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Running Head: Prevalence and Incidence of Mixed Connective Tissue Disease

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Abstract

Objective:

Epidemiologic data for mixed connective tissue disease (MCTD) are limited. Leveraging data from the Manhattan Lupus Surveillance Program (MLSP), a racially/ethnically diverse population-based registry of cases with SLE and related diseases including MCTD, we provide estimates of the prevalence and incidence of MCTD.

Methods:

MLSP cases were identified from rheumatologists, hospitals, and population databases using a variety of ICD-9 codes. MCTD was defined as one of the following: 1) fulfillment of our modified Alarcon-Segovia and Kahn criteria which required a positive RNP antibody and the presence of synovitis, myositis, and Raynaud's phenomenon, 2) a diagnosis of MCTD and no other diagnosis of another connective tissue disease (CTD), and 3) a diagnosis of MCTD regardless of another CTD diagnosis.

Results:

Overall, 258 (7.7%) of cases met a definition of MCTD. Using our modified Alarcon-Segovia and Kahn criteria for MCTD, the age-adjusted prevalence was 1.28 (95%CI 0.72-2.09) per 100,000. Using our definition of a diagnosis of MCTD and no other diagnosis of another CTD yielded an age-adjusted prevalence and incidence of MCTD of 2.98 (95%CI 2.10-4.11) per 100,000 and 0.39 (95%CI 0.22-0.64) per 100,000, respectively. The age-adjusted prevalence and incidence were highest using a

diagnosis of MCTD regardless of other CTD diagnoses and were 16.22 (95%CI 14.00-18.43) per 100,000 and 1.90 (95%CI 1.49-2.39) per 100,000 respectively.

Conclusions:

The MLSP provided estimates for prevalence and incidence of MCTD in a diverse population. The variation in estimates using different case definitions is reflective of the challenge of defining MCTD in epidemiologic studies.

Keywords: Mixed Connective Tissue Disease, Epidemiology, Prevalence, Incidence

Key messages

1) There are limited data on the epidemiology of mixed connective tissue disease (MCTD).
2) Using a multiracial/ethnic population database we report the epidemiology of MCTD using several definitions.
3) Our data shows a diagnosis MCTD is commonly found with other CTD diagnoses.

Introduction

Mixed connective tissue disease (MCTD) is an autoimmune disorder characterized by features of multiple connective tissue diseases including systemic lupus erythematosus (SLE), systemic sclerosis (SSc), polymyositis (PM), and rheumatoid arthritis (RA) and is accompanied by a high titer of anti-U1 ribonucleoprotein (RNP) antibodies. MCTD was first described as a distinct entity in 1972 by Sharp [1]. There are limited published data on the epidemiology of MCTD, likely due to the overlapping of clinical features and pathology with other diseases, misuse of the diagnosis in cases where there is overlapping connective tissue disease (CTD), the evolution of MCTD into another well-defined disease and/or simply the presence of anti-RNP antibodies [2-6]. MCTD is a distinct clinical entity as supported by genetic studies and data indicating that anti-RNP may have a central pathogenic role [3]. The characteristic clinical features of MCTD include Raynaud's phenomenon, hand edema, puffy fingers, inflammatory muscle disease, and sclerodactyly [1,4,5]. Additionally, patients with MCTD tend to have arthritis and develop pulmonary hypertension while significant renal and central nervous system involvement is less common [4,5].

To date, only four studies have been conducted to describe the epidemiology of MCTD and none have described the disease in a racially and ethnically diverse population [7-10]. A recent European effort evaluating MCTD listed epidemiological data as an unmet need [11]. Leveraging data from the Manhattan Lupus Surveillance Program (MLSP), a population-based registry comprised of cases of SLE and related connective tissue diseases [12], we provide estimates for the prevalence and incidence of MCTD.

Materials and Methods

Manhattan Lupus Surveillance Program

The MLSP is a Centers for Disease Control and Prevention (CDC) funded population-based registry used to determine the incidence and prevalence of SLE, the methodology of which has previously been reported [12]. Through the MLSP, medical records were reviewed under the health surveillance exemption to HIPAA privacy rules (45 CFR § 164.512(b)) and as authorized by New York City Charter Sections 556(c)(2) and (d)(2) with no potential cases being contacted for this project. The MLSP was deemed surveillance and thus did not require institutional review board (IRB) review at the CDC, the New York City Department of Health and Mental Hygiene (DOHMH), and the New York University School of Medicine. The DOHMH IRB reviewed and approved secondary analyses on a de-identified dataset including the analyses presented here.

