Mosaic Turner Syndrome and Treatment-Resistant Schizophrenia

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Treatment-resistant schizophrenia (TRS) is defined as nonresponse to at least 2 trials of antipsychotic medication of sufficient dose and duration and affects about 30% of people who are diagnosed with schizophrenia.[1] We describe a case of TRS in a person with Turner syndrome.

Turner syndrome, a sex chromosomal disorder that cannot occur in males, is found in nearly 1 of 2,500 live female births.[2] Turner syndrome is characterized by 45X monosomy, 45X/46XX mosaicism, or X chromosome structural abnormality in 60%, 30%, and 10% of cases, respectively. Turner syndrome primarily affects the reproductive, skeletal, and lymphatic systems. Neuropsychiatric problems including schizophrenia, attention-deficit/hyperactivity disorder, autism, and cognitive difficulties have been reported.[3] Table 1 provides an overview of findings in the medical literature relevant to the case as described below.

Case Report

Ms A is a 47-year-old woman who was admitted to an inpatient psychiatric unit of a suburban academic medical center located in the northeast United States. Her symptoms included command auditory hallucinations, disorganized behavior, agitation, and paranoid delusions. Pertinent past psychiatric history included a diagnosis of schizophrenia with 4 previous psychiatric hospitalizations for similar episodes of psychosis. Notable family history includes a maternal history of schizophrenia. In addition, the significant medical history of the patient includes hypothyroidism, type II diabetes mellitus, asthma, dyslipidemia, and irritable bowel syndrome.

Her course in the hospital was notable for progressive disorganized behavior, selective mutism, and paranoid delusions, despite the use of multiple antipsychotics including fluphenazine and quetiapine. In the past, she had also received clozapine, loxapine, lurasidone, and haloperidol. During Ms A's most recent hospitalization, she began to develop periods of confusion, during which she became disoriented to her surroundings and exhibited altered mental status. This led to bizarre behaviors for the patient including increased agitation and spreading of her feces, which was not exhibited with previous episodes of psychosis or hospitalizations. In one instance, she became agitated and threw herself to the floor, resulting in a displaced fracture of the right humerus requiring surgical intervention.

During this hospitalization, a head computed tomography scan was done as well as head magnetic resonance imaging with and without contrast, which were both negative for any acute changes. Upon further workup with karyotyping, it was determined that the patient carried 45X/46XX mosaicism for Turner syndrome. The patient's hospital course was further complicated by the treatment of cholelithiasis and urinary tract infection. Another clozapine trial was initiated following this finding; however, it was abruptly stopped due to tachycardia. Electroconvulsive therapy (ECT) was also considered but was opposed by the patient's family. Ultimately, the patient was stabilized on a combination of risperidone, quetiapine, valproic acid, and duloxetine. As Ms A became lucid and more oriented to self, place, and situation, she appeared less internally preoccupied and distressed by the symptoms of psychosis. The patient no longer endorsed command auditory hallucinations, and there was a significant reduction in the frequency and intensity of paranoid delusions.

Discussion

This patient was found to have TRS based on nonresponse to numerous trials of antipsychotic medications. After the Turner syndrome mosaicism was established, this informed further treatment course by considering ECT and reinitiating clozapine. Ultimately, a combination of second-generation antipsychotics, a mood stabilizer, and a serotonin-norepinephrine reuptake inhibitor led to remission of the acute psychotic episode for the patient. Given the complexity of the treatment course, it is likely that the genetic component of Turner syndrome mosaicism contributed to her psychosis, and this may have contributed to her suboptimal response to several psychopharmacologic interventions.

The empirical literature has hypothesized that a locus within the X chromosome defined as the pseudo-autosomal region is associated with schizophrenia due to changes in normal brain development.[7] This has led to the examination of other components of the X chromosome outside of this locus, including Xp21 associated with the development of schizophrenia.[13] In addition, the Xp13 region, where the HOPA gene is located which plays a role in fetal development, may also be involved in the pathogenesis of schizophrenia.[14]

The association of mental health conditions with Turner syndrome has been reported. Although the level of evidence remains weak, the clinical

Table 1.
Summary of Studies Associating Turner Syndrome With Mental Disorders

Authors	Findings and clinical implications
Ygland Rödström et al[4]	A possible association between Turner syndrome and bipolar disorder and comorbidity could be more complex and the treatment response slower.
Avdic et al[5]	Females with Turner syndrome have an increased risk of receiving a diagnosis of neurodevelopmental or psychiatric disorder. This warrants extensive assessment of intellectual and cognitive functions from early age, and increased psychiatric vigilance should be a part of lifelong health care for females with Turner syndrome.
Hanew et al[6]	The more exact prevalence of diverse complications in Turner syndrome was clarified, and it exceeded the prevalence of the majority of complications in the general population, specifically epilepsy (2.8%) and schizophrenia (0.9%).
Carlone et al[7]	Aripiprazole once monthly efficacy and noninferiority to oral aripiprazole have been demonstrated in preventing relapse in Turner syndrome patients with schizophrenia.
Roser and Kawohl[8]	A polymorphism of the HOPA gene within Xq13 termed HOPA^{12bp} is associated with schizophrenia, mental retardation, and hypothyroidism. Xq13 is the X-chromosome region that contains the X-inactivation center and a gene escaping X-inactivation whose gene product may be involved in the X-inactivation process as well as in the pathogenesis of sex chromosome anomalies such as Turner syndrome. These genes that escape X-inactivation may produce their gene products in excess, influencing normal brain growth and differentiation.
Wustmann and Preuss[9]	There is a relationship between Turner syndrome and psychosis. The neuropsychiatric changes are seen in individuals with Turner syndrome.
Catinari et al[10]	Mild psychosis in individuals with Turner syndrome has stress-precipitated onset and prominent mood features that may resemble organic disease.
Prior et al[3]	Turner syndrome occurs approximately three-fold more frequently in females with schizophrenia than in the general female population ($P < .02$).
Hong et al[11]	In Turner syndrome, the psychological and environmental factors, as well as genetics, may play an important role in the impairment of cognitive abilities, and the neuropsychological aspects may not be related only with the organic substrate.
Jung et al[12]	In Turner syndrome, there is possible involvement of genes on the X chromosome in the development of schizophrenia.

complexity in persons with Turner syndrome and cooccurring affective illness, cognitive impairments, neurodevelopmental disorders, and schizophrenia brings unique challenges.[15] In clinical settings, Turner syndrome with schizophrenia inspires inquiries into how genetics and antipsychotic medications may be utilized given these individuals have partial or no response to treatment.[16] There are a few reports of ECT for treatment-refractory catatonia symptoms in Turner syndrome patients, although there is a lack of evidence about specific therapeutics.[17] This case report adds to the literature on Turner syndrome and psychosis and is an example of the heterogeneity of individuals who meet the criteria for TRS.

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