Influenza A Virus: A Possible Precipitating Factor in Fibromyalgia?

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Abstract

Many fibromyalgia patients relate a history of acute febrile and congestive respiratory episodes prior to the onset of their illness. This observation prompted consideration of an influenza virus infection as a possible contributory factor in fibromyalgia. Ten fibromyalgia patients were selected at random for blood testing to determine if viral infections could play a part in development of fibromyalgia. Patient age ranged from 22 to 69, the average being 43 years. Nine of the patients were female and one was male. Screening volunteers for antibodies to influenza type A viral antigen yielded positive results in nine of ten patients. Only three of ten patients with fibromyalgia in a similarly age- and sex-matched group demonstrated positive responses to influenza type B. With the positive results obtained, it appears influenza type A viral infection, which primarily strikes the respiratory and autonomic nervous systems, might be involved in the development of fibromyalgia. In the fibromyalgia cases tested, the patients related a history of upper respiratory infection, along with associated neurological symptoms prior to the onset of fibromyalgia symptoms.
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Introduction

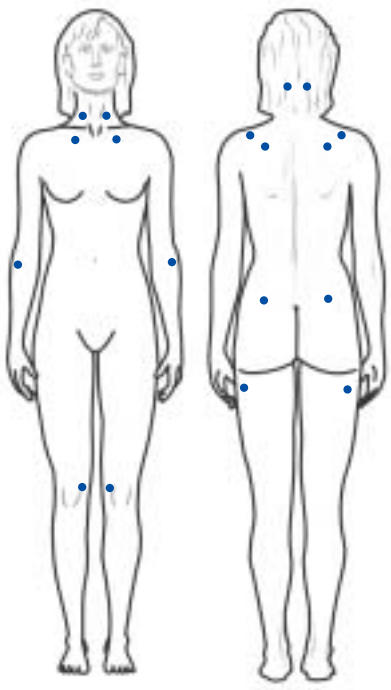
The disease entity identified as fibromyalgia is a multi-faceted disorder exemplified by symptomatology of severe pain, muscle aches, morning stiffness, and specific pathognomonic, localized tender points identified on palpation of the musculature. Related symptoms include chronic insomnia, anxiety, depression, headaches, gastrointestinal complaints and extreme fatigue. Although medical researchers have not, to date, been able to agree on specific causes of this disease, the symptoms of fibromyalgia were well documented by the American College of Rheumatology (ACR) in 1990, which devised a set of specific criteria to provide a tentative diagnosis of fibromyalgia.[1] (Figure 1)

A Search for the Cause: A Possible Viral Connection

The inability to confirm the specific cause of fibromyalgia has made it difficult to develop a satisfactory treatment protocol. The number of fibromyalgia cases encountered today is increasing rapidly, which further adds to the urgency of the situation. Viral infection as the initiating cause of fibromyalgia was considered when many confirmed patients related a history of acute flu-like febrile episodes prior to the onset of their illness. A search was initiated for a specific viral involvement in fibromyalgia, and a protocol was developed for screening patient blood samples for evidence of viral antibodies.

Three different types of influenza virus have been identified — influenza types A, B and C. Type A influenza virus is characterized as the most virulent because of its antigenic diversity

Figure 1. Specific Criteria For Diagnosis of Fibromyalgia by The American College of Rheumatology, 1990.[1]



1. History of widespread pain.

Definition: Pain is considered widespread when all the following are present: pain in the left side of the body, pain in the right side of the body, pain above the waist and pain below the waist. In addition, axial skeletal pain (cervical spine or anterior chest or thoracic spine or low back) must be present. In this definition, shoulder and buttock pain is considered as pain for each involved side. "Low back" pain is considered lower segment pain.

2. Pain in 11 of 18 tender point sites on digital palpation.

Definition: Pain, on digital palpation, must be present in at least 11 of the following 18 tender point sites:

- Occiput: bilateral, at the suboccipital muscle insertions.
- Low cervical: bilateral, at the anterior aspects of the intertransverse spaces at C5-C7.
- Trapezius: bilateral, at the midpoint of the upper border.
- Supraspinus: bilateral, at origins, above the scapular spine near the medial border.
- Second rib: bilateral, at the second costochondral junctions, just lateral to the junctions on upper surfaces.
- Lateral epicondyle: bilateral, 2 cm distant to the epicondyles.
- Gluteal: bilateral, in upper outer quadrants of buttocks in anterior fold of muscle.
- Greater trochanter: bilateral, posterior to the trochanteric prominence.
- Knee: bilateral, at the medial fat pad proximal to the joint line.

Digital palpation should be performed with an approximate force of 4 kg. For a tender point to be considered "positive" the subject must state that the palpation was painful. "Tender" is not to be considered "painful".

