1/1:5	4	3	0/2/4	1/2/3	0	6	6	3/9.3 ± 12.8	0	0
cRRMS	36	36.1 ± 10.0/14:22	15	29	0/10/26	10/16/10	0	21	0	3/26.7 ± 40.2	0	8

Abbreviations: AQP4 = aquaporin 4; cRRMS = RRMS not meeting the criteria of NMO; IFNβ-1b = interferon-β-1b; LESCL = longitudinally extensive spinal cord lesion; ND = not determined; NMO = neuromyelitis optica; NMO definite = patients who met the criteria proposed by Wingerchuk et al.[15]; NMO high risk = patients with optic neuritis and anti-AQP4 antibody or patients with optic neuritis and LESCLs; OCB = immunoglobulin G oligoclonal bands in CSF; VS = vertebral segment.

[a] Brain lesions fulfilling the criteria of Barkhof et al.[14]

(cases 1, 3, 5, and 6) had LESCLs as determined by spinal MRI. Thus, without information about positivity of AQP4 antibody, 4 of the 6 patients had already fulfilled the criteria of high-risk NMO before the initiation of IFNβ-1b therapy.

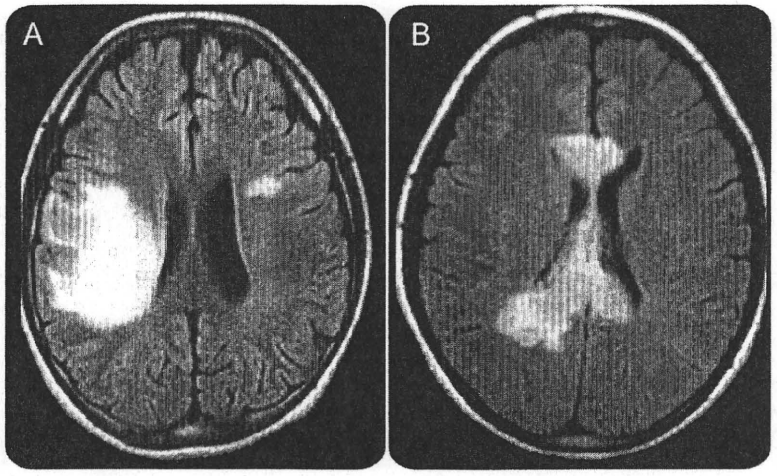
The exacerbations within 90 days were once in 3 patients (cases 3, 6, and 7) and twice in 4 patients (cases 1, 2, 4, and 5). The periods between the initiation of IFNβ-1b therapy and the following exacerbation were 2 to 60 days. Two patients (cases 1 and 3) who developed severe transverse myelitis had been stable for 11 and 36 years before initiating interferon treatment. The highest EDSS score at the time of the exacerbations ranged from 7.5 to 9.5. All the patients developed transverse myelitis, 3 patients (cases 2, 5, and 6) showed tetraplegia, and 4 patients (cases 1, 3, 4, and 7) showed paraplegia. In addition to myelitis, 2 patients (cases 1 and 2) developed optic neuritis, 2 patients (cases 4 and 5) developed tumefactive cerebral lesions (figure 1), and 2 patients (cases 6 and 7) presented with massive pleocytosis (330/mm^3 in case 6 and 3,856/mm^3 in case 7) in CSF. One of the patients (case 5), who had been initially diagnosed with RRMS, was revealed to have Sjögren syndrome in addition to RRMS after the exacerbation.

Case 2 was initially diagnosed with RRMS owing to symptoms of optic neuritis and numb sensation of her tongue with mild swallowing difficulty when she was in the United States, with the MRI showing a lesion adjacent to the fourth ventricle, which was taken just before the initiation of IFNβ-1b (figure e-2). Sixty days after the initiation of IFNβ-1b, she developed exacerbation with a lesion in the cervical cord that extended into the brainstem, followed by respiratory failure, and was intubated. Although her lesions had been confined to the optic nerve and brainstem before the initiation of IFNβ-1b therapy, from the clinical features, in addition to the positivity of the anti-AQP4 antibody, she was revealed to fulfill the criteria of definite NMO.

DISCUSSION In the present study, among the 56 patients with RRMS who had started IFNβ-1b therapy, we identified 7 who experienced unexpectedly severe (EDSS ≧7.0) exacerbation within 90 days of the initiation of IFNβ-1b.

Before the initiation of IFNβ-1b therapy, 4 of the 7 patients had already fulfilled the criteria of high-risk NMO and one patient (case 2) without spinal lesions had a history of optic neuritis and a small lesion adjacent to the fourth ventricle as determined by brain MRI. Although AQP4 antibody was detected in all the patients after the exacerbations, the clinical features before the initiation of IFNβ-1b therapy were consistent

Figure 1 **Axial brain MRI (fluid-attenuated inversion recovery) with tumefactive lesions**



Case 4 (A) developed exacerbation 67 days after the start of interferon-β-1b (IFNβ-1b) therapy; MRI showed huge tumefactive lesion in right hemisphere. Case 5 (B) developed exacerbation 32 days after the start of IFNβ-1b therapy; MRI showed tumefactive lesions in corpus callosum extending to the right parietal white matter.

with those of the NMO spectrum in 5 of the 7 patients (cases 1, 2, 3, 5, and 6).

During the episodes of exacerbations after the initiation of IFNβ-1b therapy, all 7 patients including the 2 patients (cases 4 and 7) with spinal cord lesions less than 3 vertebral segments, and 1 patient (case 2) with no spinal lesions before the initiation of IFNβ-1b therapy, developed severe transverse myelitis with LESCLs. Because assay for the anti-AQP4 antibody in serum showed positive results in all the patients, all the 7 patients after the exacerbations fulfilled criteria of NMO.[15] Furthermore, 1 patient (case 5) with LESCLs was found to have Sjögren syndrome in addition, and 2 patients (cases 4 and 5) developed tumefactive cerebral lesions in addition to spinal cord lesions. Taken together with these clinical features, the clinical features of all the 7 patients who showed unexpectedly severe exacerbation within 90 days of the initiation of IFNβ-1b were those of the NMO spectrum.[11,12] It should be noted that 2 patients (cases 4 and 7) did not initially fulfill the criteria for the NMO spectrum before the initiation of IFNβ-1b therapy, and 1 patient (case 2) was initially diagnosed with RRMS in spite of a small lesion adjacent to the fourth ventricle.

Attacks of NMO generally are more frequent and more severe than attacks of MS, even without interferon treatment. However, it is not usually experienced that such patients as cases 1 and 3, who had been stable for 11 and 36 years, suddenly develop severe transverse myelitis, and such patients as cases 4 and 5, whose main lesions had been confined to optic nerve and spinal cord, should develop tumefactive brain lesions. Furthermore, it is also unusual to observe massive pleocytosis in CSF (cases 6 and 7) and even with neck stiffness (case 7) as the natural disease courses.

The effectiveness of IFNβ-lb in Japanese patients with RRMS including OSMS was demonstrated by a randomized clinical trial.[16] A total of 205 Japanese patients with RRMS were randomized to receive a low or high dose of IFNβ-lb, and it was found that the annual exacerbation rates of RRMS were significantly lower in the high-dose group. In the subgroup analysis of 18 patients with OSMS in the 50-μg group, and 22 patients with OSMS in the 250-μg group, the annual exacerbation rate in the 250-μg group was lower than that in the 50-μg group, although the difference was not significant. Based on these observations, it was concluded that IFNβ-lb has comparable effects in patients with OSMS and CMS.

