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Unraveling Schizophrenia: Neurobiological and Genetic Factors to Consider

Ms. Baker:
Welcome to *NeuroFrontiers* on ReachMD. I'm psychiatric nurse practitioner Ashley Baker, and joining me to discuss our current understanding of the neurobiological mechanisms and genetic factors contributing to schizophrenia and how this can impact our diagnostic approach is Dr. Greg Mattingly. Not only is he an Associate Clinical Professor at Washington University, but he is also a founding partner of Saint Charles Psychiatric Associates in Missouri. Dr. Mattingly, thanks for being here today.

Dr. Mattingly:
Glad to join you.

Ms. Baker:
So let's just dive right in. Can you give us an overview of the neurobiological mechanisms underlying schizophrenia?

Dr. Mattingly:
Schizophrenia, first of all, is an illness that does not discriminate. All around the world, the global prevalence of schizophrenia is 1 percent. So it doesn't matter if you're in New York City or if you're in Los Angeles, if you're in rural Missouri or if you're in South America, Canada, or Australia. The global prevalence of schizophrenia is 1 percent. The neurobiology becomes fascinating because schizophrenia is an illness that doesn't show up in children. It doesn't show up in late life. It's an illness that begins usually when the brain is pruning back pathways that we aren't using anymore. So in that late adolescence period, those early 20s, we find that we're pruning back pathways that we're no longer using, and we're myelinating pathways that we are using. Many people think that the beginning of schizophrenia starts with abnormal synaptic pruning in the brain during late adolescence and early 20s, which then causes that first psychotic episode. Beyond abnormal pruning within the brain, we know that there are certain abnormalities within chemical systems and neural networks within the brain.

Ms. Baker:
If we zero in on each one of those mechanisms individually, how does dopamine dysregulation contribute to the pathophysiology of schizophrenia?

Dr. Mattingly:
So dopamine has a number of key networks within the brain. There's the network that gets involved with mood, motivation, and reward. Deficiencies in dopamine will leave you emotionally blunted and depressed. Too much dopamine will make you psychotic, agitated, and unable to control your emotions or perceptions. Dopamine also gets involved with a pathway that goes up to the prefrontal cortex. That gets involved with cognition, memory, and being able to remember things and process information. And where we get into schizophrenia, we see that we have too much dopamine in those pathways that involve mood. I become psychotic. I become agitated. I can't control my emotions. But we have decreased dopamine in the prefrontal cortex, so in that pathway, we find that people with schizophrenia quite often have cognitive symptoms. And those cognitive symptoms quite often start even before they have their first psychotic episode. So I have difficulties with processing speed and working memory, which is one of the reasons we see such high disability rates in schizophrenia. It's not just that I'm hearing voices or I'm paranoid, but I can't process information and keep up. I can't keep up in school. I can't keep up in a job. I can't keep up in day-to-day activities.

Dopamine also has two other key pathways that become imbalanced, quite often as a result of our treatments. Dopamine goes down to the pituitary where it controls prolactin release and hormone function. Blockade of dopamine by our antipsychotics can cause elevations

of prolactin with sexual side effects and hormonal difficulties that can occur. And then finally, dopamine in the substantia nigra and those pathways in the brain can cause motoric side effects. So blockade of dopamine as we're trying to treat schizophrenia can quite often lead to parkinsonian side effects, tardive dyskinesia, or other movement disorder side effects.

As we expand beyond dopamine, the next receptor that we started having targeted medicines for with the atypical antipsychotics was serotonin. So the atypicals, going back to clozapine, were developed to modulate specific serotonin receptors, primarily serotonin 2A and serotonin 1A. We know those receptors got involved with dopamine modulation—it's a cross-talk between serotonin and dopamine—but we also know we could minimize some of the movement disorder side effects that were resulting from antipsychotics by modulating those receptors.

Ms. Baker:
What about specifically the onset of schizophrenia? How do neurodevelopmental abnormalities play a role in that?

