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Clinical and magnetic resonance imaging features in acute ischemic stroke with early wallerian degeneration: a case-control study

Kazumichi Ota[1*], Yoshihiko Nakazato[1], Kazuhide Seo[1], Hitoshi Kawasaki[1], Mariko Okada[1], Takashi Mithufuji[1], Yasuo Ito[1] and Toshimasa Yamamoto[1]

Abstract

Background In advanced stages, Wallerian degeneration (WD) after cerebral infarction appears as an abnormality in the descending corticospinal tract on T2-weighted images. However, early WD in this region is detectable via diffusion-weighted imaging (DWI) within the first 14 days. We aimed to investigate the clinical and imaging characteristics of early WD using patient data.

Methods We retrospectively reviewed clinical characteristics and magnetic resonance imaging (MRI) features of 105 acute stroke cases. Early WD factors, including the time from symptom onset to MRI scan, Brunnstrom stage at admission and discharge, risk factors for ischemic stroke, classification per the Stop Stroke Study Trial of Org 10,172 in Acute Stroke Treatment classification, infarct location, responsible artery, and MRI slice number for small-artery disease, were evaluated. Data were analysed using Wilcoxon and chi-squared or Fisher's exact tests. Additionally, changes in MRI signals were evaluated in specific early WD cases.

Results Early WD was identified in 22 (21%) patients, and 15 cases involved small-artery disease. The infarctions were located in the paraventricular corona radiata. Patients with early WD had significantly lower Brunnstrom stage scores at admission ($p < 0.001$) and discharge ($p = 0.0012$) than those without early WD. For small-artery disease, early WD cases showed a significantly higher MRI slice number than those without early WD ($p < 0.001$), with the lenticulostriate artery (LSA) identified as the responsible artery ($p = 0.033$). In the chronic phase, high DWI signals indicating early WD disappeared in all seven patients. Nine patients with early WD exhibited concurrent high signals on DWI and fluid-attenuated inversion recovery (FLAIR) in the descending corticospinal tract. Persistent high FLAIR signals detected in two patients with early WD with follow-up indicated irreversible changes.

Conclusions The degree of pyramidal tract damage and severity of paralysis are reliable indicators of early WD. Early WD may also occur in small-artery disease, with the main responsible artery being the LSA. DWI and FLAIR imaging can reflect the progression from early WD to chronic WD.

Keywords Cerebral infarction, Wallerian degeneration, Ischemic stroke, Pyramidal tracts

*Correspondence:
Kazumichi Ota
kota24@saitama-med.ac.jp
[1]Department of Neurology, Faculty of Medicine, Saitama Medical University, 38 Morohongo Moroyama, Iruma-gun, Saitama 350-0495, Japan

Background

Wallerian degeneration (WD), a secondary degeneration affecting the axons and myelin sheath, was first described by Waller in the peripheral nerves in 1851 [1]. WD in the central nervous system is most commonly caused by cerebral infarction, followed by other factors such as trauma, tumours, haemorrhage, and demyelinating diseases [2]. WD can be identified on brain computed tomography scans as atrophy of the pyramidal tracts a few years after onset and on brain magnetic resonance imaging (MRI) scans as an abnormality along the pyramidal tracts on T2-weighted images (T2WI) approximately 4 weeks after onset [3]. Meanwhile, pre-WD can be detected in the pyramidal tracts on diffusion-weighted imaging (DWI) [4]. This change appears transiently on scans within 14 days of onset during the acute phase of cerebral infarction [5] (early WD) and is associated with poor motor function [6–9]. However, to our knowledge, reports on the differences in the clinical and imaging characteristics between patients with and without early WD are limited. Therefore, we aimed to retrospectively analyse clinical and radiological data available at our hospital to explore these features.

Methods

Study population

In this case-control study, we included patients admitted for acute ischemic stroke (within 7 days of onset) at our hospital between February 2019 and January 2022. These patients were not candidates for alteplase thrombolysis or mechanical thrombectomy as part of acute noninterventional therapy. The primary inclusion criteria encompassed patients older than 18 years, diagnosed with acute ischemic stroke via diffusion MRI scanning, and exhibiting motor paralysis. The exclusion criteria were the absence of Brunnstrom stage (BRS) evaluation [10], lack of a follow-up 1.5 T brain MRI scan obtained within 14 days of stroke onset, and inability to continue inpatient treatment. Treatment for cerebral infarction was administered immediately after MRI scanning on admission, following the Japanese treatment guidelines [11]. We defined early WD as a descending corticospinal tract (DCST) with a high-intensity signal on the axial and coronal DWI and a low-intensity signal on the axial and coronal apparent diffusion coefficient (ADC) map [6] < 14 days [5] after a stroke.

