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Prescription medication use and antinuclear antibodies in the United States, 1999–2004

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ABSTRACT

Background: Clinical reports link specific medications with the development of antinuclear antibodies (ANA), but population-based evidence is limited.

Objective: The present study investigated associations between prescription medication use and ANA in a representative sample of the adult noninstitutionalized US population, first focusing on medications previously related to ANA and then considering all medications reported in the National Health and Nutrition Examination Survey (NHANES).

Methods: Based on NHANES data (1999–2004) for 3608 adults (ages ≥18 years), we estimated odds ratios (ORs) and 95% confidence intervals (CIs) to assess associations between recent medication use and ANA (overall and in sex and age subgroups), adjusted for potential confounders and the survey sampling design.

Results: We found no evidence that most medications previously associated with ANA in specific individuals were risk factors for ANA in the general population, although statistical power was limited for some medications. Overall, ANA were less prevalent in adults who recently used any prescription medications compared with those who did not (OR = 0.73; CI = 0.57,0.93), and likewise several classes of medications were inversely associated with ANA, including hormones (OR = 0.73; CI = 0.55,0.98), thiazide diuretics (OR = 0.43; CI = 0.24,0.79), sulfonylureas (OR = 0.41; CI = 0.19,0.89), and selective serotonin reuptake inhibitor antidepressants (OR = 0.65; CI = 0.42,0.98). Positive associations with ANA were seen for loop diuretics (OR = 1.72; CI = 1.03,2.88) in all adults, and for benzodiazepines (OR = 2.11; CI = 1.09,4.10) and bronchodilators (OR = 1.83; CI = 1.00,3.38) in older (ages ≥60) adults. Estrogens were positively associated with ANA in older women (OR = 1.80; CI = 1.00,3.23) but inversely associated with ANA in younger (ages 18–59) women (OR = 0.43; CI = 0.20,0.93). Regarding individual medications, ANA were positively associated with ciprofloxacin (OR = 4.23; CI = 1.21,14.8), furosemide (OR = 1.79; CI = 1.09,2.93), and omeprazole (OR = 2.05; CI = 1.03,4.10) in all adults, and with salmeterol (OR = 3.76; CI = 1.66,8.52), tolterodine (OR = 6.64; CI = 1.45,30.5), and triamterene (OR = 3.10; CI = 1.08,8.88) in older adults. Also, in younger adults, hydrochlorothiazide was inversely associated with ANA (OR = 0.44; CI = 0.20,0.98).

Conclusions: Our findings in the general population do not confirm most clinically reported positive associations between specific medications and ANA in some individuals. However, novel positive ANA associations with other medications, as well as unexplained inverse associations with certain classes of medications and overall medication use, deserve further research to clarify the possible roles of medications as risk and protective factors in the development of autoantibodies and autoimmune disease.

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1. Introduction

Autoimmune diseases are a diverse group of disorders characterized by tissue and organ damage due to an immune response to self-antigens [1] and their causes remain incompletely understood [2]. Antinuclear antibodies (ANA) are observed in patients with many systemic autoimmune diseases. In the general US population, ANA are more common in women, older individuals, African Americans, and persons of normal weight [3]. They are also associated with childbearing [4]; certain genes [5]; and environmental agents, such as chemicals, occupational exposures, infections, and medications [6–10].

The present study focuses on prescription medications, some of which have been reported to induce ANA and symptoms of lupus or other autoimmune diseases in specific individuals. Drug challenge (ANA or disease occurrence after beginning the drug), dechallenge (resolution of ANA or disease after discontinuing the drug), and rechallenge (recurrence of ANA or disease after beginning the drug again) are often considered diagnostic for drug-induced autoimmunity [11]. However, such studies are often small and describe only case reports or case series [8,12–14]; limited data are available on a population basis to determine the extent of associations from a public health perspective. Also, few if any studies have assessed possible protective effects of medications on autoimmunity, as these cannot be performed in clinical care settings or most drug trials because they require larger sample sizes and population-based approaches.

The purpose of the present study was to investigate associations, positive or negative, between prescription medication use and ANA in the general adult population. We analyzed data from a representative sample of the noninstitutionalized US population, obtained from the National Health and Nutrition Examination Survey (NHANES). First, we examined medications previously reported to induce ANA in specific individuals and sought to determine whether corresponding positive associations could be confirmed in our large, population-based study. Second, we evaluated all prescription medications used by NHANES participants in the month preceding their interview to identify any associations with ANA. The latter analysis was mainly descriptive and exploratory; it assessed individual medications, classes of medications, and overall medication use to generate hypotheses for future studies.

