Treatment of 22q11.2 deletion syndrome-associated schizophrenia with comorbid anxiety and panic disorder

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Abstract

22q11.2 deletion syndrome (22q11DS) is a risk factor for psychiatric illnesses, including schizophrenia and anxiety. Small studies have shown that several neuroleptic medications are effective in treating psychosis in this population, but are also associated with an increased risk of adverse effects - particularly, seizures. In this case, we discuss a 34-year-old patient presenting with late onset schizophrenia, which ultimately led to her diagnosis of 22q11DS. Subsequent management of the patient's psychosis with asenapine was complicated by concurrent anxiety and panic disorder; thus, we examine the role of anxiolytic therapy in conjunction with antipsychotics in this patient population.

Introduction

22q11.2 deletion syndrome (22q11DS), a congenital microdeletion of 40-70 genes, is highly associated with the development of psychiatric disorders. The typical presentation may also include cardiac malformations, abnormal facies, palatal and pharyngeal abnormalities, hypoparathyroidism, and thymic hypoplasia.[1,2]

22q11DS is a potent risk factor for psychiatric disorders. Early onset of psychotic symptoms is common in these patients; few cases of schizophrenia with onset after age 30 in 22q11DS patients have been described.[2-4] Case reports and small studies in the literature demonstrate that typical and atypical antipsychotics are often effective in treating schizophrenia in 22q11DS patients.[5-9] However, failure of initial treatment and serious adverse effects (notably, seizure) complicated several of these studies, and none have discussed asenapine or adjunctive benzodiazepines.[5,7,8] Depression and anxiety are also extremely common in this patient population; the prevalence of concomitant cardiac abnormalities demands consideration of the potential interaction between antidepressant and anticoagulant metabolism.[10]

In the present case, we discuss the late onset of schizophrenia and the subsequent diagnosis of 22q11DS in an adult presenting with psychosis, anxiety, and panic attacks. We aim to shed light on the efficacy and safety of asenapine, clonazepam, and serotonin-norepinephrine reuptake inhibitors in this patient population.

Case Report

A 34-year-old Caucasian female presented in the outpatient setting with a 18-month history of anxiety, auditory hallucinations of voices, and paranoid ideation. The voices, which belong to the patient's neighbors and deceased members of her family, are troubling to the patient because they often instruct her to hurt herself. The patient now has frequent self-described panic attacks due to the voices. She is no longer able to be alone for short periods of time – for example, the patient's mother sits outside of the bathroom to reassure the patient while she showers. Past medication trials for these symptoms included quetiapine, valproate, aripiprazole, fluoxetine, and mirtazapine, none of which had any effect on her symptoms. Titration was at times limited by significant side effects – namely, sedation with quetiapine and reported shaking and claw-like spasms of the hands with aripiprazole.

The patient has childhood diagnoses of a learning disability and intellectual disability (IQ 87, per mother's report), and was diagnosed with autism spectrum disorder (ASD) at age 27. There is no history of psychiatric disorders or intellectual disability in her family. The patient completed high school and attained a degree from a community college on a specialized education plan. Currently, she lives with her parents and receives assistance with activities of daily living from an aide when her parents are at work.

The patient has a medical history of several congenital heart defects. At the age of 6 months, she was diagnosed with right aortic arch, bicuspid aortic valve, atrial septal defect (repaired), and mitral valve prolapse (replaced with mechanical valve). Her medical history also includes a Chiari I malformation, a right cerebellar cyst, and scoliosis. The patient's current medications are warfarin 4 mg daily and oral contraceptive pills. On physical exam, the patient was noted to have a narrow face with a hypoplastic chin and hypernasal voice. Her affect was blunted. Previous laboratory results were significant for mild hypocalcemia.

The patient was diagnosed with schizophrenia, generalized anxiety disorder, and panic disorder. She was started on 10 mg of olanzapine daily and 0.5 mg clonazepam twice daily as needed for anxiety. Genetic studies were ordered to assess for possible 22q11DS; cytogenomic SNP microarray results demonstrated loss of the 22q11.21 region, confirming the diagnosis. Follow-up calcium studies showed persistent mild hypocalcemia, normal serum parathyroid hormone, normal serum ionized calcium, and reduced 24-hour urine calcium (12.4 mg; normal range 100-300 mg).

Increasing and splitting the dose of olanzapine was found to be ineffective for the patient over the ensuing months. Clonazepam dosing was adjusted to 0.5 mg each morning and 1 mg each evening, with mild benefit. Sertraline 25 mg was prescribed in order to better control anxiety symptoms, but the patient's mother refused to allow the patient to take the medication due to fear of interaction with warfarin and increased bleeding risk.

