The information in this column is not intended as a definitive treatment strategy but as a suggested approach for clinicians treating patients with similar histories. Individual cases may vary and should be evaluated carefully before treatment is provided. The patient described in this column is a composite with characteristics of several real patients.

Clinical management of psychosis in 22q11.2 deletion syndrome

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A 17-year-old woman was referred to our centre for treatment of a recent onset psychotic episode in the context of 22q11.2 deletion syndrome. A 3 megabase A-D deletion was identified at birth through microarray-based comparative genomic hybridization, after the discovery of a tetralogy of Fallot. She had a learning disability associated with mild intellectual disability (homogeneous average intelligence quotient around 70 at age 14 yr), recurrent infections during early childhood and pervasive anxiety since adolescence. Her features were mildly dysmorphic, with a bulky nasal tip, retrognathia and an epicanthus. Her speech was hypernasal and she had a short stature.

In the previous year, she had been bullied at school and had developed depression, for which she had received fluoxetine (20 mg/d) for the previous 3 months. In the weeks before presentation, she had reported persecutory delusions toward her classmates and family, as well as mood-congruent auditory hallucinations in the form of different voices that insulted her and told her to kill herself. Brain MRI was normal.

We diagnosed depression with psychotic features, and added an antipsychotic treatment with low doses of olanzapine (5 mg) to the antidepressant, with complete remission of all psychotic and mood symptoms at 1 month. Olanzapine was kept as a maintenance treatment for 6 months, and fluoxetine was continued for 1 year. We monitored the patient closely for comorbidities, especially hypocalcemia, and for adverse effects, including QTc prolongation, constipation and metabolic anomalies. During this period, the patient gained weight (10 kg), and described attention deficit, poor quality of sleep and daytime sleepiness. Obstructive sleep apnea was diagnosed by polysomnography (Apnea–Hypopnea Index score of 6 events per hr). It improved with a mandibular advancement splint for the retrognathia. The patient lost weight after stopping olanzapine. She had no recurrence of psychosis over the next 4 years.

At age 21 years, the patient presented with a second psychotic episode that lasted more than 6 months. During this period, she received a diagnosis of schizophrenia. Her persecutory delusions did not respond to 2 lines of antipsychotics (olanzapine up to 10 mg over 8 wk and risperidone up to 3 mg over 6 wk); these could not be increased owing to her very low tolerance, including acute dyskinesia, tremors, rigidity and psychomotor slowing (described by the patient as an inability to think and to move), which coincided with starting the antipsychotics. Remission of symptoms and improvement in adverse effects were observed after slow titration of clozapine up to 100 mg/d (with plasma levels at 200 μg/L in this nonsmoker patient with a body mass index of 26).

In addition to the usual monitoring for adverse effects from antipsychotics, we regularly assessed the patient for clozapine-induced neutropenia and myocarditis.[1] Risk of seizures was prevented with 200 mg/d of lamotrigine. Hypocalcemia, which can worsen cognitive symptoms and lower the threshold for seizures, was excluded. Other psychotropic medication was avoided. The patient received cognitive behavioural therapy (CBT) to target negative symptoms (i.e., social avoidance, withdrawal, motivation deficit and anhedonia). It allowed the patient to become more aware of her symptoms, and improved her social skills, organizational skills (improved self-care at home) and ability to seek professional help when needed, as well as to more easily confide in her family and friends. The unit's social worker referred her to assisted employment, which she has steadily maintained.

Clinical management of psychosis in 22q11.2 deletion syndrome is a good example of personalized medicine, whereby knowledge of the various comorbidities associated with the genetic syndrome can lead to a more specific approach to follow-up. This condition has been reported as among the most frequent copy number variants in schizophrenia (0.5%–1% of patients with schizophrenia).[2,3] Psychotic symptoms are highly prevalent in 22q11.2 deletion syndrome, appearing in late adolescence[4] and reaching more than 40% of patients in adulthood.[5,6] However, many patients present with brief psychotic symptoms that do not qualify as a chronic psychotic disorder,[5] and that may or may not develop into one. Therefore, standard care should apply to such episodes, and long-term antipsychotic treatment should be balanced with the risk of adverse effects in a population for which the rates of obesity and type 2 diabetes are already elevated, even without antipsychotic drugs.[7,8] In addition, there is a lack of data in the literature regarding the benefit of low doses of antipsychotics in preventing chronicity after a brief psychotic episode.

We first followed recent evidence of the relevance of olanzapine maintenance to prevent relapses of psychotic depression in the general population.[9] For patients with schizophrenia, standard treatment is also recommended,[10–12] with a "start low, go slow" paradigm, especially with clozapine,[12]

because lower doses may be effective (< 250 mg/d) and because this approach decreases the risk of dose-dependent adverse effects.[13] Importantly, CBT is crucial for recovery as it may improve both disease insight and socioexecutive functions, which are often impaired in 22q11.2 deletion syndrome.[14,15] These functions, rather than psychosis, seem to be most predictive of education and employment trajectories.[16]

Although there is no clear evidence that there are higher rates of antipsychotic adverse effects or treatment resistance among patients with 22q11.2 deletion syndrome,[1,17] the syndrome itself is associated with many comorbidities. There is an increased risk of seizures, both because of an intrinsic lowering of the epileptic threshold (with more epilepsy than in the general population)[18] and because of many extrinsic factors, including hypocalcemia, fever and antipsychotic treatment, particularly clozapine.[19] This is why a preventive antiepileptic treatment can be considered.[13] Although metabolic, cardiac and hematological manifestations,[17] or movement disorders such as parkinsonism or early dystonia, can occur independently of adverse effects from treatment, treatment itself may lower the threshold to develop such symptoms.[20,21] This warrants a close monitoring of antipsychotic prescription, while trying to limit polypharmacy in a population prone to comorbidities.[22] Sleep apnea should also be suspected with subjective cognitive symptoms, considering the risk factors of dysmorphic features and obesity.[23–25]

The presence of 22q11.2 deletion syndrome in patients with schizophrenia warrants a more personalized treatment plan. People with a 22q11.2 deletion have a high risk of developing psychosis, and deserve to be integrated in the early intervention approach in psychiatry.

