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agents to improve symptoms of schizophrenia. This study provides an update regarding the efficacy of anti-inflammatory agents on schizophrenia symptoms in clinical studies performed so far.

**Results:** Our research yielded 26 double blind RCTs that provided information on the efficacy on symptom severity of the following components: asparin, celecoxib, davaunetide, EPA/DHA fatty-acids, estrogens, minocycline and N-acetylcycteine (NAC). Of these components asparin (mean weighted effect size (ES) 0.3, 95% CI 0.06-0.537, I²=0%), estrogens (ES 0.51, 95%CI 0.043-0.972, I²=69%) and NAC (0.45, 95% CI 0.112-0.779) showed significant effects. Celecoxib, minocycline, davaunetide and fatty acids showed no significant effect.

**Conclusion:** The results of aspirin addition to antipsychotic treatment seem promising, as does the addition of NAC and estrogens. These three agents are all very broadly active substances and it has to be investigated if the beneficial effects on symptom severity are indeed mediated by their anti-inflammatory aspects.

**SERUM BIOMARKERS FOR PSYCHIATRIC DISORDERS**

Sabine Bahn1,2

1Department of Chemical Engineering and Biotechnology, University of Cambridge, Cambridge, UK; 2University of Rotterdam

**Objective:** Schizophrenia is a heterogeneous disorder traditionally diagnosed using DSM criteria, which do not necessarily reflect potential differences in underlying molecular phenotypes. I will present results exploring whether schizophrenia patients can be divided into subgroups with distinct molecular alterations in growth factors or immune molecules.

**Method:** Multiplexed immunoassays were used to measure 147 molecules in the serum of 180 acutely ill antipsychotic-naive schizophrenia patients and 250 controls. 50 of these molecules were related to growth factor and immune pathways and were selected for a hypothesis driven approach to identify subgroups within the schizophrenia cohort. This analysis aimed to evaluate whether each patient subgroup had specific abnormalities in molecules associated with the two molecules classes.

**Results:** Schizophrenia patients could be separated into two significantly distinct subgroups each of which demonstrated predominant molecular abnormalities in either growth factors or immune molecules. Immune molecules were largely increased whereas growth factor levels showed both increased and decreased levels in the respective patient subgroups. Findings were validated in an independent validation cohort.

**Conclusion:** This study suggests that abnormalities in growth factors and immune molecules, which have been associated reproducibly with the molecular manifestation of schizophrenia, do not coincide in the same group of patients. This may be of relevance for intervention studies that specifically target particular molecular mechanisms and could be a first step to deconstruct the complex schizophrenia syndrome based on molecular alterations.

**THE MICROBIOME-THE MISSING LINK IN THE PATHOGENESIS OF SCHIZOPHRENIA**

Robert Yolken1, Faith Dickerson2

1Johns Hopkins School of Medicine; 2Sheppard Pratt Hospital, Baltimore, MD, USA

Recent studies indicate that individuals with schizophrenia have evidence of immune activation that may contribute to disease pathogenesis. The source of this immune activation has not been identified but is likely to be related to both genetic and environmental components. Recently it has become apparent that the composition of microbes on mucosal surfaces, termed the microbiome, represents an important modulator of the immune response in humans and in experimental animals. The microbiome has been linked to the generation of an aberrant immune response and also been shown to modulate brain development and behavior in animal model systems. We employed high throughput sequencing to characterize the complete oropharyngeal microbiome of 41 individuals with schizophrenia and 32 controls without a psychiatric disorder. We also examined the role of probiotics in modulating the microbiome. Interim analysis indicates that there are large differences between case and control individuals in terms of bacterial, viral, and fungal composition. Individuals with schizophrenia had increased levels of lactic acid bacteria including Lactobacillus casei, Lactobacillus salivarius, Lactobacillus lactis, and Streptococcus thermophilus as well as several other species of streptococci including 5 mitis and 5 mutans. Several of these bacteria have been associated with altered Th2 immune responses, an immunological change also noted in schizophrenia. On the other hand individuals with schizophrenia had decreased levels of many non-pathogenic bacteria such as strains of Neisseria, Haemophilus, Prochlororococcus, and Shewanella. Within the group of individuals with schizophrenia, altered levels of microorganisms were associated with an increased prevalence of the deficit syndrome as well as increased levels of intestinal immune activation as indicated by antibodies to food and intestinal antigens. In terms of fungi, individuals with schizophrenia had higher levels of pathogenic yeasts such as Candida glabrata and Candida tropicalis, but lower levels of the relatively less pathogenic Candida albicans. We also characterized a number of known human viruses such as Herpesviruses and Papillomaviruses, as well as bacteriophages and novel viruses. The microbiome was significantly altered by probiotic therapy, with a tendency towards normalization following treatment. Furthermore, many of the species which are increased in the oral microbiome of individuals with schizophrenia, such as streptococci, are modifiable by the administration of antibiotic medications. These studies indicate that the oral microbiome is altered in individuals with schizophrenia and that the microbiome is a potential target for novel therapies.

