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Juvenile Idiopathic Arthritis: Diagnosis and Treatment Options

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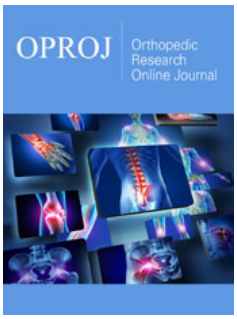

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Summary

Background: Juvenile Idiopathic Arthritis (JIA) is a prevalent pediatric rheumatological disorder characterized by inflammatory joint disease lasting over six weeks in children under sixteen years of age. Early intervention with disease-modifying anti-rheumatic medications and biologic response modifiers can alter the disease's natural course and reduce the risk of joint and ocular damage.

Methods: A comprehensive review of the literature from 2005 to 2023 was conducted using PubMed/MEDLINE and Google Scholar. The search focused on recent articles, including retrospective cohort studies, observational studies, systematic reviews, comparative studies, case reports, randomized controlled trials, and clinical trials related to JIA.

Results: JIA comprises various subtypes, each with distinct clinical features and diagnostic criteria. These include oligoarticular JIA, polyarticular JIA, systemic JIA, enthesitis-related JIA, psoriatic JIA, and undifferentiated JIA. The etiology of JIA is multifactorial, involving genetic, environmental, and immunological factors. Genetic predisposition, such as specific HLA alleles, may increase the risk. Environmental factors, including infections and exposure to toxins, can trigger or exacerbate JIA. Immunological dysregulation, with elevated proinflammatory cytokines like TNF-α, IL-6, and IL-1, plays a central role. Pharmacological treatment options for JIA encompass nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, disease-modifying antirheumatic drugs (DMARDs), and biologic agents. NSAIDs are used primarily for symptomatic relief, while DMARDs, notably methotrexate, are mainstays of treatment. Biologic agents like TNF inhibitors, IL-1, and IL-6 inhibitors have revolutionized JIA management. Physical activity and exercise can help alleviate inflammation, and some surgical interventions, including joint replacements, may be necessary in advanced cases. Dietary interventions, such as omega-3 supplements and diets rich in fruits and vegetables, may offer additional benefits. Psychological therapy can contribute to pain management and overall well-being in children with JIA.

Conclusion: JIA is a multifaceted disease with varying subtypes and complex etiology. Early diagnosis and tailored treatment plans, including NSAIDs, DMARDs, and biologic agents, can effectively manage the condition. Complementary approaches, such as exercise, surgery, dietary modifications, and psychological interventions, may further enhance the quality of life for JIA patients. Continued research is essential to deepen our understanding of JIA's pathophysiology and refine treatment strategies.

Introduction

Juvenile Idiopathic Arthritis (JIA) stands as the most prevalent rheumatic condition in pediatric patients [1-5]. It can be defined as an inflammatory joint disorder that persists for more than six weeks in children under the age of sixteen after excluding all other possible causes

of arthritis [1]. Research has consistently shown that in the initial stages of the disease, there exists a critical "window of opportunity" during which timely treatment can significantly influence the natural progression of the condition [2,3]. The early application of medical interventions, including disease-modifying anti-rheumatic drugs and biologic response modifiers, has substantially reduced the risk of both joint and ocular complications [4,5].

Materials & Methods

In April 2023, electronic databases including PubMed/MEDLINE and Google Scholar were utilized to conduct a comprehensive literature search. The primary focus was on articles published within the timeframe from 2005 to 2023, with particular emphasis on the most recent publications spanning from 2015 to 2023. The scope of the search encompassed studies conducted in the English language and included various research methodologies such as retrospective cohort studies, observational studies, systematic reviews, comparative studies, case reports, randomized controlled trials, and clinical trials.

