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Case Report

Novel neuronal cytoplasmic inclusions in a patient carrying SCA8 expansion mutation

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It has been reported that abnormal processing of pre-mRNA is caused by abnormal triplet expansion. Non-coding triplet expansions produce toxic RNA to alter RNA splicing activities. However, there has been no report on the globular RNA aggregation in neuronal cytoplasmic inclusions (NCIs) up to now. We herein report on an autopsy case (genetically determined as spinocerebellar atrophy 8 (SCA8)) with hitherto undescribed NCIs throughout the brain. NCIs were chiefly composed of small granular particles, virtually identical to ribosomes. Neurological features are comparable to the widespread lesions of the brain, including the spinal cord. Although 1C2-positivity of NCIs might be induced by reverse transcription of the CTG expansion, it remains to be clarified how abnormal aggregations of ribosome and extensive brain degeneration are related to the reverse or forward transcripts of the expanded repeat.

Key words: neuronal cytoplasmic inclusion, ribosomal aggregation, SCA8, TDP43, ultrastructure.

INTRODUCTION

We report herein on a neuronal cytoplasmic inclusion mainly composed of ribosomal aggregations (rNCIs: ribosomal neuronal cytoplasmic inclusion), in a peculiar autopsy case carrying CTA/CTG repeat expansion in the spinocerebellar atrophy 8 (SCA8) mutation. This male patient developed psychomotor retardation in early childhood. Later, he developed cerebellar ataxia and epilepsy at school age, and finally fell into akinetic mutism at the age of 23 until he died at the age of 32. On microscopic examination, there was marked neuronal loss and gliosis and white matter degeneration in the whole brain. Peculiar hitherto undescribed rNCIs were ubiquitously observed in the brain. They were basophilic on HE stain, argyrophilic on Bodian silver impregnation, positive for ubiquitin (Ub), P62 and faintly transactivation response (TAR) DNA-binding protein 43 (TDP-43), but negative for alpha-synuclein (Syn) and phosphorylated tau (AT8). Ultrastructurally, they were composed of ribosomal aggregations devoid of filamentous structures. The absence of rough endoplasmic reticula (RER) suggests that ribosomal dysfunction may play some role on formation of this novel inclusion. Regarding the pathogenesis of the current case, the abnormal gene mutation compatible with that of SCA8 mutation might modify the disease process.

The early onset of the cerebral and cerebellar symptoms and diffuse brain devastation best characterize this case, being somewhat distinct from that of common SCA8 cases that present adult onset and restricted involvement of the cerebellum.

CASE REPORT

The patient was a 32-year-old Japanese man. Parental consanguinity was denied and the family history was noncontributory. In spite of his motor and mental retardation in early childhood, he was ambulant and communicated verbally during childhood. Later, he developed cerebellar ataxia and epilepsy at school age when his motor and mental disability rapidly progressed. Neurological examination at the age of 11 on the initial visit to a general hospital identified mental disability, cerebellar ataxia, muscle atrophy and weakness of four extremities. Electroencephalography (EEG) showed spike waves on bilateral temporal lobes. Needle electromyography showed positive

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sharp waves and fibrillation potentials in the four extremities. Head CT scan demonstrated mild cerebellar atrophy.

Artificial ventilation was started at the age of 15 because of respiratory muscle weakness. His motor and mental disabilities slowly progressed. He fell into akinetic mutism at the age of 23. Head MRI demonstrated progressive atrophy of the whole brain. At the age of 31, there were neither responses to any external stimuli nor voluntary movements, including vocalization. Light, corneal, gag, cough and deep tendon reflexes were all lost. There was no electrical activity on EEG. He died of septic shock secondary to cholecystitis at the age of 32.

Serum creatine kinase, lactic acid and pyruvic acid were within normal limits. Other peripheral hematology and blood chemistry were within normal limits. Lysosomal enzymes examined were all in normal ranges. Genetic analysis of SCA8 showed pathogenic CTA/CTG repeat of 23/127 (normal 16–91). Genes for SCA1, 2, 3, 6, 7, dentatorubral-pallidolluysian atrophy (DRPLA) and Huntington's disease exhibited no pathological expansion. Abnormal fused in sarcoma (FUS) mutation was not confirmed. Thus we clinically diagnosed this case as marked psychomotor impairment, possibly related to the abnormal expansion of SCA8 mutation although other SCA8 cases reported up to now were quite distinct from the present case in clinical features.

Neuropathological findings

Autopsy was done 3 h after death. The brain weighed 400 g.

Macroscopic examination revealed diffuse atrophy of the whole brain, including the cerebellum, brain stem and spinal cord. The cerebral cortex and white matter showed atrophy. The basal ganglia, thalamus, cerebellum, tegmentum of the brainstem, midbrain (Fig. 1A), pons, medulla oblongata and spinal cord were severely devastated, obscuring the details of their internal structures.

On microscopic examination, the cerebral cortex showed diffuse neuronal loss and gliosis, and white matter atrophy was comparable to that of the gray matter (Fig. 1B). The degrees of neuronal loss and gliosis (graded into mild, moderate to severe) and the frequency of rNCIs are schematized (Fig. 2).