**INFECTIONS, INFLAMMATORY MARKERS AND SCHIZOPHRENIA**

Faith Dickerson, R.H. Yolken

Sheppard Pratt from Johns Hopkins University, Baltimore, MD

**Background:** A number of markers of infectious and inflammatory diseases have been associated with schizophrenia. However previous investigations have not yielded definitive conclusions about the role of these agents in disease pathogenesis. Previous studies have been limited by the examination of single or small groups of agents within a single population.

**Methods:** In this study, we examine multiple antibodies to infectious agents and food antigens as well as protein markers of inflammation in well-characterized cohorts of individuals with established schizophrenia (those with a duration of illness at least two years, N=261), individuals with a recent onset of psychosis (within the previous two years, N=106), and non-psychiatric controls (N=233). Some individuals had markers evaluated at several time points and some markers were not measured in some individuals due to limited sample volumes. Linear regression methods were used to calculate the association between the markers in recent onset and established schizophrenia patients in comparison with controls adjusting for demographic factors such as age, race, gender, and maternal education. Regression models were also adjusted for the performance of multiple measurements in samples obtained from the same individual at different time points.

**Results:** For the recent onset group, significant associations were found for IgG antibodies to measles (t=8.31, p<0.001), markers of intestinal inflammation, gliadin (t=5.90, p<0.001) and bovine casein (t=4.74, p<0.001); human coronavirus (t=2.89, p=0.004); Toxoplasma gondii (t=2.20, p=0.029), and the group D retroviruses, Mason-Pfizer monkey virus (t=3.97, p<0.001) and murine leukemia virus (t=3.27, p<0.001). For the established schizophrenia group, significant associations were found for a general marker of inflammation, C-reactive protein (t=7.47, p<0.001); IgG antibodies to wheat gliadin (t=2.58, p=0.010) and another marker of intestinal inflammation, Saccharomyces cerevisiae (t=3.78, p=0.006), measles (t=2.57, p=0.018), Herpes simplex virus type 2 (t=2.56, p=0.011), and human coronavirus (2.67 p=0.008). No significant case control differences were found in either group for IgG antibodies to cytomegalovirus, Epstein-Barr Virus, varicella-zoster virus, or influenza A or influenza B viruses. Case control differences were not found in the levels of antibodies to Herpes simplex virus type 1. However, antibodies to this virus were associated with lower
cognitive performance in the individuals with established schizophrenia and in controls.

Conclusions: These results indicate overlap between the markers of infectious and inflammatory diseases found in recent onset psychosis and those found in established schizophrenia. Markers of intestinal inflammation were elevated in both groups but a marker of systemic inflammation, C-reactive protein, was only elevated in the established schizophrenia patients. Future studies that assess patients from the start of the illness and throughout the illness course may further identify the infectious and inflammatory factors that contribute to disease pathogenesis.

NEUROINFLAMMATION IN TEMPORAL CORTEX OF PATIENTS WITH RECENT ONSET SCHIZOPHRENIA

Bart van Berckel
VUMc, Nucléaire geneeskunde & PET research

Background: There is increasing evidence that neuroinflammation is associated with schizophrenia. Neuroinflammation is characterized by the activation of microglial cells. Increased expression of the translocator protein is a biomarker for microglial activation and can be measured in vivo using the positron emission tomography ligand (R)-[11C]PK11195. The purpose of this study was to compare the regional distribution of (R)-[11C]PK11195 binding in schizophrenia patients with that in healthy controls.

