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Review article

Sex bias in paediatric autoimmune disease – Not just about sex hormones?

Rachel C. Chiaroni-Clarke [a, b], Jane E. Munro [c, d], Justine A. Ellis [a, b, *]

[a] Genes, Environment & Complex Disease, Murdoch Childrens Research Institute, Parkville, Victoria, Australia
[b] Department of Paediatrics, The University of Melbourne, Victoria, Australia
[c] Arthritis & Rheumatology Research, Murdoch Childrens Research Institute, Parkville, Victoria, Australia
[d] Paediatric Rheumatology Unit, Royal Children's Hospital, Parkville, Victoria, Australia

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ABSTRACT

Autoimmune diseases affect up to 10% of the world's population, and approximately 80% of those affected are female. The majority of autoimmune diseases occur more commonly in females, although some are more frequent in males, while others show no bias by sex. The mechanisms leading to sex biased disease prevalence are not well understood. However, for adult-onset autoimmune disease, at least some of the cause is usually ascribed to sex hormones. This is because levels of sex hormones are one of the most obvious physiological differences between adult males and females, and their impact on immune system function is well recognised. While for paediatric-onset autoimmune diseases a sex bias is not as common, there are several such diseases for which one sex predominates. For example, the oligoarticular subtype of juvenile idiopathic arthritis (JIA) occurs in approximately three times more girls than boys, with a peak age of onset well before the onset of puberty, and at a time when levels of androgen and oestrogen are low and not strikingly different between the sexes. Here, we review potential explanations for autoimmune disease sex bias with a particular focus on paediatric autoimmune disease, and biological mechanisms outside of sex hormone differences.

Contents

1. Introduction

Approximately 80 human diseases are considered to be autoimmune in nature [1], affecting between 5 and 10% of the Western population [2]. Many autoimmune diseases (ADs) exhibit a sexual

* Corresponding author. Genes, Environment & Complex Disease, Murdoch Childrens Research Institute, Parkville, Victoria 3052, Australia.
E-mail address: justine.ellis@mcri.edu.au (J.A. Ellis).

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dimorphism, with females carrying the majority of the AD risk burden. Over 20 ADs are strongly female biased (for example, systemic lupus erythematosus (SLE), systemic sclerosis (SS), autoimmune thyroid disease (ATD)), while a further ~25 are moderately biased towards females (e.g. rheumatoid arthritis (RA), multiple sclerosis (MS)). Approximately 20 ADs are more common in males (e.g. ankylosing spondylitis (AS)), with the remainder showing no clear bias towards either sex [1].

The average age of onset of AD is between 40 and 50 years [1]. However, many ADs that occur most commonly in adults can appear in childhood or adolescence. Conversely, other ADs show a more common, or exclusive, paediatric age of onset. While the AD sex bias tends to be more striking for adult onset diseases, biases are also evident in paediatric onset ADs (Table 1). For example, the oligoarticular subtype of juvenile idiopathic arthritis (JIA) is around three times more common, and the polyarticular subtype around twice as common, in girls than in boys [3]. Similarly, juvenile-onset dermatomyositis is around 2.5 times more common in girls than in boys [4].

The biological mechanisms behind a preponderance of one sex over another in ADs (and other diseases that exhibit sexual dimorphism) are largely unknown. For adult-onset ADs, it has long been assumed that sex hormones play a major role. This is intuitive, since levels of androgens and oestrogens are quite distinct between the sexes during middle age when AD onset is at its peak, and their role in immune modulation is recognised [5]. However, in ADs with a peak age of onset prior to puberty it could be argued that other biological mechanisms may be particularly relevant, since pre-pubertal sex hormone levels are not disparate between males and females. In this review, we consider a range of potential (and likely interconnected) mechanisms through which susceptibility to various autoimmune diseases might depend on sex. We focus particularly on paediatric-onset ADs, and on mechanisms other than sex hormone differences, which might be more relevant to driving sex-biased paediatric AD susceptibility.

2. Sex hormones and the sexually dimorphic immune response

The basic immune response is sexually dimorphic, both in type and magnitude, and appears to play an important role in the female preponderance of adult AD [73]. Females have an increased

Table 1
Reported female:male ratios in paediatric-onset autoimmune disease and comparison with adult-onset disease.

Disease	% Paediatric onset[a]	Subtypes	Mean/median age of onset	Peak ages of onset	F:M[c] (paediatric)	F:M[c] (adult)	References
Juvenile idiopathic arthritis	100[b]	Oligoarticular		2–4	3:1	N/A	[3,6,7]
		Polyarticular		2–4, 6–12	2:1		
		Enthesitis-related		Late childhood	1:2		
		Psoriatic		2–4, 9–11	2:1		
		Systemic		0–16	1:1		
Type 1 diabetes	>50			5–7, puberty	1:1.1 (5–7y) 1:1.7 (puberty)	1:1.5	[8–11]
Inflammatory bowel disease	25	Crohn's disease		<10 or ≥10 yrs[d]	1:2.4 (<10y) 1:1.6 (≥10y)	1:1.5	[1,12–14]
		Ulcerative colitis		<10 or ≥10 yrs[d]	1.7:1 (<10y) 1.1:1 (≥10y)	1.9:1	
Celiac disease	~25		Across childhood		~1:1	2–3:1 (declines in elderly)	[15–18]
Juvenile systemic lupus erythematosus	15–20			12–16 yrs	4:3 (<10y) 4:1 (10–20y)	7:1	[1,19–22]
Juvenile dermatomyositis	15–20		7y (mean)		2.5:1	2:1	[1,4,23,24]
Juvenile systemic sclerosis	5–10		8y (mean)		3.6:1	11.5:1	[1,25–28]
Multiple sclerosis	3–5			>11 yrs	0.8:1 (<6y) 1.6:1 (6–10y) 2.1:1 (11–18y)	3:1	[29–31]
Psoriasis	~35			8–11 yrs	1.5:1	1:1	[32–35]
Ankylosing spondylitis	18			Second decade	1:3	1:2–3	[36–38]
Eosinophilic esophagitis	~70			1 yr	1:3	1:3	[39–44]
Autoimmune uveitis[e]	5–10		8–9 y (median)		1.2:1	1:1	[45–49]
Autoimmune hepatitis	?	Type 1	12 y (median)		1.5:1	3:1	[1,50–52]
		Type 2 (often pre-puberty)	10 y (median)		1.5:1		
Autoimmune thyroid disease[f]	?	Hashimoto's thyroiditis Atrophic thyroiditis		Adolescence (mid-puberty)	2:1	7–10:1	[53–56]
Kawasaki Disease	100			<5 yrs	1:1.5	N/A	[57–59]
Autoimmune haemolytic anaemia	?	Warm, cold AHIA	3.1 y (mean)	<5 yrs	1:1.3	2:1	[60,61]
Behçet's disease	?		12 y (mean)		1.2:1	1:1.2	[62]
Vitiligo	~50		6 y (mean)		1:1	1:1	[63,64]
Guillain Barré Syndrome	?		6.2 y (median)		1:1.3	1:1.5	[65,66]
Myasthenia gravis	10–15	Pre-pubertal			1:1	1.5:1	[67–69]
		Post-pubertal			4.5:1		
Alopecia areata	~40		10y (median -China)		~1:1	~1:1	[70–72]

[a] 0–18 years unless defined otherwise by disease.
[b] By definition.
[c] Female:male ratio.
[d] 'Paris' classification [14].
[e] Often associated with a systemic autoimmune disease, especially JIA.
[f] Often associated with other AIDs, especially T1D.