Many remaining neurons had round to oval rNCIs. The frequency of the neurons with rNCIs was variable between 5–30% of remaining neurons. It was low in areas with severe neuronal loss, such as the thalamus, cerebellum (Fig. 1C) and motor nucleus, such as the hypoglossal nucleus (Fig. 1D), while abundant in Ammon's horn where neuronal cells were spared. It was moderate in the frontal and parietal cortices where neuronal loss was moderate in degree. This inverse relationship between neuronal loss and rNCI was similarly evident by contrasting the deep layers of the cerebral cortex where gliosis was mild with abundant rNCIs.

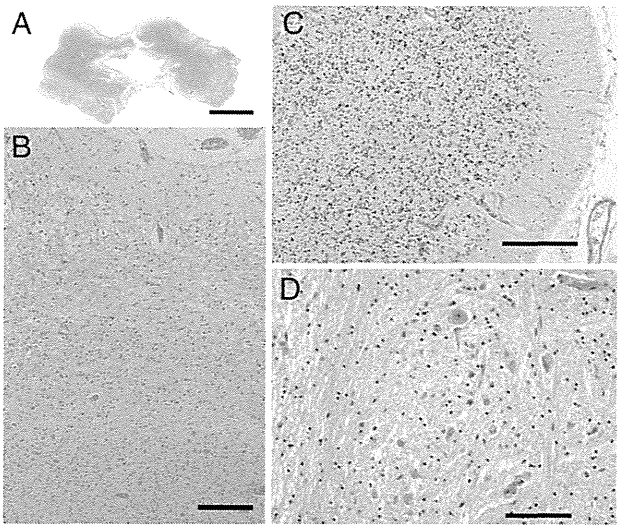

Fig. 1 (A) The tegmentum of the brainstem, red nucleus and substantia nigra are severely atrophic; it is not easy to identify their inner details. Bar = 5 mm. (B) Diffuse neuronal loss and gliosis in the cerebral cortex, associated with spongy state of superficial layers and diffuse gliosis in the white matter (HE). Bar = 250 μm. (C) Diffuse neuronal loss and gliosis in the cerebellum (HE). Bar = 250 μm. (D) Severe neuronal loss and gliosis in the hypoglossal nucleus (HE). Bar = 100 μm.

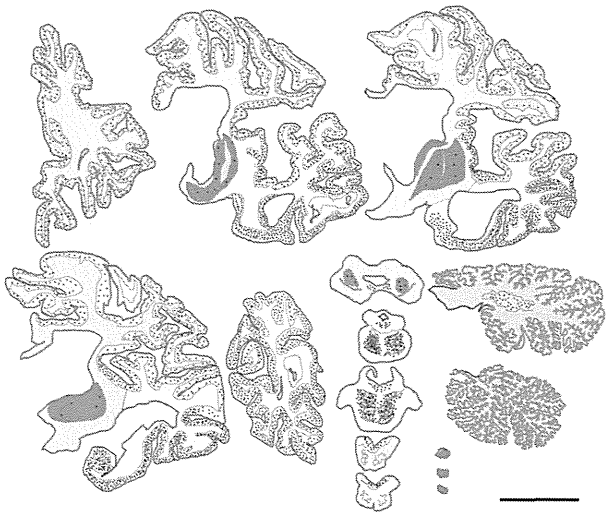

Fig. 2 Regional variability of neuronal loss and ribosomal neuronal cytoplasmic inclusions (rNCIs). Red color stands for severe devastation of the brain parenchyma, pink for moderate degeneration, and pale pink for mild degeneration. Each dot represents five inclusions. Bar = 20 mm.

The rNCIs were basophilic on HE (Fig. 3A) and KB (Fig. 3B) and argyrophilic with Bodian silver impregnation

