

Phenotypic Differences Between Flail Arm Syndrome and Upper Limb-Onset Classical ALS

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Abstract

Objective: To comparatively analyze clinical and electrophysiological differences between upper limb-onset ALS (UL-ALS) and flail arm syndrome (FAS) to improve early diagnosis and individualized treatment. **Methods:** We retrospectively analyzed 23 patients (19 UL-ALS, 4 FAS) admitted between May 2018 and April 2026, according to the 1998 El Escorial criteria. Demographic data, disease progression, neurological signs, electromyographic findings, and ALSFRS-R scores were collected and compared. **Results:** Compared to UL-ALS, the FAS group exhibited an older onset age, longer diagnostic delay, and slower progression to a second region ($P < 0.05$), with predominantly proximal upper limb involvement. FAS patients lacked upper motor neuron signs like hyperreflexia ($P < 0.05$) and showed more localized lower motor neuron involvement on electromyography ($P = 0.011$). Both groups shared high misdiagnosis rates (primarily cervical spondylosis) and similar comorbidities. However, the FAS group maintained significantly higher ALSFRS-R scores ($P = 0.046$), reflecting milder functional impairment. **Conclusion:** FAS is a slowly progressive subtype featuring an older onset, localized proximal upper limb involvement, lack of upper motor neuron signs, and a better functional prognosis. Combining clinical progression characteristics with electrophysiological markers effectively differentiates FAS from UL-ALS, helping to minimize misdiagnoses.

Keywords upper limb-onset amyotrophic lateral sclerosis; Flail arm syndrome; Clinical phenotype; Electrophysiological characteristics

1 Introduction

Motor neuron diseases are a group of fatal neurodegenerative disorders that involve both upper and lower motor neurons. Amyotrophic Lateral Sclerosis (ALS) is the most common and classic type, with various atypical variants such as Flail Arm Syndrome (FAS) and Flail Leg Syndrome (FLS)^[1]. First described in 1886, FAS is a rare subtype also known as Vulpian-Bernhardt syndrome, which is characterized by predominant lower motor neuron involvement^[2]. Its main clinical manifestations are progressive, symmetric atrophy and weakness that initially affect either unilateral or bilateral upper limbs, with no involvement of the lower limbs or bulbar function in the early disease stage^[1]. Compared with classic ALS, FAS is more prevalent in males, progresses more slowly, and is associated with longer overall survival; however, it exhibits significant phenotypic heterogeneity^[3, 4]. In the early stage, FAS often presents with muscle weakness and atrophy in unilateral or bilateral upper limb muscle groups, which easily leads to confusion

with upper limb-onset ALS, multifocal motor neuropathy, spinal muscular atrophy, and other diseases, resulting in a persistently high clinical misdiagnosis rate^[4]. Some patients even receive ineffective immunotherapy or hormone therapy^[2]. Additionally, there are ethnic differences in the age of onset, clinical phenotype, and prognosis of ALS and FAS between Eastern and Western populations, and diagnostic delay remains a prominent issue^[5]. Currently, the clinical definition of FAS is mostly based on the presence of symptoms for 12 months. However, some cases of upper limb-onset ALS with a disease duration of less than 12 months have a poorer prognosis, and a small number of FAS patients may progress rapidly to respiratory failure in the later stage, challenging the inherent perception of its relatively favorable prognosis^[4]. Based on this, this study comparatively analyzed the differences in clinical phenotypes, electrophysiological characteristics, neurological signs, misdiagnosis, treatment, and comorbidities between patients with Upper Limb-onset Amyotrophic Lateral Sclerosis (UL-ALS) and FAS. The aim was to provide a reference for improving the early diagnostic accuracy, optimizing disease assessment, and facilitating individualized diagnosis and treatment of diseases associated with upper limb atrophy.

2 Materials and Methods

2.1 Diagnostic Criteria and Case Selection

2.1.1 Case Selection

All cases were from patients hospitalized at the Seventh Affiliated Hospital of Sun Yat-sen University (Shenzhen) from May 2018 to April 2026. The diagnosis of all patients was made in accordance with the 1998 El Escorial criteria. Among them, the diagnostic criteria for FAS patients were as follows: upper limb weakness and atrophy were the core clinical manifestations, and these symptoms were progressive; positive pathological deep reflexes or Hoffmann's sign in the upper limbs could appear at a certain stage of the disease course, but there were no manifestations of upper motor neuron overexcitation such as increased muscle tone and clonus; since the onset of symptoms, the range of functional involvement had to be strictly limited to the upper limbs, and this limited state lasted for at least 12 months. A total of 23 patients were enrolled in this study, including 19 cases in the UL-ALS group and 4 cases in the FAS group.

