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Overview on Juvenile Primary Fibromyalgia Syndrome

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Abstract

JPFS (juvenile primary fibromyalgia syndrome) is a musculoskeletal pain illness that affects children and adolescents. The intricacy of the clinical picture in JPFS has not been adequately characterized in the literature. JFMS symptoms are sometimes difficult to compare to adult fibromyalgia syndrome since many of them are "medically unexplained" and frequently overlap with other medical disorders. The etiology of the illness is multifaceted, with impaired central pain processing being a significant contributor. Musculoskeletal pain that is severe and pervasive is the defining symptom. Other signs and symptoms include headaches, stiffness, subjective joint swelling, sleep and mood disorders, and headaches. Multiple sensitive spots might be found during a physical examination. The diagnosis has certain criteria and is clinical. Early detection and treatment are crucial. The gold standard of care combines a variety of modalities, but most significantly, exercise and cognitive behavioral therapy. The outlook varies, and symptoms might last well into adulthood. Discussing the epidemiology, etiology, pathophysiology, clinical symptoms, diagnosis, and management of JPFS is the goal of the review.

Keywords: *Fibromyalgia, Juvenile, JPFS, Chronic Pain, Musculoskeletal, Physical, Exercise, Juvenile Primary Fibromyalgia Syndrome.*

1. Introduction

Chronic musculoskeletal discomfort is one of the most common causes for referrals to pediatric rheumatologists. Numerous inflammatory and non-inflammatory disorders, such as arthritis, hypermobility, fibromyalgia (FM), growing pains, and complex regional pain syndrome (CRPS), might contribute to its occurrence. A general, descriptive phrase known as "amplified musculoskeletal pain" (AMP) syndrome is used to refer to chronic pain syndromes with unknown causes, including FM, CRPS, and idiopathic musculoskeletal pain. Pain signals are amplified in people with AMP, causing the body to perceive even slightly unpleasant or non-painful stimuli as extremely severe. This results in attempts to stop experiencing pain, which causes functional impairment [1].

Fibromyalgia syndrome (FM) is an idiopathic ailment with an unknown etiology that is characterized by chronic widespread musculoskeletal pain, exhaustion, and sleep disturbances. Instead of being brought on by localized inflammation, the pain may be brought on by the brain's pain receptors functioning improperly [2]. In a clinical trial from 1985, ***Yunus and Masi*** were the first to define and

utilize the term JPFS. Based on 33 young people with chronic pain, aged 17 or younger, they proposed diagnostic criteria [3].

The global prevalence of FM is 2.7%, ranging from 0.4 to 9.3% depending on region [4]. JPFS is expected to affect 1.2 to 6.2% of the population [5]. JPFS affects more females than boys. The majority of JPFS cases are Caucasian. The average age of onset is roughly 11.4 to 13.7 years, with a range of 5 to 18 years. The average age upon diagnosis is around 14.5 to 15.5 years, with a range of 7 to 18 years. JPFS has also been documented in younger children [6]. According to ***Eraso et al***., the mean age of beginning of JPFS in children younger than 10 years old was 7.5 years, while the mean age of diagnosis was 10 years. It is believed that JPFS is underdiagnosed in younger children and that its symptoms are misattributed to other conditions [7].

For FMS, a number of etiologies have been put up, however neither the etiology nor the pathophysiologic mechanism is understood [8]. Micro-trauma to the muscles or tendons with referred pain, dysfunction in the pain-processing pathways of the central nervous system, an abnormal stress response, endocrine or hormonal factors, and sleep disruption may all play overlapping roles in the development of this syndrome [9].

JFMs patients frequently have symptoms for several years before being diagnosed. Frequent medical check-ups, costly laboratory tests, and referrals to many different specialists all add up to a great deal of patient misery and expense [2]. According to current standards, the diagnosis is still clinical, and the goal of a thorough physical examination and few laboratory tests is to rule out other somatic disorders with comparable symptoms [10]. Because of this, medical personnel now feel more insecure, which causes them to order pointless tests, treat patients excessively, and send children to several pediatric experts (such as neurologists, rheumatologists, and pain specialists) before the condition is discovered. Despite the fact that children and adolescents can satisfy the criteria for FM in adults, there is still no universal agreement on how to diagnose and treat children and adolescents with chronic widespread pain [2].

