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Sex Differences in Pediatric Rheumatology

Marco Cattalini[1] · **Martina Soliani**[1] · **Maria Costanza Caparello**[2] · **Rolando Cimaz**[2]

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Abstract Autoimmune diseases affect up to 10% of the world's population and, as a whole, they are far more common in females, although differences exist according to the single disease and also in different age groups. In childhood-onset autoimmune diseases, the sex bias is generally less evident than in adults, probably for the different hormonal milieau, being estrogens strongly implicated in the development of autoimmunity. Still, some rheumatic conditions, such as juvenile idiopathic arthritis (JIA), show a strong predilection for girls (F:M = 3–6.6:1), and differences may coexist between males and females regarding disease outcome. For example, chronic anterior uveitis associated with JIA affects more commonly girls but boys tend to have a more severe course. Systemic lupus erythematosus predominantly affects girls and women (F:M = 3–5:1 in children, F:M = 10–15:1 in adults). Behçet's disease has been reported to be more prevalent in adult males (F:M = 1:1–4); in children, there are no differences. The sex ratio is equal in children and adults for Henoch-Schönlein purpura (F:M = 1:1). A higher male-to-female ratio exists for Kawasaki disease (F:M = 1:1.1–1.6 in children, F:M = 1:1,5 in adults). Juvenile dermatomyositis (F:M = 2–5:1), systemic sclerosis (F:M = 4:1 in children, F:M = 6:1 in adults), and Takayasu arteritis (F:M = 2:1 in children, F:M = 7–9:1 in adults) are more common in girls and women then in boys and men. There is no gender bias for acute rheumatic fever in children, while in adults, the F:M ratio is 2:1. Given that estrogen levels are not different between genders during childhood, pediatric rheumatic diseases could represent good models to study other mechanisms related to the development of autoimmunity. Recently, the levels of miRNA expression, and their variation according to sex chromosomes, have been linked to the development of autoimmune diseases, with different impact among sexes. This review will focus not only on the sex bias reported in the more common rheumatic conditions of childhood, focusing on differences in incidence, but also on outcome and trying to depict the mechanisms underlying those differences.

Keywords Sex bias · Estrogens · Autoimmunity · Childhood rheumatic diseases

Autoimmune diseases affect up to 10% of the world's population and, as a whole, they are far more common in females, although differences exist according to the single disease and also in different age groups. Indeed, as further discussed in this review, the sex bias is not that evident in childhood autoimmune diseases (see Table 1; Fig. 1). Sexual dimorphism seems to have an impact in mechanisms related to the development and maintenance of autoimmune diseases. The etiology of autoimmune diseases is multifactorial and closely connected to both genetic background and environmental exposures: genes usually confer disease risk, but the role of the environment and epigenetic mechanisms can mediate this interaction (Fig. 2) [1–3]. Recently, noncoding RNAs (ncRNAs) have attracted attention for their involvement in the pathogenesis of autoimmune diseases. Noncoding RNAs include microRNA (miRNA), nonprotein-coding RNAs which probably regulate a majority of human genes at the

✉ Rolando Cimaz
rolando.cimaz@meyer.it

[1] Pediatric Clinic, University of Brescia and ASST Spedali Civili di Brescia, Brescia, Italy

[2] Anna Meyer Children's Hospital and University of Florence, Viale Pieraccini 24, 50139 Florence, Italy

Table 1 Sex bias and prevalence rates in autoimmune diseases among adults and children

	Incidence/prevalence in children	Incidence[a]/prevalence in adults
SLE	0.36–1[a] (257)	3.6–30[a] (24, 256)
Behçet's disease	0.17–0.3[b] (181)	1–71[b] (274–276)
JIA	3–23[a] (259)	31–40[a] (rheumatoid arthritis) (258)
DM	2.5–4.1[b] (262)	4.6–9.63[b] (260, 261)
SSc	0.27[a] (264)	0.6–22.8[a] (263)
KD	22–69[a] (peak of 2401/100.000 in Japan) (265–267)	<100 cases described worldwide (269)
Henoch-Schönlein purpura (HSP)	20–70[a] (211)	1.3[a] (272)
Acute rheumatic fever	100–600[a] (192)	23.5[a] (208)
Takayasu arteritis	2.6[b] (238, 239)	1–3[b] (240, 241)

[a] Number/100,000/year

[b] Number/1,000,000

post-transcriptional level and play a critical role in immunity and autoimmunity [4, 5].

It has been demonstrated that males and females, in response to environmental stimuli and/or pathological events, show sex-specific miRNA expression [6–8]. The potential contribution of miRNA expression to sex differences in immune response and autoimmune diseases is under-investigated thus far. About 10% of microRNA are localized on X chromosome, suggesting a possible role in regulating sex-specific gene expression [4]. One may speculate that X-linked miRNAs, which escape inactivation or are subject to skewed X inactivation, may influence immune response in females [5].