Five months after the patient's initial presentation, olanzapine was discontinued and replaced with twice-daily sublingual asenapine, 5 mg. She began to experience relief from her psychosis and severe anxiety shortly thereafter; per her mother's report, the patient was able to spend more time alone without panic attacks, had substantially improved daily functioning, and experienced longer intervals between auditory hallucinations. These benefits persisted for about one month.

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Discussion

Psychiatric diagnoses in 22q11DS

22q11.2 deletion syndrome (22q11DS) is a congenital microdeletion of 40-70 genes on the long arm of the 22nd chromosome. The estimated prevalence is 1 in 4000 live births; most of these deletions arise de novo. There is no single clinical feature common to every patient with this disorder; rather, any of a number of identified characteristics may be present. Among these are congenital cardiac malformations, craniofacial abnormalities, intellectual disability, psychiatric disorders, hypoparathyroidism and resulting hypocalcemia, frequent infections and autoimmune disease due to thymic hypoplasia, and palatal or pharyngeal abnormalities. Patients with this disorder have normal life spans and require long-term management of complications of the condition.[1,2]

Most patients with 22q11DS are diagnosed early in life due to the interventions required for severe cardiac abnormalities, hypocalcemia-related seizures, or poor feeding due to palatal deformities. When these features of the disorder are less severe, however, patients may elude diagnosis until adolescence or adulthood. In these cases, the presenting symptom is often neuropsychiatric.[11] The prevalence of psychiatric disorders in 22q11DS is estimated to be over 50%, and a wide range of illnesses are represented (Table 1).[3] Attention deficit-hyperactivity disorder and ASD are prevalent in younger patients, while the prevalence of mood disorders increases with age. Anxiety disorders are common in every age group. Female 22q11DS patients are much more likely than males to have anxiety disorders in adulthood, and anxiety has been shown to be a significant risk factor for the development of psychosis in these patients.[3,12] Panic disorder in particular is thought to contribute to the pathogenesis of psychosis, and there is qualitative evidence that adjunctive benzodiazepines not only reduce panic symptoms but are also associated with an attenuation of the positive and negative symptoms of schizophrenia.[13,14] All of these associations are borne out in the present case.

22q11DS itself, of course, is already one of the most potent risk factors for psychosis. The prevalence of any psychotic disorder in the general population is approximately 1%, and presentation in children and younger adolescence is rare. In the 22q11DS population, however, a remarkable 42% of patients are diagnosed with a schizophrenia spectrum disorder at some point in their lives, with a quarter of these cases occurring before age 18.[3,15] It is hypothesized that the behavioral features of 22q11DS seen in childhood may in fact be an early prodrome of psychosis; negative symptoms of schizophrenia in particular are common in adolescents with the deletion.[16] The patient in the present case study did not experience the onset of psychosis until age 33, which is unusual not just in the general population, but particularly unexpected in patients with 22q11DS. Additionally, our patient was diagnosed with intellectual disability in early childhood, but was not diagnosed with ASD until age 27. ASD is thought to be over-reported in patients with 22q11DS, as the diagnosis may be made on the basis of behavioral features that overlap significantly with the features of not just intellectual disability, but also a schizophrenia prodrome.[17]

Treatment and adverse effects

Treatment guidelines for schizophrenia in 22q11DS are currently the same as those for idiopathic schizophrenia (schizophrenia not associated with the microdeletion). There have been many recent case reports and small studies reporting on the efficacy of various neuroleptic agents in 22q11DS, and some describe differences in response to treatment between the two groups. Quetiapine and olanzapine appear as efficacious in 22q11DS patients with schizophrenia as they are in idiopathic schizophrenia, while risperidone may be less efficacious.[6,7,18] Clozapine has been shown to reduce schizophrenia symptoms and hospitalizations as effectively in 22q11DS patients as it does in idiopathic schizophrenia, and at a lower average dose.[8] Three additional case reports support the efficacy of clozapine in this patient population.[5,9,19] One pattern that arises in the literature, however, is the increased likelihood of neurologic side effects with antipsychotic therapy in 22q11DS patients, and with clozapine in particular. These include generalized tonic-clonic seizures, focal seizures, myoclonus, rigidity, and tremor, with seizure being the most severe and the most common.[5,8] Given the association of 22q11DS with hypoparathyroidism and hypocalcemia, this may not be surprising; indeed, approximately half of patients with seizures in one study were retroactively identified as having had documented hypocalcemia shortly before their seizure.[8] In such patients, seizure recurrence was prevented with calcium and vitamin D supplementation, as well as an antiepileptic (valproic acid or gabapentin) in some cases.