The main treatment options for childhood fibromyalgia have been cognitive behavioral therapy and aerobic exercise [11,12]. More than 90% of children with fibromyalgia reported chronic pain in studies of long-term outcomes, and more than 90% of 33 fibromyalgia-affected children examined 2.6 years after diagnosis experienced sleep disruption. greater than 80% of children with fibromyalgia continued to experience symptoms into adulthood, and at 5.9 years following diagnosis, these children had worse physical function and greater pain, anxiety, and doctor visits compared to controls [13].

Evidence-based recommendations for adults emphasize aerobic exercise and cognitive behavioral therapy. Children are not often treated with medications, and systematic evaluations in adults are not positive. With a highly intense physical and occupational therapy (PT/OT) program and psychological counseling, we have had both short- and long-term success treating children with complicated regional pain syndrome. This approach has been copied by others. Children with this type of amplified pain are also treated in our program, and we have previously researched them. Complex regional pain syndrome is a separate pain diagnosis. Additionally, we have observed outstanding short-term functional outcomes in a small sample of fibromyalgia-affected kids who underwent sleep investigations before and after taking part in the rigorous PT/OT program [14].

Prevalence of JFM

FM affects adults in roughly 2% of cases. Women are more likely to have it (3.4%) than men (0.5%). The typical age of diagnosis is between 40 and 50 years for adults, and between 13 and 15 years for kids and teenagers. The reported prevalence of JFMS varies significantly, most likely due to variances in racial or ethnic origin, sociocultural factors, psychological characteristics of the population, and study techniques [15].

The frequency of JFMS recorded in various nations is as follows: Baseline prevalence rates for Israel were 6.2%, Mexico was 1.2%, and Finland was 1.3%. The projected frequency in the USA was 0.5 to 1% for 0 to 4 years, 1 to 1.4% for 5 to 9 years, 2 to 2.6% for 10 to 14 years, and 3.5 to 6.2% for 15 to 19 years, and Egypt was 1.2%. JPMS is more prevalent in girls and affects kids of all ages, with a frequency of about 1-6% [15].

Pathophysiology of FM

According to the most recent research, central sensitization of the central nervous system (CNS) a process that results from a genetic susceptibility and numerous external stressors is what causes FM [16]. Hyper-excitability of the central nociceptive circuits is brought on by activity-dependent

alterations in synaptic transmission, and this is a complicated phenomenon known as central sensitization. Because of this increased sensitization, even harmless non-nociceptive stimuli are perceived as painful, and the perception of noxious stimuli is exaggerated, prolonged, and widespread. This increased sensitization involves changes in receptors, neurotransmitters, ion channels, and signaling pathways in the central nervous system. A propensity for sensitization of peripheral and/or central nociceptive information, which is frequently observed in adults with FM, was shown in adolescents with FM to be more sensitive to pressure pain than their healthy counterparts. Inability to maintain stage 4 sleep, aberrant neurotransmitters, malfunction of the hypothalamic-pituitary-adrenal axis, and peripheral sensitization are other problems linked to FM [17].

They claim that in these patients, acute pain appears to engage the somatosensory, insular, and cingulate cortices, but chronic pain appears to preferentially stimulate the prefrontal and limbic cortices. The anatomy of people with various chronic pain syndromes has also been reported, including regional decreases in grey matter density, volume, or thickness in parts of the brain other than the nociceptive regions. Changes in anatomical and functional connections are probably a result of ongoing pain [18]. Effectively managing chronic pain can undo these anatomical and functional anomalies and return human brain function to normal [19].

A hereditary tendency may exist, according to family studies, since up to 25% of FM patients' relatives report having persistent, widespread pain [20]. Certain genes, such as the SS genotype polymorphism in the promoter region of the serotonin transporter gene (5- HTT) and the LL and LH genotype polymorphisms in the gene encoding the COMT (catechol-Omethyltransferase) enzyme, have been linked to fibromyalgia through a genetic predisposition [21].

Furthermore, the pathophysiology of FM may be significantly influenced by inflammatory mechanisms. Antinuclear antibody (ANA) positivity is seen in a subset of FM patients who also have constitutional symptoms resembling early lupus patients. Therefore, under some circumstances, FM might be a precursor to an autoimmune illness. Some research has attempted to show that people with FM have hormonal anomalies, however not specifically in young patients. While some studies suggest that a strong central sensitization component lies at the core of the disease, the pathophysiology of FM is yet unknown. It indicates that the pathophysiology of this condition involves the musculoskeletal system, neuroendocrine system, and central nervous system significantly [15].

