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Immunology markers that can be predictive for the diagnosis of juvenile idiopathic arthritis

<https://doi.org/10.1515/labmed-2019-0079>

Received May 10, 2019; accepted July 27, 2019; previously published online August 17, 2019

Abstract

Background: This study aimed to investigate the implications of antinuclear antibodies (ANAs) in juvenile idiopathic arthritis (JIA), the association with uveitis and the favorable evolution of the disease.

Methods: We followed 45 pediatric patients suffering from JIA, according to the International League of Associations for Rheumatology (ILAR), for a period of 2 years. ANAs were followed through immunofluorescence methods using a high-performance immunofluorescence automatic Helios device.

Results: A total of 15 of the ANA-positive patients presented an oligoarticular form of the disease, eight of them presented a polyarticular form of the disease and two of them presented a systemic form. The most severe forms have associated iridocyclitis. ANA-positive patients presented an earlier onset of disease in comparison with ANA-negative ones. ANA-positive patients from different ILAR categories had similar characteristics of the disease such as onset age (earlier), higher prevalence in females and the presence of asymmetric arthritis or iridocyclitis.

Conclusions: ANA may be an important marker for JIA and association with iridocyclitis. Following ANA titer in evolution might be a criterion for assessing the evolution of the disease. The association between positive ANA, oligoarticular JIA, iridocyclitis and a 2- to 4-year-old onset is common.

Keywords: antinuclear antibodies; juvenile idiopathic arthritis; pediatrics; uveitis.

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Introduction

Juvenile idiopathic arthritis (JIA) is a heterogeneous pathologic condition that comprises all forms of arthritis, of unspecified etiology, with the onset before the age of 16 years and lasting longer than 6 weeks. The reported prevalence of JIA varies from 8 to 150 cases per 100,000 children, with an incidence between 1–22 cases per 100,000. JIA represents one of the most frequent chronic diseases of childhood and the most common chronic rheumatologic disease in children. Without early diagnosis and appropriate treatment, JIA may result in short- or long-term disability from joint destruction, growth deficiency or blindness due to chronic anterior uveitis. One of the most common tests used in the diagnosis of JIA is represented by antinuclear antibody (ANA) titers [1–4].

ANAs represent a heterogeneous group of auto-antibodies directed against antigenic nuclear structures

(DNA, nucleosomes and histones). A positive test for ANA may indicate an autoimmune disease, such as JIA, systemic lupus erythematosus (SLE), drug-induced lupus, scleroderma (SS), Sjögren's syndrome (SjS), mixed connective tissue disease, polymyositis (PM)/dermatomyositis and rheumatoid arthritis (RA). Their presence in human blood samples have also been detected in cancers, after certain medications, in chronic infectious diseases and even in healthy persons. This is why a positive test for ANA is not diagnostic of JIA, and care should be taken in interpreting a positive result in someone who does not have clinical findings such as arthritis or uveitis. The specificity of these autoantibodies in JIA has not been fully determined so far. Some studies have shown that ANAs are associated with uveitis and correlate with disease progression. Furthermore, ANA-positive patients have common characteristics of the disease [5–8]. As Ravelli et al. presented in one of their studies, in the International League of Associations for Rheumatology (ILAR) classification system some categories of JIA seem to have some distinctive characteristics representing heterogeneous patient populations. The most well-defined and homogeneous form of JIA is considered the oligoarticular form, which is characterized by asymmetric arthritis, typically with early onset (before 6 years), higher prevalence in females, positive ANA and high risk for the development of iridocyclitis [6–10].

In this study, we investigated the implications of ANA in JIA. In particular, we tried to track the existence of some correlations between the presence of ANA in the blood samples of patients and ocular manifestations (anterior uveitis) in JIA. Other things we followed in our study were the possibility to correlate ANA levels with the evolution of the disease and whether there are similar characteristics of the disease, for different forms of JIA, due to the presence of ANA.

Materials and methods

We followed 45 patients suffering from JIA, according to ILAR, for a period of 2 years. ANAs were followed through immunofluorescence methods using a high-performance Helios device. These antibodies were determined for all patients, being part of the investigation protocol, together with the other markers. Titers higher than 1:40 after two determinations were considered positive. The associations with uveitis were followed in a retrospective way and their evolution under treatment of JIA. We also made comparisons between ANA-positive patients

and ANA-negative patients from our lot, in order to find out the specific characteristics for each category. Determination of ANA's titer on the Helios device was more accurate because of its automaticity, using the technique of immunofluorescence and also an important support, based on atlases of images of ANA. The aspect of ANA detected by immunofluorescence can indicate the existence of an autoimmune disease such as SLE, JIA, etc. This shows us that ANA can also be an immunological marker for the disease and a predictable factor for these pathologies.

The authors confirmed that they have complied with the World Medical Association Declaration of Helsinki regarding the ethical conduct of research involving human subjects.

Results

Implications of ANA in JIA

From a total of 45 patients suffering from JIA, 25 were ANA-positive. Fifteen ANA-positive patients presented an oligoarticular form of the disease, eight of them presented a polyarticular form of the disease and two of them presented a systemic form. The most severe forms had associated iridocyclitis: eight cases of the oligoarticular forms and three cases of the polyarticular forms.

