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The Etiology of Juvenile Idiopathic Arthritis

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Abstract Over the years, the commonly used term to describe juvenile idiopathic arthritis (JIA) has changed. By definition, JIA includes all types of arthritis with no apparent cause, lasting more than 6 weeks, in patients aged less than 16 years at onset. JIA pathogenesis is still poorly understood: the interaction between environmental factors and multiple genes has been proposed as the most relevant working mechanism to the development of JIA. The concept that various microbes that colonize or infect not only the mucosal surfaces, like the oral cavity, but also the airways and gut might trigger autoimmune processes, resulting in chronic arthritides, and JIA was first drafted at the outset of last century. JIA development might be initiated and sustained by the exposure to environmental factors, including infectious agents which affect people at a young age, depending on the underlying genetic predisposition to synovial inflammation. Many data from patients with JIA suggest a scenario in which different external antigens incite multiple antigen-specific pathways, cytotoxic T cell responses, activation of classical complement cascade, and production of proinflammatory cytokines. In this review, emphasis is paid not only to the potential role of parvovirus B19 and Epstein-Barr virus *in primis* but also to the general involvement of different bacteria as *Salmonella* spp., *Shigella* spp., *Campylobacter* spp., *Mycoplasma pneumoniae*, *Chlamydophila pneumoniae*, *Bartonella henselae*, and *Streptococcus pyogenes* for the development of immune-mediated arthritides during childhood. No unequivocal evidence favoring or refuting these associations has been clearly proved, and today, the strict definition of JIA etiology remains unknown. The infection can represent a random event in a susceptible individual, or it can be a necessary factor in JIA development, always in combination with a peculiar genetic background. Further studies are needed in order to address the unsolved questions concerning this issue.

Keywords Child · Infection · Juvenile idiopathic arthritis

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Introduction

Over the years, the commonly used term to describe juvenile idiopathic arthritis (JIA) has changed. By definition, JIA includes all types of arthritis with no apparent cause, lasting more than 6 weeks, in patients aged less than 16 years at onset: the estimated incidence is 2 to 20 cases per 100,000 children, and its prevalence is about 16 to 150 cases per 100,000 children [1, 2]. Nowadays, JIA is the term recommended by the International League of Associations for Rheumatology to identify eight subtypes of JIA, differentiated on the number of affected joints, associated systemic comorbidities, and biochemistry [3]. The newer classification (Table 1) includes psoriatic arthritis, enthesitis-related arthritis, and undifferentiated arthritis in addition to oligoarthritis (persistent or extended), polyarthritis (rheumatoid factor-positive or negative), and systemic variant of JIA: this classification appears useful to categorize more homogeneous groups of patients and study their possible common pathogenetic features [4, 5]. Oligoarticular JIA is the most common subtype, accounting for 50–60 % of most cohorts of JIA, while polyarticular subtype accounts for 25–40 %, although many factors may contribute to pronounced discrepancies

Table 1 Categories of juvenile idiopathic arthritis according to the International League of Associations for Rheumatology revised criteria

