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Galactosialidosis: neuropathological findings in a case of the late-infantile type

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Summary. The neuropathological findings in a 13-year-old Japanese male showing decrease of sialidase and β-galactosidase activities are reported. The patient was the product of normal pregnancy to consanguineous parents. He started to sit at 8 months, stand at 20 months and walk at the age of 2; mental retardation, visual disturbance, cerebellar ataxia, myoclonus and epilepsy developed by the age of 10, and he died at 13. Neuropathological investigation revealed neuronal loss and storage. Severe loss of neurons was observed in the thalamus, globus pallidus, lateral geniculate body, gracile nucleus, Purkinje and retinal ganglion cells. Marked ballooning was seen in the Betz cells and neurons in the basal forebrain, the motor neurons in the cranial nerve nuclei and spinal cord, and in the trigeminal and spinal ganglia. The storage material varied in staining from region to region and from neuron to neuron. Electron microscopic investigation revealed a variety of intracytoplasmic and intranuclear inclusions: membranous cytoplasmic bodies, parallel, wavy-lamellar or tortuous tubular structures, lipofuscin-like irregular-shaped pleomorphic bodies, and cytoplasmic vacuoles with fine granules and lamellar materials. The severity of the neuronal loss did not seem to correlate with the amount of the storage materials, but with the presence of tortuous tubular inclusion.

Key words: Galactosialidosis – Neuronal storage disease – Neuropathology – Ultrastructure – Neuronal loss

Galactosialidosis is an autosomal recessive disorder characterized by a deficiency of sialidase and β-galactosidase activities, and by clinical symptoms of myoclonus, cerebellar ataxia, epilepsy, visual disturbance, macular cherry-red spots, mental retardation, angiokeratoma, gargoyle-like facial features and skeletal dysplasia. Its incidence is very much higher in Japanese than in other races [8, 10, 12, 15, 17, 18]. Recent biochemical studies have revealed that the cause of the disease is a defect of a 'protective' protein which is necessary for activating sialidase and β-galactosidase, and that the amounts of the protein and its precursor are reduced more severely in the early-infantile type than in the adult/juvenile type. Its cDNA cloning has been carried out recently [2, 11, 13, 19].

Pathological findings in the central nervous system have been reported from only three patients with confirmed deficiencies of sialidase and β-galactosidase [1, 3, 12, 14, 20], and in a few possible cases without enzymatic confirmation [4, 6, 7, 16]. However, to our knowledge, pathological findings in the central nervous system of the late-infantile type have not been reported so far. In the present study, we describe the characteristic features of the heterogeneous neuronal storage material as well as the topographic distribution of neuronal loss in a case of late-infantile galactosialidosis, and discuss the particular mechanism of the progression of the disease.

Case report

The clinical history of this case and results of the ganglioside analysis of the nervous system have been reported previously [21]. The patient was a Japanese boy, the product of a consanguineous marriage, who was born after a normal pregnancy and delivery. He started to sit at 8 months, to stand up at 20 months and to walk at the age of 2. He was noticed to have spastic gait, pes planus valgus and mental retardation at 5 years. The symptoms were slowly progressive.

At the age of 9, physical examination revealed a coarse face, short neck, funnel-like chest, and mild kyphotic curvature. Radiological studies demonstrated diffuse vertebral plana with anterior beaking of the second lumbar vertebra. He was alert, but showed moderate mental retardation (Binet I.Q., 56); diffuse muscular atrophy and weakness, hyper-reflexia and cerebellar ataxia were noticed. Visual disturbance was found (rt, 0.03; lt, 0.1) with pale optic discs and corneal clouding, but macular cherry-red spots were not observed. A CT scan revealed cerebellar atrophy. Results of routine laboratory tests were normal, but sialidase and β-galactosidase activities in lymphocytes were 30% and 20% of controls,

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respectively, and in cultured skin fibroblasts less than 5% and 20%, respectively, of controls. The amount of urinary sialosyloligosaccharides was increased. Vacuoles were observed in peripheral lymphocytes. Angiokeratoma was not observed.

His gait disturbance, muscle weakness and visual disturbance gradually progressed, and myoclonic and convulsive seizures appeared at the age of 10. At 12 years, his mental abilities severely deteriorated. Action myoclonus was prominent and myoclonic seizures occurred at times. At 13, a tracheostomy was performed, but the patient died of tracheal bleeding.

Methods

Autopsy was performed 4 h post mortem. Tissue samples were taken from various parts of the central and peripheral nervous system and visceral organs, and were processed for light and electron microscopy as well as for chemical analysis. Two age-matched controls were also examined.

The tissues were fixed in 4% paraformaldehyde in 0.1 M phosphate buffer (pH 7.3), dehydrated in a graded ethanol series, embedded in paraffin, and stained with hematoxylin-eosin, Klüver-Barrera, Holzer, Bodian, ninhydrin-Schiff, cresyl violet, periodic acid-Schiff (PAS), alcian blue (pH 2.5), toluidine blue, aldehyde fuchsin, Prussian blue, luxol fast blue, diphenylcarbazide, Schmorl, von Kossa, and Fontana. Cryostat sections of the 4% paraformaldehyde-fixed tissue were stained with Bial, Sudan III, Sudan black B, Nile blue and PAS. Autofluorescence was also examined.