In the acute phase (< 14 days), early WD in the corticospinal tract can present with high intensity on DWI and low intensity on ADC maps, reflecting cytotoxic edema or axonal transport dysfunction. FLAIR signal changes may be variable at this stage. Over time, FLAIR hyperintensity becomes more prominent, reflecting tissue gliosis.

Two neurologists diagnosed early WD using these criteria, and patients without early WD were included in the control group. The Institutional Research Ethics Board of Saitama Medical University, Japan, approved the study protocol (Approval No. 2022-004). The requirement for informed consent was waived as the researchers only handled anonymized information.

Clinical assessment

Data were obtained from the registry for each patient, including age; sex; time from symptom onset to brain MRI scan; time between initial and follow-up MRI scans; time from the onset of symptoms to the start of rehabilitation; rehabilitation time; risk factors for ischemic stroke, such as hypertension, diabetes mellitus, hyperlow-density lipoprotein cholesterolemia (hyper-LDLemia), atrial fibrillation, and smoking index calculated as number of cigarettes smoked per day × smoking years; BRS on admission and at discharge; the Stop Stroke Study Trial of Org 10,172 in Acute Stroke Treatment (SSS-TOAST) classification [12]; infarction location; responsible artery; and MRI slice number for small-artery disease. Diabetes mellitus and hyper-LDLemia were diagnosed based on blood tests conducted upon admission and the medications consumed by the patients. In addition, because the typical increase in blood pressure during the acute phase of cerebral infarction interferes with the detection of pre-existing hypertension at the time of admission, the diagnosis of hypertension was based on the prescribed medications and the patient's medical history. Atrial fibrillation was identified through Holter electrocardiogram monitoring and the patient's medical history. The infarctions were sectioned into the centrum ovale, paraventricular corona radiata, internal capsule, midbrain, pons, medulla oblongata, and other sections. The responsible artery was assessed by excluding the embolic and infratentorial infarcts and categorized into three perforating vessel arteries: white matter medullary artery (WMMA), lenticulostriate artery (LSA), and anterior choroid artery (AchoA) on the tent, which is predominantly supplied by the pyramidal tract. The WMMA is located in the anterior horn-superior limb of the insular cleft (A-I line) [13, 14]. The LSA is below the A-I line and adjacent to the lateral ventricle [13, 14], and the AchoA is identified below the corona radiata area adjacent to the lateral ventricles [15].

A physical or occupational therapist measured the BRS score at admission and discharge, and the total score was used to assess the severity of paralysis. In addition, a neurologist quantified the number of axial DWI slices depicting the infarction categorized as a small-artery disease upon admission. To assess the 22 patients with early WD, we utilized coronal fluid-attenuated inversion recovery (FLAIR). Furthermore, seven patients underwent follow-up MRI scanning, including axial and

coronal DWI, along with coronal FLAIR sequences in the chronic stroke phase (after 14 days of onset).

The smoking index and medical history data could have resulted in underestimated values, which were offset when the cases and controls were selected for improved conciseness under the same conditions. Potential confounding factors for the BRS score included age, underlying disease, and effect modifier factors, such as the start time and duration of rehabilitation. A potential confounding factor for the diagnosis of early WD is the dependence of the signal intensity of a lesion on both water proton diffusion and the T2-relaxation time. This means that the lesion may have a high signal on DWI, suggesting diffusion restriction, when in fact it is due to the intrinsic long T2-relaxation time of the tissue, a phenomenon called the T2 shine-through effect. The effect modifier factors for the diagnosis of early WD included the time from onset to follow-up MRI scanning, MRI machine model, and imaging conditions.

MRI

MRI and MR angiography were performed using 1.5 T scanners, comprising Siemens Essensa (Germany, $n = 97$), Siemens Symphony Sonata (Germany, $n = 1$), and Philips Ambition (Netherlands, $n = 7$); these scanners utilized 6-, 8-, and 20-channel phased array head coils, respectively. DWI was conducted using single-shot echo-planar sequences for each scanner: (1) Siemens Essensa (isotropic b = 0, 1000 s/mm^2, repetition time (TR)/echo time (TE) 5000/59 ms, field of view (FOV) 192 mm^2, matrix 192 × 134, 5.0 mm slice thickness, 1.5 mm gap); (2) Siemens Symphony Sonata (isotropic b = 0, 1000 s/mm^2, TR/TE 4100/88 ms, FOV 230 mm^2, matrix 128 × 124, 5.0 mm slice thickness, 1.5 mm gap); and (3) Philips Ambition (isotropic b = 0, 1000 s/mm^2, TR/TE 4000/75 ms, FOV 230 mm^2, matrix 128 × 178, 5.0 mm slice thickness, 1.5 mm gap). An ADC map was then generated from the DWI datasets. In this study, T1- and T2-weighted images were not used in the diagnostic criteria or analysis for early WD; therefore, we did not provide their detailed scanning parameters. For all patients with early WD, FLAIR images were acquired using sequences with a TR of 10,000 ms, inversion recovery of 2600 ms, and TE of 96 ms.

