Demographic, Clinical, and Immunologic Correlates among a Cohort of 50 Cocaine Users Demonstrating Antineutrophil Cytoplasmic Antibodies

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ABSTRACT. ***Objective.*** Cocaine/levamisole-associated autoimmunity syndrome (CLAAS) is a poorly understood form of drug-induced autoimmunity. Our goals were to better characterize the spectrum of clinical and immunologic features of CLAAS, to identify demographic risk factors, and to generate new hypotheses regarding pathogenesis.

Methods. CLAAS subjects were identified between 2001 and 2015 at the University of Washington Medical Center, Harborview Medical Center, and affiliated clinics in Seattle, Washington, USA. Demographic, clinical, and immunologic variables were collected and correlated using contingency and logistic regression analyses. We used similar analyses to compare CLAAS subjects with all individuals exhibiting antineutrophil cytoplasmic antibodies (ANCA+) or cocaine use (Cocaine+) in an associated deidentified clinical data repository.

Results. We identified 50 CLAAS subjects. Compared to all Cocaine+ individuals (n = 2740), CLAAS subjects were more likely to be female and less likely to self-identify as black/African American. CLAAS subjects showed several ANCA patterns, including anti-MPO (myeloperoxidase)/anti-PR3 (proteinase 3) dual reactivity, a finding that appears to be specific to CLAAS. Hematologic, renal, and skin abnormalities were most frequently reported, including neutropenia and skin purpura. Finally, we observed strong, independent associations between the cytoplasmic ANCA (C-ANCA) pattern and mortality.

Conclusion. We identify sex and race as important risk modifiers in the developing CLAAS among cocaine users. The development of C-ANCA was associated with increased mortality. Moreover, we confirm the enriched presence of anti-MPO/anti-PR3 dual reactivity in CLAAS, further supporting the diagnostic utility of this feature. (First Release May 15 2019; J Rheumatol 2019;46:1151–6; doi:10.3899/jrheum.180771)

Key Indexing Terms:
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An estimated 1.5 million people in the United States abuse illicit cocaine[1]. A link between cocaine abuse and autoimmunity was noted as early as 1996 with reports of chronic inflammatory midline destructive lesions and antineutrophil cytoplasmic antibodies (ANCA) in cocaine users[2,3]. In 2008, investigators began reporting a syndrome of purpuric skin disease and neutropenia in cocaine users with high-titer ANCA[4,5]. Around the same time, it was discovered that the North American supply of illicit cocaine was adulterated by the immunomodulatory drug levamisole; as of late 2010, nearly 80% of illicit cocaine seized in the US was contaminated with levamisole[6]. Levamisole, previously used to treat nephrotic syndrome and other conditions, was removed from the market for use in humans in 1999 because of side effects of neutropenia and purpuric skin lesions, often observed in the presence of ANCA[7,8,9,10]. Thus, levamisole has been implicated in causing purpura and neutropenia in cocaine users. Since 2008, investigators across the United States and Canada have reported additional clinical and immunologic abnormalities in cocaine users, such as antiphospholipid antibodies (aPL), glomerulonephritis (GN), and pulmonary hemorrhage[11,12,13]. Together, we[14] and others[15] have termed this constellation of findings "cocaine/levamisole-associated autoimmunity syndrome" (CLAAS).

The mechanisms linking cocaine and levamisole to the development of ANCA and aPL remain unknown, but recent studies suggest drug-induced neutrophil extracellular traps could be an important source of autoantigen and a cause of tissue injury[14,16]. Direct pathogenic roles for ANCA or aPL in CLAAS remain to be determined.

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What we know of the clinical features of CLAAS comes from many individual case reports and small series defined by select clinical manifestations (e.g., purpura). Thus, the clinical spectrum of CLAAS may be larger than reported. For the same reasons, the demographic features of CLAAS remain obscure. Answering these fundamental questions will provide much-needed insight into a potentially life-threatening form of drug-induced autoimmune disease.

