Symptoms in noninfectious uveitis in a pediatric cohort: Initial presentation versus recurrences

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PURPOSE To describe the prevalence of symptoms with noninfectious uveitis (NIU) in a pediatric cohort and to assess the association between the presence of symptoms with first episode of uveitis (first-U) compared to symptoms at uveitis recurrence.

METHODS The medical records of patients with NIU treated at a tertiary referral hospital from March 2008 to November 2107 were reviewed retrospectively. Symptomaticity (eye pain, eye redness, photosensitivity) was captured at initial uveitis activation and subsequent episodes. Univariate logistic regression modeling was used to identify clinical features associated with symptomatic first-U. Ordinal regression identified patient characteristics associated with symptomatic recurrence.

RESULTS A total of 118 cases were reviewed; of these, 92 were followed for at least 6 months and had at least 1 reactivation. Juvenile idiopathic arthritis–related uveitis (JIAU) was the most common diagnosis (67/118 [57%]), followed by idiopathic uveitis (33%). In the majority, uveitis was restricted to the anterior chamber (82%). Of the 118 cases, 58 patients (49%) had symptomatic first-U, 34% JIA versus 69% non-JIA. Non-JIAU, age ≥7 years, and negative antinuclear antibody (ANA) test were significantly associated with symptomatic first-U; spondyloarthritis was not. With recurrence, half had symptoms: 41% JIA versus 66% non-JIA. Of those who had symptomatic first-U, 35% were asymptomatic at recurrence. Those with JIA had 50% or less odds of symptomaticity at reactivation. Complications did not vary based on having had symptoms at first-U.

CONCLUSIONS Non-JIA diagnosis, older age, and ANA-negativity were associated with symptomatic first-U in our study cohort, but no patient characteristics were significantly associated with symptomatic recurrence. Clinical patterns may change during disease course, with uveitis switching from symptomatic to asymptomatic, which has implications for uveitis monitoring recommendations. (J AAPOS 2019;23:220.e1-6)

Noninfectious uveitis (NIU) is the most common type of uveitis in developed countries, with childhood prevalence in the United States estimated at 29 per 100,000 persons.[1] Uveitis may be idiopathic or as part of a systemic condition. Idiopathic uveitis may be the most common type of NIU (25%-61% of tertiary-care cohorts), whereas juvenile idiopathic arthritis (JIA) is the most frequent uveitis-associated systemic disease (25%-50%).[2-4]

The most common location of childhood uveitis is the anterior chamber.[1,3,4] Pediatric uveitis is often a chronic process, insidious in onset, without heralding symptoms. It also can be symptomatic, with episodes of pain, redness, photophobia and/or blurred vision. In these cases, it is often of limited duration (acute).

To date, the specific risk factors for symptomatic NIU in childhood have not been explored. For example, adults with spondyloarthritis (SpA) are more likely to develop symptomatic acute-onset anterior uveitis (Calvo I, et al. Ann Rheum Dis 2018; THU0259), yet some SpA patients do have asymptomatic chronic uveitis.[5,6] It has been presumed that symptomatic and acute-onset uveitis is likewise more common in juvenile SpA (JSpA), but this has not been demonstrated. Nor have other factors, such as sex or anatomic uveitis location, been evaluated for their association with symptomaticity.

Regardless of underlying etiology of pediatric symptomatic uveitis, to date no study has specifically examined the course of ocular inflammation over time in symptomatic NIU. If it begins as symptomatic acute-onset uveitis, can NIU "convert" to a more insidious chronic form with further episodes of uveitis reactivation? The purpose of this study was to describe the prevalence of symptomatic NIU in children and adolescents in a single-center

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rheumatology-clinic-based uveitis cohort, with particular regard to uveitis course, relapse characteristic, and outcome.

Subjects and Methods

The study was reviewed and approved by the institutional review board of Children's Hospital of Philadelphia (CHOP). The medical records of patients (0-21 years) with NIU who were evaluated by a pediatric rheumatologist at CHOP between March 2008 and November 2017 were reviewed retrospectively; patients were evaluated by CHOP-affiliated and nonaffiliated ophthalmologists.