2.1.2 Exclusion Criteria

Patients with peripheral neuropathy (including carpal tunnel syndrome and cubital tunnel syndrome), spinal muscular atrophy, multifocal motor neuropathy, Kennedy's disease, syringomyelia, demyelinating myelopathy, cervical spondylotic myelopathy, brachial plexus neuritis, and thoracic outlet syndrome were excluded.

2.2 Research Methods

At the first visit, the following clinical data of all patients were recorded in detail: gender, age at onset, disease duration at diagnosis, origin site, time to progression to the second body region, main involved sites, fasciculation, neurological signs, electromyographic findings, misdiagnosed diseases, medication use, comorbidities, family history, and scores of the ALS Functional Rating Scale-Revised (ALSFRRS-R).

2.3 Statistical Analysis

All measurement data in this study were skewed, expressed as median (interquartile range), and the Wilcoxon rank-sum test was used for comparison between groups. Count data were expressed as cases (percentage), and the Fisher's exact test was used for comparison between groups. SPSS 28.0 software was

used for statistical analysis; all analyses were two-tailed tests, and $P < 0.05$ was considered statistically significant.

3 Results

3.1 Comparison of demographic and clinical disease course characteristics

In the UL-ALS group ($n = 19$), there were 10 males and 9 females, with a male-to-female ratio of approximately 1.11:1. In the FAS group ($n = 4$), there were 2 males and 2 females, with a male-to-female ratio of 1:1. Given the small sample size of the FAS group (4 cases), Fisher's exact test was adopted for comparison, and the results showed no statistically significant difference in gender composition between the two groups ($P = 0.662$). There was a statistically significant difference in the age of onset between the two groups ($P = 0.042$). The age of onset in the FAS group was significantly later than that in the UL-ALS group (median: 65.5 years vs. 46.0 years). In terms of diagnostic delay, the interval from symptom onset to definitive diagnosis in the FAS group was markedly longer than that in the UL-ALS group (median: 24.0 months vs. 6.0 months, $P = 0.003$), suggesting that early recognition of FAS is more challenging. Regarding disease progression rate, the time from initial symptom onset to involvement of the second affected region in the FAS group was significantly longer than in the UL-ALS group (median: 28.0 months vs. 4.0 months, $P < 0.001$), indicating a more indolent disease course of FAS.

3.2 Comparison of Affected Site Characteristics

Both groups of patients predominantly presented with upper limb onset, with unilateral involvement being the most common initial site, and no cases had bulbar onset. In terms of major affected sites, all patients in the FAS group exhibited proximal upper limb involvement, with no cases of distal or mixed involvement. In contrast, the UL-ALS group showed a more diverse pattern of involvement, including proximal, distal, and mixed involvement. Although the difference in the distribution of affected sites between the two groups did not reach statistical significance ($P = 0.283$), the highly concentrated proximal involvement pattern in the FAS group was consistent with the core clinical characteristics of its classification. Detailed data are shown in Table 1.

Table 1: Comparison of Affected Site Characteristics between UL-ALS and FAS

	UL-ALS group (n=19)	FAS group (n=4)	P value
Site of onset			1.000
Left	7 (36.8%)	2 (50.0%)	
Right	9 (47.4%)	1 (25.0%)	
Bilateral	3 (15.8%)	1 (25.0%)	
Main affected site			0.283
Proximal	7 (36.8%)	3 (75.0%)	
Distal	8 (42.1%)	1 (25.0%)	
Mixed/Unclear	4 (21.1%)	0 (0.0%)	

3.3 Comparison of Neurological Signs, Electromyographic Features and ALSFRS-R Scores

There was no statistically significant difference in the incidence of fasciculations between the UL-ALS group and the FAS group ($P = 0.630$). Fasciculations were present in 12 patients (63.2%) in the UL-ALS group and 2 patients (50.0%) in the FAS group. Regarding neurological signs, the proportions of

