Effective Treatment of Pseudobulbar affect in Pediatric ALS

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BACKGROUND

- **Pseudobulbar affect (PBA)**
  - Episodic, inappropriate laughing and/or crying
  - Well known in adult ALS
  - Can be seen in up to 50% of ALS patients
  - Also can be seen in Multiple Sclerosis, dementia, stroke, traumatic brain injury
  - Can cause distress for patient because response is out of proportion to emotion or not appropriate for the context
  - May interfere with function

- **Dextromethorphan hydrobromide/quinidine sulfate (Nuedexta)**
- FDA approved in 2010 for use in adults with PBA
- Dosing in adults is dextromethorphan/quinidine 20/10 twice per day
- Pediatric labeling for dosing is not available
- Mechanism of action –
  - Dextromethorphan (DM) is an NMDA receptor antagonist and sigma-1 receptor agonist, modulates glutamate signaling
  - Quinidine is a CYP2D6 inhibitor and increases dextromethorphan availability and prolongs half-life by preventing DM conversion to dextrorphan
  - Exact mechanism is not known
- Some risk of prolongation of QTc but in trials only small increases in QTc at doses higher than FDA recommendation

- **Pediatric ALS2**
- ALS2 encodes protein alsin
- can manifest as one of three conditions with upper motor neurodegeneration, spasticity
  - Infantile onset ascending spastic paralysis
    - Rapid progression, infantile onset, spares lower motor neurons
  - Juvenile amyotrophic lateral sclerosis
    - Lower motor neurons affected
    - Fasciculations, areflexia
  - Juvenile primary lateral sclerosis
    - Does not affect lower motor neurons
    - Oculomotor signs
    - Slow disease progression

CASE DESCRIPTION

- 9yr Male with gait abnormalities, spasticity, had previously carried diagnosis of cerebral palsy
- Diagnosis of cerebral palsy made based on spasticity and difficulties with gait
- As a young child had delayed gross motor milestones and speech, not speaking in sentences until age 3.
- However, his gait worsened as he grew and he never attained independent ambulation
- Investigated with chromosomal microarray, found to have multiple regions of homozygosity, consistent with parental consanguinity.
- Whole exome sequencing identified homozygous pathogenic mutations in ALS2 gene (c.3415C>T; p.R1139*)
- Diagnosed at 9 years with juvenile ALS, caused by ALS2, alsin protein
- Evaluated at Muscular Dystrophy Association clinic evaluation at 9yrs 9 mo, noted to have almost constant laughter which interrupted his ability to perform motor tasks, physical exam and reduced fluency of speech
- He attempted deep breaths to stop the laughter but this was ineffective
- Family recalled inappropriate laughter "for as long as they could remember"
- After evaluation at NIH/NINDS Neurogenetics branch where inappropriate laughter was also obseved, suspected to be PBA, recommendation was made to trial Nuedexta
- No pediatric FDA label or dosing recommendations for Nuedexta
- Treatment started with 10 mg dextromethorphan every other day x 1 week, titrated up to 20 mg twice daily
- This resulted in almost complete resolution of unwanted laughter
- He did not experience adverse side effects

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DISCUSSION

- In addition to ALS, PBA has also been seen in setting of cerebral palsy and extreme prematurity.
- Unclear localization for cause of PBA
  - Cerebellum – emotional expression
  - Corticopontocerebellar pathways – contextually inappropriate emotional expression
  - Frontoparietal opercula
  - Geniculate tracts in opercula
  - Corticobulbar tracts
  - Basal ganglia
- MRI changes in PBA –
  - Posterior cingulum
  - Posterior corona radiata
  - Superior corticospinal tracts
  - Cerebellar peduncles
  - Fornix
- No FDA label for pediatric use of Nuedexta in PBA
- Dose was initiated at 10 mg dextromethorphan every other day for 1 week, then titrated up to eventual dose of 20 mg twice daily

SUMMARY

9 year old boy with ALS2 mutation causative for pediatric ALS, demonstrated PBA. He was effectively treated with dextromethorphan hydrobromide/quinidine sulfate (Nuedexta) at a dose of 20 mg (dextromethorphan) twice daily. He had resolution of PBA symptoms and experienced no side effects.

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