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

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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 as well as cases of 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. The primary case definition was documentation in the medical record of meeting the Alarcón-Segovia criteria for MCTD. Prevalence was calculated using two alternate definitions.

Results: The age-adjusted prevalence of MCTD using our primary definition was 26.3 per 100,000 (95% confidence interval (CI) 17.4–38.0). The prevalence was higher in women than men using all 3 definitions, with the lowest female:male ratio of 6:1.

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.

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 truly represents a distinct clinical entity, as opposed to an early

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presentation that evolves over time into a more clear-cut connective tissue disease.[2,3] Although few long-term studies have been conducted, one study found that most patients continued to demonstrate features of MCTD without evolution into other diseases such as systemic lupus erythematosus or systemic sclerosis.[4] 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.[5] The Alarcón-Segovia criteria require positive serology (anti-RNP) 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.[6]

Few studies have investigated the prevalence or incidence of MCTD in populations. The most comprehensive study was in Norway,[7] where 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. The incidence of adult-onset MCTD from 1996 to 2005 was 2.1 per million per year. The prevalence was lower than the reported prevalence of other connective tissue diseases, including polymyositis, dermatomyositis, systemic sclerosis and systemic lupus erythematosus (SLE). This study required a strict definition of MCTD (including: 1) diagnosis of MCTD by a rheumatologist; 2) positive serum anti-RNP test; 3) fulfillment of at least one of three criteria sets for MCTD (modified Sharp's, Alarcón-Segovia, and/or Kasukawa); and 4) exclusion of other connective tissue disease) and did not include those who were diagnosed by a rheumatologist as having MCTD but did not meet one of the three sets of classification criteria for MCTD.[7] The incidence of MCTD was studied in Finland for the year 1990 and found to be 8.4 per million, higher than systemic sclerosis or polymyositis/dermatomyositis.[8] This study used less stringent criteria for case definition than the study in Norway. Finally, the incidence of MCTD in children has been investigated in both Finland[9] and Japan.[10] Other studies have followed cohorts of patients with MCTD and described the clinical features but have not focused on the epidemiology of the disease.[4,11,12]

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.[13] Because of the clinical impression of rheumatologists in the IHS and associated tribal health systems that MCTD might be more common in this population than in others, as well as previous data suggesting that "overlap syndromes" may be as common as SLE in indigenous North American populations,[14] we designed the registry from the outset to capture suspected cases of MCTD in addition to SLE. The objective of this surveillance project was to determine the prevalence of MCTD in 2007 in the IHS active clinical population from 3 regions of the United States.

PATIENTS AND METHODS:

The IHS Lupus Registry was primarily designed to determine the prevalence and incidence of SLE 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 for this report includes adults age 18 and older within the IHS Lupus Registry target areas

in 2007, including select communities as previously described[13] in the Alaska, Phoenix, and Oklahoma City IHS Areas.

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 or meet criteria for 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) in most practice settings. For each potential case of SLE or MCTD, field medical record abstraction was performed at each clinic or hospital in the 3 regions as described previously.[13] 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).[6] The treating physician's final diagnosis and the specialty of the physician making the diagnosis were also recorded.

Our primary case definition was meeting the Alarcón-Segovia criteria for MCTD[6] with documentation in the medical record. The rationale for using the Alarcón-Segovia 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.[5] Two secondary case definitions were used: 1) the treating rheumatologist's diagnosis of MCTD without other connective tissue disease diagnosis (first alternate definition); and 2) the treating rheumatologist's diagnosis of MCTD without other connective tissue disease diagnosis and with documentation in the medical record that the Alarcón-Segovia criteria were met (strict alternate definition). This strict alternate definition is the most similar to the definition used in the Norwegian population-based study of MCTD, as described above.[7]

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 population. Prevalence was calculated overall, by sex, and by age (using the following age groups: 18–24, 24–44, 45–64, and 65 and older). Age-adjusted rates were calculated overall using the 2000 projected US population.[15] 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) by the Alaska Area IRB, Phoenix Area IRB, and Oklahoma City Area IRB. Tribal approval was obtained from participating tribal health organizations.

