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Systematic Review

A systematic study on the elevated risk of ankylosing spondylitis in adolescents engaged in intense physical exercise

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ABSTRACT

This study investigates the link between intense physical activity during adolescence and the onset of ankylosing spondylitis (AS), particularly in individuals having the human leukocyte antigen (HLA)-B27 antigen, a known genetic marker for AS. The systematic literature review included studies published between 2014 and 2024. . Keywords and search terms included combinations of "ankylosing spondylitis," "HLA-B27," "adolescence," "intense physical exercise," and "genetic predisposition. Inclusion criteria focused on studies involving adolescents aged 15-24 years with genetic predispositions such as HLA-B27. Exclusion criteria included studies with unrelated outcomes such as individuals not within the target adolescent age range, non-peer-reviewed articles, and those with insufficient data on the target population. Findings revealed that adolescents with the HLA-B27 antigen who engaged in heavy weight exercise were at a heightened threat of developing AS. The mechanical stress from intense physical activity potentially triggered or exacerbated inflammation at entheses in genetically predisposed individuals. However, the onset of AS was not universally observed in all HLA-B27 positive individuals who participated in strenuous exercise, suggesting other genetic and environmental factors' involvement. The study suggests that strenuous exercise during adolescence may act as a significant contributing factor to the onset of AS in individuals having a genetic predisposition such as HLA-B27. While not all individuals having HLA-B27 develop AS, genetic and environmental factors' combination, including intense physical activity, may accelerate disease progression.

Keywords: Ankylosing spondylitis, HLA-B27, Adolescence, Intense physical exercise, Genetic predisposition

INTRODUCTION

Ankylosing spondylitis (AS) is a chronic inflammatory disease primarily distressing the spine and sacroiliac joints, causing pain, and stiffness, and potential fusion of the vertebrae.[1] The term "ankylosing" refers to stiffness, "spondyl" to the spine, and "itis" to inflammation. AS typically begins in late adolescence or early adulthood, presenting with symptoms such as inflammatory back pain and reduced spinal mobility.[2]

AS often manifests in adults under the age of 40, with over 80% of sufferers reporting their first symptoms after reaching the age of 15. Less than 5% of individuals get a diagnosis after reaching the age of 15.[3] Androgenic alopecia is more common in males than females. Furthermore, there is a heightened susceptibility to acquiring AS among family members of those who are afflicted by the condition.[4] The etiology of AS remains mostly elusive. Nevertheless, there seems to be a connection between the frequency of AS and the existence of human leukocyte antigen (HLA)-B27 in a certain community. The prevalence of AS is about 5% to 6% in those who test positive for HLA-B27.[5]

The relevance of the HLA-B27 antigen in AS is well established, as this genetic marker is found in a substantial proportion of patients with the condition. HLA-B27 is a protein that plays a crucial role in the immune system's ability to distinguish between self and non-self. Its

presence is associated with an increased risk of developing AS, making it a key factor in understanding the genetic predisposition to the disease. While not all individuals having HLA-B27 will develop AS, the presence of this antigen is a significant risk factor and helps to guide diagnosis and research into the disease's underlying mechanisms.[6] The primary objectives of this systematic literature study are to explore the potential relationship between strenuous heavy weight exercise during adolescence and the incidence of AS, and to examine the association between the HLA-B27 antigen and AS within this context.

METHODS

This study employed a systematic review and design to investigate the relationship across strenuous exercise includes high velocity or strongly resisted exercises, especially trunk flexion/rotation during adolescence and the incidence of AS, with a particular focus on the association across HLA-B27 and AS in the context of physical activity.

Data collection

Data collection for this study involved a systematic approach to gathering relevant information from multiple sources. Study utilized established databases such as PubMed, Scopus, and the Cochrane Library to identify studies related to AS, HLA-B27, and the impact of strenuous exercise during adolescence. Keywords and search terms included combinations of "ankylosing spondylitis," "HLA-B27," "adolescence," "intense physical exercise," and "genetic predisposition."

Inclusion and exclusion criteria

Inclusion criteria focused on observational studies includes retrospective, cohort studies, random clinical trials and case-control studies that investigated the relationship between intense physical exercise in adolescence and the development of ankylosing spondylitis. Studies published inside the last 10 years from 2014 to 2024 were considered to ensure the inclusion of recent data. The population focused on adolescents aged 15 to 24 years, particularly those with a genetic predisposition to AS, such as the existence of the HLA-B27 antigen. Only studies published in English were included, and the selection was limited to peer-reviewed articles and published studies to warrant the quality and reliability of the data. Exclusion criteria included studies with unrelated outcomes such as individuals not within the target adolescent age range, non-peer-reviewed articles, and those with insufficient data on the target population.