Categories	Definition	Exclusion
Systemic arthritis	Arthritis in one or more joints with/or preceded by fever of at least 2 weeks duration that is documented to be daily for at least 3 days and accompanied by one or more of the following signs: (a) non-fixed evanescent erythematous skin rash, (b) generalized lymph node enlargement, (c) hepatomegaly and/or splenomegaly, and (d) serositis	Psoriasis or history of psoriasis in the patient or in a first-degree relative; arthritis in a HLA-B27-positive male beginning over 6 years of age; ankylosing spondylitis, enthesitis-related arthritis, sacroiliitis with inflammatory bowel disease, Reiter's syndrome or acute anterior uveitis or history of one of these listed disorders in a first-degree relative; presence of IgM rheumatoid factor on at least two occasions at least 3 months apart
Persistent oligoarthritis	Arthritis affecting not more than four joints during the first 6 months of disease	Psoriasis or history of psoriasis in the patient or in a first-degree relative; arthritis in a HLA-B27-positive male beginning over 6 years of age; ankylosing spondylitis, enthesitis-related arthritis, sacroiliitis with inflammatory bowel disease, Reiter's syndrome or acute anterior uveitis, or history of one of these listed disorders in a first-degree relative; presence of IgM rheumatoid factor on at least two occasions at least 3 months apart; presence of systemic signs
Extended oligoarthritis	Arthritis affecting a total of more than four joints after the first 6 months of disease	Psoriasis or history of psoriasis in the patient or in a first-degree relative; arthritis in a HLA-B27-positive male beginning over 6 years of age; ankylosing spondylitis, enthesitis-related arthritis, sacroiliitis with inflammatory bowel disease, Reiter's syndrome or acute anterior uveitis, or history of one of these listed disorders in a first-degree relative; presence of IgM rheumatoid factor on at least two occasions at least 3 months apart; presence of systemic signs
Rheumatoid factor negative-polyarthritis	Arthritis affecting five or more joints during the first 6 months of disease with test for rheumatic factor being negative	Psoriasis or history of psoriasis in the patient or in a first-degree relative; arthritis in a HLA-B27-positive male beginning over 6 years of age; ankylosing spondylitis, enthesitis-related arthritis, sacroiliitis with inflammatory bowel disease, Reiter's syndrome or acute anterior uveitis, or history of one of these listed disorders in a first-degree relative; presence of IgM rheumatoid factor on at least two occasions at least 3 months apart; presence of systemic signs
Rheumatoid factor positive-polyarthritis	Arthritis affecting five or more joints during the first 6 months of disease with two or more tests for rheumatic factor being positive at a distance of at least 3 months	Psoriasis or history of psoriasis in the patient or in a first-degree relative; arthritis in a HLA-B27-positive male beginning over 6 years of age; ankylosing spondylitis, enthesitis-related arthritis, sacroiliitis with inflammatory bowel disease, Reiter's syndrome or acute anterior uveitis, or history of one of these listed disorders in a first-degree relative; presence of systemic signs
Psoriatic arthritis	Arthritis and psoriasis or arthritis and at least two of the following: (a) dactylitis, (b) nail pitting or onycholysis, (c) psoriasis in a first-degree relative	Arthritis in a HLA-B27-positive male beginning over 6 years of age; ankylosing spondylitis, enthesitis-related arthritis, sacroiliitis with inflammatory bowel disease, Reiter's syndrome or acute anterior uveitis, or history of one of these listed disorders in a first-degree relative; presence of IgM rheumatoid factor on at least two occasions at least 3 months apart; presence of systemic signs
Enthesitis-related arthritis	Arthritis and enthesitis or arthritis or enthesitis with at least two of the following: (a) presence or history of sacroiliac joint tenderness and/or inflammatory lumbosacral pain, (b) presence of HLA-B27 antigen, (c) onset of arthritis in a male over 6 years of age, (d) acute symptomatic anterior uveitis, (e) history of ankylosing spondylitis, enthesitis-related arthritis, sacroiliitis with inflammatory bowel disease, Reiter's syndrome or acute anterior uveitis in a first-degree relative	Psoriasis or history of psoriasis in the patient or in a first-degree relative; presence of IgM rheumatoid factor on at least two occasions at least 3 months apart; presence of systemic signs
Undifferentiated arthritis	Arthritis that does not fulfill criteria in any category or in two or more of the above-mentioned categories	

between prevalence rates across different countries [6]. JIA pathogenesis is still poorly understood: the interaction between environmental factors and multiple genes has been proposed as the most relevant working mechanism to the development of JIA. The frequency of each subtype seems to vary significantly in different countries, and ethnic differences may also depend on both genetic and environmental heterogeneity [7–10].

The starting point of autoimmunity leading to JIA is still unknown. Since the 1930s, patients with rheumatoid arthritis

were also treated with antibiotics, beginning with sulphonamide, then in the 1960s with tetracycline derivatives, and more recently with macrolides, following different observations in mammals and humans which led to suggest that this chronic disease might be caused by microorganisms [1]. Many research projects have inspected a potential link between different infections and JIA. This review will describe the etiopathogenetic factors of JIA with an in-depth look to infections.

