Synopsis for EU-GEI WP5 Publication

Synopsis no.: S5.14

Preliminary title:

Prevalence of anti-neuronal surface antibodies in people at ultra high risk (UHR) for psychosis: clinical significance, infective and inflammatory correlates and associated neuroimaging alterations

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Publication category: 3
Publications from a single work package involving only some parties (or in some cases only one party) in the Work Package

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Work Packages involved: WP5

EU-GEI Partners involved from whom candidate co-authors (*additional to working and writing group*) should be nominated: Interested parties from WP5

Objectives (scientific background, hypothesis, methods, and expected results):

Scientific background

Over the last decade there has been increasing recognition of encephalopathy syndromes caused by autoantibodies against neuronal surface targets such as the NMDA receptor (NMDAR), the voltage-gated potassium channel (VGKC) complex and the AMPA receptor. The resultant syndromes prominently feature *psychotic symptoms*, including catatonia, usually with neurological symptoms such as seizures or movement disorder. There is now evidence that these encephalopathies may present with a *purely psychiatric phenotype*. Additionally, studies of the prevalence (approx 5%) of these anti-neuronal surface autoantibodies (ANSAs) in individuals with schizophrenia or related psychoses, particularly first episode, **suggest that these antibodies can cause a clinical syndrome that *resembles first episode schizophrenia*** [1, 2]**.** A number of cases have now been described of patients with a diagnosis of psychosis (usually first episode) who have been found to be ANSA positive and have undergone immunotherapy with subsequent resolution of their psychosis ([3-5] Lennox et al., *in press*).

The current literature regarding ANSAs in psychosis is afflicted by considerable methodological heterogeneity, particularly with regards to the antibody assay used and which antibody subtype (IgG, IgM or IgA) is tested. Perhaps most concerning are recent highly divergent reports concerning the prevalence of ANSAs in healthy controls, with some studies reporting zero prevalence and others reporting comparable prevalence to psychiatric patients. Some authors have highlighted the importance of blood-brain barrier (BBB) dysfunction in determining whether peripheral antibodies can reach the CNS and exert pathogenic functional effects [6]; this may be the crucial step in explaining why healthy controls can harbour potentially pathogenic antibodies without showing signs of illness.

Putative markers of BBB dysfunction and CNS cell damage such as the glial protein S100B have been associated with psychosis, particularly first episode and acute relapses, although the literature is inconsistent [7, 8]. We suggest that one reason for this is the absence of robust *in vivo* measures of BBB dysfunction, but that another may be the following: **BBB disruption *per se* may not be harmful,**

but it confers risk of CNS disruption when it co-occurs with the presence of potentially pathogenic autoantibodies such as ANSAs. Intriguingly many established risk factors for psychosis such as viral infection, drug abuse, head injury and, more controversially, psychological stress or trauma have been shown to have effects on BBB integrity.

To date, no study has looked at the prevalence of either ANSAs or levels of S100B at individuals at high risk for psychosis.

Of the risk factors listed above, we consider viral infections to represent a fruitful area of enquiry. Viruses and other infectious agents have been implicated in the aetiology of a number of autoimmune diseases, often through a process of molecular mimicry . Further, an increasing evidence base suggests that viral infection, even subclinical, can result in the formation of anti-brain antibodies which may go on to have damaging effects on the CNS; suggested pathways linking viral infection and subsequent brain-reactive autoantibody production include non-specific adaptive immune response to neuronal damage and molecular mimicry [9]. Particular links between the formation of NMDAR antibodies and influenza [6] and herpes simplex virus 1 (HSV-1) [10, 11] infections have been demonstrated although further studies are needed to elucidate these relationships.

Serological evidence of viral or other infections have been linked with an increased risk for psychosis [12] **or with particular phenotypes within psychosis populations** such as cognitive impairment [13]. The most commonly implicated organisms include HSV-1, HSV-2, HHV, CMV, EBV, influenza, toxoplasma and rubella.