For electron microscopy, tissues were fixed in 3% glutaraldehyde in 0.1 M phosphate buffer (pH 7.3), post-fixed in 1% osmium tetroxide, dehydrated through a graded ethanol series, and embedded in Epon 812. Sections, 1 μm in thick, were stained with toluidine blue. Ultrathin sections stained with uranyl acetate and lead citrate were examined with an electron microscope.

The degree of neuronal storage and loss was divided into four grades: −, no storage or loss; +, small amount of stored materials or slight loss of neurons; ++, presence of stored materials in the whole cytoplasm or moderate loss of neurons; +++, swelling of neurons by storage substance or complete loss of neurons (Table 1).

Results

Macroscopic findings

The brain weighed 1200 g. Slight but diffuse widening of the cerebral sulci, marked atrophy of the optic nerves and thickening of the leptomeninges were observed. Coronal sections of the cerebrum revealed severe atrophy of the thalamus, lateral segment of the globus pallidus, and lateral geniculate body (Figs. 1, 2). Slight brownish discoloration was seen in the deep layer of the cerebral cortex and claustrum. In the brain stem, severe depigmentation of the substantia nigra and locus ceruleus, and atrophy of the red nucleus and pontine tegmentum were observed. The cerebellar folium, white matter and dentate nucleus were atrophic (Figs. 3, 4). The spinal cord was grossly unremarkable.

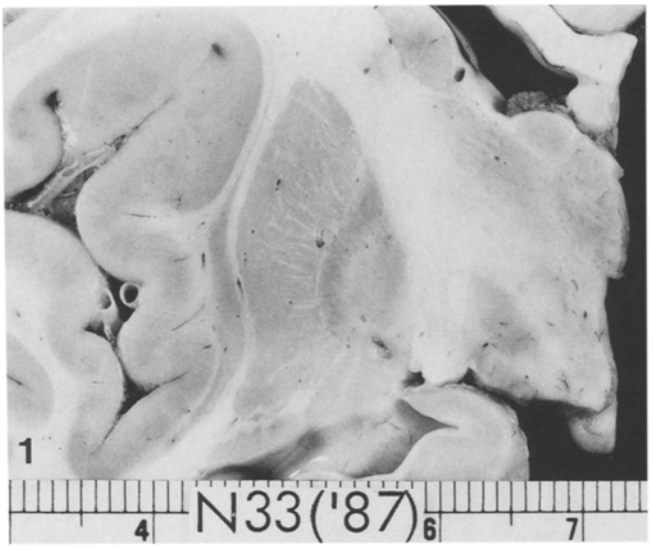
Light microscopy

Two kinds of lesions seemed to be present in the nervous system of this patient: neuronal loss and storage. The

Table 1. Topographic distribution of degree of neuronal storage and loss[a]

Sites or cells	Degree of storage	Degree of cell loss
Neocortical small neuron	+	−
Betz cell	+++	+
Hippocampus: CA 2, 3, 4	++	−
CA 1	−	−
Dentate gyrus: Anterior part	−	−
Basal nucl. of Meynert	+++	−
Diagonal band of Broca	+++	−
Neostriatum: Large neuron	++	−
Small neuron	+	−
Claustrum	+	−
Amygdaloid nucl.	+	−
Globus pallidus: Lateral segment	++	++
Medial segment	++	+
Thalamus: Anterior nucl.	++	−
Ventrolateral nucl.	++	+++
Ventral posterolateral nucl.	++	+++
Medial nucl.	++	++
Lateral geniculate body	++	++
Medial geniculate body	+	+
Hypothalamus: Anterior nucl.	+	−
Posterior nucl.	++	−
Subthalamic nucl.	+	−
Substantia nigra	++	+
Red nucl.	+	−
Superior colliculus	++	+
Inferior colliculus	+	+
Oculomotor nucl.	+++	−
Trigeminal mesenceph. nucl.	++	−
Tegmental pedunculopontine nucl.	+++	−
Locus ceruleus	++	−
Vestibular nucl: Superior	+	−
Lateral	+	−
Nucl. trapezoid body	++	−
Facial nucl.	+++	−
Pontine nucl.	+	−
Vent. Cochlear nucl.	++	−
Spinal trigeminal nucl.	++	−
Roller's nucl.	++	−
Dorsal Vagal nucl.	++	−
Hypoglossal nucl.	+++	−
Nucl. raphe magnus	++	−
Ambiguus nucl.	+++	−
Olivary nucl.	++	−
Gracile nucl.	+	+++
Cuneat nucl.	+	+
Cerebellum: Purkinje cell	+	+++
Golgi cell	+++	+
Granule cell	−	++
Dentate nucl.	++	+
Anterior horn cell	+++	−
Clarke's nucl.	++	−
Intermediolateral nucl.	++	−
Onuf's nucl.	+++	−
Sacral parasympathetic neuron	++	−
Posterior horn	+	−
Trigeminal ganglion	+++	−
Spinal ganglion	+++	+
Sympathetic ganglion	++	−
Myenteric plexus	++	−
Retina: Ganglion cell	++	++
Granule cell	−	−
Olfactory bulb: Mitral cell	++	−
Ant. olfactory nucl.	+	−
Choroid plexus epithel	+	−

[a] The degree was divided into four grades: +++, severe; ++, moderate; +, slight; −, no change