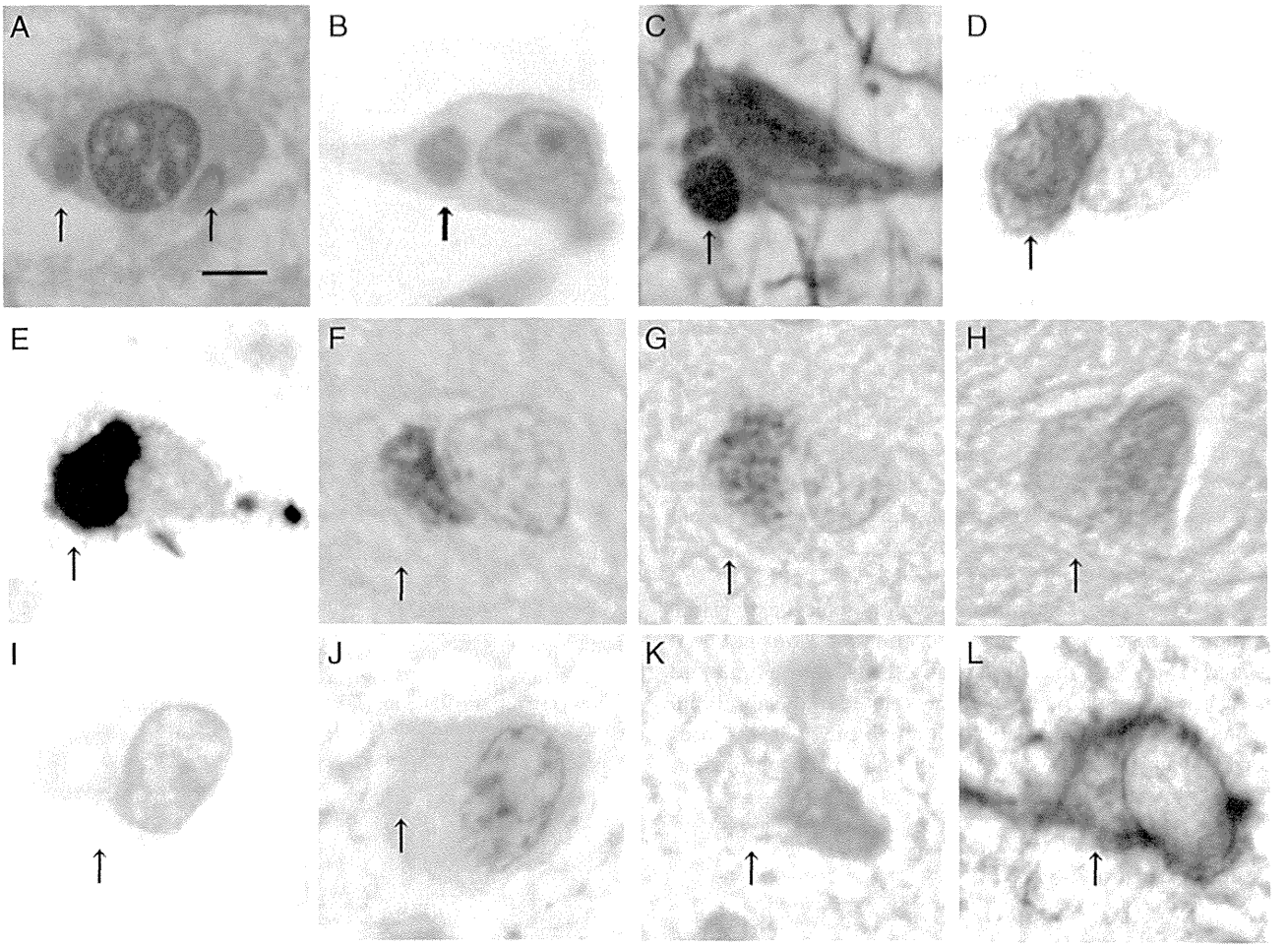

Fig. 3 The ribosomal neuronal cytoplasmic inclusion (rNCI) is basophilic on HE (A), KB (B) and brownish black for Bodian stain (C). The rNCI are positive for ubiquitin (Ub) (D), p62 (E) and faintly for trans-activation response DNA protein 43 (TDP43) (F), partly positive for 1C2 (G), and negative for alpha-synuclein (Syn) (H), phosphorylated tau (AT8) (I), fused in sarcoma (FUS) (J), neurofilaments (K) andmitogen-activated protein 2 (MAP2) (L). Bar = 5 μm.

(Fig. 3C). The rNCIs were positive: Ub ≈ 25–35% (Fig. 3D, 1:200, Millipore, Tokyo, Japan); p62 ≈ 20–30% (Fig. 3E 1:500, Abnova, Walnut, CA, USA); and phosphorylated TDP43 ≈ 3–5% (Fig. 3F, 1:10 000, Cosmo Bio, Tokyo, Japan), then positive in a few rNCIs for expanded polyglutamine ≈ 0.5–1.0% (Fig. 3G, 1–2, 1:10 000, Millopore, Tokyo, Japan) and negative for Syn (Fig. 3H, 1:10 000, Wako, Tokyo, Japan), AT8 (Fig. 3I, 1:10 000, Innogenetics, Zwijndrecht, Belgium), FUS (Fig. 3J 1:100 gift of Dr Murayama), neurofilaments (Fig. 3K 1: 200, Dako, Tokyo, Japan) and mitogen-activated protein 2 (MAP2) (Fig. 3L, 1:1000, Sigma, St Louis, MI, USA). The rNCIs were negative for alpha-internexin (1:100, Santa Cruz Biotech, Dallas, TX, USA), T cell restricted intracellular antigen-1 (TIA-1) (1:100, Santa Cruz Biotech), and poly-(A)-binding protein-1 (PABP-1) (1:100, Santa Cruz Biotech) (data not shown). The rNCIs were stained red with methylgreen-pyronine (MGP), and these positive granules disappeared after RNA-ase digestion (data not shown). Triple fluorolabeling demonstrated coexistence of Ub and 1C2 in some rNCIs, while both Ub and TDP43 frequently coexisted in the same rNCIs.

Ultrastructurally, rNCIs were composed of aggregations of small electron-dense granular particles (20–50 nm) resembling ribosomes (Fig. 4A). These aggregated granules were not membrane-bound and only seen in the neuronal cytoplasm and not in the nucleus. Most rNCIs were closely opposed to the nucleus. Some rNCIs were globular in shape, the centers of which contained degenerative organellae, surrounded by circular aggregations of ribosomes (Fig. 4B). The RER were not found in most neurons examined. Abnormal mitochondria, lipid deposits and filamentous structures were not seen. There was no similar ribosomal aggregation in glia.

