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Case Report
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Treatment of Apneas with Caffeine in a Patient with Pitt-Hopkins Syndrome

Stathos J[1,2], Pecson I[1], Galvis AE[1,2,3,*], Saqueton C[2], Holly A[1], Nakamura C[1,2]

[1]Children's Lung Specialists, Las Vegas, Nevada, USA

[2]University of Nevada Las Vegas School of Medicine, Department of Pediatrics, Las Vegas, Nevada, USA

[3]Children's Hospital of Orange County, Department of Infectious Disease, Orange, California, USA

[*]**Corresponding author:** Galvis AE, Children's Hospital of Orange County, Department of Infectious Diseases, 505 S Main St, Suite 1200 Orange, CA 92868 USA; E-mail: agalvis@choc.org

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Abstract

Pitt-Hopkins Syndrome (PTHS) is an unusual and rare genetic disorder caused by inadequate translation of the TCF4 gene, which initiates embryologic neuronal differentiation. The hallmarks of the disease include motor delays, absent speech, autism spectrum disorder (ASD), and intellectual disability. In addition to the cognitive delays, PTHS can be evidenced somatically with atypical brain imaging, abnormal facial features, and severe medical comorbidities including irregular breathing episodes. Generally, there are periods of alternating hyperventilation and apnea occurring while awake. The cause of these spells is unknown at this time. Treatment with acetazolamide has been shown to usually be effective in preventing these episodes. We present a case of a 9-year-old female with suspected PTHS admitted to the Pediatric Intensive Care Unit (PICU) for hyperventilation with severe, debilitating apneic events that were unresponsive to acetazolamide.

Keywords: Pitt-Hopkins Syndrome; Brain imaging

Introduction

Pitt-Hopkins Syndrome (PTHS) is an extremely rare neurodevelopmental disorder that is caused by a variant of the TCF4 gene, located on chromosome 18q21.2. This gene is involved in embryologic neuronal differentiation. The syndrome was originally described in 1978 with abnormal facial features, intellectual delay, and irregular breathing patterns. It can also present with seizure disorder and severe constipation. The exact prevalence of this disease is not known, but there have only been approximately 500 confirmed cases worldwide [1-3].

Currently, there is no cure for the disease, and treatment is focused on preventative and symptomatic care. Due to the rarity of the disease, common sequela resulting in hospitalization and additional care is lacking. However, it stands to reason that the most common reasons would be based on the severity of their constipation, seizures, and/or respiratory patterns. Although the etiology is unknown, treatments for constipation and epilepsy are often effective in the PTHS population [1,4]. An important, and fairly unique, feature of PTHS are the abnormal breathing spells, the exact mechanism is still under investigation.

Approximately 50% of all patients with PTHS exhibit a paroxysmal breathing pattern of hyperventilation with or without resulting apnea. It has been described as rapid breathing with a period of breath-holding afterwards, which could be either psychogenic or physiologic in nature. This period of apnea can be long enough to induce cyanosis [1,5-6]. Generally, acetazolamide has been used to treat these spells, but the mechanism for its effectiveness is hypothetical in nature [5-6].

Caffeine has been long used to reduce apneic actions in the pediatric population, generally in cases of apnea of prematurity. As a methylxanthine, its mechanism of action is well defined. It acts both centrally and peripherally to stimulate the medullary respiratory center, and thus increase carbon dioxide sensitivity, reducing hypoxic respiratory depression [7-8]. Due to this effect, caffeine can theoretically

be used to reduce other types of apnea besides apnea of prematurity.

Case Report

A 9-year-old female with a history of developmental delay and seizure disorder initially presented to the emergency department (ED) with multiple breakthrough seizures. On the day prior to admission, she was in her regular state of health until her parents noticed she was having more seizures than normal and exhibiting unusual type of activity. When she was brought to the ED, she had several more seizures with desaturations (oxygen saturation dropping into the 30-50% range) and associated cyanosis. These episodes were neither extensive nor lasting any longer than 15 seconds, but frequent enough to require the patient to be admitted to the PICU. Despite of these changes in her clinical status, all of her labs were grossly unremarkable. She remained afebrile and had no indications of infection. Her anti-epileptic medication was increased resulting in reduction of seizure activity.

The patient was initially placed on high flow nasal cannula, but was rapidly weaned to room air. She continued to have intermittent episodes of hyperventilation followed closely by apneic events, causing desaturations and cyanosis. She was started on acetazolamide, but with minimal change to her breathing patterns. The patient then underwent a polysomnogram, which was performed while she was awake. It revealed significant hyperventilation followed by central hypopneas (30 episodes, the longest lasting 38 seconds) and the lowest recorded oxygen saturation of 37%. Due to the patient's lack of response to acetazolamide, she was started on caffeine and exhibited rapid improvement. She had a 24-hour period where there were no desaturations. She was discharged with oral caffeine and a pulse oximeter for home monitoring.

Discussion

PTHS is an unusual and rare genetic disorder caused by inadequate translation of the tcf4 gene. The hallmarks of the disease include motor delays, absent speech, autism spectrum disorder, and intellectual disability. In addition to the cognitive delays, PTHS can be evidenced somatically with atypical brain imaging, abnormal facial features, and severe medical comorbidities including irregular breathing spells. Generally, there are episodes of hyperventilation and associated variable apnea occurring while awake. The cause of these spells is unknown at this time. Treatment with acetazolamide has been shown to usually be effective in preventing the episodes.

Caffeine has been given for apneic episodes in neonates for a significant amount of time, leading to understanding of its side effects. However, it is not commonly used in older pediatric populations [7-8]. Although the exact mechanism for PTHS-based apnea is still under investigation, it seems clear that the hyperventilation prior to the apneic episodes induces a hypocapnic state in patients. In similar fashion to shallow water blackouts, this allows the patient to metabolize through their store of oxygen without a significant respiratory drive [9]. Due to caffeine increasing the sensitivity of chemoreceptors to carbon dioxide, patients with hyperventilation-based apneas cannot achieve such hypoxic states as easily.

The diagnosis of PTHS was subsequently confirmed. The application of caffeine for different types of apnea needs additional research. However, the use of caffeine in patients with PTHS and apnea should be considered, especially if it is refractory to other treatment modalities.

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