Post-processing

In the post-processing stage, axial DWI and ADC map DICOM images were imported into the open-source software 3D Slicer (version 4.11.2; http://www.slicer.org), where multiplanar reconstruction was performed to obtain coronal views of these images. The corticospinal tract was then identified anatomically using standard landmarks (e.g., the posterior limb of the internal capsule and the cerebral peduncle). Two experienced neurologists independently evaluated the presence of hyperintensity or hypointensity in the corticospinal tract and resolved any discrepancies by consensus.

Statistical analysis

We first tested for normality using the Shapiro–Wilk test and found that none of the continuous variables followed a normal distribution. Therefore, we used the Wilcoxon rank sum test for group comparisons involving continuous data. Although we present these variables as mean ± standard deviation for descriptive purposes, they are not normally distributed. Categorical variables, including sex, medical history, and responsible artery, were compared using the chi-squared or Fisher's exact test. John's Macintosh Project Pro for Windows (version 16, SAS Institute Inc., Cary, NC, United States) was used for the statistical analysis, and a p-value of < 0.05 was considered statistically significant.

This article is reported following the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) statement guidelines (Additional file 1) [16].

Results

Between February 2019 and January 2022, 285 patients with acute stroke were admitted to our hospital, among which 180 were excluded based on the exclusion criteria, and 105 were included in the study. Among the 105 patients, 22 exhibited early WD, whereas 83 did not, as determined using the diagnostic criteria for early WD (Fig. 1).

Figure 2 presents MR images of a representative case of early WD. MRI scanning was conducted 11 days after the ischemic stroke infarction. Imaging of the cerebral peduncle and internal capsule revealed hyperintensity on the axial and coronal DWI and hypo-intensity on the axial and coronal ADC map in the cerebral infarction and DCST.

Early WD was identified in 21% of the patients (22 of 105 patients) in our study. Patients with and without early WD did not significantly differ in age, sex, risk factors for ischemic stroke, time from symptom onset to the first or follow-up MRI scans, time from symptom onset to the start of rehabilitation, or rehabilitation time. Infarctions categorized as small-artery disease constituted 58% ($n = 61$) of the cases, of which 15 and 46 occurred in patients with and without early WD, respectively. The primary location of the infarct was the paraventricular corona radiata (Table 1). The BRS total scores at admission and discharge were significantly lower in patients with early WD than in those without (12.5 ± 4.3 vs. 15.4 ± 2.7, $p < 0.001$, and 13.3 ± 4.5 vs. 16.1 ± 2.3, $p = 0.0012$, respectively) (Fig. 3). Patients with early WD related to small-artery disease ($n = 15$) had a significantly

