Prevalence of Mixed Connective Tissue Disease in a Population-Based Registry of American Indian/Alaska Native People in 2007

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Title: Prevalence of mixed connective tissue disease in a population-based registry of American Indian/Alaska Native people in 2007

Running head: Mixed connective tissue disease prevalence

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ABSTRACT:

Objective: The objective of this surveillance project was to determine the prevalence of mixed connective tissue disease (MCTD) in 2007 in the Indian Health Service (IHS) active clinical population from 3 regions of the United States.

Methods: The IHS Lupus Registry was designed to identify possible MCTD cases in addition to lupus. The population denominator for this report includes American Indian or Alaska Native adults within the IHS active clinical population in 2007, residing in select communities in 3 regions of the US. Potential MCTD cases were identified using a broad range of diagnostic codes and were confirmed by detailed medical record abstraction. Classification as MCTD for this analysis required both rheumatologist diagnosis of MCTD without diagnosis of other connective tissue disease and documentation of the Alarcón-Segovia criteria in the medical record. Prevalence was also calculated using two alternate definitions of MCTD.

Results: The age-adjusted prevalence of MCTD using our primary definition was 6.4 per 100,000 (95% confidence interval (CI) 2.8-12.8). The prevalence was higher in women than men using all three definitions of MCTD, and no men met the primary definition of MCTD.

Conclusion: The first population-based estimates of the prevalence of MCTD in the US American Indian/Alaska Native population show that the prevalence appears to be higher than in other populations. Additional population-based estimates are needed to better understand the epidemiology of MCTD.

Abstract word count: 225

Significance and Innovation:

- This study provides the first description of MCTD prevalence in American Indian and Alaska Native populations.
- Data from this study suggest that the prevalence of MCTD in US American Indian/Alaska Native populations may be higher than other populations studied, though the confidence intervals are wide.
- Additional studies of MCTD epidemiology in minority populations are needed.

Mixed connective tissue disease (MCTD) was first described in 1972 as a condition encompassing a set of overlapping features of connective tissue disease in patients with antibodies to ribonucleoprotein (RNP).[1] Since the initial description, there has been some debate as to whether this represents a distinct clinical entity, versus an early presentation that evolves over time into a specific connective tissue disease.[2,3] However, several studies have found that evolution of MCTD into other connective tissue diseases occurs infrequently.[4,5] Four sets of classification criteria have been developed for MCTD, most of which include a requirement for positive serology (anti-RNP) and at least three clinical features.[6] The Alarcón-Segovia criteria require positive serology and at least three of the following clinical features (of which one must be either synovitis or myositis): edema of hands, synovitis, myositis, Raynaud's phenomenon, and acrosclerosis.[7]

Few studies have investigated the prevalence or incidence of MCTD in populations. In Norway,[8] a nationwide study found the point prevalence of living adult MCTD in 2008 to be 3.8 per 100,000 (95% CI 3.2-4.4), with a female predominance. In this study, the incidence of adult-onset MCTD from 1996 to 2005 was 2.1 per million per year. A recent study in the United States described an annual incidence of MCTD of 1.9 per 100,000 from 1985-2014.[5] The incidence of MCTD in Finland was found to be 8.4 per million in 1990.[9] Other studies have followed cohorts of patients with MCTD and described the clinical features but have not focused on the epidemiology of the disease in adults.[4,10,11]

Disparities in the epidemiology of autoimmune diseases across populations can lead to insight into the pathogenesis of disease. We recently reported a high prevalence and incidence of SLE in a population-based registry of American Indian/Alaska Native (AI/AN) people receiving care through Indian Health Service (IHS) or tribal health facilities.[12] Because of the clinical impression of rheumatologists in the IHS that MCTD might be more common in this population than in others, as well as previous data suggesting that "overlap syndromes" may be common in indigenous North American populations,[13] we designed the registry from the outset to capture suspected cases of MCTD in addition to SLE. If MCTD were more common in the AI/AN population than SLE, this might lead to improved understanding of its etiology as well as guide the rheumatologic care for this population. The objective of this project was to determine the prevalence of MCTD in 2007 in the IHS Lupus Registry.

