

15. Neuronal Autoantibodies and Blood-Brain Barrier Disruption in Subjects at Ultra-High Risk for Psychosis

Background: Neuronal surface autoantibodies (NSAbs) have been identified in patients with psychotic disorders, with meta-analytical evidence indicating a higher prevalence in first-episode psychosis (FEP), probably dependent on the assay used. The causal significance of these NSAbs is unclear, with a suggestion that that blood–brain barrier disruption (BBBD) may be an important additional factor. We aimed to establish whether, prior to illness onset, NSAbs and BBBD are present in subjects at ultra-high risk (UHR) for psychosis.

Methods: Sera from 260 UHR subjects in the EUGEI study and 110 healthy controls were tested with a fixed cell-based assay (CBA) using HEK293 cells that had been transfected to express one of 30+ NSAbs; IgG, IgA and IgM binding was assessed using indirect immunofluorescence. Levels of S100B, a putative marker of BBBD, were assessed using a chemoluminescence assay in this cohort and an FEP cohort (n = 226).

Results: NSAbs were present in 8.8% of UHR subjects and 7.3% HCs (ns) with NMDAR the most frequent antigen. Serostatus did not predict transition to psychosis, and 2 of 3 seropositive patients who transitioned to psychosis had antibodies of diverse Ig isotype. Patients with brief limited intermittent psychotic symptoms (BLIPS) were twice as likely to be seropositive at baseline compared to patients who transitioned to psychosis. Interestingly, subjects who were positive on fixed CBA for any NSAb or for only NMDAR antibodies showed trends towards higher negative syndrome scores across multiple scales. These subjects had impaired verbal memory scores as measured by the Rey auditory verbal learning test (RAVLT) ($P = .0019$), a finding that mirrors patients with NMDAR encephalitis and may be reflective of hippocampal dysfunction.

Samples were also tested for NMDAR IgG antibodies using a live CBA; this detected a higher prevalence of NMDAR IgG antibodies in the total cohort than did fixed CBA (19 subjects (5.1%) vs 2 (0.5%); $P = .0025$).

Mean S100B levels were higher in FEP subjects than in UHR subjects ($P < .001$) and controls ($P < .0001$). UHR subjects with high S100B levels surprisingly showed lower total psychopathology scores (BPRS; $P = .032$), less negative symptoms (SANS; $P = .039$), and disability (GAF; $P = .009$), whereas in FEP S100B levels were associated with worse positive psychotic symptoms.

Conclusion: A minority of subjects at risk of psychosis have NSAbs detectable in serum: These individuals may have worse negative symptoms and demonstrate impaired neurocognition. Further work is required to clarify the immunological and neuroanatomical substrates of these changes. BBBD may be progressive with the development of psychosis. The paradoxical finding of improved symptoms and function in subjects with evidence of greater BBBD differentiates UHR subjects from later stage psychosis and represents an exciting avenue for further investigation.

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