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ORIGINAL ARTICLE

Biopsy histopathology in the diagnosis of adult-onset leukoencephalopathy with axonal spheroids and pigmented glia (ALSP)

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Abstract

Aim Adult-onset leukoencephalopathy with axonal spheroids and pigmented glia (ALSP) is an inherited rare disease affecting young adults. We present the clinical, imaging, and neuropathological results of our case series, emphasizing biopsy histology combined with clinical information will increase the accuracy of early diagnosis.

Methods In total, 4 females and 2 male ALSP patients with onset at ages 24–45 years were enrolled. Clinical manifestations, neuroimaging, and histopathology as well as gene mutation were analyzed and compared with literature.

Results Clinical manifestations include cognitive decline with/without psycho-behavior problems and movement disorders including paralysis, hemiplegia, parkinsonism, and pyramidal tract injury, as well as dysarthria, dysphagia, and sensory disturbances. MRI showed multiple periventricular and subcortical white matter lesions, involving the corpus callosum, with no enhancement, but with persistent hyperintensity on diffuse-weighted imaging. Histology showed widespread white matter damage and pale stain, especially destroyed axons with spheroids and funicular axons which were stained with neurofilament and ubiquitin. Foamy and pigmented macrophages were another typical change. *CSF1R* mutation was found in 4 of them. All of the patients were misdiagnosed and treated for a long time for multiple sclerosis, cerebral infarction, normal pressure hydrocephalus, etc.

Conclusion ALSP will cause rapidly progressing dementia with/without movement disorders in young adults. The definite diagnosis should be based on a comprehensive analysis of clinical manifestations, and neuroimaging, histology, and genetic results. Early biopsy will add to the accuracy of the diagnosis.

Keywords ALSP · Biopsy · White matter disease · Axon spheroids · Funicular axons

Introduction

Adult-onset leukoencephalopathy with axonal spheroids and pigmented glia (ALSP) was regarded as a distinct disease entity after the identification of pathogenic gene *CSF1R* in 2013 [1]. It includes a disease spectrum defined by clinical and pathological features previously, namely hereditary diffuse leukoencephalopathy with axonal spheroids (HDLS) and pigmented orthochromatic leukodystrophy (POLD). Both are members of orthochromatic leukodystrophy: HDLS was characterized by widespread degeneration and loss of myelin sheaths and axons, and abundant neuroaxonal spheroids, while POLD was characterized by pigmented macrophages in a background of widespread myelin loss and axon damage [2].

The clinical spectrum of ALSP includes cognitive disorder, behavior or psychiatric symptoms, and movement disorders, as well as seizure, ataxia, parkinsonism, and gait disturbance [3, 4]. Dementia and frontal release signs are predominantly found because of frontal-predominant white matter involvement, differentiated from bvFTD [5]. The characteristic MRI changes are patchy or confluent, symmetric or asymmetric

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white matter lesions with frontal periventricular predominance atrophy of the genu of the corpus callosum and enlargement of the lateral ventricle. Persistent diffuse-weighted imaging (DWI) signal increase without gadolinium enhancement is also important [4, 6]. Although *CSF1R* mutation is pathogenic, more and more mutation-negative cases were reported and *AARS2* mutation caused a similar phenotype, so genetic diagnosis was still not specific [7]. Characteristic histology manifestations, therefore, will still be emphasized [8].

Here, we present the clinical, imaging, and neuropathological results of our series from leukoencephalopathy and dementia clinics. We emphasize ALSP should be taken into account in differential diagnosis of young dementia and biopsy histology will add to the accuracy of early diagnosis.

Materials and methods

Clinical data

Six cases with biopsy-proven ALSP were included in the study. Clinical history including age onset, disease duration, family history, symptoms, and physical examinations was recorded. Laboratory results were collected, including serum analysis for biochemistry (liver function, kidney function, cholesterol, homocysteine, et al.), autoimmune antibodies (anti-nuclear antibodies, extractable nuclear antigen, anti-neutrophil cytoplasmic antibodies, aquaporin-4 antibody), endocrine and metabolism indexes (thyroid function, alpha-galactosidase, beta-galactosidase, galactocerebrosides, arylsulfatase, hexosaminidase), and CSF indexes (cell count, protein, glucose, chloride, oligoclonal band, bacterial culture, and antibodies/PCR of viruses, cytology). Otherwise, the clinical course and treatment history of the patients were also collected.

