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Comparison between Flail Arm Syndrome and Upper Limb Onset Amyotrophic Lateral Sclerosis: Clinical Features and Electromyographic Findings

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Flail arm syndrome (FAS), an atypical presentation of amyotrophic lateral sclerosis (ALS), is characterized by progressive, predominantly proximal, weakness of upper limbs, without involvement of the lower limb, bulbar, or respiratory muscles. When encountering a patient who presents with this symptomatic profile, possible diagnoses include upper limb onset ALS (UL-ALS), and FAS. The lack of information regarding FAS may make differential diagnosis between FAS and UL-ALS difficult in clinical settings. The aim of this study was to compare clinical and electromyographic findings from patients diagnosed with FAS with those from patients diagnosed with UL-ALS. To accomplish this, 18 patients with FAS and 56 patients with UL-ALS were examined. Significant differences were observed between the 2 groups pertaining to the rate of fasciculation, patterns of predominantly affected muscles, and the Medical Research Council scale of the weakest muscle. The presence of upper motor neuron signs and lower motor neuron involvement evidenced through electromyography showed no significant between-group differences.

Key words: flail arm syndrome, amyotrophic lateral sclerosis, brachial amyotrophic diplegia, electromyography, motor neuron disease

INTRODUCTION

ALS is a fatal neurodegenerative disease of motor neurons, has various subtypes, and shows a markedly heterogeneous clinical presentation and course. Despite a uniformly fatal outcome, patients with ALS display a wide range of survival times from a few months to several decades [1]. In addition, phenotypic variation is evident through different sites of onset and variable disease progression. The 3 main clinical ALS categories are classic limb onset ALS, progressive bulbar palsy (bulbar onset ALS; PBP), and a lower motor neuron dominant variant termed progressive muscular atrophy (PMA). Bulbar onset ALS tends to have a worse prognosis than limb onset, and both forms have worse prognosis than PMA. However, these 3 phenotypic categories do not fully capture the spectrum of clinical heterogeneity in ALS, which may contribute to diagnostic error. Furthermore, there are no definitive diagnostic tests or well defined biomarkers for ALS at present [2], leaving neurologists to rely on only clinical history, physical examination, and neurophysiological evidence of lower motor neuron (LMN) involvement. Apart from the 3 main

ALS subtypes, other forms have been recognized but relatively inadequately studied. Atypical ALS presentations include flail arm syndrome (FAS) and flail leg syndrome [3]. FAS, also known as brachial amyotrophic diplegia or man-in-a-barrel syndrome, is characterized by progressive, predominantly proximal, symmetric weakness and wasting of the upper limbs, with no significant lower limb or bulbar muscle involvement [4-6]. There are few reports about this phenotype. Recent studies have indicated that FAS was associated with a significantly better prognosis than typical ALS or PMA. The male to female ratio was 4~10 to 1, in contrast to the reported ratio of 1.5 to 1 for the ALS population as a whole [3].

In the initial stages of the disease, a substantial proportion of patient with ALS could be noted only upper limb weakness without bulbar or lower limb weakness, aside from those with PBP who account for approximately 20% of ALS patients [7]. Almost all progressed to lower limb, bulbar, or respiratory muscle weakness and consequently had a fatal prognosis. When clinicians encounter a patient with symptoms restricted to the upper limbs, they should consider that the possible diagnoses include classic ALS with upper limb onset (UL-ALS) or FAS. It may be difficult to differentiate between these 2 phenotypes, however, the distinction is significant importance, as they differ considerably in their prognosis. Studies investigating the clinical features and electromyographic (EMG) findings from patients with FAS are still lacking. The aim of the current study was to compare the clinical and EMG findings of patients diagnosed with FAS with those of patients diagnosed with UL-ALS. To accomplish this, a retrospective review of patients who were diagnosed with motor neuron disease and presented with progressive and symmetric weakness of the upper limbs, with no lower limb or bulbar muscle involvement, was conducted.

