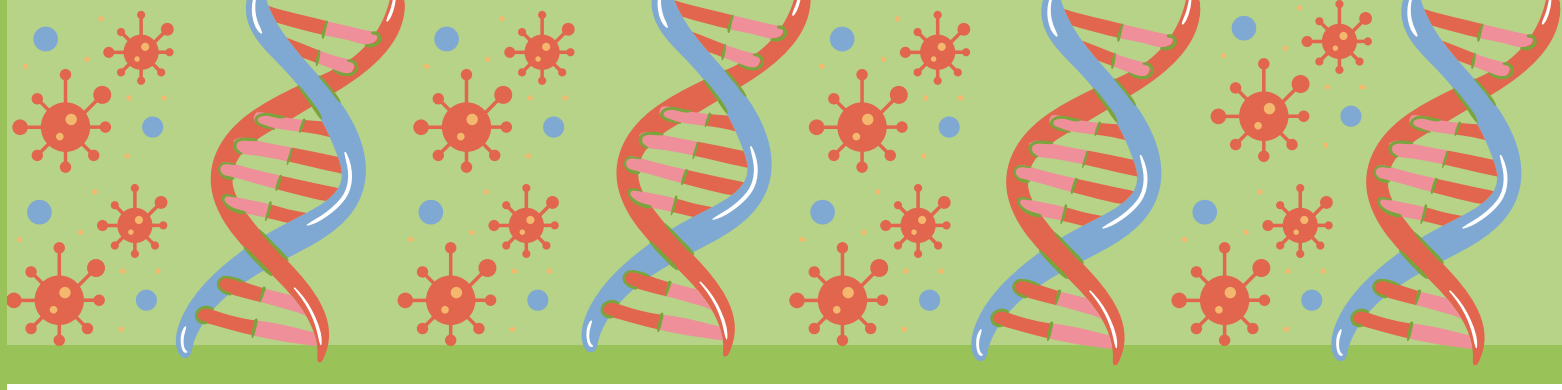

ETIOLOGICAL THEORIES OF JUVENILE IDIOPATHIC ARTHRITIS (JIA): A NARRATIVE REVIEW

MEGAN LIANG [1], AVERY RHIND [1], REEM TEHFE [1], GRACE XIONG [1], SETH YBEMA [1]

BACHELOR OF HEALTH SCIENCES (HONOURS), CHILD HEALTH SPECIALIZATION, MCMASTER UNIVERSITY

ABSTRACT

Juvenile idiopathic arthritis (JIA) is the most common pediatric rheumatic disease. It can be classified by diverse clinical presentations across subtypes classified by inflammation, swelling, and pain. This review examines current perspectives on factors impacting JIA etiology and future areas of development. Genetic and environmental factors, including early-life nutrition (i.e. breast milk), mode of infant delivery, antibiotic exposure, and infections have been proposed as etiological candidates in the literature. Various human leukocyte antigen (HLA) genes and non-HLA genes related to immune signaling are risk factors for specific JIA subtypes. The impact of infection on JIA development has also been examined; it remains unclear whether infection plays a protective or harmful role. Moreover, shorter durations of breastfeeding during childhood may be associated with an increased risk of JIA development, given that breast milk consumption favorably increases bifidobacterium, changes the composition of the microbiome, and increases microbial diversity. Additionally, mode of delivery can play a role in the onset of JIA as birth delivery through Cesarean section puts children at a higher risk of JIA compared to infants born vaginally. Lastly, antibiotic exposure and its dose- and time-dependent relationship also play a role in the microbiome and JIA pathogenesis. This research is significant, as an increased understanding of the etiology of clinically heterogeneous JIA subtypes may improve future treatments. Current limitations, research gaps, and future directions in the field are also discussed.