patients with hyperactive/exaggerated upper limb reflexes and positive pathological reflexes were significantly higher in the UL-ALS group than in the FAS group ($P = 0.016$ and $P = 0.033$, respectively), indicating prominent upper motor neuron involvement in classic ALS. In contrast, no such upper motor neuron involvement was observed in the FAS group, consistent with its clinical feature of “absence of upper motor neuron involvement”. The incidence of tongue muscle atrophy was also higher in the UL-ALS group than in the FAS group, but the difference did not reach statistical significance ($P = 0.269$). Additionally, the proportion of patients with electromyography (EMG) evidence of multi-segment lower motor neuron involvement (> 2 regions) was markedly higher in the UL-ALS group (94.7% vs. 25.0%, $P = 0.011$). In contrast, no definite upper motor neuron signs were observed in the FAS group, and the EMG involvement was more localized, predominantly affecting the cervical spinal cord segments. In terms of the ALSFRS-R score, the difference between the two groups was statistically significant ($P = 0.046$). The FAS group had a significantly higher score than the UL-ALS group (median: 43 vs. 29), indicating a milder degree of overall functional impairment in patients with FAS (Table 2).

Table 2: Comparison of Neurological Signs, Electromyographic Features and ALSFRS-R Scores between UL-ALS and FAS

	UL-ALS group (n=19)	FAS group (n=4)	P value
Fasciculations			0.630
Present	12 (63.2%)	2 (50.0%)	
Absent	7 (36.8%)	2 (50.0%)	
Neurological signs			
Upper limb reflexes (hyperactive/exaggerated)	14 (73.7%)	0 (0.0%)	0.016
Knee reflexes (hyperactive/exaggerated)	11 (57.9%)	1 (25.0%)	0.298
Positive pathological reflexes	9 (47.4%)	0 (0.0%)	0.033
Tongue muscle atrophy	7 (36.8%)	0 (0.0%)	0.269
ALSFRS-R	30.21±8.90	40.75±5.56	0.046
EMG involvement extent			0.011
Localized (≤ 2 regions)	1 (5.3%)	3 (75.0%)	
Multisegmental (> 2 regions)	18 (94.7%)	1 (25.0%)	

3.4 Comparison of Misdiagnosis and Treatment Regimens

Both groups exhibited a high rate of misdiagnosis. The misdiagnosis rate was 100% in the FAS group and 73.7% in the UL-ALS group, with no statistically significant difference between the two groups ($P = 0.298$). Cervical spondylosis was the most common misdiagnosed disease in both groups. Regarding treatment, there were no statistically significant differences in the usage rates of riluzole, edaravone, or corticosteroids between the two groups (all $P > 0.05$). The corticosteroid usage rate was low in both the UL-ALS and FAS groups, with no significant difference ($P = 0.333$). Most patients who received corticosteroids had previously been empirically treated for misdiagnosed peripheral nerve or radicular diseases, rather than receiving standard therapy for ALS (Table 3).

3.5 Comparison of Comorbidities

Regarding comorbidities, there were no statistically significant differences in the distributions of hyperlipidemia, hypertension, diabetes mellitus, emphysema, cervical spondylosis, old cerebral infarction, and family history of muscular atrophy between the two groups (all $P > 0.05$). Among them, the incidence of cervical spondylosis was 57.9% in the UL-ALS group and 100% in the FAS group. Although the incidence was higher in the FAS group, the difference did not reach statistical significance ($P = 0.269$) (Table 4).

Table 3: Comparison of Misdiagnosis and Treatment Regimens between UL-ALS and FAS

	UL-ALS group (n=19)	FAS group (n=4)	P value
Misdiagnosis status			0.298
Positive	14 (73.7%)	4 (100.0%)	-
Negative	5 (26.3%)	0 (0.0%)	-
Riluzole treatment			1.000
Used	11 (57.9%)	2 (50.0%)	-
Unused	8 (42.1%)	2 (50.0%)	-
Edaravone treatment			1.000
Used	6 (31.6%)	1 (25.0%)	-
Unused	13 (68.4%)	3 (75.0%)	-
Corticosteroid use			0.333
Used	1 (5.3%)	1 (25.0%)	-
Unused	18 (94.7%)	3 (75.0%)	-

Table 4: Comparison of Comorbidities between UL-ALS and FAS

Comorbidities	UL-ALS group (n=19)	FAS group (n=4)	P value
Hyperlipidemia	7 (36.8%)	0 (0%)	0.298
Hypertension	6 (31.6%)	1 (25.0%)	1.000
Diabetes mellitus	1 (5.3%)	1 (25.0%)	0.333
Emphysema	1 (5.3%)	0 (0%)	1.000
Cervical spondylosis	11 (57.9%)	4 (100%)	0.269
Old cerebral infarction	1 (5.3%)	0 (0%)	1.000
Family history of muscular atrophy	1 (5.3%)	0 (0%)	1.000