MATERIALS AND METHODS

The Seoul National University Hospital ALS center is located in downtown Seoul and serves a diverse community of patients from the metropolitan area. All patients diagnosed with 'motor neuron disease' in our ALS center from 2006~2011 who had initial complaints of bilateral upper limb weakness were selected for study inclusion. EMG and nerve conduction studies (NCS) were performed on this patients at the initial visit only. The simultaneous presence of spontaneous denervation potential (fibrillations and positive sharp waves) and enlarged motor unit potentials (MUPs) on EMG was considered as evidence of LMN involvement. The time of disease onset was set as the date when patients first noticed their symptoms. During the follow-up visits, we established the progression to ALS when they had evidence of bulbar or respiratory muscle involvement or lower limb weakness.

FAS was defined in patients with symmetric weakness of both upper limbs, with sparing of the lower limbs and bulbar and respiratory muscles for at least 12 months after their first visit. We also included patients who had a pattern of wasting typical for flail arm, but also had pathological deep tendon reflex or Hoffman sign in the upper limbs at some point during the disease. Patients with distal upper limb weakness or wasting without proximal involvement at presentation were excluded from this category. UL-ALS was defined in patients with limited upper limb weakness at their initial visit that spread to bulbar, respiratory, or lower limb muscles during the observation period. Those with unexplained sensory signs or symptoms, abnormal nerve conduction studies, weakness in the distribution of individual motor nerves, or any abnormality on cervical MRI suggestive of an alternate diagnosis such as spinal stenosis or cervical myelopathy were not included in the study. Patients diagnosed with conditions such as spinal muscular atrophy, Kennedy syndrome, monomelic amyotrophy, Hirayama syndrome, or multifocal motor neuropathy, which are not considered as part of the ALS spectrum, were excluded from the study.

Baseline demographics, time to hospital visit after symptom onset, the Medical Research Council (MRC) scale of the weakest muscle, the predominantly affected site between proximal and distal muscles, upper motor neuron (UMN) signs (jaw jerk, glabella reflex, snout reflex, brisk deep tendon reflexes, Hoffman sign, extensor plantar response) at initial visit, and EMG findings were specifically noted. EMG was conducted on the bulbar, cervical, thoracic, and lumbosacral regions. The FAS and UL-ALS groups were compared by data analysis using the SPSS (ver. 18) software system. Bivariate data analysis was conducted to assess factors associated with FAS and UL-ALS, and categorical variables were analyzed using chi-square and Fisher's exact tests. We considered p-values < 0.05 as statistically significant.

RESULTS

A total of 578 patients were diagnosed with motor neuron disease. Of these, 96 patients initially presented with symmetrical upper limb weakness. Eighteen (19%) patients were diagnosed with FAS, and 56 (58%) with UL-ALS. Of the remaining 22 patients, 5 had brachial plexitis, 4 had cervical radiculopathy, 2 had Charcot–Marie–Tooth disease (CMT1A), and 11 were classified as having disease of unknown origin.

All FAS and UL-ALS patients underwent brain MRI and cervical MRI to exclude the possibility of cervical myelopathy, synringomyelia, and cervical root lesions. None of the patients were positive for anti-HIV antibodies. The baseline demographic

