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Psychopharmacological Management of Problem Behaviors in Mowat–Wilson Syndrome

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To The Editor:

MOWAT–WILSON SYNDROME (MWS) IS a neurodevelopmental disorder characterized by intellectual disability (ID), Hirschsprung disease, agenesis of the corpus collosum, seizures, expressive language deficits, a distinct facial gestalt, congenital heart defects, and behavioral dysregulation, with a happy and social demeanor (Adam et al. 2006). It is caused by *de novo* heterozygous mutations in the ZEB2 gene, which is produced at high levels in postmitotic neocortical neurons and may play a role in determining neuronal cell fate in corticogenesis (Seuntjens et al. 2009). The behavioral phenotype associated with MWS was recently characterized in a systematic evaluation of 61 MWS patients (Evans et al. 2012). The MWS behavioral profile was then compared with contrast participants with ID of various etiologies. Individuals with MWS were found to have higher rates of several behaviors, such as being unrealistically happy or elated and underreacting to pain. However, overall rates of clinically significant psychopathology were similar to the general ID population at ~30% (Evans et al. 2012).

Evidence-based psychopharmacological approaches can be used to target behavioral and emotional symptoms in individuals with MWS. However, the evidence base is built on studies of individuals with ID of many etiologies (Handen and Gilchrist 2006). Reporting of anecdotal clinical successes and failures in the MWS population specifically is a first step to improving future treatment outcomes. To our knowledge, there are currently no reports in the literature on the psychopharmacological management of problem behaviors in patients with MWS. Therefore, we report our experience with a single patient in hopes that it may act as a starting point toward more precise behavioral management strategies for individuals with MWS.

Case Report

The patient was a 5-year-old nonverbal girl with ID, seizures, behavioral dysregulation, hypoaesthesia, and gastrointestinal motility difficulties. Pregnancy and birth occurred without complication. The patient rolled over at 4 months, walked at 16 months, and babbled at 6 months, but then lost her verbal language abilities until she started babbling again at 4 years of age. Her language comprehension was intact, but she is learning sign language to express herself. Her developmental course had been complicated by seizures, with early-onset absence seizures and later-onset myoclonic and atonic seizures. Serial head MRIs revealed trace thinning of peritrial white matter without progression. Exome sequencing revealed a c.73+1G>T pathogenic variant in the

ZEB2 gene, which is predicted to disrupt the canonical splice site between exons 2 and 3.

Psychotropic management was initiated by a child neurologist for seizure control and problem behaviors such as irritability, tantrums, aggression, and nighttime awakenings. In summary, levetiracetam was found to be helpful for seizure control, but was ultimately discontinued because of worsening aggression and nighttime awakenings. Ethosuximide, clobazam, and divalproex sodium were also found to be helpful in seizure control, but did not have significant effects on behavior. Risperidone was found to be moderately helpful in reducing the frequency and intensity of tantrums, but overall behavior remained significantly problematic. Melatonin and clonidine were trialed as sleep aids, without benefit. Amphetamine/dextroamphetamine salts were trialed for 3 weeks to target attention, but then were stopped because of exacerbation of irritability and tantrums. At the time of referral for ongoing behavioral management, the patient was on a regimen of risperidone 1.5 mg twice daily, ethosuximide 7 mL b.i.d., and clonidine 0.05 mg at bedtime.

On initial presentation, the patient's father reported that she frequently hit caretakers, but would then kiss them "as if to apologize." She had chronic irritability with sporadic tantrums for up to an hour, with unclear triggers. She awoke several times per night, with intermittent sleep terrors. We hypothesized that part of her irritability might be the result of difficulty keeping focus on external tasks; therefore, we started dexamethylphenidate 2.5 mg daily. She developed worse aggression and new biting behavior, and was sent home from school for being "out of control," ultimately leading to a brief hospitalization. We started the patient on olanzapine ODT 2.5 mg at night and divalproex sodium 125 mg b.i.d., up to 250 mg b.i.d., and slowly tapered her off of dexamethylphenidate and risperidone. Improvements in behavior and sleep were observed; therefore, olanzapine ODT was gradually increased to 2.5 mg in morning and 10 mg at night. On this new regimen, the patient's sleep greatly improved with fewer nighttime awakenings, almost-resolved night terrors, improved behavior and learning in school, and less intense and frequent tantrums. However, her behavior continued to fluctuate with environmental factors, such as seasonal allergies, and she has gained significant weight since initiating olanzapine ODT.

Discussion

For many MWS patients with both behavioral problems and seizures, the two can be interrelated, and patients can undergo behavioral decompensation in a post-ictal period or put themselves at increased risk for seizures by becoming agitated and stressed.

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Therefore, it is crucial to have coordinated co-management between seizure and behavioral specialists. Some antiepileptic drugs (AEDs), such as divalproex sodium, lamictal, or carbamazepine may serve a dual role for both seizure and behavioral control, and may be good first agents to try. However, as we observed with divalproex sodium, they are not always effective in this dual role, and agents targeting the symptoms separately may be necessary. Furthermore, some AEDs, such as levetiracetam, may actually exacerbate problem behaviors, as we observed. Risperidone is commonly used as a first-line atypical antipsychotic for problem behaviors in individuals with ID, but it was only moderately effective in reducing problem behaviors for our patient. Olanzapine ODT up to 12.5 mg daily provided more significant, and there was immediate improvement in both the frequency and intensity of tantrums, and nighttime waking with terrors. This may in part be because of the highly sedating properties of olanzapine compared with risperidone. However, the patient also had significant improvements in school performance after olanzapine initiation, suggesting behavioral benefit beyond sedation.

Lastly, it is unclear why our patient had such an adverse response to stimulants. It suggests that our patient's attention difficulties may be quite different from those in attention-deficit/hyperactivity disorder (ADHD). It may be that her inattention is a manifestation of overstimulation by certain environments or a frustration with her inability to communicate her needs. Based on our experience, we would recommend that providers use stimulants with great caution in individuals with MWS.

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Disclosures

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Pharmaceutical, Curemark, Forest Pharmaceuticals, Inc., Roche, Shire, Sunovion, and the Vitamin D Council. He is on advisory boards for BioMarin, BioZeus, Coronado Biosciences, Forest, Janssen, and Neuren.

Informed Consent

Consent has been obtained from both legal guardians of the patient discussed in this manuscript. They have both personally reviewed the manuscript, provided us with feedback, and given approval for publication.

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