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Case Report

Schizoaffective Disorder in an Individual with Mowat-Wilson Syndrome (MWS)

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Abstract

Mowat-Wilson Syndrome (MWS) is an autosomal dominant genetic syndrome caused by mutations in the ZEB2 gene. It is characterized by distinctive facial appearance, intellectual disability (ID), epilepsy, Hirschsprung disease (HSCR), and other congenital anomalies. The psychiatric symptoms, associated with MWS have rarely been reported. The following report highlights a case of schizoaffective disorder in a 24-year-old male with MWS and the challenges he encountered over his treatment course.

After considering numerous diagnoses including bipolar disorder and psychosis secondary to a general medical condition, the patient was diagnosed with schizoaffective disorder. Various trials consisting of atypical antipsychotics and mood stabilizers were unsuccessful in managing his symptoms. Eventually, the patient stabilized on a medication regimen consisting of clozapine 300 mg once daily, topiramate 75 mg twice per day, and lithium 1800 mg once daily.

This case report documents co-occurrence of MWS and Schizoaffective disorder.

More Information

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Introduction

Mowat-Wilson Syndrome (MWS) is a rare autosomal dominant genetic condition caused by a heterozygous mutation of the ZEB2 gene [1,2]. It is characterized by a distinctive facial appearance and moderate-to-severe intellectual disability (ID), but can also include various other features such as epilepsy, Hirschsprung disease, genital anomalies, congenital heart disease, and agenesis of the corpus callosum [1-4]. Multiple studies have detailed the associated behavioural manifestations that can also occur such as hyper-orality, bruxism, and an underreaction to pain [2,5]. Unfortunately, there is not a wealth of published evidence supporting psychiatric symptoms associated with the syndrome itself.

This case study describes a 24-year-old male with intellectual disability who was diagnosed with Mowat-Wilson Syndrome. It details the challenges that arose with regard to managing symptoms of treatment-resistant schizoaffective disorder. This study aims to bring awareness to the physical and psychiatric manifestations of Mowat-Wilson Syndrome, as well as document a stepwise general management approach to the psychiatric manifestations that could occur as part of the cluster of symptoms associated with the condition.

Methods

This case report involved a literature review that used Medline and Embase and focused on Mowat-Wilson Syndrome. Some keywords that were utilized in the search included psychosis, intellectual disability, and schizoaffective disorder. We included studies that described schizophrenia, schizoaffective disorder, bipolar affective disorder, and psychosis in cases of Mowat-Wilson Syndrome. We excluded studies that did not have a genetic diagnosis. We used multiple clinical interviews with the patient and the family and had access to his case records for longitudinal information to come to a diagnosis of schizoaffective disorder. One of the authors (MA) was his treating clinician for many years, who observed multiple episodes of illness. We used DSM-5 criteria to make the diagnosis of schizoaffective disorder [6].

Ethics approval for this case report was granted by the Health Science Research Ethics Board at Queen's University, Kingston (Reference file 6025503). Informed consent for conducting the case report was also obtained. A detailed electronic chart review was conducted.

Results

Literature review

A study by Evans, et al. [5] detailed the behavioral symptoms

associated with Mowat-Wilson Syndrome. Evans's behavioral analysis found that individuals with the genetic condition demonstrated a happy effect, were sociable, and exhibited a higher incidence of hyper-orality, stereotyped behaviors, and attention deficit hyperactivity disorder (ADHD). This study failed to mention any symptoms of psychosis in these individuals [5].

Besterman and Hendren [7] detailed the difficulties encountered when managing both the neurological and behavioral manifestations of Mowat-Wilson Syndrome [7]. They mentioned that first-line pharmacological treatment should include anti-epileptic medications such as divalproex, lamotrigine, or carbamazepine, as they can have a dual effect on both seizure reduction and behaviors [7]. According to the literature, risperidone, a second-generation antipsychotic, has been used to manage behavioral issues in individuals with ID, in particular [7]. Olanzapine, which was used in this case study, was also found to be efficacious [7].

Ivanovski described a series of 87 cases [2]. They reported rapid mood changes, unrealistic happiness and elation, and laughing for no obvious reason in their cohort. They, however, did not identify with a diagnosis of schizophrenia or bipolar disorder. They also reported some behaviours suggestive of autism spectrum disorder for example flicking, tapping, and twirling of objects, standing close to others, and eating non-food items in many of their patients.

