アクチュアル
脳・神経疾患
の
臨床

# 神経感染症を究める

総編集●辻　省次
専門編集●水澤英洋

Actual Approach to Neurological Practice

中山書店

付録 2
感染症関連ガイドラインと使用上の注意

# プリオン病

参考 「プリオン病診療ガイドライン 2014」
(厚生労働科学研究費補助金 難治性疾患等克服研究事業「プリオン病及び遅発性ウイルス感染症に関する調査研究班」「プリオン病のサーベイランスと感染予防に関する調査研究班」)
http://prion.umin.jp/guideline/guideline_2014.pdf

## ガイドライン作成の経緯

2014 年 3 月に，厚生労働科学研究費補助金難治性疾患等克服研究事業（難治性疾患克服研究事業）関連の 2 つの研究班である，「プリオン病及び遅発性ウイルス感染症に関する調査研究班」（主任研究者：山田正仁）と「プリオン病のサーベイランスと感染予防に関する調査研究班」（主任研究者：水澤英洋）の合同執筆により「プリオン病診療ガイドライン 2014」が発行された（http://prion.umin.jp/guideline/guideline_2014.pdf）．

本ガイドラインはプリオン病を専門としない一般医師向けに記載されており，大学の専門外来などではなく，市中病院の医師や開業されている医師の方々にもプリオン病診療に加わっていただき，本症に関するわが国の診療水準が向上することを目的として作成されている．

プリオン病の診療ガイドラインに関しては，いわゆる狂牛病問題が発生した 1996 年にクロイツフェルト・ヤコブ病（Creutzfeldt-Jakob disease：CJD）への一般の関心が高まり，翌年 2 月に「クロイツフェルト・ヤコブ病診療マニュアル」が作成された．その後のプリオン病の診療・疫学調査，基礎研究の進歩に伴って，2002 年 1 月に厚生労働省・特定疾患対策研究事業「遅発性ウイルス感染に関する調査研究班」（主任研究者：北本哲之）によって「クロイツフェルト・ヤコブ病診療マニュアル・改訂版」として，プリオン病の治療，検査，感染因子の滅菌法，感染防御などについて「把握し得る最大限の情報」を基に改訂が加えられた．

前マニュアルの改訂から 10 年以上が経過し，その間にわが国のプリオン病の診断技術，特に検査技術の飛躍的な進歩があり，検査の感度，および特異度は劇的に向上した．具体的には，脳 MRI 画像における高信号病変に関する画像表示条件の標準化，髄液中の 14-3-3 蛋白測定の標準化，髄液中の異常プリオン蛋白測定技術の開発など，今やプリオン病の診断技術に関して，わが国は世界をリードする立場にあるといえる．本ガイドラインでは，プリオン病の約 7 割を占める古典型孤発性クロイツフェルト・ヤコブ病に始まり，まれなタイプの孤発性クロイツフェルト・ヤコブ病，わが国の遺伝性プリオン病の特徴と診断上の注意点，世界的にも問題となっている硬膜移植によるクロイツフェルト・ヤコブ病など，プリオン病を疑った際に知っておくべき事項と調べるべき内容が簡潔にまとめられている．さらに，後半には，これまでに行われた治験の概要とミオクローヌスなどの不随意運動への対応法，心理的なサポート体制と具体的な相談窓口が掲載されており，最終章に本ガイドライン作成に携わっているプリオン病関連研究班が無料で提供している診療支援体制の内容と連絡先が明記されている（表1）．

## ガイドライン使用上の注意点

本ガイドラインはこれまでのマニュアルと異なり，生化学的基礎研究の内容などに関しては

**1**「プリオン病診療ガイドライン 2014」の目次



記載されておらず，あくまで臨床の現場で不明な点などを調べることを前提として作成されている．たとえば，孤発性クロイツフェルト・ヤコブ病には 6 型あることが知られており，各病型の特徴は記載されているが，各病型をどのように確定診断しているのか，というような事柄や病理解剖の際の補助金制度，感染対策などに関しては省かれている．感染対策に関しては，2008 年に「プリオン病感染予防ガイドライン（2008 年版）」（主任研究者：水澤英洋，編集責任者：黒岩義之）が発刊されており，プリオン対応の滅菌方法から，関連各科における注意点が詳細に記載されている．内容が多いため，要約版も作成されており，医師のみならず，検査技師や事務系の方にも読みやすいように工夫がされているので，病理解剖での対策を含めて，感染対策に関しては，こちらの感染予防ガイドラインを参照にするとよい．以下に各章に記載されている事項の概略を説明する．