Types of JIA

Juvenile idiopathic arthritis (JIA) is the most common chronic rheumatic disease that affects children and adolescents [2,3]. JIA encompasses different types, each with its own distinct symptoms and diagnostic criteria. Oligoarticular JIA occurs when there are fewer than four joints in the first six months of the disease and primarily affects girls younger than six years old [2]. The age of onset of oligoarticular JIA peaks between 2 - 4 years old [4]. Polyarticular JIA, on the other hand, involves inflammation in five or more joints in the first six months of the disease [2]. The age at onset of polyarticular JIA has a biphasic pattern, with peaks occurring between 1-4 years old and 612 years old [4]. Systemic JIA induces widespread inflammation throughout the body, and this often encompasses high fever, skin rash and other systemic symptoms [5]. Children with systemic JIA usually have two weeks of spiking fever, and the child appears ill until the fever breaks [3]. Enthesitis-related JIA results in inflammation in places where tendons and ligaments attach to bones [2]. Enthesitis-related JIA typically affects boys aged eight years or older. The clues to diagnosis include gastrointestinal symptoms, weight loss or growth failure [3]. Psoriatic JIA affects children who have psoriasis, a family history of psoriasis, and show other symptoms such as either dactylitis or onycholysis [2]. Lastly, undifferentiated JIA is diagnosed when symptoms do not align into any other subtype [2].

Etiology

Juvenile Idiopathic Arthritis (JIA) is generally considered an autoimmune disorder, wherein the body's immune system erroneously launches attacks on its own tissues [2]. While the precise origins of JIA remain elusive, various potential causative factors have been identified. Genetic elements do play a significant role, and specific genetic mutations can elevate the likelihood of developing this condition [3]. Although a single gene has not been identified as the sole instigator, certain HLA class I and class II alleles, including HLA-A2, HLA-B27, HLA-A2, DR5, and DR8, have been linked to an increased risk of JIA [1]. Environmental factors also contribute, as viral infections and exposure to substances like cigarette smoke may serve as potential triggers for JIA in certain children [6]. Furthermore, it is believed that the immune system assumes a central role, mistakenly targeting healthy cells and tissues in some individuals with JIA [1]. In essence, JIA is likely the outcome of a multifaceted interplay of genetic, environmental, and immunological factors, necessitating further research to enhance our comprehension and formulate more effective treatment strategies [1-3,6].

Pharmacological treatment of JIA

Currently, pharmacological treatment of JIA includes nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, disease-modifying antirheumatic drugs (DMARDS), and biologic agents [7]. As JIA is an umbrella term representing various distinct categories, the choice of treatment is individualized and depends on the child's age, severity of disease, and the subtype of JIA [7]. The treatment principles of successful JIA management include prompt diagnosis, early recognition of active disease, reduction of joint damage, and control of inflammation [8]. In this review, the traditional as well as conventional pharmacological options of JIA will be discussed and explored.

Non-steroidal Anti-inflammatory Drugs (NSAIDs): NSAIDs and corticosteroids were once the mainstay of treatment for JIA but are now used as adjunctive therapies alongside conventional options such as DMARDS and biologics [7]. NSAIDs are non-disease modifying and only a few NSAIDs (naproxen, ibuprofen, and indomethacin) are approved for use in children [9]. Recent guidelines discourage the use of NSAIDs as monotherapy for more than two months as the benefit to side effect ratio of NSAIDs, gastritis and tubulointerstitial nephritis, is rather low in comparison to conventional therapies [10]. However, NSAIDs are conditionally recommended as part of initial therapy for active oligoarticular JIA for ease discomfort and as initial monotherapy for systemic JIA without Macrophage Activation Syndrome (MAS) [11]. Studies associate a small sample of patients with systemic JIA without MAS responding to NSAIDs alone [11]. Overall, NSAIDs are commonly prescribed as initial therapy as the diagnosis of other etiologies are excluded [8].

Oral Corticosteroids (CS) and Intra-articular Corticosteroids (IACSs): While oral corticosteroids were once the primary treatment for JIA, they should no longer be the initial choice and, if used, should be prescribed at the lowest effective dose for the shortest possible duration due to their impact on bone growth and overall health [8]. In cases of severe polyarthritis or while awaiting the full effects of a second-line or biologic agent, a brief course of oral corticosteroids may be necessary [9]. Intra-articular corticosteroid injections (IACSs) can be a preferable option for patients with a limited number of affected joints to minimize systemic side effects [8]. Patients receiving injections of triamcinolone hexacetonide, for example,

have shown clinical improvements in arthritis for at least four months and are recommended before considering more systemic therapies like DMARDs or biologics [10]. Additionally, IACSs can be used in conjunction with DMARDs or biologics as an adjunctive treatment [8].

