REVIEW

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Tired, aching, ANA-positive: Does your patient have lupus or fibromyalgia?

ABSTRACT

The symptoms of fibromyalgia and lupus can be similar, but the treatments are very different. Although the antinuclear antibody (ANA) test has often been used to make the distinction, this approach has its pitfalls. This paper offers strategies for more accurate diagnosis.

KEY POINTS

Given that fibromyalgia is common and lupus is not, most patients with pain will be found to have fibromyalgia or an alternative pain syndrome.

Positive ANA tests are more prevalent than connective tissue diseases, and most of the abnormal results are falsely positive.

The history and physical examination are vital to establishing the pre-test probability of disease.

Fibromyalgia is not merely a diagnosis of exclusion, and can be differentiated from lupus by history, physical examination, and laboratory tests.

COMPLAINTS OF CHRONICALLY LOW ENERGY, arthralgias, and myalgias are common in any primary care setting. Physicians often investigate with a battery of laboratory tests, and if the antinuclear antibody (ANA) test is positive the patient is frequently referred to a rheumatologist with a presumptive diagnosis of lupus.

See related editorial, page 141

But in fact, few of these patients will be found to have lupus or any other inflammatory rheumatic disease, and many will be diagnosed with fibromyalgia.

Along the way there can be a great deal of confusion, since many of the symptoms of fibromyalgia resemble the symptoms of lupus, and indiscriminate use of the rheumatology laboratory can lead to unwarranted concerns about autoimmune disease. Clinicians who are comfortable with the concept of fibromyalgia, who perform thorough histories and physicals, and who interpret laboratory tests with caution are more likely to avoid diagnostic errors.

Among the key points to keep in mind:

- Patients with chronic fatigue and widespread pain are more likely to have fibromyalgia than any other rheumatic disease.
- Be prepared to diagnose fibromyalgia, while excluding autoimmune diseases by history, physical examination, and limited laboratory testing.
- Autoantibody testing is best reserved for patients whose pretest odds of an autoimmune disease are high.

- All rheumatology laboratory tests must be interpreted in the context of the history and physical examination.
- Embrace the concept of fibromyalgia: it will help you avoid errors in diagnosis and treatment and lead to a rational plan of therapy for your patient.

KNOW THE DEMOGRAPHICS

Lupus is not a common disease. The prevalence in white women in the United States is approximately 10 to 50 per 100,000; in black women the prevalence is approximately 4 to 5 times higher. Ninety percent of lupus patients are women; consequently, the prevalence in men is only one fifth to one tenth of that in women.[1]

In contrast, fibromyalgia *is* common. Wolfe et al[2] found that the prevalence of fibromyalgia in a mostly white population ranged from 1% in women 18 to 29 years old to 7% in women over age 59, for an average of 3.4%. Even the most conservative of these figures suggests that fibromyalgia is at least 20 times more prevalent than lupus in white women, and a ratio of 50:1 to 75:1 is quite plausible.

Fibromyalgia is at least 20 times more prevalent than lupus in white women

One should therefore expect that most patients with widespread pain will ultimately be found to have fibromyalgia or an alternative pain syndrome. The medical evaluation will confirm this diagnosis in most and only occasionally will yield evidence of an inflammatory rheumatic disease. In black women the prevalence of lupus is higher, and the physician should be more alert to the possibility of lupus in this population.

INTERPRET LABORATORY RESULTS WITH CAUTION

Many physicians have been taught to screen for "connective tissue diseases" with serum testing for ANAs, and then clarify the diagnosis with additional autoantibody testing. In practice, however, this approach does not work. The reason: a positive ANA test by immunofluorescence, usually defined as detectable staining at a dilution of at least 1:40, is too sensitive and not sufficiently specific to be used as a screening test.

Studies find ANA positivity common, even in healthy people

De Vlam and colleagues[3] studied 485 healthy volunteer blood donors and found that 20% of the women and 7% of the men had a positive ANA result. Of women over 40 years of age, 31% were ANA-positive.

Craig et al[4] found an ANA titer of at least 1:64 in 15% of healthy women younger than 40 years and 24% of women age 40 or older.

Tan et al,[5] in a study of healthy adults (age 20 to 60 years), found that 31.7% had a positive ANA result at a 1:40 dilution, 13.3% at a 1:80 dilution, 5% at a 1:160 dilution, and 3.3% at a 1:320 dilution. In the same study, 38.5% of patients with noninflammatory "soft tissue rheumatism" had a positive ANA result at a 1:40 dilution, and 23.1% at a 1:80 dilution.