## プリオン病とは？ プリオン病をどう診療するか？（II 章）

ほとんどの方が最も参照すると思われる章であり，プリオン病が疑われる患者を診療した際には，まずこの章を参照するとよい．最初の項目は概念の説明であるが，項目 2 に「プリオン病をどう診療するか？」が記載されており，疑った際にどのような検査をすればよいかが一目でわかるようにアルゴリズムが記載されている．この項に記載されている検査の依頼先は，「IX. 診療支援」の章に記載されており，依頼方法に関しては，各項目の最後に掲載されているウエブサイトをインターネットで検索すればわかるようになっている．項目 3 は社会資源，患者・家族支援，患者会，感染症法などに関する説明となっている．

## プリオン病各論（III〜V 章）

孤発性クロイツフェルト・ヤコブ病，遺伝性プリオン病，獲得性プリオン病の各々の分類に関して，概説と診断の項目が設けられている．プリオン病が疑われる患者を診察した際には，各病型の概説を読んでいただき，可能性のある病型の診断の章を精読するとよい．典型的な古典型孤発性は一般の医師でも比較的容易に診断をつけることができる．診断が難しい症例においては，他の領域の疾患でも同じであるが，病歴聴取が重要であり，海外渡航歴の有無，家族歴の聴取，他の遺伝性疾患の家族歴，脳外科手術歴の有無などは病型を決める際の手がかりとなるものが多い．たとえば，認知症の家族歴のある症例，脊髄小脳失調症の診断を受けた家族がいる急速進行性認知症の症例，そして家族歴はないが，症状に比べて脳 MRI 画像の高信号が目立つ症例などを見かけた際には，遺伝性プリオン病の可能性も考えなければいけない．硬膜移植によるクロイツフェルト・ヤコブ病は年々減少しているが，長いものでは潜伏期間が 30 年になるので，今後も十分な注意が必要である．（☞各病型の詳細に関しては本書 VII.「プリオン病」（p.278-285）を参照）．

プリオン病に関連した検査を依頼した場合には，偽陽性例が存在することに注意をしなければならない．脳 MRI 拡散強調画像ではてんかん発作，虚血性脳障害，低酸素脳症，MELAS（mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes：ミトコンドリア脳筋症・乳酸アシドーシス・脳卒中様発作症候群），などで大脳皮質の高信号を認めることが知られており，検査装置では 1.5 テスラの装置に比べて，近年増加している 3 テスラの装置のほうが感度は低いことが報告されている．髄液検査においても 14-3-3 蛋白は脳血管障害，脳炎，代謝性脳症，低酸素脳症，橋本脳症，傍腫瘍症候群，末梢神経障害などで陽性になることが報告されており，RT-QUIC 法による異常プリオン蛋白は感染症，痙攣，低酸素脳症などでも陽性となる場合があるので，診断においては十分な注意を払う必要がある．

## プリオン病の患者・家族に対する心理社会的支援（VII 章）

プリオン病ではプリオン蛋白遺伝子の多型が病態に関わることと，家族歴のない遺伝性プリオン病例が多数認められることより，サーベイランス調査において遺伝子検索が積極的に勧められている．さらに，発症前診断は原則として行わないことより浸透率に関する情報が少ないことで，血縁者には心理的な負担や不安を抱えている方も少なくない．そのような患者，血縁者に対し心理カウンセラーによる心理カウンセリングを行い，情報提供と理解の支援，心理的社会的支援などを厚生労働省研究班の事業として行っている（http://prion.umin.jp/prion/counseling.html）．この章では，研究班での取り組みと，患者や家族の心理的背景が概説されている．

