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Findings that shed new light on the possible pathogenesis of a disease or an adverse effect

Superficial siderosis associated with abundant τ and α-synuclein accumulation

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Summary

A Japanese male developed deafness, pyramidal signs and ataxia at age 50. A cerebrospinal fluid examination showed elevated levels of iron, transferrin and ferritin. Brain MRI showed atrophy of the cerebellum and pons as well as potential iron deposits on the surface of the brain. At autopsy, the brain weighed 1090 g and showed severe atrophy and necrosis of the cerebellum. No vascular malformation was observed. Extensive deposits of hemosiderin that were well stained with Berlin blue and ferritin immunohistochemistry were present at the surface and in the superficial layers of the cerebrum, brainstem, cerebellum and spinal cord. In these regions, numerous AT8 (p-)-immunopositive deposits were present in neurons and glia. In addition, phosphorylated -synuclein-immunopositive Lewy bodies and neurites were observed in the brainstem nuclei. In the present report, the authors derive the novel insight that superficial siderosis is a distinctive entity associated with tauopathy and synucleinopathy.

BACKGROUND

Superficial siderosis (superficial hemosiderosis) is a neurodegenerative disorder characterised clinically by a classic triad (cerebellar ataxia, sensorineural deafness, and myelopathy) as well as neuropathologically by deposition of hemosiderin, an iron-storage complex, in the subpial regions of the cerebrum and cerebellum.[1] Ever since superficial siderosis was first reported in 1908, approximately 200 English articles on the disorder have been published. Most cases have been diagnosed based on the classic clinical symptoms and neuroradiological findings. However, only a few neuropathologists have reported neuropathologic analyses of superficial siderosis.[2–11] These authors reported numerous hemosiderin deposits in the subpial regions of the cerebrum and cerebellum, and pathologic alteration of the cerebellum was particularly severe in many cases. The pathomechanism underlying the susceptibility of the cerebellum may be that Bergmann glia serve as conduits for heme. In addition, the eighth cranial nerves are also susceptible to superficial siderosis, presumably because they consist of central nervous system axons, myelin and neuroglial tissue along their subarachnoid course.[11]

One of the neuropathologic hallmarks of Alzheimer's disease is abnormal aggregation of phosphorylated τ protein in neurons. The abnormal aggregation of the presynaptic protein phosphorylated α-synuclein is a cardinal neuropathologic change of Parkinson's disease. In both pathologic conditions, several studies have indicated an association between oxidative stress and abnormal accumulation of τ or synuclein.[12–14] In particular, iron, hemosiderin and ferritin may contribute to the production of free radicals and neurodegeneration.[15]

In this paper, we report unique neuropathologic findings of superficial siderosis at autopsy. The patient showed numerous sites of τ and α-synuclein accumulation in multiple regions of the central nervous system. These sites may be associated with oxidative stress due to hemosiderin deposition.

CASE PRESENTATION

A Japanese male developed mild cognitive impairment, dysarthria, deafness, pyramidal signs and cerebellar ataxia at age 50. Although he had difficulty speaking, he was able to continue his work as an operator of a fire station without any trouble. At age 54, he was examined by an orthopedist because of lower back pain. According to the patient's medical records, MRI had shown mild degeneration of a lumbar disc. Around the same time, there were several claims about his speech that were difficult to understand over the phone. A neurological examination at age 54 revealed mild cognitive impairment (total intelligence quotient, 65; verbal intelligence quotient, 67; performance intelligence quotient, 70; Hasegawa dementia scale-revised, 25 out of 30). The patient exhibited severe dysarthria, moderate hearing loss, dysdiadochokinesis, dysmetria in the upper extremities, hyperreflexia in the upper and lower extremities and ataxic gait. Neither urinary incontinence nor anosmia was recorded. Laboratory tests showed a mild elevation of serum ferritin (256–512×; normal range, 16–128×). An examination of the cerebrospinal fluid (CSF) revealed normal cell counts, total protein levels, and glucose levels in the absence of red blood cells. The level of iron was 16 μg/dl (normal range: 0.01–0.02 μg/dl), that of transferrin was 3.0 mg/dl (0.024–0.04 mg/dl) and that of ferritin was 189 ng/ml (normal range: less than 1 ng/ml). Electromyogram and nerve conduction tests were normal. Pure-tone audiometry results were

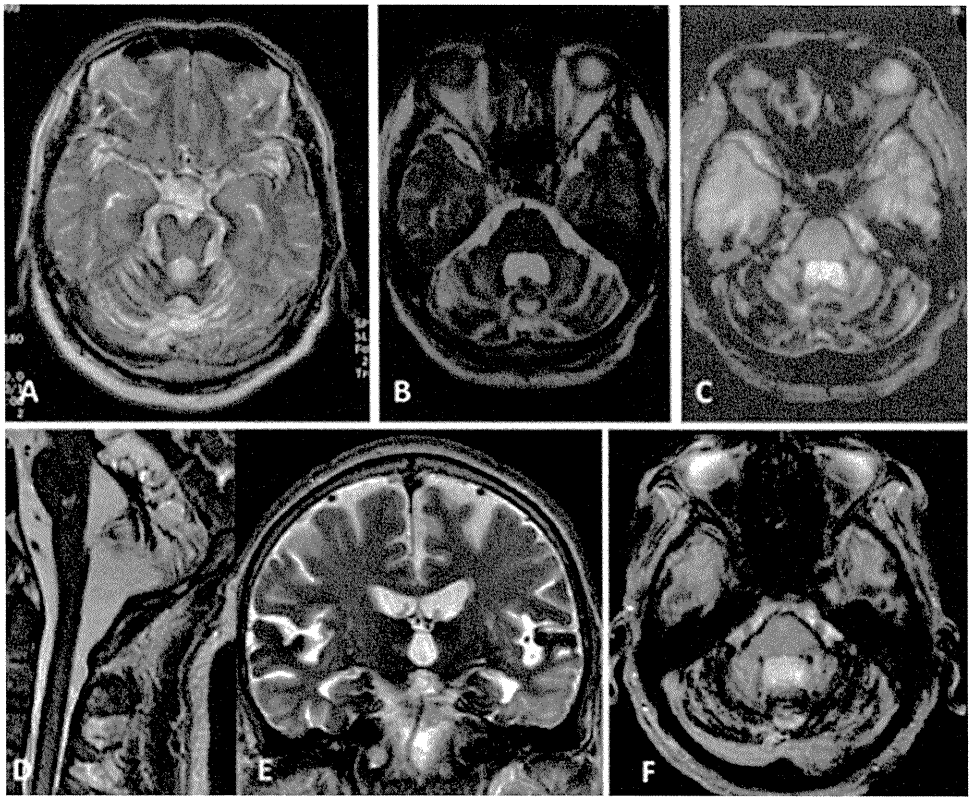

Figure 1 Brain MRI images of the patient described in this report. (A) T2-weighted image (T2WI; 1.5 T) at age 54. (B–F) T2WI (B, D, E) and T2*-weighted images (T2*WI) (C, F) obtained with a 3-T MRI scanner at ages 58 (B, C), 63 (D), 64 (E), and 66 (F). T2WI and T2*WI show hypointense rims surrounding the brainstem, cerebellum, and temporal lobes as well as the spinal cord. Severe atrophy of the cerebellum is also evident. Mild progressive atrophy of the cerebellum may have occurred over the course of the12-year period.

consistent with sensorineural deafness on both sides. An intravenous olfactory test was normal. Brain MRI showed diffuse cerebellar atrophy in T1-weighted images. MRI with T2- and T2*-weighted images showed hypointense rims surrounding the brainstem, cerebellum and cerebrum (figure 1). The patient was diagnosed as having superficial hemosiderosis without a definite causative disorder. His anamnesis revealed otitis media at age 12, appendicitis at age 17 and a motor vehicle accident at age 19. However, he had no history of surgery on the central nervous system.

TREATMENT

Although the patient was given taltirelin hydrate (a thyrotropin-releasing hormone analogue) for his cerebellar ataxia, his neurological condition showed no improvement.

OUTCOME AND FOLLOW-UP

At age 56, the patient started to use a cane, although his general neurological condition was stable. At age 60, decreased tendon reflexes were recorded in the extremities. At age 63, he was admitted to our hospital for respite care. A neurological examination showed no marked alterations in comparison to the test results at age 60. In addition, there were no obvious changes across repeated MRI exams at ages 54, 58, 62, 63 and 64 (figure 1). Repeated MRI images showed no subdural hematoma up to age 64.The MRI exam at age 63 revealed the presence of hemosiderin deposits around the spinal cord. After the patient was affected with community-acquired pneumonia at age 64, he developed disuse syndrome and needed to use a wheelchair. His condition deteriorated; ultimately, he became bedridden and remained so until his death at age 66.