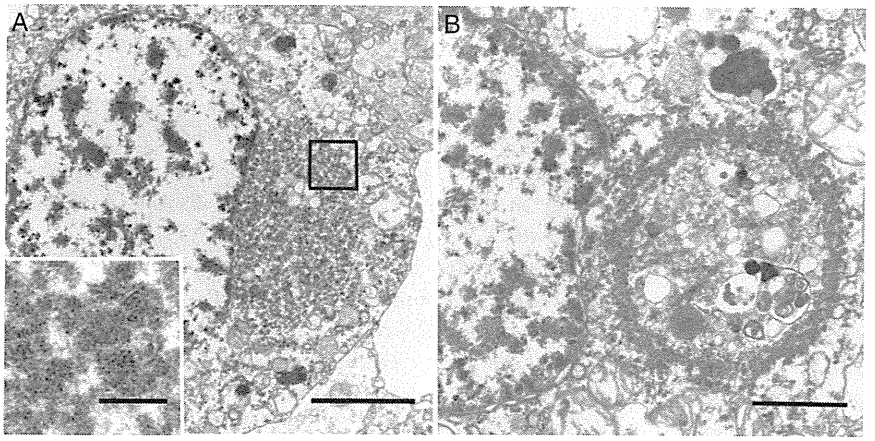

Fig. 4 (A) A ribosomal neuronal cytoplasmic inclusion (rNCI) is not membrane-bound and consists of aggregations of small electron-dense granular particles resembling ribosomal structures, and contains some degenerative organellae among ribosomes. Rough endoplasmic reticula (RER) are not related to the aggregations of the granules. Bar = 2 μm. Inset: higher magnification of granular particles. Bar = 0.5 μm. (B) A rNCI is globular in shape, the centers of which contain many degenerative organellae, surrounded by circular aggregations of ribosomes. Bar = 1 μm.

DISCUSSION

The most characteristic clinical symptoms in our case were psychomotor retardation in his infancy and epileptic attacks. Cerebellar ataxia and the mental and motor disturbances appeared and rapidly progressed in the second decade of his life. The neuroimaging study presented marked cerebellar atrophy at an early stage, but its atrophy was extended to the entire brain at an advanced stage. Abnormal CTG repeat expansion of SCA8 (23/127) was observed, but the symptoms were widespread to the whole brain which was different from those in previous autopsy reports of SCA8 that presented only symptoms in the brain stem and cerebellum.[1] The clinical symptoms of the cerebellar and motor neurons progressed concomitantly, and the pathological findings present cerebellar atrophy and neuronal loss of motor neurons (Fig. 2C,D). Because of these findings, we could not categorize this case as motor neuron disease or spinocerebellar ataxia involving motor neuron systems. However, based on clinical observations, the subjects with this abnormality of SCA8 mutation may either present no symptomatology[2,3] or be associated only with schizophrenia,[4] bipolar affective disorders,[4] Huntington phenocopy[5] or migraine.[6] This variable nature with inconsistent penetrance of the SCA8 mutation expansion suggests that corresponding phenotypes are influenced by factors other than this expansion itself. Thus, it remains unsolved whether the abnormal SCA8 mutation correlate with clinical phenotype in our case.

The most outstanding pathology was basophilic cytoplasmic inclusions, not reported to date, in the neurons. This inclusion was negative for Syn and AT8, but positive for Ub, P62 and faintly TDP43, superficially similar to basophilic inclusions (BIs) in TDP43-negative frontotemporal degeneration (FTD) or atypical amyotrophic lateral sclerosis (ALS).[7-9] The immunostain and digestion by RNAase demonstrated the content of RNA as a constituent. The negativity of FUS in our NCIs was distinct from BIs. The negativity of our NCIs for alpha-internexin, TIA and PABP-1 was different from BIs.

Ultrastructurally, these rNCIs were composed of ribosomes, not associated with the functional maturation of RER and filamentous structures,[7-9] which are different from BIs in FTD and ALS, and NCIs in multisystem atrophy (MSA) that consist of thick filamentous structures studded with electron-dense ribosome-like granules.[10] Furthermore, the distribution of BIs is quite different from that of rNCIs in our case in which they were widespread throughout all cerebral cortices, hippocampus and brain stem.[7-9]

Immunopositivity for 1C2 in NCIs may be explained by reverse transcription of the CTG repeat expansion, as in SCA8.[11,12] On the other hand, 1C2 immunorectivity related to the expansion of SCA8 mutation is nuclear in mice harboring the SCA8 expansion[11] or either nuclear[11] or cytoplasmic[1] in human autopsy cases. In any case, it is restricted to cerebellar Purkinje cells in reported cases,[1] and thus different from rNCIs in our case.

We reported novel neuronal cytoplasmic inclusions composed of ribosomal aggregations that were seen in the whole brain. Although 1C2-positivity of rNCIs might be induced by reverse transcription of the CTG expansion, it remains to be clarified how abnormal aggregations of ribosomes and extensive brain degeneration are related to the reverse or forward transcripts of the expanded repeat.

ACKNOWLEDGMENT

The abnormal CTA/CTG repeat expansion of SCA8 mutation was analyzed in Saigata National Hospital. Triple fluorolabeling for Ub and 1C2, Ub and TDP43 was performed by A. Nakamura in the Laboratory of Structural Neuropathology, Tokyo Metropolitan Institute of Medical Science.

FUS antibody was gifted by Dr. S. Murayama, Brain Bank Center of Tokyo Metropolitan Geriatric Hospital.

