

Kyoko Itoh · Kensuke Shiga · Kentaro Shimizu
Manabu Muranishi · Masanori Nakagawa
Shinji Fushiki

Autosomal dominant leukodystrophy with axonal spheroids and pigmented glia: clinical and neuropathological characteristics

Received: 19 August 2005 / Revised: 20 September 2005 / Accepted: 20 September 2005 / Published online: 23 November 2005
© Springer-Verlag 2005

Abstract We report two autopsy cases of siblings with adult-onset autosomal dominant leukodystrophy characterized by destruction of cerebral white matter, large numbers of axonal spheroids and pigmented glia in the fronto-temporal lobes. Both patients presented with motor and cognitive symptoms and aphasia, 2–3 years before death. At autopsy, the brain showed brown coloration and decreased volume of white matter in the frontal and temporal lobes as well as corpus callosum. Microscopically, marked loss of myelin and axons and abundant axonal spheroids without apparent neuronal loss were observed in the frontal and temporal lobes, which was consistent with hereditary diffuse leukodystrophy with spheroids (HDLS). In addition, glial cells, most consistent with macrophages and containing pigments that were stained by Sudan III and PAS, were found in the white matter lesions. The present cases showed overlapping features with HDLS and pigmentary type of orthochromatic leukodystrophy, suggesting that the pathomechanisms of these two diseases are closely related.

Keywords Autosomal dominant leukodystrophy · Neuroaxonal spheroids · Pigmentary orthochromatic leukodystrophy · Fronto-temporal dementia

K. Itoh (✉) · S. Fushiki
Department of Pathology and Applied Neurobiology,
Graduate School of Medical Science,
Kyoto Prefectural University of Medicine,
Kawaramachi-Hirokoji, Kamigyo-ku,
602-8566 Kyoto, Japan
E-mail: kxi14@koto.kpu-m.ac.jp
Tel.: +81-75-2515849
Fax: +81-75-2515849

K. Shiga · M. Muranishi · M. Nakagawa
Department of Neurology, Graduate School of Medical Science,
Kyoto Prefectural University of Medicine, Kyoto, Japan

K. Shimizu
Department of Neurology, Nishi-Kyoto Hospital, Kyoto, Japan

Introduction

Non-metachromatic or orthochromatic leukodystrophy is a heterogeneous group of neurological disorders characterized by progressive demyelination of the white matter. The basic biochemical or gene defect remains unknown; however, a few families with dominant inheritance have been described [1, 2, 4, 11, 14, 17]. Hereditary diffuse leukodystrophy with spheroids (HDLS), one group of orthochromatic leukodystrophy, was first described in 1984 and is characterized by widespread degeneration and loss of myelin sheaths and axons, and abundant neuroaxonal spheroids[1].

Among the orthochromatic leukodystrophies, pigmentary type of orthochromatic leukodystrophy (POLD) has been described as a disorder showing pigmented macrophages and other glia in a background of widespread myelin loss [2, 3, 5, 6, 7, 8, 9, 10, 12, 13, 15]. The dark-yellow-brown pigment was autofluorescent, sudanophilic and non-metachromatic, and ultrastructural features were similar to those of lipofuscin or ceroid. Recently, Marotti et al. [4] reported a two-generation family with apparent overlapping of these two entities. Here we report clinical and neuropathological findings from two siblings with HDLS associated with pigmented glia, who were clinically diagnosed with fronto-temporal dementia. Neuropathological findings included demyelination, abundant ubiquitin-immunoreactive spheroids and pigmented glia in the subcortical white matter, which suggested a disease spectrum including HDLS and POLD.

Case report

Case 1

The patient, a 52-year-old male, became indifferent to his sanity and his gait became unstable and he spoke far less than before. His previous medical history was unremarkable. One of his brothers died of progressive

dementia and gait instability at the age of 48 and his mother also died of dementia at the age of 64. His uncle and his two children (the patient's cousins) also died of progressive dementia (see Fig. 1). The score of a Mini Mental State Examination was 21 points. On psychological examination, verbal IQ was 71 and practical IQ was 55 in Wechsler adult intelligence scale-revised (WAIS-R). The amount of voluntary speech decreased; however, naming of objects, understanding of spoken and written language and repetition were almost preserved. On the other hand, the patient could not elaborate the meaning of simple proverbs. The magnetic resonance imaging (MRI) revealed marked atrophy of the frontal lobes and confluent T2-high-intensity in the subcortical white matter and genu of the corpus callosum (Fig. 2). SPECT showed marked hypoperfusion of frontal and temporal lobes (Fig. 3). Based on his clinical and radiological features, he was diagnosed with autosomal dominant progressive subcortical gliosis (FPSG), a subtype of fronto-temporal dementia (FTD). Two years after the

initial symptoms, he died of pneumonia and respiratory failure.