We propose a model for the development of autoimmune-mediated psychosis with the following features:

1) Genetic risk factors are present from birth. The well-replicated loci pertaining to the immune system (e.g. HLA-related polymorphisms) that have been strongly associated with schizophrenia in GWAS studies are of particular interest.
2) Maternal or early infection with neurotropic viral and/or protozoal organisms initiates a process of low-grade neuroinflammation and possible disruption of the BBB.
3) This initiates, through a process of molecular mimicry or through the presentation of damaged neuronal tissue to resident CNS immune cells, the production of ANSAs – brain reactive autoantibodies that can have direct functional effects of neural function. Due to restoration of CNS immune privilege, these antibodies are located in the peripheral circulation and may not gain subsequent access to the CNS, therefore remaining clinically silent. In some cases however the antibodies may in themselves be sufficient to cause brief, limited or subthreshold psychotic symptoms in individuals with a resilient immune system and/or an only temporarily disrupted BBB.
4) In individuals with a vulnerable immune system or a more profoundly disrupted BBB, a more permanent autoantibody-mediated dysfunction occurs and the clinical expression of a full psychotic syndrome occurs.

<u>Hypotheses</u>

Hypothesis 1: UHR subjects will show higher rates of ANSA positivity than controls.

Hypothesis 2: S100B levels will show a positive association with the extent of (attenuated) psychotic symptomatology and/or brief, limited intermittent psychotic symptoms.

Hypothesis 3: ANSA-positive UHR subjects will show increased serological evidence of previous infection relative to ANSA-negative UHR subjects.

Hypothesis 4: A composite score combining ANSA status, infective markers and S100B will be predictive of a) the severity of presenting symptoms and b) the risk of later transition to full-blown psychosis.

Hypothesis 5: The composite score will be predictive of abnormalities on a) structural MRI, potentially including hippocampal volume and lateral ventricle size. b) alterations in regional glutamate levels, as measured with MR spectroscopy

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Methods

Sera from UHR subjects (N=350) and matched controls (n=100) will be tested, blinded to group status, for

a) antibodies to the following antigens: NMDA receptor, AMPA receptor, CASPR2 (VGKC complex), LGI1 (VGKC complex), GABA-B receptor;
b) S100B level;
c) Antibodies to the following infectious agents: toxoplasma, HSV-1, HSV-2, influenza, CMV, EBV.

Analyses of group differences will be performed.

A combined autoimmune vulnerability score will be calculated for each patients and associations with clinical variables (including transition to psychosis) and structural MRI data will be assessed.

Expected results

As per hypotheses. Exploratory associations with clinical variables may also be instructive.

Association between autoimmune vulnerability and progression to psychosis would represent a highly significant and innovative methodology in the identification of vulnerable individuals within a high-risk cohort, with great potential clinical application. It may also have a role in delineating a subgroup of patients who will go on to develop an autoimmune-mediated psychotic illness with a **differential clinical profile and treatment response, allowing for the development of testing for ANSAs as basis for patient stratification and eventually targeted treatment development, possibly with immunotherapies or neurotransmitter-specific therapies based on the antibody target** (e.g. glutamatergic dysfunction with novel or established glutamatergic medications; VGKC dysfunction with potassium channel modulators; GABA receptor dysfunction with benzodiazepines or other GABA-specific compounds).

Data needed for the study: (please list the EU-GEI WP5 instruments)

Sera from WP5 UHR and control subjects: baseline and follow-up
Clinical data from subjects with serum samples, eventually including details of longitudinal clinical course

Plan for statistical analysis (overall strategy):

Chi square to compare prevalence of antibodies between groups
t-test to compare mean levels of markers of infection/S100B between groups
Principle components analysis to calculate a combined autoimmune vulnerability score
Linear regression to compare levels of the combined score between study groups
ANOVA to look at associations between the combined score and clinical variables

SPM8 will be used to perform regression analyses looking at structural MRI associations with the combined autoimmune vulnerability score

Other analyses/methods:

Serum testing for anti-neuronal surface antibodies (cell based assay; Euroimmun Inc.; testing at King's College Hospital Department of Clinical Immunology)
Serum testing for serological evidence of previous viral/protozoal infection (IgG; mainly ELISA; testing at South London Specialist Virology Centre, King's College Hospital)
Serum testing for S100B levels (chemiluminescence assay; Diasorin; testing at KingsPath)

Involvement of external Parties (non EU-GEI): Apart from the above analyses none at present

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IPR check (Intellectual property rights): N/A
Timeframe: Approximately 6 months after the clinical and biological data is ready
Additional comments: The costs of serological testing will be covered by a grant at the IoP

References

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