Case report

This patient is a 24-year-old gentleman with a past psychiatric history of ADHD, autism spectrum disorder, and epileptic seizures. He was diagnosed with Mowat-Wilson Syndrome after genetic testing was completed in 2015 when he was an adult. In several admissions to the Kingston General Hospital inpatient psychiatry unit and in outpatient follow-up appointments with the local developmental disability community mental health team he was managed for treatment-resistant schizoaffective disorder.

In 2013, soon after completing his secondary school diploma, the patient developed command auditory hallucinations, increased irritability, increased anger, "odd behavior" described as threatening and aggressive, poor sleep, and pervasively low mood. He was admitted to Kingston General Hospital as an inpatient and was diagnosed with adjustment disorder with mild intellectual disability (completed psychological testing included Wechsler Intelligence Scale for Children (WISC-IV) – the overall level of performance borderline to extremely low range, full-scale IQ at <0.1). Post-discharge, he was referred to a first-episode psychosis outpatient program but was ultimately discharged from the service as he did not engage.

After a suicide attempt in August 2014 where he presented to the emergency department after cutting his wrists and chest, he was referred to the local developmental disability community mental health team. At this time, he was taking aripiprazole 5 mg daily, escitalopram 20 mg daily, quetiapine 300 mg at night, methylphenidate 18 mg in the morning, lamotrigine 200 mg twice daily, and clonazepam 1 mg (up to 3 mg) at night as needed.

After an initial assessment at the local developmental disability community mental health team in October 2014, his aripiprazole was titrated up to 20 mg daily and quetiapine was decreased to 250 mg for better symptom management. Escitalopram was decreased to 10mg daily because the patient stated he was having increased palpitations. At follow-up visits, auditory hallucinations persisted which resulted in aripiprazole being increased to 25 mg and quetiapine being reduced to 200 mg. Around this time, the patient was also referred to a geneticist for genetic testing. A comprehensive epilepsy panel showed a missense variant in p. Thr908Ile in ZEB2, a gene associated with the autosomal dominant inherited condition Mowat-Wilson Syndrome.

In November 2014, the patient was admitted as an inpatient to Kingston General Hospital for increasing suicidal ideation. His diagnosis at this time was revised from adjustment disorder to bipolar affective disorder, as it was felt the patient was experiencing symptoms of hypomania. Medication changes included increasing his aripiprazole to 27 mg once daily, adding 5 mg of olanzapine at night, and stopping the use of quetiapine as it was yielding no benefit. Despite these changes, the patient continued to experience symptoms of hypomania resulting in the team increasing the patient's olanzapine to 10 mg and aripiprazole to 30 mg. It was difficult to balance the management of hypomanic symptoms with sleep preservation; as a result, his olanzapine was further increased to 20 mg at night. In February 2015, the patient was started on lithium, which was cross-tapered with olanzapine. Olanzapine was ultimately discontinued and lithium was increased to 1200 mg once daily. During an inpatient admission to Kingston General Hospital for an appendectomy and orchiectomy due to testicular torsion, he was also trialed on both lurasidone and ziprasidone; he did not tolerate this trial due to side effects. Ultimately, his mood symptoms and auditory hallucinations seemed to respond the best to lithium but did not resolve completely.

After proving to have numerous treatment-resistant symptoms despite the use of various antipsychotics, the patient was started on clozapine in March 2016, which was titrated up to 150 mg daily. Unfortunately, he was admitted to Kingston General Hospital again in April 2016 because of constipation and was diagnosed with both Hirschsprung's disease and renal dysfunction. It was not clear whether Lithium was responsible for the renal function impairment but as a precaution, it was stopped. This caused the re-emergence of low mood symptoms, which were previously very well controlled on lithium. To manage this, clozapine was further

increased to 175 mg daily. Clozapine, which worked well to manage his mood and psychotic symptoms, also had its fair share of side effects; the patient was started on Metformin in October 2016 to address weight gain secondary to clozapine use [8].

After considering numerous diagnoses including bipolar II disorder and psychosis secondary to a general medical condition, the patient was diagnosed with schizoaffective disorder. Various trials consisting of atypical antipsychotics and mood stabilizers were unsuccessful in managing his symptoms. Eventually, the patient stabilized on a medication regimen consisting of clozapine 375 mg once daily, topiramate 75 mg twice per day (to counteract the weight gain from the use of clozapine) [9], and lithium 1800 mg once daily (which was re-started once his kidneys function recovered). As a result, his level of functioning significantly improved; he was initially unable to work but is now working part-time. He continues to be followed in the community by the local developmental disability community mental health team.