Inclusion criteria were as follows: (1) uveitis diagnosed by an ophthalmologist; (2) chronic uveitis, as defined by SUN Working Group[5]; and (3) for assessment of reactivation, at least 6 months' follow-up. Subjects were excluded if they were >18 years of age at uveitis diagnosis or had uveitis secondary to an infection or if the record lacked of information on slit-lamp examination with cell count, visual acuity, and tonometry.

Data collected from the medical records of patients included demographics, systemic and ocular diagnoses, antinuclear antibody (ANA) and HLA-B27 status, ocular surgeries, eye disease activity at each visit in each eye, and treatment at each visit. Patients were classified as having uveitis that was idiopathic or associated with systemic inflammatory diseases. Subjects with JIA were characterized into subtypes according to the International League of Associations for Rheumatology criteria.[7] JSpA included patients with enthesitis-related arthritis (ERA), undifferentiated subtype of JIA, and uveitis associated with inflammatory bowel disease (IBDU).

Uveitis was defined as having >1 cell/hpf (≥0.5 + SUN) in the anterior or intermediate chamber (vitreous)[8] or chorioretinitis. Symptomatic was defined as having associated pain, redness, or photosensitivity. Symptomaticity was captured at initial uveitis activation and each episode of reactivation. Reactivation was defined as having an increase to >0.5 + with increased therapy for uveitis (topical or systemic). The site of inflammation was characterized using SUN categories, with one exception. A new category, *anterior and intermediate uveitis*, was created: anterior (AU), primarily anterior chamber; intermediate, primarily vitreous though may spill forward; anterior and intermediate uveitis, persistent inflammation in both; posterior uveitis; and panuveitis, inflammation involves three chambers.

Complications were considered positive if they were present at all during follow-up. They were reported as unilateral (always one eye) or bilateral (ever both eyes involved). Elevated intraocular pressure was defined as >21 mm Hg. Decreased visual acuity was collected according to Pediatric Eye Disease Investigator Group (PEDIG) and World Health Organization (WHO) guidelines. The PEDIG gradations are as follows: normal; mild decrease, 20/25-20/40; moderate decrease, 20/40-20/80; and severe decrease, 20/100 or worse.[9] The WHO gradations are as follows: normal; mild decrease, <20/60 and better than 20/400; severe decrease 20/400 or worse.

Data were analyzed using Stata 11.0 (StataCorp, College Station, TX). Differences in categorical characteristics were assessed using the χ^2 test or the Fischer exact test. Differences in continuous variables were evaluated using the Kruskal-Wallis test. McNemar's test was used to examine the relationship between paired variables (symptomatic vs asymptomatic at onset and at reactivation). Logistic regression was used to evaluate factors independently associated with the development of symptomatic uveitis. We evaluated the following factors in univariate analysis: underlying systemic disease (JIA, other, or idiopathic; JIA vs other); JIA subtype (oligoarticular, polyarticular RF+, polyarticular RF−, psoriatic [PsA], undifferentiated); JSpA (defined as ERA or IBDU); anatomic location; sex, age; ANA and HLA-B7 status. Univariate logistic regression was also used to evaluate factors independently associated with anterior location of initial uveitis; we evaluated the following factors: underlying diagnosis of JIA (and subtype) or JSpA; sex; age at diagnosis; ANA and HLA-B27 status; and symptomatic at diagnosis. Reactivated uveitis was defined as a combination of two binary options: reactivation (Y/N); presence of symptoms with activation (Y/N). An ordered variable was created to categorize reactivation: no uveitis = 0, active uveitis and no symptoms = 1, active uveitis and symptoms = 2. Reactivation was used as the outcome in a logistic regression model to identify factors independently associated with symptomaticity at reactivation. In order to account for some patients having multiple opportunities of reactivation, this was analyzed using ordinal logistic regression, with clustering by subject. Factors that were explored in univariate ordinal logistic regression analysis were the same as those in the initial univariate analysis. Statistical significance was defined as a two-tailed P value of <0.05.

Results

A total of 118 children and adolescents met inclusion criteria for this study, comprising 426 patient years. Median duration of follow-up within the database was 2.9 years (IQR, 1 week to 13.7 years; mean, 3.8 ± 3.1 years). Demographics and clinical characteristics are reported in Table 1. The majority (66%) was female, and the median age was 7.4 years of age at diagnosis. Children with symptomatic uveitis were older at onset than those who were asymptomatic. JIAU was the most common diagnosis (57%), followed by idiopathic uveitis (33%); 5% of the cohort had tubulointerstitial nephritis and uveitis (TINU), and the remainder had uveitis associated with sarcoid disease or irritable bowel syndrome. Of the 68 children with JIA, 55% (n = 37) had oligoarticular disease, 16% (n = 11) had rheumatoid factor (RF)-negative polyarthritis, 19% (n = 13) had ERA and 4% (n = 6) had PsA. Of those with ERA 23% were HLA-B27 positive.