Slater et al[6] studied 1,010 consecutive ANA results at a teaching hospital and attempted to correlate the results with clinical histories by chart review. Fifteen percent of all patients and 30% of patients older than 65 years had a positive ANA titer of 1:40 or greater, but the positive predictive value for rheumatic disease was low. The false-positive rate for any rheumatic disease was 72% in patients 65 years old or younger, and 90% in patients older than 65 years. Even ANAs that were positive at a titer of 1:320 or greater were more likely to be falsely positive (55%) than indicative of any rheumatic disease (45%).

One can draw several conclusions from these studies. Positive ANA tests are much more prevalent than connective tissue diseases, and most of the abnormal results are falsely positive. False-positive ANA tests are particularly likely to occur in the elderly. Most of the false-positive ANAs were of low titer, but even a high-titer ANA is not proof of an underlying connective tissue disease. Therefore, not surprisingly, ANA testing is frequently positive in patients with fibromyalgia. Consequently, the ANA alone is not a reliable tool for discriminating noninflammatory conditions from autoimmune diseases. Most patients with low-titer positive ANAs have no other detectable autoantibodies, and additional autoantibody testing adds to the expense but rarely clarifies the diagnosis.

Laboratory methods differ

To complicate matters, laboratory methods are constantly changing, and we often have extensive data on tests that are no longer in use but limited data on the tests currently available. The studies quoted above detected antinuclear antibodies by indirect immunofluorescence (IIF) after incubation of sera with fixed Hep-2 cells. Many laboratories now use enzyme immunoassay (ELISA) to detect ANAs, and the sensitivity and specificity vary by manufacturer.

Emlen and O'Neill[7] compared the results of immunofluorescent ANA testing to those of ELISA kits from six different manufacturers; 88% of patients known to have lupus had a positive ANA test by immunofluorescence, but the sensitivity of the ELISA kits ranged from 62% to 90%.

Similar problems have arisen in testing for antibodies to double-stranded DNA. Antibodies that were once detected by the Farr radioimmunoassay or by IIF using *Crithidia luciliae* are now detected by ELISA. Tan et al[8] tested anti-double-stranded DNA ELISA kits from eight manufacturers against stored sera. The sensitivity and specificity varied widely.

The old teaching that "antibodies to double-stranded DNA are less sensitive for lupus but are very specific" was generally true using the tests available in prior years but may not be true today. The sensitivity and specificity depend on the assay kit in use and where the laboratory chooses to draw the line that separates "positive" results from "negative." If the clinician does not know the sensitivity and specificity of the test kit used, the positive or negative predictive value of the test is difficult to assess, and one must be careful in applying the results to guide patient care.

THE IMPORTANCE OF THE HISTORY AND PHYSICAL EXAMINATION

If autoantibody testing is flawed, what is the clinician to do? Bayes theorem states that the post-test odds of a specific disease are determined by the pre-test odds and the sensitivity and specificity of the test used. When a laboratory test (eg, the ANA) is not very specific, it is essential to determine the pre-test likelihood of the disease. In the case of lupus, this is best done by a carefully performed history and physical examination, supplemented by a few simple laboratory tests.

In many areas of medicine the exhaustive history and physical of yesteryear has been replaced by a more cursory interview, a brief examination, and an extensive battery of diagnostic tests. The history and physical examination are a mere prelude to the diagnostic testing, since the test results are often believed to be more accurate and objective.

In evaluating patients for systemic autoimmune disease, however, advances in diagnostic testing have not supplanted a care-

TABLE 1

Symptoms of ANA-positive rheumatic diseases

Lupus
- Alopecia
- Oral ulcers
- Malar rash
- Photosensitivity
- Raynaud phenomenon
- Pleuritic chest pain
- Joint pain and stiffness
- Unexplained fever
- Unexplained weight loss
- Unexplained lymphadenopathy

Sjögren syndrome
- Dry eyes
- Dry mouth
- Vaginal dryness
- Parotid swelling
- Accelerated dental caries or gingivitis

Myositis
- Insidious proximal muscle weakness
- Rash
- Dyspnea

Scleroderma/CREST syndrome
- Hand stiffness
- Raynaud phenomenon
- Digital infarcts
- Calcinosis
- Telangiectasias
- Heartburn
- Dysphagia
- Dyspnea

ANA is not specific enough to use as a screening test

TABLE 2

Laboratory abnormalities in lupus

Complete blood count
- Leukopenia: usually lymphopenia, occasionally neutropenia
- Anemia: chronic disease, hemolytic
- Thrombocytopenia

Serum chemistry
- Elevated creatinine
- Low albumin
- Polyclonal hyperglobulinemia
- Elevated creatine kinase

Urinalysis
- Proteinuria
- Microscopic hematuria
- Red blood cell or hyaline casts

fully performed history and physical examination. In fact, many common rheumatologic conditions, including bursitis, tendinitis, fibromyalgia, and osteoarthritis, can be reliably diagnosed without any confirmatory laboratory or imaging tests.