Conventional Disease-Modifying Antirheumatic drugs (DMARDs): Methotrexate (MTX) is the most widely used conventional DMARD alongside Sulfasalazine (SSZ), leflunomide, and hydroxychloroquine [7]. MTX is the preferred agent for patients with poor response to NSAIDs, oral CS, and/or IACSs for oligoarticular arthritis and TMJ arthritis [11]. However, in patients with systemic JIA with/without MAS, the use of biologic DMARDs, specifically IL-1 and IL-6 inhibitors, is strongly recommended over a single or combination of conventional DMARDs [11]. A concern especially with MTX is the gastrointestinal tract side effects and monitoring blood counts and liver function tests [7].

Biologics: In patients who are intolerant to ICASs or DMARDs, biologics are indicated [7]. The commonly used biologic therapies currently available for treatment for JIA include the tumor necrosis factor inhibitors (TNFi) etanercept, adalimumab, infliximab, Interleukin-1 (IL-1), Interleukin-6 (IL-6), and Abatcept (a soluble human fusion protein) [7]. In cases of oligoarticular JIA and TMJ arthritis where there is an insufficient response to or intolerance of NSAIDs and/or IACs, it is highly advisable to consider biologic DMARDs as part of the treatment plan, provided that at least one conventional DMARD has been tried [11]. The choice of a specific biologic agent should be based on the healthcare provider's judgment and individual circumstances, as there is no universally preferred biologic option [7,11]. However, it's worth noting that TNFi agents are the most frequently utilized among them [11]. Biologic DMARDs, specifically IL-1 and IL-6 inhibitors, are extremely effective and recommended as initial monotherapy for systemic JIA with and without MAS [11]. Biologics may be combined with oral CS or calcineurin inhibitors to control MAS in some patients [11]. TNF inhibitors are more effective if administered early in the disease course and in combination with methotrexate and/or oral corticosteroids [9]. Infliximab, a chimeric TNF-a inhibitor, is associated with a greater frequency of serious adverse events and autoantibodies, therefore it is not approved for use in JIA [9]. Abatacept, a modulator that inhibits the second signal for T-cell activation, was found to be effective in the long-term phase of the trial in patients who were initially not responding to therapy [9]. An IL-6 receptor inhibitor, tocilizumab, was studied in a randomized controlled trial that showed a reduction in disease flare rates 25.6% on tocilizumab in comparison to 48% on placebo [12]. It's worth noting that tocilizumab has been approved for the treatment of polyarticular JIA in children aged two years and older [9]. Known safety concerns regarding biologics are increased risk of infection, malignancy, fatal lung disease, anaphylactic reactions, and cutaneous vasculitis [7]. However, these studies include a relatively low number of subjects and short-duration trials, therefore additional studies focusing on severe side effects associated with biologic use in JIA need to be explored [7]. Overall, the benefit to side effect ratio of biologic agents utilized to treat JIA remains high [7].

Other treatment strategies

In this section, we will give an overview of the available evidence supporting physical activity, surgical interventions, psychological therapy, and dietary alternatives to increase the quality of life in patients with JIA.

The influence of exercise on inflammation is closely tied to the activity of IL-6 [13]. Following physical activity, IL-6 promotes the creation of an anti-inflammatory environment within a relatively short span, which stands in contrast to the behavior of TNF-a and NFkB [13]. In response to acute exercise, the levels of plasma IL-6 gradually rise over time, peaking at the conclusion of the exercise and then subsiding to the pre-exercise baseline [13]. However, it's important to note a negative correlation between the extent of regular physical activity and basal plasma IL-6 levels [13].