2. Subjects and methods

2.1. Study participants

We analyzed NHANES data from 1999 to 2004, currently the only years with data on ANA. All data are publicly available and no individual follow-up outside NHANES occurred. The NHANES used a multistage strategy to select a nationally representative probability sample of the noninstitutionalized US population. A subsample of 7106 participants at least 12 years old was selected to assess serum levels of organochlorines, and 4754 of these participants gave permission for sera storage and had samples available for ANA analysis. Sampling weights were revised (https://www.cdc.gov/nchs/tutorials/nhanes/SurveyDesign/Weighting/intro.htm) to account for sampling into the organochlorine study and participation in the ANA substudy. The NHANES collected self-reported information on various sociodemographic and health-related factors. Constructed variables, such as body mass index (BMI), defined as weight (kg) divided by height (m) squared, were also included in the published dataset [15]. The NHANES protocol was approved by the human subjects Institutional Review Board of the U.S. Centers for Disease Control and Prevention, and written informed consent was obtained from all participants.

We excluded 236 women who were pregnant, as their physiology and use of medications are not representative of the general population [16,17]. We also excluded 881 participants under 18 years of age, 20 with missing medication information, and 9 with missing BMI data, which left 3608 adult participants for our analyses. Except for age and pregnancy status, which were used to define our subsample, these exclusions did not lead to any statistically significant differences in other demographic factors compared with the original ANA sample (not shown).

2.2. ANA status

Standard indirect immunofluorescence was used to measure ANA in serum specimens, based on commercial HEp-2 ANA slides (Inova Diagnostics) with 1:80 dilutions of sera and staining with DyLight 488-conjugated donkey anti-human immunoglobulin G (IgG) antibodies (Jackson ImmunoResearch), as previously reported [3]. Staining intensities were graded from 0 to 4 relative to a standard reference gallery, with values of 3 and 4 indicating ANA positivity. Two independent raters, blinded to the sociodemographic data on the subjects, agreed on > 95% of the readings for overall intensity ratings, and differences were resolved by consensus or adjudicated by a third blinded rater.

Specific autoantibodies were identified in ANA-positive participants by using immuno-precipitation of ^{35}S-methionine-labeled K562 cell extracts, as previously described [3]. They were classified as autoantibodies against extractable nuclear antigens (ENA) and included Sjögren's syndrome antigen A (Ro), Sjögren's syndrome antigen B (La), Argonaute 2 (Su), U1 ribonucleoprotein (U1RNP), Smith antigen (Sm), topoisomerase I, ribosomal proteins or RNA, replication protein A (RPA), isoleucyl-transfer RNA synthetase (OJ), nucleolar organizer region 90 kDa antigen or upstream binding protein (NOR90), histidyl-transfer RNA synthetase (Jo-1), threonyl-transfer RNA synthetase (PL-7), alanyl-transfer RNA synthetase (PL-12), glycyl-transfer RNA synthetase (EJ), signal recognition particle (SRP), p70/p80 antigen that is a DNA-binding protein (Ku), polymyositis-scleroderma antigen (PM-Scl), chromodomain helicase DNA binding protein 4 (Mi-2), RNA polymerase, and U3 ribonucleoprotein (U3RNP). The data were too sparse to analyze these autoantibodies individually, but we performed sensitivity analyses that excluded the 483 participants with any of these anti-ENA autoantibodies or certain medical disorders (described later) to focus on those without prior evidence of autoimmune disease.

2.3. Prescription medication information

Medication use was self-reported, but verified with prescription bottles, and referred to use in the month preceding the NHANES interview. Initially, we targeted medications suspected of inducing ANA in specific individuals to assess whether they also were associated with ANA in our population-based sample. After extensive literature reviews of case reports, using PubMed with search terms such as “medications and ANA” and “medications and autoimmunity” and evaluating references in sentinel papers, we (JY and FWM) compiled a list of medications that met predefined criteria for possibly inducing ANA [11,18]. We refer to this compilation as the medications-associated-with-ANA (MAWA) list. We also investigated associations with ANA for medications previously linked to lupus, an autoimmune disease associated with ANA. We created two lists of such medications: the Rubin list, which refers to medications in Table 2 of Rubin [12] or Table 1 of Rubin [13], and the Chang list, which refers to medications in Table 2 of Chang and Gershwin [8] or Table 1 of Xiao and Chang [14]. Prescription medications used by NHANES participants and included on any of these three lists are shown in our Table 1.

In addition to the targeted analysis of medications previously linked to ANA or lupus, we also performed a descriptive analysis to explore whether ANA were positively (or negatively) associated with (1) all prescription medications collectively, (2) prescription medications in established classes, and (3) individual prescription medications, possibly including some not previously reported as being associated with ANA. Overall (collective) use was defined as the use of any medication (yes/no). Medications were then categorized into three sets of classes that coincided with Level 1, Level 2, and Level 3 of the Multum Lexicon