Correlations between the presence of ANA in the blood samples of patients and ocular manifestations (anterior uveitis) in JIA

In patients with positive ANA, we found that the disease is more frequent in females, onset tends to be earlier, at a lower age, most of them develop iridocyclitis, and arthritis is asymmetric with fewer affected joints and no hip impairment (Table 1). Analyzing the association between JIA and positive ANA, there was a significant association between the type of JIA and the positive ANA ($p=0.003$). A higher frequency of oligoarticular JIA was observed in patients with positive ANA than in ANA-negative patients (60% vs. 16.7%). Regarding the occurrence of iridocyclitis in patients with positive ANA, we found an association between oligoarticular JIA and iridocyclitis ($p=0.005$). In patients with JIA, there was a significant association between the presence of ANA and the age group, with ANA being significantly more often present in patients

Table 1: Characteristics of patients with positive ANA.

	Age of onset	Gender	Iridocyclitis	Affected joints
Oligoarticular JIA (15 cases)	2–4 years: 8 patients 4–15 years: 7 patients	M: 5 F: 10	8	Asymmetric arthritis
Polyarticular JIA (8 cases)	10–18 years: 8 patients	M: 2 F: 6	3	Large joints affection
Systemic JIA (2 cases)	4 years: 2 patients	M: 1 F: 1	0	Periodic articular manifestations

ANA, antinuclear antibody; JIA, juvenile idiopathic arthritis.

between 2 and 4 years of age with the oligoarticular form ($p=0.005$).

On the other hand, in ANA-negative patients we found that JIA tends to have the onset at a higher age, is more frequent in females (like in ANA-positive patients) and none of them developed iridocyclitis. Polyarticular and systemic JIA are more common in those with negative ANA. In patients with negative ANA, there was no significant association between the type of JIA and sex, being similar in boys and girls ($p=1.00$). In patients with negative ANA, there was a significant association between the type of JIA and the age group, with the polyarticular form being more frequent in patients over 4 years of age ($p=0.004$) (Table 2).

Correlations of ANA levels with the evolution of the disease

Regarding arthritis sites, there was a significant association between the oligoarticular form, 2- to 4-year-old patients and positive ANA results. In these patients, no more than three to four joints with an asymmetric distribution were caught. Patients with negative ANA tend to develop systemic and polyarticular JIA with more than four joints affected.

Discussion

The presence of ANA in patients with JIA confers certain characteristics that may represent new diagnosing strategies. In the present study, it was found that positive ANAs are most commonly found in the oligoarticular forms, in females, with early onset between 2 and 4 years and with high risk of developing uveitis. Arthritis in this oligoarticular form is asymmetric, generally starting at a lower limb, with no more than three to four joints affected. In our study, negative ANA results were more common in females, in the oligoarticular and polyarticular forms. There was no iridocyclitis in patients with negative ANA. These patients presented extensive arthritis, initially asymmetric, affecting more than five joints.

JIA in children is much more different from RA in adults. This has been shown also through the clinical aspects, therapy response and evolution. The rheumatoid factor (RF) in JIA is positive only in polyarticular JIA, which is only a small percent of the total cases of JIA. From this point of view, the correlation between ANA and RF was not objectified. In JIA, neither anti-citrullinated protein antibody represents an immunological marker, their presence being only 2–50%, compared with RA of adults, where they are an important diagnostic marker.

Table 2: Characteristics of patients with negative ANA.

	Age of onset	Gender	Iridocyclitis	Affected joints
Oligoarticular JIA (3 cases)	2–4 years: 1 patient 4–15 years: 2 patients	M: 1 F: 2	0	Asymmetric arthritis, at least 3 joints
Polyarticular JIA (6 cases)	10–18 years: 6 patients	M: 3 F: 3	0	Large joints affection
Systemic JIA (9 cases)	4–8 years: 2 patients	M: 4 F: 5	0	Periodic articular manifestations

ANA, antinuclear antibody; JIA, juvenile idiopathic arthritis.

The importance of these ANAs in evolution and complications of JIA has been supported by ILAR and the European League Against Rheumatism (EULAR) since 1977. Studies undertaken worldwide have shown the association between the presence of ANA, uveitis and articular manifestations [11]. Another study showed the importance of the association between the presence of ANA and uveitis [12]. In an extensive article about JIA, it was shown that out of all the oligoarticular forms of JIA, about 70% are ANA-positive, with high risk of developing anterior uveitis and none with positive RF [13].

Considering all these aspects, it is important to look for and detect the ANAs in subjects with JIA. ANAs are detected using immunofluorescence and it is known that some immunofluorescence patterns are characteristic for certain types of disease. In the future, upcoming classifications will have to take into consideration these categories of JIA, with positive ANAs and negative ANAs that have a certain type of behavior and evolution [5].

Conclusions

ANA may be an important marker for JIA and the association with iridocyclitis. Iridocyclitis is more frequent in ANA-positive patients. The association between positive ANA, oligoarticular JIA, iridocyclitis and the 2- to 4-year-old onset is common. ANA-positive patients from different categories of JIA have similar characteristics of the disease. This study demonstrates the hypothesis that ANA-positive patients, classified into different JIA categories by the current ILAR criteria, constitute a homogeneous patient population. Following ANA titer in evolution might be a criterion for assessing the evolution of the disease.

Author contributions: All authors contributed equally to this work. All authors of this paper have read and approved the final version submitted. All the authors have accepted responsibility for the entire content of this submitted manuscript and approved submission.

Research funding: None declared.

Employment or leadership: None declared.

Honorarium: None declared.

Competing interests: The funding organization(s) played no role in the study design; in the collection, analysis, and interpretation of data; in the writing of the report; or in the decision to submit the report for publication.

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