Methods: (R)-[11C]PK11195 binding potential was studied in ten patients with recent onset schizophrenia and ten age-matched healthy controls. Psychopathology was measured using the Positive and Negative Syndrome Scale (PANSS). Dynamic (R)-[11C]PK11195 scans were acquired using an ECAT EXACT HR+ scanner. Binding potential was obtained using receptor parametric mapping in combination with supervised cluster analysis to derive the reference tissue input function. Subsequently, gray matter regions of interest (ROIs) were delineated on a T1-weighted structural MRI scan using an automatic procedure, resulting in the following regions: frontal, temporal, parietal and occipital cortex, and cerebellum. Multivariate analysis of variance (MANOVA) was used to test for differences in binding potential between patients and controls with group as the between-subjects factor, region of interest as the within-subjects factor, and age as covariate.

Results: MANOVA showed an overall significant effect of group (F(5)=5.7, p<0.005). Schizophrenia patients showed increased (R)-[11C]PK11195 binding potential in the temporal cortex (F(1)=5.5, p<0.03). There were no significant differences in mean (R)-[11C]PK11195 binding potential in the other areas tested. Patients with schizophrenia had minimal to moderate symptoms of the disease at the time of PET scanning (PANSS total score = 52.5±9.3).

Discussion: This study provides preliminary evidence for neuroinflammation in the temporal cortex of recent onset schizophrenia patients. This may provide an explanation for progressive tissue loss in this area in schizophrenia. Further studies are warranted to assess anti-inflammatory treatment in this disease. This is an ongoing study and results of a larger patient and control group will be presented.

IDENTIFYING BIOMARKERS OF RISK FOR AND PROGRESSION TO PSYCHOSIS USING HIGH-RISK STRATEGIES

Tyrone Cannon
Yale University

The nature of schizophrenia and related psychotic disorders is such that some factors that predispose to the illness are present premorbidly but do not change over time, while other factors show evidence of progression in the pre-onset and early phases of disorder. While at least some stable markers of risk may be necessary contributors, they are unlikely to be sufficient in provoking illness expression, given that they are present pre-onset and may also appear in clinically unaffected first-degree relatives. Markers that progress during the periods immediately preceding and following onset have the potential to play mechanistic roles in the emergence of psychosis – that is, they could represent proximal, sufficient conditions for psychosis onset – but this interpretation depends on the unambiguous dissociation of such factors as reflecting the natural course of illness rather than secondary (e.g., iatrogenic) phenomena. This talk will address criteria and research strategies used in the segregation of biomarkers of risk for versus progression to psychosis, using markers of brain structure, physiology, and metabolism as assessed by neuroimaging as primary examples and drawing upon recent evidence from genetic and clinical high-risk studies. This body of work supports that view that the emergence of psychosis is marked by a dynamic and potentially reversible process that results in a reduced structural and functional connectivity in circuits involved in cognitive control, learning and memory, emotional regulation, and auditory-verbal processing.

RELATIONSHIP BETWEEN BRAIN GLUTAMATE CONCENTRATIONS AND FUNCTIONAL OUTCOME IN INDIVIDUALS AT ULTRA HIGH RISK OF PSYCHOsis

Alice Egerton1, James Stone2, Christopher A. Chaddock3, Gareth J. Barker4, Ilaria Bonoldi5, Kate Merritt6, Paul Allen7, David J. Lythgoe4, Ruth L. O’Gorman4,5, Philip McGuire1

1King’s College London; 2Imperial College London; 3Department of Psychiatry Studies, Institute of Psychiatry, King’s Health Partners, King’s College London, UK; 4Department of Neuroimaging, Centre for Neuroimaging Sciences, Institute of Psychiatry, King’s College London, De Crespigny Park, London, UK; 5Institute of Psychiatry, King’s College London; 6MR-Center, University Children’s Hospital, Zurich, Switzerland

Background: There is increasing interest in predicting functional outcome in individuals at ultra high risk of psychosis (UHR). Magnetic resonance spectroscopy (1H-MRS) studies have indicated abnormalities in glutamate concentrations in UHR individuals. In this longitudinal study, we explored the associations between glutamate levels and functional outcome in UHR individuals.

Methods: 1H-MRS spectra (PRESS – Point REResolved Spectroscopy; TE=30 msec; TR=3000 msec; 96 averages) were acquired at 3 Tesla in voxels positioned in the anterior cingulate cortex (ACC) and left thalamus of 75 UHR participants at clinical presentation and again after a mean of 18 months. 56 age and gender-matched healthy volunteers were also assessed. Spectra were analysed with LCModel version 6.14F and metabolite concentrations were corrected for voxel cerebral spinal fluid content. Overall social