4 Discussion

As a variant of ALS, FAS accounts for approximately 10% of cases^[4, 6]. Its clinical phenotype differs significantly from that of classic UL-ALS. Due to atypical early symptoms and frequent confusion with other upper limb lesions, it is associated with persistent diagnostic delays and high misdiagnosis rates, posing challenges to clinical diagnosis and management^[1]. This study compared and analyzed the clinical data of 19 patients with UL-ALS and 4 patients with FAS, identifying the core phenotypic differences between the two conditions and providing an important reference for clinical differential diagnosis and individualized care.

The results showed that the age of onset in the FAS group was significantly later than in the UL-ALS group, consistent with previous studies and suggesting that age may be a useful reference indicator for distinguishing between the two subtypes^[2]. In terms of disease progression, the FAS group had a longer disease duration at diagnosis and a longer time to spread to a second body region, demonstrating a typical indolent course. These findings are in good agreement with those of relevant domestic and international cohort studies, and also supplement the clinical differential characteristics of the two subtypes in the local population. This is also consistent with the clinical perception that FAS has a relatively favorable prognosis^[7]. However, clinicians should be alert to the possibility of rapid progression in a small subset of FAS patients in the later stages, to avoid misjudgment of the condition based on fixed preconceptions.

In terms of affected sites, the FAS group showed highly concentrated proximal upper limb involvement, while the UL-ALS group had a more diverse pattern of involvement. Although this difference did not reach statistical significance, it can still serve as one of the key points for clinical differentiation. In particular,

elderly patients with symmetric proximal upper limb atrophy and weakness should raise clinical suspicion of FAS^[8]. Unlike previous studies which suggested that patients with FAS were younger than the ALS control group^[2], the present study found that differences between the two groups were more pronounced in neurological signs and electrophysiological features: the FAS group had no definite upper motor neuron signs, without hyperactive upper limb reflexes and positive pathological reflexes, and the EMG involvement was more localized. In contrast, the UL-ALS group exhibited significant upper motor neuron damage, with EMG mostly showing multi-segmental lower motor neuron involvement. This is consistent with the pathological feature of FAS, which is centered on lower motor neuron involvement, and is also the most critical distinguishing point between the two conditions^[7].

This study showed no statistically significant difference in gender composition between the two groups, while the age of onset was significantly later in the FAS group than in the UL-ALS group. This is consistent with the findings of the East-West ALS phenotype comparison study by Rosenbohm et al., which demonstrated ethnic heterogeneity in the age of onset of ALS and its subtypes across populations, with a generally higher age of onset among Chinese patients with FAS^[7].

Regarding the duration from symptom onset to diagnosis, the FAS group had a significantly longer interval than the UL-ALS group. Furthermore, the time from initial symptom onset to progression to a second affected region was far slower in the FAS group, indicating an indolent disease course. Previous studies have confirmed that early symptoms of FAS are mostly confined to the upper limbs, often presenting with asymmetric onset and predominant proximal involvement. The rate of disease spread to other body regions is markedly slower than in classic ALS, with symptoms remaining localized to the upper limbs for more than 18 months in over half of FAS patients, and in some cases, for 24–36 months. This represents the core reason for the difficulty in early recognition and diagnostic delay^[4, 9]. Meanwhile, a study by Chen et al. indicated that a disease duration of 12 months may serve as a key cutoff to distinguish upper limb-onset ALS from FAS. Patients with FAS-like phenotypes who have not reached a 12-month disease duration have a worse prognosis, which also indirectly confirms that a protracted disease course is an important clinical marker of FAS^[8].

In terms of clinical signs and electrophysiological characteristics, the present study found that the proportions of patients with hyperactive/exaggerated upper limb reflexes and positive pathological reflexes were significantly higher in the UL-ALS group than in the FAS group. In contrast, the FAS group showed no typical upper motor neuron involvement signs, which conforms to the classical clinical definition of FAS characterized by isolated lower motor neuron damage and absence of upper motor neuron involvement^[7]. A controlled study by Yoon et al. also confirmed that the incidences of upper motor neuron impairment signs and fasciculations were significantly higher in patients with upper limb-onset ALS than in those with FAS, which can serve as important differential diagnostic indicators^[7, 9].