Neuropathology

Gross neuropathology

The brain weighed 1090 g. There was diffuse and moderate atrophy of the cerebrum, as well as severe atrophy of the brainstem and cerebellum. The surface of the brain exhibited a diffusely brownish discolouration that was particularly conspicuous at the basilar surface, brainstem and cerebellum. In particular, the anterior portion of the cerebellar vermis showed severe tissue degradation with brownish discolouration, suggesting hemosiderin deposition. The same discolouration was also observed at the olfactory, optic, oculomotor, trigeminal, facial and acoustic nerves. There were thin, brown neo-membranes inside the right dura mater. This finding is consistent with a chronic subdural hematoma. There was minimal atherosclerosis of the major cerebral arteries, and no anomalies were present. Neither aneurysms nor vascular malformations were present. In coronal slices, there was no parenchymal haemorrhage evident in the cerebrum or brainstem. The basilar surface of the cerebrum showed a brownish colour. There was a brown rim surrounding the brainstem and spinal cord. It was difficult to identify the upper surface of the cerebellar cortex because of severe deterioration of the parenchyma.

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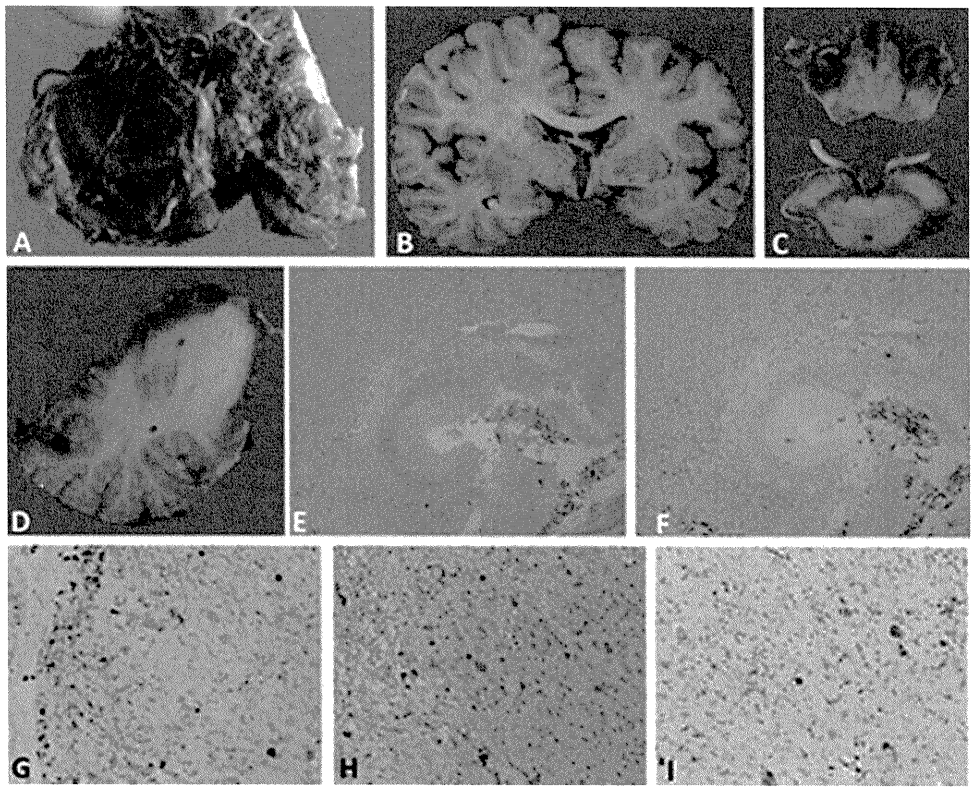

Figure 2 Neuropathology of hemosiderosis. (A–D) Gross neuropathology. (A, D) Severe degeneration and brownish discolouration, indicating hemosiderosis, were observed at the anterior part of the cerebellum. Part of the left cerebellar hemisphere was removed and stored at −80°C for future analysis. (B, C) Hemosiderosis was present at the basal part of the cerebrum as well as the surface of the brainstem and cranial nerve roots. (E, F) Microscopic neuropathology. Severe necrotic lesions and hemosiderin deposits were observed in the cerebellar cortex (E, H&E stain; F, Berlin blue stain). (G) Severe iron deposits contained in macrophages were detected in the parahippocampus. (H) Some free iron deposits were also observed. Some ovoid bodies were present, which were also immunopositive for ferritin. (G, Berlin blue stain; H, ferritin immunohistochemistry; I, CD68 (for macrophages) immunohistochemistry) (E and F, 10× objective; G–I, 40× objective).

Microscopic neuropathology

Hemosiderosis

The most remarkable finding was the extensive deposition of hemosiderins (figure 2), which are brown pigments in macrophages easily identified by the use of Berlin blue stain. The hemosiderins were present in the subarachnoid space, subpial regions and parenchyma. In the cerebrum, they were more prominent at the basilar surface, including the basilar surfaces of the frontal and temporal cortices, where the hemosiderins were observed in the upper cortical layers. They were also conspicuous in the perivascular spaces of small parenchymal vessels. The upper cortical layers displayed vacuolar changes and gliosis.

Similar alterations were observed on the surface of the brainstem and spinal cord. In addition to hemosiderin deposition, the parenchymal tissue at the anterior part of the cerebellum was lost. Hemosiderin deposits and loss of myelinated fibres were evident in the cranial nerve roots.

Although most hemosiderins were observed in macrophages, some were also detected in glia and in the cerebral parenchyma as free deposits. Hemosiderins were immunoreactive for polyclonal antibodies raised against ferritin. In the cerebral parenchyma, there were moderate numbers of pale oval bodies (ovoid bodies). These bodies were also positive for the Berlin blue stain and ferritin immunohistochemistry. In some instances, the glia were positive for Berlin blue, and ferritin immunohistochemistry revealed immunopositive deposits in the cell somata and dendrites of glial cells. There was no strong evidence of an active subarachnoid haemorrhage because only a few red cells were observed in the subarachnoid space.

There was mild thickening of the vessel walls of the basal ganglia. A monoclonal antibody raised against the synthetic peptide Aβ11-28 (IBL, Maebashi Japan) rarely stained amyloid deposits in the parenchymal and leptomeningeal vessel walls at the level of the temporal lobe. No amyloid angiopathy was detected in other regions such as the cerebellum, brainstem and spinal cord. In addition, haemorrhagic changes were absent in the brain and spinal cord. Aβ11-28–immunopositive diffuse plaques were sparse in the neocortex. A chronic subdural hematoma was present in the convexity of the dura mater. Histological examinations revealed thin membranes with hemosiderin deposits.

Tauopathy

Abundant τ deposits were notable in the present case. Neurofibrillar tangles (NFTs) and neuropil threads (NTs) were observed in the hippocampus, subiculum and entorhinal regions when the tissue was stained with a monoclonal antibody raised against phosphorylated tau (AT8, Innogenetics, Temse, Belgium). The distribution of NFTs and NTs was consistent with stage III of Braak's classification.[16] In addition, AT8-immunopositive pretangles and NFTs were observed in the cerebellar dentate nucleus and

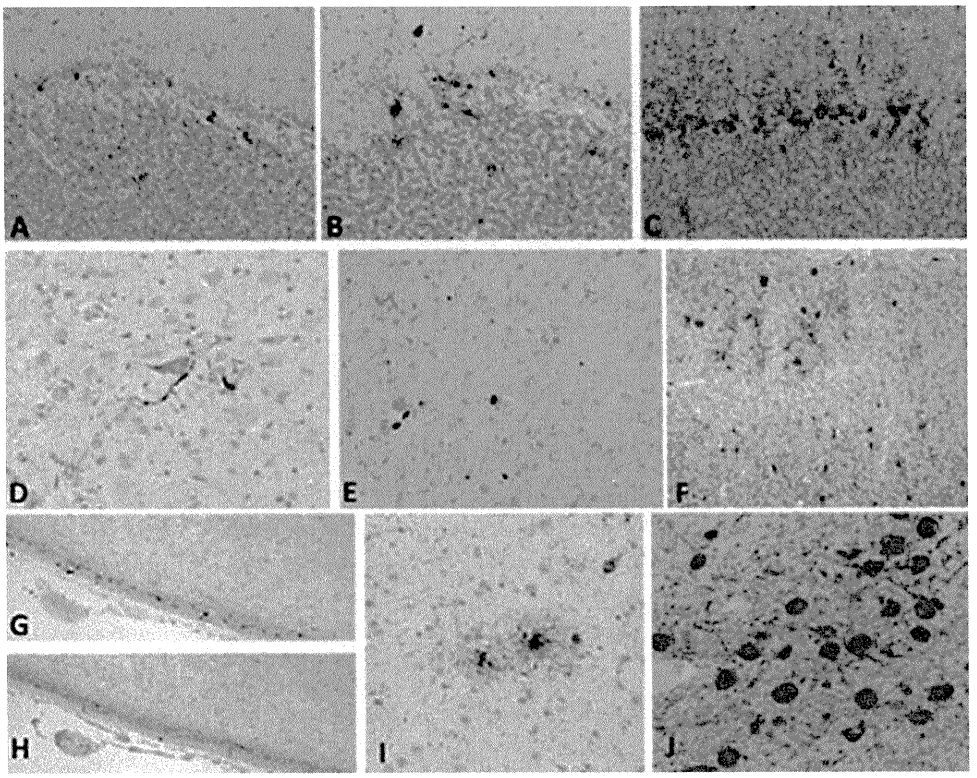

Figure 3 Microscopic neuropathology associated with tauopathy. (A–C) cerebellar cortex; (E and F) visual cortex; (G and H) parahippocampus. In areas with abundant iron deposits(A, G, E), numerous τ-immunopositive deposits were observed in the glial cells of adjacent sections (B, F, H). (D) τ-immunopositive neurons were present in the dentate nucleus of the cerebellum. (I) τ-immunopositive astrocytes were detected in the caudate nucleus. (J) Numerous τ-immunopositive neurofibrillary tangles were present in the locus coeruleus. (A and G, Berlin blue stain; B–E and H–J, immunohistochemistry using antibody (AT8) raised against phosphorylated tau protein.) (A–F, I, and J, 40× objective; G and H, 20× objective).

