International Journal of Medical Studies
Available online at www.ijmsonline.in

INTERNATIONAL JOURNAL OF MEDICAL STUDIES
ESTD 2015

IJMS 5(12), 37-44 (2020)
Print ISSN 2542-2766

Research progress on the pathogenesis of juvenile idiopathic arthritis

Cuixiang Xu[1], Jing Yuan[2], Jianying Feng[3], Fuyong Jiao[4]

[1]*Shaanxi Provincial Key Laboratory of Infection and Immune Diseases.*

[2]*Xi`an Medical University.*

[3]*Children's Hospital, 3rd Affiliated Hospital of Xi'an Jiaotong University.*

[4]*Children's Hospital, 3rd Affiliated Hospital of Xi'an Jiaotong University.*

Corresponding author: *Dr.* Fuyong Jiao

Article history
Received 15 Nov 2020
Received in revised form 29 Nov 2020
Accepted 22 Dec 2020
Available online 27 Dec 2020

ABSTRACT

Juvenile Idiopathic Arthritis (JIA) pathogenesis is not very clear, but it may be associated with specific components of various infectious microorganisms as foreign antigens for people with a genetic background, activate immune cells, and trigger an abnormal immune response by directly damaging or secreting cytokines, autoantibodies. Cause damage and degeneration of our own organization. Especially certain bacteria, viruses, special components (such as HSP) can be used as super antigens, T cells are activated directly by binding to T cell receptors (TCR) with a special variable region β chain (chain) structure and stimulate immune damage. Self-tissue denaturing components (endogenous antigens), can also be used as an antigen to trigger an immune response to its own tissue components.

Further aggravate the immune damage. Intestinal microbial groups and environmental factors may also play an important role in the pathogenesis of JIA.

Keywords: Antigens, Immune, Juvenile Idiopathic Arthritis, T Cell, T Cell Receptors.

This article reviewed by Dr. Ashish Rathore, Dr. Antim Vyas. Edited by Dr. Pradeep J., Dr. S Gaur. Available online 27 Dec 2020.

INTRODUCTION

Juvenile idiopathic arthritis is a common rheumatic disease in childhood and adolescence, characterized by chronic synovitis with systemic multiple organ dysfunction, causes serious harm to the physical and mental health of children and adolescents. It is an important cause of disability and blindness in childhood. The disease has many names, such as in Juvenile Rheumatoid Arthritis (JRA), Juvenile Chronic Arthritis (JCA), Juvenile Arthritis (JA), etc. In order to facilitate the study of the genetics, epidemiology, outcome and implementation of treatment programmes for such diseases by the international collaborative group, 2000 Expert Meeting of the International Association of Rheumatology Societies (AR) Committee of Science and Technology, "Persons with unexplained joint distention and pain in childhood and adolescence (under 16 years of age) for more than 6 weeks", named Juvenile Idiopathic Arthritis (JIA). Divided into (1) Systemic arthritis (systemic JIA); (2) Multiple joint type: rheumatoid factor negative (polyarticular JIA,); and JIA RF negative; (3) Multiple joints: rheumatoid factor positive (polyarticular JIA RF positive); (4) Less joint type (oligoarticular JIA); (5) Arthritis (enthesitis related JIA,) associated with inflammation at the attachment site ERA; (6) psoriatic arthritis (psoriatic JIA); (7) Unidentified juvenile idiopathic arthritis (undefined JIA): arthritis that does not meet either or more of the above categories [1].

Systemic Juvenile Idiopathic Arthritis (sJIA) is an autoimmune disease characterized by fever, rash, hepatosplenomegaly, lymphadenopathy, and serositis. Elevated levels of cytokine secretion are typical features of sJIA. IL-6 plays an important role in the pathogenesis and clinical manifestations of sJIA. The pathogenesis of the disease is considered to be the result of the combination of host genes and environmental factors.