Table 1. Baseline demographic, clinical and electrophysiological characteristics

	FAS (18)	UL-ALS (56)	p-value
Median age[a]	59 (48 to 76)	57 (39 to 76)	0.48
Gender (M/F)	15/3 (5:1)	36/20 (1.8:1)	0.13
Time to hospital visit[b,c]	14 (2 to 60)	12 (1 to 36)	0.30
Observation periods[c]	24 (13 to 50)	25 (17 to 51)	0.24
Dominant affected site			
Proximal	7 (70%)	6 (11%)	0.003
Distal	3 (30%)	28 (82%)	
Mixed or undefined	8	22	
MRC scale[d]	2.8	3.4	0.047
Fasciculations	3 (17%)	39 (70%)	0.001
UMN sign			
None	7/15 (47%)	8/50 (16%)	0.10
Bulbar	2/15 (13%)	5/50 (10%)	0.66
Cervical	9/18 (50%)	34/50 (68%)	0.21
Lumbar	4/16 (25%)	23/51 (45%)	0.15
2 or more regions	3/16 (19%)	19/51 (37%)	0.17
EMG[e]			
Bulbar	8% (1/12)	23% (13/56)	0.28
Cervical	100% (18/18)	100% (56/56)	1
Thoracic	71% (10/14)	87% (45/52)	0.23
Lumbar	61% (11/18)	91% (51/56)	0.060
2 regions	81% (13/16)	96% (54/56)	0.069
3 or more regions	56% (9/16)	81% (43/53)	0.054

[a]at presentation; [b]since onset of weakness; [c]in months; [d]the weakest muscle; [e]denervation evidence.
MRC, Medical Research Council; UMN, upper motor neuron; EMG, electromyography.

and clinical characteristics of the patients studied are reported in Table 1. The mean age at symptom onset was 59 years (range 48~76) in the FAS group and 57 years (range 39~76) in the UL-ALS group. The male-to-female ratio was 5:1 in the FAS group and 1.8:1 in the UL-ALS group. The FAS group showed a male predominance, however, this trend was not statistically significant (p=0.129). The mean observation period was 24 months in the FAS group (range 13~50) and 25 months (range 17~51) in the UL-ALS group. The weakness predominantly affecting the proximal muscles was observed in 70% (7/10) of those in the FAS group and 18% (6/34) of those in the UL-ALS group, while the weakness predominantly affecting distal muscles was observed in 30% (3/10) of those in the FAS group and 82% (28/34) of those in the UL-ALS group (p=0.003). MRC scale of the weakest muscle was significantly lower in the FAS group compared to the UL-ALS group (2.8 vs. 3.4 p=0.047). The rate of presence of fasciculation was 70% (39/56) in those with UL-ALS and 17% (3/18) in those with FAS (p=0.001). The proportion of UMN signs in bulbar, cervical, lumbar, and 2 or more of these 3 regions, did not differ significantly between the 2 groups. EMG studies of all 4 regions including bulbar, cervical, thoracic, and lumbar spinal segments,

were performed in 12 patients with FAS and 52 patients with UL-ALS. Between the 2 groups, there were no statistically significant differences in LMN signs on EMG.

DISCUSSION

Although FAS has been described in several reports, the current study was the first to compare FAS and UL-ALS regarding clinical features including EMG findings. In the current study, significant between-group differences were observed in the rate of fasciculation, the pattern of predominantly affected muscles, and the MRC grade of the weakest muscle. Other clinical characteristics and EMG findings did not show significant differences.

Fasciculation was noted in 17% of patients with FAS and 70% of patients with UL-ALS. Although the reasons underlying this difference are not clear, a potential explanation may be that LMN degeneration in patients with FAS was limited to the upper limbs, but had spread to 2 or more regions in those with classic ALS. UL-ALS patients may have a greater chance of feeling fasciculation than FAS patients.

The results of the current study are in line with the results of earlier studies which reported that FAS most often involved proximal muscles, while ALS usually involved distal muscles [5]. In a sense, this result is not surprising. When we initially defined FAS, the patients with distal upper limb weakness without proximal involvement were excluded. Our results indicate that the MRC grades of the weakest muscles were significantly lower in the FAS group than in the UL-ALS group, and that this is a reliable way to discriminate between these groups diagnostically. Among 7 FAS patients who had proximal dominant weakness, 6 were classified as having MRC grade 2 at shoulder abduction, and 1 as MRC grade 3. Meanwhile, among 6 UL-ALS patients who had proximal dominant weakness, 3 were classified as having MRC grade 3 at shoulder abduction, 2 as MRC grade 2, and 1 as MRC grade 4. In conclusion, in case of proximal muscle weakness, FAS patients are more severely affected than UL-ALS patients.