MRI studies

MRI examinations were performed using a 3-T MRI scanner (Avanto, Siemens, Erlangen, Germany). Axial T1-weighted, T2-weighted, T2-flair, and DWI were performed and corresponding decreased apparent diffusion coefficient (ADC) was measured. Sagittal and coronal imaging, and contrast-enhanced studies were performed.

Histopathological examination

Four-micrometer-thick paraffin sections were stained with routine stains (hematoxylin and eosin). Immunohistochemistry illustrated T and B cells CD3/CD20 (Leica), microglia/macrophages CD68 (DAKO), neurofilament protein NF (DAKO), neurons Neun (Abcam), astrocytes GFAP (Abcam), and ubiquitin (Abcam). PAS was stained in some of the cases. Photomicrographs were taken with the LEICA DM2500 microscope and a digital camera (LEICA, Germany).

Molecular genetic analysis

Written informed consent for genetic analysis was obtained from all investigated members or their legal representatives. Genomic DNA was extracted from fresh peripheral blood leukocytes. Whole exon sequencing using "next-generation" sequencing technology was performed on IlluminaHiseq (Illumina, USA), which was verified by Sanger sequencing.

Results

Clinical information

Among the 6 cases, female:male was 4:2. The age onset was from 24 to 45 years, an average of 38 ± 7.5 years, all in young adult period. The duration from onset to diagnosis was from 9 to 48 months, for an average of 20.2 ± 14.0 months. Only one patient reported family history without genetic confirmation, while the rest denied any similar patients in family. The onset clinical symptoms could be divided into two main groups: generalized cognitive decline with/without psychiatric problems and focal cortical neurological deficits. As the disease progressed, symptoms could overlap and cover all manifestations of the central nervous system. The detailed symptoms of the patients are listed in Table 1. Ataxia and parkinsonism were relatively rare while epilepsy was not reported. The laboratory examinations were all unremarkable, including serum biochemistry, antibodies, inflammatory indexes, tumor biomarkers, et al. Lumbar puncture was done in all patients and CSF indexes were all negative, including oligoclonal band and cytology. Clinical diagnosis was inflammatory demyelinating disease in cases 1, 2, 3, and 5, cerebral infarction in case 4, and hydrocephalus in case 6. Steroids, anti-infarction, and CSF drainage were given respectively without efficacy.

Neuroimaging manifestations

The neuroimaging manifestations are summarized in Table 2. MRI showed white matter lesions prominently in all patients, with widespread periventricular and sub cortical white matter involvement, except for case 2 which showed patchy periventricular localization. Four patients had frontal predominance with frontal lobe atrophy while the 2 had parietal occipital predominance with enlargement of occipital horns of the lateral ventricle. Corpus callosum (5/6) and pyramidal tract (4/6) involvements were seen in most of them. However, brain stem lesions were not common (2/6). Persistent DWI high signal was seen in all patients and almost

Table 1 Clinical results of patients

Case	Sex	Age onset	Disease duration (months)	Family history	Neurological and neuropsychiatric symptoms									
					Cognitive decline	Behavior problem	Pyramidal sign	Hemiplegia/ monoplegia	Parkinsonism	Epilepsy	Ataxia	Bulbar paralysis	Sensory disturbance	Incontinence
1	F	36	16	+	+	+	+	−	−	−	−	−	−	−
2	F	39	9	−	−	+	+	+	−	−	−	+	+	+
3	M	43	48	−	+	−	+	−	+	−	−	+	−	+
4	F	24	16	−	+	−	+	+	−	−	+	−	+	−
5	F	41	14	−	+	−	+	+	−	−	−	+	+	+
6	M	45	18	−	+	−	+	+	+	−	−	−	−	−

in all lesions, lasting more than 1 year for the longest time. All lesions were distributed asymmetrically, without enhancement and U-fiber involvement. Calcification was found in 2 of them. Illustrations of MRI are shown in Fig. 1.