The etiology and pathogenesis are still unclear and may be related to many factors

1. Infection factors

There are many reports of bacterial (Streptococcus, Yersen, Shigella, Campylobacter jejuni, Salmonella spread, etc.), viruses (parvovirus B rubella virus and EB viruses), mycoplasma and chlamydia infections associated with the disease, but none of them can be confirmed as the direct cause of the induction of the disease.

2. Genetic factors

A lot of information confirms JIA genetic background, the most studied human leukocyte antigen (HLA with HLA-DR4 (especially DR1*0401), dr8 (especially DRB1*0801), and DR5 (especially DR11104) loci are the JIA susceptible populations. Other HLA sites related to JIA pathogenesis are HLA-DR6, HLA-A2. Other HLA sites were also found to be associated with JIA onset.

The occurrence of genetic factors JIA has a certain genetic tendency, and the types of JIA between different populations are also different. The reason may be related to some genetic structural characteristics or polymorphisms. Genetic factors are helpful to determine the high-risk population and provide basis for JIA prevention and treatment. The relationship between human HLA and JIA is almost clear. I and II HLA allele changes are associated with JIA pathogenesis. Studies of siblings (sisters) with JIA in the same family show that some HLA genes have structural characteristics, such as DRB1 0801, DQB1 0402, etc.) resulting in a susceptibility to JIA of 0. Children with ankylosing spondylitis are the same as adults; HLA-B27 positive ratio reached more than 90%. The positive rate of HLA-B27 in children with less articular JIA complicated with iris ciliary body inflammation was also significantly higher than that in normal population. From a clinical perspective, the prognosis of HLA-B27 positive children was not as good as that of HLA-B27 negative children. The current study of HLA genetic structural characteristics is not enough to provide sufficient evidence related to various types of JIA [2].

Polymorphisms of other genes; Many individuals have HLA susceptible alleles but do not JIA, them and many types of JIA families are rare indicate that polygenes may have an impact on JIA pathogenesis. There are many other candidate genes, because the JIA is mainly inflammatory, thus most of the studies are cytokines in the process of immune response. Pro-inflammatory cytokines include tumor necrosis factor-interleukin (IL)-6, IL-1, etc. The

important role of TNF-α and its receptors in JIA pathology has been confirmed by many studies. Genetic analysis showed that, the polymorphism of some sites of TNF-α [promoter may be related to the onset of systemic JIA, TNF-α [promoter polymorphism sites involved include I308, I238, I1031, I863, I857, etc; Besides, TNF-α [microsatellite alleles may also be associated with JIA pathogenesis. The expression of IL-6 in sJIA serum is also abnormally high. Recently found IL-6 promoter-174 polymorphism may be the cause of IL-6 over expression [3]. But the outcome is controversial. Contrary to pro-inflammatory cytokines, IL -10 with anti-inflammatory properties decreased serum levels in severe JIA children. This phenomenon may be attributed to the formation of "ArA" IL 10 haplotypes (haplotype) IL-10 promoters I1082, I819 and I592, but there are opposite results. Polymorphism in the regulatory region of cytokine expression affects cytokine expression, these factors with HLA specific alleles, may be JIA multiple influencing factors.

3. Immunological factors

Many studies have confirmed that JIA are autoimmune diseases: some children have rheumatoid factor (RF) in serum and synovial fluid autoantibodies such as anti-denaturing IgG antibodies) and anti-nuclear antibodies (ANA); Rheumatoid arthritis cells present in synovial fluid, RAC); Serum IgG, IgM and IgA increased in most children; [4] Peripheral blood CD4T cell amplification; Serum inflammatory cytokines increased significantly.

T cells T cells are thought to play an important role in JIA pathogenesis. The relationship between JIA and HLAII antigens indicates that CD4T cells play a prominent role in JIA pathogenesis. JIA T cell subsets and dysfunction, if the polyarticular and sJIAT cell proliferation response is reduced, T cell reduction, etc. T cell function is mainly reflected by the abnormal secretion of cytokines. JIA T1/T2 immune response was abnormal. Contrary to allergic diseases, autoimmune diseases include JIA types of immune responses, T1 response enhancement, T2 response weakened, and this cytokine response was also observed in JIA children. But deep research shows that the problem is not so simple. At different stages of the disease, T1/T2 types of response may vary. A recent study found that apart from T1/T2 reactions, T cells also affect the immune response to disease, JIA CD4, CD; with less joint type T cell reduction may suggest poor prognosis. JIA the synovial fluid, T cells are activated, also indicates that T cells play an important role in joint damage.