Study selection

Relevant data were extracted systematically from selected studies. The PRISMA diagram (Figure 1) demonstrates the selection process for the investigations included in this review. Initially, 110 records were spotted via database searches and additional sources. Post duplicate removal, 100 records remained for screening, out of which 20 were excluded due to irrelevance to the specific focus on the relationship across strenuous exercise, HLA-B27, and AS. The full text of 70 articles was then assessed for eligibility, resulting in 45 exclusions based on specific criteria. Ultimately, 25 studies were included in the qualitative synthesis, providing the foundation for the analysis and conclusions of this review.

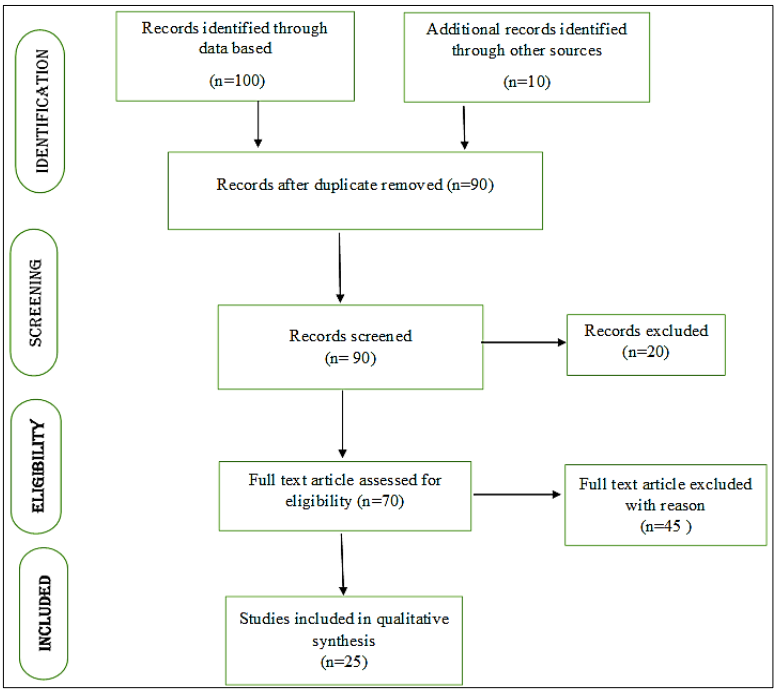

Figure 1: PRISMA diagram for article selection.

RESULTS

Clinical observations

AS is a form of arthritis that primarily affects the lower back and spine, where muscles, and tendons, along with ligaments attach to the bones. In younger individuals, it's known as juvenile AS (JAS), and it is more ubiquitous in boys than girls.[6] Symptoms typically show up between the ages of 17 and 24, with only 10-20% of cases showing signs before age 18.[6] As per the Spondylitis Association of America, AS typically develops between the ages of 17 and 45, with most people experiencing onset between 15 and 21 years old.[7] A 2022 study found that the average age of onset worldwide was 21.[3] Symptoms of adolescent AS vary widely and may include pain in the back, and joints, and buttocks, and thighs, and heels, or even shoulders, as well as morning stiffness and a slouched posture.[8] Enthesitis, or pain where muscles, ligaments, or tendons attach to bone, and swelling of large joints, especially in the legs, are also common.[6] Other symptoms can include eye pain, redness, light sensitivity, loss of appetite, anemia, fatigue, fever, and weight loss.[8]

In patients under age 24 with back pain lasting over three months, certain criteria can help identify AS with high sensitivity and moderate specificity, compared to a rheumatologist's diagnosis. These criteria include inflammatory back pain and peripheral symptoms like arthritis, and dactylitis, or even enthesitis (especially in the Achilles tendon or in plantar fascia), and the presence of psoriasis, and inflammatory bowel disease, or even uveitis. A family history of spondyloarthritis, improvement of back pain within 24-48 hours of nonsteroidal anti-inflammatory drug (NSAID) treatment, elevated C-reactive protein (CRP) levels (after excluding other causes), a positive HLA-B27 test, and sacroiliitis visible on X-ray or even magnetic resonance imaging (MRI) are also key indicators. C-reactive protein (CRP) levels in these patients may range from slightly elevated (over 6 mg/l) to significantly higher (20-30 mg/l).[9]