INTRODUCTION

Juvenile idiopathic arthritis (JIA) encompasses all chronic pediatric inflammatory diseases and is defined as arthritis that develops in children under 16 years of age for at least 6 weeks (1). JIA includes six subtypes: enthesitis-related, oligoarthritis, polyarthritis, psoriatic, systemic, and undifferentiated (2). Common symptoms include joint inflammation, swelling, pain and tenderness (2). However, certain subtypes, such as psoriatic JIA, affect the skin or internal organs rather than the joints (2). Hallmark symptoms of JIA result from overactive immune system responses where immunocompetent cells such as T Cells and macrophages proliferate and activate excessively (3). In Canada, approximately 6,200 children aged 15 years and younger have been reported to have JIA (3). The reported incidence of JIA between 2016-2017 was 17.1 in 100,000 persons, with the prevalence increasing annually (4). However, these statistics are presumed to be underreporting the true proportion of individuals affected, potentially due to inadequate disease awareness and inequitable access to rheumatologists, among other factors (5). Contrary to popular belief, JIA is not the childhood counterpart of rheumatoid arthritis (RA) despite it being formally referred to as juvenile rheumatoid arthritis (6). JIA is often concerned with child bone development, and as highlighted through the term “idiopathic”, the etiology of JIA is uncertain. Although the genetic and environmental model is most widely accepted, there are several additional theories regarding JIA pathogenesis (7). This review will examine current perspectives on JIA etiology.

GENETICS

The development of JIA may be caused, in part, by genetic factors. The heritability of JIA has been documented by several family studies, showing a monozygotic twin concordance rate of 25-40%, much higher than the population prevalence of 1 in 1000 (8). JIA has also been found to have a sibling recurrent relative risk of 15 to 30 times that of the general population, similar to that of type 1 diabetes (9,10). Although an exact set of genetic loci has not been identified as the cause of JIA, some regions of the genome have been identified in connection to JIA.

Human leukocyte antigen (HLA) genes are of particular interest since they account for 13-17% of the relative risk of familial segregation previously mentioned (10,11). The HLA region on chromosome 6 contains over 200 genes, which mostly have immune-related functions (12). HLA genes code for major histocompatibility (MHC) class I and II receptors, the latter of which are found on antigen-presenting cells (13). In many autoimmune disorders (ADs), they play a key role in self-antigen presentation (12). Specific HLA genes predispose individuals to a variety of risks, often specific to JIA subtypes and with age-specific windows of susceptibility (12,14,15). Some are protective against certain subtypes, others predispose individuals to certain subtypes, and some do both simultaneously (12). The role of HLA genes was originally derived from association and linkage studies, and have since been confirmed by genome-wide association studies (GWASs) (16).

GWASs have also been used to identify non-HLA genes, most of which are connected to immune signaling and inflammation (12). Similar to HLA, non-HLA susceptibility genes often overlap with genes involved in other ADs, but especially with RA (12). However, they do not operate via the MHC I and II mechanisms. Many studies have found associations between non-HLA loci and JIA. Recently, a 2021 study analyzed all JIA subtypes in connection with 5 novel loci, and a 2022 study identified 15 genome-wide loci between at least 2 JIA subtypes, with 10 novel loci (17,18). Although developments are being made, more studies must be conducted to verify these genomic relationships– especially to infer a causal relationship (13).

INFECTION

Exposure to infection, particularly in early life, is one environmental factor that may contribute to the development of JIA; however its role is not fully understood. A 2008 case-control study found that hospitalization for infection within one year of birth is associated with increased risk of developing JIA later in life, while another case-control study examining the same relationship did not find an association, indicating a persistent area of uncertainty (19,20). The role of specific viruses such as parvovirus B19, rubella, and Epstein-Barr virus (EBV) in JIA development has also been examined (21). In Canada, parvovirus infection leads to arthralgia (pain in the joints) in 8% of children infected (22). While some studies have reported increased prevalence of anti-parvovirus antibodies in patients with JIA when compared to patients without JIA, other studies have not been able to establish a causal relationship (21). Whether EBV plays a role in JIA pathogenesis also remains unclear, as some studies have explored a potential link through the triggering of an autoimmune response while other case studies have reported that it may have a protective role (21). Rubella infection has also been examined as a potential contributor to the development of JIA, though there is mixed evidence on this, with some studies supporting this connection and others unable to identify any relationship between rubella and JIA (21,23,24).

