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Diagnostic Criteria for Adult-onset Leukoencephalopathy With Axonal Spheroids and Pigmented Glia Due to *CSF1R* mutation

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Abstract

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Background—To establish and validate diagnostic criteria for adult-onset leukoencephalopathy with axonal spheroids and pigmented glia (ALSP) due to *colony stimulating factor 1 receptor* (*CSF1R*) mutation.

Methods—We developed diagnostic criteria for ALSP based on a recent analysis of the clinical characteristics of ALSP. These criteria provide “probable” and “possible” designations for patients who do not have a genetic diagnosis. To verify its sensitivity and specificity, we retrospectively applied our criteria to 83 ALSP cases who had *CSF1R* mutations (24 of these were analyzed at our institutions, and the others were identified from the literature), 53 cases who had *CSF1R* mutation-negative leukoencephalopathies, and 32 cases who had cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) with *NOTCH3* mutations.

Results—Among the *CSF1R* mutation-positive cases, 50 cases (60%) were diagnosed as “probable” and 32 (39%) were diagnosed as “possible,” leading to a sensitivity of 99% if calculated as a ratio of the combined number of cases who fulfilled “probable” or “possible” to the total number of cases. With regard to specificity, 22 cases (42%) with mutation-negative leukoencephalopathies and 28 (88%) with CADASIL were correctly excluded using these criteria.

Conclusions—These diagnostic criteria are very sensitive for diagnosing ALSP with sufficient specificity for differentiating from CADASIL and moderate specificity for other leukoencephalopathies. Our results suggest that these criteria are useful for the clinical diagnosis of ALSP.

Keywords

Adult-onset leukoencephalopathy with axonal spheroids and pigmented glia (ALSP); hereditary diffuse leukoencephalopathy with spheroids (HDLS); pigmented orthochromatic leukodystrophy (POLD); colony stimulating factor 1 receptor (*CSF1R*); alanyl-transfer (t)RNA synthetase 2 (*AARS2*); leukoencephalopathy; diagnostic criteria

INTRODUCTION

The differential diagnosis of leukoencephalopathy is extensive [1, 2]. Specialized investigations such as biochemical, genetic, or neuropathologic analyses are required for an accurate diagnosis. Due to recent advances in molecular genetics, genetic tests play an important role in the diagnosis of some leukoencephalopathies [1]. To perform genetic tests efficiently, it is important to understand the characteristic clinical features of a disease and establish useful diagnostic criteria.

Since the discovery of *colony stimulating factor 1 receptor* (*CSF1R*) as a causative gene for hereditary diffuse leukoencephalopathy with spheroids (HDLS) [3] and more recently for pigmented orthochromatic leukodystrophy (POLD) [4], more than 120 cases with *CSF1R* mutations have been reported worldwide but it has been relatively more common in Japan compared to other countries [5]. HDLS and POLD cases, carriers of *CSF1R* mutations are characterized as having “adult-onset leukoencephalopathy with axonal spheroids and pigmented glia” (ALSP) [4]. Interestingly, *CSF1R* mutations are not always found in pathologically-confirmed HDLS cases [6]. Mutations in other genes appear to be responsible in cases of HDLS that are negative for *CSF1R* mutations. Indeed, mutations in *alanyl-*

transfer (t)RNA synthetase 2 (AARS2) have been recently identified in 5 cases who were suspected to have ALSP, but were negative for *CSFIR* mutation [7].

Recently, we have clarified clinical characteristics of ALSP by analyzing 122 cases with *CSFIR* mutations [5]. Based on these findings, we propose diagnostic criteria for ALSP due to *CSFIR* mutation and attempt to validate them.

METHODS

Establishing diagnostic criteria

To establish diagnostic criteria, a working group was organized, consisting of board-certified neurologists from 5 institutions (Mayo Clinic, Niigata University, Shinshu University School of Medicine, Kyoto Prefectural University of Medicine, and Tokushima University Graduate School) who have observed patients with ALSP. The diagnostic criteria were created based on the clinical characteristics obtained from our case series and review of the literature and further discussions among the study working group [5]. We defined 5 core diagnostic features (Table 1). Three exclusionary findings were added to increase diagnostic specificity. Patients who had 3 of the 5 core features (Table 1, criteria 2, 3, and 4a) and had a *CSFIR* mutation were classified as definitely having ALSP or “definite.” Patients who did not have results from genetic testing were identified to have “probable” or “possible” ALSP. The “probable” criteria also requires that the patients have all 5 core features identified in Table 1, but the “possible” criteria requires that only 3 are fulfilled (criteria 2a, 3, and 4a), with the aim of preventing false-negative diagnoses and missed opportunities for the genetic testing of those who lacked typical clinical features. Although not directly used to determine the diagnosis, we added 4 supportive findings to assist clinicians in making a diagnosis. Figure 1 shows the characteristic brain CT/MRI findings of ALSP, and Table 2 provides additional comments on the diagnostic criteria.