Case 2 (the elder brother of the patient 1)

This patient had been well until the age of 45 years, when he began to have troubles with his colleagues because of his memory impairment. His superior encouraged him to visit a hospital, where a battery of intelligence testing was performed and he was diagnosed as having presenile dementia. The next year, his amnesic symptoms gradually progressed and he had to quit working. At the age of 46, he began to have sanity problems, such as urination on trains or getting lost in the neighborhood. The following year he started to have difficulty in walking and became mute. At the age of 47, he became bedridden and incapable of eating, resulting in hypoalimentation and dehydration, and he was admitted to a hospital. These conditions were alleviated with intravenous hyperalimentation;

Fig. 1 Family tree of the present cases. *Closed circles and squares* show family members with similar clinical features of dementia and gait instability. The *arrow and arrowhead* indicate case 1 and case 2, respectively. The numbers on the *right* indicate the age at their deaths

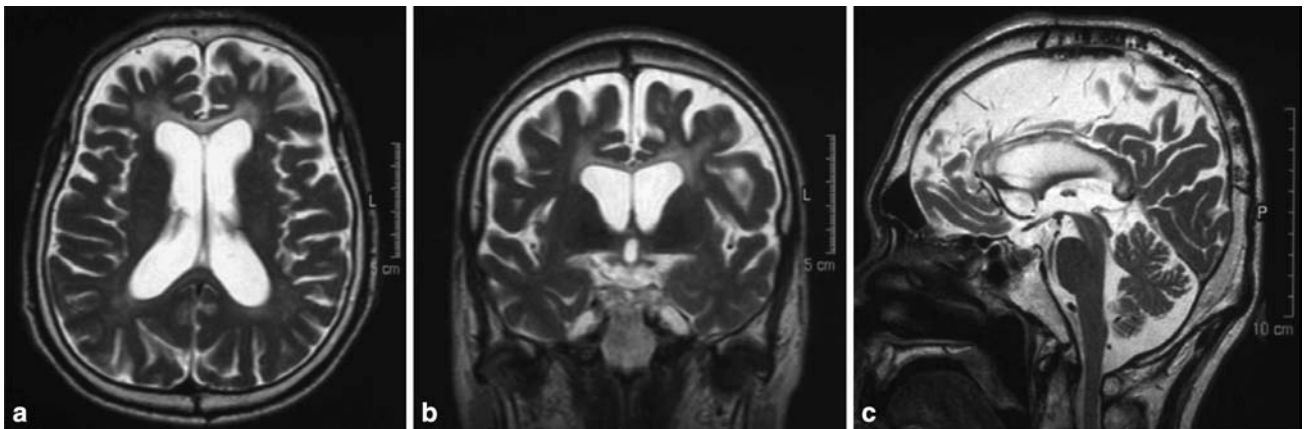
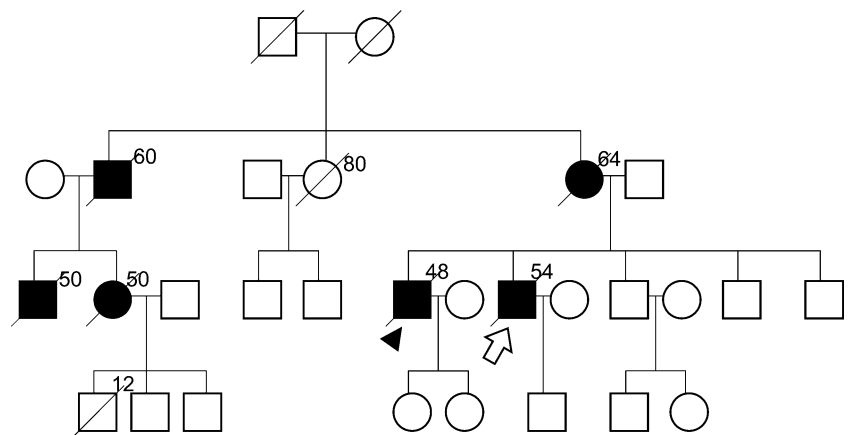


Fig. 2 a–c Axial (a), coronal (b), and sagittal (c) T2-weighted images of case 1 are presented. There is significant atrophy of the bilateral frontal lobes. There are areas of diffuse hyperintensity at the white matter of the bilateral frontal lobes and also at the corpus callosum.