PATIENTS AND METHODS:

The IHS Lupus Registry was created in 2011 with the primary objective to retrospectively determine the prevalence of SLE in 2007 and incidence of SLE from 2007-2009 in the AI/AN population. The registry was also designed to determine the prevalence of MCTD in 2007 by capturing MCTD classification elements. The population denominator includes adults age 18 and older living within the IHS Lupus Registry target areas in 2007, including select communities as previously described[12] in the Alaska, Phoenix, and Oklahoma City IHS Areas. Communities selected for inclusion in the registry were those where access to rheumatology specialist

consultation was available within the IHS system (direct care) at the time of development of the registry.

Potential cases of SLE or MCTD were ascertained from the IHS National Data Warehouse using the following International Classification of Diseases, 9th Revision (ICD-9) codes: 710.0, 710.8, 710.9, 695.4, 710.1, and 710.4. We included these codes for SLE, undifferentiated connective tissue disease, discoid lupus, systemic sclerosis, and polymyositis to capture a broader range of patients who may ultimately be diagnosed with SLE or MCTD. MCTD does not have its own ICD-9 code, but is typically coded as 710.8 (other specified diffuse diseases of connective tissue). For each potential case, field medical record abstraction was performed at each clinic or hospital in the 3 regions as described previously.[12] Specifically, medical records from each facility were reviewed from the earliest available archived paper record through the end of 2009. In addition to abstracting data elements relevant to both SLE and MCTD (including anti-RNP, synovitis, myositis, and Raynaud's phenomenon, all of which are included in the Alarcón-Segovia MCTD classification criteria), we abstracted the remaining Alarcón-Segovia clinical criteria for MCTD (edema of the hands and acrosclerosis or sclerodactyly).[7] Due to the limitations of medical record review with multiple laboratories used for anti-RNP testing, we did not require high-titer anti-RNP, differing from the Alarcon-Segovia requirement of hemagluttinin titer >=1:1600. We did exclude anti-RNP if it was marked as "equivocal/borderline" by the local laboratory. The treating physician's final diagnosis and the specialty of the physician making the diagnosis were also recorded.

Our primary case definition was the treating rheumatologist's diagnosis of MCTD without other rheumatologist-diagnosed connective tissue disease and with documentation in the medical record that the Alarcón-Segovia criteria were met. This was selected in order to best compare our results to the Norwegian population-based study of MCTD, as described above.[8] The rationale for using the Alarcón-Segovia criteria rather than other MCTD criteria was that the data elements required were more readily captured by our methods (abstraction of existing medical records, with focus on SLE-related data elements) than the other 3 sets of criteria.[6] Two secondary case definitions were used: 1) meeting the Alarcón-Segovia criteria for MCTD (criteria definition); and 2) the treating rheumatologist's diagnosis of MCTD without other rheumatologist-diagnosed connective tissue disease (rheumatologist-diagnosed definition). The first alternate definition (criteria definition) was selected for its similarity to the methods used in our analysis of the prevalence of SLE in the IHS Lupus Registry. The second alternate definition was selected to represent the burden of MCTD in a real world clinical care setting. There were no specific exclusions based on classification criteria for other diseases.

Prevalence of MCTD was calculated using the number of cases meeting the primary or alternate definitions with a date of diagnosis of 2007 or earlier divided by the number of adults in the 2007 denominator, expressed as a rate per 100,000. All individuals in the numerator and denominator were alive as of January 1, 2007. Prevalence was calculated overall, by sex, and by age. Age-adjusted rates were calculated overall

using the 2000 projected US population.[14] Male and female rates were not age-adjusted due to the small number of cases. 95% confidence intervals (CIs) were calculated around each proportion. Statistical analyses were performed using SAS version 9.3 (SAS Institute, Cary NC), and STATA (STATA/IC version 11.2 for Windows, StataCorp LP, College Station, TX).

The project was reviewed by the Institutional Review Boards (IRBs) of the participating regions and determined to be a public health activity (not research). Tribal approval was obtained from participating tribal health organizations.

