Classification Criteria for Juvenile Idiopathic Arthritis–Associated Chronic Anterior Uveitis

THE STANDARDIZATION OF UVEITIS NOMENCLATURE (SUN) WORKING GROUP[1,2,3,4,*]

• PURPOSE: To determine classification criteria for juvenile idiopathic arthritis (JIA)-associated chronic anterior uveitis (CAU).
• DESIGN: Machine learning of cases with JIA CAU and 8 other anterior uveitides.
• METHODS: Cases of anterior uveitides were collected in an informatics-designed preliminary database, and a final database was constructed of cases achieving supermajority agreement on the diagnosis, using formal consensus techniques. Cases were split into a training set and a validation set. Machine learning using multinomial logistic regression was used on the training set to determine a parsimonious set of criteria that minimized the misclassification rate among the anterior uveitides. The resulting criteria were evaluated on the validation set.
• RESULTS: One thousand eighty-three cases of anterior uveitides, including 202 cases of JIA CAU, were evaluated by machine learning. The overall accuracy for anterior uveitides was 97.5% in the training set and 96.7% in the validation set (95% confidence interval 92.4, 98.6). Key criteria for JIA CAU included (1) chronic anterior uveitis (or, if newly diagnosed, insidious onset) and (2) JIA, except for the systemic, rheumatoid factor–positive polyarthritis, and enthesitis-related arthritis variants. The misclassification rates for JIA CAU were 2.4% in the training set and 0% in the validation set.
• CONCLUSIONS: The criteria for JIA CAU had a low misclassification rate and seemed to perform well enough for use in clinical and translational research. (Am J Ophthalmol 2021;228: 192–197. © 2021 Elsevier Inc. All rights reserved.)

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Juvenile idiopathic arthritis (JIA) is a collection of inflammatory arthritic diseases characterized by onset before the 16th birthday and arthritis persisting for at least 6 weeks and includes the diseases previously known as juvenile rheumatoid arthritis and juvenile chronic arthritis.[1,2] Juvenile idiopathic arthritis encompasses at least 7 distinct diseases: (1) systemic arthritis; (2) oligoarthritis; (3) rheumatoid factor–negative polyarthritis; (4) rheumatoid factor–positive polyarthritis; (5) psoriatic arthritis; (6) enthesitis-related arthritis (ERA); and (7) undifferentiated arthritis. In addition, oligoarthritis is divided into persistent oligoarthritis and extended oligoarthritis.[1,2] The International League of Associations for Rheumatology (ILAR) criteria for JIA are outlined in Table 1.[1] The most common type of JIA is oligoarthritis, accounting for 40%-60% of cases, followed by rheumatoid factor–positive polyarthritis (20%-25%), systemic arthritis (10%-20%), rheumatoid factor–negative polyarthritis (5%-10%), ERA (5%-10%), undifferentiated arthritis (5%-10%), and psoriatic arthritis (5%).[3]

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TABLE 1. International League of Associations for Rheumatology Classification of Juvenile Idiopathic Arthritis

JIA Category	Definition
Systemic arthritis	Arthritis in ≥1 joint with daily fever of ≥2 weeks duration plus ≥1 of: 1. Evanescent, erythematous rash 2. Generalized lymph node enlargement 3. Hepatomegaly and/or splenomegaly 4. Serositis *Exclusions*: a, b, c, d (see footnote)
Oligoarthritis	Arthritis affecting 1-4 joints during the first 6 months of disease
Persistent	Affecting ≤4 joints throughout the disease course
Extended	Affecting a total of >4 joints after the first 6 months of disease
	Exclusions: a, b, c, d, e
Rheumatoid factor–negative polyarthritis	Arthritis affecting ≥5 joints during the 1st 6 months of disease; a test for rheumatoid factor is negative. *Exclusions*: a, b, c, d, e
Rheumatoid factor–positive polyarthritis	Arthritis affecting ≥5 joints during the first 6 months of disease; ≥2 tests for rheumatoid factor ≥3 months apart are positive in the first 6 months of disease *Exclusions*: a, b, c, e
Psoriatic arthritis	Arthritis and psoriasis OR arthritis plus ≥2 of: 1. Dactylitis 2. Nail pitting or onycholysis 3. Psoriasis in a first-degree relative *Exclusions*: b, c, d, e
Enthesitis-related arthritis	Arthritis and enthesitis OR arthritis OR enthesitis plus ≥2 of: 1. Sacroiliac joint tenderness and/or inflammatory lumbosacral pain 2. Presence of HLA-B27 antigen 3. Acute anterior uveitis 4. History of spondyloarthritis or acute anterior uveitis in a first-degree relative *Exclusions*: a, d, e
Undifferentiated arthritis	Arthritis fulfilling criteria in no category or in ≥2 categories

JIA = juvenile idiopathic arthritis.