Initial Episode of Uveitis

In the majority of patients, uveitis was restricted to the anterior chamber (82%). Both anterior and intermediate chambers were involved in 10%. Of those with anterior and intermediate uveitis, 8 had idiopathic uveitis, 1 had IBDU, 1 had sarcoid, and 2 had TINU. The age of onset was younger in those with AU than in those with anterior

Table 1. Characteristics of children and adolescents followed by division of rheumatology for noninfectious uveitis

Characteristic	All n = 118	Symptomatic[a] n = 58	Asymptomatic n = 60
Age at diagnosis, years, median (IQR)	7.41 (3.8-11.0)	9.1 (6.6-12.7)	5.5 (3.2-7.9)
Duration uveitis, days[b]	14 (6, 186)	14.5 (6, 92)	14 (5, 294)
	No. (%)[c]	No. (%)[e]	No. (%)
Sex, female	78 (66)	35 (45)	43 (55)
Inflammatory diagnosis			
IBD with arthritis	2 (2)	2 (100.0)	0
Sarcoid	4 (3)	1 (25)	3 (75)
Idiopathic	39 (33)	27 (69)	12 (31)
TINU	6 (5)	5 (83)	1 (17)
JIA[a]	67 (57)	23 (34)	44 (66)
Subtypes of JIA		n = 24	n = 44
Oligoarticular	37 (55)	11 (30)	26 (70)
Polyarticular (RF−)	11 (16)	3 (27)	8 (73)
ERA	13 (19)	7 (54)	6 (46)
PsA	4 (6)	1 (25)	3 (75)
Undifferentiated	3 (4)	2 (67)	1 (33)
Ocular diagnosis			
Anterior only	97 (82)	46 (47)	51 (53)
Anterior and intermediate	12 (10)	8 (67)	4 (33)
Intermediate or pars planitis	3 (2)	—	3 (1)
Posterior only	1 (1)	1 (100)	—
Panuveitis	5 (4)	3 (60)	2 (40)
HLA_B27 (positive) (n = 91)[f]			
Of all subjects	11 (12)	6 (55)	5 (46)
Of JIA subjects	8 (15)	4 (50)	4 (50)
Of ERA subjects	3 (23)	2 (67)	1 (33)
ANA (positive) of all (n = 113)[g]			
Of all subjects	54 (48)	20 (37)	34 (63)
Of JIA	42 (64)	15 (36)	27 (64)
Of oligoarticular JIA	24 (67)	15 (62)	9 (38)
Of ERA	5 (42)	2 (40)	3 (60)

ANA, antinuclear antibody; *ERA*, enthesitis-related arthritis; *IBD*, inflammatory bowel disease; *JIA*, juvenile idiopathic arthritis; *PsA*, psoriatic; *TINU*, tubulointerstitial nephritis and uveitis.
[a]Symptomatic uveitis (eye pain, redness, photophobia and/or blurred vision) at diagnosis of uveitis.
[b]Duration of uveitis at entry into cohort.
[c]Percent reflects percentage of the column.
[e]Percent reflects percent of row.
[f]With known HLA B27 status; HLA B27 includes patients positive for the class II MHC allele HLA B27.
[g]With known ANA status.

and intermediate uveitis (7.1 vs 11.1 years [$P < 0.01$]). In univariate logistic regression, the odds of AU were significantly increased in JIAU compared to idiopathic uveitis (OR = 20.3; 95% CI, 4.3-95.5) as they were for subjects with uveitis that began before age 7 years (OR = 4.7; 95% CI, 1.48-15.02; data not shown). Those with HLA-B27 positivity and symptomatic uveitis had lower odds of having AU (OR < 1), but the associations were not statistically significant.