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Case Report

Late onset GM_2 gangliosidosis presenting with motor neuron disease: An autopsy case

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Adult-onset GM_2 gangliosidosis is very rare and only three autopsy cases have been reported up to now. We report herein an autopsy case of adult-onset GM_2 gangliosidosis. The patient developed slowly progressive motor neuron disease-like symptoms after longstanding mood disorder and cognitive dysfunction. He developed gait disturbance and weakness of lower limbs at age 52 years. Because of progressive muscle weakness and atrophy, he became bedridden at age 65. At age of 68, he died. His neurological findings presented slight cognitive disturbance, slight manic state, severe muscle weakness, atrophy of four limbs and no extrapyramidal signs and symptoms, and cerebellar ataxia. Neuropathologically, mild neuronal loss and abundant lipid deposits were noted in the neuronal cytoplasm throughout the nervous system, including peripheral autonomic neurons. The most outstanding findings were marked neuronal loss and distended neurons in the anterior horn of the spinal cord, which supports his clinical symptomatology of lower motor neuron disease in this case. The presence of lipofuscin, zebra bodies and membranous cytoplasmic bodies (MCB) and the increase of GM_2 ganglioside by biochemistry led to diagnosis of GM_2 gangliosidosis.

Key words: adult onset, autopsy, GM_2 gangliosidosis, motor neuron disease, ultrastructure.

INTRODUCTION

GM_2 gangliosidosis is one of the lysosomal storage disorders with severe CNS involvement. Inherited defects in the a-subunit gene (*HEXA*, chromosome 15) or in the b-subunit gene (*HEXB*, chromosome 5) lead to the absence of hexosaminidase (Hex, E.C.3.2.1.52) isoenzymes. GM_2A deficiency (AB variant) is an extremely rare genetic disease caused by mutations of the *GM_2A* gene. Defects in any of these three genes result in excessive accumulation of GM_2 and related glycolipids in lysosomes, mainly those in neural cells, leading to a rare neurodegenerative disorder.[1–5]

In GM_2 gangliosidosis most patients present with cherry red spot, rapidly progressive neurological disorders involving motor and psycho-intellectual dysfunctions in early infancy, and die between 2 and 3 years. A few patients with GM_2 gangliosidosis develop neurodegenerative disorders starting after 1 year of age and experience a slower rate of progression than patients with the infantile forms. Those cases of GM_2 gangliosidosis present with variable neurological symptoms, such as psychomotor dysfunction, cerebellar ataxia, spastic paresis and with no cherry-red spot.[6]

In later-onset cases, the symptoms are reported as slowly progressive variables such as psychosis (often diagnosed as having schizophrenia), mood disorders, cognitive abnormality, cerebellar ataxia, dysarthria, muscle weakness, gait disturbance and dystonia, but presenting no cherry-red spot.[7–9]

Only three autopsy cases of adult-onset GM_2 gangliosidosis have been reported up to now as progressive muscular dystrophy simulating motor neuron disease or other syndromes.[10–12] We report herein on an autopsy case of adult-onset GM_2 gangliosidosis which developed slowly progressive motor neuron disease after long-standing mood disorder and cognitive dysfunction.

CASE REPORT

A Japanese male developed depressive state at 15 years old. Because of severe depression, he dropped out of high

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school and worked as a newspaper carrier, plumber, and welder and so on. Despite antidepressant and psychotropic medication, his mood disorder and cognitive dysfunction slowly progressed. At the age of 45 years old, he was diagnosed as having euphoric mood, character disorder and mild cognitive dysfunction with impaired attention. Motor dysfunction and gait disturbance were not noted.

He developed a tendency to fall and difficulty walking because of muscle weakness and atrophy of lower limbs at the age of 52 years old. His muscle weakness and atrophy slowly progressed. He had to lean on a cane to walk at the age of 60 years. He developed a shut-in because of the progression of muscle weakness, and visited the neurological clinic in National Sagamihara Hospital at the age of 62 years old. At the presentation at our hospital, his neurological findings were mild cognitive deficiency and manic state. His countenance was not gargoyle-like, suggestive of mucopolysacharidosis. Cherry-red spot was not observed. The manual muscle testing (MMT) presented 4-4 in upper limbs, 2–3 in inferior limb girdle, 3–4 in lower legs, respectively. The deep tendon reflexes mildly decreased, and there were no other pyramidal signs. There was no evidence of cerebellar symptoms, extra-pyramidal signs and sensory disturbance. The head and spine MRI presented no abnormality. Needle electromyography presented neurogenic patterns suggestive of acute denervation sign in all four limbs. The nerve conduction velocity was within normal limits. He was diagnosed as having motor neuron disease and was conservatively medicated. He died at home at the age of 67 years.

NEUROPATHOLOGICAL FINDINGS

Autopsy was performed 5 h after death. The brain weight was 1260 g. The left half of the brain was fixed in 10% formalin and representative portions were embedded in paraffin. Thin sections were stained with HE, KB, Bodian and PAS. The other half of the brain was stored at −80°C. In addition, visceral organs, such as liver, lung, adrenal glands, gastrointestinal tracts, were routinely fixed in 10% formalin and embedded in paraffin. Thin sections were stained with HE or PAS. Dorsal root ganglia, periadrenal sympathetic ganglia and Auerbach's nerve plexus in the gastrointestinal tract were also histologically examined.