The variable expression of miRNAs is only one of the possible mechanisms linking X chromosome inactivation (XCI) and autoimmunity. XCI is the random silencing of X chromosome that happens in the earlier phases of female embryogenesis [6]. In normal conditions, the XCI happens in a 50:50 ratio between maternal and paternal-derived X chromosome, but extreme skewing (inactivation of more than 90% of one allele) may happen. This phenomenon may have an impact on the development of self-tolerance, since self-antigens, and autoreactive T cells specific for the less represented chromosome may escape negative selection, and therefore activate the production of autoantibodies. This hypothesis may explain, for example, the polyclonal, nonspecific T cell activation found in SLE [7]. XCI may be linked with the development of autoimmunity also through the haploinsufficiency for X-linked genes. This hypothesis is supported by the link between autoimmune diseases and Turner syndrome. Turner syndrome (TS) is a rare genetic disorder, affecting approximately 1 out of 2500 new born females, characterized by the

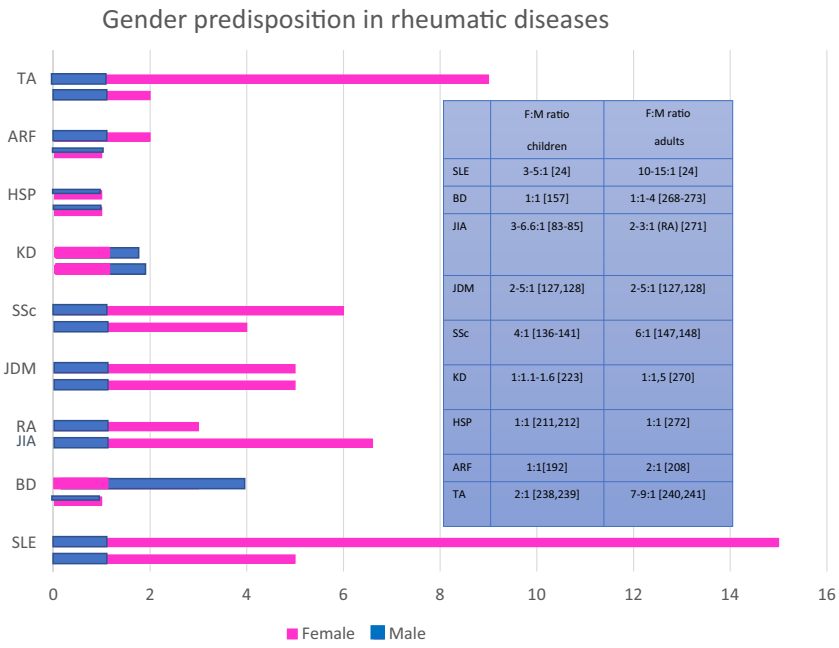

Fig. 1 This bar chart represents the gender predisposition in rheumatic diseases among adults (*top bar* for each disease) and children (*bottom bar* for each disease). When F/M ratio ranges, highest values are considered. *TA* Takayasu arteritis, *ARF* acute rheumatic fever, *HSP* Henoch-Schönlein Purpura, *KD* Kawasaki disease, *SSc* systemic sclerosis, *JDM* juvenile dermatomyositis, *RA* rheumatoid arthritis, *JIA* juvenile idiopathic arthritis, *BD* Behçet's disease, *SLE* systemic lupus erythematosus

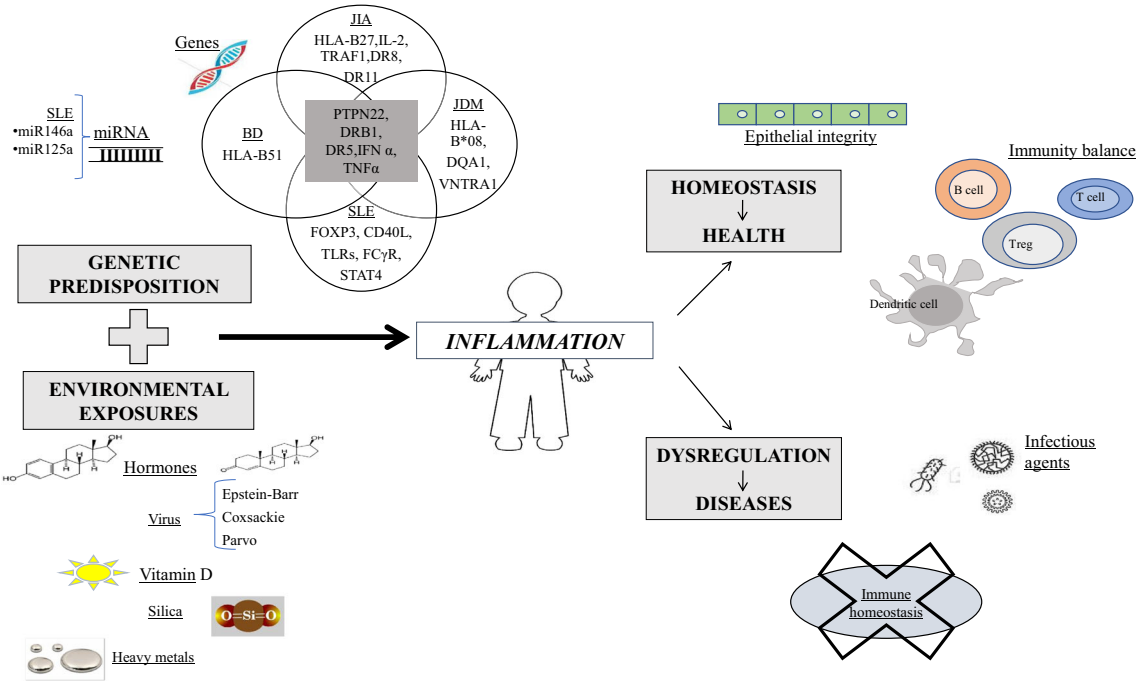

Fig. 2 The combined effect of environmental and genetic factors can lead to the development and maintenance of autoimmune diseases. Genes confer disease risk and miRNA may play a role in autoimmunity in response to environmental factors. *miRNA* microRNA, *SLE* systemic lupus erythematosus, *JDM* juvenile dermatomyositis, *JIA* juvenile idiopathic arthritis, *BD* Behçet's disease