Exclusions: (a) psoriasis or a history of psoriasis in the patient or a first-degree relative; (b) arthritis in an HLA-B27-positive male beginning after the sixth birthday; (c) spondyloarthritis, enthesitis-related arthritis, or acute anterior uveitis OR a history of 1 of these disorders in a first-degree relative; (d). presence of IgM rheumatoid factor on ≥2 occasions ≥3 months apart; (e) presence of systemic JIA in the patient.

Adapted from Petty RE, Southwood TR, Manners P, et al. International League of Associations for Rheumatology classification of juvenile idiopathic arthritis: second revision, Edmonton, 2001. *J Rheumatol* 2004;31:390-392.

Chronic anterior uveitis is a well-recognized manifestation of JIA. It typically presents in children within 4 years of the onset of the arthritis, with the highest risk in the first year. The median age of onset of the uveitis is 5-6 years.[4,5] Approximately 90% of children with uveitis will present within 8 years of the diagnosis of the arthritis, but occasionally the interval may be longer.[6] It typically presents as an asymptomatic anterior uveitis in a "white" eye, diagnosed on ophthalmologic screening.[4-8] In a small percentage (<10%) the uveitis will present before the arthritis.[4,5,7] The presence of antinuclear antibodies (ANA) in the blood is a risk factor for JIA-associated chronic anterior uveitis, and the majority of cases of JIA-associated chronic anterior uveitis are ANA-positive, but JIA-associated chronic anterior uveitis can occur in the absence of a positive test for ANA.[4-8] Among children with JIA and a positive ANA, the estimated lifetime risk of chronic anterior uveitis is ~30%-40%.[5,7] Patients with systemic JIA or rheumatoid factor–positive polyarthritis are at low risk for uveitis.[4] Among children with oligoarthritis and rheumatoid factor–negative polyarthritis, it seems that the type of arthritis is less important than the ANA; ANA-positive oligoarthritis persistent, oligoarthritis extended, and rheumatoid factor–negative polyarthritis all have an estimated risk of ~30%.[7] Conversely, ERA is an HLA-B27-associated disease, and the uveitis seen in children with ERA is an acute anterior uveitis, as in adult HLA-B27-associated diseases.[1,4] Juvenile psoriatic arthritis in younger children is a small-joint arthritis, and the uveitis phenotype typically is chronic. Conversely, older children with juvenile psoriatic arthritis may develop a psoriatic spondylitis picture, which can be associated with HLA-B27 and an acute anterior uveitis.[4]

The Standardization of Uveitis Nomenclature (SUN) Working Group is an international collaboration that has developed classification criteria for 25 of the most common uveitides using a formal approach to development and classification.[8-14] Among the anterior uveitides studied was JIA-associated chronic anterior uveitis.

METHODS

The SUN Developing Classification Criteria for the Uveitides project proceeded in 4 phases, as previously described: (1) informatics, (2) case collection, (3) case selection, and (4) machine learning.[9,12]

• **INFORMATICS:** As previously described, the consensus-based informatics phase permitted the development of a standardized vocabulary and the development of a standardized, menu-driven hierarchical case collection instrument.[9]

• **CASE COLLECTION AND CASE SELECTION:** De-identified information was entered into the SUN preliminary database by the 76 contributing investigators for each disease, as previously described.[8,11,12] Cases in the preliminary database were reviewed by committees of 9 investigators for selection into the final database, using formal consensus techniques described in the accompanying article.[12,13] Because the goal was to develop classification criteria, only cases with a supermajority agreement (>75%) that the case was the disease were retained in the final database (ie, were "selected").

• **MACHINE LEARNING:** The final database then was randomly separated into a training set (~85% of cases) and a validation set (~15% of cases) for each disease, as described in the accompanying article.[12] Machine learning was used on the training set to determine criteria that minimized misclassification. The criteria then were tested on the validation set; for both the training set and the validation set, the misclassification rate was calculated for each disease. The misclassification rate was the proportion of cases classified incorrectly by the machine learning algorithm when compared to the consensus diagnosis. For JIA-associated chronic anterior uveitis, the diseases against which it was evaluated were cytomegalovirus anterior uveitis, herpes simplex virus anterior uveitis, varicella zoster virus anterior uveitis, spondylitis/HLA-B27-associated anterior uveitis, tubulointerstitial nephritis with uveitis, Fuchs uveitis syndrome, sarcoidosis-associated anterior uveitis, and syphilitic anterior uveitis.

