Antibodies to Histone in the Pediatric Population: A Retrospective Chart Review

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Research article

Keywords: Histone, pediatric, systemic lupus erythematosus(SLE), juvenile idiopathic arthritis(JIA), drug induced lupus(DILE)

Posted Date: January 28th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-153986/v1

Abstract

Background:

Antibodies to histone have been associated in the adult literature with systemic lupus erythematosus(SLE) and drug induced lupus(DILE). Little data is available regarding the spectrum of pathology that antibodies to histone encompass in the pediatric population. Prior studies suggest an association with SLE, juvenile idiopathic arthritis(JIA), uveitis and linear scleroderma.

Methods:

Patient charts were reviewed that contained positive anti-histone antibody testing during a consecutive three year period. Patient diagnosis along with the presence of: anti-histone antibody titer, ANA, and the presence of other autoantibodies to SSA, SSB, Sm, RNP, dsDNA and chromatin were obtained. The frequency of SLE, JIA and DILE was further investigated in specific subsets.

Results:

139 individual charts were reviewed containing 41 different diagnoses. The most common diagnosis was hypermobility arthralgia with 22 patients. The most frequent rheumatologic diagnosis was JIA(non-systemic) with 19. 13 patients in this study were diagnosed with SLE and 2 with DILE. 18 patients had other autoantibody production, of these, 11 had SLE or DILE. Only one of 62 patients with a weak anti-histone antibody titer(1.0-1.5) was diagnosed with SLE. When strong titers are present(>2.5), the anti-histone antibody test was associated with a greater than 50% incidence of an underlying rheumatologic disease and ten times higher incidence of SLE than a weak titer. In regards to the frequency of SLE, there was a statistically significant difference in weak and moderate(1.6-2.5) titers(p-value 0.0113) and weak and strong titers(p-value 0.0053).

Conclusion:

The presence of anti-histone antibody was observed in a variety of diagnoses in the pediatric population. Overall, the presence of anti-histone antibodies appears to have poor diagnostic utility for any specific condition. However, diagnostic utility for SLE does improve with higher titers, when combined with other autoantibody positivity. Strength of titer did not appear to be a factor for JIA, but was the most frequently observed rheumatologic disease in this study.

Background:

Antibodies to histone have been described in the adult literature in patients with SLE and DILE. Little data is available currently regarding the spectrum of pathology that antibodies to histone encompass in the pediatric population. Prior studies suggest an association with JIA, uveitis, and linear scleroderma(LS) in addition to SLE. At present, anti-histone antibody testing is readily available and is frequently performed as part of the subsequent workup for ANA positivity, JIA, SLE and other rheumatologic diseases. Positive

results are not infrequent, often with unclear significance. The purpose of this study was to better understand the frequency of different rheumatologic diseases in the pediatric population with anti-histone antibodies. Thus, allowing for better practical application of the test in clinical practice.

Anti-histone antibodies were first detected in SLE in 1960 and subsequently re-demonstrated in 1971 and 1976(1). In 1978, a study showed higher incidence of anti-histone antibodies in patients with DILE versus SLE(2). It was suggested that anti-histone antibodies in SLE may have some correlation with disease activity(1). Histones are basic DNA binding proteins and are among the more common autoantibodies seen in patient with SLE. Individual histones H1, H2A, H2B, H3, H4 have been identified and studied within the context of SLE, but their clinical value is limited(3). Antibodies to histone detected by ELISA were present in 100% of 20 patients with DILE, 42% of 60 patients with SLE and 15% of 20 adults with rheumatoid arthritis(4).

Although adult data regarding SLE may be applicable to pediatrics, studies are lacking in regards to anti-histone antibodies in the pediatric population. It was shown in a pediatric and adolescent-onset SLE population that anti-histone antibodies correlated significantly with leukopenia, hemolytic anemia, and dsDNA antibody titers(5). There is also a suspected association between anti-histone antibodies and JIA. Antibody to histone H1 was found in 42% of the JIA serum samples(6). Another study suggested that anti-histone antibodies seen in pediatric patients with JIA may have different histone selectivity than in adult SLE. This study showed a predominance of anti-H1 and anti-H5 antibodies and relative absence of antibodies binding to core histones in JIA, in contrast to findings in adult SLE(7).

ANA positivity in JIA has long been associated with chronic anterior uveitis. An association with anti-histone antibodies has been proposed. One study showed that 58 (48%) of 121 patients with JIA tested positive for anti-histone antibodies. Twenty-eight of 30(93%) of patients with JIA with uveitis had anti-histone antibodies while only 30(33%) of 91 patients without uveitis had anti-histone antibodies. This same study also suggests that anti-H3 specific histone antibodies correlated with uveitis in the JIA population(8, 9). More recent studies have also shown higher titer anti-histone antibodies as a risk factor development of uveitis in JIA(10).

In one small study of mostly pediatric patients, results showed a high prevalence of anti-histone antibodies in LS. Ten of 14(71%) of pediatric patients with LS of the torso and/or extremities had antibodies to histone. Five of 11(45%) of pediatric patients in the study with frontoparietal LS were positive(11).