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References

1. Mosheva M, Korotkin L, Gur RE, et al. Effectiveness and side effects of psychopharmacotherapy in individuals with 22q11.2 deletion syndrome with comorbid psychiatric disorders: a systematic review. *Eur Child Adolesc Psychiatry* 2020;29:1035-48.
2. Van L, Boot E, Bassett AS. Update on the 22q11.2 deletion syndrome and its relevance to schizophrenia. *Curr Opin Psychiatry* 2017;30:191-6.
3. Rees E, Walters JTR, Georgieva L, et al. Analysis of copy number variations at 15 schizophrenia-associated loci. *Br J Psychiatry* 2014;204:108-14.
4. Gothelf D, Schneider M, Green T, et al. Risk factors and the evolution of psychosis in 22q11.2 deletion syndrome: a longitudinal 2-site study. *J Am Acad Child Adolesc Psychiatry* 2013;52:1192-1203.e3.
5. Jonas RK, Montojo CA, Bearden CE. The 22q11.2 deletion syndrome as a window into complex neuropsychiatric disorders over the lifespan. *Biol Psychiatry* 2014;75:351-60.
6. Schneider M, Debbane M, Bassett AS, et al. Psychiatric disorders from childhood to adulthood in 22q11.2 deletion syndrome: results from the international consortium on brain and behavior in 22q11.2 deletion syndrome. *Am J Psychiatry* 2014;171:627-39.
7. Van L, Heung T, Malecki SL, et al. 22q11.2 microdeletion and increased risk for type 2 diabetes. *EClinicalMedicine* 2020;26:100528.
8. Voll SL, Boot E, Butcher NJ, et al. Obesity in adults with 22q11.2 deletion syndrome. *Genet Med* 2017;19:204-8.
9. Flint AJ, Meyers BS, Rothschild AJ, et al. Effect of continuing olanzapine vs placebo on relapse among patients with psychotic depression in remission: the STOP-PD II randomized clinical trial. *JAMA* 2019;322:622.
10. Taylor DM, Barnes TRE, Young AH. *The Maudsley Prescribing Guidelines in Psychiatry, 14th Edition*. Hoboken: John Wiley & Sons; 2021.
11. Baker K, Baxendale H, Bu'Lock F, et al. Psychiatric illness. *Consens. Doc. 22q11 Deletion Syndr. 22q11DS* Stourbridge: *MaxAppeal; 2017*.
12. Fung WLA, Butcher NJ, Costain G, et al. Practical guidelines for managing adults with 22q11.2 deletion syndrome. *Genet Med* 2015;17:599-609.
13. Butcher NJ, Fung WLA, Fitzpatrick L, et al. Response to clozapine in a clinically identifiable subtype of schizophrenia. *Br J Psychiatry* 2015;206:484-91.
14. Demily C, Franck N. Cognitive behavioral therapy in 22q11.2 microdeletion with psychotic symptoms: what do we learn from schizophrenia? *Eur J Med Genet* 2016;59:596-603.
15. Buijs PCM, Bassett AS, Boot E. Non-pharmacological treatment of psychiatric disorders in individuals with 22q11.2 deletion syndrome; a systematic review. *Am J Med Genet A* 2018;176:1742-7.
16. Mosheva M, Pouillard V, Fishman Y, et al. Education and employment trajectories from childhood to adulthood in individuals with 22q11.2 deletion syndrome. *Eur Child Adolesc Psychiatry* 2019;28:31-42.
17. de Boer J, Boot E, Gils L, et al. Adverse effects of antipsychotic medication in patients with 22q11.2 deletion syndrome: a systematic review. *Am J Med Genet A* 2019;179:2292-306.
18. Bayat M, Bayat A. Neurological manifestation of 22q11.2 deletion syndrome. *Neurol Sci* 2022;43:1695-700.
19. Wither RG, Borlot F, MacDonald A, et al. 22q11.2 deletion syndrome lowers seizure threshold in adult patients without epilepsy. *Epilepsia* 2017;58:1095-101.
20. Boot E, Bassett AS, Marras C. 22q11.2 Deletion Syndrome–Associated Parkinson's Disease. *Mov Disord Clin Pract (Hoboken)* 2018;6:11-6.
21. Boot E, Butcher NJ, van Amelsvoort AMJ, et al. Movement disorders and other motor abnormalities in adults with 22q11.2 deletion syndrome. *Am J Med Genet A* 2015;167A:639-45.
22. Malecki SL, Van Mil S, Graffi J, et al. A genetic model for multimorbidity in young adults. *Genet Med* 2020;22:132-41.
23. Arganbright JM, Tracy M, Hughes SS, et al. Sleep patterns and problems among children with 22q11 deletion syndrome. *Mol Genet Genomic Med* 2020;8:e1153.
24. Moraleda-Cibrián M, Edwards SP, Kasten SJ, et al. Symptoms of sleep disordered breathing in children with craniofacial malformations. *J Clin Sleep Med* 2014;10:307-12.
25. Kennedy WP, Mudd PA, Maguire MA, et al. 22q11.2 Deletion syndrome and obstructive sleep apnea. *Int J Pediatr Otorhinolaryngol* 2014;78:1360-4.