Clinical manifestations

Widespread musculoskeletal pain with a typically extremely high subjective severity score is the defining sign of JPFS [22]. Pain has a detrimental impact on adolescent health and is linked to functional impairment, which frequently causes avoidance of routine daily tasks [23], school absences [24], and poor social functioning [25]. Research of 7753 patients registered in a worldwide registry revealed that the degree of pain, as well as measures of function and well-being, was considerably worse in children with JPFS when compared to those with other pediatric rheumatic disorders. Males had a statistically significant larger functional impairment [22].

Another typical JPFS symptom is sleep difficulties, which include generalized exhaustion, poor sleep, and feeling exhausted and un-refreshed when you get up in the morning [26]. In a study [22] of 201 JPFS patients registered in a multi-site patient registry, 84 and 82% of patients, respectively, experienced tiredness and disrupted sleep. Sleep issues may significantly lower the quality of life for FM sufferers. ***Reid et al.*** [27] discovered a link between sleep disorders and elevated functional impairment in kids with JPFS.

Prognosis of JFM

With some research suggesting a favorable prognosis and more recent data demonstrating that fibromyalgia symptoms among teenagers typically remain into adulthood, the prognosis for JFM appears to be very diverse. Although short-term symptom reduction has been shown with physical therapy, exercise-based treatment, and cognitive behavioral therapy, their long-term benefits on prognosis remain unknown. Currently, a significant experiment is being conducted to examine the interaction of various modalities [28].

Early research suggested a largely favorable long-term outlook for JFM, with 70% of kids no longer fulfilling the criterion after two years. These estimates, however, were based on studies conducted in the community on school-aged children who were not seeking treatment and may not have had symptoms severe enough to warrant seeking medical attention [29]. Studies of clinical populations (i.e., patients with JFM recruited from hospital settings) suggest a chronic and perhaps changing course, with the majority of young persons with JFM (70%) still experiencing symptoms. At a follow-up of 4 years,

controlled research of patients with JFM and matched healthy controls revealed that around 50% of JFM patients satisfied the complete ACR criteria for fibromyalgia and that >70% had persistent symptoms of pain, tiredness, or sleep problems. The JFM group significantly outperformed controls in terms of pain levels, quality of life, and anxiety and depression symptoms, indicating that JFM has a long-lasting and significant impact [30].

The diagnosis and evaluation of JPFS

JPFS is diagnosed clinically, based on a complete history, physical examination, and neurological evaluation. There shouldn't be any positive neurological indicators, such as a change in tonus, strength, or sensory perception, other than possibly sensitive areas or enhanced pain susceptibility to touch. Prior to receiving their final diagnosis, patients with JPFS frequently have evaluations by their main pediatrician and other experts. This is due to the under-recognition of JPFS by medical professionals, which can cause diagnosis delays of up to 5 years and a delay in appropriate treatment, all of which worsen the effects of the disease on patients' life (mood, functioning, academic accomplishment, etc.) [31].

Lack of acknowledgment of JPFS also drives up medical expenses for patients, their families, and the healthcare system since it necessitates more doctor visits, drugs, and diagnostic procedures. The range of functional pain syndromes, often known as central sensitivity syndromes, includes JPFS. Since JPFS symptoms typically coincide with those of other functional pain syndromes, such as irritable bowel syndrome, chronic fatigue syndrome, temporomandibular joint dysfunction, myofascial pain syndromes, premenstrual syndrome, tension-type headaches, mood and anxiety problems, JPFS is a condition that affects the myofascial system. It's important to evaluate and rule out any further medical issues. An illustration is Familial Mediterranean Fever, which can manifest as painful legs after effort [32].

A comprehensive history is crucial because the diagnosis of JPFS is clinical. The history should include information on the characteristics of pain, which often show extensive musculoskeletal discomfort with high subjective pain intensity. It is important to map the existence and severity of other symptoms, such as sleep issues, psychiatric comorbidities, and other bodily manifestations. It is important to evaluate the degree of functional impairment, which includes school absences, avoidance of routine daily tasks, and peer connections. There should be analysis of well-being indicators. Due to their significance in therapy, it is essential to incorporate information on the child's family, social, and academic settings in the first assessment [32].

