1) Inadequately fine-grained phenotyping of subjects
2) Ignoring the important moderating role of BBB permeability
3) Choosing subjects at 'too late' a stage of illness
4) Inadequately sensitive antibody detection assays

38.3 ONGOING GERMINAL CENTRE REACTIONS CONTRIBUTE TO N-METHYL-D-ASPARTATE RECEPTOR (NMDAR) ANTIBODY PRODUCTION IN NMDAR-ANTIBODY ENCEPHALITIS

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Background: Immunoglobulin G (IgG) against the NR1-subunit of the N-methyl-D-aspartate (NMDAR) receptor mediates NMDAR-antibody encephalitis (NMDAR-Ab-E). This multi-stage illness presents with an acute severe psychiatric syndrome, alongside other neurological features, similar to human and animal NMDAR antagonist models. The disease is associated with an ovarian teratoma in around 20% of cases. The cellular immunity underlying this disease is not well understood. While antibody-modifying immunotherapies often promote disease resolution, the illness can be refractory to these treatments correlating with sub-optimal outcomes.
NR1-IgG can be detected several years after clinical resolution, which may be via ongoing germinal centre reactions or the establishment of antibody-secreting cells as long-lived plasma cells in bone marrow niches. These two divergent models implicate use of differing immunotherapies to target these cells. Here we investigate the contribution of ongoing germinal centre reactions to disease progression, potentially informing disease mechanisms and guide targeted immunotherapy.
Methods: We hypothesised that recurrent antigen-driven germinal centre reactions would be associated with active generation of NR1-specific IgM and IgG and NR1-specific circulating B cells. We validated a NR1-IgM cell based assay establishing specificity cut-offs by screening healthy and disease control cohorts alongside a previously collected NMDAR-Ab-E cohort (n=46). Following this we went on to explore the temporal evolution of NR1-IgG and NR1-IgM titres in a prospective cohort (n=12).
To investigate the lymphocyte characteristics, we stimulated ovarian teratoma lymphocytes and peripheral blood mononuclear cells (PBMCs) from multiple time points under varying cytokine conditions to understand whether these circulating cells showed capacity for NR1-IgG and IgM generation.
Results: We found a 43% prevalence rate of NR1-IgM in the historic cohort. We then confirmed that NR1-IgM binding was specific by its selective depletion after anti-IgM precipitation but not with protein G. In the prospective cohort, we noted often high titres of IgM (up to 1:500) most commonly early in the disease but persisting for around 2 years. NR1-IgM levels varied in titre alongside NR1-IgG spikes. Consistently, culture experiments of patient lymphocytes (PBMCs and tumour-derived) produced varying degrees of NR1-IgM and NR1-IgG under conditions associated with B cell proliferation. The NR1-IgG levels correlated with serum NR1-titres suggesting these circulating B cells made a proportional contribution to serum levels.
Discussion: Ongoing germinal centre reactions likely contribute much of the circulating NR1-specific B cell population in NMDAR-Ab-E. Autoimmunisation at these centres represents an as yet unexplored therapeutic target in this and potentially other autoimmune encephalopathies. Regional specificity of these reactions including lymph nodes draining sources of NR1-antigen require further direct evaluation.

38.4 PREVALENCE OF ANTI-NEURONAL ANTIBODIES IN PATIENTS ADMITTED WITH FIRST EPISODE OF PSYCHOSIS AND THEIR CLINICAL OUTCOMES

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Background: Anti-neuronal antibodies are associated with psychosis although their clinical significance in first episode of psychosis (FEP) is undetermined. This study examined the prevalence of anti-neuronal antibodies in patients admitted to hospital for treatment of their first episode of psychosis and described clinical presentations and treatment outcomes of those who were antibody positive.
Methods: Between July 2013 and May 2015, all consenting patients aged between 12 and 50 admitted for their first episode of psychosis to three mental health hospitals in Queensland, Australia, were tested for anti-neuronal antibodies in serum. Antibody positive patients were referred for neurological and immunological consultation and treatment.
Results: During the study, 154 FEP patients were admitted with their first episode of psychosis and 113 consented to participate. Six patients were found to have anti-neuronal antibodies; (anti-NMDAR antibodies [n = 4], VGKC antibody [n = 1], antibody against uncharacterised antigen [n = 1]). Of these, five received immunotherapy, leading to complete resolution of psychosis in four.
Discussion: A small, but significant subgroup of patients with first episode psychosis have anti-neuronal antibodies detectable in serum and evidence of central nervous system autoimmune pathology. Early identification of these patients and referral for appropriate treatment is critical to optimise recovery.

39. VIRUSES AND SCHIZOPHRENIA: IMPLICATIONS FOR PATHOPHYSIOLOGY AND TREATMENT

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Overall Abstract: The viral hypothesis of schizophrenia posits that viral infections disrupts cortical circuits that give rise to schizophrenia psychopathology. Prenatal viral exposure during key neurodevelopmental periods, either through direct effects on fetal brain or exposure to excessive maternal cytokines and other chemokines, have been implicated. In addition, abnormal activation of dormant neuro-viruses have been linked to the pathophysiology of schizophrenia. Activation of dormant viruses has potentially important treatment implication for therapies, such as valacyclovir, that suppress viral activity. Among the viruses that have been mostly frequently associated with schizophrenia include herpes simplex virus type 1 (HSV1) and Epstein-Barr virus (EBV). The purpose of this symposium is to focus on the role of viruses in the pathophysiology of schizophrenia and results of antiviral treatment trials in this illness.
Diana Perkins will present data from the North American Prodrome Longitudinal Study (NAPLS2) which is an eight-site observational study of predictors and mechanism of conversion to psychosis and is comprised of a cohort of 763 individuals at clinical high risk for developing psychosis. This paper examines methylation of promoter regions of genes associated with gene expression and reports that 10 markers correctly classified individuals who converted to psychosis. The SIRT1 gene, that is upregulated with HSV, was among the predictive markers.

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