Fifty-eight patients (49%) had redness, pain, or photophobia at first-U. At onset, uveitis was symptomatic in 69% of non-JIAU and 34% of JIAU patients. Among patients with JIAU, the highest rates of symptomatic uveitis occurred in those with ERA (55%) and undifferentiated JIA (67%). Using univariate logistic regression, those with non-JIAU had significantly higher odds of symptomatic uveitis at onset (Table 2). Compared to those with JIA, patients with idiopathic uveitis had an odds ratio of 4.3 (95% CI, 1.84-10.03; $P = 0.001$), and patients with underlying systemic diseases other than JIA had an odds ratio of 3.8 (95% CI, 1.04-14.07; $P = 0.04$) of having symptoms at first-U (all non-JIAU 4.18 higher odds). Younger children had one-fifth the odds of symptoms at first-U than older children (OR = 0.21; 95% CI, 0.09-0.45; $P = 0.000$). There was no association of symptomaticity with sex or with anatomic location of uveitis. The odds of having symptoms at first-U were lower in ANA-positive than in ANA-negative individuals (OR = 0.4; 95% CI, 0.19-0.86). Those with spondyloarthritis or HLA-B27 + uveitis did not have an increased OR of symptomaticity at first-U. Among subjects with systemic disease, the odds of symptomaticity at first uveitis was not lower in those already on systemic medications (data not shown).

Symptoms with Uveitis Recurrence

Of the 118 enrolled patients, 92 had at least 6 months' follow-up and at least 1 reactivation. The median number of reactivations per patient during the follow-up period

Table 2. Univariate logistic regression for symptoms at uveitis onset

	Symptomatic, no. (%)	Odds ratio (95% CI)
Systemic disease		
JIA uveitis [a]	23 (34)	1 = reference
Idiopathic uveitis	27 (69)	4.30 (1.84-10.03)[b]
Uveitis with non-JIA systemic disease	8 (67)	3.83 (1.04-14.07)[b]
Systemic disease		
JIA uveitis	23 (34)	1 = reference
All other uveitis	35 (69)	4.18 (1.92-9.1)[b]
JIA subtype		
Oligoarticular JIA	11 (33)	1 = reference
Polyarticular (RF−) JIA	3 (27)	0.89 (0.20-3.98)
ERA JIA	7 (54)	2.75 (0.75-10.10)
Psoriatic JIA	1 (25)	0.79 (0.07-8.43)
Undifferentiated JIA	2 (67)	4.73 (0.39-57.69)
Spondyloarthritis		
ERA[c]	7 (53.9)	2.77 (0.80-9.54)
JSpA[d]	9 (60)	1.65 (0.54-4.50)
Location		
Any anterior uveitis	54 (50)	0.68 (0.26-1.75)
Anterior uveitis only[e]	46 (47)	1 = reference
Anterior + intermediate uveitis	8 (67)	2.5 (0.42-14.82)
Intermediate, posterior, pan uveitis	4 (44)	1.13 (0.29-4.45)
Demographics		
Sex, female	35 (47)	0.61 (0.28-1.30)
Age <7 years	16 (29)	0.21 (0.09-0.45)[b]
Biomarkers		
ANA positive	20 (37)	0.40 (0.19-0.86)[b]
HLA B27	6 (55)	1.14 (0.32-4.05)

ANA, antinuclear antibody; *ERA*, enthesitis-related arthritis; *IBD*, inflammatory bowel disease; *JIA*, juvenile idiopathic arthritis; *JSpA*, juvenile spondyloarthritis.
[a]JIA uveitis is the comparator.
[b]Statistically significant, $P < 0.05$.
[c]ERA vs other JIA.
[d]JSpA vs all other subjects. JSpA (spondyloarthritis) includes ERA JIA and IBD associated uveitis.
[e]Restricted to anterior chamber.

was 2 (IQR, 1-4; mean 3 ± 2). The median time from initial uveitis to first reactivation was 373 days (IQR, 171-1139) (mean 795 ± 962 days). Forty-nine had symptoms during at least one episode of reactivation. More than one-third of subjects with symptomatic first-U ever experienced any reactivations *without* associated symptoms. Using McNemar's test, there was no association between symptoms at first-U and ever-symptoms at reactivation (Table 3). In ordinal logistic regression, symptomatic first-U was not statistically associated with the presence of symptoms at recurrences (OR = 1.71; 95% CI, 0.75-3.91). See Table 4. Having an underlying diagnosis of JIA versus non-JIAU significantly decreased the odds of symptoms at recurrence (OR = 0.44; 95% CI, 0.19-0.99). While two-thirds of reactivations occurred in subjects being treated with a systemic immunomodulatory agent, symptomaticity was not associated with this exposure.

