Prognostic value of antinuclear antibodies in juvenile idiopathic arthritis and anterior uveitis. Results from a systematic literature review

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ABSTRACT

Aims: To analyze the prognostic role of antinuclear antibodies (ANA) for the onset of uveitis in the context of juvenile idiopathic arthritis (JIA), its correlation with uveitis course and severity and its prognostic role for the development of arthritis in children with uveitis.
Methods: We conducted a systematic review analysis of the literature on the prognostic value of ANA on JIA associated uveitis and its complications. We included series published between January 1990 and December 2011 reporting the prognostic value of ANA positivity on uveitis in consecutive patients diagnosed with JIA.
Results: We identified 246 studies from our search, of which 25 were selected for detailed analysis and only 9 fulfilled the inclusion criteria. Some authors have mentioned that uveitis could preceed arthritis and that ANA positivity might represent a predictive factor for subsequent joint involvement. A chronic course and insidious onset of uveitis are predictors for an association with JIA. Although recognized as a possible predictor of uveitis development, presence of positive ANA does not represent a predictor of severity.
Conclusions: The presence of ANAs seems to be a risk factor for ocular involvement in patients with JIA. These autoantibodies, however, did not have any correlation with the recurrence of either idiopathic anterior uveitis or JIA-related uveitis and cannot be used as a marker to predict the clinical course of ocular inflammation. Any analysis of the literature is subjected to the limitations of each of the studies under evaluation. A large, prospective population-based study of JIA patients would be certainly ideal.

Keywords: Juvenile idiopathic arthritis; Uveitis; Antinuclear antibodies; Prognosis

INTRODUCTION

Juvenile idiopathic arthritis (JIA) – associated uveitis is the most common systemic cause of pediatric uveitis in Europe and North America. JIA associated uveitis has an insidious onset and is usually asymptomatic before the development of sight threatening complications[1]. Screening for uveitis in JIA patients has been instituted for many years and may have contributed to the decrease in prevalence of patients with severe visual loss. Screening guidelines are mainly based on the perceived risk of developing uveitis: risk factors include the pattern of initial joint disease, the patients' sex, antinuclear autoantibody (ANA) status and age at onset[2].

Chronic anterior uveitis may occur in 13–34% of patients with JIA and is most often observed in young girls with oligoarticular onset JIA[3]. Uveitis is usually asymptomatic and early detection requires routine slit lamp examination. Reports suggest that up to 38% of patients with JIA associated uveitis develop severe visual impairment and up to 16–22% develop blindness[3].

We have pooled available data published in the literature in order to appraise the prognostic role of ANA for the onset of uveitis in the context of JIA, its correlation with uveitis course and severity and its prognostic role for the development of arthritis in children with uveitis.

METHODS

We conducted a systematic review analysis of the lite-

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rature on the prognostic value of ANA on JIA associated uveitis and its complications. We included series published between January 1990 and December 2011 reporting the prognostic value of ANA positivity on uveitis in consecutive patients diagnosed with JIA, according to the World Health Organization/International League Against Rheumatism (WHO/ILAR) criteria. Search was limited to studies in humans and publication in European languages. Titles and abstracts of all the studies retrieved were reviewed to identify relevant studies for inclusion. Selected articles were detailed reviewed and relevant extracted. Reference lists for the initial studies retrieved were examined to identify any additional relevant studies missed by the electronic searches. We contacted authors of the selected studies for disclosure of relevant information.

The total number of patients with JIA, the proportion of patients with each JIA subtype, the sex and age distribution, ANA detection method, the incidence of uveitis among all patients and in each subgroup of patients, duration of follow-up, visual outcome and the incidence of complications of JIA-associated uveitis were extracted.

Articles that failed to fulfill all the inclusion criteria or had insufficient data for analyses were excluded from the systematic review. Series of patients with juvenile arthritis in which the diagnostic criteria used were not specified were excluded. We did not include case reports.

The analysis was focused on 3 main outcomes: 1) ANA predictive potential for uveitis onset in JIA patients, 2) ANA correlation with the clinical course and recurrence of uveitis and 3) ANA predictive potential in idiopathic anterior uveitis and in JIA-associated uveitis

RESULTS

We identified 246 studies from our search, of which 25 studies were selected based on title and abstract. From the selected studies, the full paper was retrieved, and more detailed methodological evaluation was done. Only 9 studies were finally identified as meeting the inclusion criteria (Figure 1), and 16 studies were excluded at this stage.

