

A Case Report of Topiramate for Severe Breath Holding Spells in a Patient with Pitt Hopkins Syndrome

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Introduction

- Pitt-Hopkins Syndrome (PTHS) is an haploinsufficiency syndrome caused by loss-of-function variants of transcription factor 4 (TCF4) on chromosome 18q21.2¹
- Clinical Phenotype
 - Profound global developmental disabilities
 - Delayed onset of ambulation at 3-6 years of age
 - Absent speech.
- Medical Comorbidities
 - Early-onset myopia
 - Chronic constipation
 - Seizures
- Abnormal Breathing Spells
 - Hyperventilation followed by apnea and rapid onset of cyanosis
 - Only occur when awake
 - No ictal EEG correlate
 - Affects nearly 50% of PTHS patients²

Here we describe a patient with PTHS with previously refractory breathing spells which responded to topiramate.

Patient Case Presentation

- The patient is a 17-year-old boy with Pitt-Hopkins Syndrome and refractory breathing spells
 - Diagnosed by GeneDx Epilepsy Panel at age 10 years.
 - Heterozygous, pathogenic, non-sense variant (c.680_682delinsT, p.W227LfsX29) within exon 10 of TCF4

Developmental History

- Developmental Milestones
 - Babbled at 9-months old
 - He walked at 9-years old
 - He is non-verbal at 17-years old with severe intellectual disability
- He had onset of cyanotic spells at 4-years old that had been refractory to medication trials.
 - Spells consist of rapid, deep breathing followed by holding his breath and rapid onset of perioral cyanosis and diffuse skin mottling.
 - At the conclusion of a spell, he will suddenly take a gasping breath.
 - He can fall with prolonged spells
- Captured events never had an ictal EEG correlate and can be triggered by emotional distress.

Table 1: Detailed review of failed medication trials for breathing spells

Medication	Response
Acetazolamide	Initially was helpful, but waning benefit over time
Valproic Acid	No benefit
Levetiracetam	Allergic Response (eye swelling)
Quetiapine	No benefit
Primidone	No benefit
Clobazam	No benefit
Caffeine	Caused hyperactivity and agitation
Fluoxetine	Caused hyperactivity and agitation
Glycopyrrolate	Minimal improvement in drooling, but no benefit for apnea
Vayarin	No benefit for behavior or apnea
Gabapentin	No benefit
Amantadine	No benefit
Escitalopram	Caused hyperactivity and agitation
Aripiprazole	No benefit
Ferrous Sulfate	No benefit
Desipramine	Caused agitation
Risperidone	Reduced agitation No benefit for apnea

Treatment with Topiramate

- At peak severity, spells would last for up to a minute each and occurred nearly continuously throughout the day
- Acetazolamide was used for the longest and initially beneficial, but efficacy waned over time. It was later weaned with no clear worsening of spells.
- After failed behavioral medication trials, he was started on topiramate with remarkable response.
 - Within four weeks of starting topiramate, episode frequency improved to three or fewer per day.
 - For the first time in over a decade, he had several weeks with no observed apneic events.

Discussion

- There are no prior reports in the literature about the topiramate for respiratory dysrhythmia in PTHS
- There are reports of its use for these symptoms in Rett Syndrome, as well as a case report showing good response to acetazolamide for respiratory dysrhythmia in PTHS^{3,4,5}
- Like acetazolamide, topiramate is a carbonic anhydrase inhibitor that interferes with reuptake of bicarbonate in the kidneys which results in a metabolic acidosis⁵
- This acidosis may counteract the respiratory alkalosis that occurs with hyperventilation and leads to suppression of the respiratory drive⁵

Proposed Mechanism

- In this case, as well as in some case reports of respiratory dysrhythmia in Rett Syndrome, the respiratory symptoms had slight improvement with treatment with acetazolamide but much more effective response to topiramate³
- Compared to acetazolamide, topiramate is a weaker carbonic anhydrase inhibitor and it is specific for two of the six isoenzymes of carbonic anhydrase^{3,4}
- The stronger response to topiramate may indicate that, in certain patients, these particular isozymes are more involved in respiratory regulation and a trial of topiramate would be reasonable even in patients who failed a previous trial of acetazolamide.

References

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