locus coeruleus, respectively (figure 3). In the neurons of the locus coeruleus, NFTs and Lewy body were occasionally co-localised in the same neurons (figure 4). It is notable that τ-immunopositive deposits were observed in astrocytes and neurites (figure 3). These deposits were apparently associated with areas in the parahippocampus and occipital cortex in which hemosiderin deposits were abundant (figure 3). In the cerebellar cortex, τ-immunopositive deposits were observed in Bergmann glia (figure 3). τ-immunopositive neurites were also observed in the cranial nerve roots.

Synucleinopathy

A monoclonal antibody raised against phosphorylated α-synuclein (pSyn#64, WAKO, Japan) revealed Lewy neurites in the olfactory bulb, amygdala, parahippocampus, substantia innominata, locus coeruleus and substantia nigra (figure 4). Lewy bodies were detected in the locus coeruleus and substantia innominata. The Lewy bodies and neurites corresponded to Braak stages 2–3[17] and stage I (incidental Lewy body disease) of our brain bank method.[18] No α-synuclein-immunopositive deposits were observed in the cerebral neocortex.

DISCUSSION

According to a recent review article, most individuals with superficial siderosis show cerebellar ataxia (81%), sensorineural deafness (81%) and myelopathy (53%).[1] The clinical presentation of our patient was clearly consistent with that of superficial siderosis. We believe that his cognitive dysfunction was directly associated with superficial siderosis and not with other neurological disorders. As mentioned below, there was no advanced Alzheimer's disease, dementia with Lewy bodies, or cerebrovascular disorders. Although superficial siderosis is considered a progressive neurodegenerative disorder, the progression of clinical and neuroradiological conditions during a 12-year assessment period was very slow in the present patient.

The pathomechanism of superficial siderosis remains controversial. Generally, continuous or recurrent bleeding in the subarachnoid space is thought to be associated with siderosis in the central nervous system. In fact, some cases of superficial siderosis may be associated with brain tumours, dural tears, trauma, or brachial plexus trauma.[1 19–23] However, no definitive lesion is identified in 50% of the cases. Although we carefully carried out an autopsy, we could not identify the occult bleeding site in the central nervous system. At the time of autopsy, a chronic subdural hematoma was observed in the convexity of the dura mater. Subdural hematomas have been reported as a rare cause of superficial siderosis.[1 24] In the present case, the subdural hematoma was first recognised by MRI at age 66. That is, repeated MRI images showed no subdural hematoma up to age 64. We believe that the subdural hematoma developed in the end stage of the clinical course and was not related directly to the siderosis. In addition, the CSF analysis showed no red blood cells four years after onset (at age 54),

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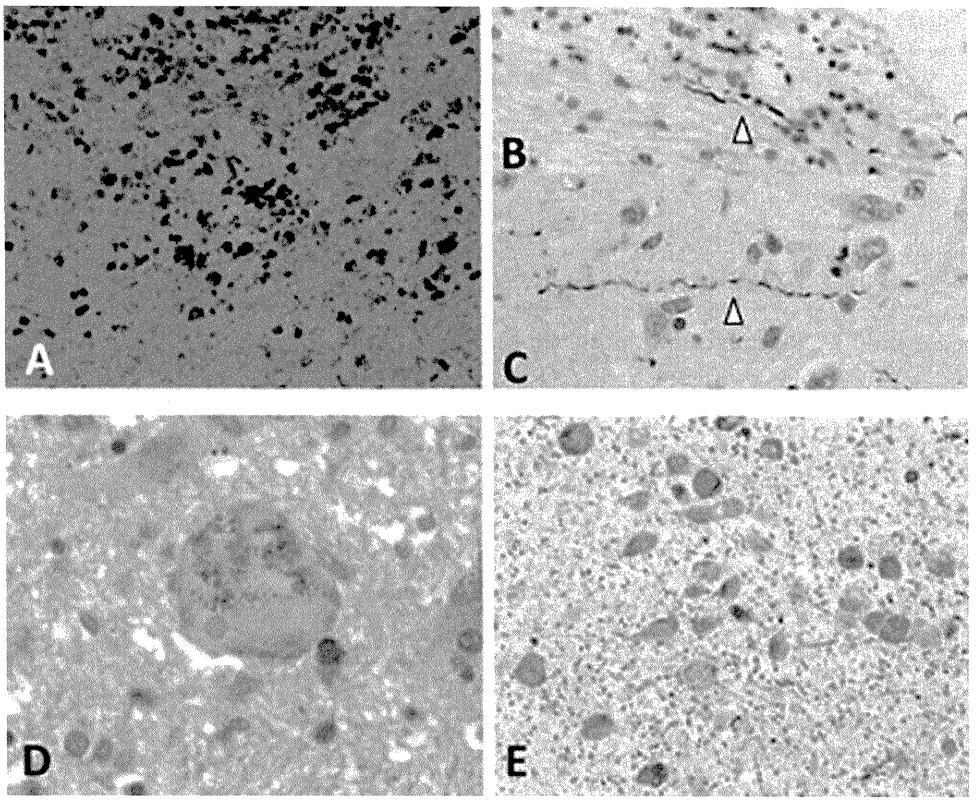

Figure 4 Microscopic neuropathology associated with α-synucleinopathy. (A) Large numbers of iron deposits were observed in the olfactory bulb. (B, C) α-synuclein-immunopositive Lewy neurites were detected in the olfactory bulb (B) and amygdala (C). (D) A Lewy body and neurofibrillar tangles are co-localised in a neuron of the locus coeruleus. (E) α-synuclein-immunopositive Lewy neurites and Lewy bodies are observed in the locus coeruleus. (A, Berlin blue stain; B, C and E immunohistochemistry using antibody (pSyn#64) raised against α-synuclein; (D) H&E stain.) (A, 20× objective; B–D, 60× objective; E, 40× objective).

although the iron and ferritin levels increased. Therefore, continuous subarachnoid bleeding did not cause the superficial siderosis in the present patient.

The basic neuropathologic findings were consistent with the well-documented pathology of superficial siderosis.[6 8 11] Hemosiderin deposits undoubtedly contribute to the parenchymal degeneration of the central nervous system. However, it remains unclear why specific anatomical regions are more susceptible than others. Koeppen *et al* concluded that the susceptibility of the cerebellar cortex is likely due to the abundance of microglia and the presence of Bergmann glia that serve as conduits for heme.[11] Revesz *et al* postulated that cerebellar pathology is associated with the dense capillary network of the cerebellum as well as the vulnerability of Purkinje and granule cells.[10] Consistent with this, the anterior part of the cerebellar vermis and hemisphere showed severe degeneration and hemosiderin deposition in our case. However, it is still difficult to explain why the pathologic changes were also severe at the basal surface of the cerebrum, brainstem and spinal cord. A compartmentalisation of CSF flow might be important for understanding how hemosiderin preferentially accumulates in specific anatomical regions.[2]

τ protein is a major component of NFTs and glial tangles in many neurodegenerative disorders. In superficial siderosis, NFTs have only been reported in the locus coeruleus.[6] However, extensive τ deposits have never been reported in cases of superficial siderosis.[11 25 26] In addition to some NFTs in the hippocampus and parahippocampus, we found abundant glial τ accumulation in the cerebellum and in nerve roots with severe hemosiderin deposits. Importantly, two papers have mentioned increased levels of τ and phosphorylated τ protein in the CSF of individuals with superficial siderosis.[27 28] An increased level of τ protein in CSF is an important biomarker for the clinical diagnosis of Alzheimer's disease because it suggests an abnormal accumulation of τ protein in the brain parenchyma.[29] Although it was impossible to evaluate the τ levels in CSF for this patient, the pathologic findings of this and other studies[27 28] strongly suggest that τ accumulation in neurons and glia may be a common pathologic alteration of superficial siderosis.