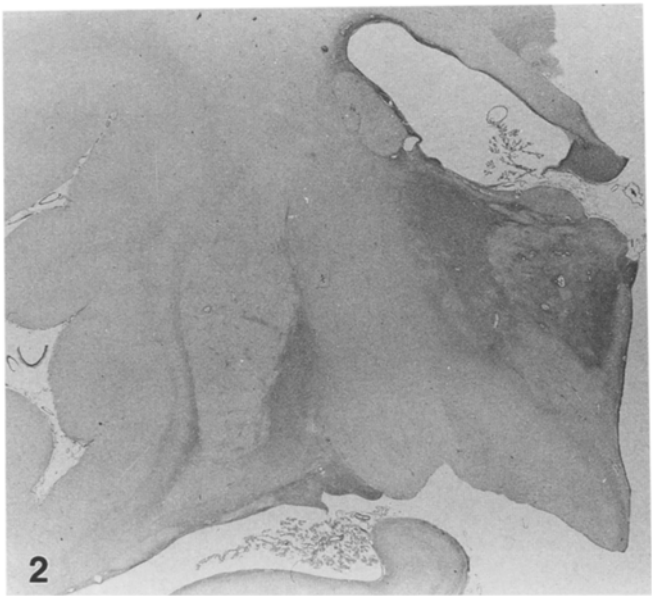
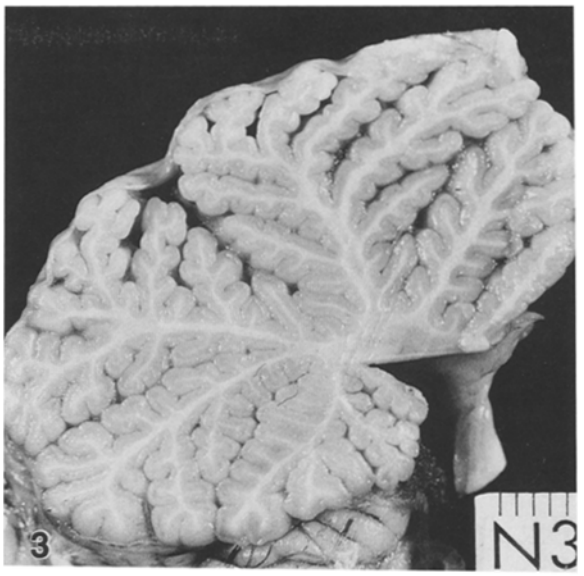


Fig. 1. Coronal section of the cerebrum revealing atrophy and brownish discoloration of the thalamus and lateral segment of the globus pallidus, and slight brownish discoloration in the deep layer of the cortex and claustrum. The subthalamic nucleus appears well preserved

Fig. 2. Severe fibrillary gliosis in the thalamus and lateral segment of the globus pallidus. Holzer preparation



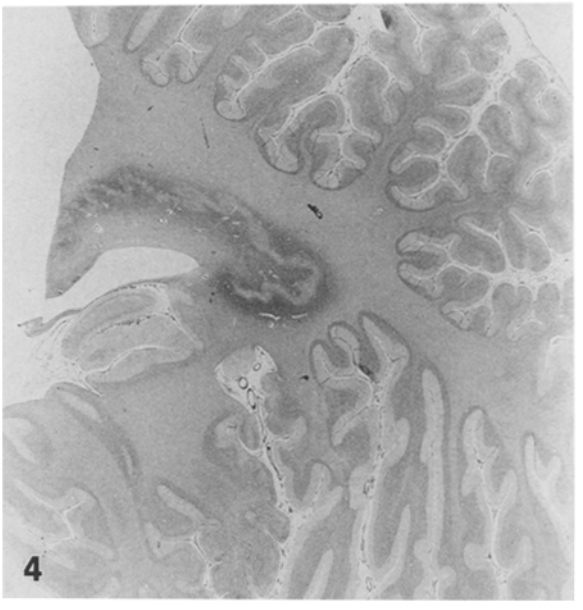


Fig. 3. Marked atrophy of the cerebellar vermis, especially in the superior

Fig. 4. Atrophy and gliosis of the dentate nucleus. Holzer preparation

topographic distribution and degree of decrease of neurons and intraneuronal storage are summarized in Table 1 and Fig. 5.

A severe decrease of neurons with fibrillary gliosis was seen in the lateral segment of the globus pallidus (Fig. 6), ventrolateral and ventral posterolateral nuclei of the thalamus, lateral geniculate body, Purkinje and granule cells of the cerebellum, gracile nucleus and ganglion cell layer in the retina. Loss of Purkinje and granule cells was diffuse, with severity in the superior vermis (Fig. 7). Moderate loss of neurons was observed in the medial segment of the globus pallidus, anterior and medial nuclei of the thalamus, the dentate and cuneate nuclei, and in the Betz cells and large neurons of the neostriatum.

Severe neuronal swelling was seen in the Betz cells, neurons of the basal forebrain and tegmental pedunculopontine nucleus, the motor neurons of the cranial nerve nuclei and spinal cord, and the neurons of the trigeminal and spinal ganglia.

