F4-01-04 MITOCHONDRIA-TARGETED MOLECULES AS POTENTIAL THERAPEUTIC TARGETS

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Background: Mitochondrial damage and synaptic dysfunction are prominent and early cellular changes in Alzheimer's disease (AD) pathogenesis. The purpose of our study was to investigate, if mitochondria-targeted molecule, SS31 could be a potential therapeutic drug for AD. **Methods:** The efficacy of mitochondria-targeted molecule SS31 was tested using amyloid precursor protein (APP) transgenic mouse model (Tg2576 line) that overexpresses human APP_{swe} mutation. APP mice were administered intraperitoneally (twice a week) with SS31 (2mg/kg body weight) for 5 months. The control APP mice were administered with phosphate buffered saline. After 5 months treatment, animals were euthanized and cortex/hippocampus were collected for immunoblotting, immunohistochemistry and biochemical analyses. We studied soluble Abeta (1-40 and 1-42) levels and Abeta deposits as well as BACE1 expression/activity and synaptic and mitochondrial proteins. **Results:** Our sandwich ELISA, immunoblotting and immunohistochemistry, and biochemical analyses revealed decreased levels of soluble Abeta, Abeta deposits in SS31 treated APP mice relative to untreated, control APP mice, indicating that SS31 has ability to reduce not only soluble Abeta (1-40 and 1-42) levels but also Abeta deposits. The BACE1 expression and activity levels were found to be reduced, and synaptic proteins, synaptophysin and PSD95 were found to be increased in SS31 treated APP mice relative to untreated APP mice. Further, Abeta degrading enzyme, NEP, was present more in SS31 treated APP mice. Mitochondrial fission proteins, Drp1 and Fis1 were reduced and fusion proteins (Mfn1, Mfn2 and Opa1) were increased in SS31 treated APP mice. These findings suggest that SS31 decreases Abeta levels, prevents mitochondrial fragmentation and enhances synaptic activity and maintains function of AD neurons. **Conclusions:** Overall, these findings suggest that SS31 reduced Abeta toxicity, which warrants the study of SS31 as a therapeutic drug to treat patients with AD.

WEDNESDAY, JULY 27, 2016
FEATURED RESEARCH SESSIONS
F4-02
RISK DISCLOSURE IN THE ERA OF ALZHEIMER'S PREVENTION STUDIES: AN INTERNATIONAL PERSPECTIVE

F4-02-01 CONNECT 4 *APOE*: A RANDOMIZED STUDY OF PHONE VERSUS VIDEOCONFERENCE DELIVERY OF *APOE* GENOTYPE DISCLOSURE IN THE GENERATION STUDY

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Background: The Alzheimer's Prevention Initiative Generation Study is enrolling *APOE e4* homozygotes age 60-75 YO and includes standardized disclosure of Alzheimer's disease risk by *APOE* genotype. Given the potential psychosocial risks and the complexity of genetic information and communication of probabilistic risk, genetic testing for disease predisposition has traditionally included in-person genetic counseling. However, some participating sites do not have genetic providers to provide counseling and test disclosure to study participants. Building off an established program for providing remote genetic counseling for hereditary cancer syndromes, The University of Pennsylvania Telegenetics Program will provide remote genetic counseling and *APOE*genotype disclosure at participating sites in the United States. Both telephone and two-way real-time videoconferencing (RTVC) have been shown to be feasible for remote delivery of genetic services, but outcomes have not been compared in a randomized trial. **Methods:** CONNECT 4 *APOE* is a multi-site randomized study to evaluate the relative short-term and longitudinal advantages of real-time two-way videoconference communication over telephone for participants who are receiving remote genetic services for disclosure of *APOE* genotype results within a large clinical trial. Participants include individuals receiving *APOE*genotype disclosure as a first step in the Generation Study. Genetic counselors will utilize standardized counseling checklists, risk estimates and visual aids for communication of genotype. **Results:** The Generation Study launched in November 2015; enrollment, genetic testing and disclosure are ongoing. The CONNECT 4 *APOE* Study is anticipated to launch in early 2016. Primary outcomes include change in genetic knowledge, disease-specific distress and satisfaction with genetic services. Secondary outcomes will include state anxiety, depression, uncertainty and psychosocial and behavioral responses to genotype disclosure. Preliminary experience and results from this study will be presented. **Conclusions:** As preventive therapies for Alzheimer's disease are developed, clinical providers will be increasingly asked to identify and counsel at-risk individuals, which will likely include genetic testing and counseling. We expect the findings from this randomized study to contribute significantly to the debate over optimal delivery models of genetic information for precision medicine and specifically to the eventual clinical implementation of *APOE* testing to benefit individuals and families at risk for Alzheimer's disease.

F4-02-02 RISK DISCLOSURE IN AD: THE PERSPECTIVE OF THE EUROPEAN PREVENTION OF ALZHEIMER'S DEMENTIA CONSORTIUM (EPAD)

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Background: The shift to focus on prodromal or 'preclinical' stages of Alzheimer's disease is associated with significant ethical challenges, including but not limited to the implications of learning AD risk status (Karlawish 2011). Within the interdisciplinary Ethical, Legal and Social implications workpackage of the European Prevention of Alzheimer's Dementia (EPAD) project we studied the effect of AD risk disclosure and developed ethics guidelines for the EPAD longitudinal cohort study and subsequent Proof of Concept trial. **Methods:** We used mixed methods. Firstly, we performed a systematic review of the literature on risk disclosure for AD. Secondly, we met several times in person and through teleconferences during 2015 to discuss ethical dilemmas encountered. Thirdly, we conducted pilot qualitative research in the UK and Spain. For this latter, eight focus groups (total n=49) were conducted with participants in cohort studies to explore attitudes, preferences and concerns related to AD risk disclosure. **Results:** Most studies we found on risk disclosure are performed in the USA. All studies involved APOE genotype risk disclosure. We did not