The association between synucleinopathy and siderosis in the present case remains unclear. Like τ aggregation, α-synuclein aggregation might be induced under conditions of oxidative stress related to iron.[13 30] In the present case, we believe that the α-synuclein accumulation in the olfactory bulb was strongly associated with oxidative stress due to severe hemosiderosis in this region. Recent studies suggest that α-synuclein accumulation may propagate along neural connections from the peripheral to the central nervous system. The olfactory bulb is one of the first anatomical regions of α-synuclein accumulation.[31] It may take 10–15 years to reach Lewy body stages 2–3 based on Braak's hypothesis.[32] If the propagation hypothesis is correct, we can speculate that the condition in the patient described in the present report was reached after a comparable duration following initial accumulation of α-synuclein in the olfactory bulb. In

fact, the clinical course of the disease in this patient was 16 years from onset to death.

To summarise, we present the first case of superficial siderosis associated with tauopathy and synucleinopathy. On the basis of neuropathologic analyses, we suggest that oxidative stress induced by hemosiderosis may contribute to abnormal aggregation of τ and α-synuclein protein. Given that many physicians are now using MRI in their daily clinical practice, the likelihood of identifying superficial siderosis will increase. However, only a few autopsy cases have been analysed to date. Further analyses will be important to understand the pathomechanism of superficial siderosis.

Learning points

- Superficial siderosis is characterised clinically by sensorineural deafness, cerebellar ataxia and myelopathy.
- MRI readily identifies hemosiderosis deposits and may aid in the clinical diagnosis.
- Neuropathologic analyses showed severe degeneration of the cerebellum, brainstem and spinal cord, as well as the basal surface of the cerebrum.
- In addition to extensive hemosiderin deposition, tauopathy and synucleinopathy may be associated with the pathomechanism of the disease.

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Competing interests None.

Patient consent Obtained.

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Spinocerebellar ataxia type 2 is associated with Parkinsonism and Lewy body pathology

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Summary

Clinical phenotype of individuals with spinocerebellar ataxia 2 (SCA2) is characterised by cerebellar ataxia and cognitive impairment. Although L-dopa-responsive Parkinsonism is considered as a rare clinical presentation in SCA2, it has been brought to the attention of many neurologists in several studies. The authors report an autopsy case of SCA2 with Parkinsonism from a Japanese family using archival materials of our Brain Bank to describe unique neuropathologic findings. The individual clinically showed Parkinsonism as a predominant phenotype instead of cerebellar ataxia. Besides the classic SCA2 neuropathologic alterations, Lewy bodies and Lewy neurites were present in the brainstem nuclei. Genetic analysis revealed shorter abnormal expansion of CAG repeats (less than 39). In contrast, the authors could not find α-synuclein pathology in two SCA2 cases without Parkinsonism. The present case will provide a neuropathologic evidence of correlation between α-synucleinopathy and Parkinsonism of SCA2 as well as shed light on understanding the pathomechanism of Parkinsonism in SCA2.

BACKGROUND

Spinocerebellar ataxia 2 (SCA2) (OMIM #183090) is an autosomal dominant cerebellar degeneration associated with expanded CAG trinucleotide repeat in *ATXN2* gene (MIM ID *601517).[1] Neuropathologic phenotype of SCA2 is characterised by degeneration of the olivopontocerebellar system as well as substantia nigra (SN), striatum and globus pallidus.[2] In addition, an abnormal aggregation of poly-glutamine is observed as 1C2 (antibody specific for poly-glutamine) immunoreactive intranuclear inclusions. Although common clinical presentations of SCA2 are cerebellar ataxia, nystagmus, slow eye movement, hyporeflexia and cognitive dysfunction,[3] recent studies have pointed out that L-dopa-responsive Parkinsonism is core clinical symptom in a subset of individuals with SCA2.[4–8] According to epidemiological and genetic studies of patients with autosomal dominant parkinsonism, an up to 10% of them showed abnormal CAG expansion of *ATXN2* gene.[5 7 9] However, the neuropathologic substrate of SCA2 with parkinsonism remains unresolved. Because the neuronal loss of the SN is commonly observed in SCA2, this kind of classic pathologic change does not sufficiently explain the cause of L-dopa responsive parkinsonism of SCA2. In this paper, we provide new insight and evidence of pathologic basis of L-dopa responsive parkinsonism of SCA2.

CASE PRESENTATION

The individual, that of a 40-year-old man, developed unstable gait and difficulty on driving a car at age 40. However, he was not seen by neurologist for approximately 20 years. Neurological examination at age 63 showed dysarthria, dysphasia, directional nystagmus as well as dysdiadochokinesis, dysmetria and truncal ataxia. Tendon reflexes were brisk in the all extremities with Babinski signs. As the most remarkable symptoms, he had severe rigidity and bradykinesia as well as stooped posture and freezing on gait. No tremor, either resting or postural, was observed. At age 66, there was severe rigidity in the neck as well as upper and lower extremities. He was able to stand and walk with full assistance. However, his gait was affected by severe bradykinesia and frozen gait. No involuntary movement was observed during his clinical course. He died of aspiration pneumonia at age 67. Anti-Parkinsonian medication was not prescribed. Because there were no neuroimages of the patient, brain MRI (figure 1) was carried out immediately after the patient's death. It showed atrophy of the cerebellum and pons with hot-cross bun sign.[10] The genetic study was permitted by the family only for the genes associated with SCA genes. Using frozen brain tissue, genetic analysis showed that he had an expanded allele with 22/37 in *ATXN2* gene.

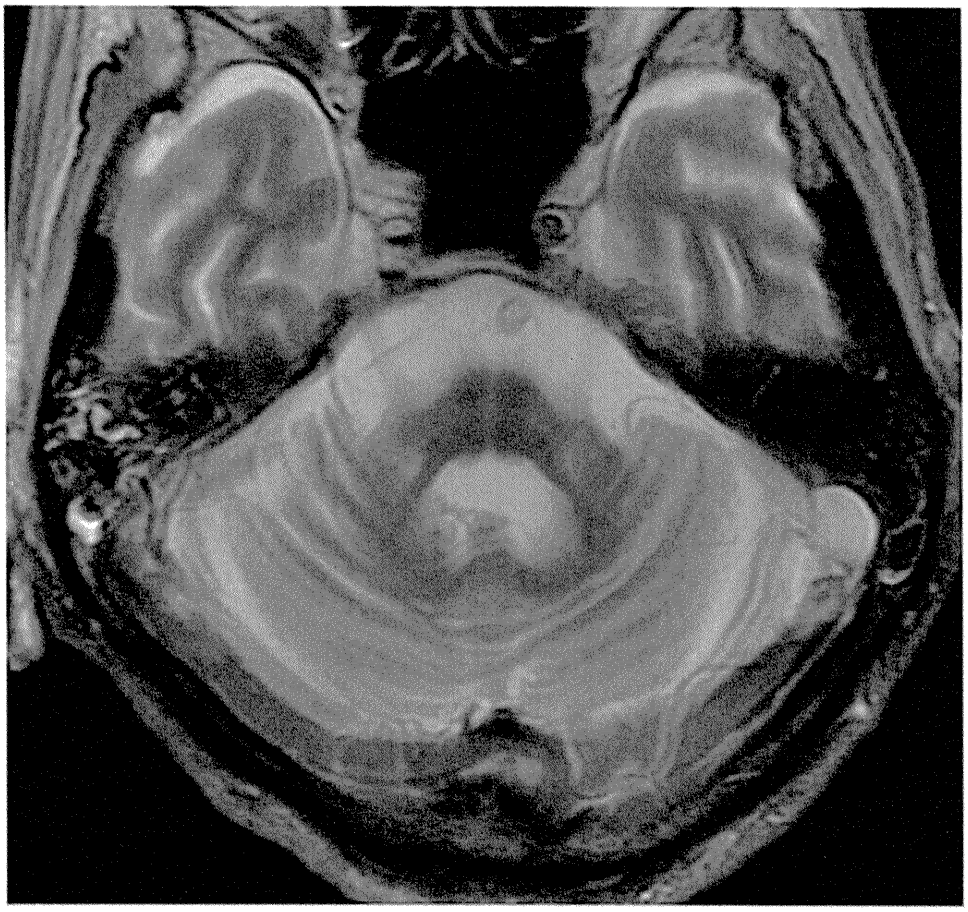

Figure 1 Brain MRI (T2 weighted image) shows severe atrophy of the cerebellum and pons with hot-cross bun sign.

His mother, brother and cousin had similar clinical presentation. His second daughter developed gait disturbance at age 18, followed by cognitive impairment, ataxia and choreic movement.

Neuropathology

Gross pathology

The weight of the fresh brain was 1220 g. The atrophy was severe in the basis pontis and middle cerebellar peduncle as well as moderate in the cerebellum. The SN and locus coeruleus appeared to have lost its pigment (figure 2A).