The surveillance period for the MLSP was 1 January 2007 through 31 December 2009 with Manhattan being chosen as the catchment area because of its racial/ethnic diversity and because it is an island on which inhabitants largely remain for their health care, making access to more complete medical records easier [12]. Based on 2010 US Census data, the population of Manhattan was more diverse than the US overall, with 48% non-Latino White, 25% Latino, 13% non-Latino Black, and 11% non-Latino Asian residents [13].

Case ascertainment, data collection, and quality control of data entry

Potential cases for the MLSP were identified through rheumatologists, hospitals, and administrative hospitalization discharge and death registry databases [12]. These sources were queried retrospectively as far back as 2004 for evidence of residence in

Manhattan and Classification of Disease Ninth Revision Clinical Modification (ICD-9CM) billing codes specific for SLE and related conditions that may evolve into SLE or have related symptoms including the ICD-9 code which is often used for MCTD (710.8) in addition to 710.0 (SLE), 695.4 (discoid lupus), 710.9 (unspecified connective tissue disease), and 710.2 (Sicca syndrome which is used for Sjogren's syndrome). Charts for patients who lived in Manhattan and had one of the respective ICD-9CM codes were fully abstracted for manifestations of lupus and the rheumatologic diagnosis. Data from this registry have provided incidence and prevalence estimates for SLE [12], primary Sjogren's Syndrome [14], and primary discoid lupus [15]. Multiple manifestations found in MCTD criteria were systematically collected as part of MLSP, including synovitis, myositis, and Raynaud's phenomenon, while acrosclerosis and "puffy fingers" were not. Abstraction was completed in 90.5% of hospitals and 75.8% of rheumatologists' practices by trained abstractors, all of whom had medical degrees and underwent extensive training and routine quality assurance as previously described [12].

Case definitions

For MCTD, the Alarcon-Segovia [16] and Kahn [17] criteria have the highest specificity and are the most widely used [18]. In addition, patients who meet criteria for MCTD sometimes meet classification criteria for other connective tissue diseases including SLE [6]. While taking this into consideration and acknowledging that acrosclerosis and "puffy fingers" aremanifestations found in MCTD criteria but were not collected in the MLSP, we derived three case definitions to estimate the burden of MCTD in the population. Our most restrictive case definition required the following: fulfillment of a modified Alarcon-Segovia [16] and Kahn [17] criteria for MCTD which

required a positive RNP antibody of any titer that was not considered equivocal or borderline, and having all three criteria: synovitis, myositis, and Raynaud's phenomenon. Our second definition required a rheumatologist or other physician stating the diagnosis of MCTD and no other connective tissue disease diagnosis such as SLE or SS. Our third definition required a diagnosis of MCTD as stated by any physician regardless of any other CTD diagnosis.

Statistical Analysis

Cases were limited to adults aged 18 and older. Prevalent cases were new or existing cases of MCTD fulfilling the definitions outlined above and residing in Manhattan January 1–December 31, 2007. Incident cases were those fulfilling the same criteria residing in Manhattan, and first diagnosed with MCTD during January 1, 2007–December 31, 2009. Denominators were calculated from DOHMH intercensal population estimates for Manhattan [12]. Annual rates overall were calculated per 100,000 person-years and age-adjusted to the standard 2000 projected US population [12]. All analyses were completed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

Results

Supplemental Table 1 provides demographic information on cases captured in the MLSP and percentage of cases who met any MCTD case definition. Using our modified Alarcon-Segovia and Kahn criteria for MCTD, the age-adjusted prevalence was 1.28 (95% CI 0.72-2.09) per 100,000 but the incidence estimate was too small to calculate, Table 1. Using our definition of a diagnosis of MCTD and no other diagnosis of another CTD yielded an age-adjusted prevalence and incidence of MCTD of 2.98

(95% CI 2.10-4.11) per 100,000 and 0.39 (95% CI 0.22-0.64) per 100,000, respectively. Finally, the age-adjusted prevalence and incidence were highest when using a diagnosis of MCTD regardless of other CTD diagnoses found in the charts and were 16.22 (95% CI 14.00-18.43) per 100,000 and 1.90 (95% CI 1.49-2.39) per 100,000 respectively.

Table 2 shows the most common other CTD diagnoses reported with MCTD among cases meeting our third definition. SLE was the most common, found in 68.6% followed by RA (29.0%), Sjogren's syndrome (28.6%), and SSc (22.9%). Supplemental Table 2 shows some of the common MCTD manifestations for our three case definitions.