RESULTS

Two hundred fifty-one cases of JIA-associated chronic anterior uveitis were collected, and 202 (80%) achieved supermajority agreement on the diagnosis during the "selection" phase and were used in the machine learning phase. These cases of JIA-associated chronic anterior uveitis were compared to 881 cases of other anterior uveitides, including 89 cases of cytomegalovirus anterior uveitis, 123 cases of varicella zoster virus anterior uveitis, 146 cases of Fuchs uveitis syndrome, 101 cases of herpes simplex virus anterior uveitis, 184 cases of spondylitis/HLA-B27-associated anterior uveitis, 94 cases of tubulointerstitial nephritis with uveitis, 112 cases of sarcoidosis-associated anterior uveitis, and 32 cases of syphilitic anterior uveitis. The characteristics at presentation to a SUN Working Group investigator of the cases with JIA-associated chronic anterior uveitis are listed in Table 2. The criteria developed after machine learning are listed in Table 3. The overall accuracy for anterior uveitides was 97.5% in the training set and 96.7% in the validation set (95% confidence interval 92.4, 98.6).[13] The misclassification rate for JIA-associated chronic anterior uveitis in the training set was 2.4% and in the validation set was 0%.

DISCUSSION

JIA-associated chronic anterior uveitis is a chronic disease often requiring long-term aggressive management to preserve vision.[4,15,16] Without treatment sufficient to control the inflammation, patients develop band keratopathy, cataracts, glaucoma, and visual loss. Even mild, "smoldering" inflammation is associated with poorer visual outcomes.[16] Among patients with mild JIA-associated chronic anterior uveitis, the median time to a sustained, drug-free remission is ~7 years, and among those with more severe uveitis, only ~25% will achieve a sustained, drug-free remission even after 20 years.[17] In a survey of pediatric rheumatologists, JIA-associated chronic anterior uveitis was associated with methotrexate use in the large majority of patients and with the need for biologic use (eg, adalimumab).[18] The duration and treatment need of JIA-associated chronic anterior uveitis contrast with the recurrent, episodic nature of spondylitis/HLA-B27-associated acute anterior uveitis, attacks of which often can be treated with topical corticosteroids alone, and which typically has prolonged periods of inactive uveitis off treatment and an average of 1 attack per year.[19] Because ERA is an HLA-B27-associated disease and is associated with acute anterior uveitis, we have made a distinction between the two, and the criteria herein are for JIA-associated chronic anterior uveitis only. Enthesitis-related arthritis-

TABLE 2. Characteristics of Cases of Juvenile Idiopathic Arthritis–Associated Chronic Anterior Uveitis

Characteristic	Result
Number of cases	202
Demographics	
Age, median, years (25th, 75th percentile)	5 (3, 7)
Age category, years (%)	
≤16	92
17-50	2
51-59	0
≥60	0
Missing	6
Sex (%)	
Male	19
Female	81
Race/ethnicity (%)	
White, non-Hispanic	79
Black, non-Hispanic	3
Hispanic	4
Asian, Pacific Islander	1
Other	6
Missing/unknown	5
Uveitis history	
Uveitis course (%)	
Acute, monophasic	0
Acute, recurrent	0
Chronic	97
Indeterminate	3
Laterality (%)	
Unilateral	34
Unilateral, alternating	0
Bilateral	66
Ophthalmic examination	
Cornea	
Normal	72
Band keratopathy	28
Keratitis	0
Keratic precipitates (%)	
None	68
Fine	22
Round	7
Stellate	0
Mutton fat	1
Other	0
Anterior chamber cells, grade (%)	
½+	34
1+	25
2+	24
3+	12
4+	3
Hypopyon (%)	0
Anterior chamber flare, grade (%)	
0	45
1+	30
2+	20
3+	5
4+	0

(*continued on next column*)

TABLE 2. (*continued*)

Characteristic	Result
Iris (%)	
Normal	71
Posterior synechiae	29
Sectoral iris atrophy	0
Patch iris atrophy	0
Diffuse iris atrophy	0
Heterochromia	0
IOP, involved eyes	
Median, mm Hg (25th, 75th percentile)	14 (12, 18)
Proportion patients with IOP > 24 mm Hg either eye (%)	6
Vitreous cells, grade (%)	
0	77
½+	14
1+	8
2+	0
3+	0
4+	0
Laboratory	
Positive antinuclear antibody (% entire population)	64
Positive antinuclear antibody (% of those tested)[a]	81

IOP = intraocular pressure.
[a]A total of 130 patients positive of 160 patients tested.