The histological characteristics of the accumulated materials were quite different in various anatomical structures (Table 2). Storage material was positive in the small and medium-sized neurons of the cerebral neocortex by PAS, but negative by luxol fast blue, and showed yellowish-light blue autofluorescence under ultraviolet

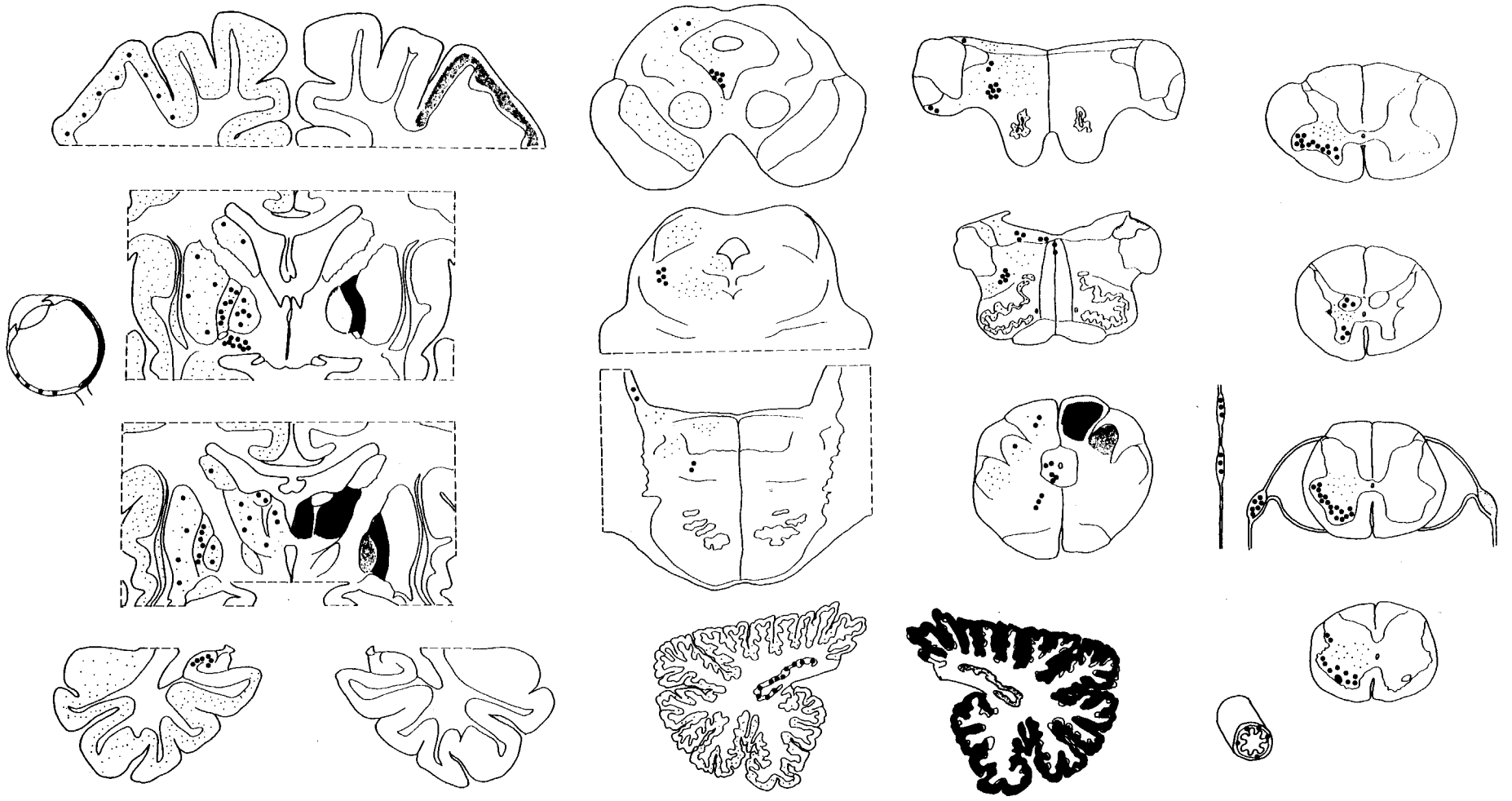


Fig. 5. Schematic demonstration of the topographic distribution of the swollen neurons (*dots* in the *left half* of the each section) and loss of neurons (*hatching* in the *right half* of the each section). Severe ballooning is indicated by *large dots*, and moderate ballooning by *small dots*. The degree of neuronal loss was divided into four grades, the severer ones represented by *darker hatching*

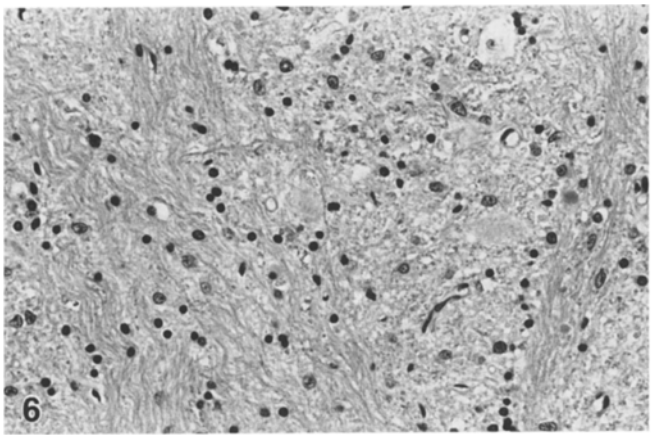


Fig. 6. Severe loss of neurons with gliosis in the lateral segment of the globus pallidus. Absence of macrophage infiltration. Hematoxylin-eosin, × 240