presence of one normal X chromosome and a missing or structurally abnormal second one, in germinal and somatic lines [8]. Autoimmunity has been recognized as one of the more prominent characteristics of women with TS. The involvement of the thyroid, and specifically Hashimoto's thyroiditis (HT), is by far the most common associated disorder, ranging between 4 and 50% compared with 1.5% of adult women in the general population [9]. Other described associations with TS are ulcerative colitis and Crohn's disease, type 1 diabetes, coeliac disease, chronic arthritis, and uveitis [10–17]. Interestingly, Jorgensen and colleagues found that the risk of autoimmunity was higher in the male-predominant types of Turner syndrome, compared with the female predominant types, arguing that the risk to develop AIDS might be partially explained by haploinsufficiency of X-linked genes [11].

For adult-onset autoimmune diseases, the differential action of sex hormones plays a major role [18]. Androgen and estrogen have been first identified as potentially responsible for the sex bias, since these hormones can directly affect the development and function of several immune cells [12–16].

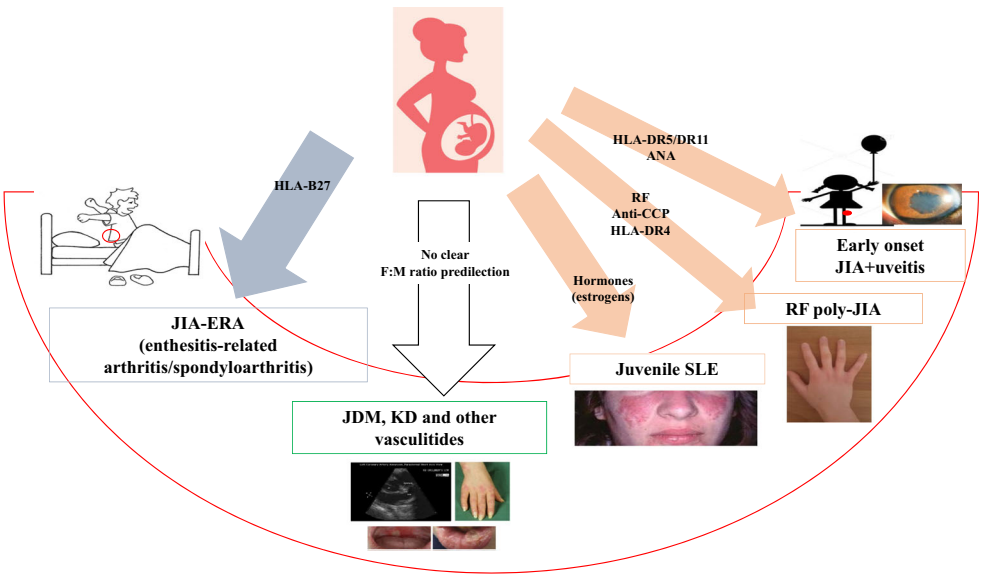

Fig. 3 There are childhood-onset rheumatologic diseases for which one gender predominates. Oligoarticular ANA-positive JIA, with an early age of onset, tends to predominantly affect girls and is frequently complicated by uveitis. Polyarticular RF-positive JIA also tends to affect young girls but in perimenarcheal age. Enthesitis-related arthritis has a much higher frequency in boys than in girls and is associated with HLA-B27. Juvenile-onset SLE predominantly affects adolescent girls. *JDM* juvenile dermatomyositis, *KD* Kawasaki disease, *SLE* systemic lupus erythematosus, *JIA* juvenile idiopathic arthritis

Androgens tend to favor a Th1 response and activation of CD8+ cells, whereas estrogens exert the opposite effect, promoting Th2 dominance, leading to antibody production [19]. In childhood-onset rheumatologic diseases, a sex bias is not as common, but there are several diseases for which one gender predominates. Since prepubertal sex hormone levels are not disparate between males and females, it is likely that other biological mechanisms, like the ones we already alluded to, may be involved. For example, it is known that sex genes makeup (XX or XY) has an effect on the immune system independent from sex hormones; this concept provides us some clues to understand the role of sex chromosomes in pediatric rheumatology [20].

Systemic Lupus Erythematosus

Systemic lupus erythematosus (SLE) is an extremely polymorphic systemic autoimmune disease, characterized by a multifactorial pathogenesis in which a genetic susceptibility interacts with environmental factors. SLE features a broad spectrum of abnormalities of both the innate and the adaptive immune system, leading to the production of nonorgan-specific autoantibodies directed against nuclear, cytoplasmic, and cell surface antigens, these being responsible for a wide range of tissue damage.