Note that there is substantial callosal atrophy, which is especially severe at the genu and body. A small focus of signal abnormality is identified within the splenium of the corpus callosum. Other parts of the brain appear to be relatively well preserved

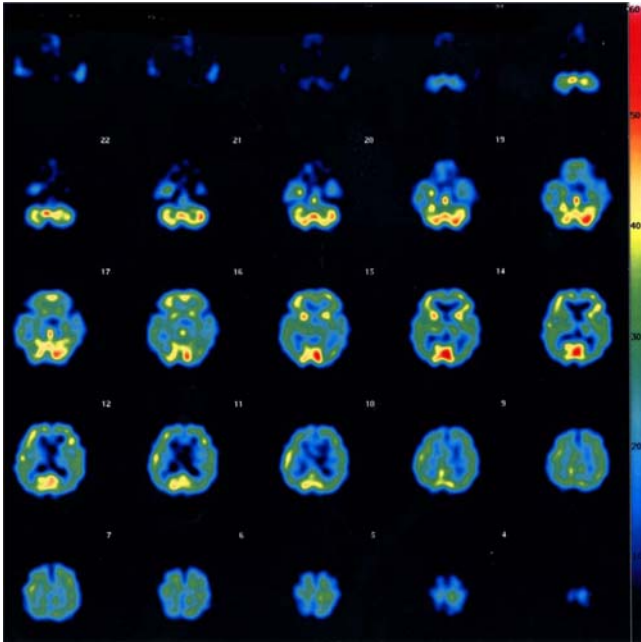


Fig. 3 SPECT images of case 1 reveal substantial decreases in flow at the bifrontal and temporal lobes in largely symmetric fashion. Relative sparing of blood flow is noted at the structures of the posterior fossa and occipito-parietal lobes

however, he soon developed bronchopneumonia and died of respiratory failure at the age of 48. The cranial MRI revealed marked atrophy in the fronto-temporal lobes and diffuse high intensity in the subcortical white matter of the frontal cortices in T2-weighted images.

Neuropathological analyses of the two cases

The brains, weighing 1170 g in case 1 and 1190 g in case 2, showed moderate atrophy of the frontal and temporal lobes, with symmetrical dilatation of the lateral and third ventricles (Fig. 4a–c). The subcortical white matter of the gyrus cinguli, gyrus frontalis superior, medius and inferior, gyrus precentralis, and gyrus temporalis medius and inferior showed marked reduction in the volume and brown coloration with relatively preserved gyrus temporalis superior, gyrus temporalis transverse, planum temporale, gyrus parahippocampalis, gyrus occipitotemporalis, and hippocampus (Fig. 4b, c). The body and genu of the corpus callosum showed marked atrophy (1.5 mm in thickness at the body) and softening. The pigmentation of the substantia nigra and locus coeruleus was normal. The brain stem, cerebellum and nucleus dentatus showed no pathological findings. The spinal cord at the level of the cervical and thoracic cord showed no marked atrophy.

Microscopically, the brains from both cases 1 and 2 showed diffuse loss of axons and myelin, numerous spheroids and intense astrogliosis in the subcortical

white matter of the frontal and temporal lobes and of the gyrus cinguli (Fig. 5a–d). Spheroids were present in the center and periphery of the white matter lesions in both cases; however, they were more pronounced in case 1 [12–13/high power field (HPF), i.e., entire field at $\times 400$ magnification; 0.196 mm^2] in the gyrus precentralis, 7–8/HPF in the gyrus temporalis medius in case 1, but 6–7/HPF in the gyrus precentralis and 3–4/HPF in the gyrus temporalis medius in case 2. The spheroids were immunoreactive for ubiquitin (Fig. 5d) and neurofilament. Within the white matter lesions, there were numerous glial cells, most of which were consistent with macrophages or microglia, containing yellow-brown granules that were positively stained by Sudan III, PAS and iron (Figs. 5e; 6a, b, d) and emitted yellow-green autofluorescence under UV light (Fig. 6c) in both cases 1 and 2. Morphologically, very few of pigmented glia appeared to be astrocytes or oligodendroglia. Choroid plexus epithelial cells and ependymal cells contained no pigment.