Validation of the diagnostic criteria

We used *CSFIR* mutation-positive cases to determine the sensitivity of our criteria. First, we applied the criteria to 26 ALSP cases who were seen by us and 96 cases previously identified in the literature [5]. Next, we applied them to 67 cases with *CSFIR* mutation-negative leukoencephalopathies to test the specificity of the criteria. These cases were suspected to have ALSP with at least white matter abnormalities on brain MRI and referred to our institutions for genetic test for *CSFIR* mutation. The primary causes of the mutation-negative leukoencephalopathies were unknown. We also applied them to 40 cases with cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) who had *NOTCH3* mutations because CADASIL is 1 of the main differential diseases of ALSP [3].

Cases diagnosed as “probable” met all 5 core features; however, in this retrospective study, the exclusion of other diseases, 1 of the core features, was not always taken into account because we could not determine whether enough assessment for a differential diagnosis had been conducted in every case. All genetic analyses were approved by the institutional review

board of each of the 5 institutions listed above. Informed consent was obtained from all the participants.

RESULTS

Among the ALSP cases with *CSFIR* mutations, 2 of 26 cases in our cohort and 37 of 96 cases from the literature were excluded due to a lack of information, including insufficient brain imaging or hereditary data. The number of cases fulfilling each designation is shown in Table 3. If we calculated the diagnostic sensitivity as a ratio of the number of cases diagnosed as “probable” or “possible” to the total number of cases, the sensitivity was 96% for our cohort and 99% when combined with the literature review cases.

Fourteen of 67 cases with mutation-negative leukoencephalopathies and 8 of 40 CADASIL cases were excluded due to missing information necessary for our evaluation. For diagnostic specificity, 22 (42%) and 28 (88%) cases did not meet either the “probable” or “possible” criteria, respectively (Table 3).

DISCUSSION

In the process of establishing diagnostic criteria, we placed a greater weight on sensitivity than specificity because a substantial number of cases with ALSP are underdiagnosed. This retrospective validation of these diagnostic criteria showed that they had high sensitivity (96%). There was almost no possibility that cases with ALSP were missed when we used these criteria. We had only 1 ALSP case who did not fit the criteria [8]. This case initially presented with gait abnormalities, and was cognitively normal in the early stages of disease when the criteria were applied. However, cognitive impairment subsequently appeared, and the patient was classified as “probable” at that time. Although cognitive impairment is inevitable in ALSP, it should be noted that it can be inconspicuous during the initial disease stages.

Thinning of the corpus callosum is characteristic to ALSP [9]; thus, we included it in a parameter of “probable.” Of the 29 cases from the literature that fulfilled the “possible” criteria, information about the corpus callosum was not obtained in 17 cases. It is estimated that more cases would have been diagnosed as “probable” if their corpus callosum had been evaluated. A majority of cases with mutation-negative leukoencephalopathy were diagnosed as “possible,” but 4 cases met the “probable” criteria, suggesting that the thinning of the corpus callosum is characteristic, but is not specific to ALSP. We assumed that brain calcifications have high sensitivity and specific diagnostic power [10, 11]; however, we could not sufficiently validate this finding due to insufficient information in the literature. Thus, we did not include it in the core features, but in the supportive findings.

When the criteria were applied to the cases who had *CSFIR* mutation-negative leukoencephalopathies or CADASIL with *NOTCH3* mutations, the specificity was 42% and 88%, respectively. We considered that the relatively low specificity for mutation-negative leukoencephalopathies was due to the minimum requirements set for the “possible” designation, which were in place to avoid missing atypical cases of ALSP. For yielding higher specificity, the brain imaging characteristics listed in Table 2 including the

distribution pattern of the white matter lesions and the brain calcifications may be beneficial. On the other hand, these criteria could successfully be used to differentiate CADASIL from ALSP. Cerebral infarction cases frequently present with diffusion-restricted lesions on brain MRI that are occasionally observed in ALSP cases as well (Figure 1E); therefore, hereditary cerebral small vessel diseases including CADASIL are part of the differential diagnoses of ALSP. One of the exclusion criteria, “stroke-like episodes more than twice,” was helpful for excluding CADASIL because there were no ALSP cases who had 2 or more stroke-like episodes. We showed additional useful points for differentiating ALSP from other leukoencephalopathies in Supplementary Table 1.

