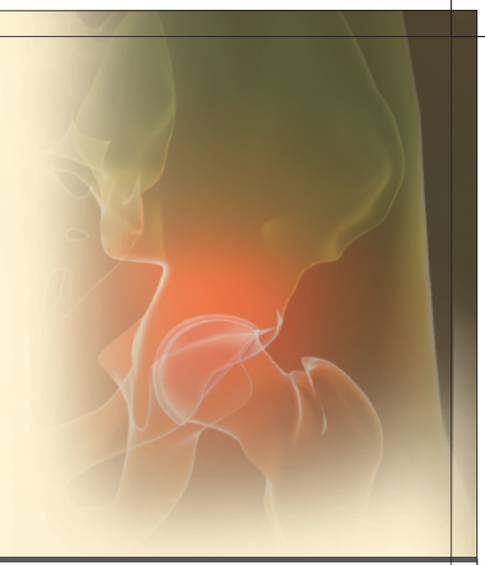
Rheuma Facts

A Quarterly Magazine

5th Issue, August 2014



Current News

Bisphosphonate compliance linked to increase in femoral fractures

4 June, 2014 Nicola Garrett

Elderly women who take bisphosphonates long-term have an increased risk of atypical femur shaft fractures, a large international study confirms, but the overall benefits of treatment still outweigh the risks.

The study of over half a million postmenopausal women found that each additional year of bisphosphonate treatment showed a progressive increase in subtrochanteric/femoral shaft fractures.

This was in contrast to a steady reduction in the rate of intertrochanteric/femoral neck (IT/FN) fractures, found the authors from the National Institute of Arthritis Musculoskeletal and Skin Diseases in Bethesda in the US.

Based on age-adjusted rates from the high and less compliant patients, the researchers estimated that during the 4th year of bisphosphonate treatment there was a decrease of 312 per 100,000 in the rate of IT/FN fractures, but an increase of 76 per 100,000 in the rate of ST/FS fractures.

The number needed to treat with high adherence to prevent an IT/FN fracture was 320, compared to 1,316 for one additional ST/FS fracture as the number needed to harm, results showed.

The association tended to depend on bisphosphonate treatment in a dose-response and duration of use manner. According to the authors, this supported the hypothesis that cumulative exposure to oral bisphosphonates may be causally related to ST/FS fractures.

However the overall benefit of bisphosphonate therapy within five years was “reassuring,” the study authors said.

“Postmenopausal women who benefited from the initiation of bisphosphonate treatment far outnumber those who might suffer subtrochanteric or femoral shaft fractures following two years or more of treatment with high adherence,” they wrote in Osteoporosis International.

“The clinical implication of this study is that adherence to oral bisphosphonates after two years of treatment remains beneficial for overall fracture reduction but needs to be monitored for possible increased risk of atypical fractures,” they concluded.

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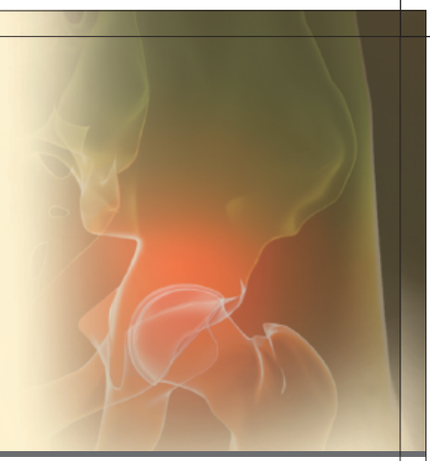

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Antiphospholipid Syndrome (APS)

Summarized by:
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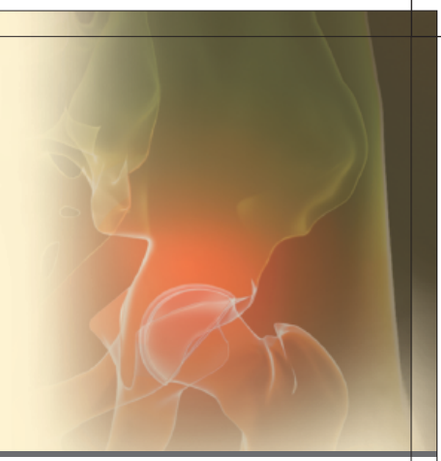


Antiphospholipid Syndrome (APS) is a disorder that manifests clinically as recurrent venous or arterial thrombosis and/or fetal loss. Characteristic laboratory abnormalities in APS include persistently elevated levels of antibodies directed against membrane anionic phospholipids (i.e. anticardiolipin [ACL] antibody, antiphosphatidylserine) or their associated plasma proteins, predominantly beta-2 glycoprotein I (apolipoprotein H); or evidence of a circulating anticoagulant.