SLE is most prevalent among women of childbearing age, though it can present at all ages. In about 15% of cases, its onset occurs before 16 years of age (juvenile-onset SLE (jSLE)) [21]. Several studies have reported that age at disease onset represents an important variable for disease progression: jSLE tends to be associated with a more severe course and young patients are more likely to have hematological, renal, and neurological involvement and to accrue renal damage, compared with adults [19–23]. The incidence of the disease is estimated at 20–50 cases/100,000 individuals, with wide variations related to both sex and age: while during fertile years, women outnumber men 10–15:1, in preadolescence and after menopause, the F:M rates decline to 3–5:1. [23]. This difference clearly points to the role of sex hormones in disease pathogenesis. Although the mechanism underlying SLE pathogenesis is still unknown, it is likely that a complex interaction between genetic predisposition and environmental agents triggers the immune dysfunction and leads to disease onset and flares. Indeed, given the gender bias mentioned above, estrogen production is nowadays considered an important factor influencing both the pathogenesis and the course of the disease. Molecularly, estrogen acts via receptor ER (ERα and ERβ). These receptors are widely distributed among human cells, and they are also present in immune system elements, such as dendritic cells, macrophages, and T and B lymphocytes [24]. ERα and ERβ show opposite effects on immune system regulation: while the first has a proinflammatory activity and seems to promote disease progression and renal damage, the latter has a mild immunosuppressive effect [25–28]. Recent studies in lupus experimental models clearly demonstrate a correlation between estrogen and the development of SLE, estrogen being disease promoter via ER, as mentioned above. Estrogen promotes CD4+ switch towards Th2, leading to antibody production, supports the survival of autoreactive T lymphocytes, and influences interferon (IFN)-γ production in NK cells. [25]. Shen et al. found that, in mice, the expression of interferon regulatory factor 5 (IRF5), which is a susceptibility factor for developing SLE and regulates the type 1 IFN production, is sex dependent, demonstrating that IRF5 mRNA levels increase simultaneously with concentration of estrogen (17β-estradiol) [26]. Moreover, estrogen seems to contribute to the sex disparity in SLE by regulating miRNA expression to promote inflammatory responses by enhancing IFN-γ production in activated splenocytes from estrogen-treated mice [3, 27]. Dong et al. found that 17β-estradiol could amplify the activation of IFN-α signaling in B cells via IKKε by down-regulating the expression of specific miRNAs [28]. In humans, Pan et al. identified that miR-21 and miR-148a are overexpressed in CD4+ T cells from SLE patients, this in turn leading primarily to promotion of cell hypomethylation by repressing DNA methyltransferase 1 (DNMT1) expression and subsequently to overexpression of autoimmune-associated methylation-sensitive genes, such as CD70 and LFA-1 [29] Conversely, other miRNAs such as miR146a and miR125a, negatively regulating respectively the IFN-α pathway and inflammatory chemokine RANTES, are profoundly downregulated in PBMCs from patients with SLE, compared with healthy controls [30, 31]. Finally, Jing et al. have recently described increased serum prolactin concentrations in lupus-prone B/W mice, triggered by ERα activation. This interaction may contribute to lupus disease progression through the stimulation of prolactin secretion [32]. Recent studies correlated the risk of developing SLE with X chromosome: XXY Klinefelter's males have been demonstrated to have a disease risk similar to female population [33]. Smith-Bouvier et al. demonstrated that this phenomenon could be attributed to the extra X chromosome in Klinefelter patients and is independent from gonadal hormone production [20]. Young et al., by treating PBMCs with 17β-estradiol, revealed an estrogen induction of a set of genes, among which toll-like receptor 8 (TLR8), an X-linked mediator of innate immunity that is known to be associated to SLE [34]. Other SLE-associated X-linked genes, such as FOXP3, CD40L, other endosomal TLRs (TLR3, TLR7, and TLR9), MECP2, and IRAK1 can be overexpressed in women, likely due to incomplete X inactivation [35–38]. On the other hand, extreme skewing may alter the process of self-tolerance, as already discussed.

As both are molecularly and genetically a distinct dualism between males and females catches a reader's eye, what about the clinical aspect? A few years ago, many authors tried to outline the clinical profile of SLE-affected men. By reviewing

a previous literature, Lu et al. observed that renal disease was frequently found to be more common among male SLE patients, in adult population. These data have subsequently been confirmed by other clinical studies [39–41]. A significantly higher prevalence of discoid lesions has been described in males compared with females, while females, in a more recent paper from a Spanish group, are more likely to have photosensitivity, malar rash, mouth ulcers, and Raynaud's phenomenon [42–44]. A male dominance in hematological involvement (hemolytic anemia, lymphopenia, and thrombocytopenia) has been reported in several studies involving adult population, while other authors observed that leukopenia and thrombocytopenia were more common in women [45–49]. Serositis has been described as more frequent at disease presentation among men, while a recent cross-sectional study by Diang et al. displayed no significant difference in gender between SLE patients with serositis versus those without serositis, while they detected a statistically significant male prevalence in pleuritis [50, 51]. A retrospective study by Specker et al. pointed out that men were more likely to have life-threatening thromboembolic complications [37]. With regard to arthritis, the gender prevalence is still a matter of debate [52–54]. Serologically, a positive detection of anti-Ro/SSA antibodies seems to be more frequent in female than in male patients [50, 55].

All the afore-mentioned differences pertain to the adult age, but what about sex differences in juvenile SLE? Probably because of the lower incidence of SLE in pediatric population and the less striking gender bias, poor evidence is available. Lo et al. conducted a retrospective analysis of 135 jSLE patients (24 boys and 111 girls): they found a female prevalence of oral ulcers, alopecia, and anti-SSA antibodies [40]. Recently, Hui-Yuen et al. analyzed transcriptional profiles obtained from SLE young patients. While girls overexpressed an IFN-α signature, boys were observed to have tumor necrosis factor-related genes up-regulated [56, 57].