RESULTS:

The prevalence of MCTD in AI/AN adults in our registry is shown in Table 1. Because of the small number of cases in men, the total number of cases is presented overall but not by gender. By the primary definition, the age-adjusted prevalence was 6.4 per 100,000 (95% CI: 2.8-12.8). The unadjusted prevalence in women was 10.7 per 100,000, with no cases found in men using the primary definition. By the criteria definition, the age-adjusted prevalence was higher at 26.3 per 100,000 (95% CI: 17.4-38.0). Using the rheumatologist-diagnosed definition, the age-adjusted prevalence was intermediate at 19.4 per 100,000 (95% CI: 12.2-29.3), not statistically significantly different from the criteria definition. Using the rheumatologist-diagnosed definition, the female to male ratio was the highest at 16:1. Using the primary definition and restricting to those with adult-onset MCTD (similar to the analysis from Norway[8]) gives a

prevalence of 5.5 per 100,000 (95% CI: 2.7-11.3) and age-adjusted prevalence of 5.7 (95% CI: 2.3-11.9) (data not shown).

Point estimates of age-specific prevalence by case definition are shown in Figure 1. Although our small numbers preclude statements of statistical significance, the primary definition had lower rates than the alternate definitions in all age groups, with the highest rates in ages 45-64 and no cases age 65 or over. The small number of cases precludes accurate description of the most common age at onset of MCTD, though the majority of cases (80-95%) had onset between the ages of 21-60. For cases meeting our primary case definition of MCTD in 2007, the median year of onset was 1999.

Table 2 shows the frequency of individual Alarcón-Segovia criteria documented in the medical record among prevalent cases by each definition of MCTD. Of note, 100% of patients meeting the primary or criteria definition had the presence of anti-RNP antibodies documented in the medical record, while only 60.9% of those meeting the rheumatologist-diagnosed definition had evidence of positive anti-RNP in the medical record. Of 9 individuals without a documented positive anti-RNP, 4 had a negative result in the medical record at some time, while 5 had missing data. Those meeting the rheumatologist-diagnosis definition had a lower prevalence of all clinical criteria as well. The most common clinical criteria met for all definitions were Raynaud's phenomenon and synovitis, while the least common criteria met for all definitions were myositis and acrosclerosis. Of the 22 cases meeting the criteria definition but not diagnosed with MCTD by a rheumatologist, 10 of those never had a documented consultation with a

rheumatologist, 7 were diagnosed with both MCTD and SLE by a rheumatologist, and the remaining 5 had diagnoses of other connective tissue disorders.

DISCUSSION:

In the IHS Lupus Registry, the age-adjusted prevalence of MCTD by our primary definition was 6.4 per 100,000 adults. The range from lowest to highest prevalence was from 6.4 (primary definition) to 26.3 per 100,000 (criteria definition). By all definitions, MCTD was more common in women, with the lowest female:male ratio of 6:1.

There is limited information about the prevalence of MCTD in populations. A recent study in the US described the incidence of MCTD.[5] Our project is the second to report on incidence or prevalence in any US population and the first to report on the AI/AN population specifically. The prevalence of MCTD by our primary case definition was higher than that found in previous studies and we suspect that given our higher point estimate, the prevalence of MCTD is truly higher in the AI/AN population than in Norway. However, given the small number of cases and wide confidence intervals in this study, we cannot determine whether this difference is due to chance. The age-adjusted prevalence using our primary definition was 6.4 per 100,000 (95% CI: 2.8-12.8), while the prevalence in Norway was 3.8 per 100,000 (95% CI: 3.2-4.4).[8] Although the prevalence of MCTD may be higher in the AI/AN population than in other US populations, no other US data on prevalence are available for comparison. A recent publication reported the incidence of MCTD in Olmsted County, Minnesota to be 1.9 per

100,000,[5] higher than studies of incidence in other countries. Based on this information, it is possible that the prevalence of MCTD in AI/AN populations is no higher than other US populations. It is important to note that although MCTD appears to be more common in AI/AN populations, as in other populations studied it remains less common than SLE. In our registry, we found the age-adjusted prevalence of SLE in 2007 to be 178 per 100,000,[12] approximately 7 times more prevalent than MCTD.