## おわりに

2013 年度からは「プリオン病に対する低分子シャペロン治療薬の開発」（主任研究者：桑田一夫）研究が本格的に開始され，現在は治験開始後の比較対象となる自然歴調査が開始されている．この研究を介した新たな治療薬の出現が期待されており，1 年間に 100 万人に 1 人という希少疾患における治療薬開発のためには，より多くの施設，そして患者と患者家族の協力が不可欠である．本マニュアルの目的である，わが国のプリオン病に対する医療水準の向上により，一人でも多くの症例が登録され，1 日でも早くこの難病中の難病であるプリオン病の治療薬が出現することを心から願っている．

（三條伸夫，水澤英洋）

Images in Neurology

# Serial Magnetic Resonance Imaging Changes in Sporadic Creutzfeldt-Jakob Disease With Valine Homozygosity at Codon 129 of the Prion Protein Gene

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**Sporadic Creutzfeldt-Jakob disease (sCJD)** accompanied by type 2 $PrP^{Sc}$ and valine homozygosity at codon 129 (VV2) of the prion protein gene (*PRNP*) is a representative sCJD having the *129VV* genotype, which does not show prominent myoclonus or periodic sharp wave complexes. Magnetic resonance imaging (MRI) findings of patients with sCJD having the *129VV* genotype have rarely been reported.[1]

A 52-year-old man initially complained of gait instability and then experienced the progression of gait unsteadiness, cognitive impairment, dysarthria, and hallucinations over a period of 4 months. Neurological examination revealed restricted eye movement, cerebellar ataxia, frontal lobe signs, and a Mini-Mental State Examination score of 18 of a possible 30, but no involuntary movements.

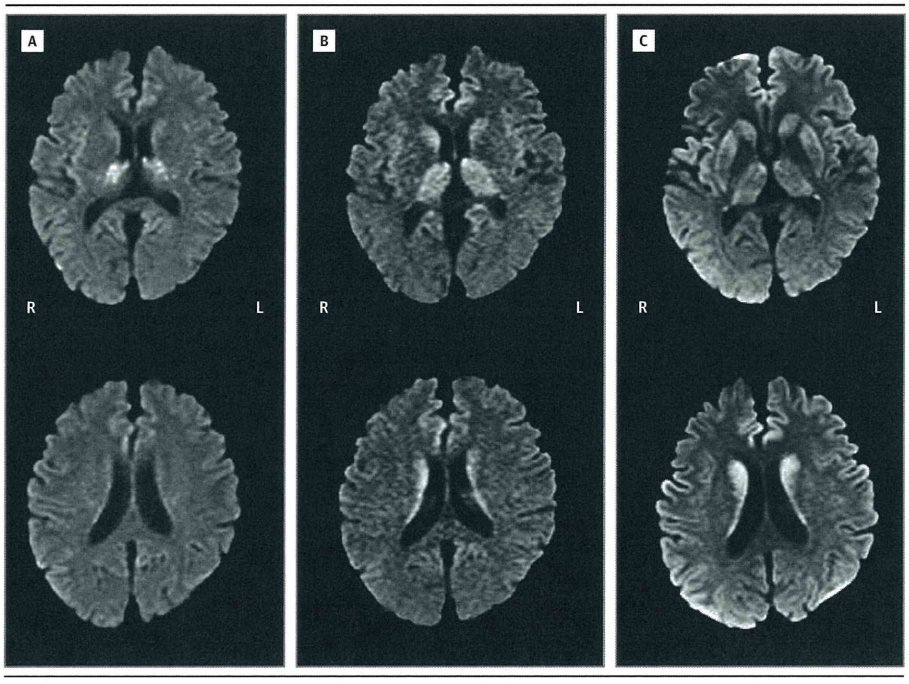
Diffusion-weighted images (DWI) of the brain showed areas of spreading hyperintensity in bilateral thalami (**Figure**). Fludeoxyglucose F 18 positron emission tomography at 5 months after onset indicated low glucose metabolism in the thalami and cerebellar cortices. Electroencephalography showed diffuse slowing but no typical periodic sharp wave complexes.

