Editorial

Uveitis Associated with Juvenile Idiopathic Arthritis: Envisioning the Future

Among the childhood rheumatic diseases chronic, non-granulomatous anterior uveitis associated with juvenile idiopathic arthritis (JIA) represents a particularly distinctive and enigmatic clinical entity. In 1910, which was 13 years after Still first documented the occurrence of chronic arthritis in children, Ohm reported cases of iridocyclitis and band keratopathy associated with childhood arthritis[1]. Subsequently, the association between arthritis and uveitis in the pediatric population became well recognized and the clinical and serologic correlates more thoroughly defined.

The group of JIA children with chronic uveitis is distinguished by a predominance of females having young onset ages, oligoarthritis, absence of ocular symptoms, and the presence of antinuclear antibodies (ANA). In the general population the prevalence and annual incidence of chronic uveitis associated with JIA have been calculated to be as high as 11 per 100,000 and 1.5 per 100,000, respectively. Uveitis associated with JIA can have debilitating ocular consequences, with past experiences indicating that of affected eyes about one-third develop substantial visual impairment and one-tenth become blind. Despite suggestions that both the frequency and severity of uveitis associated with JIA might be diminishing[2], the condition nevertheless remains a prominent clinical concern. While certain typical clinical characteristics of uveitis associated with JIA are evident, the etiology and underlying pathogenic mechanisms that account for the curious co-existence of eye and joint inflammation in a susceptible population of children and the basis for variability in expression and severity of the condition remain obscure. Insufficient knowledge about the biological basis of uveitis associated with JIA can be an impediment to providing optimal patient management. The desire to improve patient care by better understanding the clinical spectrum and etiopathogenesis of uveitis in patients with JIA is the impetus to continue to study this uniquely pediatric disease.

Identification of characteristics that correlate with the occurrence of chronic uveitis in JIA has facilitated the formulation of surveillance guidelines intended to promote prompt detection and early treatment of eye disease[3]. In JIA the features associated with a predisposition to developing uveitis (young onset age, female sex, oligoarthritis, and ANA positivity) are apparent, but characteristics that help predict the severity and prognosis of the eye disease are not as obvious. As Zulian and colleagues suggest in this issue of *The Journal*[4], identifying predictors of uveitis severity could aid in refining currently available monitoring guidelines and, by identifying those patients at risk for visual impairment, could help to justify earlier introduction of more aggressive therapy.

Attempting to identify patients at greatest risk for developing debilitating consequences of uveitis is important, but the current reality is that, despite the commendable efforts of Zulian and colleagues and of earlier investigators, proposed criteria for predicting uveitis outcomes remain limited and not yet firmly established. The conditions most consistently predictive of poor visual prognosis of uveitis associated with JIA include a short duration between the onset of arthritis and uveitis, uveitis onset prior to arthritis onset, and the severity of uveitis at first detection of ocular disease[4-8]. Other suggested predictors of uveitis severity include the presence of the histocompatibility antigen B15/w62[9], antibodies to retinal S-antigen[10] and elevated α_2-globulin[4].

As Zulian and colleagues appropriately acknowledge, and as the results of their study indicate, prospective controlled clinical assessments designed to confirm the utility of potential predictors of uveitis outcome in JIA are required. To develop a study protocol that will confirm the reliability of predictors of uveitis outcomes will necessitate the development of criteria that effectively discriminate between severe and mild uveitis. Arguably, the criteria applied in the study of Zulian and colleagues, for example, might be considered insufficient, in the context of oligoarticular JIA, to distinguish severe from mild uveitis. Chronicity is an essential characteristic of uveitis associated with JIA so that using the duration of activity of only one month to discriminate between mild and severe ocular disease might not be appropriate. Similarly, the notion presented by Zulian and colleagues that one

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episode per year of uveitis is indicative of milder disease versus having two or more episodes per year might not always be reasonable. Thus, a child having one prolonged, unremitting episode of uveitis might have more severe ocular disease than a child who has had several relatively brief episodes. Similarly, precision and consistency is required when evaluating laboratory variables as potential predictors of uveitis outcomes. Future multicenter studies that re-evaluate the predictive utility of α_2-globulin, which Zulian, *et al* purport to be a predictor of uveitis severity, will demand consistent and modern measurement methodologies, reference to current normal values, and a thorough analysis of the contributions of specific plasma proteins, which increase during inflammation, to quantitative changes in the α_2-globulin fraction.

