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Recommendations and metaanalyses

The frequency of uveitis in patients with juvenile inflammatory rheumatic diseases

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ABSTRACT

Objectives: This meta-analysis investigated the frequency and type of ocular involvement in juvenile inflammatory arthritis (JIA) and other juvenile rheumatic diseases.
Methods: Medline, Web of Science and Cochrane databases were searched from inception to September 2018 to identify publications related to juvenile arthritis and rheumatic diseases, which reported frequency of Uveitis in juvenile rheumatic conditions and contained at least 20 patients. The prevalence and type of eye complications were extracted, and random effects models estimated their frequency. Heterogeneity was evaluated using I^2.
Results: In total, 7132 unique citations resulted in 59 articles included. Pooled frequency of uveitis was: 24% in oligoarticular JIA, 12% in polyarticular JIA, 1% in systemic JIA, 50% in pediatric Bechet's, 9% in juvenile psoriatic arthritis, 24% in juvenile spondyloarthropathy and 5% in juvenile systemic lupus erythematosus. The most common uveitis in JIA was anterior uveitis, which occurred in 14%; also described as iridocyclitis in 10% of patients. Publication bias was negligible for all conditions except those with few reported studies (juvenile SLE and systemic JIA). Uveitis in JIA was more common in Europe (14%), North America (11%) and the Middle East (12%) than East Asia (7%) and Oceania (3%).
Conclusions: Ocular involvement (mostly uveitis) in juvenile inflammatory arthritis and other pediatric rheumatic diseases varied between 3% and 50% depending on the underlying condition; and was highest in pediatric Bechet's. In JIA, the highest frequency of uveitis was in oligoarticular JIA; with anterior uveitis being the most frequent type of uveitis. There was variation geographically for uveitis in JIA.

1. Introduction

Uveitis in juvenile inflammatory arthritis (JIA) and other pediatric rheumatic diseases remains a challenge due to variations in clinical presentations with potential complications such as cataracts, glaucoma and blindness causing reduced quality of life. Approximately 35% of patients with uveitis develop either complete or partial blindness when caused by inflammatory disease [1]. Juvenile idiopathic arthritis (JIA) is the most common cause of uveitis in children and also the major cause of severe visual loss [2]. JIA is an autoimmune condition that occurs children under 16 years of age and constitutes six subtypes [3]. Oligoarticular and polyarticular subtypes are distinguished by the number of affected joints (four or fewer, and five or more, respectively), and systemic-onset JIA is associated with a rash and high fevers and may also have organomegaly, serositis, lymphadenopathy and anemia [2,4]. Psoriatic JIA includes skin involvement, enthesitis-related JIA involves inflammation at tendon insertions (often called juvenile spondylarthropathy [SpA]) and undifferentiated JIA includes cases that span more than one category [3]. Behcet's disease can also onset in children. Uveitis is the most common extra-articular manifestation of JIA, particularly in the oligoarticular subtype especially young girls who are ANA positive with pauciarticular JIA. This subset is associated with chronic bilateral anterior uveitis which is often asymptomatic (no eye pain or photophobia or vision impairment) and when the joints may be in remission, but it can lead to complications such as reduced vision, corneal scars, cataracts and glaucoma. For this reason, these patients are screened with regular eye examinations.

Treatment of uveitis associated with juvenile arthritis and other rheumatic diseases has improved due to regular screening of JIA patients who are at risk and from more effective treatment. Corticosteroids (topic and orally), immunosuppres-

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sive/disease modifying drugs and biologics such as TNF inhibitors are used to manage uveitis in JIA either alone or in combination with traditional therapies [5–8]. Not all patients respond fully and uveitis may be associated with several complications such as impaired vision, cataracts and glaucoma.

In 2008, a French group investigated the prevalence of uveitis in adults with SpA and the relationship with disease activity and duration, but specifically excluded juvenile seronegative disease [9] A similar exclusion was made by another systematic review of extra-articular manifestations of ankylosing spondylitis in 2015 [10]. The aim of this study was to systematically assess the literature to determine more accurately the frequency of uveitis amongst children with different rheumatic diseases and compare the types and geographic distribution of uveitis between the diseases. We hypothesized that a higher prevalence of uveitis in Europe and North America could occur in juvenile SpA as the HLA-B27 haplotype occurs there in higher frequencies. However, in Scandanavia, pauciarticular ANA positive JIA is more common and this is the subtype of JIA, which is most common juvenile inflammatory arthritis and has a high association with bilateral uveitis. Additionally, pediatric Behcet's disease is more common in Turkey and has uveitis as a frequent manifestation. Therefore, we wanted to determine if the frequency of uveitis was different in various regions.