Neuropathological investigations

Periventricular white matter tissues with high DWI signal were biopsied in all patients. Illustrations of histology are shown in Fig. 2. Microscopically, white matter was wildly damaged and oligodendrocytes massively reduced. In severely affected areas, axon and myelin were almost dismissed, with a spongiform pattern and patchy astrogliosis. However, in mildly affected areas, axon breakdown and derangement were more obvious, while myelin was relatively preserved. Spheroid and thickened (or funicular) axons were easily found in mildly affected areas. Neither necrosis nor inflammatory lymphocyte infiltration and vascular changes were found. Scattered macrophages were found distributed in the tissue, usually single without gathering and vascular surrounding. Plasma of macrophages was enriched with axon breakdown which was stained with PAS, so-called pigmented macrophages. On immunohistochemical stain, GFAP showed extensive gliosis, and some of the reactive astrocytes had massive cytoplasm and projections. Seldom were CD3- or CD20-positive lymphocytes seen. Scattered macrophages were CD68 positive. NF showed extensive axon damage and better outlined spheroids and cord like axons. Ubiquitin was stained in 3 of the patients (cases 2, 3, and 4), showing positive spheroids.

CSF 1R gene analysis

Case 1 refused a gene analysis and no *CSF1R* mutation was found in case 3. In case 2, delCTC mutation was detected in *CSF1R* gene. In case 4, a new deletion mutation (c.2546-2548delTCT) was found that did not exist in both parents. In case 5, c.2381T>C, p.I794T was detected. In case 6, c.2563C>A missense mutation was detected.

Discussion

As a subgroup of adult-onset leukodystrophy, ALSP was first described as a clinical entity, then a pathological entity, a genetic entity, and now a clinical-pathological-genetic unity. As typical pathologic and genetic features were found, more and more cases and families were reported all around the world [9–11]. Konno et al. raised diagnostic criteria based on the clinical characteristics. Age onset, typical clinical symptoms, and typical imaging features were included in core features. Neuropathological findings were included in supporting

Table 2 Characteristics of white matter lesions

Case	Location	Distribution predominance	Corpus callosum lesions	Pyramidal tract lesions	Symmetry	Brainstem and spinal cord	Severity	DWI hyperintensity	Calcification	Enhancement	U-Fiber involvement
1	PV + SC	Frontal	+	–	–	–	C	+	–	–	–
2	PV	Frontal	–	+	–	–	P	+	–	–	–
3	PV + SC	Frontal	+	+	–	–	P	+	+	–	–
4	PV + SC	Parietal-occipital	+	+	–	+	C	+	–	–	–
5	PV + SC	Parietal-occipital	+	+	–	+	C	+	+	–	–
6	PV + SC	Frontal	+	–	–	–	C	+	–	–	–

PV, periventricular; *SC*, subcortical; *C*, confluent; *P*, patchy

features. However, other causes of leukoencephalopathy should be excluded [12].

The clinical features of ALSP covered a wide spectrum of the central nervous system. Focal neurological deficits involving pyramidal signs and motor disorders along with periventricular white matter lesions always mimicked demyelinating disease especially multiple sclerosis [13, 14]. Besides, onset of cognitive decline would make the diagnosis of neurodegenerative disease such as early-onset Alzheimer's disease, frontal temporal lobe degeneration, et al. [5, 15]. Parkinsonism and movement disorders should be differentiated [15, 16]. At last, white matter lesions should also be differentiated with central nervous system vasculitis, small vessel disease such as CADASIL, and other hereditary leukoencephalopathy and leukodystrophy [17]. In our case series, the onset age and disease progression course were similar to literature. Cognitive decline, psychiatric symptoms, pyramidal signs, and motor deficits were most frequently described in literature. However, ataxia and epilepsy were not found. All of our patients were misdiagnosed for a long time: 4 with multiple sclerosis and steroid was given with no clinical benefit. Persistent DWI hyperintensity with no enhancement and spot-like calcification were different from MS lesions. Many of them were treated as cerebral infarction in rural hospitals for DWI hyperintensity. It should be specially mentioned that case 6 was misdiagnosed as normal pressure hydrocephalus and tap test was done with no improvement.