For ultrastructural examination, small pieces taken from the frontal cerebral cortex, anterior horn of the lumbar spinal cord (L3), basal ganglia and Ammon's horn, which were formalin-fixed, were re-fixed in 2.5% glutaraldehyde solution and post-fixed in 1% osmium tetroxide and then embedded in Epon mixture. The thin sections were stained with uranyl acetate and lead citrate and observed in a JOEL 2000FX electron microscope.

The macroscopic examination revealed no atrophy of the brain, including the cerebellum, brain stem and spinal cord.

On microscopic examination, the cerebral cortex showed slight neuronal loss and gliosis. There were many neurons with ballooned cytoplasm throughout the brain, including the spinal cord. These swollen neurons were mostly seen in the deep layers of the cerebral cortex, while they were less frequent in layers II-III in contrast (Fig. 1). Swollen neurons were more frequently observed in the

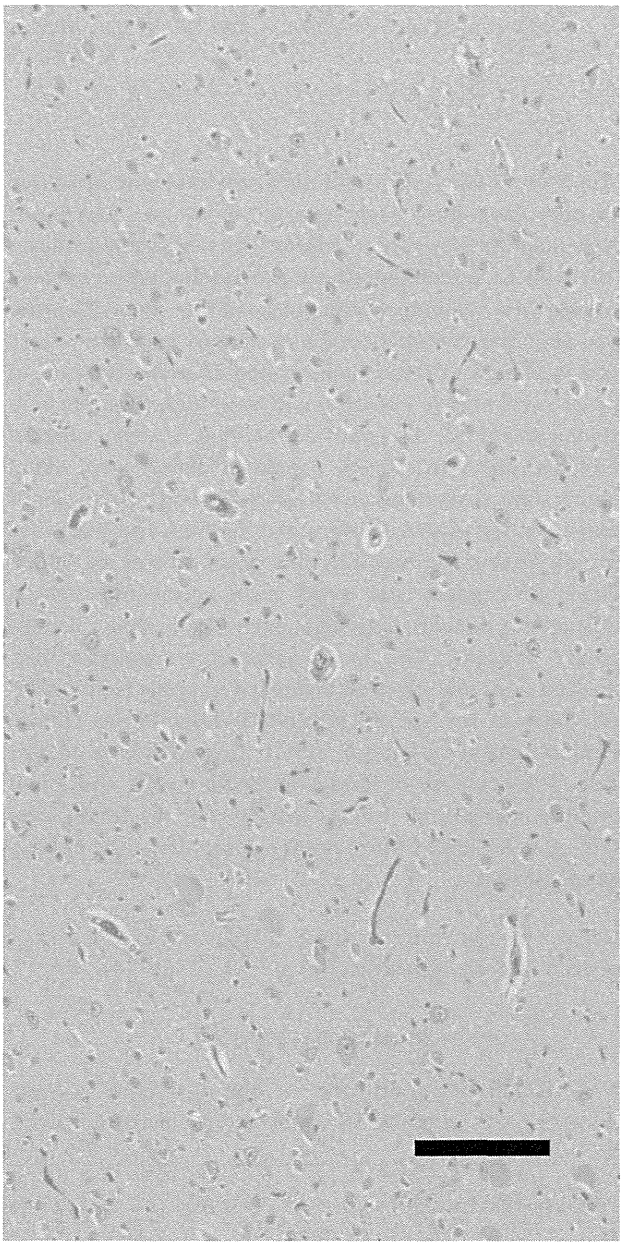

Fig. 1 Cerebral cortex: many ballooned neurons are seen in the deep layers. Bar = 100 μm.

basal ganglia, thalamus, hippocampus, brainstem and pontine nuclei, while less frequent in the olivary nuclei, cerebellar cortex, dentate nucleus, red nucleus, substantia nigra and locus ceruleus. The swollen cytoplasm was filled with coarse lipofuscin-like granules that were pale yellow-brown on HE stain, being positive for PAS and negative for KB and Bodian. These coarse granules were not observed in glial or parenchymal cells. In the visceral organs, there were many ballooned neurons in the autonomic ganglia. There were no swollen cells suggestive of lipidosis in the non-neuronal cells in the visceral organs. There were no outstanding changes in the motor cortex compared with the other cerebral cortices. The cerebral peduncles, pyramidal tracts of brain stem, lateral and anterior funiculi of the spinal cord were preserved. Severe neuronal loss and some swollen neurons were seen in the hypoglossal nuclei. In the spinal cord, severe loss of anterior horn cells was observed, more severe at the lumbar level than cervical level and motor neurons were considerably distended with PAS-positive granules (Fig. 2A–C). There were no macrophage or other inflammatory change or ischemia and so on.

Ultrastructural, lipofuscin (Fig. 3A) and zebra bodies (Fig. 3B) were observed in the majority of neurons examined in Ammon's horn, cerebral cortex, basal ganglia and anterior horn neurons in the spinal cord, but membranous cytoplasmic bodies (MCB) (Fig. 3C) were mostly found in the pyramidal cell and granule cell neurons in Ammon's horn. Membranous cytoplasmic bodies could not be found in anterior neurons examined.