2. Methods

2.1. Study selection

A search of publications related to: conjunctivitis, keratoconjunctivitis sicca, xeropthalmia, uveitis, eye hemorrhage, optic neuritis, papilledema, orbital disease, retinal artery/vein occlusion, macular edema, retinitis, chorioretinitis, scleritis, iridocyclitits, choroid hemorrhage, blindness and amaurosis fugax in patients with JIA, juvenile PsA, juvenile BD, and juvenile SLE was performed with the assistance of an information specialist [Appendix A, Table S1; see the supplementary material associated with this article online]. Medline, Cochrane and Web of Science were used searching papers that spanned from their inception (1966, 1991 and 1990, respectively) to September 28, 2018. All studies that included the frequency of ocular involvement in the setting of a juvenile inflammatory rheumatologic condition were reviewed.

2.2. Inclusion criteria

Studies were included if they provided numerical data of the prevalence, incidence or frequency of uveitis in juvenile inflammatory rheumatic diseases. Studies were excluded if they were review articles, case reports where all patients experienced the same ocular comorbidity, if different comorbidities were not grouped independently, and if the study reported on fewer than 20 patients for more common diseases such as oligo and polyarticular JIA and juvenile psoriatic arthritis (PsA). Studies with fewer than 20 patients were included if they reported on a rare condition (Behcet's disease [BD], Kawasaki disease, and systemic JIA). When the same clinic/patients were in more than one analysis, the most recent or largest sample size study was included. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist was used to assess the quality of cohort, case-control, and cross-sectional studies.

2.3. Data extraction

The following data were extracted for each study: first author, year of publication, location of study, study design, sample size, and prevalence of each ocular complication. When studies included multiple populations with various rheumatic diseases, data extraction and analysis were done separately for each condition.

2.4. Statistical analysis

After extracting the frequency of uveitis from the individual studies, meta-analysis-generated Forest plots were constructed to create a 95% confidence interval (CI) using a generic inverse variance outcome type in RevMan 5.3 [10]. Variance and study weights were determined and a random effects model was used to account for differences in study quality [10]. I-squared and tau-squared tests were used to determine heterogeneity and variance across studies. Funnel plots, Begg and Mazumbar's test, and Egger's regression were used to look for publication bias. Single factor ANOVA was used to examine differences in geographic distribution of uveitis.

3. Results

The search process identified 8951 articles where 1827 duplicate citations among the search terms/different data, of which 59 were included (Fig. 1). Table S2 (Appendix A) shows the characteristics of each study including sample size, type and frequency of ocular involvement, and geographic location.

The pooled frequency of uveitis was 13 [12–14]% in JIA overall, 9 [3–15]% in juvenile PsA, 50 [38–63]% in pediatric BD, 24 [13–34]% in juvenile SpA and 5 [0–14]% in juvenile SLE (Fig. 2). Uveitis was more common in oligoarticular JIA (24 [19–30]%) than polyarticular (12 [6–18]%) or systemic-onset JIA (1 [0–3]%) (Fig. 3). There was no evidence of publication bias in any condition aside from systemic JIA and juvenile SLE (Egger's regression intercept was 2.939, $P = 0.01$; Begg and Mazumbar's correlation was 0.144, $P = 0.14$) (Appendix A, Figure S1).