Juvenile Idiopathic Arthritis

Juvenile idiopathic arthritis (JIA) is the most common chronic inflammatory arthropathy of childhood. Although JIA is a heterogeneous disease, seven different subgroups are considered in the last classification [50], and the female preponderance is overall striking. Still, while the reason for the observed sex bias remains an opened question, few studies have investigated this phenomenon [58–61], and the observation that in the majority of cases JIA has its onset in the prepubertal age suggests that the role of sex hormones is negligible. Different studies pointed to genetic predisposition to JIA [62–77], but unfortunately the contribution of these studies in elucidating the reason of the sex bias is poor (Table 2).

Oligoarticular and polyarticular RF-negative categories of JIA have been the most often investigated for genetic associations. Oligoarticular JIA has its peak incidence between 2 and 4 years of age and has a female/male ratio in North America and Europe of 3:1. In children with uveitis, the ratio of girls to boys is even higher, from 5:1 to 6.6:1 [92–95]. However, in Asia, oligoarthritis occurs predominantly in boys, and uveitis is reported to be rare. Like oligoarticular JIA, polyarticular RF-negative JIA also tends to affect predominantly girls and has an early age of onset [96, 97]. Recently, a case-control genome-wide study on ten pediatric autoimmune diseases demonstrated

Table 2 Genes associated with the development of JIA

Gene	Protein	Function	Reference
MIF	MIF	Cofactor in T cell activation and promotes proinflammatory activity	Berdeli [78] and Donn [79]
TRAF1	Tumor necrosis factor receptor-associated factor 1	Regulates TNF pathway	Albers [80]
STAT4	Activator of transcription factor 4	Involvement in immune response	Prahalad [81]
IL2RA	CD25	Regulates development and function of regulatory T cells	Hinks [82]
WISP3	Chondrocytes from human cartilage and regulates type II collagen and aggrecan	Cartilage homeostasis	Lamb [83]
PTPN-22	Tyrosine phosphatase nonreceptor type 22	Negatively regulates T cells	Chiaroni-Clarke [84] and Goulielmos [85]
SLC11A6 (NRAMP1)	Natural resistance-associated macrophage protein	Up-regulation of TNF-a, IL-1b, iNOS, and MHC class II expression	Sanjeevi [86]
TNFA	TNF alpha	Regulation of the immune system cells	Zhou [87] and Zeggini [88]
CD226 (DNAM1)	DNAX accessory molecule-1	Costimulation of T and NK cells	Reinards [89]
IL2-IL21	IL-2 and IL-21	Dysregulation of the immune system	Hinks [90]
AFF3	Tissue-restricted nuclear transcriptional activator	Developing disease risk	Ellis [91]

that genetic variation on the X chromosome could account for around 3% of the phenotypic variance of JIA [48]. In another study aimed at exploring the skewed XCI, Uz et al. analyzed 62 JIA (oligoarticular and poliarticular) patients and 155 controls, and they found out that 13% of JIA cases had extreme skewing (90% or greater), whereas only 1% of controls showed such extreme skewing [98, 99]. Although these findings should be confirmed in other studies, they link the risk of developing JIA to XCI [49].

Enthesitis-related arthritis (ERA) has a much higher frequency in boys than in girls with a male/female ratio of 7:1 [87, 100–104]. The strong correlation of ERA with HLA-B27 does not account for this gender bias, given the equal distribution of this antigen in males and females. It has been demonstrated that spondyloarthropathies occur more frequently in men (male-to-female ratio of 3:1), but this bias decreases as age advances [105]. In women, manifestations of the disease may occur later and be less severe, and women usually have more peripheral and less axial disease [106–108]. These observations probably contribute to explain the relative lower frequency of ERA among girls. Several hypotheses have been proposed to explain sexual dimorphism, but data are conflicting [109–111].

Uveitis is a common complication of JIA, mostly in patients who are positive for antinuclear antibody (ANA) [97, 112–115]. The most typical type is chronic bilateral anterior uveitis, but other types of JIA-associated uveitis may occur, such as the recurrent acute anterior uveitis associated with enthesitis and a positive HLA-B27, which affects boys more commonly than girls [55]. In contrast, chronic anterior uveitis associated with JIA occurs predominantly in girls with persistent and extended oligoarticular arthritis [116]. Data from a Canadian registry of patients with JIA suggested that the risk of developing uveitis in girls was dependent on age at onset of JIA and ANA positivity. This association was not observed in boys, although this may be secondary to the lower number of boys with JIA-associated uveitis recruited [56]. Despite the lower number of boys affected, several reports have demonstrated worse clinical outcomes of JIA-related uveitis in boys compared with girls, although this is not universally observed. A study conducted by Woreta et al. failed to demonstrate male gender as a risk factor for developing complications related to chronic uveitis, but, again, there was a striking preponderance of girls among the recruited patients (75% girls vs. 25% of boys) [117–120]. No gender differences were reported in a study of 327 patients with JIA-associated uveitis from the Systemic Immunosuppressive Therapy for Eye Disease (SITE) Research Group [121]. Similar data were reported by Thorne and colleagues in75 patients with JIA-associated uveitis [58]. Hoeve et al. retrospectively investigated the clinical course of 62 children with JIA-associated uveitis, 22 of which were boys. The authors observed no gender-related differences in the level of cellular inflammation but there was a trend towards the increased use of immunosuppressive drug therapy in boys [59].

Juvenile Dermatomyositis

Juvenile dermatomyositis is the most common clinical phenotype of chronic myositis among children, with a prevalence of approximately 80% of all patients with juvenile idiopathic inflammatory myopathies (JIIMs). The average age at onset is 7 years, though one fourth of the patients are younger than 4 years of age when displaying the first symptoms [122, 118].