Cerebrospinal fluid analysis revealed increased levels of both total tau and 14-3-3 proteins, and $PrP^{Sc}$ was detected with the real-time quaking-induced conversion method.[2] *PRNP* analysis revealed valine homozygosity at codon 129 and glutamate homozygosity at codon 219 without any mutation or insertion. Although the $PrP^{Sc}$ type was not determined by Western blotting of brain homogenates, the patient's clinical features were compatible with sCJD with VV2 rather than VV1. He became bedridden 5 months after onset, exhibited akinetic mutism by 7 months, and died 9 months after onset.

## Discussion

Magnetic resonance imaging thalamic findings are well known as either the pulvinar sign or hockey stick sign in variant CJD and type 2 sCJD with methionine/valine heterozygosity at codon 129 (MV2). In our patient, brain MRI did not show DWI hyperintensity in the pulvinar area of the thalamus but primarily in the ventral anterior, ventral lateral, and lateral dorsal nucleus areas at 1 month after onset and then spread to the entire thalamus. Two Japanese patients with

Figure. Serial Diffusion-Weighted Magnetic Resonance Imaging of the Brain After Disease Onset




Images acquired at 1 (A), 4 (B), and 5 (C) months after onset. Hyperintense areas are first seen mainly in the bilateral ventral anterior, ventral lateral, and lateral dorsal nuclei (A, arrows), then spread bilaterally to the entire thalamus and caudate nuclei (B and C), and finally to the putamen (C).

sCJD with VV2 have previously been reported to show DWI hyperintense lesion of the entire thalamus at later stages.[3] Although MRI findings at earlier stages have not been reported in these cases, we speculate that serial MRI changes in our patient reveal the location of the pathological process and may serve for characterization of the VV2 subtype of sCJD at an early stage.

## ARTICLE INFORMATION

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*Study concept and design:* Mizusawa.
*Acquisition, analysis, or interpretation of data:* Furukawa, Ishibashi, Sanjo, Yamashita.
*Drafting of the manuscript:* Furukawa, Ishibashi, Sanjo, Mizusawa.
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*Study supervision:* Sanjo, Mizusawa.

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INTERNAL MEDICINE

□ CASE REPORT □

# Delayed Leukoencephalopathy after Carbon Monoxide Poisoning Presenting as Subacute Dementia

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## Abstract

We herein report the case of a 65-year-old woman who presented with the subacute onset of dementia and subsequently developed abnormal behavior and a gait disturbance. Her condition transiently improved; however, within one month, she became drowsy and poorly responsive, with limb chorea and urinary incontinence. Her history of frequently using charcoal led us to diagnose her with carbon monoxide (CO) poisoning. The findings of this case and a literature review suggest that subacute dementia due to CO poisoning recovers late, after a year or more, in patients above sixty years of age, and both hyperbaric oxygen and corticosteroid pulse therapy should be considered in such cases, even after one month.

**Key words:** carbon monoxide poisoning, delayed leukoencephalopathy, subacute dementia

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## Introduction

Carbon monoxide (CO) poisoning often presents as delayed encephalopathy in which neurological sequelae develop two to 40 days after an apparent recovery from acute cognitive deterioration that lasts 24 to 48 hours (1). The acute symptoms include headache, nausea, confusion and coma, depending on the blood carboxyhemoglobin (CO Hb) level, whereas delayed encephalopathy involves parkinsonism, incontinence, dementia and psychosis. The diagnosis is made based on known CO exposure and the blood CO Hb level (2).

However, problems with the diagnosis arise when there is no such evidence of exposure. In addition, how should physicians establish the diagnosis of CO poisoning in cases in which the patient does not lapse into an acute coma? We herein report the case of a patient with suspected CO exposure who exhibited the subacute onset of dementia and review the clinical course and treatment of such patients in the literature.

## Case Report

A 65-year-old woman was referred to our hospital in March due to a low-grade fever lasting for two days with the subsequent development of abnormal behavior (she drank her husband's alcohol, despite not having a drinking habit), dysarthria, lack of initiative (she stopped doing household chores) and a stooped posture while walking for over one month. She visited a local hospital ten days after disease onset and was given an intravenous drip infusion of vitamin $B_1$ for four days. Her condition immediately improved; however, she later developed urinary incontinence 14 days after onset. Her gait again worsened, and she required a wheelchair when leaving the house.