In our current study, we attempt to answer some of these questions by correlating demographic, clinical, and immunologic features of a CLAAS cohort identified within a large US academic healthcare system. Our results confirm previously reported clinical and immunologic abnormalities in CLAAS while suggesting new pathogenic mechanisms. Further, we present evidence indicating that the development of CLAAS in cocaine users is strongly influenced by sex- and race-related factors. Finally, we highlight specific ANCA features that are likely to help clinicians distinguish CLAAS from idiopathic ANCA-related disease.

MATERIALS AND METHODS

Study approval, subject identification, and data collection. Collection and analysis of protected health information was performed with ethical approval of the University of Washington (UW) Human Subjects Division (approval no. 49530). Owing to the retrospective and low-risk features of the study, written patient consent was waived.

We identified CLAAS subjects receiving care between 2001 and 2015 at UW Affiliated Hospitals and Clinics using referral records, and the deidentified clinical data repository (DCDR; 2010–2015), which is maintained by the UW Institute for Translational Health Sciences. Inclusion criteria were (1) any urine toxicology screen showing evidence of cocaine exposure, plus (2) any positive ANCA immunofluorescence test result, plus (3) age at least 18 years at time of first positive cocaine test result. While it was expected that most of these individuals would also be exposed to levamisole, we did not use toxicology evidence of levamisole exposure as an inclusion criterion because (1) the rate of levamisole testing in our cohort of cocaine users was ~80%; and (2) the length of time during which levamisole can be detected in the urine after exposure appears to be significantly shorter than that of cocaine[17,18]. Personal identifiers were obtained from rheumatology referral records (n = 12) and from a query of the DCDR (n = 39). No subjects younger than 18 years of age were identified. Inclusion criteria were confirmed through review of electronic health records (EHR). Subjects deemed by their clinicians to have idiopathic ANCA-associated vasculitis (AAV) and a supportive tissue biopsy were excluded. Fifty-one subjects met inclusion criteria. One subject was excluded because of diagnosis of AAV.

Demographic data on these 50 CLAAS subjects were recorded. Vital status for individuals in all groups was estimated by mortality information noted in the medical record in 2018, because mortality information was not available for all groups at earlier timepoints. Subjects' EHR were reviewed from the time of first positive ANCA immunofluorescence (ANCA-IF) result ± 90 days for clinical abnormalities either attributed to cocaine/levamisole exposure or otherwise unexplained. Select laboratory results within this time window were also recorded.

For some analyses, we queried the DCDR between 2010 (earliest available laboratory data) and 2015 (latest date of inclusion for CLAAS subjects) for deidentified data from individuals with at least 1 positive urine cocaine test result and no evidence of ANCA by IF testing (Cocaine+; n = 2761), or those with at least 1 positive ANCA-IF result and at least 1 anti-MPO (myeloperoxidase)/anti-PR3 (proteinase 3) result but no evidence of cocaine exposure by urine toxicology (ANCA+; n = 98). For both analyses, subjects under the age of 18 years at time of inclusion (first positive test result) were excluded; a total of 21 from the Cocaine+ group and 1 from the ANCA+ group were excluded.

Statistical analysis. Chi-square, Mann-Whitney U, and Fisher's exact tests were performed using Prism 5 software (GraphPad). Logistic regression analysis was performed using IBM SPSS Statistics 22 software (SPSS). Multivariate analysis was performed using the variables that showed statistical significance in univariate analysis.

RESULTS

Race- and sex-related factors may influence the development of CLAAS. We identified 50 subjects meeting study criteria. In our DCDR database, the estimated minimum prevalence of CLAAS was 29 per 100,000 with an incidence of 7.8 per year. Demographic features of the CLAAS cohort are shown in Table 1. The majority of subjects were female (56%) and self-identified as white (60%). The median age was 46 years old. For most subjects, route of cocaine exposure could not reliably be determined.

To identify risk factors associated with development of CLAAS, we compared demographic features of CLAAS subjects against those of all cocaine users in the DCDR (Cocaine+, n = 2740). By univariate analysis, CLAAS subjects were significantly more likely to be female or identify as Hispanic or Mexican/Mexican American. Conversely, CLAAS subjects were less likely to identify as black/African American. Moreover, despite similar median age, CLAAS subjects were far less likely to be alive 3 years after the study period. These associations between CLAAS and race, sex, and mortality were maintained, and in some cases strengthened, after multivariate analysis. Thus, both race and sex appear to independently influence the development of identifiable CLAAS in cocaine users, and the development of identifiable CLAAS in cocaine users is associated with increased mortality.