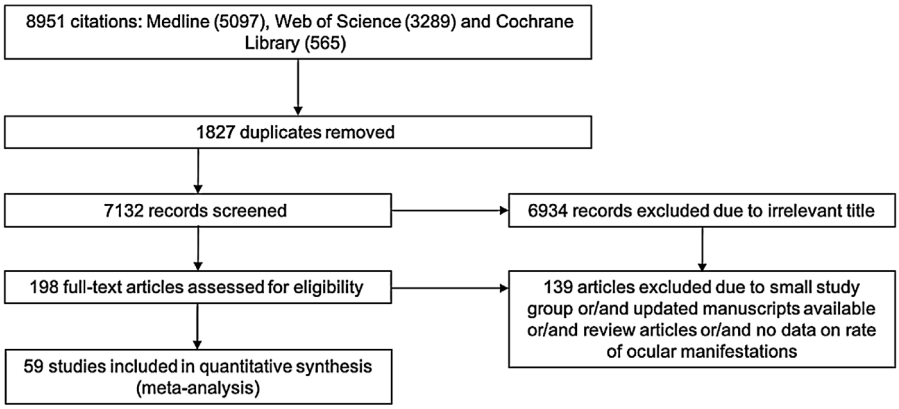

Fig. 1. Flow diagram of search results.

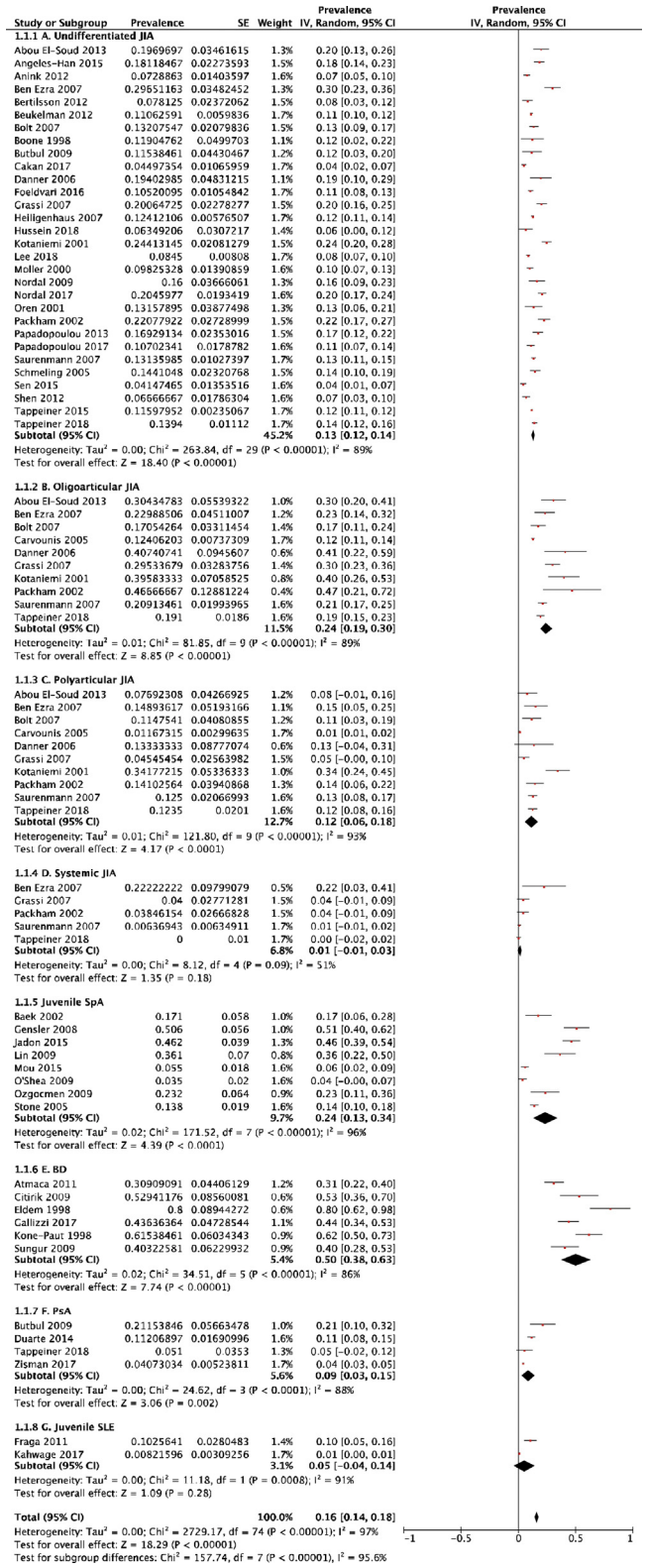

Fig. 2. Prevalence and complications of uveitis in juvenile patients with IRD. Forest plot analysis: prevalence of uveitis in undifferentiated (A) oligoarticular (B), polyarticular (C) and systemic (D) types of juvenile idiopathic arthritis. Prevalence of uveitis in patients with Juvenile SpA (E) juvenile Behcet's disease (F), juvenile psoriatic arthritis (G), and juvenile SLE (H).