On the first examination, the patient was drowsy and poorly responsive and showed forced grasping with chorea of all four limbs. She did not obey one-step commands. Her lower limbs were spastic, with an increased left Achilles tendon reflex. MRI performed 13 days after disease onset revealed bilateral symmetric hyperintensity in the subcortical white matter of the basal frontal and parahippocampal gyri, periventricular white matter and centrum semiovale (Fig. 1, upper). She was admitted to our hospital with a diagnosis of

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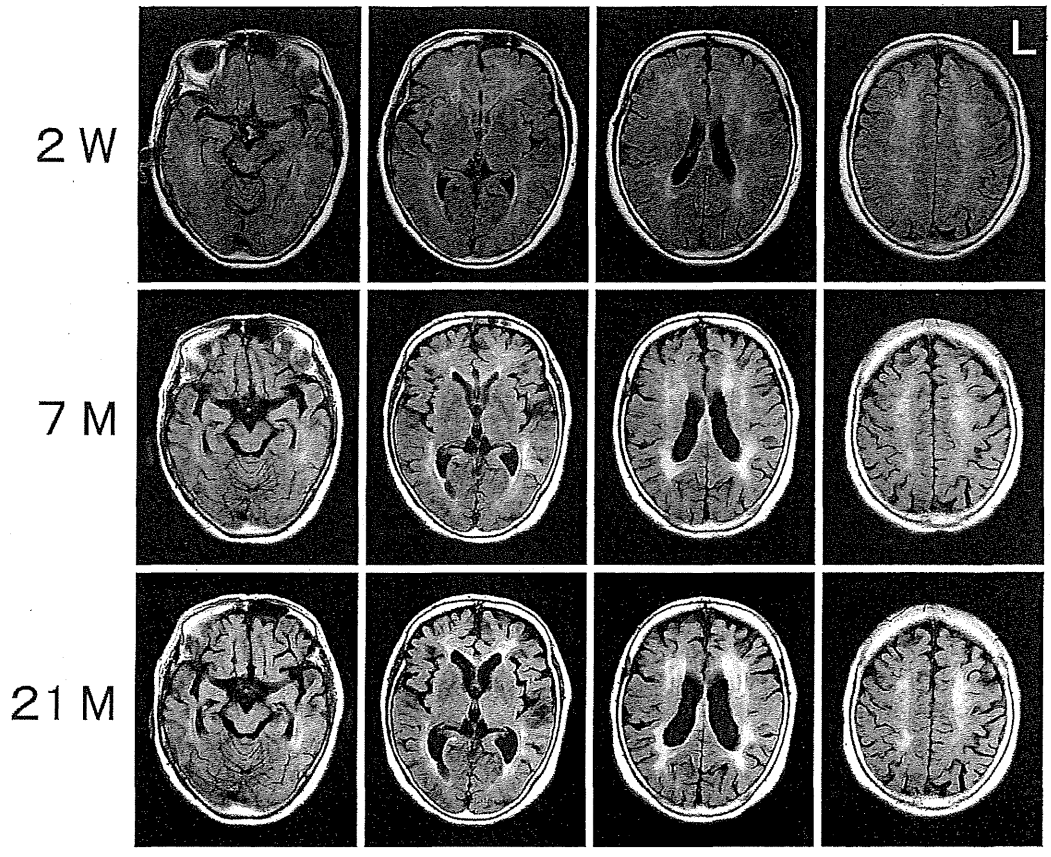


