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Management of NEM and Dystonia in Angelman Syndrome

Movement disorders in Angelman Syndrome (AS) are a recognized challenge that can be highly burdensome to patients and their caregivers, with a significant impact on quality of life. Management in both the acute setting and outpatient setting can be quite challenging. There is no gold standard treatment and much of the data we have at this time is anecdotal.

Myoclonus in Angelman Syndrome (AS) may be epileptic or nonepileptic. Epileptic myoclonus is more predominant in children whereas nonepileptic myoclonus (and dystonia) are more prevalent in late teensand adults. Differentiation of the two is an important first step in management, though this can be challenging. Epileptic myoclonic status may be associated with preservation of awareness as is seen with nonepileptic myoclonus. Further, given the involvement of the face and eyes with nonepileptic myoclonus, the EEG artifact this produces may complicate interpretation of the EEG.

Prevention

Data supports some clear triggers that increase risk for movement disorders in AS or could exacerbate them. Not limited to:

- Poor sleep
- Constipation
- Anxiety
- Menses in girls and women

Sleep

Sleep is a common challenge in AS syndrome, both initiation and staying asleep. Many treatments have been used with variable efficacy, ranging from **melatonin, diphenhydramine, clonidine, clonazepam, trazodone and others. Mirtazapine** can also be helpful in AS though can result in increased appetite and marked weight gain. **Belsomra** is a medication that is FDA approved specifically for the treatment of insomnia. There are a few anecdotes of it working very well in AS. It can be challenging to get insurance to approve this. I have a few patients I have adopted who have responded well to microdoses of 3 mg of **naltrexone**.

Anxiety

Anxiety is common in AS and can manifest in unusual ways, including episodic retching. This also seems to worsen with age. **Buspirone** is commonly used to managed anxiety in AS and in adults, can be titrated to a maximum dose of 20 mg three-times daily. **SSRIs** are also a consideration if buspirone is not helpful. Acutely, hydroxyzine is a consideration, one which can be used PRN for anxiety producing situations. **Propranolol** is another option which may help with chronic anxiety, but may also be used as needed for anxiety. Lastly, as noted above for sleep, mirtazapine is another option that may have the additional benefits of improving sleep and improving appetite (if desired).

Constipation Makes Everything Worse!

Constipation is very common in AS and can adversely affect mood, sleep, seizures and movement disorders. Thus, discussion with family to determine if worsened is very important. Having a **low threshold for a KUB** is important as there may be overflow with severe constipation which may cloud the clinical presentation. Many standard treatments for constipation are used, not limited to increasing dietary fiber, **Miralax (or generic form), lactulose, fiber supplement, or senna**. A supplement of a medium chain triglyceride **(MCT oil)** may also be considered. This can help with constipation and given how it is metabolized, may have additional benefits in reducing movement disorders and seizures. Consider starting at 2.5 ml 1x daily with a meal and increasing to 3x daily with meals. May increase as needed and tolerated to 10 ml three-times daily with meals.

- **Magnesium citrate** can also help with constipation. The citrate component of the compound may lower risk of kidney stones, a consideration if on topiramate or zonisamide. A typical starting dose is 250 mg 1x daily but you could use 250 mg 2x daily if needed.

Menses

This has been reported to be a trigger in some women. Contraceptive options which limit hormonal fluctuations may be considered. Defer to PCP or OB/Gyn for treatment and dosing options.

Acute Management of NEM / Dystonia

As noted above, differentiation of epileptic versus nonepileptic myoclonus may help guide treatment options. That being said, may agents which treat epileptic seizures may help with nonepileptic myoclonus.

- First line therapies would be **benzodiazepines**.
- If sleep is helpful, give standard sleep medications early.
- There are anecdotal reports of **IV diphenhydramine** being helpful acutely. This may be due to sleep promotion (movement disorders stop during sleep) or due in part to its anticholinergic properties.
- Typical antiseizure mediations which are helpful for myoclonus that may help with nonepileptic myoclonus acutely and can be loaded IV include **levetiracetam** and **valproic acid**. Overall, valproic acid is not a favorite for long-term management, but is a consideration acutely.
- Anecdotally, in the ICU setting, **ketamine** has been reported to be beneficial.

Subacute to Chronic Management of NEM / Dystonia

There may be an admixture of myoclonus and dystonia contributing to the nonepileptic myoclonus in AS, thus additional considerations include more traditional treatments for dystonia.

- Oral forms of **levetiracetam, brivaracetam** or **valproic acid** may be considered for daily use, though valproic acid is not favored.
- Case reports have suggested benefits of **perampanel**, though given its long half-life may not be as helpful in the subacute period.
- **Trihexyphenidyl** (Artane) is an anticholinergic used for treatment of dystonia that can be helpful in those with nonepileptic myoclonus. Side effects of worsening constipation and urinary retention are considerations.
- **Levodopa/carbidopa** (Sinemet) or dopamine agonists are additional treatment options which may be considered. Case reports support use of Sinemet in adults with AS and abnormal movements with Parkinsonian features
- **Propranolol**. As noted above if coexistent anxiety. This also may help acutely with NEM/dystonia
- **Epidiolex** or **artisanal cannabidiol (CBD)**. Anecdotal reports have noted improvements in NEM/dystonia using both prescription CBD (Epidiolex) and artisanal (over-the-counter) CBD products.