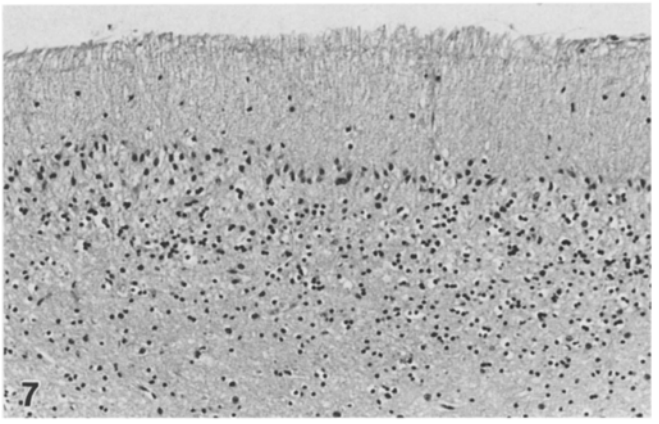


Fig. 7. Marked loss of Purkinje and granule cells in the superior vermis. Hematoxylin-eosin, × 130

Table. 2. Ultrastructural and histochemical findings[a]

	Neocortical neurons	Betz cells	Hippocampus: CA 2,3,4	Basal nucl. of Meynert	Globus pallidus: lateral seg.	Thalamus: Ventro-lateral nucl.	Purkinje cell	Dentate nucleus	Anterior horn cells	Clarke's nucleus	Spinal ganglion	Paravert. sympath. ganglion
Electron microscopy	Cytoplasmic vacuoles			Cytoplasmic vacuoles					Cytoplasmic vacuoles	Cytoplasmic vacuoles		Cytoplasmic vacuoles
			Lamellar and fingerprint like pleomorphic inclusions	Parallel and concentric lamellar inclusions	Tortuous tubular and parallel lamellar inclusions			Tortuous tubular and parallel lamellar inclusions	Parallel lamellar and pleomorphic inclusions		Wavy, and concentric and parallel lamellar inclusions	Parallel and concentric lamellar inclusions
Histochemistry												
Ninhydrin-Schiff	−		−	+	−				+/−	−		
Trypsin-Ninhydrin-Schiff	−		−	−	−				−	−		
Cresyl Violet (C.V.)	±	±	−	+/±	−	−	−	−	−/+	−	−	−
C.V.-Metachromasia	−	−	−	+/−	−	−	−	−	−/+	−	−	−
Periodic acid-Schiff (PAS)	+	−	+	+	+	+	+	+	±	+	−/+	−/±
Amylase-PAS	+	−	+	+	+				−	+	−/+	
Alcian Blue	−	±	±	+/−	±	−	−	−	+/±	−	±	
Aldehyde Fuchsin	+		+	+	+				+	+	+	
Toluidine Blue (T.B.)	+	−	+	+	+		+	+	−	−	−/+	
T.B.-Metachromasia	−	−	−	+/−	−		−	−	−	−	−	
Prussian Blue (P.B.)	−	−	−	−	+	−	−	−	−	−		
P.B.-colloidal	−		±	−	+	−	−	−	−	−		
Bial	+		+				+	+	+	+	+	
Sudan III	−		±	−	±				−	−	−	
Sudan Black B.	+		+	+	+				+/±	+	+	
Nile Blue	+		+	+	+				+	+	+	
Bleach-Nile Blue	+		+	+	+				+	+	+	
Luxol Fast Blue	−	+	+	+	+	+	+	+	+/−	+	−/±	−
Diphenylcarbazide			+	+	+				+	+	+	
Autofluorescence	+	±	+	+	+	+	+	+	±	+	+/−	±/−
Schmorl	+		+	±	+				+	+		
Bodian	−	−	+	+	+	+	−	+	+/−	+	+/−	
Kossa	−		−	−	−				−	−		
Fontana	−		±	−	−				+/−	−		
Iodine-Fontana	−		−	−	−				−	−		

[a] Degree of staining = +, positive; ±, faint; −, negative; +/−, co-existence of positively and negatively stained neurons

light. On the other hand, most of the stored material in the Betz cells was negative in PAS and toluidine blue preparations but positive with luxol fast blue. Autofluorescence was only faintly positive. The neurons in the CA2, -3 and -4 of the hippocampus were swollen and positive by PAS, toluidine blue, luxol fast blue and autofluorescence. The neurons in the globus pallidus were only positive in Prussian blue preparation. In the basal nucleus of Meynert, alcian blue-positive vacuoles showing metachromasia were separated from the diffusely accumulated amylase-digested PAS-positive fine granules in the cytoplasm. The anterior horn cells were positive by Nile blue and weakly positive by PAS and showed faint autofluorescence. In the anterior horn, neurons with alcian blue-positive vacuoles, and alcian blue weakly but diffusely positive neurons were mixed. In contrast, the neurons in Clarke's nucleus were positive with PAS staining and disclosed obvious autofluorescence. In the spinal ganglia, there was a mixture of positively and negatively stained neurons in PAS, luxol fast blue, toluidine blue or Fontana preparations. In these neurons, the storage material was generally present in the cell perikarya; however, Purkinje cells showed swelling at the proximal dendrites, with slight ballooning of the perikarya. Most of the examined neurons were positive in Bial staining (Table 2).