Increased exacerbation rates after IFNβ-lb therapy in patients with MS with clinical features of NMO and HLA DPB1*0501, which is known to be associated with NMO, have been noted in a previous report.[17] In the report, the authors examined the effectiveness of IFNβ-lb therapy in a series of 15 patients with MS, and found 5 of the 6 patients with clinical features of NMO and HLA DPB1*0501 had discontinued IFNβ-lb therapy, because of increased exacerbation rates in 3 and severe skin ulcers at the injection sites in 2. Two patients with relapsing NMO, who developed tumefactive extensive brain lesions within 2 months of the initiation of IFNβ-lb therapy, also have been reported.[18] Taken together, our studies strongly support the notion that patients with the NMO spectrum have a potential risk of developing unexpectedly severe exacerbation after the initiation of IFNβ-1b therapy. Given these observations, we should avoid IFNβ-1b therapy for patients with OSMS fulfilling the criteria for NMO spectrum. As demonstrated in our patients, 2 of the 7 patients with unexpectedly severe exacerbation did not show LESCLs, and therefore, did not fulfill the criteria for NMO, when IFNβ-1b was initiated. Thus, deliberate evaluation of the clinical features and investigations, including anti-AQP4 antibodies, would be required for patients not fulfilling the criteria for NMO.

Although the pathophysiologic mechanisms of NMO are not fully understood, a recent study showed that astrocytes are susceptible to sera from anti-AQP4-antibody–positive patients and undergo necrosis in a complement-dependent manner,[19] suggesting the primary pathogenic role of the anti-AQP4 antibody in NMO. Because there are accumulating data that IFNβ may act as an inducer

of autoantibodies, and in a few cases, symptomatic autoimmunity,[20-24] it is possible that, in patients with NMO, IFNβ therapy might stimulate pathogenic B-cell activity and induce the anti-AQP4 antibodies,[25] which have recently been suggested to play important pathogenic roles. Because all the 7 patients who showed exacerbations after IFNβ therapy were included in the NMO spectrum, it was possible that IFNβ therapy changed the immunobalance and induced the exacerbations. Further studies are necessary to reveal the effect of IFNβ-1b on the immunobalance in demyelinating disease in the NMO spectrum.

AUTHOR CONTRIBUTIONS

J.S. was involved in the study design and wrote the report. All the authors reviewed and validated data and final analyses. J.S. had full access to the complete set of data. J.S., Y.H., M.H., I.S., Y.S., H.N., Y.U., H.H., K.H., and T.K. contributed to the analysis of the data. A.I., M.H., and H.D. contributed to the assay of the anti-AQP4 antibody. J.G., T.S., M.T., and S.T. were involved in and contributed to the writing and review of the manuscript. All the authors have seen and approved the final version of the manuscript.

DISCLOSURE

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INTERNAL MEDICINE

CASE REPORT

A Case of Atypical Amyloid Polyneuropathy with Predominant Upper-limb Involvement with the Diagnosis Unexpectedly Found at Lung Operation

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Abstract

We present a patient of familial amyloid polyneuropathy (FAP) with predominant upper-limb involvement, the pattern of which resembled a mononeuropathy multiplex pattern. Sural nerve biopsy failed to diagnose the disorder, but lung partial resection performed later for other diagnostic purposes suggested FAP. A rare mutation in the transthyretin gene (S50R) was subsequently confirmed. Diagnostic challenges of FAP with atypical clinical presentations, including difficulties in pathological diagnosis, are discussed with a review of the literature.

Key words: familial amyloid polyneuropathy, transthyretin, mononeuropathy multiplex, nerve biopsy, lung partial resection

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Introduction

Familial amyloid polyneuropathy (FAP) patients usually develop small fiber neuropathy predominantly affecting the lower limbs or autonomic neuropathy between 20 and 40 years of age (1). Various atypical clinical presentations are reported (2-5), and the absence of amyloid deposits in the nerve biopsy specimen requires another measure to attain the correct diagnosis. In this report, we describe an upper-limb-predominant FAP patient with rare mutation of amyloidogenic transthyretin (ATTR), whose diagnosis was initially difficult, but was later suggested by the findings of lung partial resection conducted for other diagnostic purposes.

Case Report

A 57-year-old Japanese male from Shimane prefecture was referred to our hospital for evaluation of tingling, numbness, and poor dexterity of his hands. These symptoms developed in his right hand at the age of 51 and were progressive; similar symptoms also appeared in his left hand at the age of 56. Around the same time, mild dysesthesia occurred in his distal lower limbs, but this was neither disabling nor progressive. He lost ten kilograms in two years. Neurological examination on admission revealed weakness, muscle atrophies and decreased sensations at the right hand which mainly involved the median and ulnar nerve areas. Muscle strength was Medical Research Council (MRC) grade 2 in the right abductor pollicis brevis, 3 in the right interossei, and 4 in the right finger flexors and extensors. The lower extremities showed no weakness or atrophies, but distal dysesthesia was present. Tendon reflexes were notably diminished. He was free of autonomic dysfunctions, including orthostatic hypotension, syncope, gastrointestinal symptoms, urinary symptoms, sweating disorders, and sexual impotence. He used to drink about 250 mL of whisky and smoke 2 packs of cigarettes per day, but he had no disease history. His family history was negative for neuropathy or cardiac diseases.

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Table 1. **Nerve Conduction Study**

Sensory				
Nerve	Stimulation site	Distal latency (ms)	Amplitude (μV)	Velocity (m/s)
R median	digit 2	*Absent*	*Absent*	*Absent*
L median	digit 2	*Absent*	*Absent*	*Absent*
R ulnar	digit 5	*Absent*	*Absent*	*Absent*
L ulnar	digit 5	2.7	*0.4*	*40*
R sural	ankle	3.3	*0.4*	46
L sural	ankle	3.1	*1.3*	48
Motor				
Nerve	Stimulation site	Distal latency (ms)	Amplitude (mV)	Velocity (m/s)
R median	wrist, elbow	*Absent*	*Absent*	*Absent*
L median	wrist	*8.1*	*0.5*	
	elbow		*0.5*	*34*
R ulnar	wrist	4.5	4.1	
	below elbow		*2.7*	*33*
	above elbow		*2.3*	*29*
L ulnar	wrist	3.0	9.6	
	below elbow		7.3	48
	above elbow		6.8	*18*
R tibial	ankle	3.1	10.2	
	knee		6.7	42
L tibial	ankle	3.2	10.3	
	knee		6.3	43

Abnormal values are in Italic. L: left, R: right

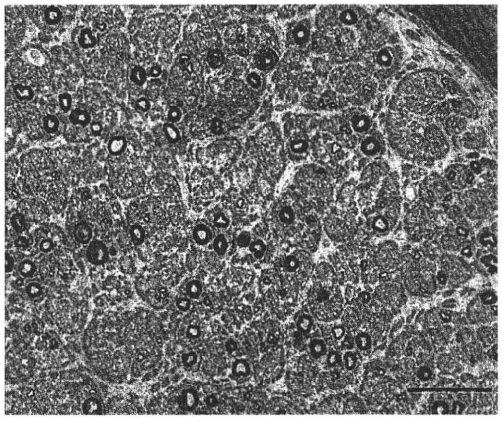

Figure 1. **Sural nerve biopsy showed a moderate loss of myelinated fibers. A few myelin ovoids were recognized. Toluidine blue staining. Bar=50μm.**

Nerve conduction study (NCS) revealed severe and diffuse damage in the sensory nerves, especially in the upper limbs (Table 1). With regard to the motor nerves, both of the median nerves were severely affected, and right ulnar nerve stimulation demonstrated an abnormal temporal dispersion and a decreased conduction velocity of 33 m/sec. Tibial nerves were normal, including maximal F wave conduction velocity of 57.0 m/s (right) and 63.8 m/s (left). Right sural nerve biopsy was performed, which showed a reduction in myelinated fiber density and signs of acute axonal degeneration (Fig. 1). There were no signs of segmental demyelination, inflammation, or endoneurial edema. Congo red or methyl violet staining revealed no amyloid deposits. Computed tomography (CT) of the chest and abdomen was performed to determine whether some malignancy underlies his neuropathy or his weight loss, and revealed an 8-mm lung nodule which was thought as inflammatory change.