Genetic Predisposing Factors to Juvenile Idiopathic Arthritis

A genetic predisposition to JIA and a peculiar gene-related response to environmental factors, such as infections, have been hypothesized to explain its origin. Delineating the genetic contribution to the risk of developing a complex disease such as JIA is complicated by the likelihood that multiple genes can be pragmatically involved. The evidence for a heritable component in JIA derives mainly from family and twin studies, showing an increased prevalence in siblings and twins of subjects affected by JIA [11]. Furthermore, there is a significant concordance in the disease course and age at onset in affected non-twin sibling pairs [12]. Nevertheless, if genetics were the only predisposing factor to JIA, it would be expected that monozygotic twins would have the identical risk of developing the disease, but the concordance rates have been estimated in the range of 25–40 % [13]. Therefore, the environmental influences should give a not negligible contribution to the pathogenesis of JIA [14]. Several associations between JIA and genes encoding the human leukocyte antigens (HLA) have been described. However, genetic variants outside the HLA also influence the overall susceptibility to JIA.

The consistency of HLA associations in different populations reported by independent investigators has provided convincing evidence of the validity of such observations. In particular, *HLA-A2* allele is associated with different JIA subtypes, especially those with earlier onset [15–17]. Enthesitis-related JIA is associated with HLA-B27, whereas oligoarticular JIA has been shown to be associated with *HLA-A2*, *DR5*, and *DR8* [15–17]. The infrequent observation of *HLA DRB1*04* and *DRB1*07* in children with oligoarthritides should suggest the protective role exhibited by these haplotypes. Rheumatoid factor-negative polyarticular JIA is mainly associated with *DRB1*08* and *DPB1*03*, whereas the rheumatoid factor-positive polyarticular variant is associated with *DRB1*04*, *DQA1*03*, and *DQB1*03* haplotypes [15–17]. In the end, *HLA DRB1*01* and *DQA1*010* have been associated with the psoriatic variant of JIA [15–17]. Taken collectively, these data suggest that genetic factors contribute substantially to JIA predisposition. The genes operative in JIA appear to have a "window-of-effect" during which time they may contribute to the risk of disease but be neutral or even protective at other times. This may be particularly true in the oligoarticular variant, in which HLA-related risks clearly differ with age [18].

Sporadic associations have also been reported between systemic-onset JIA, HLA *DRB1*04*, and the *TNF-alpha* gene, which is related to tumor necrosis factor-alpha production [19, 20]. Genetic polymorphisms also appear to influence the outcome of systemic-onset JIA: Benedetti et al. showed that a polymorphism in *MIF* gene was a poor prognostic marker in this disease [21].

A systematic review of the literature reveals that about 100 different non-HLA candidate loci have been investigated for the association with JIA in different cohorts. Nevertheless, independent confirmations have been found in only few candidate genes, including *PTPN22*, *MIF*, *SLC11A6*, and *WISP3* [22]. Thompson et al. studied a cohort of 809 JIA cases of non-Hispanic European ancestry and reported that PTPN2, COG6, and ANGPT1 were associated with oligoarticular and RF-negative polyarticular JIA [23]. Subsequently, Thompson et al. reported a new susceptibility locus at chromosome region 3q13 in their cohort of 814 JIA Caucasian patients [24]. This cohort consisted mainly of oligoarthicular JIA and RF-negative polyarticular JIA. Genome-wide association analysis was performed, and novel associations were established at 3q13 within C3orf1 and near rs4688011 regions. A new locus at 10q21 near rs647989 region was detected and associated with JIA. However, the authors did not evaluate separately oligoarticular JIA and RF-negative polyarticular JIA, probably due to limited sample size [25].

Other two studies associated *TRAF1/C5* and *VTCN1* with JIA by genome-wide analysis, but also in these cases, the study power was low [26, 27].