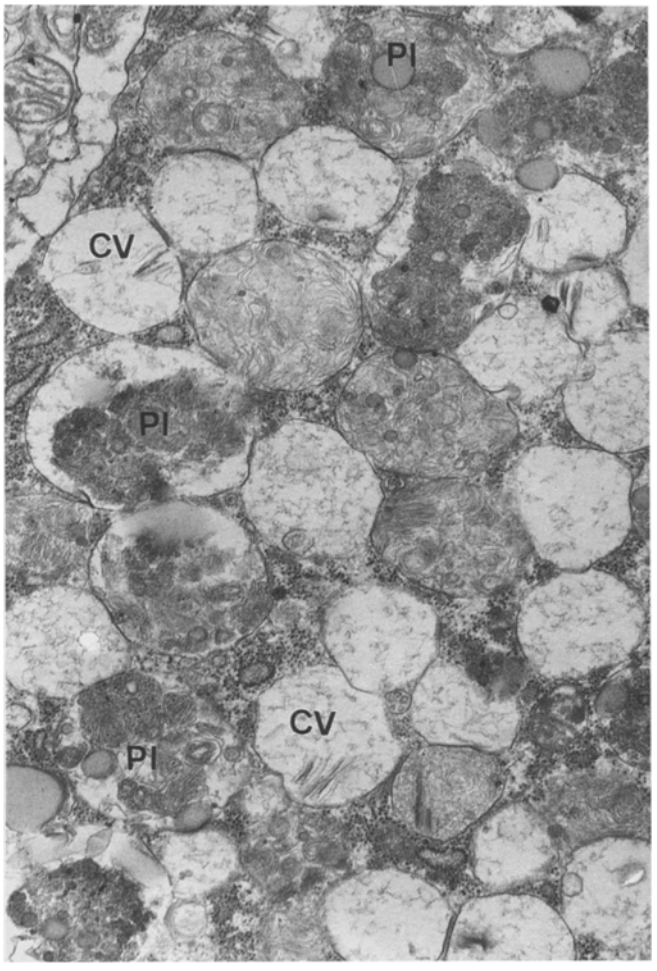


Fig. 8. Mixed accumulation of cytoplasmic vacuoles (*CV*) with fine granules and loose lamellar material, and membrane-bound fingerprint-like lamellar pleomorphic inclusions (*PI*) with tiny lipid droplets. A neuron of CA2 of the hippocampus. Uranyl-lead, × 19,000

The severity of the neuronal storage did not generally correlated with the decrease of neurons (Table 1, Fig. 5). In the globus pallidus, thalamus, lateral geniculate body and retina, the degree of neuronal storage and depletion seemed parallel. However, the Purkinje and granule cells and the neurons in the gracile and cuneate nuclei were severely decreased, although the amount of storage was samll. In contrast, neurons in the CA2 and -3, basal nucleus of Meynert, anterior nucleus of the thalamus, motor neurons of the cranial nerve nuclei and spinal cord, Clarke's and Onuf's nuclei and trigeminal ganglion showed severe ballooning, but no obvious loss of neurons.

The optic nerves and external sagittal stratum of the occipital lobe were severely atrophic and the myelinated fibers were markedly reduced. The tegmentum of the pons was severely reduced, and the cerebellar white matter was atrophic and showed gliosis. The centrum semiovale of the cerebrum and the white matter of the spinal cord showed no evident degeneration. Many spheroid bodies and globules were observed in the anterior horn, but only a few torpedoes were seen in the cerebellum. The cranial and spinal nerve roots looked well preserved, but the sural nerve showed slight loss of myelinated fibers. The skeletal muscles showed no evident alteration. No neurofibrillary tangles, spongy state, globoid cells, macrophages or lymphocytic infiltration were seen. A few PAS-positive cells were observed in the pineal body.

The areas showing no evident neuronal storage or loss were as follows; the CA1 of the hippocampus, anterior part of the dentate gyrus, anterior hypothalamus, supraoptic nuclei, and retinal granule cells.

Electron microscopy

A variety of intracytoplasmic and intranuclear inclusions was observed. These were membranous cytoplasmic bodies (MCBs), parallel or wavy-lamellar structures, tortuous tubular inclusions, lipofuscin-like irregular-shaped pleomorphic bodies, and cytoplasmic vacuoles with loose lamellar structures and fine granules (Table 2). The neurons in CA2 of Ammon's horn contained cytoplasmic vacuoles with loose lamellar structures and fine granules, membrane-bound fingerprint-like lamellar inclusions and lipofuscin-like pleomorphic inclusions, with tiny lipid droplets (Fig. 8). On the other hand, intracytoplasmic inclusions in the neurons of the basal nucleus of Meynert were MCBs, zebra bodies, myelin figures, and cytoplasmic vacuoles. In the neurons of the globus pallidus and dentate nucleus, tortuous tubular and parallel lamellar inclusions were observed in continuity (Fig. 9). The diameter of the tubular structures was 8–9 nm, the thickness of the dense line of the lamellar structure was 1.3 to 2.6 nm, and that of the clear line, 4 nm. In the spinal anterior horn, anterior horn