Multiple terms for APS exist. Unfortunately, some synonyms can be confusing. Lupus Anticoagulant (LA) syndrome, for example, is misleading because patients with APS may not necessarily have SLE (Systemic Lupus Erythematosus) and LA is associated with thrombotic rather than hemorrhagic complications. In an attempt to avoid further confusion, APS is currently the preferred term for the clinical syndrome.

Some patients with APS have no evidence of any definable associated disease, while in other patients, APS occurs in association with SLE or another rheumatic or autoimmune disorder. Traditionally, these have been referred to as primary or secondary APS, respectively.

Pathophysiology

In APS, the homeostatic regulation of blood coagulation is altered; however, the mechanisms of thrombosis are not yet defined.

Proposed mechanisms for the hypercoagulable effect of APL antibodies include the following:

- Production of antibodies against coagulation factors, including prothrombin, protein C, protein S, and annexins.
- Activation of platelets to enhance endothelial adherence.
- Activation of vascular endothelium, which, in turn, facilitates the binding of platelets and monocytes.
- Reaction of antibodies to oxidized low-density lipoprotein, thus predisposing to atherosclerosis and Myocardial Infarction (MI).

Complement activation has been increasingly recognized as a possible significant role in the pathogenesis of APS. Emerging evidence from murine models suggests that APL-mediated complement activation may be a primary event in pregnancy loss.

Clinically, the series of events that leads to hypercoagulability and recurrent thrombosis can affect virtually any organ system, including the following:

- Peripheral venous system (deep venous thrombosis)
- Central nervous system (cerebrovascular accident [CVA], sinus thrombosis)
- Hematologic (thrombocytopenia, hemolytic anemia)
- Obstetric (pregnancy loss, eclampsia)
- Pulmonary (pulmonary embolism,pulmonary hypertension)
- Dermatologic (livedoreticularis, purpura, infarcts/ulceration)
- Cardiac (Libman-Sacks valvulopathy, MI)
- Ocular (amaurosis, retinal thrombosis)
- Adrenal (infarction/hemorrhage)
- Musculoskeletal (avascular necrosis of bone)

Epidemiology

The actual frequency of APS in the general population is unknown. One to 5% of healthy individuals have APL antibodies. ACL antibodies tend to be found more frequently in elderly persons; thus, positive titer results should be interpreted with caution in this population.

APL antibodies are found in approximately 30-40% of patients with SLE, but only about 10% have APS.

Mortality/Morbidity

- APS may contribute to an increased frequency of CVAs or MIs, especially in younger individuals. CVAs may develop secondary to in situ thrombosis or embolization that originates from the valvular lesions of Libman-Sacks (sterile) endocarditis, which may be seen in patients with APS.

  Cardiac valvular disease may be severe enough to require valve replacement. Recurrent pulmonary emboli or thrombosis can lead to life-threatening pulmonary hypertension.
- Catastrophic APS (CAPS) is a rare, serious, and often fatal manifestation (mortality rate of approximately 50%) characterized by multi organ infarctions over a period of days to weeks.
- Late spontaneous fetal loss (second or third trimester) is common; however, it can occur at any time during pregnancy. Recurrent early fetal loss (< 10 weeks' gestation) is also possible.

Sex

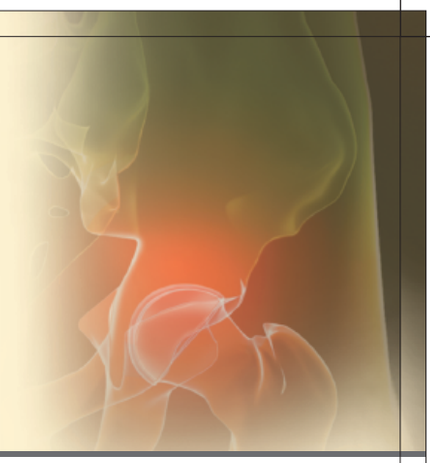
- A female predominance has been documented, particularly for secondary APS. This parallels the association of APS with SLE and other connective-tissue diseases, which also have a female predominance.