Laboratory testing does not replace a careful history and physical examination

History

When a patient with chronically low energy and widespread pain presents for evaluation, the search for an autoimmune disease begins with the history. During the history the physician should seek not only evidence of autoimmune disease but also evidence of fibromyalgia. Symptoms of ANA-positive rheumatic diseases are listed in TABLE 1.

The history must be obtained carefully, for other medical problems can cause symptoms similar to those of lupus. Hair loss might be caused by telogen effluvium or chemical injury. Oral ulcers are commonly simply aphthae. Whether a sunburn represents photosensitivity depends on the patient's natural pigmentation, the latitude, the altitude, and the duration of sun exposure. Rosacea and seborrhea are common causes of facial erythema that might be confused with the malar rash of lupus. Mild pallor of the fingers on exposure to cold is probably physiologic vasoconstriction and not the Raynaud phenomenon. Well-documented unexplained fevers support a diagnosis of lupus, but a sensation of fever without any measurement of the body temperature is less significant.

Differentiating lupus from fibromyalgia by history alone can be difficult. Patients with fibromyalgia can have a multitude of symptoms that mimic those of lupus, including fatigue, arthralgia, morning stiffness, cold intolerance, chest wall pain, and subjective deficits in memory and concentration. The likelihood of lupus increases if the patient gives a convincing history of lupus symptoms that would not ordinarily occur in fibromyalgia. Conversely, the likelihood of fibromyalgia increases if the patient has multiple risk factors for fibromyalgia, as discussed below.

Physical examination

During the physical examination the physician seeks evidence that either supports a diagnosis of lupus or suggests that the symptom or symptoms have another explanation. For example:

- The malar rash of acute lupus generally spares the nasolabial folds. Erythema involving the nasolabial folds is more likely to be rosacea.
- Oily flakes in the eyebrows or scalp suggest seborrhea.
- Alopecia in lupus can be scarring or nonscarring, localized or generalized.
- Oral ulcers in lupus are usually seen on the hard palate, but can be present on any mucosal surface.
- Acrocyanosis may be seen in lupus, particularly if the examining room is cool.
- Digital pits or ulcers are not usually seen in lupus and are more suggestive of scleroderma or the CREST (calcinosis, Raynaud phenomenon, esophageal dysmotility, sclerodactyly telangiectasias) syndrome.
- Examination of the joints may show tenderness and synovial effusion in lupus, but the arthritis is nondestructive, and impressive synovial proliferation is uncommon. Lupus, however, can lead to Jaccoud arthropathy, characterized by swan-neck deformities of the fingers without synovial pannus or joint destruction. Significant synovial hypertrophy with resulting cartilage loss is more suggestive of a synovial-based arthritis, such as rheumatoid arthritis.

• The examiner should specifically search for sites of myofascial tenderness that would suggest fibromyalgia. Muscle tenderness is not a specific symptom of lupus. When present in a patient with unequivocal lupus in the absence of myositis, it usually means that the patient also has fibromyalgia.

Laboratory testing to confirm the impression

Laboratory testing can be used to confirm the impression formed during the history and physical. Laboratory abnormalities that raise the suspicion for lupus are listed in TABLE 2. Completely normal laboratory tests are consistent with a diagnosis of fibromyalgia.

WHILE EXCLUDING LUPUS, LOOK FOR FIBROMYALGIA

Most patients with isolated chronic fatigue, diffuse pain, and a positive ANA test are ultimately found to have fibromyalgia. This is not surprising, given the prevalence of fibromyalgia and the frequency of positive ANA results in people without autoimmune disease.

As discussed above, many of the symptoms of fibromyalgia can mimic the symptoms of inflammatory rheumatic disease, leading to initial diagnostic confusion. At a university-based lupus clinic, 37 of 149 patients referred or followed for presumptive lupus were felt to have fibromyalgia with positive ANA upon retrospective chart review. The patients with fibromyalgia were slightly older (mean age 44), and more likely to be white.[9]

Fibromyalgia was also found to be the correct diagnosis in many patients referred for suspected tertiary or refractory Lyme disease,[10,11] and fibromyalgia is the most plausible explanation for the "rheumatic" symptoms reported by patients with silicone breast implants.[12,13]

Such diagnostic errors are not only due to the similarity in symptoms. Many physicians do not understand how prevalent fibromyalgia is and are not totally comfortable with using the history and physical to diagnose it.