Lewy body pathology

On microscopic examination, the SN and locus coeruleus showed severe loss of pigment and neuronal loss (figure 2A). The most striking pathologic finding was presence of α-synuclein immunoreactive Lewy bodies and neuritis in the several anatomical regions (figure 2C–E). Lewy bodies and neuritis were present in the basal nucleus of Meynert, hypothalamus, amygdala, SN, locus coeruleus and dorsal nucleus of vagus. However, neither Lewy bodies nor Lewy neurites were observed in the transentorhinal, cingulate, frontal, temporal and parietal cortex. The distribution of α-synuclein immunoreactive Lewy body pathology was consistent with stage 3 (case 2) according to Braak's staging methodology.[11]

SCA2 pathology

In the cerebellum, there was moderate neuronal loss of the Purkinje cells. Mild neuronal loss and gliosis were present in the molecular and granular cell layers. Dentate nucleus was relatively well preserved. The interlobular white matter showed severe loss of myelinated fibres. In the brainstem, there was moderate to severe neuronal loss in the basis pontis (figure 2B) and inferior olivary nucleus. The 1C2 antibody depicted intranuclear immunopositive deposits in the pontine nucleus.

In order to confirm our results, we analysed two genetically confirmed SCA2 cases without Parkinsonism using α-synuclein immunohistochemistry. Both cases showed age at onset 20 and 29 years old and died at age 50 and 55, respectively. The former had an expanded allele with 22/43 and the latter had 22/42 in *ATXN2* gene. Although there is neuronal loss in the SN in both cases, no α-synuclein immunopositive deposits were observed.

DISCUSSION

Our results give a new perspective on pathogenesis of SCA2 with Parkinsonism. Clinical phenotype of individuals with SCA2 is usually cerebellar ataxia, dysarthria, slow saccadic eye movement, hyporeflexia and cognitive impairment.[12 13] Although parkinsonism is considered as a variant clinical presentation in SCA2,[14 15] it has been brought to the attention of neurologist in several studies. In addition, L-dopa may be effective medication to improve their Parkinsonism.[4 16 17]

Because neuropathologic studies always show severe neuronal loss of the SN regardless of symptoms,[2 13] the degeneration of SN might not be a simple cause

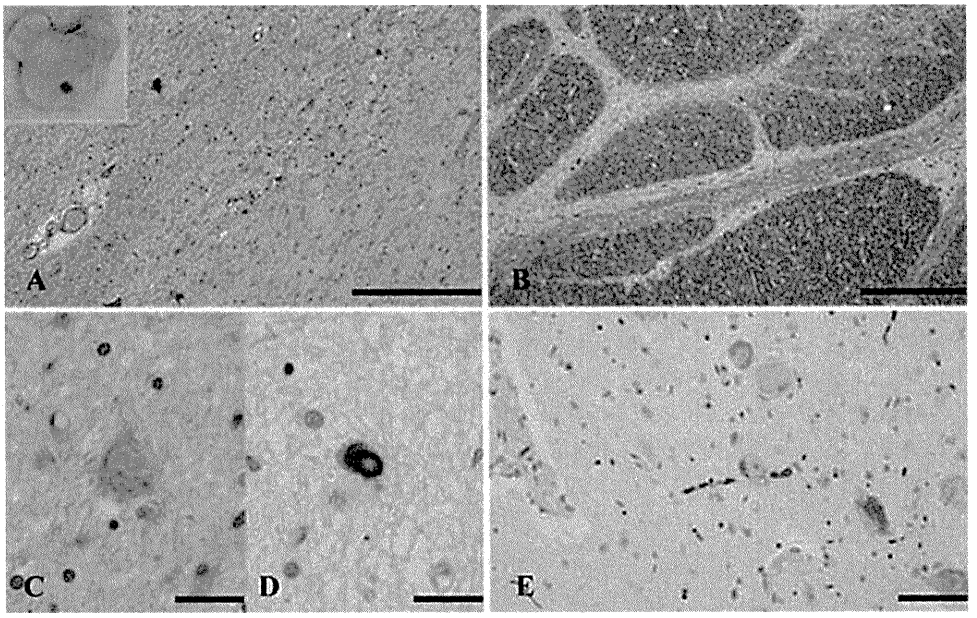

Figure 2 Neuropathologic results. Sections of the substantia nigra (A, C, D), basis pontis (B) and locus coeruleus (E). (A) Severe neuronal loss is evident in the substantia nigra. Note: The inset shows severe depigmentation at the level of the substantia nigra. (B) A photomicrograph shows severe loss of neurons and transverse fibres at the level of basis pontis. (C, D) Lewy bodies are seen in a remaining neuron. Lewy body is immunopositive using antibody raised against α-synuclein. (E) A-synuclein immunopositive Lewy neurites are seen. H&E stain (A, C), Klüver-Barrera stain (B), immunohistochemistry using monoclonal antibody specific for α-synuclein phosphorylated at Ser129 (D, E). Scale bars: A=200 μm, B=500 μm, C, D, E=25 μm.

of Parkinsonism in SCA2. In the present case, it is still problematic whether or not the distribution of LBs/LNs is enough to cause Parkinsonism. In addition, we have to leave open the possibility that the α-synucleinopathy (Lewy body pathology) of the present cases is associated with ageing instead of SCA2.[18] However, we reported another case with SCA2 in association with Parkinsonism and Lewy pathology from an unrelated family in Japanese neurology journal.[19] Briefly, the individual was diagnosed as having Parkinson's disease in the sixth decade of life. He was started on L-dopa therapy and showed mild improvement of his neurological conditions. Thereafter, genetic analysis revealed that he had an expanded allele with 22/38 in *ATXN2* gene. Neuropathologic examination showed the presence of LBs/LNs in the brainstem nuclei as well as the olivopontocerebellar degeneration.

From the genetic study point of view, the frequency of CAG expansion of ATXN2 ranges from 0% to 10% in families of autosomal dominant Parkinsonism.[5 7 9] In particular, Parkinsonism of SCA2 is strongly associated with a shorter abnormal expansion of CAG repeats (less than 39)[5]. At present, a direct interaction between α-synuclein accumulation and a shorter expansion of CAG repeats on *ATXN2* is undetermined. It might be interesting that both the present case and reported one had shorter CAG repeats expansion. In addition, we could not find LBs/LNs in genetically confirmed two SCA2 cases without Parkinsonism (longer expanded allele with 22/42 and 22/43 in ATXN2).

Based on our results, we suggest that the neuropathologic substrate of SCA2 with Parkinsonism is associated with Lewy related α-synuclein pathology in the brainstem. Further analysis may warrant genetic and pathologic correlation of SCA2 with Parkinsonism.

Learning points

- L-dopa-responsive Parkinsonism is considered as a rare but important clinical presentation in SCA2.
- We presented an individual of SCA2 with clinically prominent Parkinsonism instead of cerebellar ataxia.
- Neuropathologic findings revealed the presence of Lewy bodies and neurites in the various anatomical regions.
- The present case provides a neuropathologic evidence of correlation between -synucleinopathy (Lewy body pathology) and Parkinsonism of SCA2 as well as shed light on understanding the pathomechanism of Parkinsonism in SCA2.

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Competing interests None.

Patient consent Obtained.

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〈原　著〉

悪性腫瘍を合併した高齢者脳梗塞症例の特徴

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石原佳代子　末田　芳雅　中村　毅　山脇　健盛　松本　昌泰

要　約　目的：悪性腫瘍を合併した急性期脳梗塞症例を悪性腫瘍との関連性が高い脳梗塞と悪性腫瘍との関連性が低い脳梗塞に分類し，悪性腫瘍との関連性が高い脳梗塞の特徴を明らかとする．**方法**：観察期間は2006年1月～2009年3月．対象は急性期脳梗塞で当施設にて入院加療し，過去に悪性腫瘍と診断された症例と脳梗塞加療中または脳梗塞診断後1年以内に悪性腫瘍を新たに診断しえた症例とした．ただし脳梗塞発症から5年以上前に悪性腫瘍の治療がなされ，脳梗塞発症前5年以内に悪性腫瘍の再発，転移，治療歴を有さない症例は除外した．選択基準に合致した28例についてTOAST分類に準じて脳梗塞病型分類を行い，さらに悪性腫瘍との関連性が高い脳梗塞と悪性腫瘍との関連性が低い脳梗塞に分類した．**結果**：年齢中央値74歳（56～91歳），男性19名（68%）．脳梗塞病型はSmall-vessel occlusion 3例（11%），Large-artery atherosclerosis 5例（18%），Cardioembolism 8例（28%），Stroke of other determined etiology 5例（18%），Stroke of undetermined etiology 7例（25%）であった．悪性腫瘍との関連性が高い脳梗塞は8例（29%）に認められ，悪性腫瘍の進展度が高い症例に多いことが示唆された．悪性腫瘍との関連性が高い脳梗塞では悪性腫瘍との関連性が低い脳梗塞に比べD-dimer値は高い傾向を示した．**結論**：悪性腫瘍との関連性が高い脳梗塞は75歳未満の群で進行癌の症例に多く，D-dimer値はこの分類において有用である可能性が示唆された．

