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Flail arm syndrome with several issues related to the diagnostic process

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Flail arm syndrome (FAS), known as one of the atypical amyotrophic lateral sclerosis (ALS) variants, has a similar clinical course and pathologic findings as ALS. Therefore it is difficult to differentiate between ALS and FAS at a glance. There are few reports involving individual analysis of FAS patients to date. The findings of polysomnography (PSG) in patient with FAS are not well known. We report a male FAS patient with review of literatures and several issues related to the diagnostic process.

Key words: Flail arm syndrome; Amyotrophic lateral sclerosis; Upper motor neuron sign

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Flail arm syndrome (FAS) has a similar clinical course[1] and pathological findings as amyotrophic lateral sclerosis (ALS).[2] It is important to distinguish the two diseases because FAS patients have significantly better survival rates compared with other typical ALS variants.[1,3] We report a FAS patient confirmed by clinical and electrophysiological findings based on review of literatures. We show the findings of polysomnography (PSG) in patient with FAS. We suggest that several issues related to the diagnostic process needed to be addressed.

CASE

A 50-year-old male presented with slowly progressive weakness and muscle wasting in his arms about two years ago. At the time of the first manifestation, weakness was noted in the right proximal arm accompanied by atrophy and identical symptoms occurred in the left arm after a one year.

He had no remarkable medical history except for hypertension and there was no related family history. In neurological examination, bilateral weakness of the arms was scored as Medical Research Council grade I proximally and grade III in the distal muscles symmetrically, combined with muscle atrophy in the upper limb girdles. Both acromion processes of the scapular bone protruded beneath the skin. Both of his arms, forearms and hands were pronated. Fasciculation were absent in his all limbs and tongue. Sensory examination was normal

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and deep tendon reflexes were absent in the upper limbs but normoactive in the lower limbs. He did not show upper motor neuron (UMN) signs. There was no functional involvement of the bulbar and lumbar segments. Plantar reflexes were not observed bilaterally. Frontal release signs were absent and the jaw jerk and superficial abdominal reflex were normal. He had not cognitive dysfunction or memory impairment.

The motor nerve conduction study (NCS) revealed decreased compound muscle action potential amplitudes without conduction block in the upper extremities. The sensory NCS and F-wave latency were normal. We performed needle electromyogram (EMG) on all limbs and four body segment (bulbar, cervical, thoracic, lumbosacral). EMG revealed acute denervation potentials combined with decreased recruitment and reinnervation potentials in right flexor carpi ulnaris and biceps brachii and C5, 6, 7 paraspinalis, and left deltoid, biceps brachii and C6, 7 paraspinalis muscles. The complete blood count, blood chemistry including creatine kinase and cerebrospinal fluid tests were normal and brain and cervical spine magnetic resonance imaging (MRI) showed no significant abnormality. IgM anti-GM1 antibodies were detected at low titer. There was no abnormal trinucleotide CAG expansion of androgen receptor genes and no mutation of the superoxide dismutase gene.

After 1 year of follow up, the upper limb girdle weakness progressed slightly but there was no lower limb weakness including upper and lower motor neuron (LMN) signs. Bulbar and sensory symptoms were still absent. A pulmonary function test (PFT) to evaluate respiratory disturbance was revealed to be within the normal limit. Despite normal PFT finding, the patient complained about frequent arousal with dyspnea during sleep. Overnight PSG showed that apnea-hypopnea index (AHI) was 14.5/h (apnea 9.1/h, hopopnea 5.4/h), all of the apnea events were obstructive type (total 45 times). The sleep apnea showed position dependency (Supine AHI vs. lateral AHI, 25.7/h vs. 2.1/h) but not rapid eye movement (REM) sleep related tendency (REM AHI 2.4/h). Basal oxygen saturation was 97% whereas the lowest oxygen saturation was 79% during apnea. Total arousal index was 16.1/h which was consisted of respiratory arousal (9.9/h), respiratory effort related arousal (1.2/h) and spontaneous arousal (5.0/h). The patient's body mass index was 25.5 kg/m^2, neck circumference was 39 cm and Mallampati score II with scalloped tongue. Positive airway pressure treatment with lateral sleep positioning was recommended but the patient refused the treatment.