Although we could not reach a diagnosis, we considered the possibility of a variant of chronic inflammatory demyelinating polyneuropathy (CIDP), taking the mononeuropathy multiplex pattern into account; we performed intravenous immunoglobulin therapy without any effect. Afterwards, electron microscopy revealed obvious unmyelinated fiber loss, contrary to the diagnosis of CIDP. No amyloid deposition was evident. Thus, the etiology of the neuropathy remained unknown. The patient visited our clinic periodically with gradual worsening: owing to the deterioration of his leg symptoms, he developed the need for a cane, and he also lost his ability to use chopsticks. He had, however, no autonomic dysfunction clinically. Electrocardiogram revealed non-specific intraventricular conduction abnormality, and coefficent of variation in R-R intervals (CVR-R) was 2.83%. Transthoracic echocardiogram showed left ventricular hy-

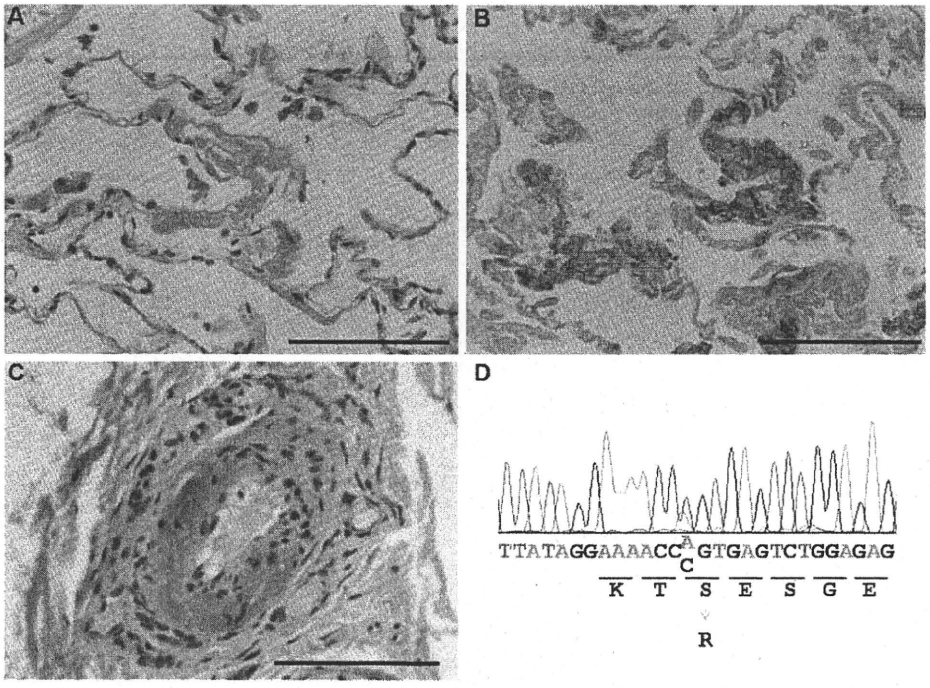

Figure 2. **A: Lung histology demonstrated alveolar septal amyloid deposits. Congo red staining. Bar=100μm. B: Transthyretin immunostaining demonstrated that the amyloid was composed of transthyretin. Transthyretin immunostaining. Bar=100μm. C: Re-examined sural nerve specimen revealed a small amount of amyloid in the epineurial small vessels. Congo red staining. Bar=100 μm. D: Transthyretin gene sequencing showed an A-to-C mutation in one allele in exon 3, which resulted in an S50R amino acid change. The upper line designates nucleotides and the lower line shows amino acids.**

pertrophy.

Two years later, the lung nodule was found to be slightly enlarged to the size of 11 mm at a follow-up CT scan. Partial resection of the lung was performed through the thoracoscope, but we could not find any nodule in the resected specimen. Postoperative CT scan did not show any nodule, and the nature of the nodule remained unclear. Histopathological examination, however, revealed some amyloid deposits in the alveolar septal region as well as in the vascular region (Fig. 2A); the amyloid deposits were immunohistochemically positive for TTR (Fig. 2B). Molecular analysis of the TTR gene using the patient's leukocyte genomic DNA revealed an A-to-C mutation in exon 3 resulting in the substitution of Arg (CGT) for Ser (AGT) at codon 50 (S50 R, Fig. 2D). Given these results, we thoroughly reinvestigated the previously obtained peripheral nerve specimen, and a small amyloid deposit was identified in the vascular walls in the epineurium (Fig. 2C), which finally confirmed the diagnosis of FAP as the cause of his neuropathy. On the other hand, TTR immunohistochemistry (IHC) was negative probably because of the paucity of the amount of the amyloid deposit.

Discussion

In this report, we presented a patient presenting with an upper-limb predominant mononeuropathy multiplex with no autonomic dysfunctions or any family histories for FAP, who turned out to have FAP. Initial hand involvement in FAP patients is mainly due to bilateral carpal tunnel syndrome (CTS), and is considered to be a feature of non-V30 M ATTR types (6, 7). Although the present patient probably had bilateral CTS, the ulnar nerves showed smaller sensory nerve action potentials than those of the sural nerves. The findings suggested the presence of mononeuropathy multiplex, which is rare in FAP and has only been reported once (4), in contrast to frequent occurrence of polyneuropathy in FAP. In addition, upper-limb neuropathy other than CTS with or without lower-limb involvement in patients with ATTR V30M has been recently reported (8, 9), and upper-limb neuropathy may be an important clue to the diagnosis of FAP.

The demyelinating feature suggested by NCS has been reported as the most common pitfall in diagnosing sporadic cases of FAP (10), and in some late-onset FAP patients with ATTR V30M, the slowing of conduction velocity and prolongation of distal latency were reported to be conspicuous (11). In fact, the electrophysiological findings of the right ulnar nerve observed in our patient also hampered the correct diagnosis in our patient. The absence of right median compound muscle action potential, however, suggests that axonal degeneration is likely the main cause of the neuropathy in the present case. These electrophysiological findings have not been previously described in FAP patients with

Table 2. **Reported FAP Cases with ATTR S50R**

Patient No.	Onset (y)	Sex	Country	FH	Initial symptom	Autonomic dysfunction	Cardiac manifestation	Ref
1	39	M	Japan	N/A	General wasting	N/A	N/A	17
2	41	M	Japan	-	Impotence	Impotence, OH, GI	First-degree AV block, hypertrophy	9
3	50	F	France	+	Lower limb paresthesia	GI	Normal ECG, Hypertrophy	10
4	38	F	Vietnam	+	Dyspnea	GI	Restrictive cardiomyopathy	11
5	42	M	Spain	+	Anorexia	OH, GI, impotence	N/A	12
6	48	M	Spain	+	Polyneuropathy	N/A	N/A	12
7	45	F	Spain	+	Anorexia	GI	N/A	12
8	53	M	Spain	+	Vitrous deposits in eyes	None	N/A	12
9	40	M	Spain	+	Polyneuropathy	N/A	N/A	12
10	48	M	Portugal	+	Pain in legs and feet	Impotence, GI, urinary incontinence	Third-degree AV block, normal TTE	12
11	68	F	Portugal	+	Loss of sensation in feet	GI, OH, urinary incontinence	N/A	12
This case	51	M	Japan	-	Right hand dysesthesia	None	Hypertrophy	-

AV block: atrioventricular block, FH: family history, GI: gastrointestinal tract dysfunction (including constipation and diarrhea), N/A: information not available, OH: orthostatic hypotension, Ref: reference, TTE: transthoracic echocardiogram

Patients 5–9 are from the same family. Patients 10 and 11 are from the same family.

ATTR S50R.

Another atypical clinical feature of the present case was the absence of autonomic dysfunctions. Misu et al reported that five of the 35 late onset Japanese FAP cases with ATTR V30M did not show autonomic symptoms (12). Another study also confirmed that late-onset patients did not note autonomic symptoms in the initial phase, but showed them in the later phase (13). However, patients with ATTR S50R have been reported to frequently present with substantial autonomic symptoms (14-17). The present patient is the first FAP case of ATTR S50R with no obvious autonomic dysfunction in his disease course lasting as long as 8 years, although absence of autonomic dysfunction is sometimes difficult to demonstrate, and a more vigorous investigation such as the Shellong test might have revealed some abnormality.