In forthcoming research endeavors, it is imperative to investigate the immediate and long-term impacts of physical activity on JIA. In a meta-analysis conducted by Kuntze et al., various types of exercises and their effects on the health status and physical function of juvenile arthritis patients were evaluated using the CHAQ, which has demonstrated sensitivity in measuring changes in juvenile arthritis [14]. The findings from this analysis suggest that supervised pilates, home exercises, and aquatic exercises led to significant enhancements in CHAQ scores. These exercise modalities capitalize on strength, flexibility, and balance, whereas aerobic exercise did not yield substantial improvements in CHAQ scores [14]. Moreover, studies have reported improved CHAQ scores in patients who attended a greater number of supervised training sessions [14].

Despite the success in treatment and physical therapy, some of the patients develop advanced, uncontrollable arthritis that can result in severe pain and disability that may warrant surgical management [15]. Surgical approaches to irreversible joint contractures, dislocations, or joint replacements may be indicated, although the role of orthopedic surgery in JIA is much more limited than in the past [9]. Minor operations such as corrective osteotomies, arthroscopic synovectomies, soft tissue release are considered first while total joint replacement is the last option for patients [15].

Arthroscopic synovectomy may prolong the duration of remission in a frequently relapsing joint [9]. Total knee arthroplasty has been a successful operation for treating end-stage arthritis [15]. It has also demonstrated survival rates of almost 95% at 10 years and just below 90% at 20 years [15]. Despite higher complication rates, patients undergoing total hip arthroplasty displayed a survival rate ranging between 96% to 100% for the femoral stem [15]. Upper limb, ankle, and spine involvement occurs less often, and literature is limited [15].

Considering that inflammatory cytokines such as IL-1 and TNF-a play an important role in the pathogenesis and progression of JIA, dietary alternatives may provide potential benefits [16,17]. A study evaluated the effect of omega-3 fatty acid supplements (2g/day for 12 weeks) on clinical manifestations, laboratory values, and disease activity in JIA patients showed reduced inflammatory response and improved clinical manifestation in patients with JIA when compared with controls [17]. The addition of omega-3 fatty acids may decrease patient daily intake of nonsteroidal anti-inflammatory drugs suggesting its use as an add-on therapy to conventional JIA treatment [17].

Consuming a diet high in fruits and vegetables offers many benefits as this can help improve intake of vitamin C and bioactive compounds that exert antioxidant and anti-inflammatory activity [17]. There is an inverse association between C-reactive protein and other inflammatory markers and increased concentrations of antioxidants and anti-inflammatory compounds [17]. In a study evaluating the efficacy and safety of blueberry and etanercept in 201 JIA patients, it showed a significant reduction in inflammatory IL-1 levels [18]. It is pivotal to highlight that fruits and vegetables can reduce the severity of JIA and should be added to JIA therapy [18].

Psychological interventions may contribute to diminishing pain complaints and improve well-being in children with JIA [19]. The intervention in this study involved a CBT program focusing on psycho-educating children and parents on pain restructuring and management and to gradually confront pain [19]. The study showed that CBT in patients with JIA found no difference in either pain or quality of life [16]. Participation in peer group activities, sporting activities, and regular attendance at school should be encouraged in order to foster a positive psychosocial and social development of the child [9].

Pathophysiology

Although the exact pathogenesis surrounding JIA is not fully known, genetic, environmental, and autoimmune factors are thought to be involved in the development of this disease [20]. Factors which have been suggested to have a protective effect against the development of JIA include practices such as breastfeeding and obtaining vitamin D and sun exposure [20]. On the other hand, factors such as the *IL2RA/CD25* and *VTCN1* genes, maternal smoking, and infections are thought to increase the likelihood of developing or exacerbating JIA [20]. With regard to infections, for many years, infections have been suspected as being triggers for the development of autoimmune diseases, including JIA [1]. However, studies that have shown a potential link between parvovirus B19 or Epstein-Barr virus and JIA have only been retrospective, and, while there has been wide debate about the role of enteric bacteria, *Chlamydophila pneumoniae*, and streptococcal infections in the development and exacerbation of JIA, results have been inconclusive [1]. Preliminary results have shown the tendency of total serum IgE levels to be increased in patients with JIA of the oligopoly articular subtype and especially in those seropositive for *M. pneumoniae* [21]. Further research is needed to find evidence that either demonstrates or disproves the association of JIA with these infectious agents [1]. On a related topic to infections, antibiotic exposure early in life - specifically during the periods of 1-12 months, 1-3 years, and 5-8 years was significantly associated with increased risk for JIA [22].