Percentage of T regulatory cells (Treg) in oligoarticular and polyarticular JIA patients appeared significantly decreased in comparison to healthy controls, but the clinical implications of these data are not completely clear [25, 28].

Moreover, it has been demonstrated that gene expression profiles in peripheral blood mononuclear cells showed differences not only between various subtypes of JIA but also within a given subtype depending of the magnitude of disease activity [21, 29].

Further genome-wide association studies involving all ethnicities across the world are urgently needed in order to clarify the associations of disease subset and outcome in JIA.

The "Suspected" Infectious Agents

Autoimmunity can be triggered by many environmental factors, infectious agents above all, and molecular mimicry is the strongest pathogenetic mechanism, combined with increased immunogenicity following infections and polyclonal lymphocyte activation [14, 30–32]. Clinical observations have shown that JIA can follow an infectious disease caused by viruses and bacteria, referred as potential triggers. The high percentage of disease-discordant pairs of monozygotic twins suggests the central role of environmental factors in the etiology of many autoimmune diseases. For instance, the study of animal models has clearly shown that Coxsackie B4 virus may trigger type 1 diabetes by increasing immunogenicity of autoantigens, as well as immunization with peptides derived from *Campylobacter jejuni* can induce a Guillain-Barré syndrome in rabbits through molecular mimicry between *Campylobacter* and peripheral nerve axonal antigens [33]. The use of various antibiotics and their efficacy in the treatment of adult patients with rheumatoid arthritis have also corroborated the theory of a pathogenetic role for bacteria in triggering a rheumatologic disease [34]. The main pathogens which have been associated with JIA have been summarized in the Table 2 and will be now discussed.

The Potential Role of Viruses in Juvenile Idiopathic Arthritis

Parvovirus B19 has been associated with a wide range of clinical entities, such as erythema infectiosum ("fifth disease") and aplastic crisis in immunocompetent children [35]. Anemia and arthropathies may occur in immunocompromised patients with chronic parvovirus B19 infection: a persistent infection might also occur in immunocompetent individuals who may develop an arthropathy. Several studies observed the relationship between parvovirus B19 infection and viral persistence in pediatric patients with chronic arthritides, including JIA [36]. Oğuz et al. enrolled 75 children with acute arthropathy and 75 healthy control children: they were all tested for serum anti-parvovirus IgM, which were detected in 22 % of patients and only 4 % of controls. All children were followed over time to assess the progress of arthropathy to JIA: seropositive cases significantly drifted to progress to chronic arthritis and more likely to receive a final diagnosis of JIA than seronegative ones. These data suggested a role of parvovirus B19 for the development of JIA [37].

Lehmann et al. analyzed serum and synovial fluid samples of 74 children with different rheumatologic diseases (68 were JIA patients of whom 39 with oligoarthritis, 16 with polyarthritis, 7 with psoriatic variants, 4 with systemic-onset, and 2 enthesitis-related arthritides): control sera from 124 children with noninflammatory bone diseases or growth retardation were also analyzed. Viral DNA and IgG-complexed virus were determined. Parvovirus B19 DNA was detected in 35 % of patients and in 7 % of controls; 62 % of patients had serum IgG against the viral structural proteins. A significantly higher rate of persistent B19 infection was noted in children affected by rheumatologic diseases, suggesting that Parvovirus B19 might be a possible trigger for JIA [38].

Angelini et al. enrolled 41 children with inflammatory arthritis lasting for more than 3 months and 93 healthy children. During a 1-year observation, 35 out of 41 patients developed JIA: 45.7 % of children who developed JIA were positive for anti-parvovirus B19 IgG, compared to 24.7 % of controls, and this difference was statistically significant [39].

More recently, in 2008, Lehmann et al. described the features of 5 girls with polyarticular arthritides: serum samples were analyzed for anti-parvovirus B19 IgG and IgM, and viral DNA. All patients showed persistent B19 infection [40]. These results are in agreement with those published by von Landenberg et al., who found 24 out of 88 patients with different forms of JIA positive for anti-parvovirus IgG, which seemed to elicit an autoimmune reaction partly mediated by anti-phospholipid autoantibodies [41].