Age

- APS is more common in young to middle-aged adults; however, it also manifests in children and elderly people. Disease onset has been reported in children as young as 8 months.

Diagnostic Criteria

In 2006, revised criteria for the diagnosis of APS were published in an international consensus statement. At least one clinical criterion and one laboratory criterion must be present for a patient to be classified as having APS.



The clinical criteria is as follow:

Vascular Thrombosis

- One or more clinical episodes of arterial, venous, or small-vessel thrombosis in any tissue or organ confirmed by findings from imaging studies, Doppler studies, or histopathology.
- Thrombosis may involve the cerebral vascular system, coronary arteries, pulmonary system (emboli or thrombosis), arterial or venous system in the extremities, hepatic veins, renal veins, ocular arteries or veins, or adrenal glands.

Pregnancy Morbidity

- One or more late-term (>10 weeks' gestation) spontaneous abortions.
- One or more premature births of a morphologically healthy neonate at or before 34 weeks' gestation because of severe pre-eclampsia or eclampsia or severe placental insufficiency.
- Three or more unexplained, consecutive, spontaneous abortions before 10 weeks' gestation.

Laboratory Criteria

Patients must have

(1) Medium to high levels of immunoglobulin G (IgG) or immunoglobulin M (IgM) anticardiolipin (ACL),

(2) Anti–beta-2 glycoprotein I,

(3) LA on at least 2 occasions at least 12 weeks apart.

Other antiphospholipid (APL) associated clinical features recognized by the 2006 consensus statement but not included in the criteria include cardiac valve disease, livedoreticularis, thrombocytopenia, nephropathy, and neurologic manifestations.

Thus, history of any of the following should raise the examiner's suspicion for APS:

- Thrombosis (e.g. DVT/PE, MI, Transient Ischemic Attack [TIA], or CVA, especially if recurrent, at an earlier age, or in the absence of other known risk factors)
- Miscarriage (especially late trimester or recurrent) or premature birth
- History of heart murmur or cardiac valvular vegetations
- History of hematologic abnormalities, such as thrombocytopenia or hemolytic anemia
- History of nephropathy
- Nonthrombotic neurologic symptoms, such as migraine headaches, chorea, seizures, transverse myelitis
- Guillain-Barré syndrome, or dementia (rare)
- Unexplained adrenal insufficiency
- Avascular necrosis of bone in the absence of other risk factors
- Pulmonary hypertension
- Livedo reticularis
- Superficial thrombophlebitis
- Leg ulcers
- Painful purpura
- Splinter hemorrhages
- Venous thrombosis
- Leg swelling
- Ascites (Budd-Chiari syndrome)
- Tachypnea (PE)
- Peripheral edema (renal vein thrombosis)
- Abnormal funduscopic examination results (retinal vein thrombosis)
- Arterial thrombosis
- Abnormal neurologic examination results (e.g. CVA)
- Digital ulcers
- Gangrene of distal extremities
- Heart murmur (frequently aortic) or mitral insufficiency (Libman-Sacks endocarditis)

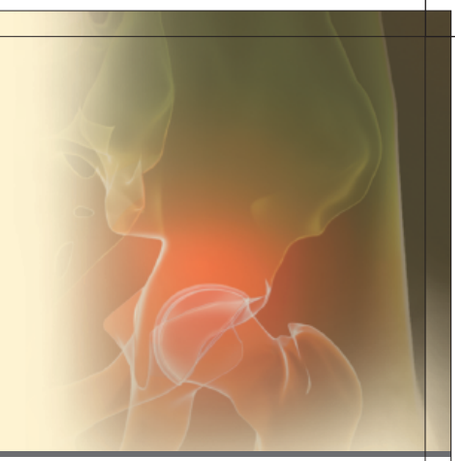
Common autoimmune or rheumatic diseases and the percentage of affected patients with APL antibodies:

- SLE - 25-50%
- Sjögren syndrome - 42%
- Rheumatoid arthritis - 33%
- Autoimmune thrombocytopenic purpura - 30%
- Autoimmune hemolytic anemia
- Psoriatic arthritis - 28%
- Systemic sclerosis - 25%
- Mixed connective-tissue disease - 22%
- Polymyalgia rheumaticaor giant cell arteritis - 20%
- Behçet syndrome - 20%
- Infections
- Syphilis
- Hepatitis C infection
- HIV infection
- Malaria
- Bacterial septicemia

Drugs

Cardiac - Procainamide, quinidine, propranolol, hydralazine
Neuroleptic or psychiatric - Phenytoin, chlorpromazine
Other - Interferon alfa, quinine, amoxicillin
Differential Diagnoses

- Disseminated Intravascular Coagulation
- Infective Endocarditis
- Thrombotic Thrombocytopenic Purpura



Laboratory Studies

The hallmark result from laboratory tests that defines antiphospholipid syndrome (APS) is the presence of antiphospholipid (APL) antibodies or abnormalities in phospholipid-dependent tests of coagulation. In addition to the clinical criteria listed in history, at least one of the following laboratory criteria is necessary for the classification of APS:

Patients with APS may have one or more abnormal results from these laboratory tests; the following laboratory tests should be considered in a patient suspected of having APS:

- ACL antibodies (IgG, IgM)
- Anti–beta-2 glycoprotein I antibodies (IgG, IgM)
- Activated partial thromboplastin time (aPTT)
- LA tests such as DRVVT (A threshold of approximately 1.6 for the DRVVT ratio has been recommended for helping discriminate APS from non-APS.[9])
- Serologic test for syphilis (false-positive result)
- CBC count (thrombocytopenia, hemolytic anemia)

Thrombocytopenia is fairly common in persons with APS and is therefore associated with paradoxical thrombosis. However, patients with platelet counts of less than 50,000/L may have an increased risk of bleeding. Hemolytic anemia has been well described in patients with APS and is associated with the presence of IgM ACL antibodies.

A low antinuclear antibody level may be present and does not necessarily imply coexisting SLE.

Additional antibodies directed against phospholipid/phospholipid-protein complexes that may be useful in selected cases include the following:

- IgA ACL
- IgA beta-2 glycoprotein I
- Anti-phosphatidylserine antibodies
- Anti-phosphatidylethanolamine antibodies
- Anti-prothrombin antibodies
- Antibodies against the phosphatidylserine-prothrombin complex

Imaging Studies

- Imaging studies are helpful for confirming a thrombotic event. A good example is the use of CT scanning or MRI of the brain (CVA), chest (PE), or abdomen (Budd-Chiari syndrome).
- Doppler ultrasound studies are recommended for possible detection of DVT.
- Two-dimensional echocardiography findings may demonstrate asymptomatic valve thickening, vegetations, or valvular insufficiency; aortic or mitral insufficiency is the most common valvular defect found in persons with Libman-Sacks endocarditis.

Medical Care

Patients with antiphospholipid syndrome (APS) may be evaluated in an outpatient setting.

Inpatient evaluation is required if the patient presents with a significant clinical event.

Patients with CAPS require intense observation and treatment, often in an intensive care unit.

In general, treatment regimens for APS must be individualized according to the patient's current clinical status and history of thrombotic events.

Asymptomatic individuals in whom blood test findings are positive do not require specific treatment.

Prophylactic Therapy

Eliminate other risk factors, such as oral contraceptives, smoking, hypertension, or hyperlipidemia.

Low-dose aspirin is used widely in this setting; however, the effectiveness of low-dose aspirin as primary prevention for APS remains unproven. Clopidogrel has anecdotally been reported to be helpful in persons with APS and may be useful in patients allergic to aspirin.

In patients with SLE, consider hydroxychloroquine, which may have intrinsic antithrombotic properties.

Consider the use of statins, especially in patients with hyperlipidemia.

Thrombosis

Perform full anticoagulation with intravenous or subcutaneous heparin followed by warfarin therapy.

