VA RR&D Merit Review

Project Title: Longitudinal Changes in Auditory Function Among Veterans with Diabetes (#3422)

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Objectives: Goals of our ongoing research include providing benchmark measures of longitudinal declines in auditory function at peripheral, central, and cognitive levels of processing, and their influence on auditory perception and quality of life. Previously published results from our group demonstrate effects of diabetes at peripheral and central-auditory processing levels found in Veterans under age 50 that are more typical of changes from presbycusis among non-diabetics who are much older. Though our current grant provides longitudinal contrasts over a 3 year period in a group of 150 Veterans, approximately half with diabetes, measures over a longer period are necessary to precisely benchmark prevalence rates of diabetes-related auditory impairments, age of auditory dysfunction onset and changes in the magnitude of effects over time. Proposed research will address 3 objectives. **Specific Aim 1:** Contrast presbycusis among non-diabetics with accelerated presbycusis from DM, including differences in temporal processing ability. **Specific Aim 2:** Determine the extent that an animal model corroborates the hypothesis that microvascular changes are an important cause of change from DM in the stria vascularis and auditory nerve, and whether these changes are associated with declines in brainstem temporal processing. **Specific Aim 3:** Determine the DM-related characteristics and comorbidities that are risk factors for premature auditory system senescence, and thus distinguish the DM phenotype that includes auditory disability.

Plan: We propose a continuation project to maintain longitudinal surveillance measures of auditory function and DM in the valuable cohort of younger Veterans participating in our current study and to expand the hearing range surveilled to more precisely define the auditory system consequences of DM in a typical Veteran primary care population. In order to determine the specific physiologic and histologic mechanisms of DM-related auditory dysfunction and how they interact with the onset and progression of age-related hearing loss, we also plan a concurrent biological program of research of type 2 DM (C57 mice fed a high-fat diet). Mouse data will augment the physiological and perceptual information obtained non-invasively in humans, and will facilitate understanding of associated vasculature and histological changes affecting the inner ear.

Methods: Human Subjects. A total of 176 participants will be newly recruited or re-recruited from a pool of participants in our ongoing longitudinal study and/or in two previous cross-sectional studies of DM and hearing loss at the NCRAR. Part of this new group will be chosen from specific categories of DM, age, and hearing ability. Exclusion criteria are: (1) active ear pathologies; (2) history of treatment for cancer, multiple sclerosis or other neurologic diseases; (3) use of medication that might impact assessment of auditory function or ability to perform experimental tasks (e.g., medication that the subject reports causes him/her to feel drowsy or confused); inability to complete the auditory assessment or experimental tasks (e.g., non-English speaking or those with dementia). We will perform audiometric tests bilaterally to quantify hearing. We plan to continue with fruitful peripheral and central-auditory measures (distortion-product otoacoustic emissions and auditory brainstem responses, cortical evoked potentials), and will add a new temporal processing test. We will continue time compressed speech testing, but will add a speech-related release from spatial masking test sensitive to deficits in auditory temporal and spectral encoding. Finally, we will continue to behaviorally measure auditory working memory and sequencing ability. Participants will complete a questionnaire to determine DM-related disease and treatment history. Foot neuropathy testing will be done using standard methodology. From computerized medical charts, laboratory tests, including interim HbA1c, urinary microalbumin, and clinical exams, including retinal findings will be obtained. **Mice.** C57/B6 mice fed a high fat diet for 6 wks usually develop type 2 DM. However we plan to alter the administration of the diet to begin 6 wks prior to the time when age-induced presbycusis typically affects the C57/B6 mouse. Hearing will be assessed using ABR at five frequencies from 8 to 40 kHz as well as gap detection using tone burst stimuli. Blood and urine samples will be taken at 2 week intervals for determination of fasting HbA1c, blood glucose levels, cholesterol panel as well as urinary microalbumin and creatinine levels. An age-matched cohort fed a normal mouse diet will undergo the same testing. Measures of cochlear histology include ultrastructural analysis with transmission and scanning electron microscopy as well as immunohistochemistry for markers of microvascular and neural/synaptic pathologies.

Finding to Date: This is a new project.

Clinical Relevance and Relevance to VA's Mission

DM is a metabolic syndrome affecting 20-30% of Veterans receiving care at VA producing devastating complications of vascular and neurologic malfunction. Hearing loss is one of the most common service-related disabilities and can lead to communication difficulties that result in problems with employment, social isolation, depression, and overall reduced quality of life. Hearing loss could be particularly disabling among individuals

with diabetes because of the insidious nature of even a mild hearing loss when combined with central-auditory and cognitive declines, and due to the potential for dual sensory loss of vision and hearing in this population. Information gained from this research will guide future decisions as to how to diagnose and rehabilitate communication impairment and whether to routinely screen for it in Veterans with diabetes. If successful, it will also provide information about specific mechanisms that lead to DM-related auditory dysfunction, which is necessary to prevent or delay the increased burden of hearing loss among Veterans with DM.

MESH Terms: Diabetes, hearing loss, auditory nerve, central-auditory processing, cognition