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Illuminating the Etiology and Pathophysiology of Schizophrenia: Neurodevelopmental, Structural, and Neurochemical Abnormalities

Announcer:
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Dr. Correll:
Welcome to Illuminating the Etiology and Pathophysiology of Schizophrenia: Neurodevelopmental, Structural, and Neurochemical Abnormalities. My name is Christoph Correll. I'm Professor of Psychiatry and Molecular Medicine at the Zucker School of Medicine at Hofstra Northwell in New York, and I'm also Professor and Chair of Child and Adolescent Psychiatry at the Charite University of Medicine in Berlin, Germany.

Let's start by reviewing what are the risk factors for schizophrenia. In an umbrella review, reviewing 683 studies and 170 risk factors from 55 meta-analysis, Radua, et al, reviewed many of the potential risk factors. Those that came out having odds ratios that are believable and relevant, included, among others, in an odds ratio range of 10 or higher, ultra-high risk state for psychosis, just made it with 9.3 odds ratio. So the attenuated positive symptoms are risk factors for future psychosis, although we've seen these rates go down. There's also lower, between 2 and 10 odds ratios, urbanicity black race, and being immigrants, so having social and environmental stressors. Childhood trauma, also with a risk factor score of about 2.5.

Now, what is really higher, though, more interestingly, diabetes during pregnancy, and several antibodies against either viral or also other infectious agents. So there might be an infectious component for at least some schizophrenia patients. And that is also seen because of the winter birth in the northern hemisphere and in the southern hemisphere.

It is also seen by whole genome association studies, where the towering Manhattan plot winner was really the major histocompatibility complex, which has to do with autoimmunity and immunity, again, pointing to at least some environmental infectious potential reason that might actually affect pregnant women, so that maybe in the future, we could even have vaccination against schizophrenia.

The problem with schizophrenia is wherever it starts, that it affects neural development. And that has to do with the myelination of the brain, but also the excitation/inhibition in this balance, because we know that in the beginning, there's a lot of excitatory synapses that need to be pruned down, whereas inhibitory synapses are being built up, so that we can fine tune our mental capacity and abilities more and more. And that seems to go awry during the developmental phase in patients who later have schizophrenia.

We also know that these genetic risk factors aren't brought out by environmental stressors, either in utero, during birth, or also later. And drug abuse, stressors, childhood abuse can also all play into this. Now, there are some people who have very little genetic risk, and whatever the stressors are, no psychoses ensues and there are others where these stressors are not even needed, because of the very strong genetic risk, which could be either transmitted from family to family, or very often, it seems to be also a just spontaneous aberration.

We also know that during development, but also after the schizophrenia has hit, brains of people with schizophrenia change. There is a shrinkage of gray matter, and also an enlargement of ventricles with cortical atrophy. This unfortunately, has to do both with gray matter and total brain volumes. And that has to do then also with decreased mental capacity and abilities.

We know that in terms of electrophysiology, there is an increase of presynaptic dopamine tone, and that increased production of dopamine seems to be the problem. Our current treatments are more on the postsynaptic dopamine receptor side, and then we don't think really that much is wrong, so that we're maybe not treating the illness where the actual problem is. This increased dopamine tone presynaptically can also be brought out by psychosocial stressors that sensitize dopamine system, then leads to an aberrant processing of stimuli, which can lead to paranoid interpretation and psychosis. There is also the problem between differentiating of foreground and background, meaning the mismatch negativity is a key concept of schizophrenia. Usually when a tone or a stimulus is presented several times, the response is attenuated because it's known. But in people with schizophrenia, this doesn't seem to be the case, so continuous or repeated stimuli seem to be novel, and that is threatening and is then built into often a systematized delusional system.

Finally, we know that schizophrenia doesn't stop at the neck. It's not just a brain disease. It's also a whole system and physical disease. We know that there are cardiometabolic disturbances, even in the first episode in untreated patients never been treated with antipsychotics, we have increase of insulin resistance, dyslipidemia, but there are also immune disturbances and also hypothalamic-pituitary-adrenal axis stress response abnormalities, which are in the range between a small effect size for the cardiometabolic risk, to large to very large effect sizes for the stress response and immune disturbance.

It's unclear whether a risk factor gives rise to both the CNS and peripheral problems, whether the CNS disruption then filters down to the non-CNS dysfunction, or whether these are separate lines of developmental abnormalities that originate from a risk factor in utero and later.

So let me sum up. Unfortunately, even now, the exact pathophysiology of schizophrenia remains unknown, but it's likely highly heterogeneous with a common pathway at the end, presenting clinically similarly. There are data points that both neurodevelopmental and neuro-progressive components are relevant for schizophrenia. Schizophrenia is associated with both central as well as peripheral multisystem dysfunctions involving structural, neurochemical, and cellular brain abnormalities. Treatments targeting the pathophysiology beyond dopamine blockade are clearly needed to address more expressions of schizophrenia, both centrally and also peripherally, and likely also are needed to target specific subtypes so that we have precision psychiatry.

Let me thank you for your attention. Thanks for watching, and I hope that this was helpful.

Announcer:
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