Cortical laminar architecture was well preserved without apparent neuronal loss. A few ballooned-like neurons, showing abundant and achromatic cytoplasm, were observed in the fronto-temporal cortices (Fig. 7a–c) in cases 1 and 2. The ballooned-like neurons showed faint immunoreactivity for ubiquitin (Fig. 7b), but no immunoreactivity for phosphorylated tau or α -synuclein. Gallyas-Braak and Bodian staining did not demonstrate argentophilic inclusions in the neurons and glia, senile plaques, neurofibrillary tangles, astroglial plaques or neuropil threads. No inclusions or substances immunoreactive for phosphorylated tau were found. Intense astrogliosis, immunoreactive for glial fibrillary acidic protein (GFAP), was observed in the subpial cortical zone and at the junction of the cortex and white matter. Mild hypoxic changes without apparent neuronal loss were observed in the CA1–3, hilus and dentate gyrus of the hippocampus. No ballooned neurons containing Pick bodies were found in the hippocampus. The corpus callosum was remarkably decreased in volume, accompanied by diffuse loss of axons and myelin, numerous spheroids, pigmented macrophages and intense astrogliosis. The capsula interna, externa and extrema showed myelin pallor and intense astrogliosis with numerous spheroids. The basal ganglia and thalamus showed moderate astrogliosis without marked neuronal loss. The substantia nigra showed neither loss nor degenerative changes of pigmented neurons. The pyramidal tract of the midbrain, pons and medulla oblongata showed axonal loss with microvacuolation and numerous spheroids (Fig. 8a, b) in cases 1 and 2. The bilateral tractus pyramidalis lateralis showed diffuse loss of myelin and axons, deposition of spheroids and intense astrogliosis at the cervical, thoracic and lumbar cord (Fig. 8c, d) in case 1. No loss or degenerative changes of the motor neurons were observed in the anterior horn of the cervical, thoracic, and lumbar cord of either case.

Fig. 4 a-c Gross findings of the brain from case 1. **a** Dorsal view of the brain showing moderate atrophy of the frontal lobe. **b, c** Coronal sections of the fixed brain showing decreased volume and irregular brown coloration of the frontal and temporal white matter with marked thinning of the corpus callosum and symmetrical ventricular dilatation. The area indicated by an *asterisk* was dissected for storage as frozen material. *Bar* 2.5 cm

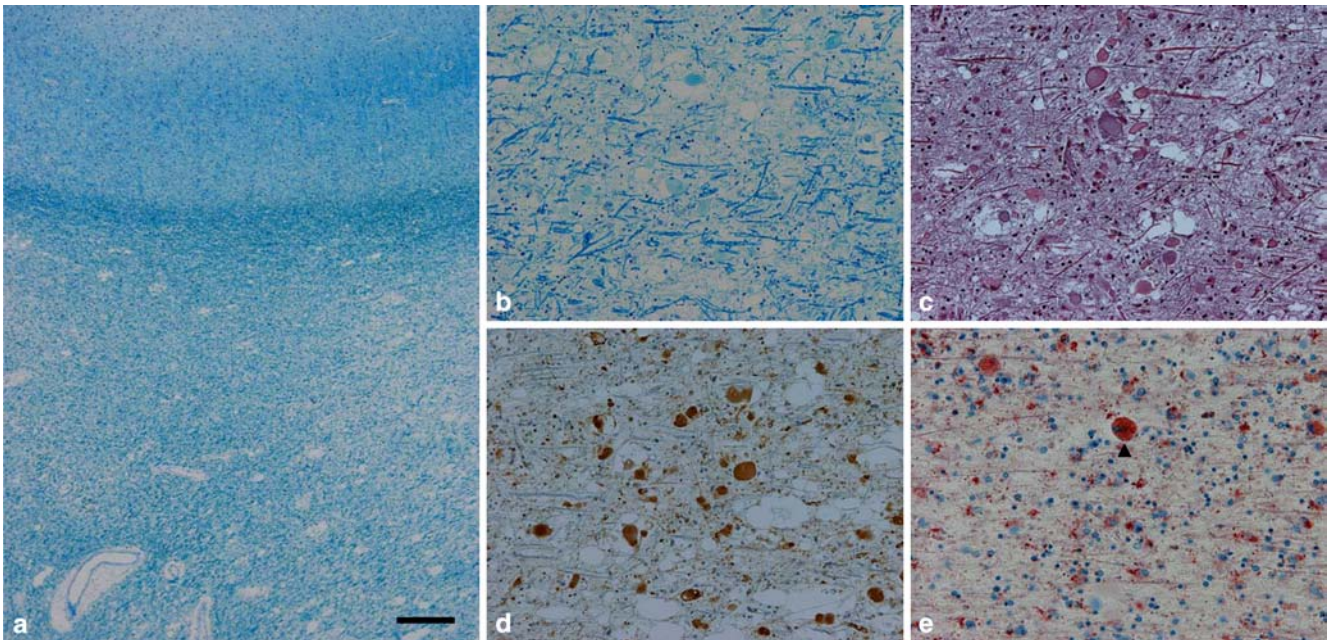
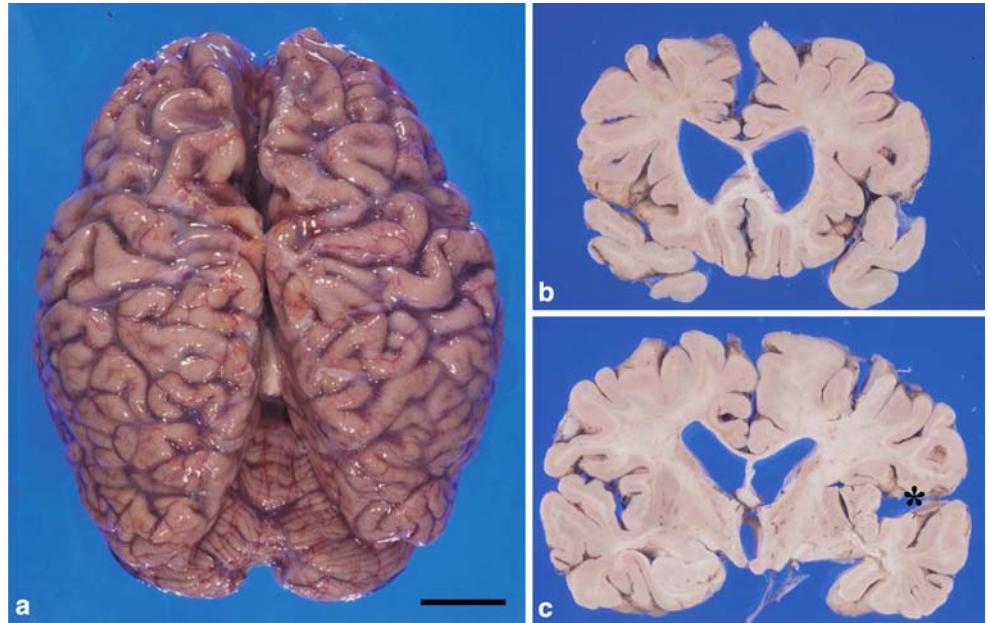