Even if the results of an optimally designed study revealed a constellation of characteristics that could reliably predict the severity of uveitis and guide the aggressiveness of therapy, the advanced treatment options currently available for consideration are not of certain efficacy in uveitis. Despite the lack of substantive histopathologic proof, uveitis associated with JIA is considered to be a consequence of inflammatory and immune-mediated mechanisms. Consequently, for children afflicted with progressive ocular disease that is refractory to conventional corticosteroid therapy or for whom the duration and dose of steroid therapy becomes associated with intolerable toxicity, there is an understandable inclination to experiment with the use of other treatments that modulate immune and inflammatory pathologic processes[11-13]. However, selecting alternate therapies, even if poor ocular outcomes could be reliably predicted, cannot currently be based on a strong rationale because of limited insight into the underlying pathogenesis of uveitis, imprecise knowledge about modes of pharmacologic action of certain advanced drug therapies, and insufficient information about the distribution in the eye of drugs delivered systemically. Further, there are indications that, at least in some subjects, there is the potential that certain immunomodulatory therapies could induce or aggravate the expression of uveitis. The use of tumor necrosis factor-α (TNF-α) inhibitor agents, for example, while showing promise in controlling uveitis in patients with JIA[13], has been associated with the first appearance of uveitis in both experimental animals and human subjects, suggesting that inhibition of TNF-α might contribute to inducing or exacerbating uveitis in certain circumstances[14,15].

Our understanding of the arthritis of JIA and the uvetiis that might be associated with it remains rudimentary. The challenge is to achieve a better understanding of the cause and pathogenesis of uveitis associated with JIA so that more effective, rationally conceived treatments can be devised. There are sufficiently intriguing results from earlier studies that support the view that identifying a cause and explaining the pathogenesis of uveitis associated with JIA are realistically achievable goals. In isolation the results of earlier studies provide incomplete and fragmentary insights into uveitis. When considered together, however, the bits of independently acquired information about uveitis could be integrated to help formulate a unifying hypothesis upon which future collaborative research could be based. There is sufficient existing information, for example, that could invoke a hypothesis that could include the concepts of exposure of a genetically predisposed subject to an environmentally encountered infectious agent, a component of which shares amino acid sequence similarity and uveitogenic potential with uveitogenic components of the eye and of chromatin, and which might be rendered more pathogenic by interactions with type II collagen, an arthritogenic and possibly uveitogenic protein present only in the joint and the eye. To be successful, testing such multifaceted hypotheses requires multicentered collaboration to ensure the recruitment of a sufficient number of subjects and the involvement of an eclectic array of collaborators representing, in part, the disciplines of pediatric rheumatology, ophthalmology, immunology, immunogenetics, microbiology, molecular biology, and epidemiology.

Endeavoring to understand uveitis better is itself important, but it is also enticing to contemplate the prospect that uveitis associated with JIA could serve as a valuable model for the study of other childhood rheumatic diseases. Exploring uveitis associated with JIA has the potential to provide insights into the origins of rheumatic diseases that begin at a young age, an understanding of mechanisms that account for linkages between inflammatory joint disease and associated extraarticular organ involvement, an explanation for sex disparity in childhood rheumatic diseases, and elucidation of the relationship between inflammatory arthropathies and ANA positivity.

Efforts to better characterize and explain uveitis associated with JIA, such as those presented in this issue of *The Journal*, help to highlight uveitis as a continuing clinical concern and to provide focus for future research initiatives. Children with JIA afflicted with associated uveitis, particularly those predisposed to severe outcomes, will be the ultimate beneficiaries of such undertakings.

ALAN M. ROSENBERG, MD,
Professor of Pediatrics,
Department of Pediatrics,
University of Saskatchewan,
Saskatoon, SK, Canada S7N 0W8.

Address reprint requests to Dr. Rosenberg.

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