TABLE 3. Classification Criteria for Juvenile Idiopathic Arthritis–Associated Chronic Anterior Uveitis

Criteria
1. Evidence of anterior uveitis
   a. anterior chamber cells
   b. if anterior vitreous cells are present, severity is less than anterior chamber inflammation

AND

2. Chronic anterior uveitis or, if at initial diagnosis, uveitis is of insidious onset and asymptomatic / minimally symptomatic

AND

3. Juvenile idiopathic arthritis of the following subtypes[a]
   a. Oligoarthritis, persistent or extended, OR
   b. Rheumatoid factor–negative polyarthritis, OR
   c. Juvenile psoriatic arthritis, other than psoriatic spondylitis

Exclusions
1. Enthesitis-related arthritis
2. Positive serologic test for syphilis using a treponemal test
3. Evidence of sarcoidosis (either bilateral hilar adenopathy on chest imaging or tissue biopsy demonstrating noncaseating granulomata) or other granulomatous disease (eg, familial juvenile systemic granulomatosis)[19-22]
4. Aqueous specimen PCR positive for cytomegalovirus, herpes simplex virus, or varicella zoster virus

PCR = polymerase chain reaction.
[a]See Table 1.

associated acute anterior uveitis should be considered as one of the spondylitis/HLA-B27-associated uveitides and reported separately from JIA-associated chronic anterior uveitis.

Chronic anterior uveitis occurs in children without JIA and often is treated in a similar fashion.[20,21] More problematic is the occurrence of occasional children with chronic anterior uveitis and a positive ANA but no evidence of JIA even with follow-up. Whether or not they represent a *forme fruste* of JIA-associated chronic anterior uveitis is unknown. Some may have had a short-lived, mild oligoarthritis, which was undiagnosed, but this hypothesis cannot be verified. Therefore, the criteria currently require the presence of JIA for a diagnosis of JIA-associated chronic anterior uveitis. Long-term prospective cohort studies demonstrating similar genetic risk factors, similar course, and/or a substantial rate of JIA might lead to a revision and inclusion of these cases, but absent such data, children without JIA, even those with a positive ANA, have not been included in the criteria.

The presence of any of the exclusions in Table 3 suggests an alternate diagnosis, and the diagnosis of JIA-associated chronic anterior uveitis should not be made in their presence. In prospective studies many of these tests will be performed routinely, and the alternative diagnoses excluded. However, in retrospective studies based on clinical care, not all of these tests may have been performed. Hence the presence of an exclusionary criterion excludes JIA-associated chronic anterior uveitis, but the absence of such testing does not exclude the diagnosis of JIA-associated anterior uveitis if the criteria for the diagnosis are met. Although no cases of familial juvenile granulomatosis (Jabs syndrome or Blau syndrome) were included in the SUN database, this is a genetic disorder distinct from JIA, sometimes initially misdiagnosed as JIA.[22-25] Biopsy of affected tissue (eg, synovium or skin) or genetic testing for a *NOD-2/CARD15* mutation can confirm the disease.

Classification criteria are employed to diagnose individual diseases for research purposes.[14] Classification criteria differ from clinical diagnostic criteria in that although both seek to minimize misclassification, when a trade-off is needed, diagnostic criteria typically emphasize sensitivity, whereas classification criteria emphasize specificity,[14] in order to define a homogeneous group of patients for inclusion in research studies and limit the inclusion of patients without the disease in question that might confound the data. The machine learning process employed did not explicitly use sensitivity and specificity; instead, it minimized the misclassification rate. Because we were developing classification criteria and because the typical agreement between 2 uveitis experts on diagnosis is moderate at best,[12] the selection of cases for the final database ("case selection") included only cases that achieved supermajority agreement on the diagnosis. There may be occasional cases that clinicians in the course of clinical care believe have the disease, but that do not meet criteria, and therefore would not be included in a research study.

In sum, the relatively low misclassification rate of the SUN criteria suggests their appropriateness for use as classification criteria in clinical and translational research.

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