STUDY CHARACTERISTICS
The methodological quality of the studies meeting the inclusion criteria was variable. With the exception of
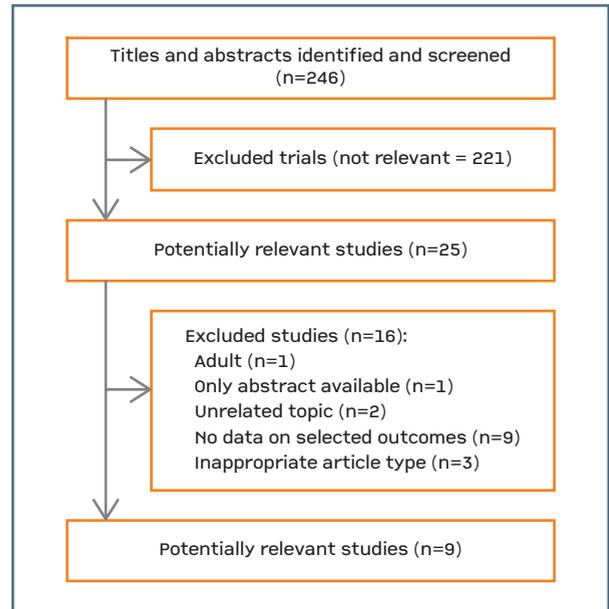

FIGURE 1.

a single prospective study the remaining were retrospective studies (Table I).

The total number of patients reported in the studies was 4534, with the largest study reporting 3271 patients and the smallest one characterizing 22 patients. Five studies were multicentric, two came from a terciary center and two were population-based. The majority of the series came from Europe: three from Italy[3,5,9], two from Germany[8,12], one from France[6], one from Norway[7], one from Switzerland[10] and just one from America (Canada)[11].

STUDY FINDINGS
Our main outcomes were ANA predictive potential for uveitis onset in JIA patients, ANA correlation with the clinical course and recurrence of uveitis and ANA predictive potential in idiopathic anterior uveitis and in JIA-associated uveitis.

ANA PREDICTIVE POTENTIAL FOR UVEITIS ONSET IN JIA PATIENTS
Heiligenhau et al[8], *Saurenman et al[11]* and *Bolt et al[10]* demonstrated that ANA can be predictive of uveitis onset as an independent predictor variable (univariate analysis) and as part of a multivariate logistic regression analysis. *Heiligenhau et al* characterized, by multivariate analysis, predictors of uveitis in a large cohort (3271 patients) of JIA patients: age at onset (OR 0.95, CI

TABLE I. CHARACTERISTICS OF STUDIES RETRIEVED

Study	Type of study	Participants	Interventions	Methods used for detection	Outcomes
Manzotti 2002[5]	Retrospective cohort study, population based	22 children (10 with JIA uveitis and 12 with IU). ANA positive >1:80, from 1990 to 2000 in Parma	Paediatric and ophthalmologic review 4 t/y; ANA detection 4 t/y and in uveitis recurrences; cyclosporine (2.5-4.5mg/kg/day) and fluocortolone (0.5-1mg/kg/week)	Indirect immunofluorescence (HEp2 cell). Threshold of 1:80 was considered positive	ANA seropositivity, clinical course of ocular disease; and ANA levels during the ocular recurrences in JIA and IU groups
Zulian 2002[3]	Retrospective case-control study, multicenter	316 patients with Oligo-JIA; minimal follow up of 2 years. ANA positive >1:80. 239 patients in study-group and 77 in validation group (no signicant differences between them)	3 groups: severe uveitis, mild uveitis and no uveitis. Analysis of variables that were significant with univariate tests or were clinically relevant for each outcome underwent multivariate logistic regression analysis	Indirect immunofluorescence (HEp2 cell). Threshold of 1:80 was considered positive	2 final models: the first predicts the onset of uveitis and the second its outcome (severe or mild)
Guillaume 2000[6]	Retrospective cohort, multicenter	207 oligo-JIA patients; follow-up 10 years	Paediatric and ophthalmologic review; articular and ocular progression	Tested on rat liver sections. IF-ANA considered positive when titers were 1:100	Clinical course of ocular and articular disease; Predictors of disease severity.
Nordal 2009[7]	Prospective population-based cohort study, multicenter	100 children with JIA	Paediatric and ophthalmologic review 2-4 t/y; ANA detection by IF and ELISA; AHA detection	ANA by indirect immunofluorescence using HEp-2 cells (IF-ANA) and by ELISA (E-ANA). Threshold of 1:80 and 1:101, respectively, was considered positive	Predictors of chronic asymptomatic uveitis
Heiligenhau 2007[8]	Retrospective cohort study, multicenter	3271 JIA patients; follow-up 1 year	Paediatric and ophthalmologic review; ANA detection	Not described	Predictors of uveitis and its complications; screening intervals
Grassi 2007[9]	Retrospective cohort study, population-based	309 JIA patients; from 1987 to 2007 in Milan	Paediatric and ophthalmologic review 2-4 t/y; ANA detection 4 t/y and in uveitis recurrences	Indirect immunofluorescence	Predictors of uveitis and its complications; ANA levels during the ocular recurrences