Table 3. Association between Symptoms at initial vs. subsequent activation

	Initial uveitis[a] (%)[b]	
	Symptomatic (n = 49)	Asymptomatic (n = 43)
Symptomatic at reactivation (≥1)	32 (67)	16 (33)
Asymptomatic at reactivation	17 (39)	27 (61)

[a]Number of subjects with ≥6 months' follow-up, episode of reactivation, and data on symptoms at reactivation. N = 92.
[b]*P* value of McNemar's test = 0.81.

Table 4. Univariate ordinal logistic regression for symptoms at any uveitis reactivation

	OR (95% CI)
Symptoms at diagnosis	1.71 (0.75-3.91)
Systemic disease	
JIA uveitis[a]	0.44 (0.19-1.99)[b]
JIA uveitis	1 = reference
Idiopathic uveitis	2.27 (0.91-5.65)
Uveitis with non-JIA systemic disease	1.64 (0.85, 6.52)
JIA subtype	
Oligoarticular JIA	1 = reference
Polyarticular (RF−) JIA	1.4 (0.40-4.77)
ERA JIA	2.0 (0.44-8.8)
Psoriatic JIA	$4.6e^{-07}$ ($8.58e^{-08}$ to $2.47e^{-06}$)[b]
Undifferentiated JIA	1.32 (0.11-16.23)
Spondyloarthritis	
ERA	2.01 (0.51-8.00)
JSpA	1.43 (0.48-4.23)
Location	
Anterior uveitis[c]	0.75 (0.31-1.80)
Anterior uveitis only	1 = reference
Anterior + intermediate uveitis	1.26 (0.28-5.68)
All other uveitis	2.16 (0.73-6.42)
Demographics	
Sex, female	1.4 (0.64-2.88)
Age ≥7 years	2.03 (0.88-4.67)
Biomarkers	
ANA	1.32 (0.58-3.0)
HLA B27	1.7 (0.44-6.58)
Current systemic medications[d]	1.2 (0.58-2.54)

ERA, enthesitis-related arthritis; *JIA*, juvenile idiopathic arthritis.
[a]JIA vs all other non-JIA-associated uveitis.
[b]$P = 0.05$.
[c]Inflammation restricted to the anterior chamber versus all other location of uveitis (including anterior + intermediate uveitis).
[d]Systemic medication treatment during reactivation, including treatment with: systemic corticosteroids, methotrexate, infliximab, adalimumab, and/or mycophenolate mofetil.

Complications

Complications developed in at least one eye as follows (data not shown): increased intraocular pressure (15%), band keratopathy (21%), cataract (26%). The percentage of those with decreased visual acuity varied by classification system; 10% had mild or moderate decreased vision unilaterally by WHO criteria (9% bilateral), whereas 42% had at

least moderately decreased visual acuity unilaterally by the PEDIG criteria (17% bilateral). Neither the prevalence of ever-complications nor of any individual complication varied based on having had symptoms at disease outset.

Discussion

We describe the symptomaticity of NIU over time in a North American tertiary referral center. JIA accounted for the majority of cases, and most inflammation was confined to the anterior chamber. About half of subjects presented with symptomatic first-U. This was more likely if the patient did not have JIA, was older at the age of onset (≥7 years), and was ANA negative. That almost 90% of patients experienced an episode of uveitis reactivation reflects the chronic course of NIU in our cohort. One-third of those who had symptoms with first-U experienced at least one episode of reactivation without symptoms. Those with JIA had decreased odds of symptomaticity at uveitis recurrence, but no other patient characteristics were associated with symptomaticity at recurrence. Rates of complications were similar regardless of whether uveitis was symptomatic.

Ocular inflammation most often involved the anterior chamber (82%). This rate of AU is higher than that described in earlier North American uveitis cohorts (45%-58%)[3,10-12] and in the most recent cohort, reported earlier this year by Ferrara and colleagues[4] (62%).The increased prevalence AU, relative to that in Ferrara and colleagues,[4] may be partially attributable to the increased prevalence of JIAU in our cohort (57% vs 36%, resp.). In addition, 10% of subjects, although none with JIAU, had involvement of both the anterior and intermediate chambers, a distribution of uveitis not previously described. These children may not respond as well to topical agents as do those with isolated AU and may require more intensive treatment.