Discussion

Mowat-Wilson Syndrome is a rare autosomal dominant genetic syndrome that has many medical complications and can have psychiatric implications, as well [1,2]. It is caused by a mutation in the ZEB2 gene [1,2]. The mutation identified in our case was a missense variant, which we believe contributed to our patient's presentation and diagnosis [1,2]. In Ontario, microarray genetic testing for copy number variants is universally available for individuals with intellectual disability. This patient has a single nucleotide change that would not have been detected by that method. Targeted sequencing for epilepsy genes helped with the diagnosis. The molecular diagnosis of the syndrome triggered further clinical evaluation and identification of multisystem features of the syndrome. This case emphasizes the need for genetic testing of individuals presenting with a cluster of symptoms including intellectual disability that should go beyond microarray and include exome sequencing to identify changes that will be missed in microarray testing [2]. A thorough assessment of both behavioral and physical health conditions should help with early identification of the syndromic features and guide genetic testing [2]. In this case, the patient was not diagnosed with Mowat-Wilson Syndrome until he was an adult. The diagnosis resulted in significant changes in monitoring potential health problems and improved his care. To the best of our knowledge, there is no previous report of schizoaffective disorder in a patient with MWS. One obvious question is whether it is a chance association or there is a causative link. Only further evidence can help to address that question. Rare genetic conditions should not be overlooked in a broad differential that includes symptoms of psychosis in someone with pre-existing intellectual disability.

When it came to choosing a psychiatric diagnosis for this patient in particular, it was challenging to tease out the different criteria. It is important to remember that psychosis is more common than bipolar disorder in individuals with intellectual disability [10]. Diagnosing mental health conditions in individuals with dual diagnoses is also quite complex. Ultimately, diagnostic criteria overlap and have similar treatments, which makes it challenging to commit to a single diagnosis [11]. Our patient in particular met the criteria for several psychiatric disorders including schizophrenia, bipolar II disorder, and autism spectrum disorder. In addition, the patient had the physical complications of Mowat-Wilson Syndrome, which made it difficult to fit his presentation under a single diagnostic label.

Brain imaging studies have identified structural brain changes in patients with Mowat-Wilson syndrome. These changes include anomalies of the corpus callosum, hippocampal abnormalities, enlarged cerebral ventricles, and white matter abnormalities [12]. These changes are associated with mood abnormalities for example happiness despite serious illness. In our patient, however, the mood symptoms were cyclic, and full-blown manic and depressive episodes were observed. The patient was taking anti-convulsant medication that can cause mood instability [13]. We considered this possibility but the presentation in this patient was consistent with a diagnosis of schizoaffective disorder with clear episodes instead of ongoing mood instability.

As this is only a single case, we cannot infer any causation. It is an association and can be a coincidental finding.

The management of psychiatric manifestations in these conditions can be quite treatment-resistant. It is important to optimize a treatment regimen that targets symptoms, especially behavioral problems such as aggression; when managed appropriately, it can improve a patient's quality of life, minimize symptom burden, decrease distress, and optimize patient safety [2]. Behavioral measures and antipsychotics, such as clozapine, can be used to manage aggression in individuals with intellectual disability [14,15]. Clozapine not only works well to control these behaviors but ultimately helps to decrease the hospitalization rate in this population, as well [14,15]. It is important to find a treatment regimen that balances the efficacy of treatment and side effects in order to work best for the patient; this, in turn, requires frequent reassessment over a long period of time. In this case, this patient was trialed on numerous medications before his optimal regimen was discovered. These medications included antipsychotics (aripiprazole, quetiapine, olanzapine, lurasidone, ziprasidone, clozapine), mood stabilizers (lamotrigine, lithium), selective serotonin reuptake inhibitors (escitalopram), stimulants (methylphenidate), and benzodiazepines (clonazepam). The combination of clozapine, topiramate, and lithium worked well and allowed the individual to return to an improved level of functioning.

Conclusion

This case study highlights the importance of genetic testing in individuals with intellectual disability and psychiatric symptoms, as the management and prognosis of these individuals can be quite treatment-resistant and complex. Rare genetic conditions, such as Mowat-Wilson Syndrome, should not be overlooked in a broad differential that includes symptoms of psychosis in someone with pre-existing intellectual disability [2]. In individuals with dual diagnoses, it can also be quite difficult to establish the criteria for certain psychiatric conditions. This can make psychosis challenging to diagnose, which when left undiagnosed and untreated, can negatively impact a patient's level of function and quality of life. It is important to remember that optimization of management can be a lengthy and discouraging process. Finding the perfect regimen that works well for the individual can decrease patient distress, minimize symptom burden, improve safety, and ultimately improve patient quality of life and level of functioning.

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