Fig. 5 a-e White matter lesions of the motor cortex from case 1. **a** Marked myelin loss of the subcortical white matter with spared U-fiber, KB staining. **b-d** Numerous axonal spheroids in the white matter lesion; **b** KB staining, **c** Bodian staining, **d**

immunohistochemistry for ubiquitin. **e** Abundant sudanophilic macrophages (*arrowhead*) in the white matter, Sudan III (*KB Klüver-Barrera*). *Bar* **a** 400 μ m, **b-e** 90 μ m

Discussion

The neuropathological findings in the present cases showed marked loss of myelin and axons, abundant spheroid deposition and numerous pigmented macrophages with preferential involvement of the frontal and temporal white matter. The fronto-temporal localization of the lesions might have led to a clinical diagnosis of a

type of fronto-temporal dementia, such as Pick's disease, FTDP-17, motor neuron disease type dementia or familial progressive subcortical gliosis. However, the pathology of these two cases showed a marked loss of axons and myelin without loss of neurons, including cortical as well as motor neurons, and a lack of abnormal inclusions in neurons or glia immunoreactive for phosphorylated tau. These neuropathological findings suggested a type of adult-onset dysmyelinative

Fig. 6 a-d White matter lesions of the motor cortex from case 2. **a, b** Axonal spheroids (*arrow*) and pigmented macrophage (*arrowheads*); **a** HE staining, **b** PAS. **c, d** Pigmented macrophages (*arrowheads*) showing autofluorescence under UV light (**c**) and pigments containing iron (**d**); **c** fluorescence micrograph, **d** Berlin blue staining (*HE* hematoxylin and eosin, *PAS* periodic acid-Schiff). *Bar* **a-d** 50 μ m