Diagnostic difficulties on nerve biopsies deserve further discussion. Previous autopsy studies reported that the proximal portion of the peripheral nerve showed more amyloid deposition than the distal portion. Therefore, considering the small amount of amyloid deposit found in the specimen (i.e. distal portion of the nerve), the cause of the neuropathy in the present patient might be ascribed to possible deposition of amyloid in the more proximal region of the peripheral nerve (18). With regard to biopsy of the distal portion of the nerve, a retrospective study demonstrated that six of the 35 peripheral nerve biopsies obtained from patients with amyloid neuropathy required electron microscopy to detect an amyloid deposit, although 4 of the six reinvestigations of the specimen using light microscope could reveal it (19). Another study demonstrated that TTR IHC could reveal amyloid deposits in the sural nerve that could not be detected by Congo red staining, supporting increased sensitivity of TTR IHC (20). In the present case neither electron microscopic observation nor TTR IHC detected amyloid deposition. The distribution of amyloid deposits was also characteristic in our case. Amyloid deposits are usually found in the endoneurium, but in our case they were restricted to the vascular walls of the epineurium. Although several studies have shown epineurial amyloid deposition (19, 21), its frequency is as low as two out of 40 (21). The two cases, in which epineurial amyloid deposition was noted, were elderly (68 and 73 years old) and showed amyloid deposits only around the capillaries as in our patient.

The diagnosis of FAP patients often requires a tissue specimen other than peripheral nerves such as rectal or fat tissue; however, lung tissue is almost always the last to be obtained for FAP diagnosis. Note that there was as much amyloid deposition in the alveolar septal region as in the vascular walls. An autopsy series demonstrated that alveolar amyloid deposition is more often observed in elderly patients with FAP (22). Thus, the uncommon deposition pattern, that is, in the alveolar septum in the lung and in the epineurium in the peripheral nerve, may be due to aging or a rare mutation of S50R. In fact, another non-V30M mutation (D38A) was reported to demonstrate diffuse pulmonary amyloid deposition (23), indicating a possible correlation between non-V30M ATTR and pathological findings of diffuse pulmonary amyloid deposition.

How could we diagnose FAP earlier in the present patient? At least two issues should have been addressed. First, if we had considered neuropathy and a cardiac (i.e. ECG or echocardiographic) abnormality derived from the same origin, the possibility of FAP might have been explored further. A previous study revealed that patients with non-V30M ATTR often present with cardiac amylodosis (24). Second, to further explore the etiology of the neuropathy, it would be useful to include rectal or fat biopsies, which are less invasive than lung partial resection.

ATTR S50R is a rare mutation and has been mentioned in only five other reports in the literature (14-17, 25). In general, the patients with an ATTR S50R mutation in the literature showed more typical presentations as FAP (Table 2), hence our patient added another spectrum of FAP with ATTR S50R mutation as discussed above. Further investiga-

tion of the phenotype-genotype correlation in additional cases will be needed.

In conclusion, we emphasize the diverse clinical presentations and the diagnostic challenge of FAP associated with an ATTR S50R mutation. Because FAP can be treated with liver transplantation earlier in the course, we should conduct vigorous investigations when we encounter apparently sporadic, immunotherapy-resistant patients with atypical clinical presentations such as mononeuropathy multiplex predominantly involving the upper limbs.

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Letters to the Editor Related to Published Articles

Reply: Based on the Available Randomized Trial Patients Should Say No to Glutathione for Parkinson's Disease

One of the most commonly asked patient-driven questions about Parkinson's disease (PD) therapy has been whether to use glutathione. Glutathione acts as an antioxidant and has been found reduced by as much as 50% in the brains of patients with PD, other parkinsonian disorders and even incidental Lewy body disease and thus is not specific for PD.[1] A small group of physicians have been promoting this therapy and charging a fee for infusion of glutathione service in their office practices. Despite the lack of evidence for efficacy, the lack of data that glutathione crosses the blood brain barrier, the requirement for the placement of an intravenous line, and the need for patients to pay out of pocket, many medical practices have persisted in offering the therapy. Hauser and colleagues presented the long-awaited, first randomized, double blind placebo-controlled trial of intravenous glutathione therapy in PD in the May 15th, 2009 edition of *Movement Disorders*.

Twenty-one patients in the trial were randomly assigned to glutathione therapy or placebo (one withdrew). Glutathione proved safe and well tolerated; however, there was no improvement evidenced in any outcome variable. The authors mention in the abstract the change in UPDRS units when combining two Parkinson subscales, however in the study, they report a *P*-value of 0.66 for the comparison. This *P*-value fails to meet a significant level or a trend level for improvement. In fact, no outcome variable in this study met even a trend level of improvement. The clinical global impression scales for the patients were similar for the two groups especially when considering the sample size was small. Given the small nonsignificant changes, we are, therefore, perplexed about why the authors included the following statement in the abstract "preliminary efficacy data suggest the possibility of a mild symptomatic effect."[2] and how the reviewers permitted these conclusions to be emphasized in the only part of the article that most people coming across the article will ever read.

In the discussion, the authors stated that "we did not observe a significant improvement in parkinsonian signs and symptoms in the glutathione group when compared to placebo,"[2] and we completely agree with this conclusion. We do not however agree that combining two subscales and using change of UPDRS points for a comparison would lead one to conclude that there is a "possibility that glutathione may provide a symptomatic benefit."[2] We agree that this trial did not assess the potential for glutathione as a neuroprotective agent or the potential efficacy of other treatment schedules.

In the end, we must consider our patients and their overall well being as the most important issues when assessing the risks versus benefits of any new therapy. Thus, there is only one conclusion; this glutathione study failed to meet a minimum clinical efficacy criteria that would allow doctors to offer, promote, and charge for the therapy in their office practices. On the basis of these results, patients with PD should be encouraged to say no to an IV placed in their arm for the false hope of a symptomatic glutathione treatment.

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Higher-Dose Glutathione Therapy for Parkinson's Disease in Japan: Is It Really Safe?

We read with great interest the manuscript by Hauser et al.,[1] who performed a randomized, double-blind, pilot evaluation of intravenous glutathione (GSH; 1,400 mg) administered three times a week for 4 weeks in patients with Parkinson's disease (PD). Although their preliminary data on the efficacy of GSH remain to be evaluated in a larger study, the authors stressed the safety and tolerability of higher-dose GSH therapy.

We report a Japanese patient with PD who presented with severe hepatic injury after GSH therapy. A 73-year-old man had suffered from PD for 6 years. He initially presented with tremor, bradykinesia, and disturbance of gait and was given L-dopa/DCI and cabergoline, which relieved these symptoms. With gradual progression of disease, entacapone was initiated because of wearing-off symptoms. He was well-controlled with L-dopa/DCI 300 mg, cabergoline 1 mg, and entacapone 300 mg daily. However, he was anxious concerning disease progression and consulted another private clinic that he found on an internet service, from which he received intravenous GSH (1,200 mg daily) injection per week, but exhibited no relief of symptoms. After GSH therapy for 5 months, he complained of general malaise and anorexia. He exhibited severe hepatic injury with elevated AST of 1,040 IU/l and ALT of 890 IU/l, and all drugs except L-dopa/DCI 300 mg/day were therefore discontinued. He was bedridden for a week, but gradually recovered after resumption of anti-parkinsonian drugs. Glutathione appeared to be the drug responsible for hepatic injury, since he had been in good health for months before GSH treatment without addition of any other drugs, and DLST yielded negative results for entacapone but equivocally positive results for glutathione. Liver function returned to normal in 2 months after discontinuation of GSH therapy.