Main clinical manifestations are symmetric proximal and axial muscle weakness, usually insidious and misinterpreted, and often recognized late; pathognomonic Gottron's papules in small joints of the hands, heliotrope rash of the eyelid, erythematous malar rash with a mask-like distribution are also observed [60]. There can be associated impairment of smooth muscle function, in both respiratory and gastrointestinal apparatus, manifesting as speech difficulty, abdominal pain, constipation, or diarrhea. Juvenile dermatomyositis (JDM) can also be associated with a small-vessel vasculopathy, evidenced by dilated and tortuous periungual capillaries [60]. Approximately 20–50% of patients with JDM develop calcinosis, which consists of subcutaneous calcium deposits in tissues and muscles [61, 62]. The development of calcinosis seems to be influenced by both a young age at disease onset and the presence of anti-NXP2 autoantibodies [63]. While in adults an association between DM and malignancy is well documented, in children affected by JDM, no such association has been established. By surveying previous literature, Stübgen detected a possible, though rare, association between JDM and limphoma [64].

In JDM, the F:M estimated ratio is 2–5:1, with girls outnumbering boys. During adulthood, dermatomyositis (DM) affects women three times more often than men, resulting in a F:M ratio stable in time [65]. The reason of this sexual dimorphism is still unknown.

DM shows common association within the human leukocyte antigen (HLA) region: two large HLA imputation studies have recently confirmed a strong association with the 8.1 ancestral haplotype (AH) in clinical subgroups of myositis, including DM, suggesting multiple independent associations on this haplotype [66]. The HLA class II gene DRB1 allele *0301 (also known as DR3) has been identified as a major immunogenetic risk factor for JDM [67]. Lintner et al. recently investigated the potential association with low gene copy number variations of complement C4 gene in 105 JDM patients [68]. They pointed out a correlation between C4A deficiency and

elevated serum muscle enzymes such as creatine kinase and aldolase. Niewold et al. investigated the association between high serum IFN-α and genetic polymorphisms of both osteopontin (OPN) rs28357094G and tumor necrosis factor alpha (TNF-α) –308 A allels, in newly diagnosed JDM patients [69]. Both OPN and TNF-α polymorphisms were associated with a higher serum IFN-α and were more commonly detectable in females. Dourmishev et al. investigated the role of *Xba*I and *Pvu*II polymorphisms of the *ESR1* gene (which encodes for the estrogen receptor-α), as possible disease-modifying factors in women with DM, being more detectable in a subgroup of patients with electromyography (EMG) findings and elevated muscle enzymes [70].

No clear-cut differences have been observed in children with JDM, regarding clinical manifestations of disease related to gender.

Systemic Sclerosis

Systemic sclerosis (SSc) is a rare multifactorial and heterogeneous disorder affecting the immune system, the microvascular system, and the connective tissue, resulting in skin and internal organ fibrosis [71]. SSc is associated with a strong female predominance; data from patients registered in the EUSTAR database as of November 2013 [72] showed a sex ratio (women/men) in SSc of about 6:1, whatever age at disease onset, concordant with previous literature [73–77, 92]. It is also known that the sex ratio can be higher during childbearing years and decreases in the postmenopausal years, suggesting that the female hormonal milieu and the pregnancy-related events will be possibly related to disease susceptibility [73]. The roles of sex chromosomes and reproductive hormones, genetic and epigenetic differences, environmental exposure, and lifestyle have all been investigated, in order to explain this sex bias, but with inconclusive results [93–95]. The female preponderance is not associated with disease severity, since male patients usually have a more severe prognosis [77, 96]. SSc onset in childhood is very uncommon, with less than 10% of patients with SSc developing the disease before the 20th birthday. The mean age at onset in the pediatric cases is 8.1 years, the disease is more frequent in females with a rate of 4:1. As for the adult population, the reasons for this sex bias are far for being understood [97, 123].

Juvenile Localized Scleroderma

Juvenile localized scleroderma (JLS), often called morphea, encompasses different conditions characterized by skin thickening: linear scleroderma, plaque morphea, and *en coup de saber* scleroderma. In the largest pediatric cohort reported so far, the disease showed a female predilection, with an overall female-to-male ratio of 2.4:1. This bias was more evident in deep vs. generalized and plaque morphea and in children younger than 10 years at disease onset [98]. Probably due to the relative rarity of this disease, no studies have specifically addressed neither the role of sex on disease characteristics nor the possible reasons for the sex bias.

Behçet's Disease

Behçet's disease (BD) is a rare immune-mediated small-vessel systemic vasculitis of unknown etiology, characterized by oral and genital ulceration, skin lesions, and uveitis, with a strong association with HLA-B51 [99, 100]. A recent meta-analysis indicated that HLA-B51/B5 was more common among male patients and was associated with higher prevalence of genital ulcers, ocular and skin manifestations, and lower prevalence of gastrointestinal involvement [101]. Children are rarely affected by BD [102]. The exact prevalence is unknown, and the usual age at disease onset is around 30 years [103]. The recent discovery of A20 protein haploinsufficiency as a cause of autosomal dominant "Behçet-like" disease supports the idea that the spectrum of disorders included in BD may not be related to a single gene and that a very early and atypical disease onset may underlie a monogenic disorder [87].

