

ANALYSIS OF 26 CASES OF ANKYLOSING SPONDYLITIS COMPLICATED WITH FIBROMYALGIA

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ABSTRACT

Introduction: To summarize the clinical characteristics of patients with ankylosing spondylitis (AS) combined with fibromyalgia (FM), in order to provide clues and a basis for early diagnosis and standard treatment.

Materials and methods: A total of 26 patients with AS complicated with FM who were treated in Jiangsu Province Hospital of Traditional Chinese Medicine from January 1, 2017 to December 31, 2021, were collected. The clinical data of the patients were retrospectively analyzed, including epidemiological characteristics, clinical manifestations, diagnostic characteristics, drug conditions and treatment effects.

Results: The onset age of AS combined with FM was concentrated between 19 and 40 years old (73%), and the ratio of male to female was close to 1:1 (54% vs 46%). When FM was diagnosed, all patients did not show typical inflammatory low back pain, and most of the patients could not relieve the pain after activity (88%), but no patient (0%) recorded waking up with pain at night. All patients (100%) had dorsoaxial pain, most patients also had shoulder girdle pain (69%) and buttock pain (54%). A small number of patients had chest pain (31%), upper limb pain (46%), and lower limb pain (35%). Most patients had sleep disorders (62%), fatigue (69%), neuropsychiatric symptoms (54%), and self-reported paresthesia (81%). Prior to diagnosis, most patients had used 1-2 NSAIDs (81%) and most had used biologics (74%). After the diagnosis of FM, the symptoms of most patients (77%) were improved after adding the indicated drugs (pregabalin and duloxetine).

Conclusion: In patients with AS who present with diffuse pain, especially diffuse pain that does not show a clear tendency to improve with rest after activity, nor does it show a tendency to wake up with pain and difficulty turning over at night (especially 3-5 am). In cases where there is no improvement with multiple NSAIDs, biologics, the possibility of comorbid FM needs to be considered with emphasis. In patients with AS combined with FM, anti-FM drugs are required to improve the patient's symptoms.

Keywords: Ankylosing spondylitis, fibromyalgia.

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Introduction

Fibromyalgia (FM) is a common chronic diffuse pain syndrome and is considered to be one of the most common physical and mental diseases. In addition to pain in multiple areas, patients are often accompanied by a variety of clinical symptoms such as fatigue, sleep and mood disorders. Due to the lack of clear specific laboratory indicators, diagnosis is mostly based on clinical symptoms, so it is prone to missed diagnosis and misdiagnosis. In particular,

FM can coexist with other systemic diseases, posing challenges in diagnosis and management. Ankylosing spondylitis (AS) is one of the most common rheumatic diseases, with inflammatory pain and often an insidious onset. The onset of this disease is less than 45 years old. The pain in the neck and back can be decreased after activity and cannot be relieved after rest. However, AS can also be complicated with many diseases, and FM is one of the important ones⁽¹⁾, which has been reported in the literature to reach 29.6%⁽²⁾. However, we did not find any reports

of AS combined with FM through keyword search in major Chinese databases, suggesting that there may be insufficient understanding of the comorbidity of AS combined with FM in China, and misdiagnosis and missed diagnosis may be common.

Materials and methods

Through the electronic medical record system, a total of 26 patients with AS complicated with FM who were treated in Jiangsu Province Hospital of Traditional Chinese Medicine from January 1, 2017, to December 31, 2021, were collected. These patients included both inpatients and outpatients. For hospitalized patients, the discharge diagnosis was also required to include "ankylosing spondylitis," "fibromyalgia syndrome," or "fibromyalgia."

The clinical data of the patients were collected, and their age, gender, clinical manifestations, case characteristics, and treatment regimens were retrospectively analyzed. The missing data in some outpatient medical records were inquired and recorded by telephone.