Gonzalez et al. studied the presence of parvovirus B19 infection in 50 JIA patients and 39 healthy controls. IgM antibodies were found in 20 % of cases and viral DNA in 10 %, but none in controls. On the other hand, they observed IgG antibodies in 32 % of JIA patients and 44 % of controls: the percentage of parvovirus B19 IgG positivity was not significantly higher in the disease subgroups compared with healthy controls [42].

Other studies failed to identify a cause-effect relationship between parvovirus B19 infection and JIA. Weissbrich et al., in fact, evaluated the prevalence of anti-parvovirus B19 IgG in the sera from 406 children with rheumatologic diseases, including 159 cases with JIA, and 146 healthy controls. Comparing the percentage of IgG between children with JIA and control group, the authors found no significant differences, rejecting the hypothesis of a pathogenetic role of parvovirus B19 for the development of JIA [43].

Epstein-Barr virus (EBV) is another candidate to explain the pathogenesis of JIA. The association of EBV infection with adult rheumatoid arthritis and other autoimmune diseases has been reported in many scientific papers, but EBV role in JIA has not been extensively examined. Aghighi et al. enrolled 50 patients with JIA, hospitalized in Tehran during the years 2001–2002: all patients were tested for EBV capsid-specific antigens. Forty-four patients (88 %) had recent (82 %) or previous (6 %) EBV infections; the overall EBV infection rate was higher in JIA patients if compared with healthy 0- to 14-year-old children living in the same geographical area, which was 70 %. However, this result could be only a casual association and not a clear evidence of a pathogenetic link between EBV and JIA [44]. In addition, Massa et al. analyzed the role of EBV in the pathogenesis of the oligoarticular subtype of JIA: their aim was to show that the autoimmune

Table 2 Main pathogens associated with juvenile idiopathic arthritis (JIA) and references correlated with each report

Type of pathogen	Etiologic agent	Author (reference number)	Location	Case description, number of patients	Control group description, number of patients
Virus	Parvovirus B19	Oğuz et al. [37]	Turkey	Cases with acute arthritides, *n*=75	Healthy controls, *n*=75
		Lehmann et al. [38]	Germany	Cases with rheumatologic diseases, *n*=74	Controls with noninflammatory bone diseases or growth retardation, *n*=124
		Angelini et al. [39]	Italy	JIA cases, *n*=41	Healthy controls, *n*=93
		Lehmann et al. [40]	Germany	JIA cases, *n*=5	No controls
		von Landenberg et al. [41]	Germany	Cases with different subtypes of JIA, *n*=88	Controls with noninflammatory bone diseases or growth retardation, *n*=135
		Gonzalez et al. [42]	Chile	JIA cases, *n*=50	Otolaryngology ward patients, *n*=39
		Weissbrich et al. [43]	Germany	JIA cases, *n*=172	Children from endocrinology or pediatric rheumatology hospital units presenting without articular complaint and without infections, *n*=146
	Epstein-Barr virus	Aghighi et al. [44]	Iran	JIA cases, *n*=50	No controls
		Massa et al. [45]	Italy	Cases with active oligoarticular JIA and serological evidence of past Epstein-Barr virus infection, *n*=17	Non-JIA controls carrying at least one JIA-associated HLA allele and serological evidence of a previous Epstein-Barr virus infection, *n*=20
		Kawada et al. [46]	Japan	JIA cases, *n*=3	No controls
Bacteria	Enteric bacteria	Pacheco-Tena et al. [52]	Mexico	Cases with active juvenile-onset spondyloarthropathy, *n*=22; patients with adult-onset spondyloarthropathy, *n*=9; cases with rheumatoid arthritis, *n*=9	No controls
		Saxena et al. [53]	India	Cases with enthesitis-related arthritis, *n*=26 and cases with rheumatoid arthritis, *n*=10.	Healthy controls, *n*=10
		Singh et al. [54]	India	Cases with JIA—enthesitis-related arthritis, *n*=25	No controls
	Chlamydia trachomatis and *Chlamydophila pneumoniae*	Taylor-Robinson et al. [55]	Great Britain	JIA cases, *n*=19	No controls
	Chlamydophila pneumoniae	Altun et al. [56]	Turkey	JIA cases, *n*=60	Controls with familiar Mediterranean fever, *n*=22; healthy controls, *n*=35.
	Bartonella henselae	Tsukahara et al. [57]	Japan	One case of systemic-onset JIA	No controls
	Mycoplasma pneumoniae	Postepski et al. [58]	Poland	JIA cases, *n*=19	Controls with digestive tract complaints, *n*=20
	Streptococcus pyogenes	Riise et al. [59]	Norway	Cases with recent onset of arthritis acute rheumatic fever, post-streptococcal arthritis, JIA, transient arthritis), *n*=173	No controls
		Barash et al. [60]	Israel	JIA cases, *n*=41	No controls

