

- 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.