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

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Abstract

Pitt-Hopkins syndrome is a rare genetic neurodevelopmental disorder characterized by intellectual disability, delayed motor development, and absent speech. Patients often show symptoms of respiratory dysrhythmia, including episodes of hyperpnea followed by apnea with cyanosis. These spells occur while awake and do not have ictal correlate on electroencephalogram (EEG). The episodes can become quite frequent and can be challenging to treat. We present a case of a teenage patient with Pitt-Hopkins syndrome who had very frequent apneic spells that responded well to treatment with topiramate after limited response to acetazolamide.

Keywords

intellectual disability, neurodevelopment, developmental disability, genetics, autism

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Introduction

Pitt-Hopkins Syndrome (PTHS) is a haploinsufficiency syndrome caused by loss-of-function variants of *TCF4* (transcription factor 4) on chromosome 18q21.2. It was first described in 1978 by Drs. Pitt and Hopkins, and *TCF4* was identified as the causative gene in 2007.[1] The phenotype has remained relatively homogenous with profound developmental disabilities including global developmental delay (100%) with markedly delayed onset of ambulation and absent speech. Medical comorbidities including early-onset myopia (54-88%), chronic constipation (70-83%) and seizures (35-38%) are also commonly reported. Additionally, nearly half of patients with PTHS have spells of abnormal breathing including hyperventilation which is sometimes followed by apnea with rapid onset of cyanosis.[1] Abnormal breathing spells are consistently only reported while awake and have not had an ictal EEG correlate, so despite often concomitant presence of epilepsy, they do not seem to be seizures and their mechanism is unknown, although may be related to disruption of central chemoreception.[2,3] Respiratory dysrhythmia is also common in patients with Rett syndrome[2,4,5] and has been reported in 2 cases of *HNRNPU* associated epileptic encephalopathy.[6] Here we describe a patient with PTHS with medically refractory spells of abnormal breathing which responded to topiramate.

Case

The patient is a 17-year-old boy who was diagnosed with Pitt-Hopkins Syndrome by a commercially available genetic epilepsy panel at age 10 years. He carries a nonsense deletion within exon 10 of the *TCF4* gene (c.680-682 del). His developmental milestones were markedly delayed. He walked at 9-years-old, babbled at 9-months-old, and currently does not have any expressive language. He had onset of cyanotic spells at 4-years-old that have been refractory to medication trials (Figure 1). His 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. Initially, spells were believed to be epileptic, but captured events never had an ictal EEG correlate. The patient had two EEGs. The first EEG at age 6-years showed intermittent bifrontal slowing, but did not capture the events of respiratory dysrhythmia. The second EEG at age 10-years captured >50 events of

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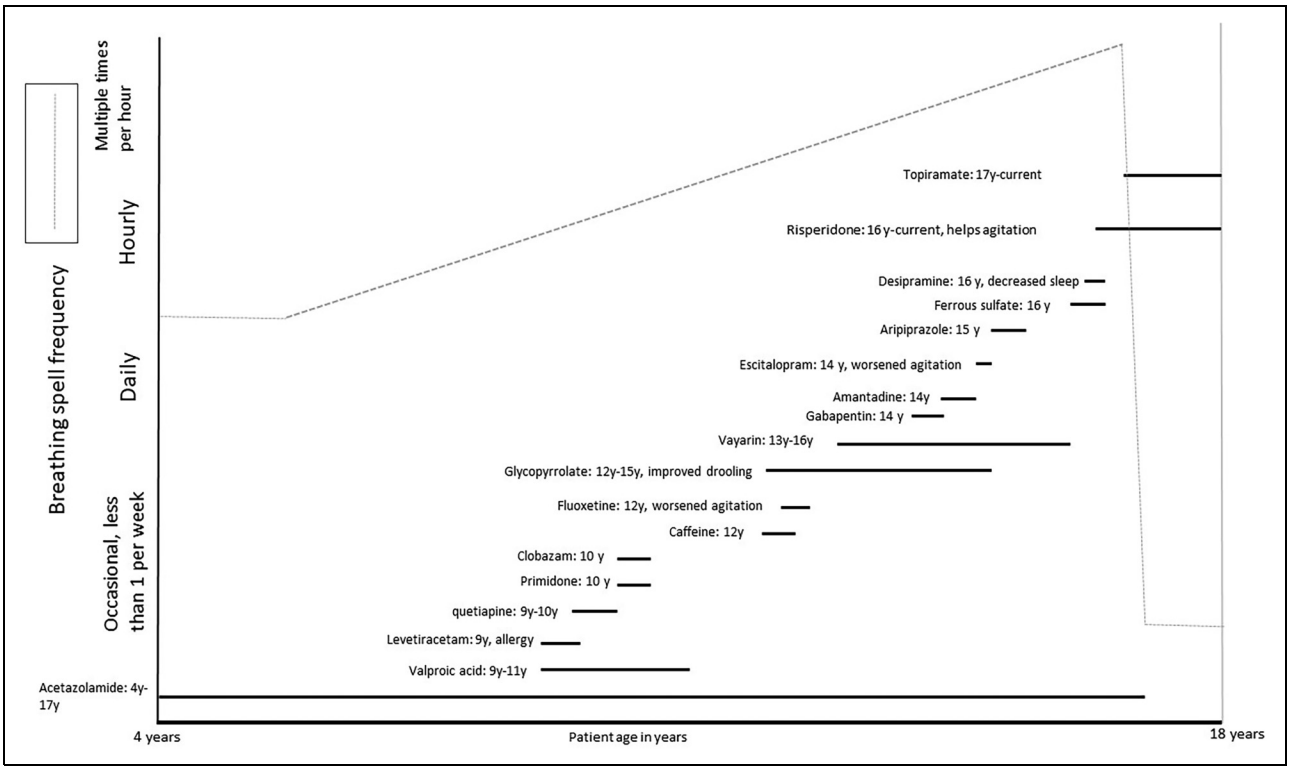