For classification purposes, patients will be said to have fibromyalgia if both criteria are satisfied. Widespread pain must have been present for at least three months. The presence of a second clinical disorder does not exclude the diagnosis of fibromyalgia.

and the three variants or sub-types which all infect humans. Type B and C viruses have no sub-types, hence the variant factor is not a concern. In addition, influenza C is rarely encountered. Positive titers to influenza A normally last less than a year after infection. Therefore, positive serological findings are not prevalent in the general population without recent infection.[2]

Method

Ten patients were selected at random for blood testing. All patients met the diagnostic guidelines for fibromyalgia developed by the American College of Rheumatology. Patient age ranged from 19 to 70, the average being 45 years of age. Nine of the candidates were female and one was male. A test for influenza type B was the first choice, since this is the most common flu virus seen currently.

The second viral screening procedure again involved ten patients, a group of 9 females and one male ranging in age from 22 to 69, with an average age of 43. These fibromyalgia patients were tested for influenza virus type A. All tests were performed by the Seattle-King County Communicable Disease Laboratory using the complement fixation methodology.

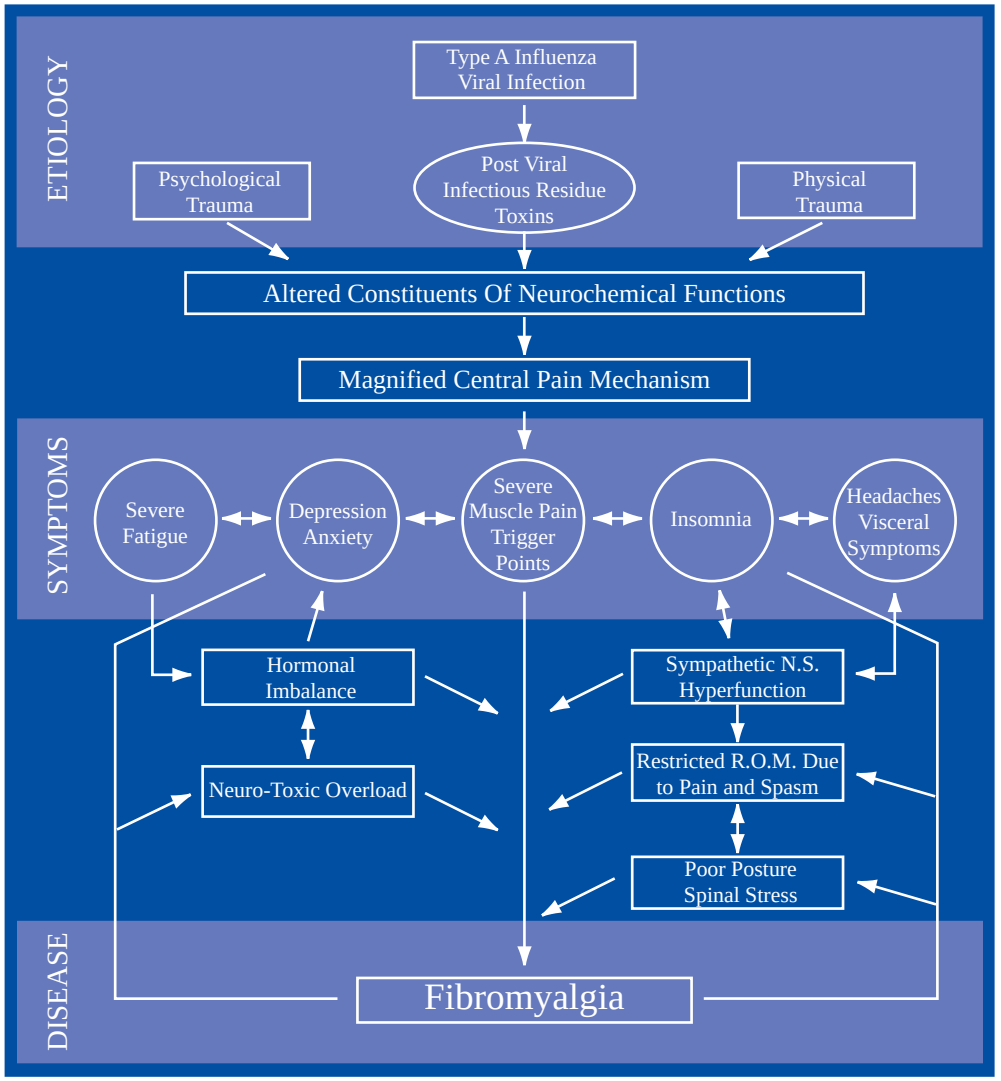
Results

Three of the 10 fibromyalgia patients tested had positive antibody titers (<1:8) for the influenza type B virus and seven were negative. On the other hand, 9 of 10 fibromyalgia patients in a similarly age- and sex-matched group tested positive for influenza type A.