Children with FM may have numerous TP and occasionally show signs of JH, but their physical examinations are otherwise uninteresting and show no signs of arthritis or other pathological abnormalities [33]. When compared to their healthy contemporaries, adult and pediatric FM patients have more than one TP, which indicates a generalized sensitivity to pain [32]. The average number of TP in a study [34] of 47 female adolescents with JPFS was 11, vs. an average of 2-3 in healthy controls. TP may be lower in children with FM than in adults. Children and teenagers with FM were found to have a mean of 9.7 TPs added together throughout all visits, which is lower than the standard of 11 for adults at one visit. It is debatable whether the manual TP examination should be used as a diagnostic standard because it is commonly carried out improperly. The amount of pressure used, the degree of subjectivity, and lack of consistency over time and amongst examiners are all inconsistent. Men are less likely to benefit from it as well since they often tolerate less intense pressure-related pain [32].

The diagnosis of JPFS is frequently relatively evident following a thorough history and physical examination, with no additional testing. Blood-work and imaging, on the other hand, are frequently assessed when the diagnosis is ambiguous or when a different pain diagnosis is suspected. A complete blood count, blood chemistry, C-reactive protein, erythrocyte sedimentation rate, and creatinine kinase are among the standard laboratory examinations. Antinuclear antibody (ANA) testing should be done if anamnesis points to systemic constitutional symptoms like lupus. While some FM patients have a low positive ANA titer, the majority of FM patients have normal test results. However, as there is no clinical indication of an inflammatory or autoimmune illness, this is insignificant and only occurs accidentally in around 5% of the general population. Imaging tests are often normal, but if immobilization is extended, disuse osteoporosis may be present [32].

Clinical measures of JFM

The main basis for assessing symptoms, such as pain, exhaustion, sleep, functioning, and quality of life, is patient reporting [35]. Functional Disability Inventory, Modified Fibromyalgia Impact Questionnaire

Child Version, and Pediatric Quality of Life are among the tools that may be used to evaluate FM in young people (3.0) Pain and Hurt Scale from the Rheumatology Module [36].

Diagnostic criteria of JMF

There is not much literature describing JFM diagnostic standards. The ***Yunus and Masi*** criterion, which was initially published in 1985 and is still frequently used today, served as the first diagnostic standard for fibromyalgia in children [3]. More recently, the 2010 Adult Fibromyalgia Criteria of the American College of Rheumatology (ACR) were assessed for use in female pediatric patients [34].

Both criteria call for symptom-based diagnosis [34]. According to the ***Yunus and Masi*** criteria [3], patients must have generalized musculoskeletal pain at three or more areas, five or more "tender points," and three other minor criteria in order to be diagnosed with JFM; four tender points and five minor criteria are also adequate [3].

Treatment

Enhancing quality of life through pain reduction and better function is the main aim of JPFS therapy. The current gold standard of therapy for JPFS is a multimodal approach integrating behavioral and exercise-based modalities. Exercise should be the first non-pharmacologic modality used in treatment. Cognitive Behavioral Therapy (CBT), movement and meditation therapies, and other non-pharmacologic modalities are also available. Reassurance, which emphasizes that the patient's suffering is not hazardous while yet recognizing that it is genuine, is crucial. The discomfort may endure for an undetermined amount of time, and there is no known instant treatment, but there are therapeutic choices that might lessen the pain over time. It is essential to set objectives for living a complete life, emphasize the significance of lifestyle choices, and address emotional problems [37].

It is possible to establish multidisciplinary programs in an outpatient or inpatient environment. Children with significant pain-related disability were enrolled in a study comparing an intensive day-hospital rehabilitation program of physical, occupational, and psychological therapies to outpatient treatment. The results showed that those in the day-hospital rehabilitation program experienced significantly greater improvements in functional disability, pain-related fear, and readiness to change. Children with JPFS have reported better pain, function, and quality of life in intensive, multidisciplinary outpatient programs [37].

Physical therapy

Physical therapy and exercise are the pillars of every patient with JPFS's treatment. Studies of FM therapy in adults have mostly shown the benefits of exercise, which typically include aerobic training, strength/resistance training, or movement-based treatments like yoga and tai chi. There was a noticeable increase in everyday function and quality of life, as well as a decrease in pain and exhaustion. The American Pain Society recommends at least 30 minutes of moderate-to-vigorous aerobic activity two to three days a week for kids with FM. Despite suggestions for exercise to alleviate juvenile FM discomfort, people with FM have poor long-term exercise adherence. Children with chronic pain are less physically active than their classmates are, according to actigraphy research [37].