DISCUSSION

According to the operational definitions with standardized inclusion and exclusion criteria for FAS, which were proposed by Wijesekera et al.[1] in 2009, FAS shows common signs of LMN disease in the upper limbs with little or no involvement of the bulbar and lower limb muscles during the early stages of the disease.[3] It is difficult to differentiate between ALS and FAS based on LMN signs at first presentation, especially upper limb onset ALS, which is diagnosed by the El Escorial criteria.

Possible differentiating clinical features between ALS and FAS have been reported. First, whether prominent weaknesses of the intrinsic hand or bulbar muscles, rather than limb girdle weakness, is the primary symptom. This is mainly observed in ALS.[1,3] Second, during the clinical course of ALS, weakness spreads asymmetrically over other segments of the body.[3] In addition, ALS is faster than FAS with regard to the spreading of weakness to a different region of the body.[3] Third, FAS is more common in men and has a younger age onset, which is very different from typical ALS.[1,3]

EMG cannot discriminate between FAS and ALS patients, because more than a half of FAS patients exhibit LMN signs in both upper and lower extremities, similar to typical ALS.[3,4] NCSs and EMG revealed acute and chronic neuropathic changes in our patient. However, the changes occurred in the upper extremities only.

Our patient showed a slowly progressive proximal upper limb girdle wasting pattern. The symptoms did not spread to other segments including the bulbar region or lower extremities until 3 year after the symptom onset. These clinical phenotypes are in accordance with the operational clinical criteria.[1] Based on the operational criteria, another report proposed additional remarkable phenotypic differential points between FAS and ALS, suggesting that the first manifestation in patients with FAS is most frequently found on the dominant side.[3] Fasciculation does not tend to appear in FAS, unlike ALS.[4] Our patient is right handed, the side in which the symptoms started, and fasciculation was not found even during the follow up periods.

We performed PSG to identify sleep disordered breathing (SDB) in this patient. Our patient showed moderate obstructive sleep apnea (OSA) and sleep fragmentation on PSG. PSG findings in ALS patients include central, obstructive, or mixed apnea, increased sleep fragmentation.[5] The most common form of SDB in ALS is nocturnal hypoventilation, secondary to palsy of the diaphragmatic, intercostal and accessory respiratory muscles.[6] Recent study also revealed that the presence of OSA especially at the initial stages of the disease (disease duration < 1 year), weakness of upper airway dilator muscle controlled by cranial nerve is regarded as the mechanism.[7]

Unlike ALS patients, it is well known that respiratory muscle weakness and bulbar weakness are relatively less frequent in FAS as in the case of this patient. And considering that OSA is relatively prevalent among 50-70-year-old men,[8] it could not be regarded as the same as ALS. For these reasons, it is unclear whether OSA was concurrent and unrelated to FAS or an early symptom of FAS as in ALS. But according to recent study, diagnosed with OSA at the early stage of ALS related to poor prognosis,[7] so it could be worth to investigate that the finding also applies in FAS. Additionally, diagnosis of SDB of FAS through PSG has not been reported so far, further researches are required to identify specific sleep patterns in FAS patients.

We reviewed the published literature about FAS. In the process, we realized that several issues related to the diagnostic process needed to be addressed. First, 41.8% of FAS patients developed at least one UMN sign in the flail region,[1] but the UMN sign was not observed during 3-years of follow up in our patient. While 85% of ALS patients were observed UMN signs in some body segments at the time of diagnosis,[9] FAS patients with UMN sign were usually revealed UMN sign at some point since been diagnosed.[1] Therefore maximal interval period from disease onset to UMN sign occurrence in FAS patients who was observed only LMN signs may be help to differential diagnosis. Second, brain MRI in our patient showed no significant findings. Recently, the owl's eye sign, which refers to intramedullary hyperintensity in T2 weighted images, representing gliosis of the anterior horn cell was reported.[10] If the clinical value and statistical relationship between this characteristic finding and FAS are proven, it will be easy to diagnose FAS. Third, IgM anti-GM1 was detected at low titers in our patient. To date, statistically significant differences in phenotypes, progression rate, and survival rates have not been found between ALS patients with and without anti-ganglioside antibodies.[11] However, if clinical significance of positivity of IgM anti-GM1 antibody from FAS patients is identified, it may be help to differentiation between FAS and ALS.[2]

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