Psychosis and biological markers

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Conflict of interest statement:
Henrik Zetterberg is co-founder of Brain Biomarker Solutions, a GU Venture-based platform company at the University of Gothenburg, Sweden, and has served at advisory boards for Roche Diagnostics, Eli Lilly and Pharmasum Therapeutics.

In the current issue of *Lancet Psychiatry*, Lennox and colleagues present a report in which 228 patients with a first episode of psychosis (FEP) were compared with 105 matched healthy control individuals in regards to prevalence of serum auto-antibodies to neuronal surface antigens.[1] Serum anti-NMDA receptor antibodies were specifically seen in FEP patients (not in healthy controls) without any clear association to phenotypic characteristics of the patients. The results call for large scale longitudinal studies.

When looking for biological markers to evaluate a disease, knowledge on the pathology and/or pathophysiology makes biomarker discovery easier and increases the interpretability of the results generated during the discovery process. In psychiatry, the clear and abundant pathology of Alzheimer's disease has facilitated the development of imaging and fluid biomarkers for the disease.[2] In regards to schizophrenia and several other central nervous system diseases, this has been much harder.

For many years, schizophrenia was regarded a functional disorder with no structural basis. However, during more than a century of research, a number of macroscopic brain

abnormalities have been established, including ventricular enlargement and decreased cortical and hippocampal volumes.[3] Imaging studies suggest that these changes are present also in drug-naïve first episode of psychosis (FEP) patients,[4] suggesting that they are not simply downstream of lifelong schizophrenia, which was a common criticism against findings in autopsy studies. The structural brain changes are not correlated with Alzheimer's disease pathology,[5] and there is no firm evidence of gliosis (a much debated topic some 20 years ago).[3] No other protein pathologies characteristic of proteopathic neurodegenerative diseases have been identified. Instead a number of microscopic changes, including reduced neuropil and neuronal size, have been identified.[3] Whether these are neurodevelopmental or related to altered neuronal network activity is presently unknown. Nevertheless, functional neuroimaging in patients with schizophrenia can detect aberrant activity in neuronal circuits involving the prefrontal cortex, hippocampus and also some subcortical structures.[4]

Although functional neuroimaging may be the most tangible biomarker for schizophrenia, we should not give up on fluid biomarkers. The synaptic changes in autopsy studies are clear and also reflected in the cerebral proteome; for example strongly reduced Rab3a expression in the thalamus has been observed in schizophrenia.[6] Recent advances in analytical technology have made it possible to develop quantitative methods to measure synaptic protein concentrations in cerebrospinal fluid (*e.g.*, the dendritic protein neurogranin) that correlate with imaging evidence of structural and functional synaptic changes in Alzheimer's disease.[7] Perhaps such sensitive tests could generate data that reflect the synaptic pathology in schizophrenia and give complementary information to neuroimaging? There is also abundant literature on a potential role of microglial activation and neuroinflammation in the pathogenesis of schizophrenia;[8] processes for which cerebrospinal fluid biomarkers do exist.

There are additional aspects that underscore the need of in depth medical evaluation of patients with suspected schizophrenia. Schizophrenia-like psychoses may be the dominating presenting symptom of, not only encephalitides, but also other neurological disorders, such as temporal lobe epilepsy, neurosyphilis, Wilson's disease and metachromatic leukodystrophy.[3]

Lennox *et al*. have now extended these studies to auto-antibodies in serum.[1] The knowledge that auto-antibodies against neuronal cell surface receptors and related proteins may cause encephalitic syndromes that frequently present with psychosis,[9] led Lennox and colleagues to hypothesise that (i) such auto-antibodies are overrepresented in the serum of FEP patients

without clinical signs of encephalitis and (ii) antibody-positive FEP patients would be phenotypically different from antibody-negative patients. Seven out of 228 patients had serum auto-antibodies against the NMDA receptor, detected using a live cell-based assay, compared to none of the controls, whereas the prevalence of a number of other neuronal surface protein antibodies was not significantly different between the two groups.[1] Antibody-positive and –negative patients were largely similar in terms of clinical characteristics and treatment response over 6 months, but it should be noted that the numbers for comparison were small.

The study does not tell if the anti-NMDA receptor antibodies are a cause or consequence of psychosis but the result of increased prevalence in FEP resonates well with a recent meta-analysis of the literature,[10] and calls for large scale longitudinal studies, as well studies examining the specificity and pathogenicity of the antibodies. If causality is demonstrated, a new field of immunomodulatory treatment opportunities for a subset of FEP patients may have been opened, especially since we know that this form of treatment usually leads to remission of antibody-mediated encephalitides.

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