Risk factors

Risk factors for ankylosing spondylitis in adolescence include a family history of the disease, with those having affected relatives at higher risk. The onset typically occurs between ages 17 and 24, often beginning in the teenage years, earlier than most other forms of arthritis. Males are at least twice as likely as females to develop AS.[12] Heavy weight lifting during adolescence may also be a risk factor, particularly in individuals having a genetic predisposition like the HLA-B27 gene. The strain from intense physical activity could contribute to joint and spinal inflammation, which are the key areas affected by AS. While not all who engage in heavy lifting develop AS, this exertion might trigger or worsen the condition in those genetically susceptible.[13] Additionally, low back pain (LBP) is common in adolescents, with prevalence rates between 30% to 70%. Early onset LBP in adolescence is linked to chronic LBP in adulthood, making it a predictor of future back pain. Growth patterns during puberty, particularly after age 10, may also influence the incidence of back pain, which often originates from the paraspinal muscles rather than the spine itself.[13]

Diagnosis

Diagnosing ankylosing spondylitis in adolescence can be challenging because its symptoms often resemble those of other conditions. The process typically begins with a physical examination and a detailed review of the patient symptoms and medical history. X-rays are commonly used to create images of the spine and pelvis, helping to detect changes associated with AS, although early onset changes may not always be visible.[10] Additional imaging tests, such as MRI, may also be utilized to provide more detailed images, especially when X-rays do not reveal early changes. Blood tests, though not specific for AS, can offer valuable insights. Tests like the erythrocyte sedimentation rate (ESR) measure inflammation in the body, where elevated levels may suggest active disease. HLA-B27 antigen testing checks for a genetic marker associated with autoimmune conditions like JAS, but its presence alone is not definitive for the disease, as it can also be found in healthy individuals.[11]

Strenuous exercise and ankylosing spondylitis

High-impact activities and contact sports should be avoided, as they can strain the joints. It's also important to focus on maintaining good posture during exercises, be mindful of pain levels, start gradually, and consider balance and stability to ensure safe and effective workouts. High-impact and spine-stressing exercises, such as running, tennis, and weightlifting, can exacerbate ankylosing spondylitis symptoms.[14] AS symptoms compared to traditional therapies, while others like Exergame and Swiss ball exercises show no significant difference.[14] Additionally, strenuous exercise in adolescence, particularly in those genetically predisposed, may contribute to the onset of AS by causing joint microtrauma and inflammation. Avoid engaging in activities that involve excessive twisting of the spine or put excessive strain on the back and spine, as they may lead to potential issues. It is advisable to carefully evaluate high-impact workouts like jogging, as well as sports that include jarring and twisting movements, such as tennis, and weightlifting, and squash, along with racquetball. However, the effectiveness of exercise as a treatment for AS varies, and its benefits depend on the type and intensity of the activity, as well as the duration of the disease.

HLA-B27 and ankylosing spondylitis

The association of back pain with a positive HLA-B27 test is significant, particularly in the context of AS and other related forms of axial spondyloarthritis. HLA-B27 is a genetic marker found in a high percentage of individuals

having AS, and its presence increases the likelihood of developing this condition.[19] When a patient, especially a young adult, presents with chronic back pain lasting more than three months, a positive HLA-B27 test can strongly suggest the presence of AS or a related disorder. This back pain is often inflammatory in nature, typically worsening with rest and improving with physical activity. However, it's important to consider not everyone with a positive HLA-B27 will develop AS, and the marker can also be present in individuals having out the disease, making it one of several factors considered in the diagnosis.[20]

Examination of genetic studies on HLA-B27 prevalence in AS patients

HLA-B27 is an antigen found in around 8% of individuals who are in good health. Out of every 20 individuals who have HLA B27, only one will develop ankylosing spondylitis.[15] The percentage rises to 20% if there is an afflicted parent (or other first-degree relative). HLA antigens, a cluster of genes, significantly influence the likelihood of your kid developing a certain illness. The specific HLA antigen linked to JAS is referred to as B27.[16] If your kid has the HLA-B27 gene, they may have an inherent predisposition (higher likelihood) to develop JAS. However, it is crucial to bear in mind that while the majority of individuals having JAS possess HLA-B27, only a small proportion of those with HLA-B27 actually develop JAS.[16] This indicates that your kid may have a positive HLA-B27 test result, but may not necessarily have JAS.[16] A cluster of genes located on chromosome 6 is responsible for encoding HLA antigens, which significantly influence an individual's vulnerability or resilience to diseases. HLA antigens have a direct impact on the development of several prevalent illnesses. Certain illnesses, including JAS, are both autoimmune and inherited in a multifactorial way.[17]