process in JIA starts from T cell cross-recognition of exogenous and self HLA-derived antigens. The authors chose EBV as the exogenous trigger since the encounter with the virus usually occurs during the first years of life, and the usual onset of oligoarthritis is before 6 years; they included in the study 17 patients with active oligoarticular JIA, all with serologic evidence of a previous EBV infection and 20 healthy subjects with a serologically confirmed previous EBV infection,

showing at least one of the HLA class II alleles associated with oligoarticular JIA (*HLA-DRB1*1101*, *DRB1*0801*, or *DPB1*0201*). The authors found homologies between the oligoarticular JIA HLA class II alleles and EBV proteins, and a cytotoxic response against EBV-derived peptides was shown both in patients and controls, while, when stimulated by the HLA derived peptides, only patients' cells showed a cytotoxic T cell response and a significant increase in the production of IFN-γ. Furthermore, the expansion of EBV-specific T cells led to the generation of self HLA-directed cross-reactive responses. These data supported the hypothesis that EBV antigens might trigger an autoimmune response through the induction of autoreactive cells against HLA-derived peptides [45].

Conversely, EBV has been advocated as a protective factor for the risk of JIA. In fact, Kawada et al. reported three cases of JIA (two oligoarthritis and one poliarthritis) who experienced remission after a primary EBV infection. Indeed, although they had mildly active arthritis at the onset of EBV infection, they went into remission during the follow-up period (2 years, 18 months, and 3 years, respectively) [46]. As showed in a murine model, a defective control of Th17 cells and production of interleukin-17 are prominent in chronic inflammation and several immunoinflammatory disorders: in particular, Th17 cells with their proinflammatory actions might have a role in the pathogenesis of JIA and are inhibited by IFN-γ. It has been hypothesized that EBV infection might induce IFN-γ production by CD8+ T cells and inhibit the Th17 pathway, leading to the remission of JIA [47].

Two further viruses for which a possible association with JIA onset has been considered are cytomegalovirus (CMV) [48, 49] and rubella [50, 51]. In childhood, such viral infections are quite frequent and, in consequence, the prevalence of corresponding antibodies. Considering also time-dependent factors such as seasonality of infections and the delay between acute infection and JIA development, the available data do not support the participation of CMV and rubella virus in the pathogenesis of JIA.

The Potential Role of Bacteria in Juvenile Idiopathic Arthritis

The role of bacteria in the pathogenesis of JIA has been largely investigated, and different source sites in the body have been considered, such as the mucosal surfaces, respiratory tract, and gut. Pacheco-Tena et al. examined the synovial fluid cells of 22 patients with active juvenile-onset spondyloarthropathy: 9 specimens contained bacterial DNA; in particular, 5 samples had DNA of one single bacterium, 2 DNA of two bacteria, and 2 DNA of three bacteria. The bacteria involved were *Salmonella* spp., *Shigella* spp., *Campylobacter* spp., *M. tuberculosis*, and *Chlamydia trachomatis* [52].