Key words：悪性腫瘍，脳梗塞，TOAST分類，D-dimer

（日老医誌　2011；48：57-62）

緒　言

悪性腫瘍と血栓塞栓症の関連はTrousseauら[1]によりはじめて報告された．中枢神経腫瘍を除く悪性腫瘍患者3,426例の剖検例によると，担癌患者における中枢神経合併症として脳血管障害は約15%を占め，転移性脳腫瘍に次いで2番目に多い[2]．また担癌患者における脳梗塞は血液凝固異常を呈している例が多く，特に非感染性血栓性心内膜炎（nonbacterial thrombotic endocarditis；以下NBTEと略す）は悪性腫瘍に合併した脳梗塞の原因として27%を占め最も多いとされている[2]．しかし実地臨床においては担癌高齢者の増加に伴い，悪性腫瘍に起因する血液凝固異常のみならず加齢や生活習慣病に伴う動脈硬化性疾患を合併した症例を多く経験し，担癌高齢者における脳梗塞の病因は一層複雑化している．近年，画像診断技術の進歩により低侵襲的な検査で脳梗塞の病因精査が可能となったが，担癌患者における脳梗塞について悪性腫瘍との関連性を詳細に検討した報告はみられない．

また担癌脳梗塞症例における凝血学的異常を検討した報告が近年みられる．渡邉ら[3]の検討によると担癌脳梗塞症例においてD-dimer値が明らかな高値を示し，血液凝固異常が脳梗塞発症の一因になっている可能性が示唆された．

今回，我々は当院で脳梗塞の急性期治療を行った症例のうち悪性腫瘍を合併した症例を，その脳梗塞病型により悪性腫瘍との因果関係を検討し，悪性腫瘍との関連性が高い脳梗塞と悪性腫瘍との関連性が低い脳梗塞とに分類した．そして，悪性腫瘍に起因した脳梗塞の特徴を検討することを目的とした．

方　法

観察期間は2006年1月から2009年3月，対象は急性期脳梗塞で当施設にて入院加療し，過去に悪性腫瘍と診断された症例と脳梗塞加療中または脳梗塞診断後1年以内に悪性腫瘍を新たに診断しえた連続30例を抽出した．

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表1　患者背景

		全体 (n=28)	75歳未満 (n=15)	75歳以上 (n=13)
年齢		中央値74歳 (56～91歳)		
性別	男/女	19/9	11/4	8/5
心血管危険因子	高血圧	15	6	9
	脂質異常症	8	3	5
	糖尿病	7	4	3
	心房細動	6	4	2

ただし脳梗塞発症から5年以上前に悪性腫瘍の治療がなされ，その後脳梗塞発症前5年以内に悪性腫瘍の再発，転移，治療歴を有さない2例を除外し，最終的に28例で検討を行った．

悪性腫瘍の臨床病期は，既知の悪性腫瘍は脳梗塞発症時，悪性腫瘍切除後のものは切除時，脳梗塞発症後1年以内の新規発症の悪性腫瘍は診断時の評価を用いた．複数癌を有する症例では脳梗塞発症時点で最も活動性が高い悪性腫瘍，また2つ以上の原発悪性腫瘍を5年以内に切除し，いずれの悪性腫瘍も再発が確認されていない症例は脳梗塞発症からより近い時期で切除された悪性腫瘍を選択した．

脳梗塞発症の危険因子である高血圧，糖尿病，脂質異常症，心房細動の診断はそれぞれの診断基準を満たした症例，または脳梗塞発症時に各疾患に対する治療薬を内服中の症例とした．

脳梗塞病型は頭部CT/MRI検査，頸動脈エコー，経胸壁心エコー，経食道心エコー，心電図の結果よりTrial of Org 10172 in Acute Stroke Treatment（以下TOASTと略す）分類[4]に準じて行った．今回，悪性腫瘍との関連性が高い脳梗塞とは以下の①～②のいずれかを満たす症例とした．

① Cardioembolismのうち，心エコー検査で僧帽弁または大動脈弁に疣贅を認め，臨床症状および検査所見から感染性心内膜炎が否定的な症例．

② Stroke of undetermined etiologyのうち，各検査により精査を行っても悪性腫瘍以外に脳梗塞の原因を指摘しえなかった症例．

従って心原性脳塞栓症の原因となる明らかな心疾患を有する症例，脳動脈解離や血管炎による脳梗塞症例は悪性腫瘍との関連性が低い脳梗塞とした．

悪性腫瘍との関連性が高い脳梗塞の血液凝固異常の特徴を検討するために，入院時血漿D-dimer値をラテックス凝集反応を用いて測定した（測定機器：シスメックス社XE7000，試薬：リアスオートDダイマーネオ）．

統計解析はJMP 8.0を用いた．連続変数は平均値±標準偏差または中央値（最小値～最大値）で表した．連続変数の有意差検定はStudent t 検定にて行った．分布の偏りに関してはWilcoxson順位和検定にて行った．統計学的有意差は$p<0.05$にて判断した．

結　果

患者背景を表1に示す．年齢の中央値は74歳(56～91歳)，男性19例，女性9例であった．心血管危険因子の有病率は高血圧15例（54%），脂質異常症8例（29%），糖尿病7例（25%），心房細動6例（21%）であった．頭部MRIは27例（96%），経胸壁心エコーは23例（82%），経食道心エコーは12例（43%）に実施した．

悪性腫瘍の診断から脳梗塞発症までの平均期間は16.6±21.9カ月であった．悪性腫瘍の内訳は肺癌・大腸癌がそれぞれ4例（14%）と最多であった（表2）．悪性腫瘍の組織型は腺癌が23例（82%）を占め，臨床病期はStage IVが14例（50%）であった（表3）．患者背景について75歳以上と75歳未満の群で比較を行ったところ，75歳未満の群で悪性腫瘍の臨床病期Stage IVの占める割合が75歳以上の群に比べ多い傾向が示された（$p=0.06$，表3）．

脳梗塞病型分類の内訳はSmall-vessel occlusion 3例（11%），Large-artery atherosclerosis 5例(18%)，Cardioembolism 8例(28%)，Stroke of other determined etiology 5例（18%），Stroke of undetermined etiology 7例（25%）であった（表4）．

本検討にて分類した悪性腫瘍との関連性が高い脳梗塞に合致する症例は28例中8例（29%）であった．Cardioembolismのうち，心エコー検査で僧帽弁または大動脈弁に疣贅を認め，感染性心内膜炎が否定的な症例は2例，Stroke of undetermined etiologyのうち，精査しても脳梗塞の原因を指摘しえなかった症例は6例であった．悪性腫瘍との関連性が高い脳梗塞は75歳未満の症例（15例）のうち5例，75歳以上の症例（13例）のうち3例

表2　脳梗塞合併悪性腫瘍の内訳

	全体 (n＝28)	75歳未満 (n＝15)	75歳以上 (n＝13)
肺癌	4	2	2
大腸癌	4	0	4*
胃癌	3	1	2
肝臓癌	3	3**	0
胆嚢癌	3	2	1
膵臓癌	3	2	1
乳癌	2	1	1
食道癌	1	1	0
腎臓癌	1	1	0
膀胱癌	1	1	0
成人T細胞リンパ腫	1	1	0
咽頭癌	1	0	1
前立腺癌	1	0	1

*大腸癌症例のうち1例は脳梗塞発症2年前に胃癌を内視鏡的粘膜切除術にて切除し，その後胃癌の再発は確認されていない．

**肝臓癌症例のうち1例は脳梗塞発症1年前に食道癌を内視鏡的粘膜切除術にて切除し，その後食道癌の再発は確認されていない．

表3　悪性腫瘍の組織型と臨床病期

		全体 (n＝28)	75歳未満 (n＝15)	75歳以上 (n＝13)
組織型	腺癌	23	12	11
	非腺癌	5	3	2
臨床病期	Stage I	8	2	6
	Stage II	1	0	1
	Stage III	4	2	2
	Stage IV	14	10	4
	不明・分類不能	1	1	0

であり，高齢者における明らかな分布の差異は認めなかった（p＝0.69）．

さらに悪性腫瘍の臨床病期と，担癌と脳梗塞の因果関係について検討を行った．この結果，悪性腫瘍に起因した脳梗塞には悪性腫瘍の臨床病期Stage IVの症例が多く，悪性腫瘍の進展度が高いことが示唆された（p＝0.02，図1）．

入院時血漿D-dimerは25例（89%）で測定した．異常高値（＞1 μg/m l）を示した症例は19例（76%）であった．悪性腫瘍との関連性が高い脳梗塞症例にてD-dimer値は悪性腫瘍との関連性が低い脳梗塞症例に比して高い傾向を示した（p＝0.13，図2）．悪性腫瘍の臨床病期Stage IV群とStage I～III群でD-dimer値を比較したところStage IV群のD-dimer値は明らかに高値であった（Stage I～III：中央値 1.2 μg/m l（0.3～29.0），Stage IV：中央値 9.9 μg/m l（0.4～81.5）p＝0.01）．さらに悪性腫瘍との関連性が低い脳梗塞に限った検討においてもStage IV群のD-dimerは高値を示した（Stage I～III：中央値 1.15 μg/m l（0.3～29.0），Stage IV：中央値 7.1 μg/m l（1.9～81.5）p＝0.02）．