TABLE I. CONTINUATION

Study	Type of study	Participants	Interventions	Methods used for detection	Outcomes
Bolt 2008[10]	Retrospective cohort study, terciary center	309 JIA patients; from 1997-2005 in Switzerland	Paediatric and ophtalmologic review; ANA detection	Not described	Risk of uveitis; treatment and course of uveitis.
Saurenman 2010[11]	Retrospective cohort study, terciary center	1047 JIA patients (onset uveitis before arthritis excluded) in Toronto	Paediatric and ophtalmologic review; ANA detection	ANA by indirect immunofluorescence. A titer of 1:40 was considered positive.	Uveitis risk factor differences between male and female
Heinz 2008[12]	Retrospective cohort study, multicenter	137 with AU; from 1995-2005 (88 JIA + 49 IAU) in Germany	Paediatric and ophtalmologic review in both groups; ANA detection	Not described. Threshold of 1:160	Risk factor differences between IAU and JIA-uveitis

IF - indirect immunofluorescence; AHA – antihistone antibodies; IU – idiopathic uveitis; JIA – juvenile idiopathic arthritis; t/y – times per year; AU – anterior uveitis; IAU – idiopathic anterior uveitis

0.90–0.99, p=0.03), disease duration (OR 1.11; CI 1.07–1.15, p<0.01) and ANA-positivity (OR 2.63, CI 1.83–3.79, p<0.01) (besides the JIA subgroup (p=0.04)). The method of ANA detection and ANA threshold positivity was not described. The predictors of uveitis were additionally examined for the group of early cases (disease duration <24 months) in which oligoarticular JIA appeared to be at a particularly high risk for uveitis. In this subgroup, as determined by multivariate analysis, ANA-positivity again (OR 10.7, CI 3.1–37.1, p<0.001) was a predictor of uveitis, whereas HLA-B27 (p=0.06), age at onset (p=0.42), gender (p=0.23), number of joints with arthritis (p=0.38) and ESR (p=0.08) had no significant influence.

Saurenman et al showed that age at diagnosis (LR 16.7, p=0.0001), ANA positivity (LR 13.1, p=0.0003), female sex (LR 8.0, p=0,004), and the combination of female sex and young age at diagnosis (LR 6.7, p=0.009) were significantly associated with the development of uveitis. Among the subgroup of patients in whom JIA was diagnosed at the age of 6 years old or younger, ANA positivity (LR 16.3, p=0.0001), age at diagnosis (LR 7.2, p=0.007), and female sex (LR 6.8, p=0.008) but not oligoarticular JIA (LR 0.3, p=0.59) were significantly associated with the development of uveitis. For patients older than 6 years old at the time of the diagnosis of JIA, only age at diagnosis (LR 4.7, p=0.03) was associated with the development of uveitis, whereas ANA status (LR 0.39, p=0.53), sex (LR 1.28, p=0.26) and oligoarticular JIA (LR 0.22, p=0.64) were not.

Bolt et al[10] evidenced only positive ANA as a strong risk factor for the development of uveitis in their model (relative risk 16.7 for positive ANA, p<0.00001). The method of ANA detection and ANA threshold positivity was not described. The age at JIA diagnosis was the second most important factor but did not reach statistical significance (risk ratio 0.9, p = 0.056).

Grassi et al[9] revealed that oligoarticular-onset JIA, the early phase of arthritis, and the presence of ANA were the main risk factors for development of uveitis. Statistical analysis was not performed in patients with polyarticular- and systemic-onset JIA, because uveitis was rare among these subjects.