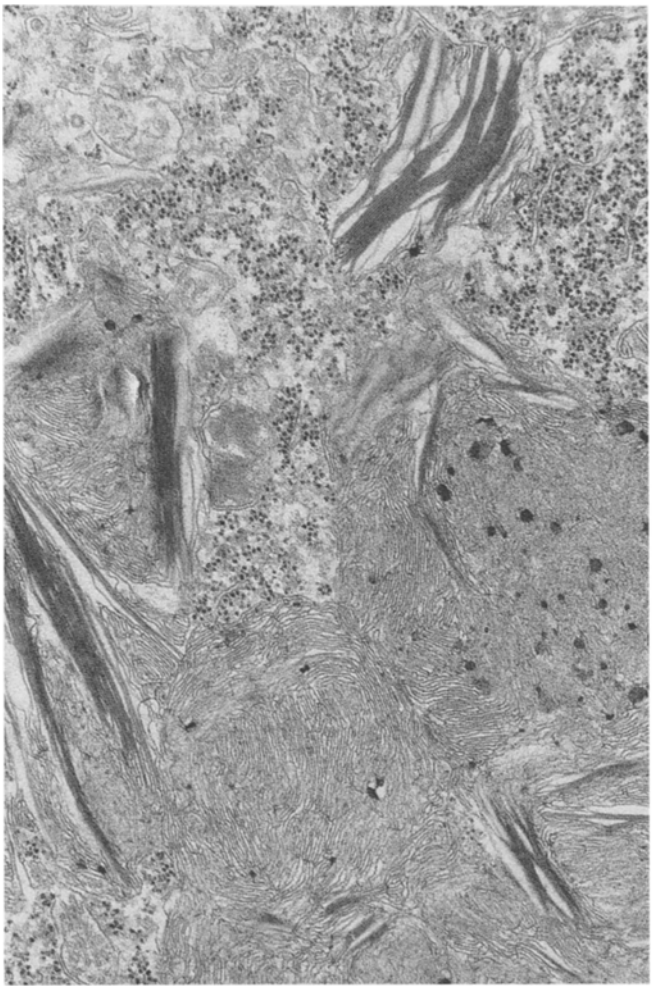


Fig. 9. Tortuous and parallel lamellar inclusion in continuity in a neuron of the dentate nucleus. Uranyl-lead, × 28,000

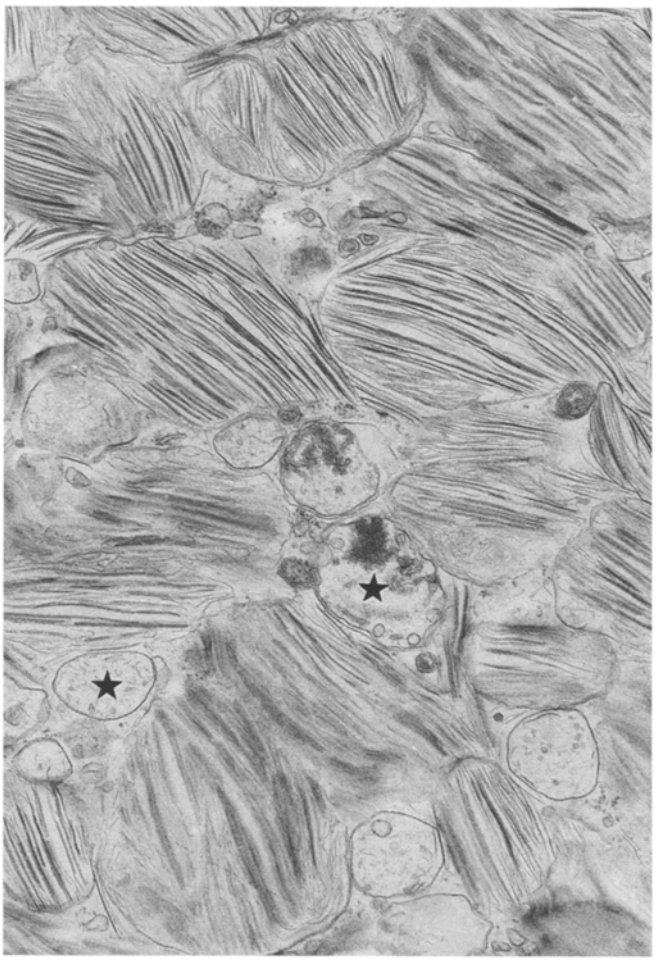


Fig. 10. Membrane-bound parallel lamellar inclusions and tiny cytoplasmic vacuoles (★) with fine granules in an anterior horn cell. Uranyl-lead, × 12,000

cells containing membrane-bound parallel lamellar structures and tiny cytoplasmic bodies with reticular substance and fine granular materials (Fig. 10) co-existed with cells storing large cytoplasmic vacuoles and pleomorphic inclusions. Inclusion bodies in the spinal ganglia were also heterogeneous. Some ganglion cells contained concentric or wavy-lamellar inclusions with lipid droplets, and others stored cytoplasmic vacuoles with fine granules and loose lamellar structure. The thicknesses of the dark and light lines of the parallel lamellar structures were each about 2.5 nm, and the periodicity of the alternating dark and light lines about 5 nm. Astrocytes and Schwann cells contained cytoplasmic vacuoles with fine granules. None of the neurons had curvilinear profiles.

Discussion

This patient was diagnosed as having galactosialidosis on the basis of clinical manifestations and biochemical findings of a deficiency of sialidase and β-galactosidase in the lymphocytes and cultured fibroblasts [21].