The glutathione system is the primary mechanism in the brain of clearing H_2O_2 and protecting against the formation of hydroxyl free radicals. Previous studies demonstrated a specific reduction of glutathione in the substantia nigra of patients with PD and a correlation with disease activity.[2] However, there have been few clinical trials on the efficacy and safety of glutathione for treatment of PD. Sechi et al. reported a 42% reduction in PD-related disability with intravenous glutathione (1,200 mg daily for 30 days; total of 36,000 mg) which lasted for 2 to 4 months.[3] Hauser et al. attributed the lack of beneficial effects in this study in part to the relatively smaller total dosage (16,800 mg) and suggested that longer trials are needed. However, it should be noted that a total dose in a range similar to this (24,000 mg) may produce severe adverse effects. While this approach offers hope to patients with PD, sufficient attention to the safety and tolerability of higher-dose GSH is needed, and clinical use of it should not be performed before larger controlled trials.

Author roles: Yutaka Naito: conception and design, data acquisition and analysis, drafting, editing and revising of the text. Ko Matsuo, Yasumasa Kokubo, and Yugo Narita: data acquisition, drafting of text. Hidekazu Tomimoto: conception and design, drafting, editing and revising of text.

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Reply: Intravenous Glutathione in Parkinson's Disease

We appreciate the careful reading of our manuscript by Okun and colleagues.[1] However, their letter contains a number of inaccuracies that require correction. We clearly state

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in the abstract that "there were no significant differences in changes in Unified Parkinson's Disease Rating Scale (UPDRS) scores.[2]" The authors seem to imply that we arbitrarily combined "two Parkinson's subscales," but the combination of UPDRS ADL + motor scores is a relatively common outcome measure previously used by us and others.[3,4] In fact, the change in UPDRS ADL + motor scores from baseline to week 4 was the predefined outcome of greatest interest in our study, as stated in the manuscript. Our main efficacy result was that over the 4 weeks of study medication administration, UPDRS ADL + motor scores improved by a mean of 2.8 units more in the glutathione group than the placebo group ($P = 0.32$). In addition, over the subsequent 8 weeks, UPDRS ADL + motor scores worsened by a mean of 3.5 units more in the glutathione group than the placebo group ($P = 0.54$). We note that the P value of 0.66 to which Okun and colleagues refer appears to come from our table reporting baseline characteristics and is not relevant to efficacy. Nonetheless, we are left with the vexing issue of how to interpret preliminary, nonsignificant, efficacy data in a small pilot study that was not powered for efficacy. We were struck by the fact that the direction of mean change relative to placebo was positive during the course of glutathione administration and negative following its discontinuation. In addition, the magnitude of these changes was somewhat greater than that described as a minimal clinically relevant difference.[5] Therefore, we feel these findings should not be completely ignored and a reasonable interpretation is that these "preliminary efficacy data suggest the possibility of a mild symptomatic effect, but this remains to be evaluated in a larger study," as our full sentence states. The possibility of a mild symptomatic effect may be a particularly important consideration for the design of a "neuroprotective" trial. We reiterate that we did not observe statistically significant differences across groups in this small pilot study.

We thank Naito and colleagues for bringing a case of possible glutathione-induced hepatotoxicity to our attention.[6] Although intravenous glutathione appeared to be safe and well tolerated in our study, our experience was limited to 10 subjects treated for 4 weeks. It is certainly possible that the full range of potential adverse events related to glutathione extends beyond what we observed.

Both letters highlight the limitations of small pilot studies. Although these trials can provide useful preliminary information, it is only through adequately powered, rigorous, randomized, double-blind trials that we discern the true efficacy and safety of therapeutic interventions.

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Author Roles: RAH drafted the text and KEL reviewed and revised the draft.

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Long-Standing Paraphilia Induced by Dopamine Agonists in Parkinson's Disease

Among impulse control disorders (ICDs), hypersexuality related to antiparkinsonian therapy has been well-described.[1,2] Most of these patients with Parkinson's disease (PD) have modification of sexual behavior in a hyperactive direction. Occasionally, they can also have other changes in sexual behaviors, including gender identity disorder, as recently reported by Odiyoor et al.,[3] and various paraphilic disorders.[4–8] For example, 3 patients developed transvestic fetishism associated with selegiline intake.[6,8] Another patient developed frotteurism and delusional jealousy associated with pergolide intake.[7] ICDs are usually promptly recognized and improve after cessation of the causal dopaminergic medication.

A 60-year-old man had PD since 1982 (onset at age 33 years). He had no history of psychiatric or behavioral disorder. Before the introduction of dopamine agonist (DA) medication, he had only engaged in heterosexual activities and had no tendency toward transvestic fetishism. PD was initially treated with levodopa. In 1991, lisuride was started in

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TABLE 1. *Diagnostic criteria for transvestic fetishism, as defined by the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV)*[9]

A. Over a period of at least 6 months, in a heterosexual male, recurrent, intense sexually arousing fantasies, sexual urges, or behaviors involving cross-dressing.
B. The fantasies, sexual urges, or behaviors cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

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addition to levodopa, and the daily dose was gradually increased up to 2 mg. A few months later, the patient began to dress occasionally in women's underwear. This persisted over years. He also had associated ICDs, namely, compulsive shopping and risk-seeking behavior. For example, he engaged in extreme sports like paragliding, despite his motor difficulties. In 1999, entacapone was added. Subsequently, he bought women's clothes and lost 22 kg in few months to be "a good looking woman." He then began to frequent parking lots each night, wearing make up, fully dressed in women's clothes, and wearing external artificial breasts. At these moments, he had an extreme pleasure to be seen as a desirable woman and had sexual intercourse with other men. Because of motor complications, lisuride 2 mg/day was replaced by pergolide 3 mg/day (2003) and then pramipexole 2.1 mg/day (January 2007); entacapone was definitively stopped in 2006. These treatment changes induced no significant modification of his abnormal behavior. During this 16-year period, he had no manifestations of depression although it was not formally assessed.

He concealed these behaviors from his wife, his children, and his neurologist until March 2007. Pramipexole was then stopped and the patient was treated with levodopa alone. Transvestic fetishism and the others ICDs gradually resolved within a few months. One year later, low dose of ropinirole was introduced due to motor fluctuations. Paraphilia recurred rapidly. DAs were definitively stopped and paraphilia disappeared within 1 month. One year later, there had been no recurrence of these behaviors on levodopa monotherapy.

The persistent behavioral disorder described in our patient fulfils the diagnostic criteria for transvestic fetishism (Table 1).[9] Paraphilias are a group of psychiatric syndromes characterized by recurrent, intense sexual urges, fantasies or behaviors that involve unusual objects, activities, or situations. Transvestic fetishism is a paraphilia focused on cross-dressing. The link between paraphilia and DAs intake is robust in our case: (1) It was absent before DAs administration; (2) it occurred after DAs administration and persisted, regardless of the DAs used; (3) it disappeared after DAs withdrawal; (4) it reappeared after reintroduction of DAs.

The main originality of this report is the very long duration of the disorder: transvestic fetishism persisted during 16 years which represents about one third of his sexually active life. In the literature, the duration of the drug-induced ICDs in patients with PD ranges from a few months to a few years with a median duration of 2–3 years. Only one similar case with paraphilia over more than 10 years has been reported.[5] Both patients were men with young-onset PD, their paraphilic behavior worsened with increasing doses and persisted with various dopaminergic medications. As suggested for other ICDs,[10] male gender and young-onset PD may be risk factors for paraphilia. Motor fluctuations, which have also been tentatively linked to hypersexuality,[2] were present at the time of paraphilia onset in our patient, but not in the previously described patient.[5] In our patient, the very long duration is likely linked to the reluctance to report these problems. Paraphilias are likely under-reported because they are of stigmatizing nature and hold many more taboo within our society than do any other group of behavioral disorders. Not only neurologists but also the patients themselves and their families should be aware that changes in sexual behavior are a potential side effect of dopaminergic medication.