Factors that increase the likelihood of fibromyalgia

Fibromyalgia is *not* merely a diagnosis of exclusion. The history and physical may reveal a number of findings that increase the likelihood that fibromyalgia is present. Fibromyalgia symptoms often occur in a setting of stress, depression, anxiety, lack of sleep, lack of exercise, and traumatic life experiences.

Stress. Patients should be specifically asked about potential sources of stress, including job dissatisfaction, financial difficulties, conflicts in personal relationships, and overwhelming responsibilities.

Depression. The patient may reveal symptoms of low mood, emotional lability, anhedonia, hopelessness, or suicidal ideation suggestive of depression.

Anxiety. Past episodes of chest pain or shortness of breath might represent panic attacks caused by an underlying anxiety disorder.

Lack of sleep, lack of exercise. The interviewer should ask about any difficulties obtaining restorative sleep, and inquire about recreational exercise.

Traumatic life experiences. A history of physical, emotional, or sexual abuse is quite common in fibromyalgia patients and should be investigated using open-ended questions.

The family history may reveal depression, anxiety, or fibromyalgia in close relatives.

Related symptoms. Fibromyalgia patients, in addition to reporting widespread pain and fatigue, often report chronic headaches, memory loss, loss of concentration, paresthesias in the extremities, and symptoms of irritable bowel or bladder.

Soft-tissue tenderness. Physical examination usually reveals diffuse soft tissue tenderness, particularly over the posterior neck, the trapezius and supraspinatus muscles, the proximal forearms, the anterior chest, the posterior pelvis, the greater trochanters, and the medial femoral condyles.

Normal laboratory values. Blood counts, serum chemistry, and urinalysis are normal in fibromyalgia, which helps to differentiate it from lupus when the diagnosis is not clear.

When the history, examination, and routine laboratory tests support a diagnosis of fibromyalgia, autoantibody testing is not necessary.

Reserve ANA testing for those whose odds of having lupus are high

REFERENCES

1. **Hochberg MC.** The epidemiology of systemic lupus erythematosus. In: Wallace DJ, Hahn BH, editors. Dubois' Lupus Erythematosus. 5th edition. Baltimore: Williams and Wilkins, 1997:50–52.
2. **Wolfe F, Ross K, Anderson J, Russell IJ, Hebert L.** The prevalence and characteristics of fibromyalgia in the general population. Arthritis Rheum 1995; 38:19–28.
3. **De Vlam K, De Keyser F, Verbruggen G, et al.** Detection and identification of antinuclear autoantibodies in the serum of normal blood donors. Clin Exp Rheumatol 1993; 11:393–397.
4. **Craig WY, Ledue TB, Johnson AM, Ritchie RF.** The distribution of antinuclear antibody titers in "normal" children and adults. J Rheumatol 1999; 26:914–919.
5. **Tan EM, Feltkamp TEW, Smolen JS, et al.** Range of antinuclear antibodies in "healthy" individuals. Arthritis Rheum 1997; 40:1601–1611.
6. **Slater CA, Davis RB, Shmerling RH.** Antinuclear antibody testing. A study of clinical utility. Arch Intern Med 1996; 156:1421–1425.
7. **Emlen W, O'Neill L.** Clinical significance of antinuclear antibodies. Arthritis Rheum 1997; 40:1612–1618.
8. **Tan EM, Smolen JS, McDougal JS, et al.** A critical evaluation of enzyme immunoassays for detection of antinuclear antibodies of defined specificities. I. Precision, sensitivity and specificity. Arthritis Rheum 1999; 42:455–464.
9. **Calvo-Alen J, Bastian HM, Straaton KV, Burgard SL, Mikhail IS, Alarcon GS.** Identification of patient subsets among those presumptively diagnosed with, referred and/or followed up for systemic lupus erythematosus at a large tertiary care center. Arthritis Rheum 1995; 38:1475–1484.
10. **Hsu VM, Patella SJ, Sigal LH.** "Chronic Lyme disease" as the incorrect diagnosis in patients with fibromyalgia. Arthritis Rheum 1993; 36:1493–1500.
11. **Sigal LH.** Summary of the first 100 patients seen at a Lyme disease referral center. Am J Med 1990; 88:577–581.
12. **Wolfe F.** "Silicone related symptoms" are common in patients with fibromyalgia: no evidence for a new disease. J Rheumatol 1999; 26:1172–1175.
13. **Wolfe F, Anderson J.** Silicone filled breast implants and the risk of fibromyalgia and rheumatoid arthritis. J Rheumatol 1999; 26:2025–2028.

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