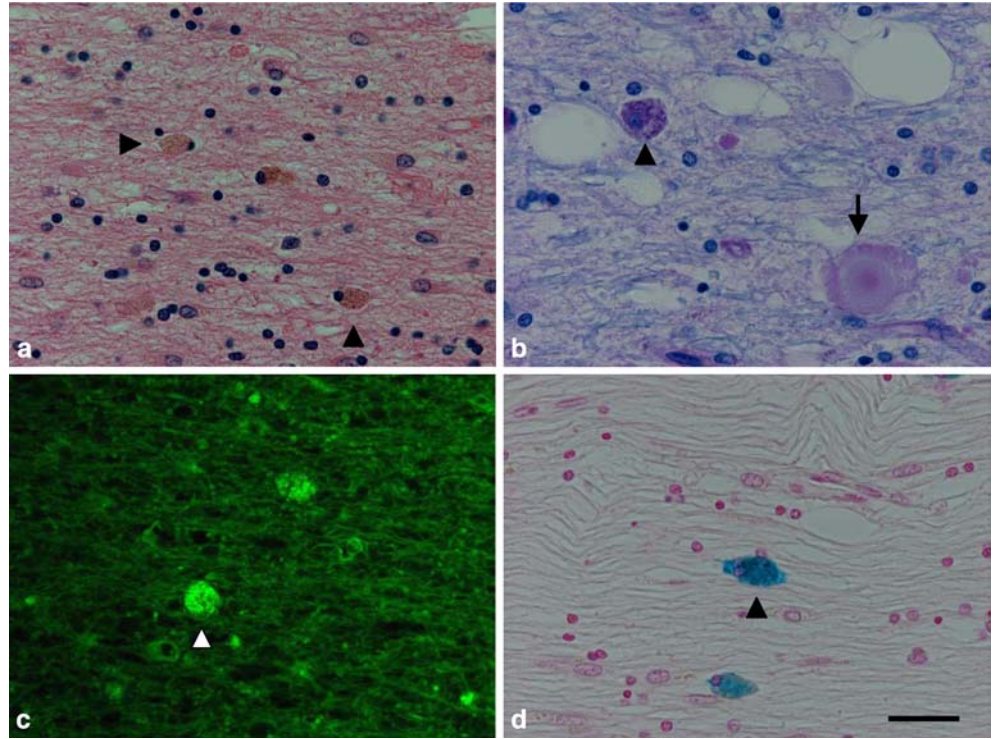
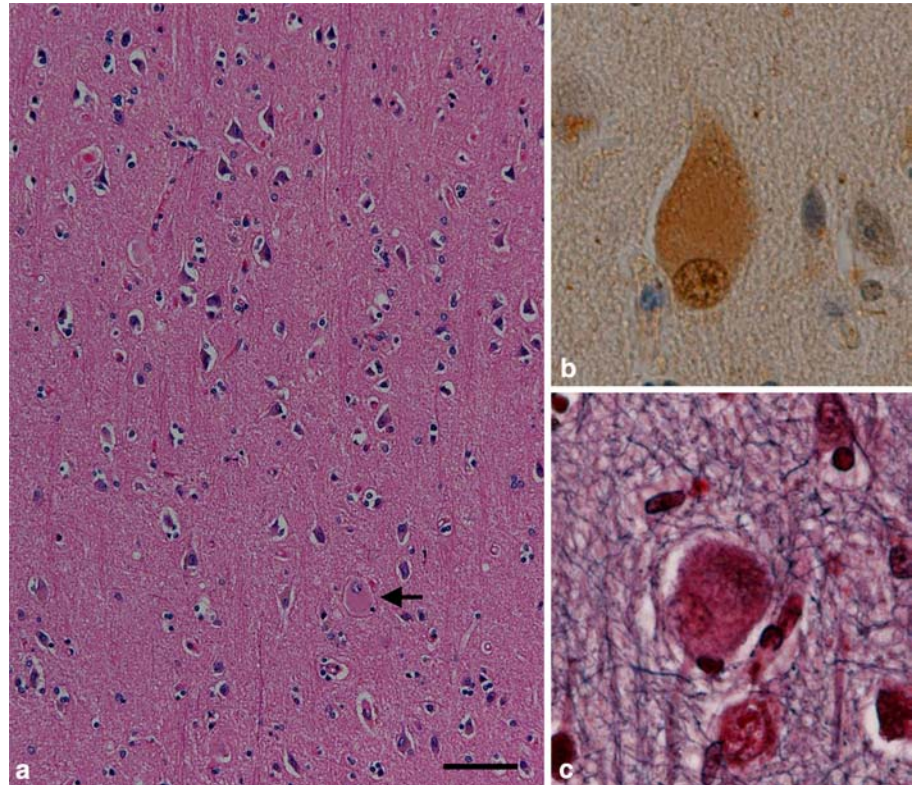