If a kid has a certain HLA antigen type linked to the condition, it is believed that they have a heightened likelihood of developing the ailment. Children that possess the B27 HLA antigen are believed to have a heightened likelihood (or genetic predisposition) of developing JAS; nevertheless, it is crucial to note that a kid without this antigen may still acquire JAS. HLA antigen testing is neither diagnostic nor accurate for predicting the disorder. Male individuals are afflicted with JAS at a frequency three times higher than that of females.[18]

Complex relationship between HLA-B27, strenuous exercise, and ankylosing spondylitis: pathogenesis and clinical implications

The relationship across HLA-B27 and exercise is complex thus the association focuses on the potential increased risk of developing ankylosing spondylitis in individuals having this genetic marker who engage in strenuous physical activity. The association across HLA-B27 and AS has been recognized since the early 1970s. The primary pathology involves enthesitis, or inflammation at the sites where tendons and ligaments attach to bone. The heritability of spondyloarthritis (SpA) is well-documented, particularly with the high association of the HLA-B27 antigen. Although this connection has been established for over four decades, the specific pathophysiological mechanisms of different HLA-B27 allotypes are not fully understood. Theories include the presentation of arthritogenic peptides, ER stress caused by misfolded HLA-B27, and the interaction of HLA-B27 with immune receptors to drive IL-17 responses. Additionally, several non-HLA susceptibility loci have been identified, such as endoplasmic reticulum aminopeptidases (ERAP) and those related to the IL-23/IL-17 pathway. This review explores the clinical aspects of SpA, counting gut inflammation, and enthesitis, along with new bone formation, and discusses how HLA-B27 contributes to disease pathogenesis, incorporating recent insights into HLA class I proteins.[21]

Studies investigating the combined impact of HLA-B27 and heavy weight exercise during adolescence reveal how genetic along with environmental factors interact in the onset of ankylosing spondylitis.[22] Adolescence is a crucial period for skeletal and immune system development, and the existence of HLA-B27 is known to increase susceptibility to AS. Research indicates that heavy weight exercise, which imposes significant strain on the spine and joints, may act as a stressor that triggers or exacerbates inflammation in individuals having this genetic predisposition.[22]

Participants with HLA-B27 who engaged in intense physical activity during their adolescent years frequently reported an earlier onset of back pain and AS-related symptoms. The mechanical stress from heavy lifting can cause microtrauma at the entheses, where tendons and ligaments attach to the bone—areas particularly vulnerable to inflammation in AS. This inflammation may be more pronounced in those with HLA-B27, potentially accelerating disease progression.[23] However, not all individuals having HLA-B27 who partake in heavy weight exercise develop AS, suggesting that additional factors such as other genetic predispositions, environmental exposures, or variations in immune response also play a role. These findings highlight the complexity of AS pathogenesis, suggesting that while heavy weight exercise may not directly cause AS, it could be a significant contributing factor for those genetically predisposed.[19]

AS is associated with a prevalence of HLA-B27 in individuals over 85%. Over 170 HLA-B27 alleles have been identified, although most of them are not well represented for genetic association research.[21] In meta-analysis aggregates data from numerous studies to quantify the strength of the association between HLA-B27 and AS. It presents statistical analyses of the odds ratios for AS in HLA-B27-positive individuals compared to controls, offering insights into how significant this genetic marker is in predicting AS.[20] In another study explores the different subtypes of the HLA-B27 antigen and their

varying impacts on AS. It includes data on how specific HLA-B27 subtypes correlate with disease severity and progression, providing a detailed look at the complex relationship between HLA-B27 subtypes and AS.[17] This longitudinal study tracks AS patients over time, examining how the presence of HLA-B27 affects clinical outcomes such as disease progression, response to treatment, and quality of life. The study includes statistical data on disease activity scores and functional outcomes based on HLA-B27 status. This study focuses on how HLA-B27 status can predict early onset AS and its progression. It includes data on the age of onset, disease severity, and progression rates in HLA-B27-positive versus HLA-B27-negative patients, providing valuable insights into early diagnosis and prognosis.[23]

These studies provide a broad spectrum of data and analysis on HLA-B27 in the context of ankylosing spondylitis, covering genetic associations, disease mechanisms, clinical outcomes, and extra-articular manifestations.