Exercise may be linked to greater short-term pain in FM patients due to neurobiological changes. However, if FM patients can get past the short-term pain increases following exercise and avoid the increased fear of movement that prevents them from participating in physical activity, studies suggest that neurobiological changes connected to regular exercise may be able to result in long-term pain reduction. The majority of research on exercise for FM are rather brief. To ascertain if exercise adherence and its advantages can be sustained over time, more research on long-term exercise programs is required. Multidisciplinary pain treatment programs frequently include combined CBT and exercise-based therapies. Despite being successful in helping adolescents with JPFS cope with their everyday lives and manage their pain, CBT did not result in an increase in physical activity on its own, as was demonstrated in a clinical trial via actigraphy monitoring. In order to boost physical therapy, a multidisciplinary strategy integrating CBT and other therapies is advised [37].

Fibromyalgia Integrative Training for Teens, a CBT and neuromuscular training regimen, first showed potential in adolescents with JPFS. Neuromuscular training is a specialized method that tackles biomechanical impairments in gait, posture, balance, and mobility to lower the risk of injury or discomfort in JPFS patients. It is adapted from evidence-based injury prevention protocols in pediatric sports medicine. So, using biomechanical evaluation to establish visible changes in performance following such an intervention may be done objectively [38].

Psychological therapy

The most effective evidence-based therapy options for JPFS are psychological treatments, most notably CBT. They are advised as a crucial component of the multidisciplinary therapy strategy. Short-term, goal-oriented treatment using CBT approaches emphasizes altering thought and behavior patterns. It has been discovered that CBT helps teenagers with JPFS manage with pain better and experience less functional impairment. Programs for treating chronic pain frequently include a rehabilitative strategy. With the idea that pain reduction will follow, the first focus is on reducing pain-related impairment. In contrast to pain relief following CBT, research that tested this concept in young people with chronic pain showed a large, quick improvement in functional impairment in functional impairment [37].

Pharmacological treatment

JPFS should be managed with a focus on non-pharmacological methods, while judicious pharmaceutical usage may be taken into consideration for symptom control. **Non-opioid analgesics and anti-inflammatory medications:** FM has been treated with topical analgesics as well as oral over-the-counter analgesics including paracetamol and non-steroidal anti-inflammatory medications, but these are ineffective, because they operate peripherally, whereas FM's underlying pain mechanism is centrally mediated. Adult FM has not been successfully treated with prednisone [39]. **Anticonvulsants:** Although gabapentinoids were initially recommended for treating epilepsy, they are now often used to treat chronic pain. Pregabalin and gabapentin have both shown to be effective and tolerable in treating adult FM, according to studies. Pregabalin has FDA approval for the treatment of adult FM, and it is advised in adult FM treatment recommendations [37]. Few studies have been done to determine if gabapentin and pregabalin are safe and effective for relieving pain in young children and adolescents [40]. **Anti-depressants:** There are three primary kinds of anti-depressants used to treat FM in adults, but there is little evidence to support their use in children. These include **SNRIs** (serotonin-norepinephrine reuptake inhibitors), which the FDA has licensed for use in treating adult FM but which the European Medical Agencies have not. There are little statistics on the pediatric population. **SSRIs**, there is fewer solid data supporting the efficacy of SSRIs like fluoxetine and paroxetine in treating FM in adults. Only modest dosages of the medicine were tolerated in an open-label, exploratory study of fluoxetine in juvenile FM, which raises the possibility that kids are more sensitive to side effects. **Tricyclic antidepressants,** FM is treated with tricyclic antidepressants like amitriptyline. Antidepressants are effective in treating concurrent mental problems, such as anxiety and depression, which are frequent in children with FM, even though there is no evidence to support their use in the treatment of JPFS. Consider carefully the black box warning for increased suicidal inclination in young people with serious depressive illness using SSRIs. **Acupuncture:** A multimodal treatment plan that includes acupuncture may be clinically beneficial for pediatric children with chronic pain disorders. Acupuncture might be a helpful adjuvant in the care of these kids [37].

4. Conclusion

JFMS is distinguished by the appearance of several identifiable sensitive sites on physical examination, as well as chronic generalized musculoskeletal discomfort, sleep problems, and exhaustion. Despite the fact that the pathophysiology of it is not fully known, it is presently thought to be caused by a dysfunction of the central nervous system (CNS) that intensifies pain transmission and perception. According to current recommendations, the diagnosis is still clinical, and the goal of the physical exam and the few laboratory tests is to rule out any other somatic diseases that may adequately explain the symptoms. The current gold standard of therapy for JFMS is a multidisciplinary strategy that combines pharmacological, behavioral, and exercise-based approaches.

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