B cell JIA are considered to be autoimmune diseases, especially some types JIA the presence of rheumatoid factors (RF) or occult types RF, and the presence or absence of RF is also associated with the prognosis of JIA. B cells and their secreted antibodies also play an important role in JIA pathological processes. The relationship between antinuclear antibodies (ANA) and less articular JIA and uveitis is very clear. Studies have found that blocking signaling between T cells and B cells by antibody binding CD or its ligands can alleviate the clinical symptoms of human rheumatoid arthritis. However, whether it can play a role in clinical practice needs further study and confirmation. The relationship between JIA and CD, CD ligands has not been studied. Most JIA children have not found characteristic autoantibodies in their bodies. Some special types of arthritis, such as X linkage without C globulinemia, are prone to autoimmune diseases, mainly arthritis. Its clinical manifestation is consistent with systemic JIA. A large amount of monocyte and granulocyte infiltration can be seen around the vessels in the early stage of sJIA involvement of joint inflammation, lymphocytes are almost absent. JIA infiltrating polymorph nuclear neutrophils (PMN) and mononuclear cells in the synovium during the course of the disease can release pro-inflammatory cytokines to cause synovial inflammation. Among them, important cytokines are IL-1, TNF-α and so on. Under these cytokines, it can stimulate the release of metalloproteinases by neutrophils, phagocytes and so on. Aggravate joint damage, removal of neutrophils can completely block or reverse joint inflammation. The study found, in the affected joint, activation of pro-inflammatory factors by local immune complexes with activated complement fragments, damaged tissues, or fear cross-linked mononuclear cells, such as IL-1B and INF; they can induce lower levels of neutrophil recruitment. These little activated neutrophils ooze blood vessels and back into the joint to form a proinflammatory environment. This is necessary for the persistence and expansion of arthritis. Except for local effects, in recent years, different from other rheumatic diseases SLE, Kawasaki disease, different types of peripheral blood neutrophils exist in different types of JIA, activation of peripheral blood neutrophils during active JIA especially sJIA neutrophil activation is very obvious.

4. Involvement of gut microbiota in JIA pathogenesis

The pathogenesis of the disease is considered to be the result of the combination of host genes and environmental factors. But what causes the body's sensitivity to JIA is unclear.

Microbiome has received increasing attention as a potential enabler of immune-mediated disease development, including inflammatory bowel disease [5], type 1 diabetes, and rheumatoid arthritis. Also in JIA, there is growing evidence that the composition of the microbiome is different from that of healthy individuals. There is growing evidence that the microbiome may influence the development of the immune system, the integrity [6] of the intestinal mucosal barrier, and the differentiation of T cell subsets, which may lead to dysregulation of the immune system and thus may play a role in JIA development. Controlling the effects and effects of altered microbial groups, such as fecal microbial transplantation, may provide prospects for future therapeutic interventions. A report suggests that the microbiome is involved in JIA pathogenesis, and the microbiome affects autoimmune development in general and micro-local [2, 7].

5. Research progress of high migration rate B1 in children with rheumatoid disease [4]

High migration rate group protein B1 as a non-histone expressed in eukaryotic nucleus, can promote inflammatory response after release to extracellular, participate in the positive feedback loop of cytokines, and are closely related to the pathogenesis of many autoimmune and inflammatory diseases. Recent studies have found that it may become a serum marker of purpura nephritis and lupus nephritis, and may predict the prognosis of juvenile idiopathic arthritis and the lack of response to intravenous gamma globulin in children with Kawasaki disease.