Our second alternate definition was a rheumatologist's diagnosis of MCTD without any other rheumatologist-diagnosed connective tissue disease. Unlike the other definitions, not all individuals in this category had documented anti-RNP positivity. In addition, a smaller proportion met each of the individual clinical criteria. It is possible that this definition overestimates the prevalence of MCTD and that some of these individuals would be better categorized as having undifferentiated connective tissue disease. For this reason we did not consider rheumatologist-diagnosed MCTD as our primary definition, but we included this definition because we felt that this may be a better representation of real world burden of diagnosed disease.

This project has some limitations in addition to those related to rheumatologist-diagnosed MCTD. First, data collection was limited to the existing medical record. Some criteria for MCTD might have been met but not documented in the medical record, and we were not able to examine, interview, or collect serum from patients to validate the criteria. For example, in cases identified by rheumatologists as MCTD for which we were unable to locate a positive anti-RNP result in the medical record, it is

possible that anti-RNP was positive at one point in time but was not available in the medical record, either because of long duration of disease or related to accessing care in different locations over time. The median duration of follow-up for prevalent cases was 10 years. Second, MCTD does not have a specified ICD-9 code. We drew from a set of codes likely to include all codes used for MCTD, but it is possible that we missed some cases that were coded differently. For possible cases, detailed medical record abstraction was performed, reducing the risk of misclassification found in studies using administrative data only. Third, we did not specifically exclude individuals who met classification criteria for SLE or other connective tissue diseases. It is possible that we are overestimating the prevalence of MCTD by including patients with SLE or other connective tissue diseases. However, due to the nature of connective tissue diseases and the limitations of classification criteria in clinical practice, and given that we excluded those with rheumatologist-diagnosed connective tissue diseases, we believe that our estimates are reasonable. Fourth, for the cases diagnosed more recently, we were not able to follow them longitudinally to know if their diagnoses might evolve over time. Fifth, the small number of cases limited the precision of our estimates. This affected our ability to make comparisons to existing studies, precluded us from calculating incidence, and did not allow us to determine whether the lower prevalence by our primary definition in those 65 and older was due to chance or an effect of MCTD on longevity. This limitation is inherent in studies of small populations, especially AI/AN populations. Finally, although we used multiple definitions of MCTD, we only included one of the four criteria sets for MCTD in this study. The strengths of this project include the opportunity to assess the prevalence of MCTD in a population-based registry in the

US and the ability to use several different case definitions to determine the range in prevalence and burden of disease.

In summary, we found the prevalence of MCTD in the IHS Lupus Registry to be higher than described in the few previous studies of MCTD prevalence. MCTD was more common in women, and was at least 7 times less common than SLE in this population. This study significantly adds to the limited literature on MCTD epidemiology. Epidemiologic studies of MCTD in other populations are warranted, and ideally would be able to add surveillance for differential outcomes to advance our knowledge of possible health disparities in MCTD prognosis in minority populations. Finally, the high prevalence of SLE and MCTD in AI/AN populations suggests that studies investigating genetic and environmental factors in these populations could lead to insights into the pathogenesis of autoimmune diseases.

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Table 1: Unadjusted and age-adjusted prevalence of MCTD in AI/AN adults in 2007 overall and by gender, by three case definitions

	Overall			Female	Male	Female: Male Ratio
Case Definition	# of cases	Unadjusted (95% CI)	Age-adjusted (95% CI)	Unadjusted (95% CI)	Unadjusted (95% CI)	
Primary: Rheumatologist diagnosis of MCTD AND Alarcón-Segovia criteria documented	8	6.2 (3.2-12.3)	6.4 (2.8-12.8)	10.7 (5.4-21.2)	0.0 (0.0-7.2)	Undefined (male = 0)
Criteria: Alarcón-Segovia criteria for MCTD documented in the medical record	30	23.4 (16.4-33.4)	26.3 (17.4-38.0)	36.1 (24.8-52.6)	5.6 (1.9-16.5)	6.4
Rheumatologist-diagnosed: Rheumatologist diagnosis of MCTD alone	23	17.9 (12.0-26.9)	19.4 (12.2-29.3)	29.4 (19.4-44.6)	1.9 (0.3-10.6)	15.7

