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Authors
LaHue, Sara C
Albers, Kathleen
Goldman, Samuel
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Title: Cervical Dystonia Incidence and Diagnostic Delay in a Multiethnic Population

Sara C. LaHue, M.D.,[1,2] Kathleen Albers, M.P.H.,[3] Samuel Goldman, M.D., M.P.H.,[1,4,5] Raymond Lo, M.D.,Ph.D.,[6] Zhuqin Gu , M.D., PhD.,[7] Amethyst Leimpeter, M.Sc.,[3] Robin Fross, M.D.,[8] Kathleen Comyns, M.P.H.,[1] Connie Marras, M.D., Ph.D.,[9] Annelie de Kleijn M.D.,[10] Robin Smit M.D.,[10] Maya Katz, M.D.,[1,2,4] Laurie J. Ozelius, Ph.D.,[11] Susan Bressman, M.D.,[12,13] Rachel Saunders-Pullman, M.D., M.P.H., M.S.[12,13] Cynthia Comella, M.D.,[14] Jeffrey Klingman, M.D.,[15] Lorene M. Nelson, Ph.D.,[16] Stephen K. Van Den Eeden, Ph.D.,[3] Caroline M. Tanner, M.D., Ph.D.[1,2,4]

[1]Department of Neurology, School of Medicine, University of California, San Francisco, CA, USA

[2]Weill Institute for Neurosciences, Department of Neurology, University of California,

San Francisco, San Francisco, CA, USA

[3]Division of Research, Kaiser Permanente Northern California, Oakland, CA, USA

[4]San Francisco Veteran's Administration Medical Center, San Francisco, CA, USA

[5]Occupational and Environmental Medicine, School of Medicine, University of California, San Francisco, CA, USA

[6]Buddhist Tzu-Chi General Hospital, Hualien, Taiwan

[7]Department of Neurobiology, Xuanwu Hospital of Capital Medical University, Beijing, China

[8]Kaiser Permanente Hayward Medical Center, Hayward, CA, USA

[9]Morton and Gloria Shulman Movement Disorders Centre and the Edmond J Safra Program in Parkinson's Research, University of Toronto, Toronto, Canada

[10]Radboud University Nijmegen, Nijmegen, Netherlands

[11]Department of Neurology, Massachusetts General Hospital, Charlestown, MA, USA

[12]Mount Sinai Beth Israel, New York, NY, USA

[13]Icahn School of Medicine at Mount Sinai, New York NY, USA

[14]Rush University Medical Center, Chicago, IL, USA

[15]Kaiser Permanente Walnut Creek Medical Center, Walnut Creek, CA, USA

[16]Department of Health Research and Policy, Stanford University, Stanford, CA, USA

Corresponding Author:

Caroline M. Tanner, M.D., Ph.D.

Address: Movement Disorders and Neuromodulation Center

Department of Neurology, University of California, San Francisco

1635 Divisadero Street, Suite 515

San Francisco, CA 94115

Phone: 415-514-6966

Email: caroline.tanner@ucsf.edu

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ABSTRACT

Background: Current cervical dystonia (CD) incidence estimates are based on small numbers in relatively ethnically homogenous populations. Frequency and consequences of delayed CD diagnosis is poorly characterized.

Objectives: To determine CD incidence and characterize CD diagnostic delay within a large, multiethnic integrated health maintenance organization.

Methods: We identified incident CD cases using electronic medical records and multistage screening of more than 3 million Kaiser Permanente Northern California members during January 1, 2003–December 31, 2007. Final diagnosis was made by movement disorders specialist consensus. Diagnostic delay was measured by questionnaire and health utilization data. Incidence rates were estimated assuming a Poisson distribution of cases and directly standardized to the 2000 United States census. Multivariate logistic regression models were employed to assess diagnoses and behaviors preceding CD compared to matched controls, adjusting for age, sex and membership duration.