Results

Epidemiological characteristics of AS combined with FM

A total of 26 patients with AS combined with FM were collected, including 12 females (46%) and 14 males (54%). The ratio of male to female was close to 1:1, which was higher than the ratio of male to female of 2-3:1 described by Chinese guidelines⁽³⁾ and higher than the registration data of Corrona registry in the United States⁽⁴⁾, suggesting that female AS patients are more likely to be complicated with FM. In terms of age, there were no cases under 18 years old, 19 cases (73%) between 19 and 40 years old, 7 cases (23%) between 41 and 65 years old, and no case over 65 years old. The age distribution was basically consistent with the age distribution of AS reported in the literature, and the age distribution of FM was also basically consistent with the age distribution of FM⁽⁵⁾.

Diagnostic characteristics of AS combined with FM

According to the information recorded in the electronic medical record, 26 patients were diagnosed AS first, and then FM. The interval between the two diagnoses was less than 1 year in 1 case (4%), 1-3 years in 12 cases (46%), and more than 3 years

in 13 cases (50%). In terms of diagnostic criteria, 25 cases (96%) recorded the tender points at diagnosis, which were in line with the American College of Rheumatology classification criteria for FM in 1990⁽⁶⁾, and 1 case (4%) recorded the patient's pain area, tender points, fatigue and sleep, which were in line with the American College of Rheumatology diagnostic criteria for FM in 2010⁽⁷⁾.

However, the number of tender points did not meet the American College of Rheumatology classification criteria for FM in 1990. Among the diagnostic departments, 25 patients (96%) received their first diagnosis of FM in the rheumatology department and 1 patient (4%) in the neurology department.

Clinical manifestations of AS combined with FM

All 26 patients (100%) reported pain. In terms of the nature of pain, 26 cases (100%) recorded that the pain could not be relieved after rest, and 23 cases (88%) recorded that the pain could not be relieved after activity. No patient (0%) reported waking up for pain at night. In terms of pain location, all 26 cases (100%) had dorsoaxial pain (neck, back and waist), 8 cases (31%) had chest pain, 18 cases (69%) had shoulder girdle pain, 12 cases (46%) had upper limb pain, and 14 cases (54%) had buttock pain.

Lower limb pain was recorded in 9 patients (35%). In terms of complications, 16 cases (62%) had sleep disorders, 18 cases (69%) had fatigue, and 14 cases (54%) had psychiatric symptoms (such as poor mood, irritability, and anxiety). Twenty-one patients (81%) had self-reported paresthesia, such as fear of wind, fear of cold, soreness and swelling of limbs, numbness, foreign body sensation in throat, chest distress and chest tightness.

Medication of AS combined with FM

Before the diagnosis of FM, 1 case (4%) had used ≤ 1 Non-Steroidal Antiinflammatory Drugs (NSAIDs), 21 cases (81%) had used 1-2 NSAIDs, and 4 cases (15%) had used ≥ 3 NSAIDs. Eight patients (31%) had used ≤ 1 biological agent, 9 patients (35%) had used 1-2 biological agents, and 2 patients (8%) had used ≥ 3 biological agents.

It showed that before the diagnosis of FM, the use of biological agents in patients was much higher than 15-25% reported in the literature of general AS patients⁽⁸⁾, and more than 1/3 of patients had undergone at least one conversion of biological agents. After the diagnosis of FM, 16 patients (62%)

were initially treated with pregabalin, 8 patients (31%) were initially treated with duloxetine, and 2 patients (7%) were initially treated with duloxetine and pregabalin.

Treatment effect of AS combined with FM

After 26 patients were diagnosed with FM and added duloxetine or pregabalin, 20 (77%) experienced pain improvement at follow-up, and NSAIDs or biologic tapering or complete discontinuation were recorded. Three patients (12%) had no significant improvement in pain.

Three patients (7%) had no follow-up records. After telephone contact, one of them (4%) went to the department of physical and mental medicine of another hospital, and the pain was improved after duloxetine was stopped and replaced by paroxetine. One patient (4%) was referred to another hospital for treatment, and the pain was improved after the addition of duloxetine and pregabalin. One case (4%) was lost to contact.