考　察

今回，我々は当院で脳梗塞の急性期治療を行った症例のうち悪性腫瘍を合併していた症例について，その病因を精査し，悪性腫瘍との関連性が高い脳梗塞の分布と特徴を検討した．その結果，悪性腫瘍との関連性が高い脳梗塞は28例中8例（29%）に認められた．また悪性腫瘍との関連性が高い脳梗塞には悪性腫瘍の進展度が高い

表4　担癌脳梗塞症例における脳梗塞病型についての本検討結果ならびに既報との比較

		本検討	Cestari et al (2004)[9]	Zhang et al (2006)[10]	Oberndorfer et al (2009)[11]	Seon et al (2010)[6]
TOAST 分類	Small-vessel occlusion（%）	11	12	19.6	20	10.6
	Large-artery atherosclerosis (%)	18	10	21.4	41	24.2
	Cardioembolism（%）	28	15	26.8	18	14.3
	Other determined etiology（%）	18	39	10.7	21	1.2
	Undetermined etiology（%）	25	19	21.4		49.7
患者背景	症例数（n）	28	96	69	131	161
	年齢	74（56～91）	67（27～91）	77.1±7.1	68.1（28～96）	67.2（56～78）
	男性（%）	68	61	68	58	65
	心房細動（%）	21.4	5	27.5	27	12.4
検査実施率	経胸壁心エコー（%）	82	64	不明	57	100
	経食道心エコー（%）	43	0	不明	0	不明
	MRI/MRA（%）	96	24	不明	100	100

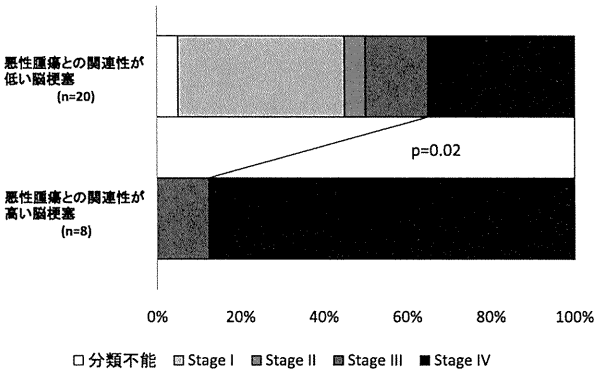

図1　悪性腫瘍との関連性が高い脳梗塞と臨床病期の関係
悪性腫瘍との関連性が高い脳梗塞は悪性腫瘍の臨床病期 Stage IV の症例に多い（p＝0.02）.

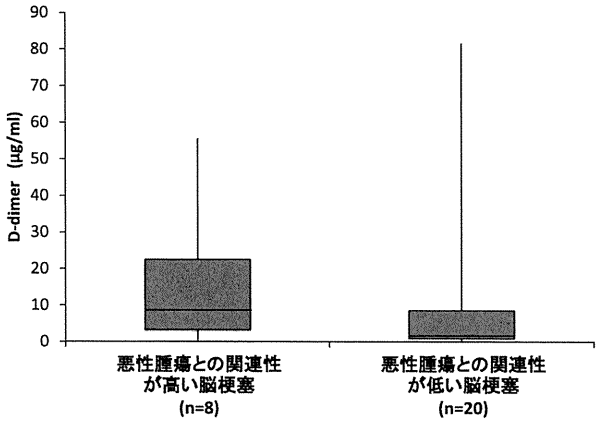

図2　悪性腫瘍との関連性が高い脳梗塞と D-dimer 値の関係
悪性腫瘍との関連性が高い脳梗塞症例にて D-dimer 値は悪性腫瘍との関連性が低い脳梗塞に比して高い傾向を示した（悪性腫瘍との関連性が高い脳梗塞：中央値 9.4 μg/ml（0.4～55.5），悪性腫瘍との関連性が低い脳梗塞：中央値 1.9 μg/ml（0.9～81.5），p＝0.13）

症例が多いことが示唆された．悪性腫瘍との関連性が高い脳梗塞では悪性腫瘍との関連性が低い脳梗塞に比べ D-dimer 値は高い傾向を示した．

近年の担癌患者の高齢化に伴い，担癌脳梗塞症例の中には悪性腫瘍が脳梗塞の原因となった症例だけではなく，動脈硬化性疾患や心房細動が主な原因となった脳梗塞も多数混在していることが考えられる．悪性腫瘍との関連性が高い脳梗塞の病態を解明し，その予防法の検討を行うためには，担癌脳梗塞症例の中で悪性腫瘍との関連性が高い脳梗塞と悪性腫瘍との関連性が低い脳梗塞とに分類する必要がある．この分類は上記のように容易ではないが，今回我々は過去の報告をもとに，脳梗塞病型より悪性腫瘍との因果関係を検討し，その分類を試みた．ただし本分類法は確立したものではなく，今後更なる検討を加える必要がある．

悪性腫瘍は凝固系を活性化し血栓塞栓症を発症すると考えられているが，その機序は複雑である．腫瘍細胞は凝固カスケードを活性化する組織因子，腫瘍プロコアグラント，第Ⅴ因子受容体などの細胞性プロコアグラントや線溶蛋白，線溶阻害因子およびそれらの受容体を発現するとともに，各種サイトカインや腫瘍抗原とその免疫複合体を介して血小板，単球，内皮細胞との細胞間相互作用を惹起してさらに凝固活性化を促進し，血栓形成をもたらすと考えられている[5]．D-dimer は架橋化フィブリンの分解産物であり，D-dimer 値の測定は血栓塞栓症の診断に有用である．担癌患者脳梗塞患者の D-dimer 値は非担癌脳梗塞患者に比べ高値を示すことが報告されている[3)6)]．本検討の結果，D-dimer 値は悪性腫瘍との関連性が高い脳梗塞で高い傾向が示された．ただし本分類

法では悪性腫瘍との関連性が高い脳梗塞にNBTEを合併した症例が含まれており，これによりD-dimer値が高値を示した可能性がある．そこで悪性腫瘍の臨床病期Stage IV群とStage I～III群でD-dimer値を比較したところ，悪性腫瘍の臨床病期Stage IVではD-dimer値が高値を示した．さらに悪性腫瘍との関連性が低い脳梗塞に限った検討においてもStage IV群のD-dimer値は高い結果が示された．このことより，悪性腫瘍との関連性が高い脳梗塞におけるD-dimer値の上昇はNBTE合併による上昇のみではなく，悪性腫瘍の臨床病期の悪化によってもD-dimer値が高値となり易血栓形成を示す可能性が示唆された．D-dimer値は動脈硬化性疾患や心房細動を原因とする脳梗塞でも上昇するが，悪性腫瘍との関連性が高い脳梗塞では更に高い傾向を示したことから，D-dimer値は悪性腫瘍との関連性が高い脳梗塞を鑑別する上で有用な指標となる可能性が示唆された．

担癌患者は経過中に約15%（3.8%～30.7%）の症例で脳血管障害を合併すると報告されている[2]．担癌患者を対象にした剖検例において脳梗塞の原因は血液凝固異常，特にNBTEが多いと報告されている[2]．担癌脳梗塞患者を対象に，TOAST分類を用いて脳梗塞病型分類を行った本検討の結果と共に過去の報告を表4にまとめた[6)～9)]．TOAST分類を用いた担癌患者の脳梗塞病型分布は各報告の間で異なる．本検討の結果は他の報告に比べCardioembolismが多い傾向が示された．その原因として対象患者の年齢が他の報告と比べ高いことが挙げられる．またTOAST分類上Cardioembolismに含まれるNBTEはその診断において，経食道心エコーが経胸壁心エコーよりも有用な検査法であることが知られている[10]．本検討において経食道心エコーは43%の症例で実施されており，他の報告と比較して高い施行率であったことから，本検討ではCardioembolismの診断率が高かったと考える．

今回，我々は脳梗塞の病型より悪性腫瘍との関連性が高い脳梗塞を分類し，その分布は75歳未満の群で進行癌の症例に多く，D-dimer値は悪性腫瘍との関連性が高い脳梗塞で有意に高いことを示した．しかし，悪性腫瘍との関連性が高い脳梗塞の分類方法については更なる検討が必要である．本検討の結果，この分類にD-dimerが有用である可能性が示唆された．しかしながら今回の分類法では心房細動を有する症例は悪性腫瘍との関連性が高い脳梗塞から除外されているが，心房細動合併例の中にも悪性腫瘍が原因で凝固系が活性化されている症例が含まれている可能性がある．悪性腫瘍との関連性が高い脳梗塞を正確に鑑別するには経食道心エコーや下肢静脈エコーなどの塞栓源検索精査を可能な限り全例で行い，D-dimer値に加えてトロンビン・アンチトロンビン複合体（thrombin-AT complex；TAT）などその他の凝固系に関わる分子マーカーについて検討した多施設前向き研究が必要である．

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Clinical characteristics of ischemic stroke in elderly patients with cancer

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Abstract

Aim: We classified acute ischemic stroke patients with cancer according to their causal relations, and attempted to evaluate the clinical characteristics of ischemic stroke associated with cancer.