RESULTS:

The prevalence of MCTD in AI/AN adults residing in the regions included in our registry and receiving care through IHS or tribal health systems is shown in Table 1. The total population denominator was 128,123, with 30 cases identified by the primary definition. Because of the small number of cases in men, the total number of cases in Table 1 is presented overall but not by gender. By the primary definition (documentation of Alarcón-Segovia criteria in the medical record), the age-adjusted prevalence was 26.3 per 100,000 (95% CI: 17.4–38.0). The unadjusted prevalence in women was 6.4 times higher than in men (36.1 vs. 5.6 per 100,000). By the first alternate definition (rheumatologist diagnosis of MCTD without other connective tissue disease diagnosis), the age-adjusted prevalence was slightly lower overall at 19.4 per 100,000 (95% CI: 12.2–29.3), not statistically significantly different from the primary definition. Using the first alternate definition, the female to male ratio increased to 16. Finally, using the strict alternate definition (requiring both rheumatologist diagnosis of MCTD without other connective tissue disease diagnosis as well as documentation of the Alarcon-Segovia criteria in the medical record), the age-adjusted prevalence was lower at 6.4 per 100,000 (95% CI: 2.8–12.8). There were no cases of MCTD in men that met this strict definition. Using the strict alternate definition and restricting to those with adult-onset MCTD (similar to the analysis from Norway described above[7]) 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).

To provide some sense of possible differences in age-specific prevalence rates by definition, we show the point estimates (Figure 1) although our small numbers preclude statements of statistical significance. For the primary definition, the highest prevalence was in individuals age 65 and over, but the prevalence was similar for all age groups 25 and over. For the first alternate definition, the highest rates were found in ages 35–64. The strict alternate definition had lower rates than the primary definition in all age groups, similar rates to the first alternate definition in ages 18–34, and the highest rates in ages 45–64. The small number of cases precludes accurate description of the most common age at onset of MCTD, though the majority of cases (80–95%) by all definitions had onset between the ages of 21–60.

Table 2 shows the frequency of individual Alarcón-Segovia criteria met and documented in the medical record among prevalent cases by each of the three definitions of MCTD. Of note, 100% of patients meeting the primary or strict alternate definition had the presence of anti-RNP antibodies documented in the medical record, while only 60.9% of those diagnosed by a rheumatologist but not meeting criteria had evidence of positive anti-RNP in the medical record. The most common clinical criteria met for all definitiions were Raynaud’s phenomenon and synovitis, while the least common criteria met for all definitions were myositis and acrosclerosis.

DISCUSSION:

In this surveillance project of the IHS active clinical population from 3 regions of the United States in 2007, we found the age-adjusted prevalence of MCTD by our primary definition

was 26.3 per 100,000 adults. The range from lowest to highest prevalence based on alternate definitions was from 6.4 (strict alternate definition) to 26.3 per 100,000 (primary definition). Our first alternate definition gave an intermediate prevalence of 19.4 per 100,000. 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, and our project is the first to report prevalence in any US population. Our primary definition was based on having documentation of meeting the Alarcón-Segovia criteria in the medical record. We elected to use this as our primary definition as it utilized methodology most similar to what we used in our previous report from the IHS Lupus Registry,[13] using the presence of classification criteria in the medical record as our primary case definition. In this report, we used two alternate definitions. The first alternate definition was a rheumatologist's diagnosis of MCTD without any other connective tissue disease. Although fewer criteria for MCTD were documented in the medical record in cases meeting this definition, we felt that it may be a better representation of real world burden of disease. The strict alternate case definition was more stringent and more closely aligned with the previous prevalence study in Norway. We found the lowest rates using this case definition.

The prevalence of MCTD found by our primary case definition was significantly higher than that found in previous studies. Furthermore, given the small number of cases and wide confidence intervals in this study, we cannot determine whether the prevalence of MCTD in the AI/AN population included in this registry is truly higher than that found in Norway. The age-adjusted prevalence using our strict 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).[7] Although the prevalence of MCTD may be higher in the AI/AN population than in other US populations, as clinicians had suspected, MCTD was not more common than SLE. We found the age-adjusted prevalence of SLE in 2007 to be 178 per 100,000 total population,[13] approximately 7 times more prevalent than MCTD.