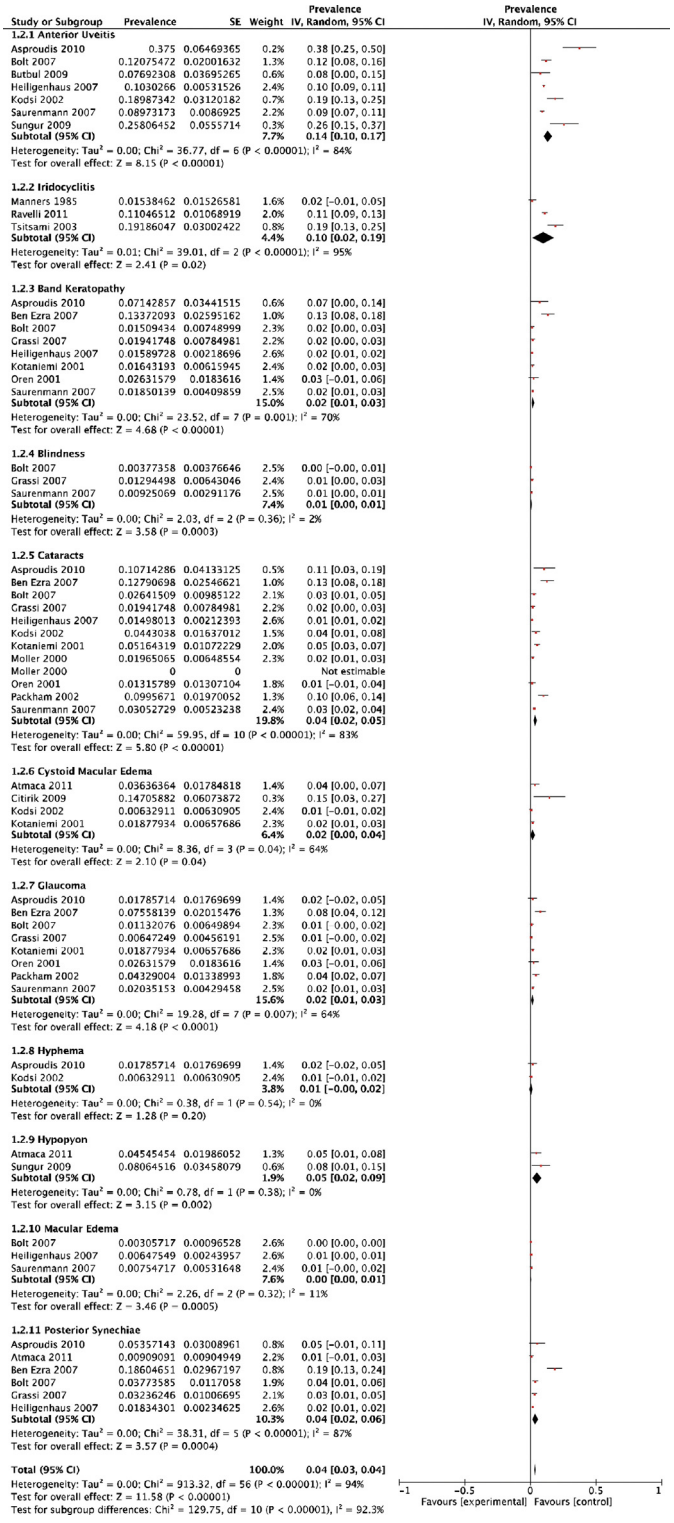

Fig. 3. Ocular manifestations of JIA including complications of iritis. Anterior uveitis (A), iridocyclitis (B) band keratopathy (C), blindness (D), cataracts (E), cystoid macular edema (F), glaucoma (G), hyphema (H), hypopyon (I), macular edema (J), posterior synechiae (K).