Patients with leukoencephalopathy due to *AARS2* mutations, termed as AARS2-L [12], develop similar clinical and radiologic features to those of ALSP; however, some differentiating points were present in the cases with AARS2-L; for example, autosomal recessive pattern of inheritance, relatively younger age at onset including childhood onset, and the presence of ovarian failure in all female cases [7, 12, 13]. On brain MRI, white matter rarefaction, tract involvement, spared middle section of the brain, and cerebellar atrophy seemed to be more frequently observed in cases with *AARS2* mutation [13]. Brain calcifications observed in ALSP have not been seen in patients with AARS2-L [12]. Only 1 biopsied case showed pathologic findings comparable with ALSP [7], while another biopsied case failed to provide any specific findings [14]. Thus, pathologic characteristics of AARS2-L remain unclear. Notably, mutations in *AARS2* can also cause infantile mitochondrial cardiomyopathy [15]. Therefore, further studies would be warranted to determine clinical, radiologic, and even pathologic similarities and differences between ALSP and AARS2-L.

This study had the following limitations. First, we retrospectively extracted the clinical data; thus, there may be variations or bias in the volume of information depending on the medical records or the literature. In particular, the disease duration at the time of applying the criteria varied in cases (we could not calculate the mean disease duration due to insufficient data). If the criteria were applied to patients with the very early stage of the illness, the sensitivity would become lower. Second, except for cases with CADASIL, we could not validate these criteria to cases with other specific leukoencephalopathies. To clarify the differential points among leukoencephalopathies, establishing diagnostic criteria for other leukoencephalopathies and assessing the utility of these criteria for each disease would be preferable.

Comprehensive genetic testing using the panel or exome sequence analyses has become technically available and facilitated genetic diagnosis of adult-onset leukoencephalopathies. While panel testing for these genetic disorders is becoming more popular, its application to clinical practice may be limited due to the cost and availability. Accurate clinical suspicion will facilitate gene testing of the target gene, and eventually reduce the cost and time of diagnostic process. We believe that these criteria are useful for the clinical diagnosis of ALSP; however, the criteria should be validated in larger prospective cohorts and further refined, especially for achieving higher specificity.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. Characteristic brain MRI/CT findings in patients with ALSP

(A–E, MRI; F, CT) Fluid attenuated inversion recovery imaging of a 43-year-old case with p.Ile794Thr mutation in *CSF1R* (A–C, axial; D, sagittal). Abnormal signals are observed in frontal white matter around anterior horn of the lateral ventricles, in the posterior limb of the internal capsule (arrow, A), and in the splenium of the corpus callosum (arrow, B). A thinning of the corpus callosum is shown (arrow, D). (E) Diffusion-restricted lesions in a 22-year-old case with the splice site mutation (c.2442+1G>A) in *CSF1R*. (F) Calcifications are revealed by thin-slice CT of the 43-year-old case with p.Ile794Thr mutation (arrows). ALSP, Adult-onset leukoencephalopathy with axonal spheroids and pigmented glia; *CSF1R*, colony stimulating factor 1 receptor; CT, computed tomography; MRI, magnetic resonance imaging

Table 1**Diagnostic Criteria for ALSP**

Core features	
1	Age at onset ≥ 60 years
2	More than 2 findings of the following clinical signs and symptoms <ol style="list-style-type: none"> Cognitive impairment or psychiatric symptoms Pyramidal signs Parkinsonism Epilepsy
3	Autosomal dominant inheritance or sporadic occurrence
4	Brain CT/MRI findings <ol style="list-style-type: none"> Bilateral cerebral white matter lesions Thinning of the corpus callosum
5	Other causes of leukoencephalopathy including vascular dementia, multiple sclerosis, or leukodystrophy (e.g. adrenoleukodystrophy, Krabbe disease, metachromatic leukodystrophy) can be excluded
Exclusionary findings	
1	Age at onset < 10 years
2	Stroke-like episodes more than twice except for epilepsy
3	Prominent peripheral neuropathy
Supportive findings	
1	Frontal lobe dysfunction shown by clinical features or cognitive battery test
2	Rapidly progressive course. Become bedridden within 5 years after onset
3	Spotty small calcifications in the white matter shown by brain CT
4	Neuropathologic findings compatible to ALSP
Diagnosis by the criteria	
Definite: Fulfill core features 2, 3, and 4a and confirmation of <i>CSF1R</i> mutation	
Probable: Fulfill core features 1–5, but genetic tests have not been performed	
Possible: Fulfill core features 2a, 3, and 4a, but genetic tests have not been performed	