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Reply: The 'Plait Sign' of Neurostimulator Torsion

Goyal et al. reports a rare case of neurostimulator torsion which they postulate is secondary to their patient's uncontrolled head tremor.[1] However, tremor per se may not be sufficient to cause neurostimulator torsion. Any factor that allows the neurostimulator to twist within its subcutaneous pocket such as accumulated fluid can predispose to this condition and this is illustrated in the following case.

A 72-year-old man with severe essential tremor confined to his arms (tremor score 90) underwent bilateral posterior subthalamic area deep brain stimulation. The Kinetra neurostimulator (Medtronic, Minneapolis) was inserted into a subcutaneous pocket in the left infraclavicular region and secured to the pectoralis fascia with nylon sutures. Following surgery, the neurostimulator settings were adjusted such that his tremor improved by 73% (tremor score 24).

Three months after surgery, he woke up to find sudden worsening of his arm tremor. Additionally, the neurostimulator no longer responded to his personal Access programmer. Clinical examination showed that his arm tremor had returned to pre-surgical levels. There was no head tremor. There was a moderate sized subcutaneous fluid collection over the neurostimulator. The overlying skin, especially on the lateral side, was slightly bruised. The patient could not recall injuring himself in that area but had noticed increasing swelling and bruising in that area the week before his tremor worsened. There was nothing to suggest that the patient had been tampering with his neurostimulator. He admitted that he had a propensity to "toss and turn" in his sleep and the edge of the neurostimulator had previously hit the edge of the bed. This raised the possibility that the lateral edge of the neurostimulator may have repeatedly impinged on his bed during sleep. Interrogation of the device using the physician N'Vision programmer indicated an open circuit (impedance $>4000\ \Omega$, $<15\ \mu A$).[2] Radiographs taken of the entire DBS system did not show any fracture of the electrodes or the proximal portions of the connecting leads although the distal leads could not be easily seen due to the superimposed image of the neurostimulator. However, the connecting leads were twisted around each other (Fig. 1A), and the direction of the connection between the connecting leads and neurostimulator was opposite to that expected for its position (Fig. 1B–C). This suggested torsion of the neurostimulator. The DBS system was re-explored, and intraoperatively, we found that the subcutaneous pocket around the neurostimulator was distended and filled with approximately 20 mL of serosanguinous fluid. The neurostimulator had rotated 180° around a pedicle formed by the connecting leads and both connecting leads had fractured close to the point where they connect with the neurostimulator. The connecting leads were replaced, and the neurostimulator was repositioned. The potential dead space around the neurostimulator was decreased by tightly stitching the pectoralis fascia to the

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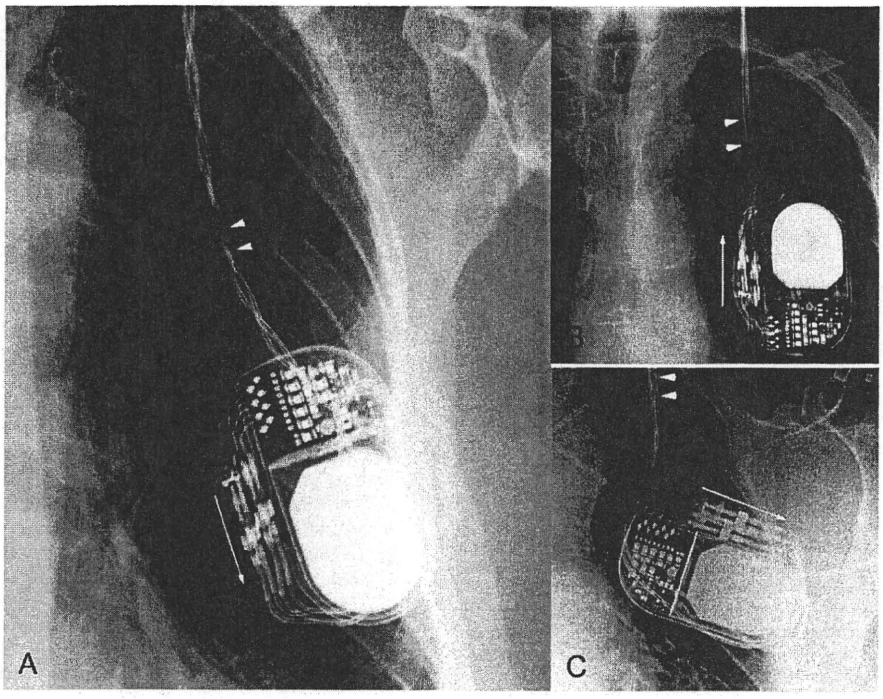

FIG. 1. Radiograph of the left chest depicting a rotated neurostimulator (**A**) and non-rotated neurostimulators in the two most common positions of insertion: vertical (**B**) and horizontal (**C**). The connecting leads of the rotated neurostimulator are plaited around each other (Fig. 1A arrowheads) whereas the leads for non-rotated neurostimulators run parallel to each other as shown (Fig. 1B–C arrowheads). Additionally, the direction of the axis of the neurostimulator to connecting lead (long arrows) differs between rotated and non-rotated neurostimulators.

overlying subcutaneous fascia with nylon sutures. The wound was closed after intraoperative testing indicated that the device was functioning and that test stimulation controlled the arm tremor. Microbiological analysis of the fluid failed to show an infection. The patient's tremor control has now returned to optimal levels.

The radiological signs of neurostimulator torsion we described are also seen in Goyal's case. Neurostimulator torsion should be considered in any patient with a DBS who presents with the triad of sudden worsening of symptoms, an 'open circuit' on neurostimulator interrogation and plaiting of DBS connecting leads as seen on radiographs. Attempts to reduce the dead space around the neurostimulator should be part of the treatment plan.

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Hypoglycemia-Induced Choreoathetosis Associated with Hyperintense Basal Ganglia Lesions in T1-weighted Brain MRI

In a recent article in this journal, Kandiah et al.[1] reported a case series of patients with choreoathetosis associated with nonketotic hyperglycemia. They showed basal ganglia hyperintensities in T1-weighted MR-images (MR-T1) in all patients and discussed hyperviscosity as the most likely pathogenetic mechanism. However, we found a similar clinical presentation and basal ganglia hyperintensities in MR-T1 (Fig. 1d,i) in a young male type I diabetic patient with recurrent episodes of nocturnal hypoglycemia during the dose finding period with an insulin pump. The minimal blood glucose levels ranged from 1.9 to 2.2 mmol/L at five

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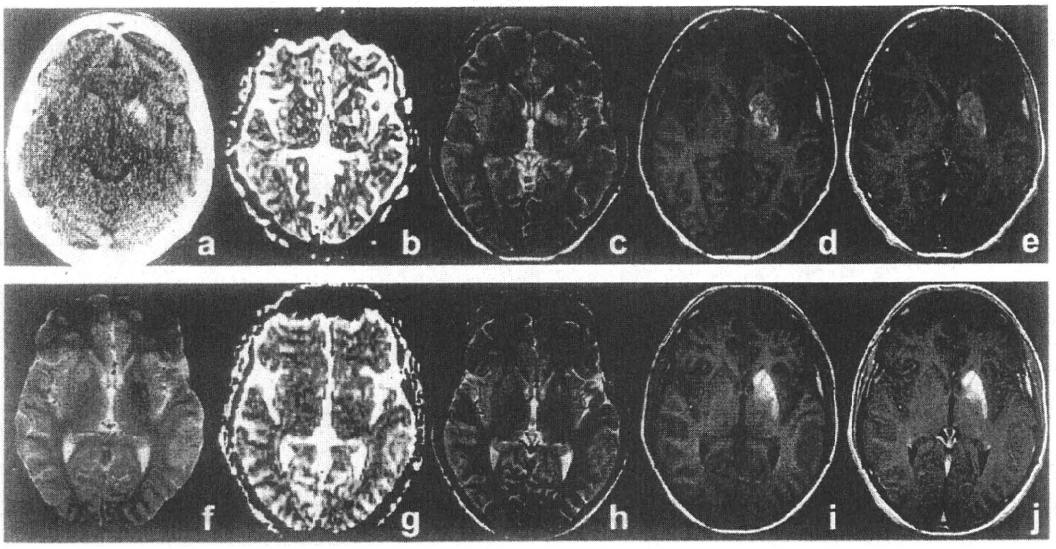