Methods:

All charts from the Cardinal Glennon Children’s Hospital Pediatric Rheumatology clinic from 1/1/2016 to 12/31/2019 with positive anti-histone antibody tests were reviewed. In addition to the anti-histone antibody titer, age, diagnostic codes, and the presence of ANA, anti ds-DNA, chromatin, SSA, SSB, Sm and RNP antibodies were recorded. In the case of multiple available antibody profiles, the most recent was used. Charts were manually reviewed for the treating Rheumatologist’s most recent diagnosis which was

recorded and used for statistical analysis rather than the diagnostic codes. In the case of multiple diagnoses, each relevant diagnosis was recorded and some patients had more than one diagnosis. Patients whose charts specifically noted being on medications associated with DILE, but did not have manifestations of SLE were considered as possible drug induced autoantibody formation and not DILE.

In addition to individual diagnoses, diagnoses were also grouped into the category of rheumatologic diagnoses and autoimmune diagnoses. Rheumatologic diagnoses were defined as SLE, Sjogren's syndrome, chronic recurrent multifocal osteomyelitis(CRMO), inflammatory bowel disease(IBD)/IBD arthritis, Behcet's, rheumatoid arthritis, JIA(all subtypes except systemic), systemic JIA, DILE, uveitis, psoriasis/psoriatic arthritis, undifferentiated connective tissue disease, inflammatory myopathy, LS and Henoch Schonlein Purpura. Autoimmune diagnoses were defined as autoimmune hepatitis, autoimmune thyroid disease, celiac disease and type 1 diabetes in addition to the previously mentioned rheumatologic diagnoses. This was done to allow calculation of a positive predictive value for a positive anti-histone antibody test in reference to any autoimmune or rheumatologic disease given the low incidence of specific diagnoses observed in the population.

Weakly positive anti-histone titers were defined as a level from 1.0-1.5 units. Moderate titers were defined as 1.6–2.5 units and strongly positive titers defined as greater than 2.5 units in accordance with how results are reported back to the clinician. Anti-Histone antibody tests were performed by LabCorp using an IgG class ELISA test.

Positive predictive value was calculated for SLE, JIA(non-systemic), DILE, and any rheumatologic or autoimmune diagnosis. Some specific subsets were also evaluated. This included patients with positive anti-histone antibodies in conjunction with other autoantibodies, along with patients with low titer anti-histone antibodies and negative ANA testing without other autoantibodies present.

This study was approved by the Saint Louis University Institutional Review Board, protocol #30713.

Results:

139 individual charts were reviewed. There were 41 different diagnoses present in the study group. The most common diagnosis recorded was hypermobility arthralgia which was present in 22 patients. This was followed by arthralgias(without JIA) in 21 patients. The most frequent rheumatologic diagnosis was JIA(non-systemic) with 19. The other diagnoses are enumerated in Table 1.

A total of 13 patients in this study were diagnosed with SLE and 2 with DILE. 56 patients had a rheumatologic diagnosis and 61 were considered to have had an autoimmune diagnosis including autoimmune hepatitis, autoimmune thyroid disease, type 1 diabetes, and celiac disease. Positive predictive values for SLE, DILE and JIA were all very low(Table 2).

Only 69 patients out of 139 had a + ANA in addition to a positive anti-histone antibody level. 70 patients were ANA negative. 18 patients had other autoantibody production in addition to anti-histone antibodies.

Of these patients with other autoantibody production, 14 had an autoimmune diagnosis and 11 had SLE or DILE(Table 3).

34 patients in the study had weakly positive anti-histone antibodies, negative ANA titer and no other autoantibody production. Of these 34, 10 had a rheumatologic diagnosis, 1 had a diagnosis of DILE and none had a diagnosis of SLE(Table 3).

When separated out by strength of anti- histone antibody titer, 62 patients had low positive titers. 34 patients had moderate titers and 43 had strongly positive titers(Table 4). Of those with weak positive titers, 19 out of 62 carried a rheumatologic diagnosis. 13 out of 34 patients with a moderate titer had a rheumatologic diagnosis and 24 of 43 with strongly positive titers had a rheumatologic diagnosis. The lowest titer observed in a patient with SLE was 1.3. Only one of 62 patients with a low titer histone antibody were diagnosed with SLE. This increased to 5 out of 34 and 7 out of 43 in the moderate and strong titer groups respectively. A patient with a strong titer anti-histone antibody was approximately ten times more likely to have SLE than a patient with low titer in this study population, but only about twice as likely to have an autoimmune disease. The incidence of JIA in the strong titer group was the highest, but followed closely by the weak titer groups with 8 of 43 patients and 10 of 62 patients respectively. The lowest incidence of JIA was in the moderate titer group.

Using a Chi-square test, statistical significance between weak, moderate, and strong titers of anti-histone antibodies and the frequency of autoimmune disease and SLE was evaluated. In regards to the frequency of overall autoimmune disease, there was no significant difference between weak and moderate titers (p-value 0.187) or moderate and strong titers(p-value 0.102). However, there was a statistically significant difference between weak and strong titers (p-value 0.000028).