Anterior uveitis was the most common subtype of uveitis present in patients with JIA 14% [10%–17%] having this feature, followed by iridocyclitis (10%) cataract (4%) and synechiae (4%) (Fig. 3). Glaucoma, blindness, macular edema, hyphema, and band keratopathy all occurred at 2% or less. When analyzing geographic trends in prevalence of uveitis in JIA, it appeared more common in Europe, North America and the Middle East (14%, 11%, and 12%, respectively) than East Asia and Oceania (7% and 3%, respectively). Europe and North America had a statistically higher prevalence of uveitis compared to Oceania ($P = 0.0064$ and $P = 0.0331$, respectively) (Appendix A, Figure S2).

4. Discussion

Uveitis is common in many juvenile rheumatic diseases and the prevalence varied by disease from 4% to 50% in our meta-analysis. The frequency of uveitis was the highest in pediatric BD which is a multisystemic inflammatory disease characterised by oral and genital ulcerations, skin lesions, ocular and gastrointestinal involvement, and neurological manifestations. Eye involvement is the presenting feature of BD in one-fifth cases [11]. Recurrent, bilateral iridocyclitis with or without panuveitis is the most common clinical manifestation of BD [11]. However, the proportion of childhood BD among all BD cases is very low (between 3.3 and 26% even in Mediterranean and Far and Middle East countries with the highest disease incidence of 77–350 per 100,000) [12,13].

JIA remains the most common cause of pediatric uveitis and also major cause of visual impairment in children. The pooled prevalence of uveitis in JIA was 13%. The highest pooled prevalence of uveitis was found in oligoarticular type (25%), followed by polyarticular (11%) and systemic (3%) types. Oligoarticular arthritis is a major risk factor for developing uveitis in patients with JIA, along with sex (girls), early age (5 years or less) of disease onset, antinuclear antibody positivity and rheumatoid factor seronegativity [14]. Chronic anterior uveitis was the most common subtype present in patients with JIA by our meta-analysis.

Although publications were combined using a random effects model, high heterogeneity was observed in some studies, possibly due to their small size, diverse patient populations, and non-standardized definitions of uveitis. For instance, uveitis and anterior iritis may have similar meaning. Therefore, we extracted the terms that were used in their referenced studies to avoid our bias or misinterpretation. We eliminated smaller studies by setting a minimum sample size as an inclusion criterion for JIA subsets (oligarticular and polyarticular) in order to reduce heterogeneity. Publication bias may have occurred. Studies with low frequencies of uveitis may not have been published. Therefore, the reported rates of uveitis may not be fully representative. Another limitation is the absence of data on disease activity and duration, treatment and other cofounders. The length of follow-up was variable between studies. Some eye complications could have been due to uveitis disease activity (decreased vision, glaucoma) or from complications of the uveitis and/or its treatment (blindness, glaucoma, cataracts). We did not determine if the use of TNF inhibitors has decreased uveitis. In oligoarthritis that is ANA positive, it is more likely that TNF inhibitors would be used for the treatment of uveitis and less likely for joint involvement. Certainly, in adults with SpA monoclonal antibodies to TNF have reduced new and recurrent acute anterior iritis. Newer treatments with biologics in JIA have preliminarily shown to be associated with uveitis in some rare cases [15]. We could not estimate incidence, only a cumulative prevalence or overall frequency. The geographic variability may be partially explained by the presence of the HLA-DRB1 genotype in Scandinavian patients with pauciarticular JIA [16,17]. The correlation of this haplotype with oligoarticular JIA may explain an increased comparative prevalence of uveitis in Europe [18–20]. There is also heterogeneity in the subsets of JIA as traditionally uveitis is common in pauciarticular ANA positive girls with JIA onset very young; whereas teens with oligoarthritis may be more likely to be HLA-B27 positive boys [21].

5. Conclusion

This meta-analysis calculated the frequency of various ocular problems in children with JIA and other rheumatic diseases. There should be standardized definitions of JIA subsets and descriptions of ocular involvement using the same terms (i.e. iritis, uveitis, anterior iritis and iridocyclitis may all be describing the same thing but the terms were not combined as we used what the authors of papers reported). Uveitis was most common in JIA (predominantly oligiarticular type) and pediatric Bechet's disease, and least frequent in juvenile SLE. Recognition of uveitis may help in early referral and prompt initiation of treatment for prevention of vision threatening complications.

Disclosure of interest

The authors declare that they have no competing interest.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at https://doi.org/10.1016/j.jbspin.2019.06.001 [22–78].

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