Dr. Mattingly:
The earliest symptoms we tend to see in schizophrenia if you have high genetic loading—let's say you have a mom or an uncle or a sibling with schizophrenia—the earliest symptoms will be subtle cognitive changes. There are studies going back to age 7, 8, and 9 where we can see subtle cognitive changes in the brains of children. We have high genetic loading of schizophrenia. When we first start seeing the onset, though, of those first psychotic symptoms, it tends to be in those areas we talked about—late teens, early 20s—where we're having abnormalities of pruning pathways back in the brain. So that's a time when all of us have critical expression of pathways we're trying to use. I'm trying to concentrate, I'm trying to focus, and I want to be socially engaged. I have to keep those pathways in the brain, and I prune back pathways I'm not using, so the pathways I am using are more efficient.

The theories are right now that schizophrenia presents in those years because we have an abnormal pruning process in part due to genetics, in part due to neuroinflammation, and in part due to environmental experiences. We know that childhood trauma plus genetics are worse than either one by itself. So I think some of the really interesting research, when we look at how do we help with those early onset of symptoms, it comes back to holistic treatment for our patients. I may have genetic loading, but I can help to compensate for trauma, social deprivation, and social economic status by having positive life events, increased structure, increased daily routine, exercise, and nutrition and avoiding things that cause inflammation in the brain. All tend to be some of the holistic solutions to help the outcomes for our patients.

Ms. Baker:
Thinking back about genetic factors, have specific genes or mutations been identified, and if so, how do they influence the risk of developing schizophrenia?

Dr. Mattingly:
The number one gene, if you look at loading of genes, is this gene called C-4, which gets involved with the immune system and seems to be involved with neural pruning. So in a large study done by the NIMH, that was the highest candidate gene. You then start seeing genes around dopamine—dopamine transmission, dopamine release—which makes sense because we've had a lot of interest in dopamine throughout the years. And beyond that, we see genes involved with glutamate and genes involved with monoamine metabolism, the MAO system. All of those seem to have some genetic risk. I think what's important to realize, though, is schizophrenia is not going to be a single gene illness. It's going to be multiple risk genes laying over the top of each other plus environmental exposure and environmental risk added together.

Ms. Baker:
For those just tuning in, you're listening to *NeuroFrontiers* on ReachMD. I'm psychiatric nurse practitioner Ashley Baker, and I'm speaking with Dr. Greg Mattingly about the neurobiological mechanisms and genetic factors behind schizophrenia.

So, Dr. Mattingly, given everything we've discussed so far, how can this knowledge of the neurobiological and genetic factors influence our diagnostic approach as clinicians and help us to identify patients with schizophrenia earlier?

Dr. Mattingly:
So the important part of this message is, like any other health condition, early intervention is key. If you have cardiac disease or if you have metastatic cancer, early intervention makes a difference. The same thing is true with schizophrenia. So the earlier we can pick up those at-risk patients, say listen, I can tell there's things that are starting to change in the brain, cognitively, emotionally, the way I perceive things around me.

So there's a term we now call the duration of untreated psychosis—DUP. The longer your duration of illnesses before you receive your first intervention, the worse your long-term outcome is. So we want to look at genetic risks. I have family members that have mental

health issues. We want to look at subtle cognitive changes in someone before they've ever become ill, especially if they have those genetic risks. And then in our teenagers, our early adults, and our college-aged students, we want to make sure we pick up those first psychotic episodes and get holistic appropriate treatment for our patients.

Ms. Baker:
And if we look ahead for just a moment before we close, are there any ongoing areas of research that may uncover new insights into the underpinnings of schizophrenia?

Dr. Mattingly:
It's an exciting time to be in mental health right now. We're learning more about the brain every day, and so people are looking at not just presynaptic and postsynaptic modulation, but why is the brain becoming ill?

Some of these new treatment options, I think, are truly going to be disease-modifying. So instead of using symptomatic treatments, we're daring to move beyond symptoms and talk about how to recall functional recovery, life engagement, and disease modification with some of these new medications that modulate presynaptic dopamine release.

Ms. Baker:
With those forward-looking thoughts in mind, I want to thank my guest, Dr. Greg Mattingly, for joining me to discuss the early identification and diagnosis of schizophrenia based on our understanding of its contributing neurobiological mechanisms and genetic factors. Dr. Mattingly, it was great speaking with you today.

Dr. Mattingly:
It is an exciting time to be in the field, and thank you for letting me join you today.

Ms. Baker:
For ReachMD, I'm psychiatric nurse practitioner Ashley Baker. To access this and other episodes in our series, visit *NeuroFrontiers* on ReachMD.com, where you can Be Part of the Knowledge. Thanks for listening.