This surveillance project has some limitations. 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. It is possible that having a clinical assessment, as was done in Norway, might have identified more patients with MCTD. 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. Finally, the small number of cases limited the precision of our estimates, making comparison with the few available studies difficult. 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 active clinical population in 3 regions of the US by our primary definition 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

using similar methodology are warranted, and ideally would be able to add surveillance for differential outcomes to advance our knowledge of possible health disparities in AI/AN and other minority populations.

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Disclaimer:

The findings and conclusions in this report are those of the authors and do not necessarily reflect the official position of the US Centers for Disease Control and Prevention or the Indian Health Service.

REFERENCES:

1. Sharp GC, Irvin WS, Tan EM, Gould RG, Holman HR. Mixed connective tissue disease--an apparently distinct rheumatic disease syndrome associated with a specific antibody to an extractable nuclear antigen (ENA). The American journal of medicine 1972;52:148–59. [PubMed: 4621694]
2. Cappelli S, Bellando Randone S, Martinovic D, et al. "To be or not to be," ten years after: evidence for mixed connective tissue disease as a distinct entity. Semin Arthritis Rheum 2012;41:589–98. [PubMed: 21959290]
3. Aringer M, Steiner G, Smolen JS. Does mixed connective tissue disease exist? Yes. Rheumatic diseases clinics of North America 2005;31:411–20, v. [PubMed: 16084315]
4. Burdt MA, Hoffman RW, Deutscher SL, Wang GS, Johnson JC, Sharp GC. Long-term outcome in mixed connective tissue disease: longitudinal clinical and serologic findings. Arthritis Rheum 1999;42:899–909. [PubMed: 10323445]
5. Ortega-Hernandez OD, Shoenfeld Y. Mixed connective tissue disease: an overview of clinical manifestations, diagnosis and treatment. Best Pract Res Clin Rheumatol 2012;26:61–72. [PubMed: 22424193]
6. Alarcon-Segovia D, Villareal M. Classification and diagnostic criteria for mixed connective tissue disease. In: Kasukawa R, Sharp GC, eds. Mixed connective tissue disease and anti-nuclear antibodies. Amsterdam: Elsevier; 1987:33–40.
7. Gunnarsson R, Molberg O, Gilboe IM, Gran JT, Group PS. The prevalence and incidence of mixed connective tissue disease: a national multicentre survey of Norwegian patients. Ann Rheum Dis 2011;70:1047–51. [PubMed: 21398332]
8. Kaipiainen-Seppanen O, Aho K. Incidence of rare systemic rheumatic and connective tissue diseases in Finland. J Intern Med 1996;240:81–4. [PubMed: 8810933]
9. Pelkonen PM, Jalanko HJ, Lantto RK, et al. Incidence of systemic connective tissue diseases in children: a nationwide prospective study in Finland. J Rheumatol 1994;21:2143–6. [PubMed: 7869325]
10. Fujikawa S, Okuni M. A nationwide surveillance study of rheumatic diseases among Japanese children. Acta paediatrica Japonica; Overseas edition 1997;39:242–4. [PubMed: 9141265]
11. Maldonado ME, Perez M, Pignac-Kobinger J, et al. Clinical and immunologic manifestations of mixed connective tissue disease in a Miami population compared to a Midwestern US Caucasian population. J Rheumatol 2008;35:429–37. [PubMed: 18260175]
12. Tani C, Carli L, Vagnani S, et al. The diagnosis and classification of mixed connective tissue disease. Journal of autoimmunity 2014;48–49:46–9.

13. Ferucci ED, Johnston JM, Gaddy JR, et al. Prevalence and incidence of systemic lupus erythematosus in a population-based registry of American Indian and Alaska Native people, 2007–2009. Arthritis Rheumatol 2014;66:2494–502. [PubMed: 24891315]

14. Atkins C, Reuffel L, Roddy J, Platts M, Robinson H, Ward R. Rheumatic disease in the Nuu-Chah-Nulth native Indians of the Pacific Northwest. J Rheumatol 1988;15:684–90. [PubMed: 3260954]

15. Klein RJ, Schoenborn CA. Age adjustment using the 2000 projected U.S. population. Healthy People 2000 Stat Notes 2001:1–9.