Discussion

The diagnosis of FM usually faces challenges. Literature has reported that it often takes more than 2 years and an average of 3.7 doctors to be diagnosed⁽⁹⁾. However, this is still the data of western countries with a high proportion of FM diagnosis, and the diagnostic delay rate of FM in our country may be higher⁽¹⁰⁾. FM is not a diagnosis of exclusion, and it is often accompanied by other diseases. Especially when FM is combined with rheumatic diseases, because rheumatic diseases often have pain symptoms, the diagnostic requirements are higher, so the possibility of delay in the diagnosis of FM is greater. AS combined with FM may not be rare, and a study⁽¹¹⁾ showed that about 4.4% of AS patients had FM. However, using “fibromyalgia” + “ankylosing spondylitis” keywords to search the mainstream databases of China: CNKI, Wanfang, VIP, no literature report or statistical analysis of AS combined with FM was found. In this study, only 26 patients were found to have AS combined with FM, which was less than 1% of the number of AS patients who visited the hospital during the same period. It was suggested that there may be a large number of patients with FM and AS who are missed diagnosed.

The first diagnosis of AS combined with FM was mainly concentrated in the department of rheumatology and neurology, and there was no case diagnosed in the department of orthopedics,

acupuncture rehabilitation department, pain department and other related departments that may receive AS and FM. For these departments, the diagnosis of AS was often unclear in the past, and missed diagnosis and misdiagnosis were very common^(12, 13). After medical education in recent years, the recognition of AS has been improved, and the misdiagnosis rate has decreased. However, most doctors still have a serious lack of understanding of FM, and the rate of misdiagnosis and missed diagnosis is very high. It has been reported that the correct diagnostic rate of Grade III Grade A hospitals is 9.3%, and the correct diagnostic rate of Grade III Grade B and Grade II hospitals is zero⁽¹⁴⁾. The diagnosis of FM alone is so “difficult”. For AS patients with FM, it may be a serious challenge for non-rheumatoid, neurologic and psychiatric doctors to achieve “no misdiagnosis and no missed diagnosis”. It is suggested that the education of doctors aiming at FM urgently needs to be strengthened.

The common symptom of AS and FM is pain. However, the characteristics of pain are different between the two groups. AS is mainly manifested as inflammatory low back pain⁽¹⁵⁾, which usually starts at the age of less than 45 years old, worsens after occult, alleviates after activity, and does not relieve after rest. Many patients will wake up for pain at night (especially 3-5 a.m.), turn over difficulty, with morning stiffness and strong specificity. In addition to a small number of peripheral arthritis, metatarsophalangeal arthritis (enthesitis), most of the AS pain in the spine, namely the neck, back and waist. FM is diffuse pain, not limited to the spine, the pain is not inflammatory pain, there is no obvious improvement after activities and the tendency to get worse after rest, and generally does not wake up for pain at night (especially at 3-5 am) and turn over difficulty. Although some patients respond to the symptoms of morning stiffness, but often for a short time. Therefore, for the diagnosis of AS, the presence of diffuse pain beyond the spine, such AS thigh, upper arm, front chest, shoulder, etc., especially when the nature of pain is not consistent with AS, the possibility of FM should be highly vigilant. In this study, the pain of most patients (89%) could not be improved after activity, which was contrary to the pain characteristic of AS, which is “not improved after rest, but relieved after activity”. It may be one of the key points in the diagnosis of FM.

FM often has more subjective symptoms, such as fatigue, headache, neuropsychiatric symptoms, headache, sleep disorders, and a variety of subjective

discomfort⁽¹⁶⁾. However, some symptoms, such as AS fatigue, can also be seen in AS patients. However, when a lot of subjective discomfort occurs at the same time, such as vertigo, paroxysmal dizziness, foreign body sensation in the pharynx, chest tightness, shortness of breath, etc., the possibility of FM should be highly vigilant.