The median age and time to hospital visit did not differ between the 2 groups. Patients with FAS showed a male predominance pattern as compared to patients with UL-ALS (5:1 vs. 1.8:1, p=0.129). These results are consistent with those reported in previous studies [3, 8, 9]; however, the small sample size of the current study may have impacted our ability to observe a statistically significant difference. Another remarkable finding was that UMN signs showed no significant between-group differences. Although UMN signs tend to be more frequent in UL-ALS than in FAS, many FAS patients also had UMN signs. At time of initial

diagnosis, 8 (44%) FAS patients showed at least one UMN sign. The previous study, which tested 20 patients with FAS, 50% met the EL Escorial criteria for probable ALS [6]. This means that at least 10 (50%) patients had an UMN sign. FAS is considered a lower motor neuron disease, but about half of FAS patients may have at least one UMN sign.

In addition, when the FAS group was categorized according to the revised El Escorial criteria, 8 patients were classified as clinically probable–laboratory supported ALS and 3 as possible ALS [10]. The remaining 10 patients could not be classified. In the UL-ALS group, 36 patients were classified as clinically probable–laboratory supported ALS, and 3 as possible ALS. The remaining 11 patients could not be classified.

Before the study began, we expected that LMN involvement evidenced through EMG would be more wide-spread to other regions including the brainstem and thoracic and lumbar spine in patients with UL-ALS compared to those with FAS. However, our findings did not support this prediction. Many patients with FAS had electrophysiological evidence suggestive of LMN involvement of 2 or 3 segments (81% and 56%, respectively). We believe that the reasons for this are as follows. Since the mean age of patients with FAS was 59 years, these findings may have been attributable to patient age, as the elderly are known to have higher prevalence rates of lumbar or thoracic radiculopathy. The LMN involvement in their EMGs may have been caused not by anterior horn cell degeneration from motor neuron disease, but rather from lumbar or thoracic radiculopathy associated with degenerative changes. In fact, only 1 patient with FAS had EMG LMN involvement in the bulbar region. Although the difference lacked statistical significance in our study, more patients with UL-ALS had LMN involvement of other segments, especially the bulbar region.

Three patients with UL-ALS died during the study's observation period. Mean survival time in our population was higher than in other studies [1, 3]. This might be related to a selection bias, as patients managed in ALS centers tend to survive longer. This in turn may be related to greater use of non-invasive positive pressure ventilation, percutaneous endoscopic gastrostomy placement, and riluzole.

This study has several limitations. First, the number of patients was insufficient for reliable data analysis. In the future, clinical and electrophysiological studies on FAS are needed. Second, this study was performed by retrospective chart review. We could not evaluate the whole information because of the lack or missing of some clinical data such as checking upper motor neuron signs. Third, as mentioned above, the MRC grade of the weakest muscle was significantly lower in the FAS group than in the UL-ALS group. Most patients with FAS showed proximal muscle weakness.

On the other hand, most patients with UL-ALS had distal muscle weakness. The comparison of MRC grades of different muscles between the two groups has obvious limitations. Fourth, we have not paid sufficient attention to fasciculation potentials in the EMG study. Fasciculation potentials are relevant for the diagnosis of ALS. The lack of information on fasciculation potentials in the EMG study prevented comparison to clinical fasciculation.

It is important to recognize FAS because the natural history differs from that of classic ALS. Bilateral upper limb weakness could be a frequent presenting symptom of ALS cases [7]. Therefore, we could not predict the slow clinical course during the early stages. It is difficult to differentiate between progression to the lower limb, bulbar, or respiratory muscles characteristic of classic ALS and restriction to the upper limb muscles observed in FAS. The results of the current study may help in discriminating between the 2 groups, but are not sufficient to do so with certainty. Future studies will be required to find factors (genetic, laboratory, radiographic) that further distinguish between FAS and UL-ALS.

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