**Figure 1. MR images of the patient. Fluid-attenuated inversion recovery (FLAIR) axial images obtained two weeks after onset (upper) revealed bilateral symmetric hyperintensity in the subcortical white matter in the basal frontal and parahippocampal gyri, periventricular white matter and centrum semiovale. On FLAIR axial images obtained seven months after onset (middle), the periventricular and deep white matter hyperintense regions remained, although they had decreased in size. However, the lateral ventricles had slightly enlarged. At 21 months after onset (lower), the ventricular enlargement had progressed further. 2W: two weeks after onset, 7M: seven months after onset, 21 M: 21 months after onset**

leukoencephalopathy of an unknown etiology. The chorea worsened, and she was restless in the evening, necessitating frequent sedation with an intravenous drip infusion of haloperidol for 10 days after admission. Over the course of one week, the chorea remained limited to the lower limbs. The patient exhibited echolalia in response to a doctor's questions, as well as environmental dependency behavior, e.g., trying to place a toothbrush in her mouth upon seeing it. The laboratory data disclosed elevated serum lactate dehydrogenase (LDH) (253 U/L) and soluble IL2-receptor (281 IU/mL) levels; however, the C-reactive protein level (0.1 mg/dL) and white blood cell count (6,000/μL) were normal. A cerebrospinal fluid (CSF) analysis showed a normal cell count of 1/μL and a total protein level of 14 mg/dL, with an elevated myelin basic protein level (567 pg/mL) and IgG index (0.85, normal <0.7), calculated according to the formula: (CSF-IgG/CSF-albumin)/(serum IgG/serum albumin). Antibodies associated with paraneoplastic neurological syndromes, i.e., Ma2, Ma1, amphiphysin, CV2, Ri, Yo, HuD and anti-N-methyl-D-aspartate-receptor (NMDAR), as well as herpes simplex virus (HSV)-IgM, herpes zoster virus (HZV)-IgM and HIV antibodies, were all negative.

Detailed history-taking from the patient's husband revealed that they had used charcoal at home for heating and boiling water for a private samisen (Japanese traditional lute) lesson for four or five hours a day from November of the previous year to February (four months). The patient had always made the fire. Therefore, it is possible that she had unknowingly been exposed to low levels of CO. Although the patient's husband and students may also have inhaled low-dose CO, they did not show any symptoms of CO intoxication (e.g., headache) because they frequently opened the door for air ventilation.

The possible CO exposure, together with characteristic biphasic consciousness disturbances and symmetric leukoencephalopathy on MRI, strongly suggested CO poisoning. The patient was administered intravenous corticosteroid pulse therapy (methylprednisolone, 1,000 mg a day) for three days starting at 51 days post-onset. Subsequently, the echolalia and chorea mostly disappeared. However, she was