Spheroid axons and pigmented macrophages were key pathological features of ALSP. Pyramidal tract and corpus callosum were usually affected. In white matter, diffuse loss of axons and myelin, numerous spheroids, and intense astrogliosis were seen. Cortical lamination was usually kept and neuron loss was not usually found. However, a few balloon-like neurons could be seen [18]. The cytoplasm of pigmented macrophages was positively stained by PAS, Sudan III, Berlin blue, and ubiquitin [18]. Besides, it was reported that enlarged unmyelinated axon was also found in skin tissue, which meant peripheral nervous system involvement [19]. As we know, axon damage and spheroid axons were not specific, and may be caused by lots of pathophysiologic process such as Wallerian degeneration, traumatic axon damage, and other secondary reactions. However, the widespread distribution and frequency were specific. Also, the scattered distribution of macrophages was distinct without perivascular accumulation, which was not usually seen in other metabolic leukoencephalopathy and demyelinating disorders. Autopsy material from asymptomatic member of a Japanese family showed patchy axonal degeneration and myelin loss, predominantly in the subcortical white matter; however, pigmented microglia was distributed diffusely throughout the cerebral white matter, suggesting microglia pathophysiologic changes came earlier [20]. Axon loss was a pathologic result and progressed from patchy localization to widespread

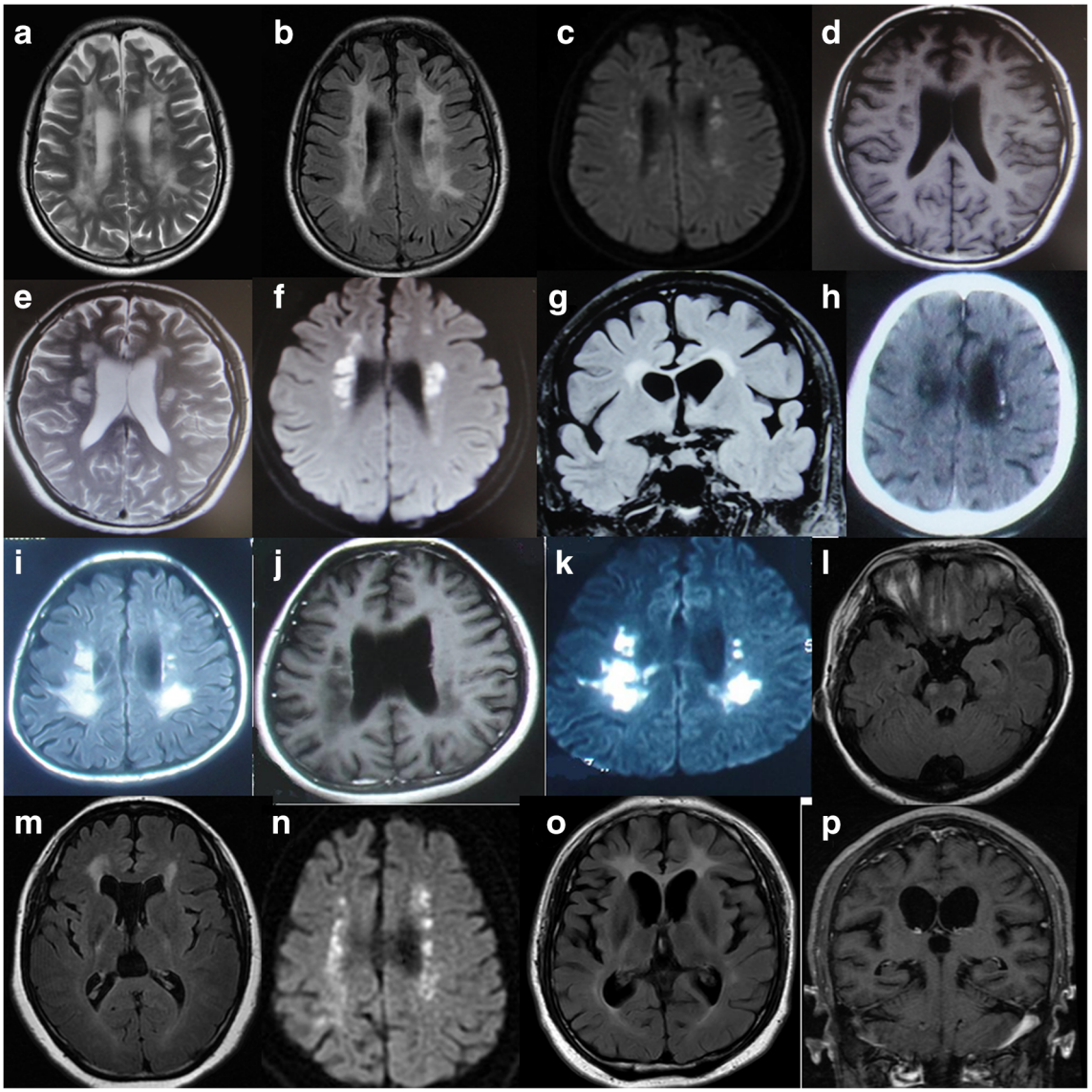

Fig. 1 MRI of patients. **a–c** Case 1: confluent periventricular white matter lesions with subcortical involvement and DWI hyperintensity (T2, FLAIR, DWI). **d–f** Case 2: frontal predominant patchy white matter lesions with DWI hyperintensity (T1, T2, DWI). **g**, **h** Case 3: frontal periventricular white matter lesions with corpus callosum