The best described pathogenesis of JIA is the cell-mediated release of proinflammatory cytokines, such as tumor necrosis factor-alpha (TNF-α), interleukin (IL)-6, and IL-1 secondary to T-cell activation as evidenced by radiographic models which show a higher percentage of activated T cells in the synovium of patients with JIA as well as diagnostic tests that show higher levels of TNF-α, IL-6, and IL-1 specifically in patients with the polyarticular and systemic JIA subtypes [20]. In addition, aberrant microRNA (miRNA) levels have been observed in patients with JIA [23,24]. Recent studies point toward the potential of certain miRNAs to be used as diagnostic biomarkers as well as provide information regarding the activity and progression of this disease [25].

Diagnosis

Juvenile Idiopathic Arthritis (JIA) is the most common childhood rheumatic disease with a diagnostic criteria requiring symptom development prior to the age of sixteen and episodes of chronic inflammatory arthritis persisting for a minimum of six weeks [25,26]. JIA is diagnosed by a thorough history and physical examination with lab tests and imaging studies confirming the initial suspicion [27]. Seeing that JIA is derived from the intricate interplay of genetic elements and environmental influences, medical history will focus on specific factors such as age of symptom onset, gender, living conditions, and known familial conditions [27].

Females have a higher predisposition to JIA [28,25] and although inheritance is thought to be sporadic, individuals with affected siblings are twelve times more likely to develop JIA than general society [29]. In a study analyzing data extracted from a Norwegian Population, Human Leukocyte Antigen (HLA) testing has shown DR8 allotype as an associated risk factor for JIA [30]. Specifically, early-onset oligoarticular JIA is most distinct to HLA-DR8, HLA-DR11, HLA-DR13, and HLA-DPw2, with active Epstein-Barr virus (EBV) infections further heightening the risk due to protein sequence similarities to said HLA types [31,32]. Despite variable sensitivity, HLA-B27 has demonstrated a genetic risk factor for the enthesitis-related form of JIA where inflammatory processes affect tendon-ligament connection points [27]. Prior bacterial infections with *Shigella flexneri, Salmonella Typhimurium, Salmonella Enteritidis, Yersinia enterocolitica, Campylobacter jejuni* correlate with HLA-B27 autoimmunity for reactive arthritis [30]. Notably, HLA-B27 delays JIA onset and increases the likelihood of various forms of JIA in males later in life [32]. Polyarticular RF-negative JIA is linked with HLA-DPw3 while systemic JIA is connected with HLA-DRB1*11, MHC class II variants, and HLA-DR4 (Northern European region) [32]. Rheumatoid Factor (RF) and Anti-Cyclic Citrullinated Peptide (CCP) autoantibodies rarely manifest in children diagnosed with JIA [27]. History of trauma, exposure to elevated stress, and

vitamin D deficiency also contribute to the etiology of JIA [25,31]. Laboratory tests will frequently depict elevated Erythrocyte Sedimentation Rate (ESR) and C-Reactive Protein (CRP), indicating inflammation [27]. Although Antinuclear Antibodies (ANAs) are highly sensitive for other autoimmune conditions like SLE (>95% positive), ANA has a reported incidence of positivity in 4 - 88% of JIA cases [32,32]. Due to the broad nature of ANA testing results in JIA populations, ANA is not used to diagnose or predict JIA development [33]. However, ANA positivity is more common in early-onset JIA females and can be used as a prognostic value indicating one's risk for chronic anterior uveitis [33].