In regards to the frequency of SLE, there was a statistically significant difference in low and moderate titers(p-value 0.0113) and between weak and strong titers(p-value 0.0053), but not between moderate and strong titers(p-value 0.850).

Discussion:

Anti-histone antibodies are seen in a variety of conditions both rheumatologic and non-rheumatologic in the pediatric population. The two most frequent diagnoses were hypermobility arthralgia and arthralgia(without JIA) suggesting that the anti-histone antibody can be present in a significant number of patients who have arthralgia, but do not have underlying JIA or SLE.

Positive predictive values calculated for SLE, JIA and DILE were low despite this population being patients strictly in a rheumatology clinic undergoing evaluation for autoimmune disease. The most common rheumatologic diagnosis encountered was JIA(all subtypes excluding systemic), which had a positive predictive value of only 0.136. Even when combining all autoimmune conditions, the percentage

of patients with a positive anti-histone antibody test and an underlying autoimmune disease was still less than half at 43.9%. The titer of anti-histone antibody does seem to be a factor for both the overall occurrence of autoimmune disease and SLE with statistically significant differences between weak and strong titers. This did not appear to be a factor for JIA. A strong titer anti- histone antibody level was associated with an approximately ten times higher frequency of SLE than a weak titer.

The anti-histone antibody test did perform differently when specifically examined in the group of patients with the presence of other autoantibodies. 78%(14/18) of patients with other autoantibody production including antibodies to SSA, SSB, Sm, RNP, Chromatin, and dsDNA did have an underlying rheumatologic diagnosis. Of these, 10 were diagnosed with SLE.

It's still not entirely clear what significance the presence of anti-histone antibodies signifies in pediatric lupus patients since the classic association with DILE was seldom observed in this population. Only 2/139 patients in this study were diagnosed with DILE. There was a considerable amount of suspicion for drug induced autoantibodies leading to positive anti-histone antibody levels. Seventeen patients in the study had positive anti-histone antibody tests without features of SLE, but were on medications associated with DILE. Data about the frequency of specific medications was not collected in this study but does provide an opportunity for further investigation.

Patients with low titer anti-histone antibodies, negative ANA, and no other autoantibody production had a low incidence of underlying autoimmunity (10/34 patients). This was less than one third, but interestingly not non-existent as might be expected suggesting some association of the anti-histone antibody with autoimmune disease in general. Five of these patients were diagnosed with JIA and one with SLE.

Conclusion:

Anti-histone antibodies were observed in a variety of diagnoses in the pediatric population, many of which are considered benign or not rheumatologic. Most frequently, anti-histone antibodies were present in patients without underlying autoimmunity, especially at weak titers. DILE was uncommon in this study with only two cases. Not surprisingly, the positive predictive value of the anti-histone antibody test for SLE did improve in the subpopulation that demonstrated other autoantibody production. Similar to the ANA test, positive results were present in significant numbers of patients without underlying autoimmunity and testing should be reserved for cases in which there is a high underlying clinical suspicion of autoimmune disease. The clinical situation in which the test is ordered will obviously influence interpretation of the results.

Even within the subset of patients with underlying autoimmunity, the presence of anti-histone antibodies were not exclusive to SLE and had presence in multiple autoimmune diseases. Most frequently this was JIA(non-systemic) and not SLE. At strongly positive titers, the anti-histone antibody test was associated with a greater than 50% incidence of an underlying rheumatologic disease and ten times higher incidence of SLE than when present at weakly positive titers. Both the overall rate of autoimmune disease and SLE

were significantly higher in patients with strongly positive versus weakly positive titers of anti-histone antibodies.

Further research is still needed to investigate if the presence of anti-histone antibodies has any association with clinical phenotype or other factors in JIA. Association with uveitis has been proposed previously, but other factors may also exist. The increasing availability and sharing of patient data within pediatric rheumatology might make this possible. JIA was the most frequent rheumatologic disease seen in this study. It's possible this trend could be secondary to the increasing use of TNF inhibitors leading to autoantibody formation or just a reflection of higher prevalence of JIA in general when compared to SLE in the pediatric population.

The results of this study show that anti-histone antibodies in the pediatric population alone are a poor predictor of any specific condition, especially at weakly positive titers. However, this does improve with titer strength. The frequency at which JIA was observed should prompt consideration for additional research among a larger cohort of JIA patients as to possible significance within the JIA population.

Abbreviations

SLE: systemic lupus erythematosus

DILE: drug induce lupus

JIA: juvenile idiopathic arthritis

LS: linear scleroderma

CRMO: chronic recurrent multifocal osteomyelitis

IBD: inflammatory bowel disease

HSP: Henoch Schonlein Purpura

Declarations

Ethics approval and consent to participate:

This study(protocol#30713) was approved 10/4/19 by the St. Louis University Institutional Review Board as Bio-Medical research – exempt.

Consent for Publication:

Not Applicable

Availability of data and materials:

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request

Competing Interests:

None

Funding:

None

Authors' Contributions:

CJ was the primary investigator and author of this study.

TM assisted with study design, editing and statistical analysis.

Acknowledgements:

Howard Williams who helped facilitate data collection from the EMR.

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Tables

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