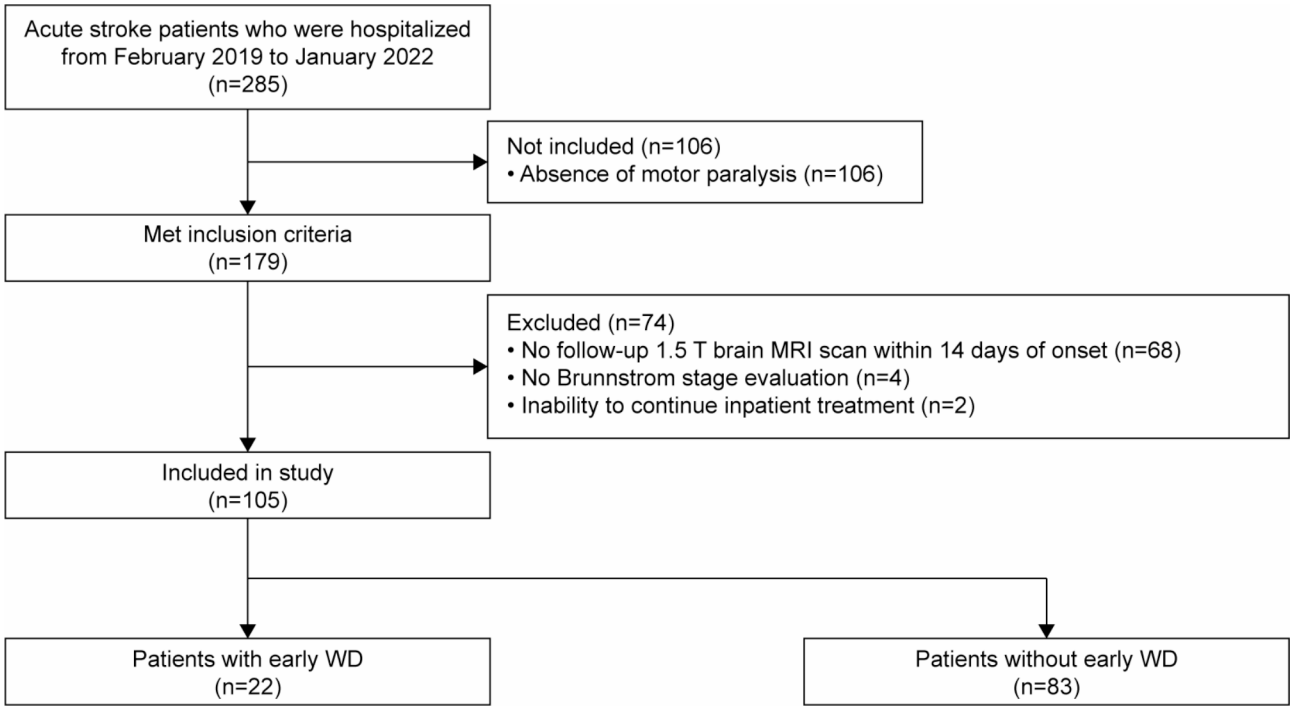

Fig. 1 Study design. MRI: magnetic resonance imaging, WD: Wallerian degeneration

higher number of MRI slices compared with patients without early WD ($n = 25$) ($p < 0.001$), with the LSA as the most common responsible artery ($p = 0.033$) (Fig. 4).

Seven patients underwent follow-up MRI scanning during the chronic stroke phase, and the time duration from stroke onset to the third MRI scan was 20, 22, 36, 48, 210, 566, and 808 days. The high DWI signal indicating early WD disappeared in all patients. Of the 22 patients with early WD, 9 exhibited simultaneous high DWI and FLAIR signals in the DCST. In two patients who were followed up from stroke onset to the fourth MRI scan performed after 48 and 210 days, the axial and coronal high DWI signals disappeared, and the coronal high FLAIR signal was more defined (Fig. 5).

Discussion

Herein, we retrospectively analysed the data collected at our hospital, revealing the clinical and imaging characteristics associated with early WD. First, the incidence of early WD was approximately 21% (22 of 105 patients), which is consistent with the rate previously reported in a study with a smaller sample size (approximately 20%, 2 of 11) [4]. The relatively high incidence of early WD (21%) may be partly explained by our inclusion of only patients with motor paralytic stroke, many of whom were ineligible for acute revascularization. Therefore, these findings might not represent the incidence of early WD in the entire stroke population.

Second, early WD was specifically associated with the severity of transient pyramidal tract symptoms presenting clinically and on imaging findings. Previous studies [6–9] have detected an association between early WD and motor paralysis, consistent with the results documented in this study. However, those studies used semi-quantitative assessments and the Pediatric Stroke Outcome Measure [17] and National Institutes of Health Stroke Scale [18], which include items other than the motor function. In this study, only motor function was assessed using the BRS, which is more accurate. Our findings suggest that early WD on DWI is closely associated with more severe corticospinal tract injury and motor impairment. Therefore, rather than serving as an independent prognostic factor, it may be a useful imaging surrogate marker for the severity of infarction and, hence, poor motor outcomes. Cardiogenic embolism is more likely to cause early WD than large-artery atherosclerosis or small-artery disease owing to a larger infarct area and greater DCST impairment [19]. Small-artery disease with early WD has received less attention.

In our study, the number of cardiogenic entries was reduced, given that patients undergoing recombinant tissue-type plasminogen activator treatment and those eligible for endovascular treatment were excluded. However, cases of early WD were identified, and small-artery disease was more common in the SSS-TOAST classification, with the LSA of the perforating branch being the responsible artery. Early WD is more likely to appear in infarcts