6. Environmental factors

The effect of environmental factors on the incidence of rheumatism is not very clear. It is generally believed that families with relatively poor socio-economic conditions are at increased risk of rheumatic diseases. Growth in cold and humid areas of the disease is relatively more. As with other rheumatic diseases, the incidence of JIA population has increased in recent years. The reasons for the increase in the incidence of this population are unclear. According to one view, environmental factors and lifestyle may be the cause of increased JIA morbidity. The environmental one gene interaction (environmental genetic interaction) hypothesis suggests that environmental factors may make phenotypes (phenotype) different under the same genotype (genotype) premise. But at present, this only exists in the conceptual and theoretical stage, and needs careful and in-depth research

data support. The increase in the incidence of rheumatic diseases is related to the abnormal immune response caused by environmental factors, which is similar to the "hygiene hypothesis" in allergic diseases: environmental factors cause not only T2 response tendency, but also T1 response. Recent epidemiological studies suggest that the evidence for this hypothesis is inadequate.

While infection has been thought JIA may be associated with infection, infection as a JIA cause has not been confirmed. The causes of association JIA and infection include: Lyme disease, reactive arthritis and so on, which are infected by pathogenic microorganisms, are very similar to JIA, and some studies have shown that epidemiological and serological antibody tests suggest that some JIA children have a history influenza virus infection. Studies of infection are not well documented, possibly because infection often occurs early and is systemic rather than intra-articular, whereas arthritis is due to subsequent autoimmune responses.

CONCLUSION

To sum up, the pathogenesis of JIA is not very clear, but it may be associated with specific components of various infectious microorganisms as foreign antigens for people with a genetic background, activate immune cells, and trigger an abnormal immune response by directly damaging or secreting cytokines, autoantibodies. Cause damage and degeneration of our own organization. Especially certain bacteria, viruses, special components (such as HSP) can be used as super antigens; T cells are activated directly by binding to T cell receptors (TCR) with a special variable region β chain (chain) structure and stimulate immune damage. Self-tissue denaturing components (endogenous antigens), can also be used as an antigen to trigger an immune response to its own tissue components. Further aggravate the immune damage. Intestinal microbial groups and environmental factors may also play an important role in the pathogenesis of JIA.

DECLARATION OF COMPETING INTEREST

All authors declare no conflicts of interest.

REFERENCES

1. Li Hongwei & Zeng Huasong regulation of JAK/STAT signaling pathways by miR-21 in the pathogenesis of juvenile idiopathic arthritis volume16, pages 502, world journal of pediatrics 513 (2020).

2. Correspondence author: Debby Bogaert all authors: Anouk Verwoerd Debby Bogaer childhood rheumatism [IF : 2.595] human microbiome and juvenile idiopathic arthritis. Springer Nature Switzerland AG. Part of Springer Nature 2021© human flora and juvenile idiopathic arthritis.

3. Gui Zhen, Zhang Shuping, Chen Xiaojie. Progress of IL-6 Inhibitors in the Treatment of Systemic Juvenile Idiopathic Arthritis Modern Immunology, 2020, (No .2).

4. Ruan Xiaoxia, Tang Xuemei. Research Progress of High Migration Rate Protein B1 in Children with Rheumatic Diseases [J].]; and Chinese Journal of practical Pediatrics, 2020 (No.5).

5. Verwoerd, A. a; Ter Haar, N. M. a; de Roock, S. a; Vastert, S. J. a, b; Bogaert, D. c the human microbiome and juvenile idiopathic arthritis Vol. 14 (No .1).

6. Ricciuto, Amanda1, 2; Sherman, Philip M1, 2; Laxer, Ronald M2, 3 Gut microbiota in chronic inflammatory disorder, A focus on pediatric inflammatory bowel diseases and juvenile idiopathic arthritis. Clinical Immunology 2020 Vol. 215.

7. Majumder, Sanjukta; Aggarwal, Amita Majumder, Sanjukta; Aggarwal, Amita Juvenile idiopathic arthritis and the gut microbiome, Where are we now? Best Practice & Research: Clinical Rheumatology.