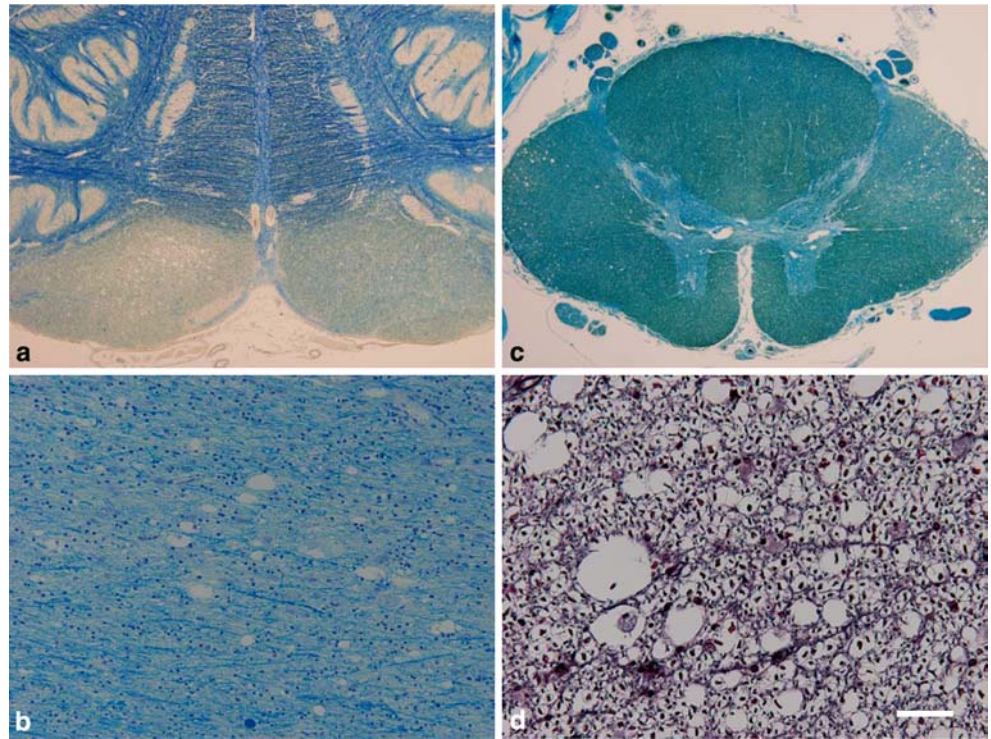
Fig. 7 a-c Frontal cortex of case 1. Ballooned neurons (*arrow*) showing immunoreactivity for ubiquitin (**b**), but containing no argentophilic inclusion (**c**), are occasionally observed without apparent neuronal loss. **a** HE staining, **b** immunohistochemistry for ubiquitin, **c** Bodian staining. *Bar* **a** 90 μ m, **b, c** 30 μ m



leukodystrophy, such as metachromatic leukodystrophy or some orthochromatic leukodystrophy. Pigmented granules in macrophages showed no metachromasia, but

were positively stained by Sudan III, which supported the possibility of some type of sudanophilic leukodystrophy [4, 5, 6, 8, 9, 11].

Fig. 8 a–d Asymmetric degeneration of the corticospinal tract. **a, b** Medulla oblongata from case 2 showing asymmetric loss of myelin in the pyramis; **a, b** KB staining. **c, d** Cervical cord of case 1 showing loss of large axons and myelin; **c** KB staining, **d** Bodian staining. *Bar a, c* 800 μ m, *b, d* 80 μ m



The present cases showed abundant spheroid deposition in addition to marked loss of myelin and axons in the frontal and temporal white matter, which was consistent with HDLS except for the existence of pigmented macrophages and the unique localization of the white matter lesions. Previous reports described the lesions of white matter in HDLS as being severer in the frontal and parietal lobes [1, 4, 11, 14, 17]. In the present cases, the white matter lesions were severest in the motor area as well as cingulate cortex, resulting in asymmetric pyramidal degeneration in the spinal cord, as previously reported [16, 17]; however, motor neuron disease-like signs were not observed throughout the clinical course. Characteristic findings in POLD include pigmented glia containing yellow-brown granules, which show both sudanophilia and autofluorescence present, within the white matter lesions [2, 3, 5, 6, 7, 8, 9, 10, 12, 13, 15]. Recently, Marotti et al. [4] reported three cases of adult-onset autosomal dominant leukodystrophy with neuroaxonal spheroids and pigmented glia, whose neuropathological findings were quite similar to those of our cases. They suggested that both HDLS and POLD were rare adult-onset diseases of the white matter with sporadic and autosomal dominant forms, and were not different from each other. The varying localization of white matter lesions as well as numbers of spheroids and pigmented macrophages might reflect the stage of the disease and accompanying neuropathological events. Furthermore, we have found abundant spheroid deposition in the lamina VI, subcortical white matter, corpus callosum, capsula interna, externa, and extreme and corticospinal tract of the brain stem and spinal cord,

which makes it likely that neuroaxonal degeneration of long projecting and association fibers underlies this disease entity [4, 14]. Although ballooned neurons immunoreactive for ubiquitin were found in the frontal cortex, they might reflect dying back degeneration secondary to destruction of the white matter.