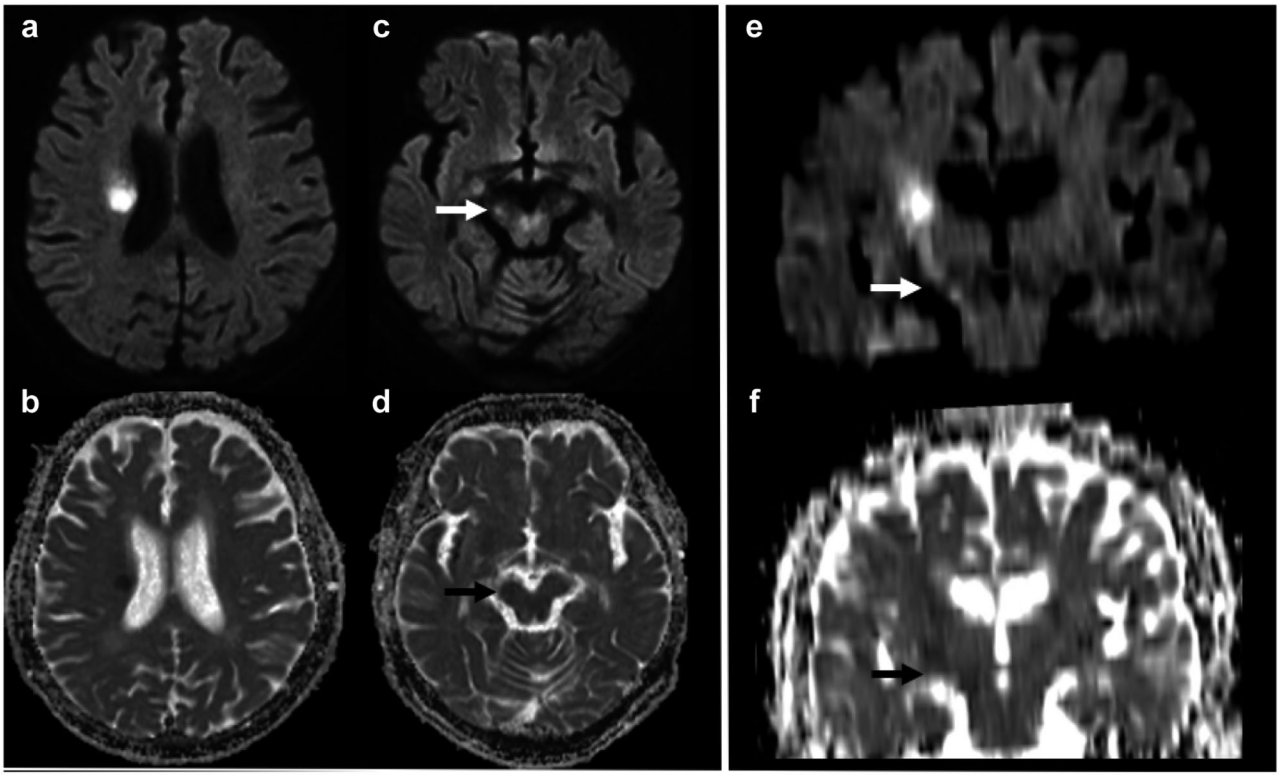

Fig. 2 Findings of a representative case. Cerebral infarction is observed in the right lenticulostriate artery (LSA) area of a 72-year-old woman. Diffusion-weighted MRI scanning was performed 11 days after ischemic stroke infarction experienced by the patient. Axial diffusion-weighted imaging (DWI) reveals an acute infarction, classified as a small-artery disease in the right paraventricular corona radiata (**a**), with a decreased axial apparent diffusion coefficient (ADC) map (**b**). Imaging of the cerebral peduncle and internal capsule demonstrates hyperintensity on the axial and coronal DWI (**c and e**), as well as hypo-intensity on the axial and coronal ADC map (**d and f**), in the descending cortical tract. Multiplanar reconstruction generated coronal DWI and ADC map section images (**e and f**). MRI: magnetic resonance imaging

of the LSA because the LSA is a perforating branch that vertically passes over the horizontal part of the middle cerebral artery, which nourishes an area where the pyramidal tract converges (paraventricular corona radiata) and has more infarct slices than the other two vessels (WMMA and AchoA), resulting in greater damage to the pyramidal tract. The early WD group exhibited a lower BRS on admission and at discharge and greater paralysis, corroborating the damage to the pyramidal tracts. Cardiogenic embolism is characterized by cortical damage as the main embolic mechanism, and the cortex may exhibit a lower degree of total pyramidal damage, depending on the case, owing to the dispersion of the pyramidal tract, which does not consistently induce early WD. Therefore, paraventricular corona radiata area converging pyramidal tracts and extensive cortical infarcts are more likely to induce severe pyramidal tract damage and early WD.

In this study, the high DWI signal and low signal on ADC map of the DCST, indicating early WD, exhibited DWI signal normalization in all seven cases. In addition, a high FLAIR signal was identified in 41% (9/22) of the cases with early WD within 14 days of acute stroke onset. Early WD depicts the degeneration attributed to cytotoxic oedema of axons [5] or dysfunction of the axonal transport [7] within 14 days of onset and presents as a transient high DWI signal. Four weeks after onset, a high T2WI signal can be detected [3], indicating increased water content in the extracellular space enlarged by myelin and axons loss [20]. However, studies have reported pyramidal tracts exhibiting a high T2WI signal in the acute phase earlier than 4 weeks after onset [7, 21, 22]. The FLAIR images were T2WI with suppressed water signals, which was similar to the results of our study. The DCST below the cerebral peduncle is often adjacent to the cerebrospinal fluid and more easily detected on FLAIR images, which are T2WI with suppressed water signals. Therefore, increased water content in the extracellular space may be detected earlier on FLAIR images than on T2WI, as observed in this study.