Based on the most recent evidence, a reasonable target for the international normalized ratio (INR) is 2.0-3.0 for venous thrombosis and 3.0 for arterial thrombosis. Patients with recurrent thrombotic events, while well maintained on the above regimens, may require an INR of 3.0-4.0. For severe or refractory cases, a combination of warfarin and aspirin may be used. Treatment for significant thrombotic events in patients with APS is generally lifelong.

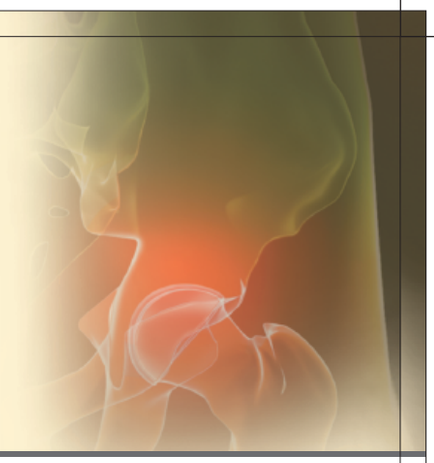
Obstetric Considerations

Guidelines from the American College of Obstetricians and Gynecologists

(Based primarily on consensus and expert opinion) regarding prenatal and postpartum care for women with APS recommend prophylaxis for those with no history of thrombosis and full anticoagulation for those with a history of thrombosis.

Patients with pregnancy loss receive prophylactic subcutaneous heparin (preferably low–molecular-weight heparin [LMWH]) and low-dose aspirin. Therapy is withheld at the time of delivery and is restarted after delivery, continuing for 6-12 weeks postpartum. Warfarin (Coumadin) is contraindicated in pregnancy.

Patients with a history of thrombosis receive therapeutic doses of heparin during pregnancy; long-term anticoagulation is then continued postpartum.
Corticosteroids have not been proven effective for persons with primary APS, and they have been shown to increase maternal



morbidity and fetal prematurity rates.
Breastfeeding women may use heparin and warfarin.

Surgical Care

Recurrent DVT may necessitate placement of an inferior vena cava filter.

Consultations/Referral

- Rheumatologist
- Hematologist
- Neurologist, cardiologist, pulmonologist, hepatologist, ophthalmologist (depending on clinical presentation)
- Obstetrician with experience in high-risk pregnancies

Diet

- If warfarin therapy is instituted, instruct the patient to avoid excessive consumption of foods that contain vitamin K.

Activity

- No specific limitations on activity are necessary.
- Individualize the activity according to the clinical setting.
- Instruct the patient to avoid sports with excessive contact if taking warfarin.
- Limit activity in patients with acute DVT.
- Instruct the patient to avoid prolonged immobilization.

Patients who require heparin administration throughout pregnancy should receive calcium and vitamin D supplementation to help avoid heparin-induced osteoporosis. When monitoring heparin therapy, note that the aPTT may be unreliable in the presence of circulating LA with a baseline elevated aPTT. In this case, factor Xa may be helpful.

The antithrombotic properties of hydroxychloroquine have long been recognized and may be considered in the prophylactic treatment of a patient with SLE and a positive APL antibody test result. Case reports suggest that clopidogrel may be effective because of its antiplatelet effect. Recently, statins have been suggested to have potential antithrombotic effects. In addition to full anticoagulation, plasma exchange and corticosteroids are generally used in the treatment of CAPS. Intravenous immunoglobulin or cyclophosphamide may also be considered in selected patients with CAPS. For example, a recent retrospective study reported a decrease in late pregnancy complications in women with APS who received 0.2g/kg of intravenous immunoglobulin.

Rituximab has shown promise in the treatment of APS. Trials of rituximab for APS are in progress.

Aspirin

Although not proven effective when used alone, most clinicians use aspirin with SC heparin in pregnant patients with APS. Begin aspirin as soon as conception is attempted.

Immunosuppressive Agents

Consider immunosuppressive agents in select cases (e.g. refractory APS, CAPS).

Cyclophosphamide

Chemically related to nitrogen mustards. As an alkylating agent, mechanism of action of active metabolites may involve cross-linking of DNA, which may interfere with growth of normal and neoplastic cells. Has not been shown to be effective in APS.