involvement and calcification (FLAIR, CT). **i–l** Case 4: parietal occipital predominant white matter lesions with no enhancement and DWI hyperintensity, and brain stem lesions (FLAIR, T1+C, DWI,FLAIR). **m**, **n** Case 5:periventricular lesions with DWI hyperintensity and pyramidal tract (internal capsule) involvement (FLAIR, DWI). **o**, **p** Case 6: confluent white matter lesions with corpus callosum involvement and ventricle enlargement, no enhancement (FLAIR, T1+C)

diffusion. Based on these, the Japanese researchers raised a pathological staging system of ALSP, mainly considering distribution of axon damage and atrophy [21]. In our series, all pathological features were in the advanced stage, for delayed clinical diagnosis. We found typical spheroid axons, and thickened axons in longitudinal section which we called funicular axons. The distribution and morphologic features of pigmented macrophages were all as described in literature.

CSF1R is a tyrosine kinase receptor expressed on the surface of microglia, which was found to be the pathogenic mutation of ALSP [1]. Konno et al. studied 90 families with ALSP and found 58 mutations located in the tyrosine kinase domain of *CSF1R* [22]. However, 40% of the patients have no family history. The detailed pathogenesis of *CSF1R* mutation was unknown. *TREM2*, another gene involved in activation of microglias, was found to cause Nasu–Hakola disease while mutated. Nasu–Hakola disease is characterized by marked degeneration of cerebral white matter with spheroids, bone fracture, and peculiar membranous structures in the bone marrow and adipose tissue [21]. Besides, mutations in the alanyl-tRNA synthetase 2 (*AARS2*) gene causing ovarioleukodystrophy were also reported to cause similar clinical and pathological changes as ALSP [7, 23, 24]. In our series, most of them were sporadic without family history and