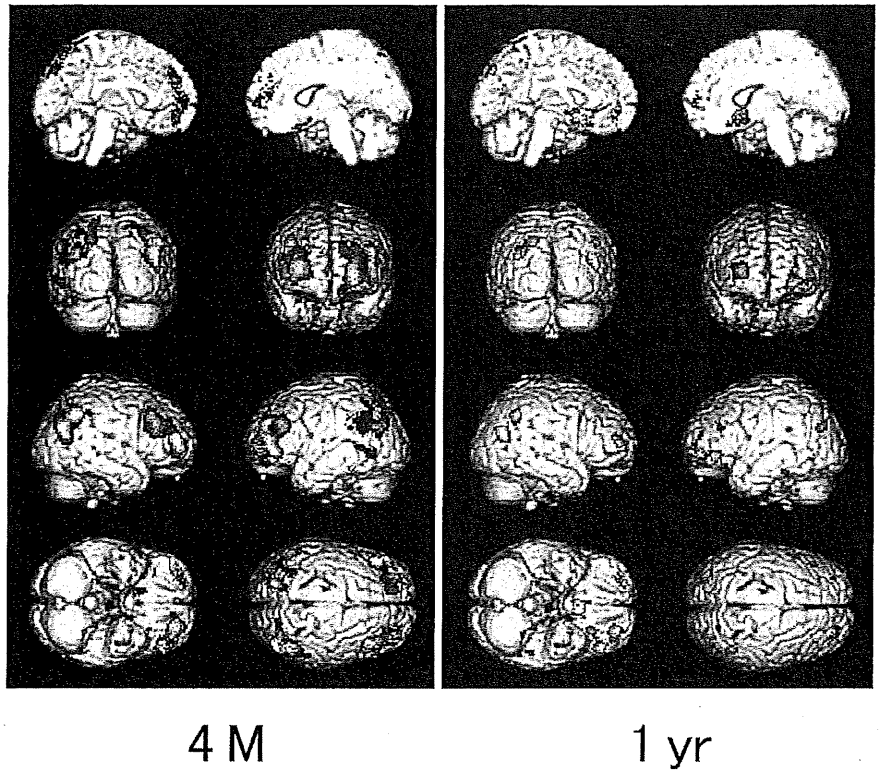


**Figure 2.** $^{99m}$Tc-ECD-SPECT images obtained at four months and one year after onset. The SPECT data were transformed into the Analyze format and normalized, smoothed and corrected for inter-laboratory differences with a three-dimensional conversion map using the easy Z score imaging system (eZIS) (14) version 3. The images were then compared with those of a normal subject database of the same generation and gender (n=22) with a two-sample t-test of Statistical Parametric Mapping (SPM) 2 (15) to show areas with a significant decrease in blood flow (uncorrected $p<0.001$) on standard brain surface images. The SPECT images obtained four months after onset (left) revealed hypoperfusion in the bilateral frontal convexity and mesial frontal and temporoparietal areas. The regions with hypoperfusion had markedly reduced in size at one year after onset (right). 4M: four months after onset, 1yr: one year after onset

euphoric, persisting in fiddling with a blanket continuously with her right hand (frontal alien hand sign) (3) despite a doctor talking to her (attentional disorder), stirring an empty cup with chopsticks when presented with the cup and chopsticks (compulsive manipulation of tools) (4) and continuing to show forced grasping. She was able to read aloud her kana (Japanese phonograms) name written on a sheet of paper; however, when asked to write her name, she wrote lines repeatedly (motor perseveration).

The patient was transferred to the Department of Neurology at the Medical Hospital of Tokyo Medical and Dental University, Tokyo for hyperbaric oxygen therapy. She was given a total of 19 oxygen therapy sessions during hospitalization for one month; however, she still wandered at night. She was then transferred again to our hospital for a reevaluation. She required sedation with quetiapine for four months after onset, when she became relatively independent in her activities of daily living.

The Mini-Mental State Examination (MMSE) conducted four months after onset for the first time during hospitalization revealed moderate cognitive impairment (11.4/30), consisting of disorientation of time and space, agraphia [perseveration and neographism of kanji (Japanese morphograms) characters], acalculia, recent memory impairment (the 5-minute delayed three-word reproduction score was 0/3). The Frontal Assessment Battery (FAB), conducted at the same time, showed a severe dysexecutive function (6/18; word fluency, 1 word). The patient's digit span forward score on the Wechsler Adult Intelligence Scale-III (WAIS-III) was three. Single photon emission computed tomography with a $^{99m}$Tc-ethylcysteinate dimer (ECD-SPECT) performed four months after onset revealed hypoperfusion in the bilateral frontal convexity and mesial frontal and temporoparietal areas (Fig. 2). Electroencephalogram (EEG) performed during this period showed a small amount of 8-9-Hz $\alpha$ waves in F-C-P-O, which contrasted markedly with that of the moderate amount of 4-Hz $\theta$ waves with occasional 2-3-Hz $\delta$ waves in Fp-C-O observed at onset.

After discharge, the patient became independent in activities of daily living; the Barthel Index improved from 25 at

**Table. Patients with CO Poisoning Presenting as Subacute Dementia**

| Reference | Patient | Treatment | | Outcome |
|---|---|---|---|---|
| | | HBO (time p.o./counts) | PSL (time p.o.) | |
| (5) | 48W | n.d. | 12 days* | 90 days, recovery |
| (6) | 45W | 50 days/6 | n.d. | 60 days, recovery |
| (7) | 57M | 30 days/15 | n.d. | 90 days, recovery |
| (8) | 52W | n.d. | n.d. | 120 days, HDS-R 17/30 |
| (9) | 75W | 15 days/50 | n.d. | 80 days, disorientation |
| (10) | 67W | 40 days/3 Mos | n.d. | 5 Mos, HDS-R 20/30 |
| Our patient | 65W | 51 days/19 | 37 days# | 4 Mos, MMSE 11.4/30<br>14 Mos, MMSE 27.7/30 |