X-ray and Magnetic Resonance Imaging (MRI) provide details on JIA inflammatory involvement in bones, cartilage, and joints [27,34]. Imaging is most useful for the detection and observation of JIA bony degenerative disorders [35]. Potential radiologic findings may include periarticular soft tissue swelling, demineralization, joint space narrowing, erosion, geodes, and/or Joint malalignments [35]. As noted in a systematic review regarding the appearance of JIA involving the Temporomandibular Joint (TMJ), MRI will show acute changes in synovial membrane enhancement, articular disc deformities, and condylar head erosion with flattening [25]. The JIA-affected TMJ joints will also display osteophytes described as enlarged bony growths with sclerotic edges and exophytic protrusions originating from the condylar surface [25,34]. In another study analyzing 2223 JIA patients, 15% of patients displayed hip inflammation and arthritis, carrying both poor prognosis and high risk of disability [36]. Therefore, imaging results are important indicators of JIA progression [36].

Prognosis

The prognosis of JIA has been trending upward due to the development of biologic therapies, such as TNF, IL-1, and IL-6 inhibitors [37]. These studies suggest an important predictor of a positive prognosis is outlined by a "window of opportunity" for diagnosis and treatment that may improve remission rates and long-term outcomes [38]. This theory is based on a biphasic model of JIA in which early and late JIA may be differentiated by their core immunological mechanism [39]. This window is thought to vary based on characteristics and severity of the disease [7].

Due to these newer biologic treatments, complications have been minimized [7,11]. Patients are less frequently requiring surgical intervention; however, long-term problems may still result [40]. Complications include leg-length discrepancy, joint contracture, macrophage activation syndrome, and other less common complications, such as growth retardation, bone mineral insufficiency, and amyloidosis [38].

Discussion

Extensive research has revealed that JIA is a multifaceted autoimmune condition with a significant impact on the quality of life in pediatric patients [1,7,20,27]. A comprehensive understanding of JIA, encompassing its various subtypes like oligoarticular JIA, polyarticular JIA, systemic JIA, enthesitis-related JIA, and psoriatic JIA, is crucial [2-4]. The treatment landscape for JIA has evolved, with an increasing preference among healthcare providers for DMARDs, such as methotrexate, over the solitary use of NSAIDs or corticosteroids [7]. Surgical interventions are considered only in severe cases marked by irreversible complications, such as uncontrolled arthritis [9,15].

Moreover, the introduction of biologics, particularly TNF inhibitors, has brought about a paradigm shift in the management of JIA, particularly when administered proactively or in combination with other therapeutic modalities [7,11]. As mentioned earlier, JIA arises from a complex interplay of genetic, environmental, and immunological factors [20]. Consequently, factors like dietary considerations, omega-3 supplementation, psychological interventions, and specific exercise regimens hold promises as complementary treatments to mitigate pain and enhance the overall well-being of children grappling with JIA [16-19]. A holistic approach that integrates all these strategies is essential for providing comprehensive care and formulating personalized treatment plans that cater to the distinct needs of individual patients [7-15].

Vigilant attention to a patient's medical history, physical examination findings, laboratory results, and imaging studies can expedite the diagnostic process, thereby minimizing the risk of future complications [4,5,9,33]. The timely diagnosis and intervention are pivotal for optimizing the chances of achieving remission and elevating the quality of life for individuals living with JIA [9,38].

Conclusion

This comprehensive meta-review provides a thorough overview of the intricate clinical features and diverse subtypes of JIA, along with the transformative advancements in treatment strategies for this condition. The introduction of DMARDs and biologics has significantly improved the management of JIA, offering enhanced symptom control and superior long-term outcomes. Additionally, the meta-review underscores the importance of complementary interventions, including physical activity, surgical procedures, psychological therapy, and dietary modifications, in enhancing the overall quality of life for individuals with JIA. Nonetheless, it is essential to acknowledge the inherent limitations of a meta-review study. While it synthesizes existing research, there remains a compelling need for large-scale randomized trials to delve deeper into the underlying causes of JIA and to further refine the therapeutic approaches for this complex condition. These endeavors have the potential to yield more effective and personalized treatment strategies, ultimately resulting in improved clinical outcomes for JIA patients. The findings of this study pave the way for future investigations in this relatively less-explored realm of JIA etiology and management, promising valuable insights and advancements in the field.

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