Thin layer chromatography of total glycosphinogolipids from frozen brain tissue (frontal cortex) sulfatide and cerebroside (Fig. 4A) revealed a thick band of GM_2 ganglioside. Asialo GM_1 (GA1) and Asialo GM_1 (G1) were not increased. Sulfatide and glucocerebroside were slightly increased. Ganglioside (GM_2) from the patient was purified with columns of diethylaminoethyl (DEAE)-Toyopearl and Iatrobeads 6RS-8060, successively. The

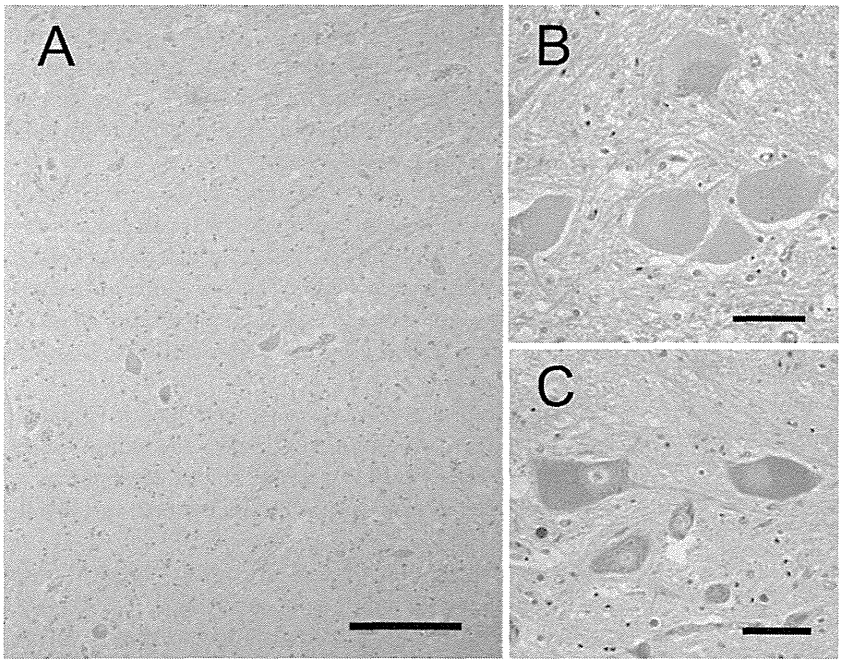

Fig. 2 (A) Considerable neuronal loss and gliosis in the anterior horn in the spinal cord (lumbar level). High-power view of ballooned neurons in the anterior horn. Bar = 100 μm. (B) HE. Bar = 20 μm. (C) PAS. Bar = 20 μm.

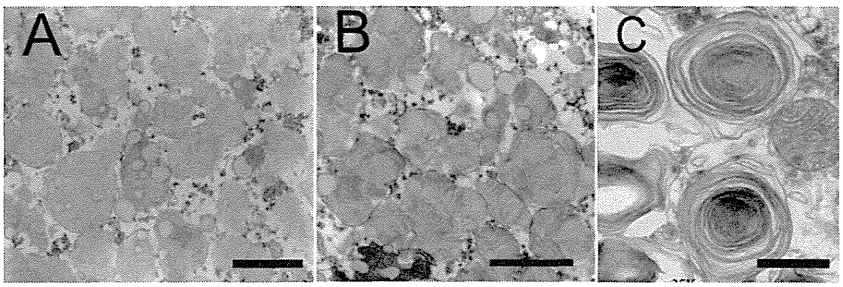

Fig. 3 Fine structures of neuronal deposits. (A) Lipofuscin-like. Bar = 1 μm. (B) Zebroid. Bar = 1 μm. (C) Membranous cytoplasmic bodies. Bar = 0.5 μm.

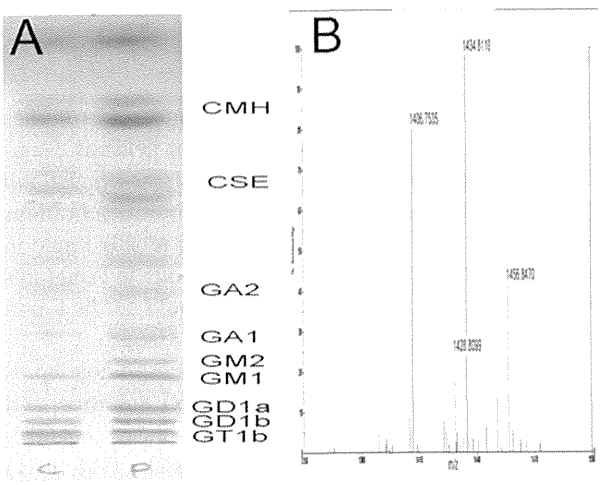

Fig. 4 (A) TLC of glycosphongolipids from brain. Lane A: control, Lane B: patient. Total lipids were extracted from brain tissues using mixtures of chloroform/methanol (1:2, by volume) and treated with 1/10 volume of 0.5 N NaOH in methanol for 30 min to remove alkali labile phospholipids. Glycosphinogolipids were separated on a silica-gel high performance thin layer chromatography (HPTLC) plate. The plate was developed to 5 cm with a solvent mixture of chloroform: methanol: 0.2% $CaCl_2$ (60:40:9, by volume), then, after air-drying, to 8 cm with a solvent mixture of methyl acetate: propanol: chloroform: methanol: 0.25% KCl (25:25:25:10:9, by volume). Glycosphingolipids were visualized by orcinol-H_2SO_4 reagent followed by heating. (B) Matrix-assisted laser desorption ionization – time of flight (MALDI-TOF) mass spectra of GM_2 from patient. Intact GM_2 was analyzed by positive mode MALDI-TOF mass spectrometer (2,5-dihydroxybenzoic acid was used as matrix).