Because these associations might reflect propensity for ANCA testing, we compared demographic features of all Cocaine+ individuals (18 yrs or older) in the DCDR, comparing demographic features of those with at least 1 ANCA-IF result (n = 97) versus those with no ANCA-IF result (n = 2643; Supplementary Table 1, available with the online version of this article). The population of 97 cocaine users undergoing ANCA-IF testing included some but not all of our 50 CLAAS subjects. This discrepancy relates to the fact that some CLAAS subjects were identified by referral records prior to 2010, the earliest date for laboratory data in the DCDR. By univariate and multivariate analyses, ANCA-IF–tested individuals were more likely to be female, and less likely to be living at the end of the study period. There were no statistically significant differences in age or self-identified race. Thus, female cocaine users were more likely than male cocaine users to undergo ANCA-IF testing, and ANCA-IF testing was independently associated with mortality.

To assess demographic features associated with development of ANCA among cocaine users, we compared

Table 1. Demographic features of CLAAS cohort versus all cocaine users.

Characteristics	CLAAS, n = 50	Cocaine+, n = 2740	Univariate		Multivariate	
			OR (95% CI)	p[1]	OR (95% CI)	p[2]
Age[3], yrs, median (min, max)	46 (21, 63)	45 (18, 85)	NA	0.6373[4]	NA	NA
Sex, female	28 (56)	895 (32.7)	2.62 (1.49–4.61)	0.0005	3.15 (1.74–5.69)	0.0001
Vital status, alive[5]	35 (70)	2511 (91.64)	0.21 (0.11–0.40)	< 0.0001	0.20 (0.11–0.38)	< 0.0001
Race, self-identified						
White	30 (60)	1335 (48.7)	1.58 (0.89–2.79)	0.1139	1.55 (0.86–2.79)	0.149
Black/African American	10 (20)	1083 (39.53)	0.38 (0.19–0.77)	0.0051	0.37 (0.18–0.77)	0.007
Nonwhite/nonblack	10 (20)	322 (11.75)	1.82 (0.90–3.68)	0.090	1.92 (0.94–3.92)	0.074
Hispanic and Mexican/ Mexican American	4 (8)	35 (1.28)	6.72 (2.29–19.70)	< 0.0001	8.46 (2.71–26.47)	0.0002
Native American/Alaska Native	4 (8)	134 (4.89)	1.69 (0.60–4.77)	0.315	4.46 (1.51–13.17)	0.007
Asian	1 (2)	NA	NA	NA	NA	NA
Other/Unknown	1 (2)	NA	NA	NA	NA	NA

Values are n (%) unless otherwise specified. [1] Chi-square test, 2-sided (except where otherwise indicated). [2] Logistic regression analysis, controlling for age, sex, vital status, and race. [3] Age at first positive cocaine test result. [4] Mann-Whitney U test, 2-sided. [5] As of March 2018. CLAAS: cocaine/levamisole-associated autoimmunity syndrome; NA: not assessed.

ANCA-IF results among those tested (n = 97; Supplementary Table 2, available with the online version of this article). Those demonstrating at least 1 positive result were more likely to be female and less likely to self-identify as black/African American.

Anti-MPO/Anti-PR3 dual reactivity is a unique feature of CLAAS. Consistent with CLAAS case reports[19], the majority (60%) of our CLAAS subjects had a perinuclear (P)-ANCA IF pattern, often in high titer (Supplementary Table 3, available with the online version of this article). However, we also identified 7 individuals (14%) with cytoplasmic (C)-ANCA pattern and 13 (26%) with atypical (A)-ANCA pattern. Of those with a P-ANCA IF pattern, only 67% had associated anti-MPO antibodies; of those with C-ANCA IF pattern, 86% had associated anti-PR3 antibodies. Those with A-ANCA-IF pattern showed variable anti-MPO and anti-PR3 reactivity. Interestingly, we identified 13 subjects with both anti-MPO and anti-PR3 antibodies. Querying the DCDR, we compared these frequencies with those among all ANCA-IF+ individuals lacking evidence of cocaine exposure by urine toxicology (ANCA+, n = 97). Compared to this population, CLAAS subjects were over 30 times more likely to show dual reactivity (Table 2). The dual-reactive pattern was able to discriminate CLAAS subjects from the ANCA+ population with a specificity of 99% and sensitivity of 26% (data not shown).