Five years later, Saxena et al. analyzed the involvement of enteric bacteria in enthesitis-related arthritis, evaluating the lymphoproliferative response of synovial fluid and blood cells in 26 patients, using crude lysates of the enteric bacteria *Salmonella typhimurium*, *Yersinia enterocolitica*, *Shigella flexneri*, and *Campylobacter jejuni* as antigens. An antigen-specific lymphoproliferative response was observed in 14 out of 26 patients: among these patients, 12 showed a response in the synovial fluid (4 each to *Salmonella typhimurium* and *Campylobacter jejuni*, and 2 each to *Shigella flexneri* and *Yersinia enterocolitica*), and 2 in the blood (to *Salmonella typhimurium* in both) [53].

A similar study was carried out in 2011 by Singh et al., who isolated mononuclear cells from the synovial fluid and peripheral blood of 25 patients with enthesitis-related arthritis. Peripheral blood mononuclear cells from 13 out of 25 showed an antigen-specific response to different enteric bacteria: 8 to *Salmonella typhimurium*, 3 to *Yersinia enterocolitica*, and 2 to *Shigella flexneri*, while 6 patients showed a cross-reactive response to more than one bacterial antigen. Among these 19 patients, 12 showed a specific response to *Salmonella typhimurium* outer membrane protein (OMP). As regards synovial fluid mononuclear cells, in 3 out of 15 patients, there was an antigen-specific response to enteric bacteria: 2 to *Salmonella typhimurium*, 1 to *Shigella flexneri*, while in the remainder 9 patients, there was a cross-reactive response to more than one bacterial antigen. Among these 12 patients, 11 showed a proliferative response to OMP. These outer membrane proteins are accessible to the immune system and might represent a T cell-mediated target of synovial fluid and peripheral blood mononuclear cells in patients with enthesitis-related arthritis [54].

Taylor-Robinson et al. evaluated the involvement of *Chlamydia trachomatis* and *Chlamydophila pneumoniae* in JIA, investigating 19 children (10 with pauciarticular disease, 5 with poliarticular one and 4 with spondyloarthropathies): neither antibodies against *Chlamydia trachomatis* in the sera and synovial fluid samples, nor IgM against *Chlamydophila pneumonia* were detected. However, the authors found IgG antibodies against *Chlamydophila pneumoniae* in 10 patients and its DNA in one synovial fluid sample taken from 1 HLA B27-positive child with spondyloarthropathy, who showed recurrent knee effusions poorly responsive to intra-articular corticosteroids [55].

Altun et al. also investigated the role of *Chlamydophila pneumoniae* in JIA development and exacerbation. Blood samples from 60 JIA patients during an active disease period were tested for IgG, IgM, and IgA against *Chlamydophila pneumoniae*. Synovial fluid samples were taken from 20 of them and were analyzed for anti-*Chlamydophila pneumoniae* IgG and underwent real-time polymerase chain reaction assay for *Chlamydophila pneumonia* DNA. The control group included 22 patients with familiar Mediterranean fever and 35 healthy children. IgG levels were found to be significantly higher among familial Mediterranean fever patients than those

with JIA, and no significant results could be observed between healthy controls and JIA patients. Only one JIA patient had anti-*Chlamydophila pneumoniae* IgM, and all synovial fluid specimens were negative for *Chlamydophila pneumoniae* DNA. High IgG levels were found in the blood and synovial samples of one patient. Three other patients with serum IgG level of 1/16 had a synovial fluid IgG level of 1/128, suggesting that these antibodies were produced within the joints. Therefore, the authors concluded that *Chlamydophila pneumoniae* is not a significant trigger or an exacerbating factor in JIA patients [56].

The role of *Bartonella henselae* infections in the systemic-onset JIA was speculated too. Tsukahara et al. described the case of a 4-year-old girl who received a scratch from a cat 1 month before the disease onset. Serum anti-*Bartonella* antibodies were tested: IgM levels were negative, while IgG were 1:4096, suggesting that *Bartonella henselae* infection might have triggered a systemic inflammatory response in the patient [57].