purified sample was analyzed by matrix-assisted laser desorption ionization – time of flight (MALDI-TOF) mass spectrometer (Fig. 4B) and showed the monoisotopic spectra of GM_2 from the patient. Ions were detected as cationized ones ($(M + Na)^+$). The two major ions corresponded to GM_2 with two different ceramide species, m/z = 1406.75 corresponding to GM2 with C18:0-d18:1 (calculated m/z = 1406.81) and m/z = 1434.81 corresponding to GM2 with C18:0-d20:1 (calculated m/z = 1434.84). Ions of m/z = 1428.80 and 1456.84 were $(M + Na)^+$ of sodium salt of GM2 with two species of ceramides described above, respectively.

GM_2 structure was further confirmed by carbohydrate composition analysis which revealed the composition of galactose : glucose : *N*-Acetylgalactosamine = 1:1:1, which confirmed the structure of GM2 (data not shown).

Unfortunately, hexosaminidase activity was not examined since cerebral lipidosis was not suspected antemortem.

DISCUSSION

This patient developed slowly progressive motor neuron disease-like signs and symptoms at adult age after longstanding mood disorder and cognitive dysfunction. The neuropathology and biochemistry on the frozen brain tissue confirmed GM_2 gangliosidosis. Neuropathological examination presented neuronal loss and cytoplasmic lipid deposit in neurons throughout the nervous system, including peripheral autonomic neurons. Abnormal deposits of lipids were seen only in the neuronal cytoplasm, including peripheral neurons, excluding other neuronal lipidoses.

In the literature, late-onset and slowly progressive GM_2 gangliosidosis has been reported as a rare type of GM_2 gangliosidosis. These patients present with various symptoms such as psychosis, congenital dysfunction, motor dysfunction, cerebellar ataxia and spastic paresis. In the previous reports of late-onset cases, about half the patients are diagnosed with psychosis. Mostly psychosis symptoms appear at the second decade, most of which are diagnosed as schizophrenia. One-fourth of patients present with psychosis, such as mood disorders, and one-eighth severe depression, respectively.[8]

Up to now, only a few cases of late-onset GM_2 gangliosidosis have been reported as progressive muscular dystrophy mimicking motor neuron disease. In these reports, the patients show slowly progressive heterogeneous clinical course, such as lingual atrophy, upper and lower neuron signs. One report documented only lower neuron symptoms. Gene analysis has shown unprecedentedly some mutations on GM_2 gangliosidosis.[13–15]

The latest onset of the disease starts at the fourth decade. In our case, motor neuron disease-like symptoms first appeared at the sixth decade which is the oldest reported in GM_2 gangliosidosis. There was marked degeneration in the anterior horn of the spinal cord. The distended neurons contained massive lipofuscin-like granules in their cytoplasm.

Ultrastructurally, the neuronal cytoplasmic granules consisted mainly of lipofuscin granules and zebra bodies. MCBs were found only in Ammon's horn, the findings of which are quite distinct from those in infantile or juvenile GM_2.

In our knowledge, there are only three reports that document late onset and slowly progressive GM_2 gangliosidosis,[10–12] two of which presented motor neuron disease-like course. In comparison with the previous autopsy report, diencephalon and brain stem lesions that were more severe than those in the cerebral cortex, was a common finding in our case (Table 1). Massive neuronal loss and swollen neurons in the anterior horn of the spinal cord support lower motor neuron disease-like symptoms, in this case as in other two cases. No outstanding changes in the motor cortex and pyramidal tracts have been reported for the present.

In summary, we reported on a rare autopsy case of late-onset and slowly progressive GM_2 gangliosidosis,

Table 1 Distributions of balloned neurons

Authors	This case	Jellinger	Kornfeld	Suzuki
Cereberal cortex	+~++	+	+~++	+~++
Caudate	+~++	±	±	±
Putamen	++	±	±	±
Globus pallidus	++	±	±	±
Subthalamic nucleus	+++	+++	++	++
Thalamus	++	+++	±	++
Dentate gyrus	±	±	ND	ND
Ammon's horn	+~++	+++	ND	++
Oculomotor nuclei	+++	+++	+++	
Red nucleus	+	+++	ND	
Substantia nigra	+	+++	ND	+++
Pontine nuclei	++	±	ND	
Hypoglossal nucleus	+++	+++	+++	
Cerebellum	±	+++	±	+++
Spinal cord anterior horn	+++	ND	+++	++
Posterior horn	±	ND	++	ND

ND, not described; ±: 5% < in this case; +: 10% < of neurons; ++: 20% < of neurons; +++: <20% of neurons.

clinically simulating motor neuron disease. Albeit very rare, it should be borne in mind that motor neuron phenotype occurs in adult onset GM_2 gangliosidosis.

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