Screening for Psychosis Among Individuals With Rare Genetic Disorders That Confer Risk for Schizophrenia-Like Phenotypes

To the Editor: Numerous rare genetic variants confer significant risk for schizophrenia. While clinically oriented reviews on this topic have traditionally focused on suggestive features and the implications of making a correct diagnosis, little has been written about how best to monitor for the emergence of psychotic symptoms in this high-risk population. However, early identification is critical given the association between duration of untreated psychosis and a variety of treatment outcomes.[1]

Although numerous specialists may be involved in the care of such individuals, given the frequent co-occurrence of developmental abnormalities and variable neurological/medical problems, primary care physicians are uniquely positioned to perform periodic psychiatric screens, given their longitudinal involvement in patient care from an early age. At the first signs of psychosis, a referral to appropriate psychiatric services should be made (ideally an "Early Psychosis Intervention Program") for further assessment and management.

While compiling an exhaustive list of all genetic disorders that carry risk for psychosis is beyond the scope of this letter, notable examples include Kleefstra syndrome, Lujan-Fryns syndrome, Prader-Willi syndrome, and monogenic forms of Parkinson disease, in addition to certain inborn errors of metabolism, a subset of copy number variant (CNV) disorders, and numerous less well-described but emerging monogenic conditions.[2] Guidelines concerning the surveillance of potential medical/neurological comorbidities exist for many of these disorders (often included in their respective GeneReviews articles), but recommendations regarding psychosis screening have seldom been published. Notable exceptions include 22q11.2 deletion syndrome, the most common and well-described schizophrenia-associated CNV syndrome, and Prader-Willi syndrome. Specifically, recent guidelines suggest screening for psychosis in 22q11.2 deletion syndrome at the time of diagnosis, subsequently (where applicable) between age 1 and 5 years, 6 and 12 years, and 13 and 18 years[3] and every 1–2 years thereafter,[4] compared to annually in adolescents and adults with Prader-Willi syndrome.[5]

Despite the magnitude of risk and typical age of onset varying between disorders, these recommendations can reasonably be extrapolated for use in other genetic conditions that predispose to psychosis. In situations where pediatric patients are seen more often than once per year for other clinical reasons, screening at each visit should be considered where feasible, given that deleterious CNVs[6] and rare loss-of-function variants in schizophrenia-related genes[7] appear to be associated with an earlier illness onset.

Patients should also be educated with respect to modifiable psychosis risk factors within their control, such as abstaining from cannabis and other psychotomimetic substances. Relatedly, the use of nonstimulant medications in the management of concurrent attention-deficit/hyperactivity disorder should be favored (eg, atomoxetine or clonidine/guanfacine), or at a minimum, extra caution should be exercised if a stimulant trial is deemed necessary.

In conclusion, routine monitoring for the development of psychotic symptoms among individuals with rare genetic disorders that confer risk for psychosis by primary care providers may allow for early intervention and should be considered standard of practice.

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