There are numerous mechanisms through which infection may influence the risk of developing JIA. For example, the molecular mimicry theory describes the potential for immune cells to mistakenly attack the self as infectious agents with peptides, producing an autoimmune response. (25,26). On the other hand, increased provocation of immune responses by organs may be a mechanism connecting JIA pathogenesis to infection. Another possible mechanism of action is polyclonal lymphocyte activation, where non-specific antibody-producing lymphocytes proliferate in response to microbes in the body, may also be at play (25,27).

Alternatively, the hygiene hypothesis suggests that the adaptive immune response can be strengthened through increased exposure to pathogens during childhood (25). Typically, children with siblings are thought to be exposed to more microbes and pathogens compared to children without siblings, as they spend more time interacting with one another (25). The relationship between exposure to siblings and risk of JIA development was evaluated in a systematic review examining environmental factors associated with JIA, and suggests a protective effect (28).

MICROBIOTA

A biodiverse microbiome is required to create a stable system which is resistant to agitation (29). The composition of the gut microbiota, when altered, causes dysbiosis (29). Gut dysbiosis, or continuous imbalance within the gut microbiota, has gained interest as a potential pathogenic factor for JIA (30). Gut dysbiosis also triggers inflammation and increases the permeability of gastrointestinal tissue. Inflammation is then triggered through the cell movement to extraintestinal sites, including the joints (29).

BREAST MILK

Recent studies have explored the role of early childhood nutrition and duration of breastfeeding in the development of JIA. A recent prospective cohort study conducted by *Kindgren et al.* in 2017 found that shorter durations of childhood breastfeeding were associated with an increased risk of JIA development in adolescents (31). This study found that children who had been breastfed for less than 4 months were found to be at an increased risk for JIA relative to those breastfed for longer than 4 months (31). Breast milk contains a multitude of immune-modulating compounds that contribute to the maturity of an infant's immune system (31). Along with these favourable compounds, breast milk contains natural prebiotics and probiotics that improve an infant's gut microbiota (32). In particular, the consumption of breast milk results in increased bifidobacterium in the gut microbiota and the intestine (33). Bacteria present in the gut microbiota play a vital role in the development of an infant's immune system by stimulating the gut-associated lymphoid tissues to produce antibodies against pathogens (33). When an infant's immune system is weak, the immune system attacks body cells and tissues. This results in the release of inflammatory chemicals that attack the tissue around a joint leading to inflammation (2).

Past studies have also investigated the association between breast milk and JIA. However, limitations of these studies include smaller sample sizes, and have led to weak associations between childhood nutrition through breastfeeding and the onset of JIA (34). Studies dating back to 1996 have suggested that non-breastfed children are at increased risk to develop juvenile arthritis compared to infants who have been breastfed (34).

ANTIBIOTICS

The association between antibiotic exposure and JIA development has been heavily theorized. This is especially relevant within the first three years of life (35). The presence of antibiotics may disrupt the gut microbiota through alterations of the composition of the microbial community, which plays an important role in maintaining homeostasis (29). Exposure to prescription drugs can disrupt the maturation of the microbiome, antibiotics, for example, can target and eliminate beneficial bacteria leading to a reduction in microbial diversity (29). In addition, some prescription drugs have been linked to an increased risk of dysbiosis (29). Moreover, antibiotic exposure has lasting impacts on the microbiome, specifically antibiotics targeting anaerobic microorganisms (29). These long-term changes include antibiotic resistance, further contributing to the damage and alteration of the microbiome composition (29). Frequent exposure may increase mucosa permeability within the gut microbiota, causing antigen leakage, and contributing to the pathogenesis of JIA, such as triggering inflammation of the joints (29). Children who had developed JIA were more likely to have been exposed to increasing courses of antibiotics before the age of 9, compared to those who had not (35). A study conducted by *Kindgren et al.* suggested that the type of antibiotic is inconsequential, as both penicillins and non-penicillins had equal effects on the risk of JIA development (35). This demonstrates a dose- and time-dependent relationship and corroborates claims to support policies that restrict antibiotic use earlier in life (29). The association between the number of infections and use of antibiotics during childhood should be further investigated, as well as maternal antibiotics and its effects on the microbiome diversity of the child.

