Alzheimer's & Dementia: Diagnosis, Assessment & Disease Monitoring 4 (2016) 109-117

Diagnostic Assessment & Prognosis

Systemic and localized extra-central nervous system bacterial infections and the risk of dementia among US veterans: A retrospective cohort study

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Abstract

Introduction: Emerging evidence indicates associations between extra-central nervous system (CNS) bacterial infections and an increased risk for dementia; however, epidemiological evidence is still very limited.

Methods: This study involved a retrospective cohort of a national sample of US veterans ($N = 417{,}172$) aged $\geq$56 years. Extended Cox proportional hazard models adjusted for demographic characteristics and medical and psychiatric comorbidities determined the associations between systemic and localized extra-CNS bacterial infections occurring >2 years before the initial dementia diagnosis and the risk for dementia.

Results: Exposure to any extra-CNS bacterial infection was associated with a significantly increased risk for dementia (hazard ratio [HR] = 1.20 [95% confidence interval = 1.16–1.24]). Independently, septicemia (HR = 1.39 [1.16–1.66]), bacteremia (HR = 1.22 [1.00–1.49]), osteomyelitis (HR = 1.20 [1.06–1.37]), pneumonia (HR = 1.10 [1.02–1.19]), urinary tract infections (HR = 1.13 [1.08–1.18]), and cellulitis (HR = 1.14 [1.09–1.20]) were associated with a significantly increased risk for dementia.

Discussion: Both systemic and localized extra-CNS bacterial infections are associated with an increased risk for developing dementia.

Keywords: Dementia; Bacterial infections; Septicemia; Bacteremia; Pneumonia; Osteomyelitis; Urinary tract infections; Cellulitis; Veterans

1. Introduction

Dementia is a chronic degenerative disorder that is characterized by progressive global cognitive dysfunction. Emerging evidence from animal models indicates associations between extra-central nervous system (CNS) inflammatory events such as extra-CNS bacterial infections and the neuropathogenesis of dementia syndromes. For example, systemic inflammation—induced by extra-CNS injection of bacterial lipopolysaccharide—has been found to induce, potentiate, and exacerbate the development and propagation of dementia neuropathology in the brain of transgenic mice [1–4]. Moreover, experiments also indicate that extra-CNS inflammatory events can induce various cognitive decrements including impaired memory [4–6], attention [7,8], and executive functioning [8]. These findings suggest that extra-CNS bacterial infections could trigger, exacerbate, and potentiate the development and spread of dementia neuropathology, cause cognitive impairments, and possibly increase the risk for dementia among humans.

Indeed, emerging epidemiological research has linked extra-CNS bacterial infections to an increased risk for subsequent dementia among humans. For example, history of two or more extra-CNS infections was associated with a significantly increased risk for dementia among individuals aged 84 years or older [9], whereas collectively, previous

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http://dx.doi.org/10.1016/j.dadm.2016.08.004

hospitalization for cellulitis, urinary tract infections (UTIs), septicemia, and bacteremia was associated with a significantly increased risk for dementia in a community-based cohort [10].

Epidemiological evidence also shows significant associations between severe or systemic extra-CNS bacterial infections and increased risk for both cognitive impairments and dementia in humans. For example, sepsis significantly increased the risk for long-term cognitive moderate–severe cognitive impairments up to 8 years after the infection [11]. In addition, sepsis significantly increased risk for dementia among intensive care recipients after discharge (hazard ratio [HR] = 1.40 [95% confidence interval {CI} = 1.28–1.53]) [12].

Hospitalization for pneumonia has also been associated with a significantly increased risk for subsequent dementia [10,13], as has chronic osteomyelitis that was demonstrated in a retrospective cohort study involving 17,238 newly diagnosed patients and 68,944 age- and gender-matched controls (relative risk = 1.6 [95% CI = 1.4–1.83]) [14].

Nevertheless, the epidemiological evidence for the association between extra-CNS bacterial infections during adulthood and the risk of dementia is still very limited; thus, further investigation is required. Moreover, the independent associations between less severe localized (e.g., cellulitis and UTIs) and other outpatient extra-CNS bacterial infections on the risk for dementia remain undetermined. Prior research also lacked sufficient adjustment for psychiatric comorbidities such as posttraumatic stress disorder, depression, and psychotic disorders (e.g., bipolar disorder) that have been associated with the risk for infections [15–17] and dementia [18–21]. Thus, the purpose of this study was to conduct a comprehensive assessment of the associations between several systemic and localized extra-CNS bacterial infections including septicemia, bacteremia, pneumonia, osteomyelitis, septic arthritis, cellulitis, and UTIs and the risk for developing dementia in a national sample of United States (US) veterans with adjustment for demographic characteristics and medical and psychiatric comorbidities.

2. Methods

2.1. Study design and population

The study used a retrospective cohort study design. The sample population that comprised 3,139,780 veterans aged 56 years and older during fiscal year (FY) 2003 enrolled and receiving health care at any Veterans Health Administration (VHA) care facility in the US veterans were excluded (Fig. 1) if 1) they died or had clinical encounters containing *International Classification of Diseases*—9th edition (ICD-9) diagnosis codes for dementia or mild cognitive impairment during the baseline observation period (i.e., from October 01, 2002 through September 31, 2004); 2) had less than one VHA encounter every 2 years during the follow-up period (FY 2004–2012); and 3) had an ICD-9 code (Appendix A, Table A.1) for other neurodegenerative disorders, cancer, chronic inflammatory diseases, or conditions associated with potentially reversible or non-neurodegenerative cognitive impairments at any time during the study period. Thus, the final sample consisted of 417,172 veterans with complete information on all variables of interest. The Institutional Review Board of the University of Iowa and the Research and Development Committee of the Iowa City Veterans Affairs Health Care System reviewed and approved this study.

2.2. Data sources

Data were derived from the VHA national repository of databases including 1) the Patient Treatment File (PTF) Bed Section Files and 2) the Outpatient Care Files (OCF). The PTF Bed Section Files identify all VHA inpatient admissions and include data elements such as demographic characteristics and principal and secondary ICD-9 diagnoses. The OCF database contains data including demographic characteristics and principal and secondary ICD-9 diagnoses for each outpatient encounter at all VHA facilities. Unique identifiers allowed the linkage of the individual databases to create a comprehensive longitudinal medical record for each subject's health and health-care utilization.

2.3. Diagnosis of extra-CNS bacterial infections

Systemic and localized extra-CNS bacterial infections of interest included septicemia, bacteremia, pneumonia, osteomyelitis, septic arthritis, UTI, and cellulitis and were diagnosed using ICD-9 diagnosis codes [22,23] (Appendix A, Table A.2) in the PTF Bed Section Files and OCF. All participants with ICD-9 diagnosis codes for the extra-CNS bacterial infections of interest either as primary or as secondary diagnosis during the follow-up period were classified as having an extra-CNS bacterial infection. To account for the association between preclinical (or the delayed diagnostic recording of) dementia and the increased risk of certain extra-CNS bacterial infections, only infections occurring >2 years before the date of the first dementia diagnosis were considered among participants with a diagnosis of dementia. Controls were participants without a diagnosis of an extra-CNS bacterial infection during the study period.

2.4. Follow-up and censoring

We collected data from the veterans' medical records until a code for dementia was identified in the medical record or until they were censored. Veterans were considered censored if they 1) did not develop dementia by the end of the 9-year follow-up period, 2) ceased to have any contact with a VHA facility during the follow-up period, or 3) died during the follow-up period.

2.5. Dementia diagnosis

The diagnosis of dementia was determined from the PTF Bed Section Files and OCF using ICD-9 diagnosis codes for