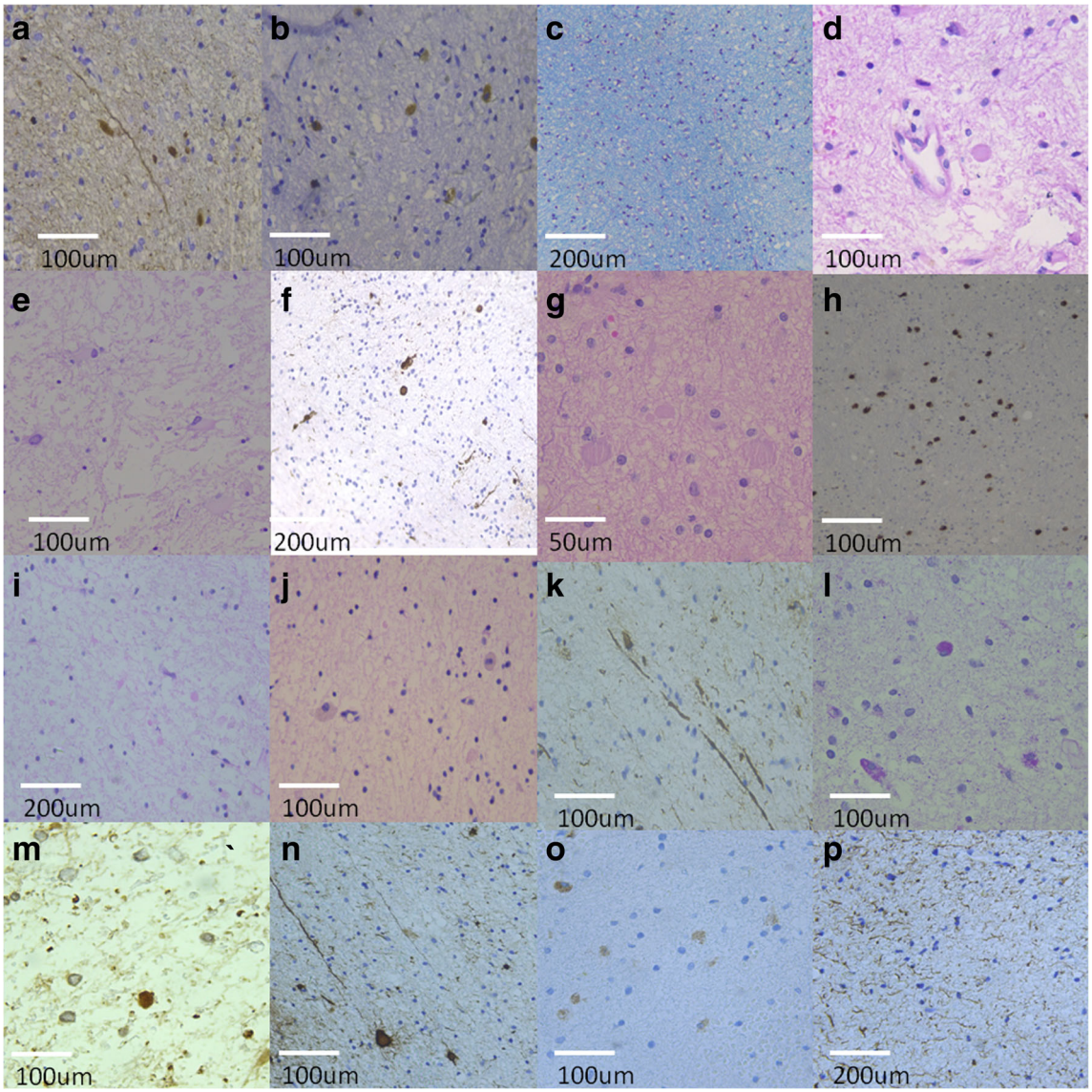

Fig. 2 Histology of patients. **a–c** Case 1: diffuse white matter damage with funicular, spheroid axons and pigmented macrophages, myelin relatively kept in mild affected area (NFX200, CD68 X200, LFB X100). **d–f** Case 2: axon damage and spheroid axons without vasculature inflammation, severe gliosis in widespread spongiform white matter background (HE × 200, HE × 200, NF × 100). **g**, **h** Case 3: spheroid axons and scattered pigmented macrophages (HE × 400, CD68 × 200). **i–m** Case 4: spheroid, funicular axons and pigmented macrophages in severely destroyed white matter; PAS-positive granules in macrophages and Ub-positive stain of spheroid axons (HE × 100, HE × 200, NF × 200, PAS × 200, Ub × 200). **n**, **o** Case 5: spheroid, funicular axons and pigmented macrophages (NF × 200, CD68 × 200). **p** Case 6: severe destruction and derangement of axons (NF × 100)

CSF1R mutations were found in 4 of them. In case 4, no *CSF1R* mutation was found, suggesting other underlying genetic mechanisms. Indeed, as a clinical pathological nomenclature, ALSP is a genetic heterogeneous entity.

In conclusion, ALSP represents a subgroup of adult-onset leukoencephalopathy with distinct histological characteristics, but with a wide spectrum of clinical manifestations and genetic heterogeneity. We should take ALSP into account with diagnosis of rapid progressing dementia with/without movement disorders in young adults. Asymmetrical white matter lesions with persistent DWI hyperintensity without contrast as well as corpus callosum involvement are characteristic MRI features. Spheroid or funicular axons and pigmented macrophages are typical histology changes. However, secondary axon changes should be ruled out on biopsy. The definite diagnosis should be based on a comprehensive analysis of clinical manifestations, and neuroimaging, histology, and genetic results. To avoid misdiagnosis and delayed diagnosis, we suggest early biopsy in these patients to get rid of side effects and costs of wrong treatment and help them keep a relatively high quality of life.

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Compliance with ethical standards

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

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee (PUMC ethics committee 2017006) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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