Table 2:

Individual criteria met

Frequency of meeting individual Alarcón-Segovia criteria in the medical record (1 serologic and 5 clinical), by three case definitions of MCTD.*

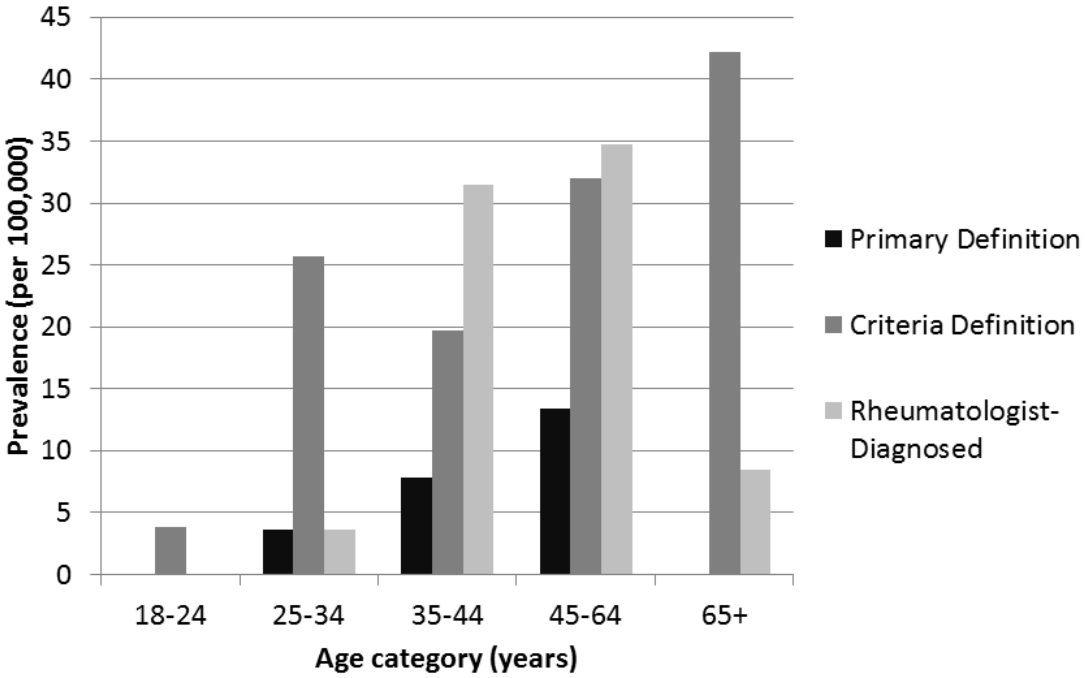
Alarcón-Segovia criterion	**Primary Definition:** Rheumatologist Diagnosis MCTD and Alarcón-Segovia criteria documented n=8	**Criteria Definition:** Alarcón-Segovia criteria documented n=30	**Rheumatologist-Diagnosed Definition:** Rheumatologist Diagnosis MCTD alone n=23
	%	%	%
Serologic: positive anti-RNP antibody	100.0	100.0	60.9
Clinical: 1. Edema of the hands	62.5	70.0	26.1
2. Synovitis	100.0	93.3	69.6
3. Myositis	25.0	26.7	17.4
4. Raynaud's phenomenon	100.0	100.0	69.6
5. Acrosclerosis	25.0	33.3	17.4
All criteria fulfilled	100.0	100.0	34.8

* No statistical comparisons between case definitions are provided because some patients are included in more than one group.

Figure 1 legend:

Age specific rates (prevalence) per 100,000 population. Prevalence per 100,000 adult population in 2007 by age group for the primary definition, first alternate (criteria) definition, and second alternate (rheumatologist-diagnosed) definition.

Figure 1:


45
40
35
30
25
20
15
10
5
0
Prevalence (per 100,000)
18-24
25-34
35-44
45-64
65+
Age category (years)
Primary Definition
Criteria Definition
Rheumatologist-Diagnosed