This study had some limitations. First, this retrospective study was conducted at a single institution, which may have introduced bias. Second, selection bias may have affected the results, given that patients ineligible for alteplase thrombolysis for acute noninterventional therapy and mechanical thrombectomy were included. Third, while assessing early WD, we investigated a

Table 1 Summary of patient demographic and clinical characteristics

	With early WD	Without early WD	*p*-value
Number (n)	22	83	
Age (years)	74.1 ± 9.7	73.9 ± 11.6	0.87
Sex (males: females)	10:12	34:49	0.33
Time from symptom onset to first MRI (days)	1.1 ± 1.1	1.3 ± 1.4	0.84
Time from symptom onset to follow-up MRI (days)	8.8 ± 1.5	9.3 ± 2.5	0.28
Time from symptom onset to start of rehabilitation (days)	3.0 ± 1.5	3.4 ± 1.9	0.56
Rehabilitation time (days)	15.8 ± 10.5	12.5 ± 7.1	0.09
Hypertension	17	66	0.78
Diabetes mellitus	4	26	0.29
Hyper-LDLemia	13	47	0.84
Atrial fibrillation	4	9	0.46
Smoking index	280.8 ± 87.2	328.0 ± 46.6	0.67
Brunnstrom stage on admission	12.5 ± 4.3	15.4 ± 2.7	< 0.001
Brunnstrom stage on discharge	13.3 ± 4.5	16.1 ± 2.3	0.0012
SSS-TOAST classification			
Large-artery atherosclerosis	3	16	
Cardioaortic embolism	2	10	
Small-artery disease	15	46	
Other causes	0	2	
Undermined causes	2	9	
Infarction locations			
Centrum ovale	0	6	
Paraventricular corona radiata	15	15	
Internal capsule	4	12	
Midbrain	0	1	
Pons	0	13	
Medulla oblongata	0	3	
Multiple sections	3	33	
Responsible artery			
Number	19	26	
White matter medullary artery	1	7	
Lenticulostriate artery	14	8	
Anterior choroid artery	4	11	

Hyper-LDLemia, hyper-low-density lipoprotein cholesterolemia; MRI, magnetic resonance imaging; SSS-TOAST, The Stop Stroke Study Trial of Org 10,172 in Acute Stroke Treatment classification; WD, Wallerian degeneration

high-intensity DWI signal and low-intensity signal ADC map on coronal and horizontal MRI scans to avoid misinterpreting the T2 shine-through effect. However, identifying MRI signal changes depended on the judgment of the diagnostician. Similar limitations apply to the FLAIR imaging. Fourth, the MRI machine models and imaging conditions used were not identical for all patients. Fifth, although patient age and the timing and duration of rehabilitation initiation were assumed to be potential confounders and descent modifiers of the BRS score, they had little impact, with no significant difference between the groups with and without early WD. Finally, musculoskeletal diseases other than lifestyle-related diseases were not investigated in this study but may have affected the score values.

Nevertheless, this study revealed that early WD is a poor prognostic factor for pyramidal tract disorders associated only with infarct size and paralysis severity on admission. Thus, early therapeutic intervention and penumbra salvage may reduce infarct expansion and prevent early WD. Moreover, the findings of our study indicating that MRI scanning may support the assessment of early pyramidal tract pathology can contribute to the therapeutic evaluation of modern neuroprotective drug research.

Conclusions

Our study demonstrates that the degree of pyramidal tract damage and severity of paralysis are the only reliable indicators for early WD. Notably, early WD may occur not only in cardiogenic embolism but also in small-artery disease, with the main responsible artery being the LSA, and has a poor prognosis. Our study indicates that MRI evidence of early WD is closely associated with more severe corticospinal tract damage and worse motor outcomes. Recognizing early WD as a surrogate marker of CST injury can help clinicians identify patients at higher risk of poor recovery. Consequently, these patients may benefit from more aggressive or specialized rehabilitation approaches. Although early WD may not be an independent prognostic factor outside the context of baseline stroke severity, its imaging signature provides practical insight into early tissue changes and can guide therapeutic decision-making.