Results: CD incidence was 1.18/100,000 person-years (95% confidence interval [CI] 0.35, 2.0; women: 1.81, men: 0.52) based on 200 cases over 15.4 million person-years. Incidence increased with age. Half of the CD patients interviewed reported diagnostic delay. Diagnoses more common in CD patients before index date included essential tremor (odds ratio [OR]

68.1, 95% CI 28.2, 164.5), cervical disc disease (OR 3.83, 95% CI 2.8, 5.2), neck sprain/strain (OR 2.77, 95% CI 1.99, 3.62), anxiety (OR 2.24, 95% CI 1.63, 3.11) and depression (OR 1.94, 95% CI 1.4, 2.68).

Conclusions: CD incidence is greater in women and increases with age. Diagnostic delay is common and associated with adverse effects.

INTRODUCTION

Cervical dystonia (CD) is among the most common forms of focal dystonia in the neurology clinic.[1-9] However, the true frequency of CD is not established.[10, 11] Most estimates of CD prevalence are based on referral clinic populations.[2-5, 7, 12-14] There are many advantages to studying population incidence, including the minimization of bias. Previous studies estimating CD incidence are based on small numbers of cases in homogenous populations, or rely on decades-old data that may now poorly represent increased awareness of dystonia among medical providers.[15-17] The aims of this study were to determine the incidence of CD in a large, ethnically diverse population, identify the characteristics associated with a delayed diagnosis of CD, and delineate possible risk factors for developing CD.

METHODS

Study Population and Data Extraction

Kaiser Permanente Northern California (KPNC) is an integrated healthcare system with over 3 million members that serves a diverse population across 14 Northern Californian counties. Based on data from the 2003 California Health Interview Survey, Kaiser Permanente member demographics are similar to the non-Kaiser Permanente population.[18]

Cases and controls were ascertained through a review of the comprehensive clinical and administrative databases of KPNC. The multistage case identification process used by this study is detailed in Figure 1 and is based on our preliminary work[15].

Case Selection

Incident cases of CD were identified through a three-stage case identification procedure. First, inpatient and outpatient visits and pharmacy records for all KPNC and non-KPNC services were screened for specific diagnostic codes and write-in diagnoses for primary dystonia. Second, for all individuals with a CD diagnosis, a complete chronological list of all health service utilizations from the beginning of KPNC membership was generated for each individual. Each individual's list was reviewed by one or more movement disorders specialists to classify individuals as likely or unlikely to have cervical dystonia. Third, individuals judged likely to have cervical dystonia underwent a more extensive review by a movement disorders expert, including when possible a neurological examination in person or via review of a standardized videotape data collection by a trained research assistant during a home visit. Research diagnostic criteria appropriate to epidemiologic studies were developed by an expert panel convened by the Dystonia Medical Research Foundation (including CMT, SB, CC) and operationalized for use in KPNC. A final diagnosis of cervical dystonia required: a) Diagnosis by a neurologist; b) No consistent change in neurologist's diagnosis after index date; c) No antecedent

neuroleptic use; d) No identifiable associated medical or neurologic disorder known to include dystonia. Individuals were excluded if their dystonia was diagnosed prior to January 1, 2003 (i.e. prevalent cases) or after December 31, 2007, or if they were not members of the KPNC system at the time of CD diagnosis.

Medical records review, videotaped exam review and clinical examinations, conducted by movement disorders experts in subsets, included characterization of the abnormal posture, the presence or absence of superimposed movements, presence or absence of geste antagoniste, presence or absence of associated features, type of therapy and response to therapy as well as absence of another cause for the movement abnormality.

In these validation subsets, agreement between utilization-defined cervical dystonia and medical record review was 88%, and between utilization defined CD and examination was 96%.

Control Selection

Two control populations were assembled. For analyses based on the electronic medical record,
control subjects were identified in order to determine the relative risk of clinical diagnoses preceding a diagnosis of CD. Ten controls were selected at random from the entire KPNC member base and matched to each case on birth year, sex, membership length, facility, and zip code (as a proxy for socioeconomic status). Electronic medical record (EMR) information was then

pulled from the KPNC databases. For analyses based on interview data, control subjects were selected at random from the KPNC member base and matched one-to-one to enrolled cases based on birth year, sex and membership length. If a control did not complete the entire interview, another matched control was selected for the participating case.