Clinical and immunologic features of CLAAS cohort. Clinical manifestations potentially attributable to CLAAS are listed in Table 3. Hematologic abnormalities were observed in 92% of subjects, with anemia being the most common (84%), followed by leukopenia (66%). Neutropenia, a widely reported feature of CLAAS, was observed in only 46% of subjects. Renal abnormalities (abnormal serum creatinine or urinalysis) were common, observed in 78% of subjects. Two subjects had pauciimmune GN attributed to CLAAS. Dermatologic abnormalities were noted in 58% of subjects, most of whom had purpura or ulcers. Musculoskeletal (MSK) abnormalities such as arthralgia or myalgia were frequently reported. There were 2 subjects who carried a diagnosis of spondyloarthropathy.

CLAAS subjects displayed a wide variety of laboratory abnormalities. However, not all subjects were tested for all variables. Variables in which data were available for at least 50% of subjects are shown in Table 3. Of those tested, most showed evidence of IgM anticardiolipin antibodies or lupus inhibitor (LI), consistent with previous case reports[15,19]. Evidence of hepatitis C virus (HCV) exposure was observed in 32 of the 48 subjects, 47% of whom also had evidence of

Table 2. Comparison of ANCA-associated antibodies: CLAAS versus all ANCA+ individuals.

Anti-MPO/PR3 Status		CLAAS, n = 50	ANCA+, n = 97	OR (95% CI)	p[1]
Anti-MPO	Anti-PR3				
–	–	17 (34.0)	38 (39.2)	0.80 (0.40–1.63)	0.592
+	+	13 (26.0)	1 (1.0)	33.73 (4.26–267.2)	< 0.0001
–	+	9 (18.0)	26 (26.8)	0.60 (0.26–1.40)	0.308
+	–	11 (22.0)	33 (34.0)	0.55 (0.24–1.21)	0.183

Values are n (%) unless otherwise specified. [1] Fisher's exact test, 2-sided. CLAAS: cocaine/levamisole-associated autoimmunity syndrome; ANCA: antineutrophil cytoplasmic antibodies; MPO: myeloperoxidase; PR3: proteinase 3.

Table 3. Clinical and demographic features of CLAAS cohort.

Features	N (%)
Clinical features	
Hematologic (any)	46 (92)
Anemia	42 (84)
Leukopenia	33 (66)
Neutropenia	23 (46)
Renal	39 (78)
Dermatologic (any)	29 (58)
Purpura/ulcers	21 (42)
MSK	20 (40)
ENT	5 (10)
Pulmonary	2 (4)
Laboratory features	
Antiphospholipid antibody (any)	19/28 (68)
Anticardiolipin IgM	18/28 (64)
Anticardiolipin IgG	5/28 (18)
Anti-β_2 glycoprotein IgM	9/24 (38)
Anti-β_2 glycoprotein IgG	3/28 (11)
Lupus inhibitor	15/19 (79)
Evidence of HCV exposure	32/48 (67)
HCV viremia	23/49 (47)
Evidence of HIV infection	3/47 (6)
Low C3 or C4	15/33 (45)
Cryoglobulinemia	8/28 (29)
RF	8/33 (24)
ANA	11/48 (23)
Levamisole detected in urine	14/36 (39)

CLAAS: cocaine/levamisole-associated autoimmunity syndrome; MSK: musculoskeletal; HCV: hepatitis C virus; HIV: human immunodeficiency virus; RF: rheumatoid factor; ANA: antinuclear antibody; IgM: immunoglobulin M.

active HCV viremia. Low complement (C3 or C4) levels were observed in 15 subjects, mostly in association with HCV viremia. Similarly, of the 8 subjects showing cryoglobulinemia, all but one had evidence of HCV infection. We were unable to compare frequencies of these abnormalities in the Cocaine+ population because testing rates in that population were very low. Finally, levamisole was detected in the urine of only 39% of the 36 CLAAS subjects who underwent an extended toxicology screening.