Due to the hematologic and seizure side effects associated with clozapine, the patient's prior failed trial of quetiapine, and the evidence in the literature that 22q11DS patients are more likely to fail risperidone, our initial choice of treatment for the present patient was olanzapine with adjunctive clonazepam. No benefit was seen at five months, and at this point olanzapine was replaced with asenapine, which has not yet been characterized in the 22q11DS-associated schizophrenia literature. The patient and her parents reported vastly improved daily functioning for a period of about one month, which suggests that asenapine with adjunctive clonazepam may be a viable treatment option in refractory schizophrenia in 22q11DS. Approximately one month after beginning asenapine, however, the patient complained of increased anxiety with auditory hallucinations and dystonic reactions, including shaking and claw-like spasms of the hand. She stated that these

Table 1. Neuropsychiatric manifestations of 22q11.2 deletion syndrome and prevalence in this population by age group (adapted from Schneider *et al.*, 2014).[3]

Disorder	Prevalence (%) by age group				
	6-12	13-17	18-25	26-35	36+
Schizophrenia spectrum disorders	1.97	10.12	23.53	41.33	41.73
Major depressive disorder	2.19	8.96	10.84	12.00	15.75
Bipolar disorder	0	0.32	1.88	2.00	3.94
Generalized anxiety disorder	8.28	10.49	9.83	12.16	11.02
Panic disorder	1.20	0.87	6.30	8.76	14.41
Post-traumatic stress disorder	0.36	1.35	0.83	0	2.74
Obsessive-compulsive disorder	5.52	5.94	5.08	5.37	6.30
Specific phobia	21.94	17.02	7.22	3.82	2.83
Attention deficit/hyperactivity disorder	37.10	23.86	15.59	-	-
Autism spectrum disorder	12.77	26.54	16.10	-	-
Oppositional defiant disorder	14.25	14.79	6.09	-	-
Conduct disorder	0	0	1.45	-	-

dystonias begin within 5 minutes of taking asenapine and recede over the next hour. They were worsened when environmental stressors were present – *e.g.,* when the patient's parents leave for work in the morning, and have progressed to include transient unresponsiveness. Subsequent 24-hour EEG monitoring did not demonstrate epileptiform activity during these episodes, and the clinical features themselves further suggest that the movements do not reflect seizures. The symptoms also did not respond to benztropine, which reduces the likelihood that they represent unmasked parkinsonism reported in other 22q11DS patients treated with dopamine antagonists.[8,18]

It is still possible that these symptoms reflect a side effect of asenapine therapy; however, given the timing of the symptoms and their association with the patient's experience of stress, they may also be a manifestation of her comorbid panic disorder. Patients with both schizophrenia and panic disorder demonstrate significantly higher levels of functioning than do patients with schizophrenia alone, reflecting a distinct cognitive profile and psychosis etiology for which ideal treatments have not yet been identified.[13] The patient benefited only temporarily from treatment with asenapine and clonazepam, and emotional stimuli appear to have played a role in determining this response; as such, better control of her anxiety may simultaneously reduce psychosis symptoms. As the patient has had valve replacement surgery and will be on warfarin therapy indefinitely, antidepressant/anxiolytic choice must be made with liver enzyme interactions in mind, as warfarin is a substrate. Some selective serotonin reuptake inhibitors, such as fluoxetine and paroxetine, have been linked to clinically significant bleeding risks and/or increases in prothrombin time (PT) and international normalized ratio (INR).[10] Moreover, the patient had not tolerated a past trial with the atypical antidepressant mirtazapine. Therefore, sertraline, desvenlafaxine, and duloxetine were chosen for their more favorable interaction profiles (*e.g.*, mild 2D6 inhibition only), though reports of INR increases without bleeding do exist.[20] The patient and her family were so concerned about the theoretical risk of bleeding that each of these therapies were refused. Anxiolysis with clonazepam was mildly beneficial in this patient, but it is possible that better control of anxiety and panic symptoms may have been achieved with an SSRI/SNRI. The fact that anxiety is a risk factor factor for psychosis suggests that prioritizing anxiolysis, and helping these patients and their families overcome concerns about bleeding risk, is critically important in refractory cases.

Conclusions

Patients with 22q11DS have a significantly elevated risk of developing psychosis and anxiety. In cases where the diagnosis is missed until adulthood, psychiatric features may indeed be the presenting symptoms, and obtaining an accurate diagnosis confirmed with genetic analysis is of the utmost importance. Asenapine may be a reasonable choice of neuroleptic medication in treatment-resistant psychosis for 22q11DS patients with schizophrenia. Adequate management of concomitant anxiety may be a critical factor in the response of these patients to antipsychotic pharmacotherapy.

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