There have been several reports of pathological findings in the central nervous system of individuals who showed deficiencies of both sialidase and β-galactosidase activities [1, 3, 12, 14, 20], as well as other possible cases without enzymatic data [4, 6, 7, 16]. The patients with the adult/juvenile-type disease showed marked swelling and storage of the motor neurons of the brain stem and spinal cord, and of the neurons of CA1 to -4 of the hippocampus, basal nucleus of Meynert, thalamus, hypothalamus, lateral geniculate body, pontine nucleus, Purkinje cells, dentate nucleus, dorsal vagal nucleus, Clarke's nucleus, and spinal ganglia. The main components of the stored materials were thought to be phospholipids and glycolipids, and the histochemical characteristics of the storage materials varied in staining from region to region. Electron microscopically, these stored materials were composed of membrane-bound lamellar or lipofuscin-like structures [1, 3, 4, 6, 7, 10]. Loss of neurons was observed in the cerebral cortex, dentate nucleus and Purkinje cells [1, 6, 7]. In a case of early infantile-type galactosialidosis, neuronal swelling was seen in the spinal cord, paraganglia and Auerbach's myenteric plexus, the storage materials being composed

of lamellar structures and membrane-bound vacuoles. The number of Purkinje cells was reduced [20].

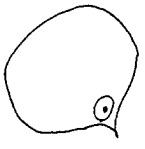
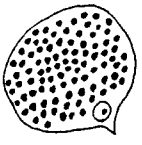
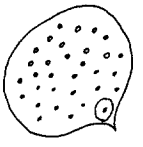
The intraneuronal-stored materials in the present patient seemed to be classified into five groups morphologically (Table 3). In each neuron various ratios of these groups of inclusions were found: Group I comprised materials which were faintly stained in PAS and alcian blue preparation and mainly composed of concentric, wavy- or parallel-lamellar structure, and which were located in the motor neurons, basal nucleus of Meynert, and spinal and sympathetic ganglia. PAS-positive and alcian blue-negative granular materials were composed of two kinds of inclusions (Groups II a & b). Group IIa consisted of lipofuscin-like pleomorphic inclusions in the hippocampal pyramidal and neocortical small neurons. Group IIb comprised tortuous tubular inclusions observed exclusively in the dentate nucleus and globus pallidus. Gruop III comprised alcian blue-positive and PAS-negative large cytoplasmic vacuoles in the neurons of the basal nucleus of Meynert and the motor neurons of the brain stem and spinal cord. Group IV consisted small cytoplasmic vacuoles with lamellar structure observed in the motor and hippocampal pyramidal neurons and the neurons of spinal and sympathetic ganglia.

The heterogeneity of the stored materials in various anatomical structures and neurons may be reflections of the difference in metabolic pathways and amount of synthesized substrates in these sites; it may also indicate the occurrence of secondary storage by successive suppression and/or hyperactivation of some enzymes other than sialidase and β-galactosidase. The neuropathological findings indicated that not only glycolipids, but also mucopolysaccharides were stored in the neurons. The galactose residues of keratan sulfate, which is one of the mucopolysaccharides, were removed by β-galactosidase. Although total absence of β-galactosidase activity results in G_{M1} gangliosidosis, a different molecular defect of β-galactosidase could lead to the accumulation of keratan sulfate, known as mucopolysaccharidosis IVB [5]. Further biochemical study is needed to identify the mucopolysaccharides accumulated in the present case.

In the present patient, the severity of the neuronal loss was not uniformly correlated with the amount of the storage materials. On the mechanism of loss of neurons, the occurrence of tortuous tubular inclusions, which were observed in the dentate nucleus and globus pallidus showing severe decrease of neurons, seemed to correlate with neuronal degeneration (Tables 1–3). In addition, there could be three possible mechanisms of neuronal loss. The first is that it arose in regions where the accumulation occurred earlier; the second is that the decreased neurons were especially vulnerable to the stored materials; and the third is that some toxic substance, such as psychosine in Krabbe's disease [9], was formed exclusively in these depopulated neurons.

In the previously reported cases of galactosialidosis, loss of neurons in the cerebral cortex, dentate nucleus and Purkinje cells was observed in the adult/juvenile type [1, 6, 7], and decrease of Purkinje cells in the early infantile-type [20]. However, severe-to-moderate loss of neurons with marked gliosis in the globus pallidus, thalamus, lateral geniculate body, gracile nucleus, and retinal ganglion cells that was revealed in the present patient of the late infantile-type has not been previously reported. Such a constellation of findings has not been observed in disorders other than galactosialidosis. These findings may reflect the nature of the disease; however, elucidation of the significance of these findings in the

Table 3. Intraneuronal stored materials classified into five groups histochemically and ultrastructurally

Types of stores material	I	II_a	II_b	III	IV
Histological characters of stored materials in PAS or alcian blue preparation					
PAS	±	+	+	+	±
Amylase-PAS	−	+	+	−	−
Alcian blue	−	−	−	+	±
Sudan, Nile blue	+	+	+	−	+
Autofluorescence	−	+	+	−	−
Electron microscopic findings	Concentric, wavy or parallel lamellar inclusion	Pleomorphic body	Tortuous tubular inclusion	Large cytoplasmic vacuole	Cytoplasmic vacuole with lamellar structure
Localization	Betz cell, Meynert, motor neuron in brain stem, ant. horn cell, spinal ggl., symp. ggl., myenteric plexus	Hippocampus, cortical small neuron, Clarke's nucl.	Globus pallidus, dentate nucl.	Meynert, motor neurons in brain stem, ant. horn cell	Hippocampus, Betz cell, motor neurons in brain stem, ant. horn cell, spinal ggl., symp. ggl.

disease process is not yet possible. Further studies are needed to clarify the mechanism of neuronal storage and loss caused by the primary defect of a 'protective' protein in this disease.

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