Clinical, epidemiologic, and immunologic correlates among CLAAS subjects. To identify potential disease mechanisms in CLAAS, we analyzed relationships between select demographic, clinical, and immunologic features using Fisher's exact tests (Supplementary Table 4, available with the online version of this article). To avoid the confounding effects of indication bias, we analyzed only those variables for which we had complete or nearly complete datasets. We found several statistically significant associations between vital status, race, and ANCA-IF pattern. Specifically, subjects with P-ANCA pattern were more likely than others to be alive 3 years after the study; conversely, those with C-ANCA pattern were less likely than others to be alive at the same timepoint. Race was also associated with ANCA-IF patterns, with P-ANCA pattern being more likely in white subjects and less likely in black/African American subjects; the opposite pattern was observed for C-ANCA pattern. Controlling for race, the relationships between vital status and ANCA-IF pattern remained strong and statistically significant (Table 4).

We also observed a strong, positive correlation between the presence of purpura/ulcers and anti-MPO antibodies (Supplementary Table 4, available with the online version of this article). In addition, MSK manifestations were positively correlated with P-ANCA-IF and anti-MPO antibodies, and negatively correlated with C-ANCA-IF. The relationship between MSK anti-MPO was independent of ANCA-IF pattern (Table 4).

DISCUSSION

Our study is unique in its approach to understanding CLAAS. In contrast to most published studies on this topic, which selected subjects based on clinical manifestations (purpura, renal disease, etc.), we defined our CLAAS cohort based solely on ANCA and cocaine status. McGrath, *et al*[12] described a similarly selected cohort of 30 CLAAS subjects. However, we were also able to compare our cohort to the ANCA+ and Cocaine+ populations from which it was derived. Together, these approaches allowed us to better understand current observations in CLAAS, define a broader array of associated immunologic and clinical abnormalities, and generate new hypotheses regarding pathogenesis.

Little is known about genetic and environmental risk factors for developing CLAAS among cocaine users. Our demographic analysis suggests that female sex and white race are positive risk factors, and that black/African American race is a negative risk factor. The female bias of our CLAAS cohort appeared to reflect both an increased rate of ANCA testing and increased rate of positive results among female cocaine users. Thus, sex-related factors may influence the development of clinical manifestations prompting ANCA testing as well as the propensity to develop autoantibodies. This finding contrasts with idiopathic AAV, which does not show a similar sex bias[20].

We observed a broad range of clinical and immunologic abnormalities in our CLAAS cohort. Features previously reported as characteristic of CLAAS, such as neutropenia and skin disease[13,15], were reported in only half of subjects. Pulmonary disease was reported in just 2 subjects. Mild renal abnormalities were common, but GN attributed to CLAAS was reported in only 2 subjects.

These results confirm previously associated clinical manifestations (e.g., neutropenia and skin purpura), further supporting the idea that ANCA antibodies alone are insufficient to cause disease in this setting. Moreover, it is interesting to note that among cocaine users who underwent ANCA testing, only one-third had had a positive result (Supplementary Table 2, available with the online version of this article). This indicates that exposure to cocaine can induce clinical signs/symptoms prompting ANCA testing

Table 4. Select demographic, clinical, and immunologic correlates within CLAAS cohort.

Outcome	Predictor	Univariate[1] OR (95% CI)	Covariable p	Multivariate[2]	OR (95% CI)	p
Vital status (alive)	P-ANCA	7.94 (2.01–31.36)	0.0036	Race[3]	5.76 (1.25–26.58)	0.025
	C-ANCA	0.04 (0.01–0.42)	0.0018	Race[3]	0.06 (0.01–0.66)	0.022
Purpura/ulcers	Anti-MPO	5.56 (1.62–19.03)	0.0092	NA	NA	NA
MSK	Anti-MPO	7.00 (1.95–25.14)	0.0034	ANCA-IF pattern[4]	4.24 (1.04–17.20)	0.044