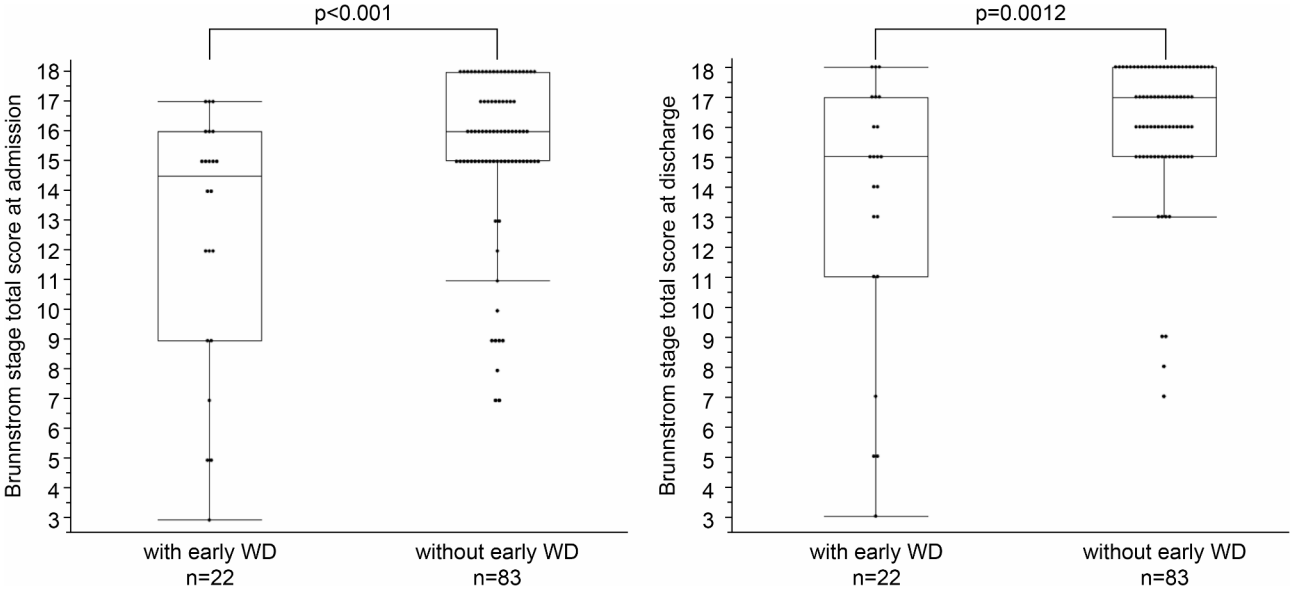

Fig. 3 Brunnstrom stage scores at admission and discharge with and without early Wallerian degeneration (WD)

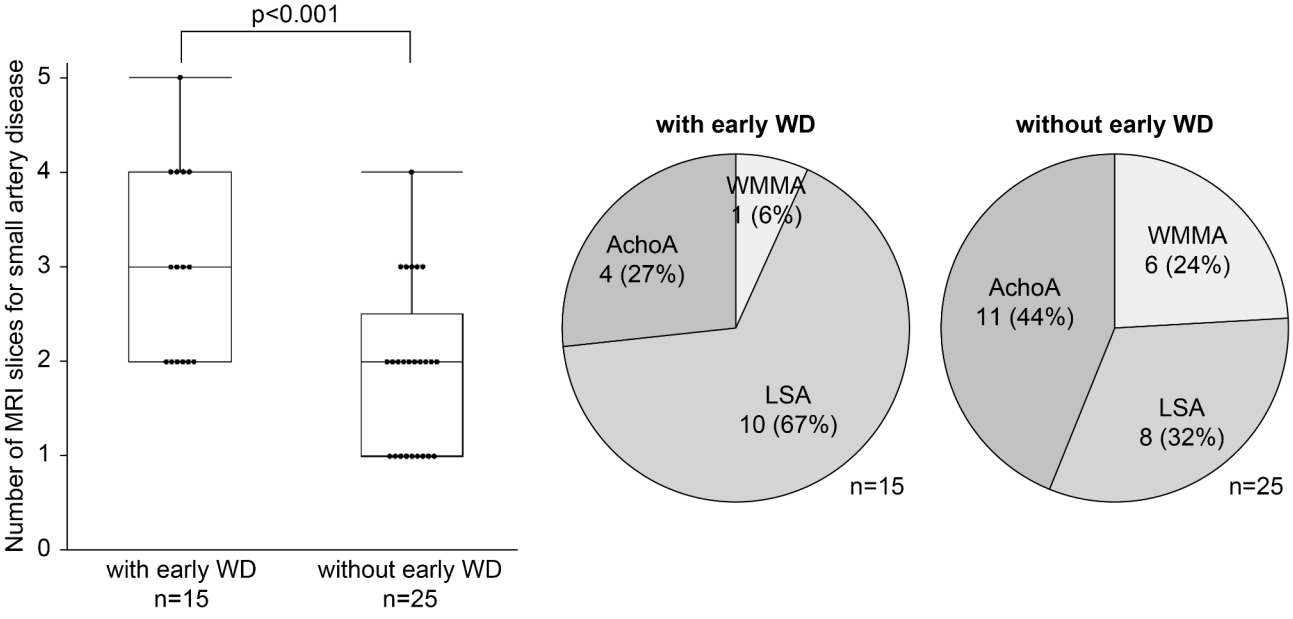

Fig. 4 Magnetic resonance imaging (MRI) slice counts and responsible artery for small-artery disease. Cases are divided according to whether they showed early Wallerian degeneration (WD). WMMA, white matter medullary artery; LSA, lenticulostriate artery; AchoA, anterior choroid artery