Data Acquisition

Data were acquired from review of the EMR, health services utilization reports and mailed questionnaire. Information regarding incidence and antecedent clinical diagnoses was obtained from the EMR. The patient questionnaire provided detailed information on the frequency, character and impact of diagnostic error in persons with CD, as well as data regarding family history and demographics.

Standard protocol approvals, registrations, and patient consents

This study was conducted with approval from the KPNC Institutional Review Board. Informed consent was obtained from each participant.

Statistical Analysis

All statistical analyses were conducted using the SAS/STAT statistical software package, version 9.1 (SAS Institute Inc). Average annual incidence was calculated overall, and for sex-, race/ethnicity- and age-specific groups.[19] Incidence rates and confidence intervals were estimated assuming a Poisson

distribution of cases within the Kaiser Permanente population. Direct standardization of rates for age, race/ethnicity and sex used the 2000 U.S. census population. Incidence rates were presented per 100,000 person-years.

Behaviors and antecedent diagnoses were compared between CD cases and their interviewed controls (1:1) or EMR-control (1:10). Adjusted odds ratios (ORs) and 95% confidence intervals were calculated adjusting for birth year, sex, membership length, facility, and zip code (as a proxy for socioeconomic status).

RESULTS

Cervical Dystonia Incidence and Subject Demographics

Two hundred cases of incident primary cervical dystonia were identified over 15,489,433 person-years of observation. Incidence standardized to the US 2000 Census population was 1.18 per 100,000 person-years (95% C.I.: 0.35, 2.0). The age-, sex-, and race/ethnicity-specific rates are summarized in Table 1. CD incidence was significantly greater in women and Caucasians. The difference between mean age at incident diagnosis between men and women approached significance (men = 47 years, 95% C.I.: 42.29, 51.85; women = 54 years, 95% C.I.: 51.61, 56.43). Incidence appeared to increase with age through the 7th decade.

Cervical Dystonia Diagnostic Delay

Of 200 CD cases, we had permission to contact and approach 114 cases. A total of 80 cases agreed to respond to questionnaires concerning risk factors, diagnosis and treatment (70%); of those, a total of 58 cases (51%) responded to the survey addressing details of diagnosis. Diagnosis of CD was delayed a median of 730 days after the onset of self-reported symptoms; a median of 3 physician visits occurred before the diagnosis was made. Characteristics of diagnostic delay derived from the patient questionnaire are outlined in Table 2. Fifty percent of patients reported unpleasant or harmful effects due to this delay. Sixty-six percent of those surveyed reported receiving treatment for an incorrect diagnosis prior to being diagnosed with CD. The most common treatments included muscle relaxants, physical therapy, anti-inflammatories, acupuncture, antidepressants, and trigger point injections. A quarter of those who received treatment prior to CD diagnosis reported unpleasant or harmful side effects from those treatments. Following CD diagnosis, 83% of patients received botulinum toxin injections; of these, 89% reported that botulinum toxin injections were helpful. The features associated with diagnostic delay are summarized in Table 3.

Medical Conditions Preceding Cervical Dystonia Diagnosis

Patients ultimately diagnosed with cervical dystonia were more likely to be given certain diagnoses compared with controls. These diagnoses included

essential tremor (OR 68.1, 95% C.I. 28.2, 164.5), cervical disc disease (OR 3.8, 95% C.I. 2.83, 5.17), neck sprain/strain (OR 2.68, 95% C.I. 1.99, 3.62), anxiety (OR 2.24, 95% C.I. 1.63, 3.11) and depression (OR 1.94, 95% C.I. 1.4, 2.68). Patients with CD were significantly more likely to have a diagnosis of neck trauma or pathology three and five years preceding the index date compared with controls ($p=0.000$ and $p=0.002$, respectively). Three years prior to diagnosis, patients with CD were significantly more likely than controls to be diagnosed with tremor, essential tremor, depression and anxiety ($p < 0.001$ for each), but not migraine ($p=0.577$).