FIG. 1. Sequential neuroimaging. **(a)** Initial computerized tomography: left striatal hyperdensity indicating blood. **(b)** Initial MRI [parameter map of the apparent diffusion coefficient (ADC)]: slight diffusion restriction in the left basal ganglia. **(c)** Initial MRI (T2): inhomogeneous signal characteristics of the left basal ganglia with an area of hypointensity consistent with blood particles. **(d)** Initial MRI (T1): left striatal and pallidal hyperintensities sparing the anterior horn of the internal capsule. **(e)** Initial MRI (T1 with contrast agent): contrast enhancement can be seen in the left putamen. **(f)** Follow-up MRI (susceptibility weighted image, T2*): signal drop out in part of the basal ganglia indicating hemosiderin. **(g)** Follow-up MRI (ADC): no diffusion restriction left in left basal ganglia. **(h)** Follow-up MRI (T2): diminishing edema of the left basal ganglia compared to (c). **(i)** Follow-up MRI (T1): homogeneous striatal hyperintensity consistent with early chronic stage of hemorrhage development. **(j)** Follow-up MRI (T1 with contrast agent): no contrast enhancement left in the basal ganglia lesion.

consecutive nights. During this period, the patient developed a slowly progressive right-sided choreoathetosis, which persisted even after normalization of blood glucose levels. Apart from insulin, the patient did not take any drugs and had no family history of movement disorders; other metabolic disorders and thyroid dysfunction were excluded. CSF was normal. We started symptomatic treatment with tiapride (100 mg t.i.d.) for 4 weeks. Six weeks later, we reviewed the patient and found almost complete remission of clinical symptoms with only minimal residual chorea of the right hand.

Cranial CT performed immediately after admission at our Neurology Department 1 week after symptom onset showed hyperdensity in the contralateral striatum sparing the intercalated part of the internal capsule (Fig. 1*a*). In contrast, signal changes in MRI at the same time were inhomogeneous: Within a larger area of hyperintensity in the striatum and pallidum (both on MR-T1 and MR-T2), a hypointense area on MR-T2 extended from the ventrolateral putamen into the lateral part of the caudate nucleus including a small part of the internal capsule (Fig. 1*c*). This area had lower apparent diffusion coefficient (ADC) and showed contrast enhancement. The follow-up MRI 6 weeks later showed T1-hyperintensities in the left striatum and the lateral part of the pallidum and only a slight signal dropout in MR-T2* in a small part of the lesion (Fig. 1*f*). There was no contrast enhancement left (Fig. 1*j*) and the initial swelling of the left basal ganglia had diminished. No area of lowered ADC was present anymore (Fig. 1*g*). Considering the images alone, the signal development of the basal ganglia lesion to the point of homogeneous hyperintensity in MR-T1 and slight signal dropout in MR-T2* in the follow-up scan is in favor of an extravasation of blood particles, compatible with hemorrhagic transformation in subacute brain infarction. The hyperdense lesion in cranial CT supported this, as this scan was already taken in the subacute phase. The pathophysiology of brain lesions following hypoglycemia is however suggested to be a combination of substrate deficiency and excitotoxicity leading to a different ultrastructural lesion pattern as in ischemia.[2] Substrate deficiency such as hypoglycemia or general hypoxia predominantly affects cells carrying excitatory receptors, thus leading to selective neuronal damage.[3] In contrast, selective neuronal cell death and delayed hyperintensity in MR-T1 has also been described in the striatum of rats 7 days after a brief focal ischemia along with proliferation of reactive astrocytes and microglia without infarction (pannecrosis), hemorrhage, or apparent calcification on histology.[4] The brain imaging appearance of substrate deficiency and ischemia have overlapping features. In our case, the predominant involvement of gray matter without restriction to a vascular territory, and the clinical presentation with slow progression and without stroke-like symptoms pointed to the recurrent hypoglycemic states as the major pathogenetic factor for the basal ganglia lesion.[5] Imaging information alone can thus not reveal the etiology, as it is not specific and several brain pathophysiologies share final common pathways.[6]

Together, the pathogenesis of the T1-hyperintensities as well as the clinical manifestation seems variable with nonke-

totic hyperglycemia being the most common pathogenetic cause most likely mediated by hyperviscosity [Ref. 1 and literature within]. However, our case together with previous reports on hyperintense basal ganglia lesions in MR-T1 due to hypoglycemia[6] or after cardiopulmonary resuscitation with general hypoxia[7] strongly suggest substrate deficiency as another pathogenetic factor leading to basal ganglia MR-T1 hyperintensity and choreoathetosis.

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前頭側頭型認知症の診断と病理

Diagnosis and pathology of frontotemporal dementia

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Summary

前頭側頭型認知症のプロトタイプとされたピック病は，病理学的に，3リピートタウオパチー(ピック嗜銀球を伴うピック病)，4リピートタウオパチー(皮質基底核変性症，進行性核上性麻痺，嗜銀顆粒性認知症)，TDP 43プロテイノパチー(孤発性・家族性ユビキチン陽性封入体を伴う前頭側頭葉変性症，認知症を伴う筋萎縮性側索硬化症)からなることが明らかとなり，最近さらにFUS/TLSプロテイノパチー(好塩基性封入体病，神経中間線維封入体病)が加わった。また，本来非アルツハイマー型認知症として分離されたが，アルツハイマー病理を有する症例が最も頻度が高いとする報告もある。臨床的に治療上特別な配慮が必要な点と，大脳病変局在との関連上重要な疾患であるが，背景となる病理は多様である。剖検による厳密な臨床病理学的分類に基づき，サロゲートバイオマーカーを同定していくことが，今後の根治療法の開発には必須である。

Key words

- 前頭側頭葉変性症(FTLD)
- タウ
- ユビキチン
- TDP43
- FUS/TLS
- FTDP-17

I 前頭側頭型認知症(FTD)の命名に関する混乱について

前頭側頭型認知症(frontotemporal dementia：FTD)は，アルツハイマー病(Alzheimer's disease：AD)が頭頂葉を病変の首座とする後方型認知症に分類されるのに対し，前頭・側頭優位を病変の首座とすると考えられてきた症状を示す症例の総称である。

基本的には，ADが記憶障害を呈するのに対し，病識の欠如，脱抑制，性格変化，行動異常，言語障害を基本とし，そのプロトタイプはピック病(図1)である。

ADは，Alois Alzheimerが，綿密な臨床観察と神経病理学的検索に基づいて分離した疾患である[1]。アルツハイマー型神経原線維変化(Alzheimer-type neurofibrillary tangle：ADNFT)と，老人斑(senile plaque：SP)を基本とする点で，疾患の病態機序が共通する一群が定義された結果，その後の大きな発展の基盤を形成することになった。

一方，ピック病に関してはArnold Pickにより，臨床症状と，肉眼病理学的病変部位の記載により最初に分離された[2]。ピック(嗜銀)球をピック病に最初に記載したのはAlzheimerであり[1]，もしピック病をピック球を伴う疾患と定義すれば，その後の大きな混乱は防げた可能

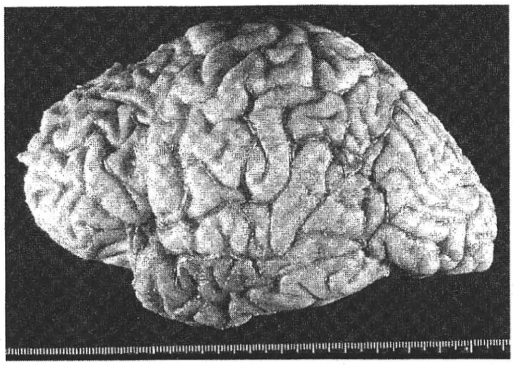

図1　ピック病(ピック球を伴う)脳の肉眼所見
中心前回より前の前頭葉が著明に萎縮し，側頭極と，第2・第3側頭回の萎縮が強いが，第1側頭回後方は萎縮より免れている。頭頂葉では，縁上回・角回は萎縮を認めるが，他の部位はよく保たれている。