Drugs can also help us to identify AS combined with FM. Inflammatory low back pain in AS is often sensitive to NSAIDs⁽¹⁷⁾, and if they are ineffective, TNF- α inhibitors or IL-17 inhibitors (biological agents) can be used. However, if you use NSAIDs, the pain is not relieved, or not completely relieved; If the effect of switching to other NSAIDs or biological agents still fails to relieve pain symptoms, it should first be aware of the accuracy of the diagnosis of AS. In determining the definite diagnosis of AS, it should also be aware of the pain caused by other diseases. In this study, most patients (96%) used two or more drugs, NSAIDs, and the vast majority of patients (74%) used biological agents. More than one-third of the patients underwent biologic conversion (using the two kinds of biological agents or higher), and the vast majority of these cases were diagnosed AS combined with FM. After using drugs for the treatment of FM, symptoms have improved. Therefore, if doctors can be more familiar with and alert to FM and make a clear diagnosis in advance, many patients may not need to undergo repeated conversion of NSAIDs and biological agents, which will bring tangible benefits to patients.

According to the author's experience, when FM is suspected above, the doctor can first "follow the trend" to conduct a physical examination and press 18 tender points. If more than 11 tender points can be found, the diagnosis can be made. Although it is no longer emphasized that >11 tenderness points must be met for the diagnosis of FM⁽¹⁶⁾, the number of pain areas and the severity of symptoms can also be used as a diagnostic basis. However, the author found that for combined rheumatic diseases with pain as the main manifestation, patients will appear the phenomenon of inaccurate pain positioning sometimes, especially for patients with a low degree of education, when asking about the pain area, they often give a plausible answer, which brings difficulties to the diagnosis. In the case of limited time of general outpatient treatment in China, when considering AS combined with FM, rapid physical examination of 18 tenderness points may be able to quickly improve the diagnostic rate and ensure the accuracy of diagnosis.

If the FM classification criteria of the American College of Rheumatology in 1990 are not met, which means at least 11 pains out of 18 tenderness points are not met, and other symptoms of the patient are highly suspicious of FM diagnosis, in this case, the pain area, and the frequency and severity of accompanying symptoms such as fatigue, sleepiness, and emotional state are carefully inquired, patients with FM can be detected to the greatest extent. In accordance with the clinical reality, the missed diagnosis is avoided to the maximum extent. Of course, in practice, we should not only consider the case of AS combined with FM, but also carefully consider whether the diagnosis of AS is clear before diagnosis. The misdiagnosis of FM to AS was excluded⁽¹⁸⁻²²⁾.

In terms of treatment, once AS combined with FM is diagnosed, the activity degree of AS and FM should be evaluated respectively, and corresponding treatment should be given respectively. However, in most of the above cases, when AS combined with FM was diagnosed, powerful AS treatment drugs, including NSAIDs and biological agents, were often given. Therefore, most of the remaining symptoms of patients are caused by FM, and their pain characteristics are also consistent with the pain characteristics of FM, but not with the inflammatory pain characteristics of AS. At this point, rheumatologists need to give standard anti-FM drugs, such as pregabalin, duloxetine, most patients can be relieved with the use of stepwise increase of drug or combination. A small number of patients cannot be relieved by using the on-label drugs, they may be considered to be transferred to the psychosomatic medicine department or the department of psychiatry and other related departments.

Psychiatrists may give some off-label psychotropic drugs, which can sometimes have better efficacy. At the same time, the efficacy of physical therapy in AS and FM should not be ignored, which may be beneficial to both AS and FM.

Conclusion

In conclusion, in patients with AS who present with diffuse pain, especially diffuse pain that does not show a clear tendency to improve with rest after activity, nor does it show a tendency to wake up with pain and difficulty turning over at night (especially 3-5 am). In cases where there is no improvement with multiple NSAIDs, biologics, the possibility of comorbid FM needs to be considered with emphasis.

For AS combined with FM that cannot be improved by using a variety of NSAIDs and biological agents, anti-FM drugs are needed to improve the symptoms of patients.

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