Title

39.1 DNA METHYLATION OF IMMUNE CELLS IN PERSONS AT CLINICAL HIGH RISK FOR PSYCHOSIS

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Faith Dickerson will focus on the association between HSV1 exposure and cognitive impairment in schizophrenia and the potential link between EBV and this illness. In a large cohort of 828 individuals and 573 controls, a significant relationship between HSV1 exposure and cognitive impairment was found. The strongest linkage was in the domain of immediate memory. In 397 subjects with schizophrenia who were compared to 289 controls, significantly higher levels of antibodies to the EBV viral capsid antigens (VCA) was discovered in the schizophrenia cohort.

Vishwajit Nimgaonkar will examine the relationship between HSV1 infection and cognitive performance in a mixed cohort of 226 individuals and present the results of a randomized clinical trial of the anti-viral agent valacyclovir. HSV1 infected participants had significantly lower scores on Emotion Identification and Discrimination (EMOD), spatial memory and spatial ability irrespective of schizophrenia diagnoses. Valacyclovir treatment (1.5 grams BID, 16-week trial) improved EMOD.

Alan Breier will report the results of the VISTA study – 12-site, double-blind, placebo controlled, 16-week trial of the anti-viral medication valacyclovir (3 grams/day) in early phase schizophrenia. 170 subjects were randomized of whom 74 were HSV-1 seropositive and 96 were seronegative. Baseline working memory scores (letter number sequence) were significantly lower in HSV1 positive as compared to HSV1 negative subjects. Analysis of valacyclovir treatment outcomes have only recently commenced and are ongoing. The complete data set (cognitive domains, role function, symptoms and safety) will be presented in full at the meeting.

39.1 DNA METHYLATION OF IMMUNE CELLS IN PERSONS AT CLINICAL HIGH RISK FOR PSYCHOSIS

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Background: A dysregulated immune system is implicated in the development of psychotic disorders. Persons with schizophrenia have altered levels of circulating immune cell signaling molecules (cytokines), and elevation of specific cytokines predict conversion to psychosis in persons at clinical high risk. Whether these peripheral signals are a causal or a secondary phenomenon is unclear. But, subpopulations of circulating immune cells do regulate the brain from meningeal and perivascular locations influencing cognition, mood, and behavior, and thus may be relevant to schizophrenia vulnerability. Hematopoietic stem cells in the bone marrow differentiate into cascading subtypes depending on signals from other organs, especially the brain. For example, a monocyte subpopulation emerges with repeated social defeat that establish the persistence of anxiety-like behaviors; blocking their release or inhibiting their attachment to brain vascular endothelium prevents the emergence of anxiety-like behaviors. In humans, a similar monocyte subpopulation is associated with social isolation and other adversities including low SES, chronic stress, and bereavement.

Methods: The North American Prodrome Longitudinal Study (NAPLS2) is an eight-site observational study of predictors and mechanisms of conversion to psychosis The full cohort includes 763 at clinical high risk (CHR) based on the Criteria of Prodromal State (COPS) and 279 demographically similar unaffected comparison (UC) subjects. Methylation of whole blood DNA collected in PAXgene tubes at baseline was analyzed with the Illumina 450k array in a subgroup of 59 subjects who converted to psychosis (CHR-C), 84 CHR subjects followed for 2 years who did not develop psychosis (CHR-NC) and 67 unaffected subjects (UC). Our analyses focused on methylation of promoter regions of genes, associated with gene expression. Classifier construction used Coarse Approximation Linear Function (CALF) with bootstrapping of 1000 random 80% subsets with replacement to determine statistical likelihood.

Results: We found highly overlapping sets of differentially methylated promoter regions in CHR-C subjects compared to CHR-NC and to UC subjects. A set of 10 markers correctly classified CHR-C and CHR-NC subjects with high accuracy (AUC=0.94, 95% CI 0.89–0.98). Included was SIRT1, a gene that is upregulated with HSV reactivation.

Discussion: Circulating immune cells excerpt powerful influences on mood, cognition and behavior. An obvious example is the experience of most human with "sickness syndrome", characterized by apathy, avolition, and withdrawal, and triggered by immune-cell-released cytokines producing an adaptive, resource conserving, behavioral response. While at an early stage, our findings further implicate immune system dysregulation as a mechanism in the development of psychosis.

39.2 VIRAL EXPOSURES AND SCHIZOPHRENIA

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Background: Epidemiological, immunological, and microbiological studies indicate that infections with members of the family Herpesviridae may be associated with schizophrenia and with cognitive impairment. Herpesviruses are enveloped, double-stranded DNA viruses which are widely prevalent and which are capable of causing persistent infections. The most highly replicated association is that between the alpha herpesvirus Herpes Simplex Virus Type 1 (HSV-1) and cognitive impairment in schizophrenia. Acute HSV-1 infection results in oral lesions which usually resolve spontaneously. However, latency can occur in nerve root ganglia leading to cycles of reactivation in later life. Other herepsviruses may also be associated with schizophrenia. Epstein Barr virus (EBV) is a gamma herpesvirus usually acquired in childhood or adolescence. Acute EBV infection is often associated with fever and adenopathy leading to a vigorous immune response and the suppression of viral replication. However, latency can occur with long term consequences to the infected individual.

Methods: We examined the association between HSV-1 seropositivity and cognitive functioning in 828 individuals with schizophrenia from the Sheppard Pratt cohort and 573 control individuals. We also studied antibodies to EBV in a recently enrolled subset of the Sheppard Pratt cohort consisting of 397 individuals with schizophrenia and 289 without a psychiatric disorder. Antibodies to HSV-1 and EBV proteins were measured by immunoassay and confirmed by Western blot. Cognitive functioning was measured by the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS). Regression models were employed to define the independent association between virus exposure and outcome.

Results: Serological evidence of exposure to HSV-1 was associated with significantly lower levels of cognitive functioning as measured by the RBANS Total score (coefficient =-3.84, 95% CI -5.60, -2.09, p<.0001). The strongest association was in the domain of Immediate Memory (coefficient= -4.95, 95% CI -7.24, -2.66, p<.0001.) There was a smaller but statistical significant relationship between serological evidence of exposure to HSV-1 and RBANS Total score in control individuals. (coefficient =-1.98, 95% CI -3.88, -.094, p=.04).

In terms of EBV, we found that individuals with schizophrenia had significantly higher levels of antibodies to the EBV viral capsid antigens (VCA) as compared to controls (coefficient= .57, 95% CI .37- .77, p<1.7 10-8). On the other hand, the level of antibody to the EBV Nuclear Antigen (EBNA) and EBV Early Antigen (EA) did not differ between the groups. Within the schizophrenia group, increased levels of EBV VCA antibodies were associated with older age, female gender, and cigarette smoking but not with clinical or cognitive measures.

Discussion: The mechanism of the association between HSV-1 exposure and cognitive deficits in individuals with schizophrenia may be due to