Discussion

Our analysis of the MLSP dataset provides prevalence and incidence estimates of MCTD using multiple case definitions among Manhattan residents who constitute a diverse population in the United States. Our prevalence estimates were lower using more restrictive case definition that required fulfillment of our modified Alarcon-Segovia and Kahn criteria, while the incidence rate was too small to reliably calculate. Incidence and prevalence were higher when the case definition had the MCTD diagnosis stated with the exclusion of other CTD diagnoses and without needing to fulfil our modified criteria. Lastly, incidence and prevalence were notably higher when the case definition had a diagnosis of MCTD regardless of other CTD diagnoses. This likely reflects the variability in how MCTD is defined with clinical practice definitions that may not align with existing classification criteria, evolution of MCTD into other CTDs, and misuse of

the diagnosis in cases where there is overlapping connective tissue disease and/or presence of anti-RNP antibodies becomes the defining criteria [2-6].

The first epidemiologic study of MCTD was performed in Finland and used the Finnish National Health Insurance Database to identify incident cases of MCTD. The age- and sex-adjusted incidence of MCTD was 0.84 (95% CI: 0.41-1.71) per 100,000 person-years [7]. The second was conducted in Norway: based on a nationwide cross-sectional retrospective study, the prevalence of MCTD in 2008 was 3.8 (95% CI 3.2–4.4) per 100,000, and the incidence during 1996–2005 was 0.21 (95% CI 0.17–0.25) per 100,000 per year [8]. One of two reports in the U.S. was performed in Olmsted County, MN, and found the annual incidence rate was 1.9 (95% CI 1.0–2.7) per 100,000 population [9]. Most recently, data from the Indian Health Service provided a prevalence estimate of MCTD in 2007 among Alaska Native or American Indian people of 6.4 (95% CI 2.8–12.8) per 100,000 [10].

Compared to those prior epidemiologic studies, our prevalence and incidence estimates were similar when using a physician's diagnosis of MCTD without any other CTD diagnoses. When other CTD diagnoses were included, the prevalence and incidence rates were likely overestimated. The Olmsted County report required fulfillment of at least one set of four different criteria without fulfillment of classification criteria for other connective tissue diseases, and found a higher incidence rate compared to our population [9]. More cases could have been captured using multiple criteria or it is possible there is a higher incidence rate in Olmsted County due to racial/ethnic population differences. The Indian Health Service study utilized a more restrictive primary case definition that consisted of a rheumatologist's diagnosis of

MCTD and the documentation that the Alarcon-Segovia criteria had been met [10]. They found a higher prevalence rate of MCTD compared to prior studies as well as our study which could indicate that the prevalence of MCTD is possibly higher in the Alaska Native/American Indian population, similar to what has been shown in SLE [19,20]. The Norwegian study required the clinical diagnosis of MCTD to be verified by a rheumatologist with the fulfillment of at least one of 3 criteria for MCTD and their prevalence and incidence rates were slightly more in line with our estimates [8]. The Finnish study, in comparison, used the least specific definition and captured patients with MCTD based on the presence of anti-RNP as well as the presence of clinical features of more than one connective tissue disease, which is reflective of a higher incidence rate than found in our study [7]. Overall, comparability is limited given the variability in case definitions and population differences across studies.

There were several limitations of the MLSP which have been previously described which include underestimating incident and prevalent cases as not all case finding sources participated and the tremendous differences across medical records systems and abstracting several years after the surveillance period. [12]. Our modified criteria may not have captured as many patients with MCTD given that we did not collect data on acrosclerosis or “puffy fingers” which are included in both the Alarcon-Segovia and Kahn criteria [16,17]. Requiring myositis in our first case definition, albeit studies support its present in less than a third of MCTD patients [4], likely resulted in reduced estimates. However, we chose to include myositis since we did not collect all the criteria elements used in the various classification criteria and thus felt compelled to use all the data elements available. Additionally, our more liberal case definitions could

have captured more patients that may have had another CTD rather than MCTD including cases which did not have anti-RNP antibodies. The true burden of MCTD likely falls within the range of the three case definitions. Given the MLSP was designed to capture cases with SLE it is not surprising that SLE was the most commonly found other CTD diagnosis. It remains possible that patients who presented with symptoms more consistent with SSc or inflammatory myositis might not have been found through the MLSP methodology. Despite these limitations, our analysis benefitted from the design and composition of the MLSP, a population-based registry with a diverse population [12]. However, we could not provide reliable estimates among racial/ethnic groups and gender due to the small number of cases meeting our criteria.