Nordal et al[7] have studied the predictive value of ANA tests (by indirect immunofluorescence using HEp-2 cells - IF-ANA and ELISA for ANA - E-ANA) in particular antihistone antibodies (AHA) as risk factors for development of chronic asymptomatic uveitis of insidious onset in JIA. They have verified that AHA≥ 8 U/ml, IF-ANA titer≥ 1/320, and young age at onset of

arthritis were significant predictors for development of chronic uveitis. No association was found between E-ANA and uveitis.

Zullian et al[3] highlighted that among the laboratory variables, the presence of IF-ANA and high ESR were independent predictors of uveitis (OR 2.07 and 1.71, respectively). However when a multivariate analysis was done the best-fitting model for the prediction of the onset of uveitis included the age at onset (OR 0.96), α2- globulin level (OR 1.34), and HLA-A19 (OR 2.87), B22 (OR 4.51), DR9 (OR 2.33) and HLA-DR1 (OR 0.13) but not ANA (OR 0.51). Although this model was robust (concordant nodes 75.2%, p=0.001), it couldn't clearly predict the development of uveitis in an early stage of JIA (sensitivity 78%, specificity 61%, efficiency 65%).

In the study of *Guillaume et al*[6] IF-ANA positivity was not predictive of uveitis occurrence (p=0.56). A family history of psoriasis was shown to be predictive of uveitis occurrence. They found joint erosion as being strongly associated with a polyarticular course. A high ESR as well as involvement of more than 1 joint or involvement of an upper limb at disease onset were predictors of disease extension. A high ESR was also a strong predictor of a destructive course.

CORRELATION WITH CLINICAL COURSE AND RECURRENCE OF UVEITIS

Four studies evaluated ANA association with the clinical course and/or recurrence of uveitis. *Heiligenhau et al* demonstrated that while ANA was a strong predictor for the onset of uveitis, complications in ANA-negative JIA associated uveitis were as common as in ANA-positive children. They considered that screening intervals in the ANA negative patients should be also shorter than in the previous guidelines[13,14] in order to avoid a delay of the recognition and treatment of recurrence[15]. *Grassi et al* found that, while the presence of IF-ANA represented a risk factor for the development of uveitis, an increase in titer was not associated to uveitis relapses. ANA were determined at the time of 84 uveitis relapses and were positive in 66/84 episodes and negative in 18/84; ANA titer increased before uveitis in 14 cases, decreased in 13, and was unchanged in 18, while in the remaining 21 cases the preceding ANA titer was dated back to more than 4 months, thus preventing comparison. They have verified that IF-ANA positivity represents a risk factor for the development of uveitis, but changes in titers were not associated with uveitis relapses. When patients

with and without ocular complications were compared, no significant differences appeared in ESR values at onset or regarding the presence of ANA.

Manzotti et al showed that IF-ANA positivity (1:80) is a risk factor for ocular involvement in those patients with JIA. These autoantibodies, however, did not have any correlations with the recurrence of either IU ou JIA-related-uveitis and cannot be used as a marker to predict the clinical course of ocular inflammation.

Zullian et al, showed that, the presence of ANA and high ESR were risk factors for uveitis. However only an increased alfa2-globulin concentration at disease onset could predict a more severe uveitis course. The best-fitting model for the prediction of severity of AU included only 2 variables: α2-globulin concentration at disease onset and time interval between onset of arthritis and first uveitis, but no ANA positivity.

ANA PREDICTIVE POTENTIAL DIFERENCES IN IDIOPATHIC ANTERIOR UVEITIS AND IN JIA-ASSOCIATED UVEITIS

Manzotti et al[5] and *Heinz et al*[12] analyzed children with idiopathic anterior uveitis (IAU) and with JIA-associated-anterior uveitis (AU). Demographic information, age at onset of uveitis, ANA titers, uveitis course and complications were recorded. *Manzotti et al* verified that IF-ANA positivity was a very frequent finding in JIA patients and that it was present from the onset of ocular involvement. In this study, the presence of ANA was found to be quite high (8 out of 10) in patients with JIA-associated uveitis, at baseline and throughout the study, without variations in the titer. This figure was notably different from that found in paediatric patients with IAU. In their study ANA positivity was found in 1 out of 12 patients with IAU at baseline and increased to 6 during the follow-up. From those who became ANA positive, two developed late articular involvement. The study was not intended to discuss the therapeutic effect of immunossupressive drug combination therapy. However, it is interesting that treatment had no influence in changing or supressing ANA production, neither in JIA-related uveitis nor idiopathic arthritis (IU).