In conclusion, we have reported here familial non-diffuse leukodystrophy with axonal spheroids and pigmented glia. Although the biochemical and genetic pathomechanisms remain unknown, POLD and HDLS could be classified as closely related disease entities. More intensive investigations on both the molecular and histological features will be required to understand the pathology of these diseases, which would then enable us to make a proper diagnosis.

Acknowledgement The authors would like to thank Dr. Kei Yamada for his critical comments on the manuscript.

References

1. Axelsson R, Roytta M, Sourander P, Akesson HO, Andersen O (1984) Hereditary diffuse leucoencephalopathy with spheroids. *Acta Psychiatr Scand Suppl* 314:1–65
2. Constantinidis J, Wisniewski TM (1991) The dominant form of the pigmentary orthochromatic leukodystrophy. *Acta Neuropathol* 82:483–487
3. Knopman D, Sung JH, Davis D (1996) Progressive familial leukodystrophy of late onset. *Neurology* 46:429–434
4. Marotti JD, Tobias S, Fratkin JD, Powers JM, Rhodes CH (2004) Adult onset leukodystrophy with neuroaxonal spheroids and pigmented glia: report of a family, historical perspective, and review of the literature. *Acta Neuropathol* 107:481–488

5. Okeda R, Matsuo T, Kawahara Y, Eishi Y, Tamai Y, Tanaka M, Kamaki M, Tsubota N, Yamadera H (1989) Adult pigment type (Peiffer) of sudanophilic leukodystrophy. Pathological and morphometrical studies on two autopsy cases of siblings. *Acta Neuropathol* 78:533–542
6. Peiffer J (1970) The pure leucodystrophic forms of orthochromatic leucodystrophies (simple type, pigment type). *Handb Clin Neurol* 10:105–119
7. Pietrini V, Tagliavini F, Pilleri G, Trabattoni CR, Lechi A (1979) Orthochromatic leukodystrophy with pigmented glial cells. An adult case with clinical-anatomical study. *Acta Neurol Scand* 59:140–147
8. Seiser A, Jellinger K, Brainin M (1990) Pigmentary type of orthochromatic leukodystrophy with early onset and protracted course. *Neuropediatrics* 21:48–52
9. Shannon P, Wherrett JR, Nag S (1997) A rare form of adult onset leukodystrophy: orthochromatic leukodystrophy with pigmented glia. *Can J Neurol Sci* 24:146–150
10. Sotrel A (1988) On the dual nature and lack of specificity of intracytoplasmic inclusions in a case of adult onset orthochromatic leukodystrophy. *J Neuropathol Exp Neurol* 47:490–492
11. Terada S, Ishizu H, Yokota O, Ishihara T, Nakashima H, Kugo A, Tanaka Y, Nakashima T, Nakashima Y, Kuroda S (2004) An autopsy case of hereditary diffuse leukoencephalopathy with spheroids, clinically suspected of Alzheimer's disease. *Acta Neuropathol* 108:538–545
12. Tunon T, Ferrer I, Gallego J, Delgado G, Villanueva JA, Martinez-Penuela JM (1988) Leucodystrophy with pigmented glial and scavenger cells (pigmentary type of orthochromatic leucodystrophy). *Neuropathol Appl Neurobiol* 14:337–344
13. Van Bogaert L, Nyssen R (1936) Le type tardif de la leukodystrophie progressive familiale. *Rev Neurol (Paris)* 65:21–45
14. van der Knaap MS, Naidu S, Kleinschmidt-Demasters BK, Kamphorst W, Weinstein HC (2000) Autosomal dominant diffuse leukoencephalopathy with neuroaxonal spheroids. *Neurology* 54:463–468
15. Vergheze J, Weidenheim K, Malik S, Rapin I (2002) Adult onset pigmentary orthochromatic leukodystrophy with ovarian dysgenesis. *Eur J Neurol* 9:663–670
16. Yamashita M, Yamamoto T (2002) Neuroaxonal leukoencephalopathy with axonal spheroids. *Eur Neurol* 48:20–25
17. Yazawa I, Nakano I, Yamada H, Oda M (1997) Long tract degeneration in familial sudanophilic leukodystrophy with prominent spheroids. *J Neurol Sci* 147:185–191