In summary, MCTD is a connective tissue disease with limited epidemiologic data. The MLSP allowed us to estimate prevalence and incidence in a diverse population. The variation in estimates using both restrictive and liberal case definitions is reflective of the challenges of defining and diagnosing MCTD.

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Data Availability Statement: The data underlying this article is from a public health surveillance registry stored at the NYC DOHMH and will not be shared to protect patient confidentiality.

Conflicts of Interest:

Hasan: None, Ferucci: None, Buyon: None, Belmont: None, Salmon: None, Askanase: None, Bathon: None, Geraldino-Pardilla: None, Ali: None, Ginzler: None, Putterman: None, Gordon: Centers for Disease Control and Prevention, AbbVie, AstraZeneca, MGP, Sanofi, UCB, grants from UCB and Sandwell and West Birmingham Hospitals NHS Trust. Helmick: None, Parton: None, Izmirly: GlaxoSmithKline, Momenta/Janssen

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Table 1: Prevalence and incidence of MCTD among Manhattan residents aged 18 and older			
Prevalence, 2007			
Definition	N	Crude rate per 100,000 person-years (95% CI)	Age-adjusted rate per 100,000 person-years (95% CI)
1. Modified Alarcon-Segovia and Kahn criteria	16	1.20 (0.68-1.94)	1.28 (0.72-2.09)
2. Diagnosis of MCTD and no other diagnosis of another connective tissue disease	38	2.84 (2.01-3.9)	2.98 (2.10-4.11)
3. Diagnosis of MCTD regardless of other CTD diagnoses	210	15.70 (13.58-17.83)	16.22 (14.00-18.43)
Incidence, 2007-2009			
Definition		Crude rate per 100,000 person-years (95% CI)	Age-adjusted rate per 100,000 person-years (95% CI)
1. Modified Alarcon-Segovia and Kahn criteria	2	*	*
2. Diagnosis of MCTD and no other diagnosis of another connective tissue disease	16	0.40 (0.23-0.64)	0.39(0.22-0.64)
3. Diagnosis of MCTD regardless of other CTD diagnoses	75	1.86 (1.46-2.33)	1.90 (1.49-2.39)

*Rates were not calculated due to small case counts.

Table 2: Other connective tissue disease diagnoses reported among mixed connective tissue disease cases		
Other diagnosis (not mutually exclusive)	N=210	% of total
SLE	144	68.6
Rheumatoid Arthritis	61	29.0
Sjögren's Syndrome	60	28.6
Systemic Sclerosis or Scleroderma	48	22.9
Fibromyalgia	24	11.4
Antiphospholipid Syndrome	14	6.7
Polymyositis/Dermatomyositis	12	5.7
Discoid Lupus	7	3.3
Systemic Vasculitides	2	1.0

Supplemental Table 1: Characteristics of eligible MLSP cases overall and of those meeting any of three MCTD case definitions				
	Overall		Meeting any of the three MCTD case definitions	
	N	%	N	%
Eligible cases, aged 18 and older	3,460		266	7.7%
Male	372	10.8	11	4.1
Female	3,088	89.3	255	95.9
White	1,193	34.5	102	38.4
Black	760	22.0	65	24.4
Latino	842	24.3	61	22.9
Asian	271	7.8	23	8.7
Other	394	11.4	15	5.6
18-29 years old	530	15.3	40	15.0
30-39 years old	622	18.0	46	17.3
40-49 years old	675	19.5	52	19.6
50-59 years old	705	20.4	61	22.9
60-69 years old	504	14.6	38	14.3
70+ years old	424	12.3	29	10.9

Supplemental Table 2: Manifestations among Manhattan residents aged 18 and older with MCTD									
	Modified Alarcon-Segovia and Kahn criteria			Diagnosis of MCTD and no other diagnosis of another connective tissue disease			Diagnosis of MCTD regardless of other CTD diagnoses		
	Total	N	%	Total	N	%	Total	N	%
Overall	16			47			258		
Anti-RNP*	16	16	100.0	34	15	44.1	195	105	53.8
Arthritis	16	16	100.0	46	14	30.4	257	151	58.8
Myositis	16	16	100.0	46	2	4.3	256	25	9.8
Raynauds	16	16	100.0	47	18	38.3	258	138	53.5
Interstitial lung disease or pneumonitis	16	3	18.8	46	8	17.4	256	57	22.3
Pulmonary hypertension	16	2	12.5	46	2	4.3	256	35	13.7

* N reflect the cases in which a laboratory value was found in the abstracted chart. % reflects the cases with a positive RNP antibody of any titer that was not considered equivocal or borderline or negative.