A lower percentage of those with JIA had symptoms at first-U than those without JIA (34% JIAU vs 69% non-JIAU), an association that was statistically significant in logistic regression analysis. While this observation is similar to what has been reported previously,[13,14] this is the first report demonstrating that younger children and those who were ANA-positive are less likely to have symptoms at first-U. This is unlikely to simply reflect a reporting bias based on age, as redness and photosensitivity can be appreciated in nonverbal children. Stratified analyses suggest that ANA modifies the relationship between JIA and symptomaticity, although the study was underpowered for this to reach significance. In non-JIAU, the likelihood of symptomaticity was higher in those who were ANA negative than positive, but the likelihood of symptomaticity was not affected by ANA status in those with JIAU (data not shown).

As expected, the prevalence of symptomaticity was higher in ERA (50%) and undifferentiated JIA (67%) than in other types of JIA, but neither was significantly associated with symptomatic uveitis in regression models. It is possible that the lack of significance is due to the small number of patients in these groups, because the OR were >1. Contrary to the expectation that uveitis associated with JSpA is symptomatic, and hence requires less frequent screening,[13] our data showed that patients with ERA frequently develop uveitis without symptoms (50%). This rate was higher than in a German cohort, in which one-third of ERA-U patients were asymptomatic[13]; this may reflect a difference in the study populations, as our population with uveitis had a lower prevalence of HLA-B27 positivity. This will require further evaluation in a larger ERA cohort, but it might suggest that children with ERA would benefit from more frequent uveitis screening than those more recently proposed by Heiligenhaus and collegues.[13]

By analyzing the pattern of uveitis over the time, we demonstrate that clinical features may change, switching from symptomatic to asymptomatic and vice versa, during the course of disease. One-third of patients with the presence of symptoms at first-U experienced at least one reactivation without any symptoms during follow-up. That symptomatic first-U was not statistically associated with the presence of symptoms at recurrences, indicates that uveitis presentation can vary within an individual. Currently, consensus recommendations do not exist to guide the frequency of monitoring in patients with known uveitis. Many practitioners, though, recommend that patients with "controlled" uveitis who initially presented with symptoms, return for follow-up care less frequently than those who did not have symptoms at the outset. Our data suggest that because the clinical pattern of uveitis may change over the time, monitoring parameters should not be less stringent for patients who initially have symptomatic uveitis.

Our study was limited by its retrospective nature and the number of subjects in each subset. Because ophthalmologic assessments were not subject to an established protocol, longer inter-examination intervals may have resulted in delayed diagnosis of asymptomatic uveitis; however, because time to reactivation was not an outcome, this should not affect results. Patient race was not collected. Our population was heterogenous racially and ethnically, and review of the electronic medical record suggested that patient/family self-reporting may have been a poor proxy even for self-identified race. Another limitation of the study is the absence of concurrent articular disease activity. The temporal relationship between arthritis and uveitis activity is not well described and is an area for future investigation. Although there were no significant associations between patient or disease characteristics and symptomaticity at reactivation, the OR were relatively higher in those with symptoms at first-U, non-JIAU, spondyloarthritis, and nonanterior uveitis. Patients with PsA did have a significantly decreased OR of symptomaticity at reactivation, but this encompassed a small number of patients

(n = 4, episodes of reactivation = 6). In a larger cohort, with smaller confidence intervals, clearer associations might be detected. The relatively small number of subjects with ERA and the lower-than-expected prevalence of HLA-B27 were also limitations.[13] This may lead to misclassification bias of ERA since the diagnosis may be driven by enthesitis. However, analyses of the association between uveitis symptomaticity at first-U and at reactivation were performed restricted to those with HLA-B27 and was not significantly associated with symptomatic uveitis. Future work may evaluate whether concomitant medications impact the odds of symptoms with uveitis recurrence.

Literature Search

PubMed was searched for English-language results in January 2018, without date restriction, using the following terms and combinations: *uveitis* AND *pediatric*, *non* AND *infectious* AND *uveitis*, and *idiopathic* AND *uveitis*.

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