Postepski et al. considered also *Mycoplasma pneumoniae* infection in the etiopathogenesis of JIA. Nineteen patients aged between 6 and 17 years and a control group of 20 children of similar age, hospitalized due to digestive symptoms, were tested for IgM and IgG against *Mycoplasma*. IgG positivity was observed in 58 % of patients and 15 % of controls: the authors stated that *Mycoplasma pneumoniae* infection might have had a role in triggering the disease [58].

Finally, there is some evidence suggesting that streptococcal infections may contribute to JIA pathogenesis or exacerbation. Riise et al. studied 173 children with recent onset arthritis, with 33 of them diagnosed as having JIA. Of these 33 cases, only 9 % was positive for a recent streptococcal infection [59]. Another study that examined all cases of JIA hospitalized during a period of 10 years found a high correlation between disease exacerbations and streptococcal infections, concluding that "arthritogenic" streptococci may cause flare-ups of chronic arthritides [60].

At last, it has been observed that periodontal infections by *Porphyromonas gingivalis*, unique among oral bacteria as it produces an enzyme capable of citrullinating human peptides, might lead to autoimmune reactions: unfortunately, data related to *Porphyromonas gingivalis* infections in children are poor, though results from a case-control study with 332 people showed that immunity to *Porphyromonas* was significantly associated with the presence of rheumatoid arthritis-related autoantibodies [61].

Although Reiter's syndrome (RS) represents an exclusion criteria for JIA, some bacteria that underlying RS have been hypothesized to be involved in JIA pathogenesis [62, 63]. Molecular mimicry is an attractive mechanism for triggering autoimmunity that could explain these findings [64]. The wide distribution of the highly conserved stress proteins or enzymes among the members of the normal flora and common infectious microorganisms raises a new question on how cross-reactive autoantibodies are not produced during the immune response to these bacteria in most healthy people. Understanding the mechanisms that deselect autoreactive B cell clones during the germinal center reaction to homologous foreign antigens may provide a novel strategy to treat autoimmune diseases.

Conclusive Remarks

JIA development in genetically susceptible individuals could be triggered by the exposure to environmental factors, including infectious agents. Although there are ethnical and cultural differences in researches performed in different countries, several studies support the role of infection in triggering or increasing the risk of JIA. Nevertheless, the mechanism remains speculative and may be different among the wide set of infectious agents. The infection can represent a random event in a susceptible individual, or it can be a necessary factor in JIA development, always in combination with a peculiar genetic background.

On the other hand, some epidemiological and clinical data support the hygiene hypothesis according to which the decrease of infections observed over the last three decades is the main cause of the incessant increase in immune disorders [65–68]. The hypothesis does not exclude an etiological role for specific pathogens in a given immune disorder. Even in this setting, infections could still have a nonspecific protective role. Independent of the need for confirmation by epidemiological prospective studies, the hygiene hypothesis still poses numerous questions concerning the nature of protective infectious agents, the timing of their involvement with regard to the natural history of immune diseases and, most importantly, the mechanisms of protection.

The current knowledge of the involved infectious agents and the genetic characteristics of susceptible children is currently not complete. Further studies are needed in order to address the unsolved questions concerning this issue. A better understanding of pathogenetic pathways in JIA will probably lead to the development of targeted therapies, leading to a decrease in the incidence of short- and long-term morbidities and functional articular impairment.

Summary

- Infections have long been suspected as being trigger factors in the development of autoimmune processes, including juvenile idiopathic arthritis (JIA).
- The potential link between parvovirus B19 or Epstein-Barr virus and JIA has been studied, mostly in a retrospective manner.

- The role of enteric bacteria, *Chlamydophila pneumoniae*, and streptococcal infections in JIA development and exacerbation has been widely debated with inconclusive results.
- No unequivocal evidence favoring or refuting the association of JIA with infectious agents has been clearly confirmed.
- Future research has to be done to improve our knowledge about the genetic elements of childhood inflammatory arthritis.

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