While other autoimmune diseases are more common among women of childbearing age, the most recent epidemiological studies tend towards an equal sex ratio in pediatric BD but with significant gender differences in clinical manifestations and severity [104]. For certain geographic regions and particular ethnic groups, Behçet's disease has been reported to be more prevalent in males [106, 124] with a more severe course and higher mortality rate, especially from the second to the fourth decade, among young male patients [107]. In a retrospective cohort study of 817 children and adults followed up for a median of 7.7 years, death was associated with younger age (15–25 years), male sex, arterial involvement, and a high number of flares [108]. In contrast with this report, a recent large Chinese population-based study showed no significant gender differences in the incidence or prevalence of the disease [109]. The most common manifestation in adult onset is recurrent oral ulcer (OU), and data from a retrospective review of 3527 patients showed that oral ulcers were more common in females and exacerbations correlated with menstrual cycles [110–113]. OU may be the only manifestation of disease for an average of 6 to 7 years before the second major manifestation arises [114, 115, 125]. In the pediatric population, OU is not exceptional and remains a major clue for the diagnosis of BD. Similar to oral ulcers, genital ulcers are also more frequent in females, being observed in 55 to 83% of children with BD [126]. Other mucocutaneous manifestations in children are necrotic folliculitis and acneiform lesions, which are more commonly reported in females, and erythema nodosum, which seems to be more common in males [127].

Males with BD are at a higher risk of developing uveitis and of evolving in complications such as posterior synechiae (32.4%), cataract (31.5%), and cystoid macular edema (19.8%); neuro-Behçet's manifestations are described more commonly in younger boys [117, 127]. Gender could also have an impact on response to treatment, as suggested by few therapeutic trials [118–120, 122, 128, 129].

Despite the fact that numerous studies evidenced a gender bias, there is no clear evidence as to what is the cause of this difference [126, 127, 130–132]. Both genetic and environmental factors (smoking, infection, vitamin D, and immune dysregulation) have been investigated [99, 103, 133–137] but with no clear results.

Acute Rheumatic Fever

Acute rheumatic fever (ARF) is the consequence of a group A streptococcal pharyngitis. Cardinal manifestations are arthritis, usually of large joints, cardiac involvement, mainly characterized by inflammation of the valvular apparatus, skin disease (eritema marginatum and subcutaneous nodules), and chorea [138]. ARF and rheumatic heart disease (RHD) continue to be major causes of morbidity and mortality among young people in developing nations and can be regarded as a manifestation of poverty and social inequality. There are over 15 million cases of RHD worldwide, with 282,000 new cases and 233,000 deaths annually [139, 140]. In a systematic review based on a meta-analysis of 37 populations, the mean age was 11 years and there was no sex bias [141]. Prevalence of rheumatic heart disease progressively increases between the ages of 5 years and 16 years [142–152]. Some other studies reported a higher incidence of ARF among females, particularly in adulthood [153–158]. This is probably a mirror of economic disparities and social inequality. For example, it might be explained by underschooling of girls or a greater exposure to β-haemolytic streptococci of young mothers compared with men [140, 145, 159].

Henoch-Schönlein Purpura

Henoch-Schönlein purpura (HSP) is the most common pediatric vasculitis and usually affects children from 3 to 10 years of age, with a mean age of 6.5 years at disease onset and no gender predilection [160, 161].

HSP is a systemic leucocytoclastic small-vessel IgA-mediated vasculitis, usually manifesting with nonthrombocytopenic purpura predominantly evident on lower extremities and buttocks, associated with joint, gastrointestinal, or renal involvement; the latter, when persistent, is responsible of the major long-term complications [162]. Blistering eruptions can occur in a small percentage of patients and, when present, blisters develop concomitantly with purpura or within 2 weeks from its appearance and tend to overlap on the same body areas [163]. Although etiopathogenesis is still poorly understood, some authors consider infective agents, vaccinations, drugs, and insect bites to play as triggers, being responsible for the elevation of circulating immunoglobulin A (IgA) and complement activation [164]. A familial occurrence of HSP has been reported in some cases [165]. HSP has an abrupt onset, and in most cases, a benign self-limiting course, with a complete recovery within few weeks. The chronicity of the disease and the long-term prognosis depend on the severity of renal involvement, usually manifesting with hematuria and/or proteinuria within the first month after disease onset but rarely appearing years after the diagnosis of HSP. Chen et al. aimed to develop a biomarker panel for renal involvement in HSP. They found increased levels of both urinary cystatin C and neutrophil gelatinase-associated lipocalin in HSP patients with renal involvement, compared with healthy controls and HSP patients without renal disease [166]. Other risk factors that were associated with renal involvement were male gender, disease onset after 10 years of age, severe gastrointestinal symptoms, arthritis or arthralgia, persistent purpura or relapse, and low serum C3 levels [167]. Central nervous system (CNS) involvement in HSP is rare (0.65–8%) and occurs mainly in patients with arterial hypertension or atypical presentation. Main CNS manifestations in HSP are posterior reversible encephalopathy syndrome (PRES) and hypertensive encephalopathy [168, 169].

Kawasaki Disease

Kawasaki disease (KD) is the second most common vasculitis occurring during pediatric age. KD exhibits a specific predilection for the coronary arteries and results in coronary artery abnormalities in up to 25% of untreated children, representing the leading cause of childhood-acquired heart disease [170]. KD is more common among young children and in 80% of cases the disease occurs before the age of 4 [171]. The incidence of KD varies considerably between ethnic groups, with incidence rates in North East Asia up to 20 times higher than in Europe. A slight male predominance is observed, with a M:F ratio ranging from 1.1 to 1.6 [172, 173]. Even though the exact pathogenesis is still unknown, it is generally accepted that KD might be triggered by an infectious agent that activates the immune system in a genetically predisposed host. Few disease-susceptibility genes have been discovered, such as inositol 1,4,5-trisphosphate 3-kinase C (ITPKC), CASP3, B-lymphoid kinase (BLK), and CD40 polymorphisms, the latter being involved in KD progression, through the CD40L–CD40 signaling [174–180].