Corticosteroids

In selected cases with specific nonthrombotic autoimmune manifestations (e.g. clinically significant thrombocytopenia), corticosteroids may be considered.
Immunosuppressant for treatment of autoimmune disorders. May decrease inflammation by reversing increased capillary permeability and suppressing PMN activity.Useful in treating cytopenias.

Prognosis

- With appropriate medication and lifestyle modifications, most individuals with primary Antiphospholipid Syndrome (APS) lead normal healthy lives. However, subsets of patients continue to have thrombotic events despite aggressive therapies. In these patients and in patients with CAPS, the disease course can be devastating, often leading to significant morbidity or early death.
- A retrospective study suggested that hypertension or medium-to-high titers of IgG anticardiolipin antibody are risk factors for a first thrombotic event in asymptomatic patients with antiphospholipid (APL) antibodies. Primary prophylaxis against thrombosis appears to offer significant protection in such cases.
- Patients with secondary APS carry a prognosis similar to that of patients with primary APS; in the former, however, morbidity and mortality may also be influenced by these patients' underlying autoimmune or rheumatic condition. In patients with SLE and APS, APL antibodies have been associated with neuropsychiatric disease and have been recognized as a major predictor of irreversible organ damage.
- Women with APL antibodies who experience recurrent miscarriages may have favorable prognoses in subsequent pregnancies if treated with aspirin and heparin.

Patient Education

- Stress the importance of early recognition of a possible clinical event.
- Educate the patient about anticoagulation therapy.
- Discuss the importance of planned pregnancies so that long-term warfarin can be switched to aspirin and heparin before pregnancy is attempted.

References

1. Giannakopoulos B, Passam F, Rahgozar S, Krilis SA.Current concepts on the pathogenesis of the antiphospholipid syndrome. Blood. Jan 15 2007;109(2):422-30. [Medline]<http://reference.medscape.com/medline/abstract/16985176>.
2. Ruiz-Irastorza G, Crowther M, Branch W, Khamashta MA. Antiphospholipid syndrome.Lancet. Oct 30 2010;376(9751):1498-509. [Medline]<http://reference.medscape.com/medline/abstract/20822807>.
3. Girardi G, Redecha P, Salmon JE. Heparin prevents antiphospholipid antibody-induced fetal loss by inhibiting complement activation. Nat Med. Nov 2004;10(11):1222-6. [Medline]<http://reference.medscape.com/medline/abstract/15489858>.
4. Lockshin MD. Update on antiphospholipid syndrome. Bull NYU HospJt Dis. 2006;64(1-2):57-9. [Medline]<http://reference.medscape.com/medline/abstract/17121491>.
5. Avcin T, Cimaz R, Silverman ED, Cervera R, Gattorno M, Garay S, et al. Pediatric antiphospholipid syndrome: clinical and immunologic features of 121 patients in an international registry. Pediatrics. Nov 2008;122(5):e1100-7.

Treatment of Fibromyalgia

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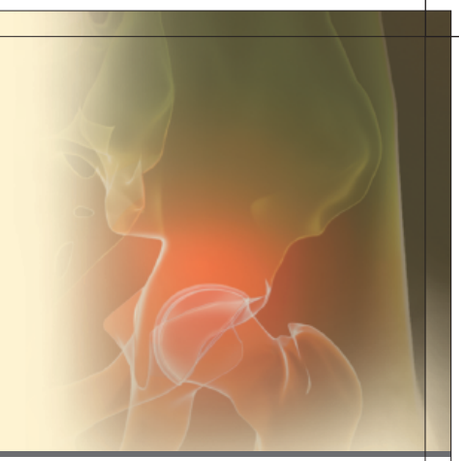


Fibromyalgia Syndrome (FMS) is a medical syndrome constituting a constellation of symptoms, including pain and fatigue, which often overlap with a number of other conditions. Patients are diagnosed with this condition in increasing numbers and it has been identified in approximately 2 to 4% of the general population. Fibromyalgia is most often diagnosed in female patients between the ages of 20 to 60 years old. In fact, women are diagnosed three times more often than men. This condition can be difficult to treat and quite debilitating for patients. Approximately 62% of patients have difficulty climbing stairs, 55% have difficulty walking two blocks, and 35% have difficulty with activities of daily living. The challenge of treating FMS requires a high quality patient-physician relationship combined with a multidisciplinary approach in order to improve the patient's symptoms and quality of life.