MODE OF DELIVERY

The mode of birth may influence the maturation of the infant's immune system and gut microbiota. It has been proposed that infants delivered through Cesarean section (C-section) have an increased risk of developing JIA in comparison to infants born vaginally (36). According to a review conducted by Coelho et al. in 2021, infants born vaginally present greater concentrations of Bacteroides including Bifidobacteria and Lactobacillus in the first few days of life following birth, contributing to microbial variability in the weeks following birth (36). Microbial variability is important in the development of an infant's immune system as a weak immune system may lead to inflammation (29). In contrast, infants born through C-section showed a deficiency of these Bacteroides and have a microbiome resembling the maternal skin (36). These Bacteroides play a part in composing the infant's gut microbiota, helping to regulate gut immunity and inflammation (29). Childhood is a significant developmental stage for the infant microbiota, and microbial diversity is important for the maintenance of intestinal homeostasis (29). A lack of gut microbiota diversity may cause dysbiosis resulting in an immunological imbalance, thus putting infants at risk for JIA or other inflammatory diseases (29). A study conducted by Horton et al. in 2019 further supports this hypothesis, suggesting that infants born by C-section present with less microbial diversity (32). Along with reduced microbial diversity, infants born via C-section have lower levels of circulating cytokines and leukocyte responsiveness. This predisposes those children to immunologic dysfunction and disorders relative to infants born vaginally (32).

Moreover, a 2016 study conducted by Dominguez-Bello et al. suggested that exposure to maternal vaginal microbiota can partially restore bacterial communities in infants delivered by C-section (37). This suggests that regardless of the mode of delivery, protective microbiomes can be developed upon exposure to vaginal fluids (37). Nonetheless, further investigation of the infant gut microbiota is needed as current studies look at this association from a descriptive lens, resulting in challenges in drawing directional links between microbiota composition and JIA.

DISCUSSION

II. Infection and SARS-CoV-2

While the connection between various viruses and JIA development has been explored, no clear causal links have been established. However, comparing the prevalence of JIA with that of other viruses may provide insight into potential causal links.

Previously, the association between viruses such as rubella and the development of JIA had been explored, though whether a clear link can be established remains uncertain (21). Over the past century, the prevalence of rubella has decreased drastically with no cases of rubella being reported during 2022 in Canada (38,39). Thus, given the relatively low prevalence of JIA in the population this makes it challenging to examine whether a relationship exists between rubella infection and JIA (39). Additionally, while the prevalence of rubella has remained low in recent decades, the prevalence of JIA has been steadily increasing, suggesting that rubella may not be a major etiologic factor in JIA development in Canada today (4). However, in recent years new pathogens and viruses such as SARS-CoV-2, which has infected over 70% of the Canadian population as of 2022, have emerged (40). The potential link between COVID-19 infection and symptoms of arthritis was recently explored in a case report study of a patient who experienced multisystem inflammatory syndrome (MIS-C) and atypical Kawasaki syndrome following complications of a COVID-19 infection (41). After beginning treatment for MIS-C, the patient developed symptoms of severe inflammatory arthritis and persistent polyarthritis (41). This case report supports the notion that viral infection could potentially play a role in the onset of arthritis in children; however further research is needed to explore the impact of COVID-19 infection on the development of symptoms of arthritis. This field of research may be increasingly relevant given that SARS-CoV-2 remains a novel virus that continues to evolve, with many long-term effects which are not yet understood.

Additionally, it may be worth investigating whether new viruses might provide a clearer link between the relationship of JIA and viruses. For example, it may be worth exploring whether a connection exists between JIA and respiratory syncytial virus (RSV), a virus currently significantly affecting children in Canada (42).