From a clinical point of view, KD is characterized by fever, persisting more than 5 days despite antibiotic treatment. Fever is mandatory for diagnosing KD [181]. The conjunctival hyperemia is mostly bilateral and nonexudative, whereby a mild acute iridocyclitis or anterior uveitis can coexist [182]. A typical strawberry tongue and a diffuse erythema of oropharyngeal

cavity are usual findings, together with cracked and dry lips. Edema and erythema of the extremities, lasting from 1 to 3 days and followed by "gloves-and-socks" periungueal desquamation, a scarlatiniform maculopapular rash, and a nonsuppurative cervical lymphadenopathy complete the clinical presentation of typical KD [183]. The disease course of KD is triphasic. The acute phase is characterized by the clinical manifestations mentioned above. Then subacute phase occurs, in which patients are at the most risk for developing coronary artery lesions (CAL). Finally, in convalescent phase, most children are asymptomatic and, when present, coronary involvement discloses itself [184].

In KD, male sex may be a risk factor, together with age at onset within the first year of age, incomplete KD, and unresponsiveness to IVIG, for the development of cardiac lesions. Yamashita et al. found that onset in the first year of life and male sex were associated with acute cardiac involvement (within the 30 days from disease onset) [185]. The reason for this association between male sex and worse prognosis is unknown.

Takayasu Arteritis

Takayasu arteritis (TA) is a chronic, granulomatous vasculitis of large vessels, with a typical localization to the aorta and its major branches at their origin. TA mostly affects women, usually within the 4th decade of life and is rare in patients younger than 16, though it represents the third most common cause of vasculitis in the pediatric age group. In fact, TA with a childhood onset (c-TA) has been described in any age group, ranging from the younger patient described in literature, diagnosed at the age of 6 months to late adolescence [186].

The M:F ratio in c-TA is 1:2, as reported in the Indian and South African series [187, 188]. During adulthood, women outnumber men at 7–9:1 [189, 190]. The pathogenesis of the disease is still unclear. An infectious agent has been considered to play a role, especially tuberculosis (TB), as granulomas giant cells within the vessel wall resemble TB lesions. Moreover, a high prevalence of TB, both previously and ongoing infection, has been reported in TA patients and, recently, genetic sequences of *Mycobacterium tuberculosis* have been detected in aortic tissue from a number of individuals with Takayasu arteritis [191, 192]. A viral trigger of vasculitis has also been speculated [193]. The evidence for a genetic contribution to TA etiology comes from a well-defined genetic association with different human leucocyte antigen (HLA) alleles. HLA-B*52 is the most significantly associated, especially in Japanese population, and seems to characterize a subset of individuals with an earlier disease onset, a more severe disease course, and a higher incidence of left ventricular wall abnormalities/aortic regurgitation [194, 195]. By genotyping two indipendent cohorts of TA patients, Saruhan-Direskeneli et al. established a genetic association in the Fc-gamma receptor IIA and Fc-gamma receptor IIIA (FCGR2A/FCGR3A) and IL12B loci [196]. Renauer et al. discovered other three susceptibility loci for TA. Two of these loci are located in genes coding for IL6 and RPS9/LILRB3, both involved in immunoregulatory pathways. Moreover, a possible role for IL-6 in TA pathogenesis has been recently hypothesized, because of the increased serum IL-6 levels in TA individuals compared with the controls [197, 198].

The disease course of c-TA is characterized by two phases: during the acute phase, constitutional and nonspecific symptoms, such as fever, hypertension, fatigue, myalgia, arthralgia, abdominal pain, headache, and vomiting are common, while during the second and chronic phase, organ-specific manifestations develop, due to the progressive stenosis and subsequent ischemia [199]. Absence of extremity pulses is the most common sign in c-TA [200]. Children are less likely to experience bruit, claudication pain, and eye involvement, compared with adults [201]. In children, no gender differences in clinical presentation are described and abdominal aorta and renal arteries are the most affected arterial segments, while in adult population, vascular involvement seems to depend on gender. In a recent Korean survey, females resulted more often affected in the thoracic segment of aorta and its branches, while men were more likely to present with an involvement of the abdominal aorta and its branches [202, 203]. Considering the angiographic classification according to the International TA Conference in Tokyo 1994, male patients are more likely to develop type IV lesions, while females have a higher incidence of types I, IIa, and IIb. In addition, adult males experience hypertension more often than women [204].

Conclusions

In the adult population, autoimmune diseases are far more common in women, while for some diseases, male gender is a risk factor for a more severe course. This sex dimorphism is less common in childhood diseases, probably because at this age, the hormonal milieu differences between males and females are negligible (Fig. 3). JIA is one of the few disorders where the predominance of females is more striking. Although the exact mechanism for this difference is far from being understood, JIA could be a good model to study the role of factors other than estrogens, such as miRNA expression or XCI, on the development of autoimmunity. Unfortunately, many childhood autoimmune diseases are so rare that it is very difficult to explore any possible difference in outcome secondary to gender predominance.

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Compliance with Ethical Standards

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