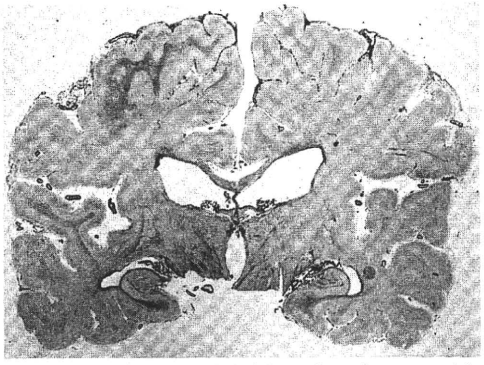

図2　皮質基底核変性症(巻頭グラビアページ参照)
視床下核を通る割面のHolzer染色。左右差を伴う白質病変が，片側優位に強調されている。

性がある。しかし実際は，Onariら[3]により，葉性萎縮を示す認知症として括られ，その一部にピック球が出現するという疾患概念形成がなされた。すなわち，神経細胞死とピック球形成に関連はないという立場であり，これにはピック球が歯状回の顆粒細胞層が好発部位でありながら，その部位には細胞脱落がみられないという観察も1つの根拠となった。現在ではこの部位は，成年における神経再生(adult neurogenesis)が起きる部位であることは，ラットではほぼ確立しており，またヒトてんかん病理からもそれを支持する見解が得られており，ピック球が神経変性に結びつかないという根拠にはならないことが明らかとなっている。

その後Escourollらにより，ピック病は，ピック球と腫大神経細胞を伴う群，ピック球を欠くが，腫大神経細胞は伴う群，どちらも伴わない群に分類された。次いでConstantinidisらはこれに陽性萎縮のパターンを加え，前頭葉下面と側頭極に変性が強調されピック球を伴う1型と，前頭葉弓隆面が障害され腫大神経細胞を伴う2型，ピック球も腫大神経細胞もどちらも伴わない3型に分類し，3型にも1型のパターンと2型のパターンの両方が存在するとした。近年の蛋白化学的研究の進歩により，1型は3リピートタウオパチー(後述)としてのピック病，2型は4リピートタウオパチー(後述)としての皮質基底核変性症(corticobasal degeneration：CBD)，3型は，ユビキチン陽性封入体を伴う前頭側頭葉変性症(frontotemporal lobar degeneration with ubiquitinated inclusions：FTLD-U)にほぼ合致することが明らかになった。つまり，少なくとも3つ以上の疾患が，同一名で括られていたわけである。

現在これらをピック症候群として総括する立場もあるが，混乱が混乱を呼ぶ可能性があり，基礎科学的観点から，3リピートタウオパチーとしての，ピック球を伴う症例のみを，ピック病と呼ぶことが神経科学の世界では一般的である。

ここで問題となるのは，CBDであり，前頭葉優位の大脳皮質弓隆部を病変の首座とし，高頻度に左右差を示すことが病変の基本である。この疾患の中で，中心前回・後回に病変が強調された一群を抜き出し，いわゆる片側の肢節運動失行を強調して，Gibbら[4]がCBD(**図2**)と記載したのは，ピック病の2型として記述がされたより歴史的にははるかに後である。さらに，左前頭弁蓋の病変が強調された群が，緩徐進行性失語[5]と記載された結果，本疾患には3つの臨床診断名が存在することとなった。Mayo ClinicのBoeveらは，臨床的なCBDをCBD syndromeとして，病理学的CBDと区別して記載しており[6]，これも1つのアプローチであろうが，どちらの

意味で記載されているかについては，注意が必要である。

Ⅱ 前頭側頭型認知症(FTD)と前頭側頭葉変性症(FTLD)をめぐる混乱

FTDは臨床症候名である。一方FTLDは，ピック病をめぐる混乱を収拾するため，神経病理学的に，前頭側頭葉に変性型病変を有する症例をまとめるかたちで，スウェーデンのLund大学と，イギリスのManchester学派が共同で提出した疾患概念である[7]。

このFTLDを呈する症例の中に属した，家族性疾患の一群が，17番染色体にリンクすることが明らかとなり，FTDP-17(frontotemporal dementia with parkinsonism, linked to chromosome 17)と命名された[8]。連鎖解析研究において，臨床症状を重視するのは当然である。そして，この変異家系の大部分において，責任遺伝子がタウ(MAPT)であることが明らかとなった。結果的に，FTDという言葉が病因とリンクした結果，あたかも病理学的背景をもつような誤用を生むこととなった。しかし，FTDをきたす疾患で，神経病理学的に最も頻度が高いのは，ADであるとする報告は数多く存在する。一方，FTDP-17(MAPT)に分類されるR406W変異の多くはADと診断されている[9]。ブラックボックスの部分が多いヒト脳を，臨床症状のみから診断することが危険であることは自明である。しかし，根治療法が存在せず，対症療法が主体となる現時点で，FTDの臨床徴候を正確に捉え，的確に介入することについて，臨床上の有用性は高い。

Ⅲ ユビキチン陽性封入体を伴う前頭側頭葉変性症(FTLD-U)をめぐる混乱

FTLD-Uは，抗ユビキチン抗体免疫染色の適用により，いわゆるピック球を伴わないピック病(Pick disease without Pick body)の大部分を占めることが明らかとなった。これは，蛋白を病理組織上で可視化する免疫組織化学の応用が，新たな原因蛋白の発見につながる最近のトレンドの1つを形成する。ユビキチンは細胞内プロテオームパスウェイのキー蛋白であり，ADNFTの形成において必須の役割を果たす機能が明らかとなった[10]。次いで，レビー小体に存在することが示された[11]。FTLD-Uに関しては，ユビキチン化されている蛋白自体は明らかではなかった。ユビキチン化封入体は，筋萎縮性側索硬化症(amyotrophic lateral sclerosis：ALS)でも存在が明らかにされ[12]，さらに認知症を伴うALS(ALS with dementia：ALSD，湯浅・三山症候群)で歯状回顆粒細胞にユビキチン陽性封入体が記載された[13]。FTLD-Uは，ALS/ALSDとの関連が強調され，運動ニューロン疾患型ユビキチン陽性封入体をもつ一群と命名された。

FTLD-Uのユビキチン化蛋白については，2種の方法で明らかにされた。1つは，ALSDのプロテオーム解析により，蓄積蛋白として同定された[14]。もう1つはFTDP17-non tauの一部がprogranulin変異であることが明らかとなり，遺伝子異常を有する脳における蓄積蛋白の解析から明らかにされた[15]。蓄積蛋白として同定されたのはTDP43であり，さらにTDP43遺伝子変異がALS/ALSDの原因となることが明らかとなった。これにより，本邦においてはFTLD-Uの大部分が，TDP43細胞内蓄積を示すことが明らかとされた。最近の命名では，FTLD-TDP43の名称を用いることが提唱されている。

TDP43は核内蛋白で，RNA編集への関与が想定されている。実際ALSではRNA editingの異常が報告されている。一方，家族性ALSの責任遺伝子として，最近FUS/TLS(fused in sarcoma/translated in liposarcoma)が責任遺伝子として同定された[16][17]。本邦においては家族性ALSで，basophilic inclusion body disease(BIBD)に属する症例が，FUS/TLS変異症例として報告されている[18]。一方欧米では，FTLD-U non-TDP43の症例の大部分がFUS/TLSで陽性であり，これらはFTLD-FUS/TLSと呼ぶべきであるという提唱がなされた[19]。当然ながら，ユビキチン化される蛋白は種々あり，それに基づき疾患を分類すべきであるという点まではよい。ただし，FUS/TLSについては，TDP43との関連での議論以上の