Discussion

The first influenza type A virus was isolated from chickens with so-called "fowl plague" in 1901,[3] but it was not recognized as an influenza viral infection until 1955.[4] The cause of the great 1918 flu epidemic was also later identified as a type A influenza viral infection, sub-group H7N7.[5] Of the several sub-groups identified under the type A virus, currently only two remain active, H1N1 and H3N2, and both are considered highly

Figure 2. Hypothetical Progression From Influenza A Infection to Fibromyalgia



infectious. The last severe type A influenza epidemic to invade North America was in 1978, named the "Texas Flu." Other subsequent type A flu epidemics occured in the Philippines in 1980, Bangkok in 1982 and Victoria, Australia in 1983. These incidents were prevented from reaching epidemic status in North America by a vaccination program. The type A influenza virus is currently active in a less virulent form. It is interesting to note that fibromyalgia as a disease did not exist in the form encountered today until after the severe influenza epidemic of 1918. At that time there were confirmed reports of myalgias, poliomyositis, and muscular rheumatism. Reported epidemics of type A influenza which followed were not as devastating as the 1918 episode, but neither was the virus dormant.

Since not all those infected with influenza A develop fibromyalgia, differences in host immunity might allow certain individuals to avoid development of fibromyalgia. It is logical to assume that because of lack of specific immune resistance to combat viral illness, in this case influenza, the organism flourishes and the illness is more virulent. Both encephalopathy and myositis associated with the influenza type A infection are seen in adults.[6-11] As the flu and the symptoms associated with it subside, residual effects from infection are experienced. Previous physical or psychological trauma can compromise resistance. Moreover, influenza viral infections carry an increased risk for a person with deficiencies in either humoral or cell-mediated immunity. Severity of the influenza infection does not seem predictive of the development of fibromyalgia. Perhaps it is the residual effect of the virus which manifests the fibromyalgia syndrome and precipitates the symptomatology we have come to recognize as this disease.

If influenza type A infection is a primary factor in the development of fibromyalgia, then the symptomatology found

in fibromyalgia should be explainable in terms of viral infection. Of course, the answer is not a straightforward description of verified facts. Nevertheless, there is ample evidence in scientific research to substantiate the premise that a viral infection in humans can be ascribed to development of the symptomatology described.

A hypothetical sequence of events (see Figure 2) leading to fibromyalgia after a person has been exposed to a virus might be constructed as follows: First, there is development of fever in response to the viral invasion, followed by general multifaceted pain and severe loss of energy. Initial symptoms may include nonspecific autonomic nervous system effects of postural hypotension, blurred vision, abdominal pain and loss of sweating (which may be preceded by excessive sweating). The onset of true fibromyalgia may be rapid, over a period of days, or may occur more gradually over a period of weeks. Not every case is the same, but in many cases there seems to exist a prodromal fever due to viral illness. From the symptoms described it appears that the pain portion of fibromyalgia involves the autonomic nervous system. But how does the sympathetic nervous system involvement contribute to the total pain syndrome? The sympathetic nervous system is not known to be involved in the generation of pain under healthy conditions. However, under a pathological condition this change is possible.[12] The proposed answer is neurologically interpreted as follows. The sympathetic nervous system can be involved in the generation and maintenance of pain states. This is well documented in the disorder known generically as reflex sympathetic dystrophy (RSD), and in related disorders which follow trauma, both with and without nerve lesions. The syndrome consists of pain, abnormal blood flow in the skin and deeper tissues and some motor function disturbances. Thus, it includes many of the known fibromyalgia symptoms. In the case of RSD, Dr. Bonica of the University of Washington suspected that sympathetic noradrenergic neurons were involved. He often obtained prolonged relief, and in some cases continued ease of acute pain syndrome by doing a sympathetic nerve block with local anesthetic.[13,14] When the sympathetic nervous system is involved, pain from such disorders can become continuous. In some cases, there may also be neurological changes in the motor system, including weakness, wasting of the musculature and in rare instances, tremors.

Depression, anxiety and emotional lability are frequently observed in fibromyalgia. It appears fibromyalgia patients may suffer from lowered serotonin levels.[15-17] The decrease in serotonin may be a result of antibodies to serotonin receptors. At least two studies have determined that patients with fibromyalgia demonstrated anti-serotonin antibodies.[18,19] In the studies, 73% [18] and 74% [19] of subjects tested positive for the antibodies, which occurred in only 18% of healthy individuals.[18] Is it possible the anti-influenza A antibodies cross-react with serotonin receptors?

Conclusion

In many cases of fibromyalgia there exists a history of a flu-like episode as well as a history of trauma or prolonged stress, severe infection or a persistent inflammation of the digestive, respiratory or endocrine system. Autonomic nervous system dysfunction, possibly precipitated by an initial viral infection and compounded by additional factors, can play a role in the manifestation of symptomatology. This disease is a complex phenomenon which cannot be treated lightly, nor should any facet of it be overlooked. Consideration of viral infection as part of the basic cause of fibromyalgia provides a better understanding of the disease itself, and might offer some insight into treatment options for

this condition. The complex muscular pain conditions present in fibromyalgia are most likely not initiated solely by viral infection. The etiology of fibromyalgia is multi-factorial and related to both somatic and possible psychological factors. However, the existence of influenza type A antibodies in 9 of the 10 cases tested is preliminarily suggestive of its involvement in fibromyalgia. When these factors are combined, the stimulus can be perpetuated, thereby triggering the mechanism of chronic pain. Further research into the viral component of this syndrome is warranted in an effort to isolate the mechanisms which may be involved in the development of fibromyalgia symptoms.

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