Methods: This is a retrospective study of all acute ischemic stroke patients admitted to our hospital between January 2006 and March 2009. Among acute ischemic stroke patients, we identified 30 patients with a history of cancer, or who developed cancer within 1 year from their ischemic stroke onset. There were 2 patients excluded from our evaluation because they had undergone extirpation of their cancer more than 5 years before stroke onset, and no recurrence of cancer within 5 years of stroke onset was noted. Finally, 28 patients were enrolled and evaluated in this study. Ischemic stroke was classified based on the Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria. In addition, we classified the patients according to their causal relations of ischemic stroke with cancer.

Results: The median patient age was 74 years (range, 56 to 91 years); 68% of patients were men. Of these, 8 (29%) were classified into an ischemic stroke related to cancer group. There was a higher prevalence of ischemic stroke related to cancer in patients under 75 years old with clinical stage IV cancer ($p = 0.02$). D-dimer tended to be higher in those patients with ischemic stroke related to cancer in this study ($p = 0.13$).

Conclusion: Ischemic stroke related to cancer was found more frequently in patients under 75 years old with advanced cancer. Additionally, D-dimer tended to be higher in those patients with ischemic stroke related to cancer.

Key words: *Cancer, Cerebral infarction, TOAST criteria, D-dimer*

(Nippon Ronen Igakkai Zasshi 2011; 48: 57–62)

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LETTER TO THE EDITORS

Neurological deficits in a patient with selenium deficiency due to long-term total parenteral nutrition

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Dear Sirs,

The neurological symptoms of selenium deficiency are unclear. We report a patient with neurological deficits associated with selenium deficiency following long-term total parenteral nutrition (TPN).

A 40-year-old man was referred complaining of visual loss followed by slurred speech and staggering gait that had developed over the preceding 2 months. He had suffered from Crohn's disease for 22 years and had received home TPN management for 3 years following extensive surgical resection of the gastrointestinal tract. As a result of short-bowel syndrome, he received only a little water and gastric coating agents.

Neurological examination showed visual loss, bradyarthria, truncal and limb ataxia, and loss of limb proprioception. Physical examination showed curly hair and whitened nail beds on the fingers and toes, which had developed 3 months before the neurological manifestations (Fig. 1a, b). Brain magnetic resonance (MR) imaging and MR spectroscopy appeared normal. Ophthalmological examination showed large optic disc cupping, concentric visual field constriction and diminished flicker sensitivity without elevation of intraocular pressure, suggesting optic nerve disorder. Blood examination revealed an elevated mean corpuscular volume (MCV) of 109.1 fl. Blood concentrations of vitamins A, B_1, B_2, B_6, B_{12}, C and E, folic acid and trace metals (Fe, Cu, Zn, Pb and Al) were all normal. Serum inflammatory and autoimmunological markers, including antineuronal antibodies, and cerebrospinal fluid findings showed no abnormalities. Clinical history, nail and hair abnormalities, and macrocytosis were suspicious for selenium deficiency. The serum selenium level was below the detection limit of 2.0 μg/dl.

He was diagnosed with systemic dysfunctions caused by selenium deficiency, and 100 mg/day sodium selenite was administered intravenously. By continuous administration, his curly hair and whitened nail beds gradually disappeared (Fig. 1c, d), and the MCV returned to normal over several months. Although deterioration of his neurological symptoms stopped shortly after initiation of replacement, improvements were insufficient to allow resumption of daily activities. Visual, speech and gait disturbances were unchanged by 3 years of selenium replacement.

Selenium is an essential trace element that acts as an antioxidant in tissues [1, 2]. Selenium deficiency may occur as a result of long-term unphysiological nutrition, and is known to present macrocytosis [3], nail bed or hair abnormalities [3–5], skeletal muscle disorders [6, 7] and cardiomyopathy [8], between 1 month and 6 years [6, 8, 9]. The scarcity of cases, however, means that the neural symptoms of selenium deficiency remain unknown. To the best of our knowledge, only seven cases with neurological symptoms have been reported, including the present and three in Japanese abstracts (not available via MEDLINE) [10, 11]. Visual disturbance was the major symptom in six of these, and other neurological symptoms included consciousness disturbance, dysarthria, spasticity of the extremities, ataxia and sensory disturbances. These were manifested over 1–12 years after initiating TPN or

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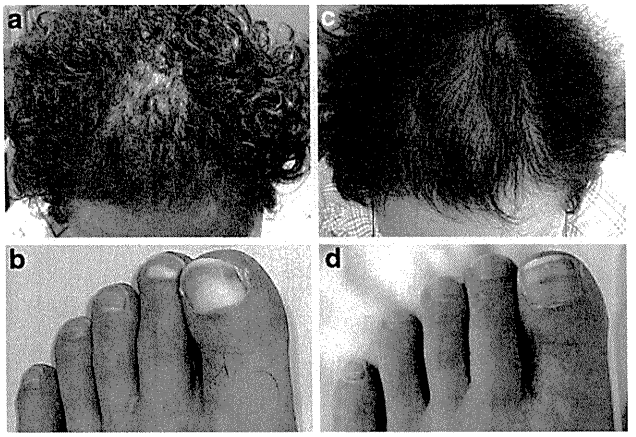

Fig. 1 Hair and nail beds before and after selenium replacement. Curly hair (**a**) and whitened nail beds (**b**) gradually disappeared after selenium replacement (**c**, **d**)

elemental enteral nutrition. It remains uncertain why the visual system is vulnerable to selenium deficiency; however, its constant use might increase glucose metabolism at a higher rate, resulting in more generation of toxic oxygen derivatives [11–13].

Long-term neurological outcomes following selenium replacement are not necessary favorable. Four of the reported patients underwent selenium replacement; one showed no improvement, and the other three patients only slight neurological amelioration; none were able to resume normal daily activities [10]. Pathological changes such as neural loss or gliosis might underlie the irreversible neurological features [11].

Although reports of further cases are needed to confirm the clinical features and appropriate treatment of selenium deficiency, we believe that selenium replacement should be initiated if deficiency is suspected. Clinical history and specific features, including visual disturbances, macrocytosis, curly hair and whitened nail beds, might aid the diagnosis.

Conflicts of interest The authors declare that they have no conflict of interest.

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INTERNAL MEDICINE

□ CASE REPORT □

Akinetic Mutism Caused by HIV-associated Progressive Multifocal Leukoencephalopathy was Successfully Treated with Mefloquine: A Serial Multimodal MRI Study

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Abstract

We report a case of a patient with highly active anti-retroviral therapy-resistant human immunodeficiency virus (HIV)-associated progressive multifocal leukoencephalopathy (PML). The patient showed an improvement in imaging findings and clinical symptoms after mefloquine was introduced as an additional treatment. Serial assessment of white matter lesions was conducted by proton magnetic resonance spectroscopy (^{1}H-MRS) and diffusion-weighted imaging (DWI). As the clinical symptoms improved, the N-acetylaspartate/creatine ratio increased, the choline/creatine ratio decreased, and the elevated ADC value decreased. These concomitant changes suggested that ^{1}H-MRS and DWI were useful for the assessment of the therapeutic effect on PML.

Key words: progressive multifocal leukoencephalopathy (PML), human immunodeficiency virus infection (HIV), highly active anti-retroviral therapy (HAART), mefloquine, proton magnetic resonance spectroscopy (^{1}H-MRS), apparent diffusion coefficient (ADC)

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Introduction

Progressive multifocal leukoencephalopathy (PML) is a demyelinating disease of the central nervous system caused by JC virus (JCV). PML occurs among immunocompromised patients with leukemic disease, malignant lymphoma, human immunodeficiency virus (HIV) infection or patients receiving immunosuppressive therapy. HIV-induced immunodeficiency is the most common precipitating condition that leads to PML, and in an analysis of 9,675 cases of PML in the US Nationwide Inpatient Sample database (1), it was reported that HIV-associated PML (HIV-PML) accounted for 82% of all PML cases. Highly active anti-retroviral therapy (HAART), which uses a combination of more than three drugs, is a central component for the treatment of HIV and is effective for prolonging the life of patients. Obviously, the introduction of HAART is also effective for prolonging the life of HIV-PML patients (2). On the other hand, the frequency of PML has not decreased as compared to other opportunistic infections (3), and HAART is not effective for about 50% of HIV-PML patients (2). In 2009, the anti-malarial drug mefloquine was revealed to have anti-JCV activity in in vitro culture (4). Some cases in which mefloquine has had an effect on PML have been reported (5, 6); however, there is no detailed report that mefloquine has an effect in HIV-PML. There have been many reports of using diffusion-weighted imaging (DWI) and proton magnetic resonance spectroscopy (^{1}H-MRS) for imaging PML; however, there are only a few studies on white matter lesions assessed by ^{1}H-MRS during the therapeutic period. We studied the serial changes of ^{1}H-MRS and DWI in white matter lesions of a patient with HAART-resistant HIV-PML to whom mefloquine was introduced.

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