DISCUSSION

In this study of cervical dystonia in patients within the Kaiser Permanente Northern California system, we found an estimated CD incidence of 1.18/100,000 p-y based on 200 cases over 15.4 million p-y. This study incorporates the largest, most ethnically diverse cohort of incident cases of CD to date. Our estimated incidence of 1.18 per 100,000 person-years is similar to the preliminary incidence estimate we previously published for the years 1997-1999 (1.07 per 100,000 person-years).[15] This current report is based on three times as many incident cases of CD, over twice as many person-years of observation, compared with our prior estimate. Due to the larger sample size, we are now able to evaluate differences among subgroups with more confidence and precision.

We found that the incidence of CD differs by sex. The incidence of CD was 3.5 times greater for women than for men. This strengthens our previous finding that the minimum estimated incidence of CD was 2.5 times greater for women.[15] The majority of prior studies estimated CD prevalence, not incidence; these studies found sex prevalence ratios (female:male) ranging from 1.1-3.6:1.[4, 7, 16, 20] However, unlike our study, these data were mostly derived from homogenous populations or from a small number of centers[20]. While the incidence of CD is higher for women, the age of CD onset may be later for women than for men. The sex difference observed in our study may have several explanations. One possibility is rooted in genetics. While most cases of CD have no known cause, family history of dystonia remains an important risk factor.[21] There are genetic links for many forms of dystonia, but these are not usually inherited on sex chromosomes.[22] However, our observation that the incidence of CD differs by race also raises the possibility of genetic contributions. Currently identified CD-related genetic mutations and variants are not sufficient to explain the observed sex difference, though variable penetrance, epigenetic modification of gene expression, or gene-environment interactions may play a role. Differences in sex hormones are another possible explanation for this sex discrepancy. Rodent studies suggest that estrogen may protect the nigrostriatal dopaminergic system from damage through enhancing dopamine synthesis, increasing dopamine receptor sensitivity, and stimulating plasticity in this circuit.[23-26] The decrease in estrogen during the peri- and post-menopausal

periods may be a driver of the observed increase in CD incidence for women later in life as compared to men.[4, 7, 13] Sex differences may also result from differences in health-seeking behaviors or medical provider diagnostic bias. These could affect both the overall sex-specific incidence rates as well as apparent differences in age distribution. Lastly, these observations may also be due to exogenous risk factors, such as occupation. Additional study of genetic, molecular and environmental factors is necessary to better understand the relationship of sex to the development of CD.

Diagnostic delay is an important barrier to appropriate treatment for patients with dystonia, but few studies have characterized the magnitude of this obstacle. Our study suggests a greater percentage of misdiagnosis than prior studies, with 50% of patients endorsing harmful effects due to the delay.[3, 27, 28] The consequences of diagnostic delay can be severe and include unnecessary healthcare costs, such as inappropriate testing and treatment. There are many reasons for CD delayed diagnosis, including mild or slowly progressive symptoms, fluctuation of symptoms not seen during a physician visit, focus by the physician on managing pain rather than the underlying cause of pain, and misdiagnosis as a psychogenic illness[28, 29]. Even in healthcare systems with equal access to care, such as KPNC, delayed diagnosis remains an important barrier. Given the significant improvement in health-related quality of life in patients who receive botulinum toxin therapy for dystonia, it is imperative that physicians maintain a high level of suspicion for CD when examining a patient with neck muscle spasm.[30, 31]

Possible interventions to mitigate diagnostic delay include more robust education on diagnosing dystonia in medical school or through continued medical education courses.

Participants in this study were given multiple diagnoses preceding the diagnosis of CD. These alternate diagnoses may reflect comorbid conditions, diagnostic errors or etiologic factors. For example, depression and anxiety could represent a misattribution of CD symptoms to a psychogenic cause, or may reflect the prominent mood disorders that can accompany a disabling neurological disease.[28, 32] Potential triggers of CD in the literature include peripheral trauma, such as neck sprain or whiplash.[21, 33-35] We found that patients diagnosed with CD were significantly more likely to be diagnosed with cervical disc disease or neck trauma preceding CD diagnosis compared with controls. A relationship between peripheral trauma and development of CD has been previously observed,[35-37] such as in one case-control study, where 16 of 95 respondents reported a history of injury within four weeks of CD development.[38] The pathophysiology of a peripherally – rather than centrally – mediated association remains unclear, and there continues to be debate regarding its existence.[39] One possibility is a gene-environment interaction, where the peripheral trauma incites development of CD in someone with a genetic predisposition.[40, 41] Aberrant peripheral inputs – such as from trauma – may provoke reorganization of neuronal circuitry more centrally.[41, 42] There is suggestion that patients with dystonia have aberrant synaptic plasticity mediated by acetylcholine resulting in altered basal