II. Genetics

Further investigations into relevant regions of the genome should also be conducted. Many HLA and non-HLA genes have already been identified as potentially relevant, however, a large number of studies include insufficient sample sizes (16). Previously, it was difficult to generate studies that assessed the genome comprehensively while simultaneously addressing the differences between JIA subtypes. However, this is now possible through GWASs, which have been used to discover new relevant loci (14,17,18). Future GWASs should utilize larger sample sizes to discover new loci while increasing their power (12). Additionally, meta-analyses can be used to overcome the barrier of smaller sample sizes by consolidating existing research, such as the one conducted in 2015 by De Silvestri et al. (16).
Another relevant aspect to genetics is the role of ethnicity and sex in predisposition to JIA. Similar to other HLA-associated diseases, evidence has shown that ethnic groups have different subtype susceptibility. For example, North American and European studies have found that patients of African and Indigenous descent have an increased risk of RF-positive polyarticular JIA than those of European descent (43). Large, multi-ethnic studies are needed to better understand the relationship between JIA subtypes and various ethnic groups (15). With regard to biological sex, research has shown that females may be at a higher risk for certain JIA subtypes. According to Arthritis Society Canada, some JIA subtypes, such as oligoarticular–persistent, RF-negative and RF-positive polyarticular JIA, are more common in females than males (44). Further studies among diverse populations should be conducted to analyze sex differences in JIA subtype risk.

Epigenetics are also important to consider. DNA methylation and histone modifications, triggered by environmental factors, can affect genes which are relevant to JIA. However, the connections between genetics and environment are not well understood (12). Future research should integrate previously identified genetic loci and environmental factors to better understand the nature of their relationship.

The significance of research investigating the genetic makeup of JIA subtypes is underlined by implications for patients. However, this effort may be hindered by a lack of evidence caused by diagnostic inequities, with numerous studies illustrating the role of social determinants in access to rheumatologic care (7,45,46). The uncertainty associated with current JIA incidence and prevalence rates is well explored, but the consequent knowledge gaps are not (47). Firstly, differences in care access due to social inequities or health systems design may contribute to statistics that both under-report and misrepresent the quantity and demographics of the true patient population. One such determinant is community poverty level. A 2021 cohort study conducted by Balmuri et al. identified that community poverty was associated with longer times before the first pediatric rheumatology (PR) appointment in polyarticular JIA cases (46). It is notable that Balmuri et al. also controlled for confounding variables including sex and ethnicity, both of which have been commonly tied to JIA etiology (43,44). Differences in time before first PR visit are also corroborated by high-level evidence syntheses, with one systematic review suggesting that disparities in time to access may depend on factors affecting the referral pathway: parental background and family history of

heumatologic diseases, amongst others (48). Furthermore, disparities in time to diagnosis may also result from such referral inconsistencies (49,50). Finally, Canada and the United States are facing serious shortages of pediatric rheumatologists (51,52). This poses challenges towards JIA diagnosis and thus, the collection of patient data required to better understand etiology and treatment. This is necessary to discuss to improve patient care at the systems-level (53). Time to access and diagnosis are only two dimensions of PR care accessibility, however, these findings emphasize the need to decrease individual, societal and educational barriers to accessing PR care. More research is required to improve our understanding of JIA etiology and ultimately, improve patient outcomes.

III. Considerations for Future Research

Another important factor to consider when examining the etiology of JIA is the limitations of observational study designs, which are often used to investigate links between JIA and various environmental factors. A 2019 review investigating environmental factors linked to JIA discussed the many limitations of observational studies that may limit what conclusions can be drawn about etiology (32). For example, their review discussed the magnitude of studies evaluating JIA etiology that do not consider confounding variables, such as socioeconomic status (32). Thus, it may be valuable for future research and reviews to consider the relationship between socioeconomic status (such as income level, geographic region, and education level) in relation to the development of JIA to reduce the potential for confounding bias and to understand whether socioeconomic status itself acts as a risk factor for disease.

An article conducted by Horton and Shenoi conducted in 2019 also suggested that case-control studies are vulnerable to selection bias based on how control study populations are chosen (32). This review identified inconsistency in results between case-control studies looking at the link between hospitalization for infection during the first year of life and risk of JIA development, where two studies, each of which were conducted in different countries (and therefore had different study populations) found conflicting results.

CONCLUSIONS

This review examined the various etiological theories of JIA. It highlighted genetic and environmental factors, including nutrition (breast milk), mode of delivery, antibiotic exposure, and infections as etiological candidates for the pathogenesis of JIA. Future research on the role of infections, viruses, and genetics is required to better understand JIA etiologies.

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