Pathogenesis of Pediatric Rheumatologic Diseases

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KEYWORDS

• Inflammation • Autoimmunity • Tolerance • Rheumatic diseases

KEY POINTS

- Inflammation is due primarily to changes in microcirculation.
- Autoimmunity implies that the normal tolerance checkpoints have been breached.
- Autoinflammation can promote autoimmunity.
- Therapeutic advances depend on knowledge of pathogenesis of the rheumatic diseases.

INTRODUCTION

Inflammation is inherently understood by anyone who has burned their hand, had a localized infection, or suffered a large cut. The skin becomes red, there is swelling, and the site is tender. These are the hallmarks of inflammation. At a cellular level, inflammation is well understood to reflect activation of pain fibers, vasodilation, and increased vascular permeability. This article also describes the current understanding of loss of tolerance and the evolution of autoimmunity, as well as autoinflammation and the consequences of elevated cytokine expression. In many cases, current understanding is incomplete and there have been great advances coupled with increasingly perplexing questions. As anticipated, the improved understanding of pathogenesis has translated, in some cases, to improvements in therapeutics.

HISTORICAL UNDERSTANDING OF ARTHRITIS

Arthritis clearly affected ancient civilizations (**Table 1**); however, a medical appreciation of pediatric arthritis did not occur until 1545. The first inklings that inflammation was part of a pathologic process occurred after microscopy was developed and invading white cells could be observed. Dutrochet identified white cells that accumulate in inflammation in 1824. Currently, the character of the invading cells is still used to define the type of inflammation requiring treatment. Pathologists reference the cell types in

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Table 1
Rheumatic diseases in the ancient era

Findings	Therapy	Key People	Time
Earliest skeletal findings of rheumatoid arthritis (RA)		Native Americans, Tennessee River	4500 BCE
Gout (podagra) described; Mummies with spondyloarthropathy (SpA) and osteoarthritis (OA) found from this era.	Water therapy, willow extracts	Egyptian hieroglyphs	3000–2000 BCE
Gout recognized as related to gender, affluence	Diet therapy	Hippocrates	400 BCE
Charaka Samhita text describes an entity resembling RA	Diet, lifestyle, and herbal remedies	Ayurvedic texts Greek physician Dioscorides	200 CE
First use of term "rheumatismos" meaning "to flow" and associating respiratory disease with painful maladies	Colchicine used for gout	Galen Alexander of Trailes	200 CE 600 CE
Madhav Nidan describes amavata: rheumatic fever	Diet, lifestyle, and herbal remedies	Ayurvedic texts	700 CE
Earliest skeletal findings of psoriatic arthritis PsoA		Saxon village	1200 CE
Pediatric arthritis described as "stiffness of lymmes" and thought to be due to cold exposure		Thomas Phaer	1545 CE
Recognition that gout, RA, and rheumatic fever are distinct entities		Guillaume do Baillou	1600 CE
"Inflammation of the lymphatic arteries" described as the cause of rheumatic fever Chronic rheumatism recognized as a distinct entity		Thomas Sydenham	1666 CE

their descriptions. Synovial fluid neutrophil count, lymphocytic infiltration into muscle, and granulomas in skin are revealed by pathologic evaluation and are used diagnostically and to determine therapy in some circumstances. The migration of cells has proven to be a pivotal facet that has been mined therapeutically (see later discussion).

If inflammation represents an ancient concept that has been refined over the years, autoimmunity represents a much more recent concept. The overall concept of immunity sputtered through history, beginning with Thucydides' description of the plague of Athens, which rendered sufferers immune to a second attack.[1] Autoimmunity as a concept was not recognized until quite recently. In 1900, Paul Ehrlich stated flatly that antibodies could not be generated to self but in the 1950s autoantibodies were clearly demonstrated in human disease states.[2] In the intervening time, it has become understood that T cells also can be autoreactive. As the understanding of host defense and immunity has improved, the ability to manipulate the immune system has also improved (**Table 2**). This rapid evolution in immunology has translated into improved therapeutics specifically for pediatric rheumatology. Perhaps the best argument for pursuing studies on pathogenesis is to develop new and better therapeutics that lessen the burden of disease, improve outcomes, and allow children to live the life they envision for themselves. It is in this spirit that this article reviews pathogenesis.