ganglia networks.[43] It is also possible that pain secondary to CD resulted in neck imaging that revealed cervical disc disease, which is common in the general population, and so this radiographic finding may be present but not contributory. Overall, the relationship between peripheral trauma and dystonia remains a challenging topic to study due to recall bias, and cause-effect bias -- for example, unrecognized dystonia may result in injury, rather than the converse. A larger prospective study is warranted to better elucidate this potential association.

This investigation includes several strengths. We chose to minimize survival bias and differences in diagnostic practices by studying incident cases of CD during a specified five-year period rather than all prevalent CD cases. Our strict case definition and physician review of all suspected cases minimized the false-positive rate. In addition to its large size, there are many advantages to studying CD in the KPNC population. All Kaiser Permanente members receive essentially equal access to health care and membership is precisely enumerated. Members benefit from equal access to expert care, including movement disorders specialists. The multiethnic KPNC cohort is demographically similar to the non-Kaiser Permanente population,[18] maximizing the generalizability of our findings. Centralized data collection within the Division of Research that spans across the Kaiser Permanente organization is another strength.

This study has several limitations. We did not conduct population-wide examinations, so individuals never diagnosed are not included in our study.

This may result in an underestimation of CD incidence. The sample sizes for racial groups other than Caucasian were small and the categories were broad – for example, the classification of Asian within KPNC includes persons from multiple regions including the Indian subcontinent and the Pacific Islands – limiting our conclusions on racial differences. Lastly, our questionnaire characterizing diagnostic delay, mailed to the 114 of the 200 CD cases we had permission to contact, was only answered by 58 cases. This is a potential source of bias as there is a possibility of over- or underestimating the burden of delay.

In conclusion, cervical dystonia is a disease with a female and Caucasian preponderance, with an incidence that increases with age. Despite increased awareness of this common movement disorder, there remain significant delays with diagnosis and treatment for patients with CD. Quality of life can greatly improve with simple therapies. Education of primary care physicians and general neurologists on recognition of CD, and screening tools with increased sensitivity and specificity, are needed to assist with making an accurate and timely diagnosis in this vulnerable patient population.

AUTHOR CONTRIBUTIONS

S.C. LaHue: Acquisition, analysis, or interpretation of data, drafting of the manuscript; critical revision of the manuscript for important intellectual content

K. Albers: Conception or design; acquisition, analysis, or interpretation of data; critical revision of the manuscript for important intellectual content; statistical analysis

S. Goldman: Conception or design; acquisition, analysis, or interpretation of data; critical revision of the manuscript for important intellectual content; no additional contributions

R. Lo: Acquisition, analysis, or interpretation of data; critical revision of the manuscript for important intellectual content; no additional contributions

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A. Leimpeter: Acquisition, analysis, or interpretation of data; critical revision of the manuscript for important intellectual content; administrative, technical, or material support; supervision

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C. Tanner: Conception or design; acquisition, analysis, or interpretation of data, drafting of the manuscript, critical revision of the manuscript for important intellectual content, obtaining funding, supervision

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FIGURES

Figure 1. Case identification process for patients with cervical dystonia (CD) obtained from a multiethnic membership of a health maintenance organization in Northern California.

Figure 2. Incidence of cervical dystonia by decade standardized to the US population during the year 2000.

TABLES

Table 1. Demographics of patients with cervical dystonia derived from the Kaiser Permanente electronic medical record.

Table 2. Characteristics of diagnostic delay in patients ultimately diagnosed with cervical dystonia derived from patient questionnaire.

Table 3. Consequences of diagnostic error derived from patient questionnaire.