No significant differences were observed in the incidences of tongue muscle atrophy and fasciculations between the two groups, suggesting that tongue muscle involvement is not a specific marker for distinguishing the two subtypes. Electrophysiologically, the UL-ALS group had a significantly higher proportion of patients with multi-segmental lower motor neuron involvement on electromyography, indicating more extensive lower motor neuron damage after disease onset in UL-ALS. In comparison, lower motor neuron involvement in FAS was mostly confined to the upper limbs with a relatively limited distribution, and this electrophysiological feature can provide objective evidence for clinical differentiation^[9]. Although some studies have indicated that both FAS and classic ALS exhibit cortical and peripheral nerve hyperexcitability, this indicator cannot be applied to early differential diagnosis, and clinical comprehensive judgment still relies on neurological signs and electromyography^[10].

In the analysis of comorbidities, misdiagnosis and treatment, cervical spondylosis was the most common comorbidity in both groups. The comorbidity rate reached 100% in the FAS group and nearly 60% in the UL-ALS group, with no statistical difference between groups. Both groups presented an extremely high

misdiagnosis rate, and cervical spondylosis was the leading misdiagnosed disease in both, which is consistent with previous studies [2]. Characterized merely by upper limb weakness and atrophy without obvious upper motor neuron signs, FAS is highly prone to being confused with spinal degenerative diseases such as cervical spondylosis and radiculopathy. Literature has reported that the early misdiagnosis rate of FAS exceeds 54.8%, with cervical spondylosis ranking first among misdiagnosed etiologies; some patients even receive non-targeted empirical treatments such as immunoglobulin and corticosteroids[2]. There was no significant difference in the utilization rates of standard ALS medications including riluzole and edaravone between the two groups in this study. Corticosteroid treatment was only an empirical intervention after misdiagnosis with no definite therapeutic value for the disease, reflecting the current status of insufficient early recognition and lagging standardized management of FAS in clinical practice.

In terms of functional status assessment, the ALSFRS-R scale was adopted in this study to evaluate patients' overall function. The results showed that the ALSFRS-R score at diagnosis was significantly higher in the FAS group than in the UL-ALS group, indicating a milder degree of disability, which is highly consistent with the biological characteristics of FAS, including an indolent disease course and slow progression. Multiple studies have confirmed that patients with FAS have a significantly better overall survival than those with classic ALS, with a median survival of 53 months, far longer than 33 months in upper limb-onset ALS. Meanwhile, the rate of decline of ALSFRS-R scores is more gradual, and the process of functional deterioration is slower^[4, 11]. Kornitzer et al. further pointed out that the rate of vital capacity decline in flail limb subtypes is much lower than that in classic ALS, with a relatively mild functional deterioration course, which mutually verifies the conclusion of better overall functional preservation in FAS patients in this study^[2].

This study has certain limitations. It is a single-center retrospective study with a limited sample size and a small number of cases in the FAS group. Long-term follow-up and survival prognosis analysis were not performed; therefore, further exploration of long-term survival differences, the pattern of respiratory function decline, and dynamic changes in electrophysiological indicators between the two groups was not feasible. In addition, quantitative indicators such as cognitive function, diaphragmatic function, and CMAP amplitude were not included, which can assess the risk of progression from FAS to typical ALS^[3]. Future research should expand the sample size through multicenter collaboration and conduct prospective follow-up studies. By combining electrophysiological, respiratory functional, and imaging parameters, an early differential diagnostic system for UL-ALS and FAS can be further established, providing evidence-based references for precise clinical diagnosis, treatment, and prognostic evaluation.

5 Conclusion

There are significant differences in clinical phenotypes between FAS and UL-ALS. FAS is characterized by an older age of onset, an indolent disease course, proximal upper limb involvement only, absence of typical upper motor neuron damage, limited extent of involvement on electromyography, and a better overall functional prognosis. Clinically, both conditions are easily confused with diseases such as cervical spondylosis, leading to high misdiagnosis rates. Combining the age of onset, disease progression characteristics, neurological signs, and the extent of electrophysiological involvement can effectively differentiate UL-ALS from FAS, helping to shorten diagnostic delays, reduce misdiagnoses, and provide an important reference for clinical individualized management and treatment planning.

To Cite This Article Chenghui Ye, et al. (2026). Phenotypic Differences Between Flail Arm Syndrome and Upper Limb-Onset Classical ALS. *Medical Research*, 8(2), 26–33. <https://doi.org/10.6913/mrhk.080204>

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