Heinz et al. reported differences in the clinical course of IAU and JIA-associated AU. Their observations showed that ANA positivity (threshold of 1:160, but method not described) but presence of uveitis complications, insidious onset of uveitis, duration longer than 3 months, visual acuity of 20/50 or less and age 6 years old or younger at diagnosis of uveitis were as-

sociated with JIA-related AU. This may also apply for patients in whom uveitis onset is manifested prior to arthritis. JIA uveitis manifests earlier, has more complications, and more often requires systemic immunosuppression and surgical intervention.

DISCUSSION

In this systematic review, we aimed to find all available evidence on the prognostic role of ANA in JIA-associated uveitis, by using a strict methodology of systematic literature search and selection criteria.

Some authors have mentioned that uveitis could preceed arthritis and that ANA positivity might represent a predictive factor for subsequent joint involvement. In both IAU and JIA-associated-uveitis group of patients, a chronic clinical course, as defined by duration ≥ 3 months, was noted more often in the JIA group. Further, insidious course was more frequent in patients with JIA. A chronic course and insidious onset of uveitis are predictors for an association with JIA. *Manzotti* and *Heinz* showed that ANA positivity was associated with development of JIA. However, in the *Manzotti* study, due to the small number of patients enrolled, it was not possible to perform statistical analysis and look for statistical significance of the results presented. A larger number of patients is needed.

In patients with oligo-JIA, anterior uveitis has been reported with a frequency ranging between 12% and 20.1% (*Grassi et al.* 2007; *Heiligenhaus et al.* 2007). Among predictors for its development, early age at disease onset, ANA positivity, DRB1*11 HLA-haplotype and female gender have been identified (*Heilligenhaus et al.* 2007, *Saurenmann et al.* 2007; *Bolt et al.* 2008, *Grassi et al.* 2007). Three quarter of patients develop uveitis within 1 year and 90% by 4 years after arthritis onset (*Zulian et al.* 2002; *Heilligenhaus et al.* 2007). Although recognized as a possible predictor of uveitis development, presence of positive ANA does not represent a predictor of severity (*Zulian et al.* 2002; *Heilligenhaus et al.* 2007). Several studies tried to assess possible risk factors for severe course uveitis. The most frequently reported are symptomatic onset, diagnosis of uveitis before or concomitant to arthritis, chronic course, presence of complications at first visit, degree of inflammation at the initial ocular examination and a short interval time between the diagnosis of arthritis and uveitis (*Zulian et al.* 2002; *Heilligenhaus et al.* 2007). *Zullian* highlighted that among the laboratory varia-

bles, the presence of ANA was an independent predictor of uveitis. When a multivariate analysis was done, the best-fitting model for prediction of onset of uveitis included alfa2-globulin concentration at disease onset and time interval between onset of arthritis and first uveitis but did not include ANA positivity. The model confirmed a good sensitivity, and it is also reliable to predict a mild course uveitis. However, <50% of patients assigned to the high-risk group by the model had severe uveitis. It may be underlined that more than half of the children with predicted severe course had a follow-up <2 years. We may speculate that, in some of these patients, a longer follow-up might reveal a severe course.

In contrast to that found in previous studies, *Guillaume et al* have showed that ANA was not a predictive factor for uveitis occurrence. No correlation between ANA titer and any of the clinical manifestations of the disease, particularly relapses, could be identified. These observations indicate that the relationship between ANA and uveitis is far from clear-cut.

Integration of immunogenetic data, with clinical and laboratory risk factors for occurrence of JIA associated uveitis (such as JIA disease onset subtype, female gender, age of onset of arthritis, ANA positivity, serum concentrations of inflammatory markers) into a model that predicts patients who will develop uveitis would be highly desirable[16].

Any analysis of the literature is subjected to the limitations of each of the studies under evaluation. A large, prospective population-based study of JIA patients would be certainly ideal to determine the incidence, outcomes and prognostic development of JIA associated uveitis. However, the relative rarity of the disease and its complications make it impractical, if not impossible.

CONCLUSION

In summary, the presence of ANAs seems to be a risk factor for ocular involvement in patients with JIA. They are present in most cases from the onset of the disease. Furthermore, some studies[5,12] highlighted that in children, uveitis can be the single initial clinical manifestation of an indolent connective tissue disease that will only be symptomaticaly apparent latter on. The detection of ANA can be a marker of the future development of a full blown connective tissue disease[5]. These autoantibodies, however, did not have any cor-

relation with the recurrence of either IAU or JIA-related uveitis and cannot be used as a marker to predict the clinical course of ocular inflammation.

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