ALSP, Adult-onset leukoencephalopathy with axonal spheroids and pigmented glia; CSF1R, colony stimulating factor 1 receptor; CT, computed tomography; MRI, magnetic resonance imaging

Table 2**Additional Comments on Diagnostic Criteria****1. Age at onset**

The mean age at onset of ALSP was 43 ± 11 years (range, 18–78), but was significantly younger in women than in men (40 vs. 47 years) [5]. Ninety-five percent of the cases develop their disease by age 60 years [5].

2. Clinical signs and symptoms

Cognitive impairment or psychiatric symptoms are cardinal features and are seen with high frequency. Psychiatric symptoms include anxiety, depression, apathy, indifference, abulia, irritability, disinhibition, distraction, and other behavioral and personality changes. Pyramidal signs include hyperreflexia, spasticity, increased tone in extremities, and pseudobulbar palsy. Parkinsonism includes resting tremor, rigidity, bradykinesia, and postural instability. Parkinsonian symptoms are not responsive to levodopa (6). Seizure is observed in approximately 30% of cases [5], but it may characterize ALSP from other leukoencephalopathies.

3. Mode of inheritance

Sporadic cases are not uncommon. *De novo* mutations have been reported [5].

4. Brain CT/MRI findings

On brain MRI scans, the white matter lesions without gadolinium enhancement can be scattered and asymmetric during the initial stages of the disease but later become confluent, diffuse, and more symmetric. Frontal and parietal lobe predominance is observed with involvement of the periventricular deep white matter and dilation of the lateral ventricles. Thinning of the corpus callosum with signal abnormalities is observed even in the early stages of the disease [9, 11]. Fluid attenuated inversion recovery sagittal imaging is recommended to evaluate changes in the corpus callosum. Abnormal signaling in the pyramidal tracts and diffusion-restricted lesions are observed in some cases [5, 11]. None of ALSP cases showed middle cerebellar peduncle lesions, which are known as a characteristic finding of some leukoencephalopathies.

On brain CT scans, calcifications are often observed bilaterally in the frontal white matter adjacent to the anterior horn of the lateral ventricle and the subcortical region of the parietal lobe. Calcifications can be very small. Thus, thin-slice CT (1 mm) is recommended to detect those [5, 11]. Characteristic “stepping stone appearance” can be seen on sagittal view [10].

5. Neuropathologic findings

Neuropathologic findings include prominent white matter lesions with myelin and axon damages, neuroaxonal swelling (spheroid formation), and pigmented macrophage and glia [4].

6. *CSF1R* mutation

All reported mutations were located within the tyrosine kinase domain of *CSF1R* except for 2 frameshift mutations [5].

ALSP, Adult-onset leukoencephalopathy with axonal spheroids and pigmented glia; *CSF1R*, colony stimulating factor 1 receptor; CT, computed tomography; MRI, magnetic resonance imaging

Table 3

Validation of the Diagnostic Criteria for Clinical Diagnosis of ALSP

	Number of Cases	Probable, n (%)	Possible, n (%)	Not Fulfilled, n (%)	Sensitivity ^a (%)
Our case series	24	20 (83)	3 (13)	1 (4)	96
Literature search	59	30 (51)	29 (49)	0 (0)	100
Total	83	50 (60)	32 (39)	1 (1)	99
Leukoencephalopathy without <i>CSF1R</i> mutation	53	4 (8)	27 (51)	22 (42)	42
CADASIL with <i>NOTCH3</i> mutation	32	0 (0)	4 (12)	28 (88)	88

ALSP, Adult-onset leukoencephalopathy with axonal spheroids and pigmented glia; CADASIL, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; CSF1R, colony stimulating factor 1 receptor

^aSensitivity was calculated as a ratio of the number of cases who were diagnosed as probable or possible to the total number of cases.