HBO: Hyperbaric oxygen therapy, PSL: Prednisolone administration, W: Woman, M: Man, p.o.: Post-onset, Mos: Months, n.d.: Not done, HDS-R: Hasegawa Dementia Scale Revised, MMSE: Mini-Mental State Examination
*After corticosteroid pulse therapy (methylprednisolone, at 1,000 mg/day for three days), oral prednisolone (initial dose, 60 mg/day) was administered for ten days.
#Methylprednisolone 1,000-mg pulse therapy for three days only

one month after onset to 100 at six months after onset. Follow-up MRI performed seven months after onset showed that the periventricular and deep white matter hyperintense regions remained, although they had decreased in size (Fig. 1, middle). However, the lateral ventricles had become slightly enlarged, and the ventricular enlargement was found to have progressed further on MRI performed one year and nine months after onset (Fig. 1, lower). ECD-SPECT performed one year after onset revealed that the regions with hypoperfusion in the bilateral frontal and parietal areas had markedly reduced in size (Fig. 2). The MMSE score improved to the normal range (27.7/30) and the digit span forward score was four at 14 months after onset, although the FAB score remained low (14/18), even at 18 months after onset.

## Discussion

The present patient presented with the subacute progression of dementia lasting for one month. We diagnosed her with delayed leukoencephalopathy due to CO poisoning based on the facts that: i) she had used charcoal for four to five hours a day over a period of four months and was believed to have frequently been exposed to low levels of CO during that period; ii) biphasic consciousness disturbances occurred; and iii) MRI showed symmetric leukoencephalopathy.

The delayed neurological sequelae observed after 40 days in this case included dementia with nocturnal delirium and dysexecutive syndrome characterized by environmental dependency behavior, the alien hand sign and the compulsive manipulation of tools. Four months later, when we were able to first evaluate the patient's cognitive function, she exhibited agraphia, acalculia, reduced verbal short-term memory and recent memory impairment. These findings were consistent with the ECD-SPECT results obtained at the same time, which revealed hypoperfusion in the bilateral dorsolateral frontal, mesial frontal and temporoparietal areas. She became independent in activities of daily living within six months, and her cognitive function improved to a nearly normal level, except for the executive function, within 14 months, in accordance with the reduction of high-intensity white matter regions on MRI and areas with hypoperfusion on SPECT.

The patient did not develop an acute-phase comatose state and exhibited subacute dementia a few days to weeks after exposure to CO. Subacute dementia due to CO poisoning, lacking an acute coma, is a rare disorder. A MEDLINE and ICHUSHI (Japan Medical Abstracts Society) search for articles published between January 1960 and September 2013 was conducted using the key words "CO poisoning" and "dementia." Among the obtained articles, we selected cases with subacute (progression more than one week to as long as six weeks) dementia without witnessed acute coma. The table shows these reported cases. All patients were Japanese; this is because charcoal is frequently used in Japan for barbecues.

It is noteworthy that the patients under 60 years of age normally recovered within two to three months (5-7), except for one patient (8) who did not receive hyperbaric oxygen or corticosteroid pulse therapy. In contrast, the patients above 60 years of age had poor prognoses and did not recover completely within six months (9, 10). It should be noted, however, that our patient became independent in activities of daily living within six months, and her cognitive function recovered almost completely within 14 months. Therefore, a follow-up study lasting over one year is needed to determine the prognosis of patients with subacute dementia caused by CO poisoning.

Another important point is that most of the patients received hyperbaric oxygen or corticosteroid pulse therapy. Although the efficacy of chronic-stage hyperbaric oxygen therapy is debatable, all patients undergoing hyperbaric oxygen recovered to various extents, whereas one patient under 60 years of age who was not given hyperbaric oxygen or corticosteroid pulse therapy remained mildly demented at four months after onset (8). It is notable that hyperbaric oxygen was administered as late as 50 days after disease onset (6). Since the immediate effect of hyperbaric oxygen therapy is limited and the recovery process is slow and lasts