Though an exact etiology is unknown, a number of pathophysiological mechanisms contributing to the syndrome have been postulated. In 1990 Wolfe et al published the first American College of Rheumatology (ACR) criteria which included a history of chronic widespread pain and the presence of 11 out of 18 defined tender points upon physical examination. With this publication came a new paradigm of understanding FMS as not simply a psychological phenomenon—as previously thought—but also a neurobiological entity. The most commonly cited explanation of FMS is that of a central sensitization in which an impairment in the nervous system's inhibitory mechanisms of ascending sensory pathways—via gaba-amino-butyric acid (GABA) and other inhibitory neurotransmitters—causes oversensitivity of pain and other stimuli. The syndrome has also been correlated with low CSF levels of serotonin and norepinephrine and high levels of substance P, an amine known to increase pain sensation. Liptan in 2009 attributed central sensitization to fascial inflammation. It is this inflammation, he proposed, is the initial nociceptive noxious input that leads to the reflex hyper excitability of the sensory system as described above.

Diagnosing FMS requires keen clinical investigation of patients complaining of chronic pain, fatigue, impaired sleep, and morning stiffness. The diagnostic criteria as outlined in the 1990 ACR guidelines includes a complaint of wide spread pain lasting more than 3 months along with 11 out of 18 defined palpable tender points using about 4kg of pressure (enough to make the palpating thumb blanch white). Wide spread pain is characterized by pain on both sides of the body, above and below the waist, and includes axial pain. It is important that other causes of pain are ruled out such as Rheumatoid Arthritis (RA), Systemic Lupus Erythematosus (SLE), Polymyalgia Rheumatic (PMR), or any other inflammatory or autoimmune diseases.

Once the diagnosis of Fibromyalgia is made, the physician has a number of options available to manage these patients. A multidisciplinary approach to treatment includes addressing impairment of sleep and fatigue as well as physical exercise, behavioral and psychological therapies. Pharmacological management primarily involves antidepressant medications but also may include usage of medications such as Pregabalin, Duloxatine, and others.

Hauser et al performed a meta-analysis with 18 randomized controlled trials (RCT) investigating usage of antidepressants for FMS. There was strong evidence that antidepressants reduced pain, fatigue, depressed mood, and sleep disturbances as well as improved quality of life. These effects were most evident with tricyclic antidepressants.

Treatment

With a thorough understanding of the above, a physician may develop a comprehensive treatment plan.
The treatment should be holistic, patient-centered, and specially focused on the structural impairments which may impede functional recovery. This general philosophy is especially appropriate for the FMS patient who may have a multitude of contributing factors involved.

1- Exercise and Physical Activity for Fibromyalgia

Massage therapy, aerobics, yoga, psychological therapies, education, cognitive-behavioral therapy, relaxation training, and social support are usefull in treating patients with FM.
Exercise also has been shown to improve patients' symptoms and quality of life in multiple studies.

2- Pharmacological Treatment

- Duloxatine
- Pregablin
- Milnacipran

are endorsed by multiple health regulatory authorities as standard treatment for FM. Analgesics rarely give some benefit to patients.

Conclusion

In conclusion, Fibromyalgia is a difficult syndrome to manage and treat effectively. A comprehensive, multidisciplinary approach to treatment is essential for successful improvements in the patient's overall condition. A combination of psychological, physical, and pharmacological interventions may be required. The treatment of somatic dysfunction is understood to help facilitate the body's natural ability to heal itself.

References

Brecher, L.; Cymet, T. Practical Approach to Fibromyalgia. *JAOA* **2001**, 101:S12-S17.

Smith, H.; Barkin, R. Fibromyalgia Syndrome: A Discussion of the Syndrome and Pharmacotherapy. *American Journal of Therapeutics* **2010**, 17:418-439.

Wolfe, F. Fibromyalgia: A clinical syndrome. *Rheum Dis Clin North Am* **1989**, 15, 1:1-18.