Figure 1. Timeline of medications tried, listed by patient age in years.

apnea and cyanosis with hypoxia to SpO_2 of 37% on pulse oximetry, and did not demonstrate any epileptiform discharges or slowing. The EEG remained normal before, during, and after these events. He never had epileptiform discharges on EEG. Spells were not responsive to multiple anti-seizure medication trials including valproic acid, levetiracetam, primidone, clobazam, or gabapentin. Spells appeared to be triggered by emotional distress or anxiety, however, did not improve with behavioral medications including quetiapine, fluoxetine, amantadine, escitalopram, desipramine, aripiprazole, or risperidone. Additionally, medications to stimulate the respiratory drive including acetazolamide, caffeine, and ferrous sulfate were used with limited efficacy (Figure 1).

At the peak of severity, spells would last for up to a minute each and occurred nearly continuously throughout the day. Acetazolamide was used for the longest and was initially beneficial. Efficacy waned over time despite escalating doses and was ultimately weaned without a clear correlation to worsening of clinical symptoms. He was then started on topiramate 2 mg/kg/day with reduction in spell frequency to fewer than three per day within four weeks. For the first time in over a decade, he had several weeks with no observed apneic events. He does not have epilepsy and in addition to the topiramate, he currently takes risperidone 1.5 mg daily for aggression.

Discussion/Conclusions

Although there is a report of topiramate's effective treatment of epilepsy in PTHS,[7] there are no prior reports in the literature about the use of topiramate for respiratory dysrhythmia in PTHS. There are reports of its use for these symptoms in Rett Syndrome, which can be associated with similar episodes of hyperventilation, apnea, and cyanosis.[4,5] There are also case reports showing good response to acetazolamide for respiratory dysrhythmia in Pitt-Hopkins Syndrome[8,9] and in *HNRNPU* epileptic encephalopathy.[6] Like acetazolamide, topiramate is a carbonic anhydrase inhibitor that interferes with reuptake of bicarbonate in the kidneys which results in a metabolic acidosis.[8] Studies of acetazolamide in treatment of sleep apnea have demonstrated that this acidosis induces mild hyperventilation, which lowers blood partial pressure of carbon dioxide, and in turn stabilizes ventilation so that changes in the respiratory pattern are less likely to lead to apnea or periodic breathing.[8,10,11] 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 topiramate.[4] Compared to acetazolamide, topiramate is a weaker carbonic anhydrase inhibitor and it is specific for the type II and type IV isoenzymes of carbonic anhydrase.[4,5,12] In addition to its carbonic anhydrase activity, topiramate also blocks voltage-dependent sodium channelsenhances GABA transmission resulting in increased CNS levels of GABA, antagonizes the AMPA receptor, and downregulates L-type calcium channels.[12] A preclinical study of PTHS in a mouse model demonstrated that abnormal expression of NaV1.8 sodium channels occurs centrally in the brains of mice with *TCF4*

mutations and disrupts central chemoreceptors, and that this sodium channel may be an effective treatment target for respiratory dysrhythmia in PTHS.[2]

This patient's response to topiramate may indicate that, in addition to the carbonic anhydrase activity that it shares with acetazolamide, the sodium channel blocking activity of topiramate may contribute to its effective treatment of respiratory dysrhythmia. A trial of topiramate would be reasonable even in patients who failed a previous trial of acetazolamide for treatment of apneic spells in Pitt-Hopkins syndrome.

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Author Contributions

MB and KG were both involved in conception of the project, reviewing literature and patient chart, writing and editing the manuscript, and creating the figure.

Declaration of Conflict of Interest

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Not applicable, because this article does not contain any studies with human or animal subjects.

Informed Consent

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Trial Registration

Not applicable, because this article does not contain any clinical trials.

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