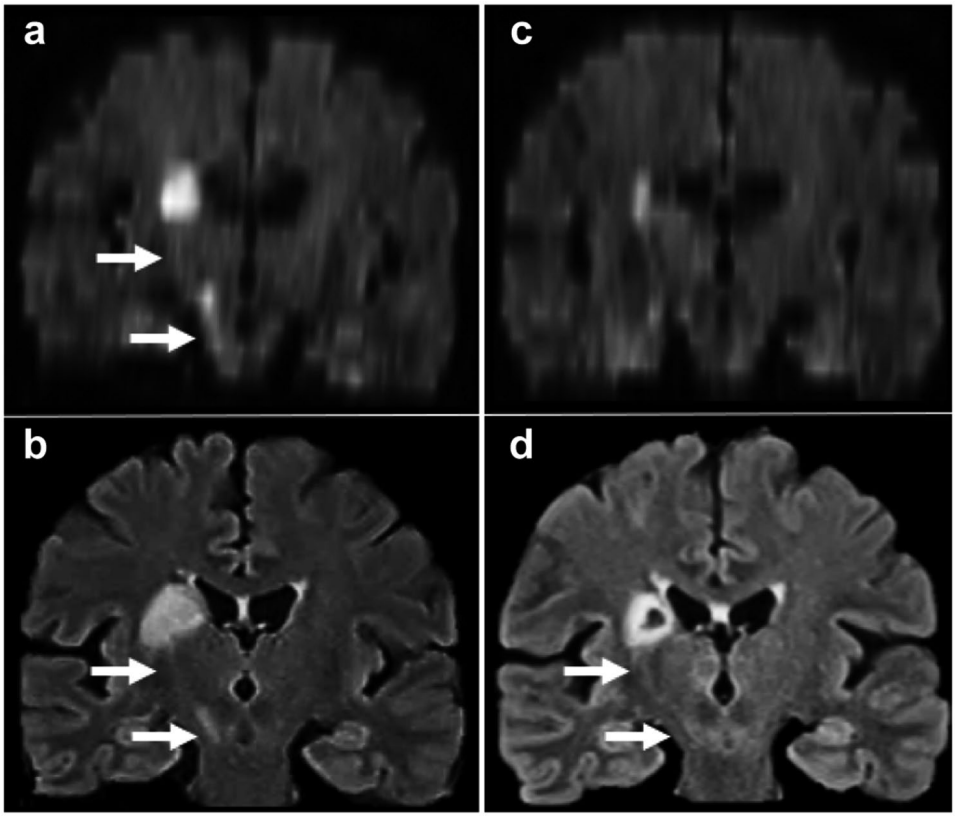

Fig. 5 Long-term follow-up MRI scan and tracking of changes on DWI and FLAIR imaging. A 65-year-old woman underwent axial follow-up magnetic resonance imaging (MRI), including diffusion-weighted imaging (DWI) and coronal fluid-attenuated inversion recovery (FLAIR) imaging during the acute and chronic phases of stroke. The second coronal DWI (**a**) and coronal FLAIR (**b**) were obtained 9 days after stroke onset. Each sequence demonstrates a high signal in the pyramidal tract descending from the infarction. The third DWI (**c**) and FLAIR (**d**) were performed 48 days after onset. The high DWI signal disappeared, and the high FLAIR signal is more defined. All coronal DWI images (**a and c**) were created using multiplanar reconstruction

Abbreviations

AchoA	Anterior choroid artery
ADC	Apparent diffusion coefficient
BRS	Brunnstrom stage
DCST	Descending corticospinal tract
DWI	Diffusion-weighted imaging
FLAIR	Fluid-attenuated inversion recovery
FOV	Field of view
hyper-LDLemia	Hyper-low-density lipoprotein cholesterolemia
LSA	Lenticulostriate artery
MRI	Magnetic resonance imaging
SSS-TOAST	Stop Stroke Study Trial of Org 10172 in Acute Stroke Treatment
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
T2WI	T2-weighted images
TE	Echo time
TR	Repetition time
WD	Wallerian degeneration
WMMA	White matter medullary artery

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12883-025-04179-4.

Supplementary Material 1

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Author contributions
KO, KS, HK, MO, TM and TI were involved in the study concept and design, collection of data, and drafting, reviewing, and critiquing the manuscript. YN was involved in the study concept and design, collection of data, drafting, reviewing, and critiquing the manuscript and supervision. TY revised and critiqued the manuscript. All authors have read and approved the final manuscript.

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Data availability
The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
The Institutional Research Ethics Board of Saitama Medical University, Japan, approved the study protocol (Approval No. 2022-004). The requirement for informed consent was waived by the Institutional Research Ethics Board because the researchers only handled anonymized information.

Consent for publication
The release of information on this clinical study was posted on the website from May 9, 2022, to March 31, 2023, providing participants with the opportunity to opt out of the release of information. There were no refusals to disclose this information. https://saitama-med.bvits.com/rinri/publish.aspx?BOARD_ID=1

Competing interests
The authors declare no competing interests.

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