DISCUSSION

This study systematically examines the elevated risk of AS in adolescents who engage in intense physical exercise. The literature reviewed highlights a significant correlation between intense physical exercise during adolescence and an increased risk of developing AS, particularly in individuals having the HLA-B27 antigen. Our study discusses adolescence age between 15 to 21 usually beginning of AS due to heavy exercise. Similarly, in observation that AS typically develops during late adolescence and early adulthood. A study by Wata et al noted that AS symptoms often manifest between the ages of 15 and 30, with the average age of onset around 24 years.[24] Similarly, the Spondylitis Association of America reports that the most common age of onset for AS is between 17 and 45, with a notable peak in the late teenage years and early twenties. A study by Hillberdink et al found that patients who developed AS before the age of 16 had more extensive radiographic damage and were more likely to experience severe functional impairment compared to those with later onset.[25] This suggests that the early onset of AS, particularly during adolescence, may lead to a more aggressive disease course.

Based on the findings of this study, managing exercise in adolescents with a genetic predisposition to ankylosing spondylitis requires a careful balance between maintaining physical fitness and minimizing the risk of triggering or exacerbating symptoms. Adolescents who carry the HLA-B27 antigen or have a family history of AS should be advised to engage in low-impact, spine-friendly exercises that promote flexibility and core strength without placing undue stress on the joints and spine. In a study by Wrobel et al, AS often presents in early adolescence, sometimes asymptomatically, but it usually manifests as aching low back pain, worsened by hyperextension of the spine and relieved by rest.[26] This condition is notably prevalent among adolescent athletes, with one orthopaedic series reporting that AS accounts for 47% of cases involving acute low back pain. While the exact cause is unclear, intense physical exercise such as particularly in sports that involve repetitive flexion, and extension, or even hyperextension of the spine—such as gymnastics, football, cricket (especially fast bowlers), and weightlifting—can contribute to the onset of AS. The strain placed on the spine during such activities is thought to exacerbate underlying genetic predispositions, particularly in individuals carrying the HLA-B27 antigen, which is strongly associated with AS. Similarly, in another study by Assadiasl et al suggests that strenuous activity could cause microtrauma or stress on the joints, triggering an inflammatory response.[27] In genetically susceptible children, this inflammation may not resolve normally and could lead to chronic conditions like AS. However, the connection between intense exercise and AS is not fully understood, as not all physically active children develop the condition, indicating the involvement of other genetic or environmental factors. Although, HLA-B27 is strongly linked to JAS, not all children with the antigen will develop the disease, highlighting the complexity of its causes.[28] This investigation's conclusions have vital implications for clinical practice. So, healthcare providers should consider screening for AS in adolescents who present with persistent back pain and have a history of intense physical activity, particularly if they carry the HLA-B27 antigen.[29] Early detection of AS in this high-risk group could enable timely intervention, potentially slowing disease progression and improving quality of life. Clinicians should also educate young athletes and their families about the potential risks associated with intense physical exercise and the importance of monitoring for early signs of AS.[30]

Overall, this study underscores the need for a multidisciplinary approach to managing AS risk in adolescents, integrating genetic screening, lifestyle assessment, and early clinical intervention to mitigate the long-term impact of this chronic condition. Further investigation is needed to explore the mechanisms underlying the relationship between intense exercise and AS, as well as to develop targeted strategies for prevention and early treatment.

Limitations

The study's findings are constrained by a small sample size, limiting their generalizability across diverse populations. The reliance on retrospective data introduces potential recall bias, affecting the accuracy of reported associations between exercise habits and AS onset. Additionally, the focus on the HLA-B27 antigen may overlook other genetic factors, while the lack of consideration for environmental influences such as diet and lifestyle further limit the study's scope. Future research should involve larger, more diverse cohorts and employ prospective studies to reduce bias. Expanding genetic analysis and incorporating environmental factors will

provide a more comprehensive understanding of AS risk in adolescents. Also, specific exercise interventions like Pilates, Yoga, and Tai Chi can significantly improve flexibility, core strength, and overall well-being, while helping to manage pain and reduce stiffness in individuals having ankylosing spondylitis.

CONCLUSION

This investigation highlights the complex relationship between heavy weight exercise during adolescence and the threat of AS, particularly in those with HLA-B27 positivity. It suggests that while not all adolescents who engage in strenuous exercise will develop AS, those genetically predisposed may face an increased risk, with mechanical stress potentially triggering or worsening inflammation. These findings emphasize the need to consider both genetic and environmental factors in AS diagnosis and management, calling for further research to enhance early detection and treatment in at-risk populations.

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