[1] Fisher's exact test, 2-tailed. [2] Logistic regression analysis controlling for listed covariables. [3] White vs others; Black/African American vs others. [4] P-ANCA vs C-ANCA vs A-ANCA. CLAAS: cocaine/levamisole-associated autoimmunity syndrome; ANCA: antineutrophil antibodies; P-ANCA: perinuclear ANCA; C-ANCA: cytoplasmic; MSK: musculoskeletal; IF: immunofluorescence; NA: not assessed.

even in the absence of ANCA. Further comparison of clinical manifestations prompting ANCA testing in cocaine users with positive versus negative results could provide important insight into the pathogenic roles of autoantibodies in CLAAS.

Consistent with previous case reports[13,19], we observed high rates of LI and aPL in CLAAS subjects who were tested. However, the low rate of testing precluded meaningful correlation with clinical manifestations. The rate of HCV infection (> 60%) in our cohort was much higher than that reported among recreational cocaine users in another US urban center (33%) and in Brazil (32%)[21]. Thus, HCV infection may be a risk factor for developing CLAAS. Larger studies are needed to examine this association.

Although this is the largest CLAAS cohort published to date, to our knowledge, we were limited in our ability to correlate certain immunologic, clinical, and demographic features. Nevertheless, the high overall rate of LI/aPL positivity among those tested, together with known mechanisms of thrombotic skin disease in aPL syndrome, suggest a pathogenic link in CLAAS. The associations between anti-MPO antibodies and MSK or skin manifestations described in the current investigation also suggest a pathogenic link.

CLAAS subjects displayed unique ANCA patterns. Consistent with reported cases, ANCA-IF patterns in our CLAAS cohort were predominantly perinuclear (P-ANCA), often in high titer, but with variable anti-MPO reactivity. In contrast, we observed 7 subjects with a C-ANCA-IF pattern. The independent association of this pattern with decreased survival in our study remains unexplained, in part because we were unable to discover the cause of death in most cases. Most, but not all, cases showing the C-ANCA-IF were observed before 2008, when the prevalence in levamisole in seized cocaine in the US began to rise rapidly[6]. The significance of this finding remains unclear, but these results are consistent with the idea that levamisole or cocaine alone may induce different forms of ANCA-associated autoimmunity, as suggested by *in vitro* studies[14]. The A-ANCA pattern was associated with both anti-PR3 and anti-MPO reactivity, but it was not associated with mortality or specific clinical features. Finally, we were able to confirm previously published reports[12,22] of high rates of anti-MPO/anti-PR3 dual reactivity in CLAAS subjects and compare these rates to those in other ANCA+ individuals. The high specificity of dual positivity for cocaine users in our study suggests that clinicians encountering dual reactivity when evaluating vasculitis should suspect CLAAS.

A major limitation of our study (and previous similar studies) is the impossibility of reliably and accurately determining levamisole exposure. Because of this, we were unable to discern which cohort features were associated with cocaine exposure, levamisole exposure, or both. Another study limitation is selection bias. First, selecting subjects based on ANCA reactivity and/or referral to rheumatology consultation likely biased the cohort toward individuals with symptoms suggestive of CLAAS or idiopathic AAV. The rate of ANCA reactivity among cocaine users remains unknown; our study estimates only the lower limit of prevalence. Within our CLAAS cohort, not all subjects were tested for all immunologic variables. While we limited statistical analysis to variables for which we had at least 50% of the results, testing was almost certainly influenced by presence of certain clinical manifestations (e.g., LI testing in patients with purpura). Our deidentified patient database offered a useful tool for assessing certain features in comparator populations, but individual results could not be verified. Finally, this cross-sectional, retrospective study did not permit analysis of temporal relationships between cocaine exposure, autoimmunity, and clinical disease.

Our study offers new insight into the diagnosis and pathogenesis of CLAAS. Further studies are needed to improve the care of patients with CLAAS and to better understand the mechanisms of tissue injury and loss of immunologic tolerance to neutrophil-associated antigens.

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ONLINE SUPPLEMENT

Supplementary material accompanies the online version of this article.

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