Wolfe, F.; Smythe HA; Yunus, MB; Bennett RM; Bombardier, C.; Goldenberg, DL; Tugwell, P.; Campbell, SM; Abeles, M.; Clark, P. The American College of Rheumatology 1990 Criteria for the Classification of Fibromyalgia.Report of the Multicenter Criteria Committee. *Arthritis Rheum* **1990**, 33, 2:160-172.

Ablin, J.; Neumann, L.; Buskila, D. Pathogenesis of fibromyalgia – A Review. *Joint Bone Spine* **2008**, 75:273-279.

Liptan, G. Fascia: A missing link in our understanding of the pathology of fibromyalgia. *Journal of Bodywork & Movement Thereapies* **2010**, 14:3-12.

Hauser, W.; Bernardy, K.; Uceyler, N.; Sommer, C. Treatment of fibromyalgia syndrome with antidepressants: a meta-analysis. *JAMA* **2009**, 301, 2:198-209.

Nelson K., & Glonek, T. (2007). *Somatic Dysfunction in Osteopathic Family Medicine.* Baltimore, MD: Lippincott Williams & Wilkins.

Gamber, R.; Shores, J.; Russo, D.; Jimenez, C.; Rubin, B. Osteopathic manipulative treatment in conjunction with medication relieves pain associated with fibromyalgia syndrome: Results of a randomized clinical pilot project. *JAOA* 102, 6:321.

Dardzinski, JA; Osrov BE; Hamann, LS. Myofascial pain unresponsive to standard treatment: successful use of a strain and counterstrain technique with physical therapy. *J Clin Rheumatol* **2000**, 4:169-174.

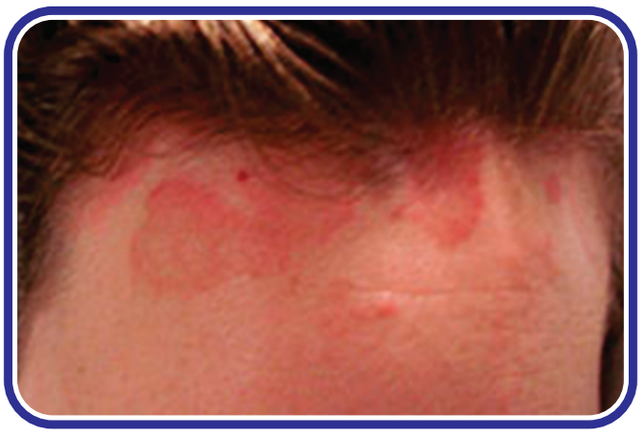
Pickar, J. G. Neurophysiological effects of spinal manipulation. The Spine Journal **2002, 2**, 5:357-371.

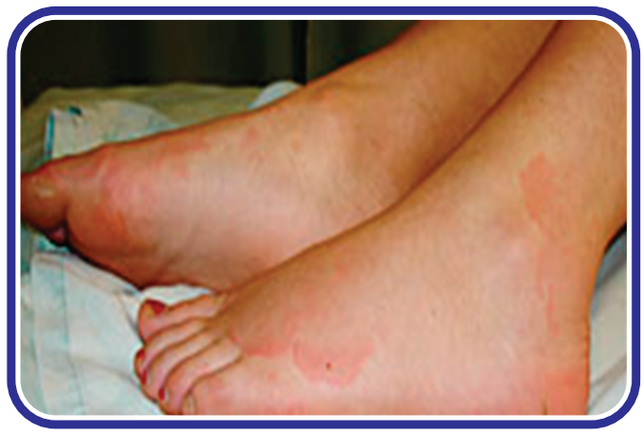
DiGiovanna, D., Schiowitz, S., & Dowling, D. (2007) *An Osteopathic Approach to Diagnosis and Treatment 2nd Ed.* Lippincott.

Photo Quiz

Rash and Fever in a School Student

A 15-year-old female school student presented to the hospital with rash and high fever. Severe arthralgias and a nonpruritic rash appeared on her lower extremities shortly after the pharyngitis developed. The rash migrated to her chest and head a few days later.





Question

Based on the patient's history and physical examination, which one of the following is the most likely diagnosis?

A. Disseminated tineacorporis

B. Erythema marginatum

C. Erythema migrans

D. Erythema multiforme

E. Erythema nodosum