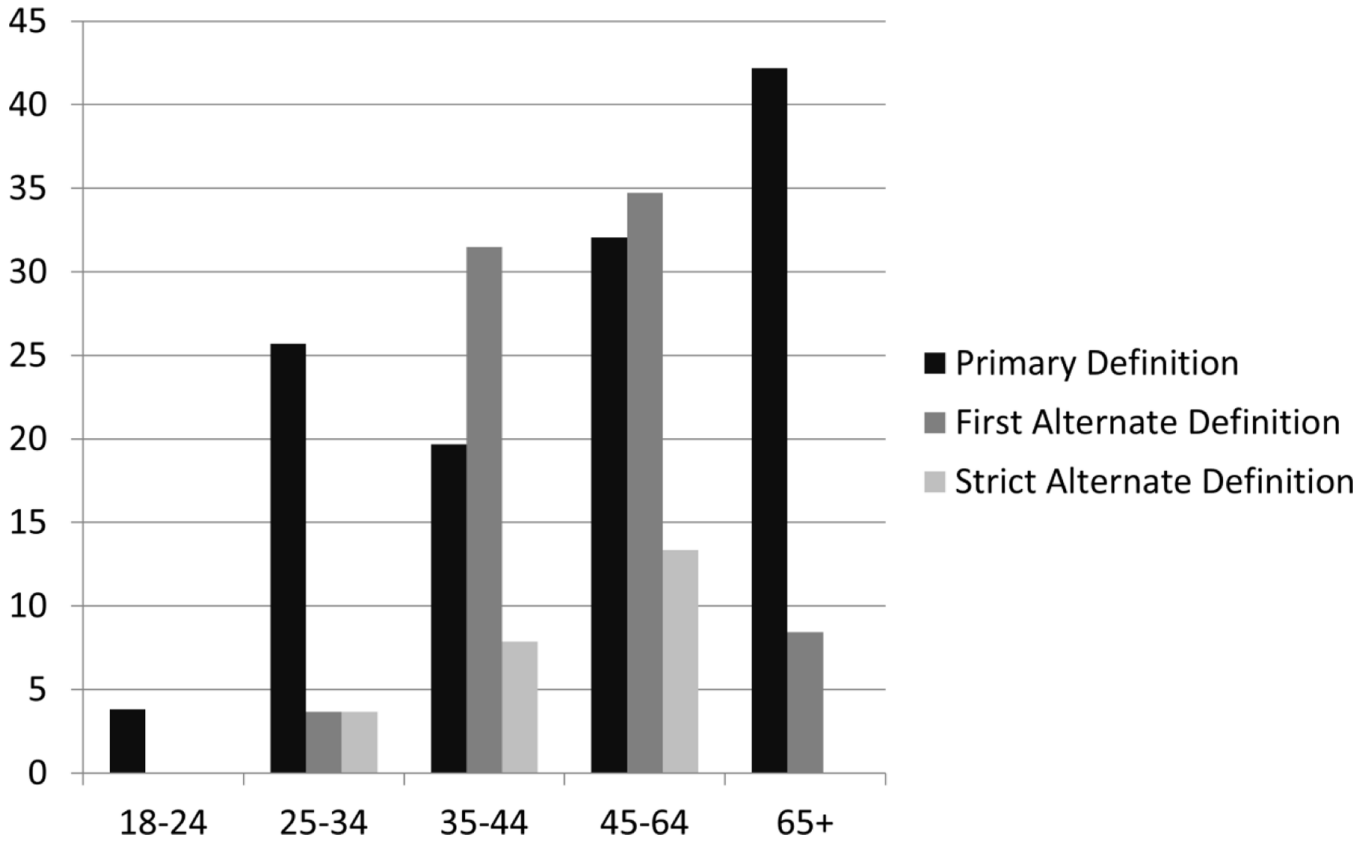

Figure 1. Age specific rates (prevalence) per 100,000 population.

Prevalence per 100,000 adult population in 2007 by age group for the primary definition (Alarcon-Segovia criteria documented in medical record), first alternate definition (rheumatologist diagnosis of MCTD without any other connective tissue disease), and strict alternate definition (rheumatologist diagnosis of MCTD without other connective tissue disease and Alarcon-Segovia criteria documented in medical record).

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: 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
First Alternate: Rheumatologist diagnosis of MCTD	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
Strict Alternate: 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)

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

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