Case Report

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Acetazolamide for *TCF4* Mutation-Related Apneas

Coca E, Ruiz C, Díaz A, García del Cerro G, Turon E and Boronat S*

Department of Pediatrics, Hospital de la Santa Creu i Sant Pau, Universitat Autònoma de Barcelona, Spain

***Corresponding author:** Boronat S, Department of Pediatrics, Hospital de la Santa Creu i Sant Pau, Universitat Autònoma de Barcelona, Barcelona, Spain

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ABSTRACT

Pitt-Hopkins syndrome (PTHS) is due to a loss-of-function mutation in *TCF4* (transcription factor 4). It is characterized by severe intellectual disability, dysmorphic features and episodic hyperventilation with apnea while awake. Acetazolamide for controlling apnea episodes have been reported in 3 previous cases. We report the case of a girl with a *TCF4* mutation who had a colloid cyst in the third ventricle, which has not been previously reported in this syndrome. She had more than 50 episodes/day of hyperventilation/apnea which completely disappeared for 2 months after treatment with acetazolamide (250 mg/12 h). After this time the episodes recurred but only occasionally.

Keywords: Colloid cyst; Treatment; *TCF4*; Pitt-Hopkins

Introduction

Pitt-Hopkins syndrome (PTHS) is due to a loss-of-function mutation in *TCF4* (transcription factor 4). It is characterized by severe intellectual disability, dysmorphic features and episodic hyperventilation with apnea while awake. Acetazolamide for controlling apnea episodes have been reported in 3 previous cases [1,2] and valproate in one [3]. We report the case of a girl with a *TCF4* mutation who had a colloid cyst in the third ventricle, which has not been previously reported in this syndrome. She had more than 50 episodes/day of hyperventilation/apnea which disappeared for 2 months after treatment with acetazolamide (250 mg/12 h).

Case Report

Thirteen-year-old girl, daughter of healthy non-consanguineous parents, born at 41 weeks with weight: 3285 g, height 52 cm and occipitofrontal circumference of 33.5 cm. She presented with severe global developmental delay in the first months of life and postnatal poor growth. She could sit unaided at 3 years of age and walked independently at 8 years. At 13 years of age, she understands a few simple commands, but she has no expressive language. Stereotypical movements of clapping and flapping of the hands are frequent, mainly when she is nervous. She recognizes familiar faces. She has myopia (-4 diopters). She had dysmorphic features, including deep-set eyes, a broad and beaked nose with flared nostrils, a wide mouth with a cupid´s bow shaped upper lip, small and widely spaced teeth, cupped ears with broad helices. Her occipitofrontal circumference growth followed the p3-p10 centile. Her teeth were widely spaced, and she had a bifid inferior canine. She had slender fingers and bilateral single palmar creases. A brain MR performed at 9 years of age showed a cystic image of 13x11mm with inferior wall calcification in the 3rd ventricle, without hydrocephaly, suggestive of a colloid cyst. Eight months later, cyst enlargement (19 mm) was detected, and it was surgically removed. This cyst was not present in an MR scan performed at 2 years of age. The neuroimaging also showed an ectopic neurohypophysis.

From the age of 6, when she had not yet been diagnosed with Pitt-Hopkins Syndrome, she developed episodes of staring, hyperventilation followed by apneas and intense cyanosis while awake, lasting 1-4 minutes. Although these episodes were not recorded in the EEG, which was otherwise normal, she was started with lamotrigine (50 mg/12 h) in another center, but the episodes' frequency did not change. These events were progressively more frequent until up to 30 times/hour, increased with emotions or fatigue. These lead to the diagnosis of Pitt-Hopkins syndrome and a mutation in exon 13 c.1049_1050delCG (p.G350VfsX13) was detected when she was 10 years old. An EEG ruled out the presence of epileptic discharges associated with these apneic-hyperpneic events, so lamotrigine was discontinued. At the age of eleven she had approximately 50 intense episodes/day, so a trial of treatment with acetazolamide 250 mg/12 h was started. Her parents noted a complete disappearance of the episodes within 2 weeks. Episodes were completely absent for two months approximately and she restarted occasional episodes that were scarce and very mild.

This treatment lead to a marked improvement in the quality of life and after 2 years of treatment there has been no deterioration in symptom control and continues on the same dose of medication.

Discussion

In 2012, Verhulst, et al. [1] reported the successful use of acetazolamide in two patients with Pitt Hopkins syndrome for controlling severe episodes of central apnea. Another case of an important reduction in episodes with this treatment was reported in 2015 [2]. Both authors used a dose of 250 mg/24 h, lower than in our patient. This may account for the more intense response in our case, with complete disappearance of the episodes, although episodes returned after 2 months, but they were much milder and scarcer. The carbonic anhydrase inhibitor acetazolamide interferes with the reuptake of bicarbonate by the kidneys resulting in metabolic acidosis. It regulates blood pH and CO_2 levels, thus impacting the respiratory rate [1]. Improvement of breathing abnormalities were reported after treatment with valproate in one case [3], but no other patients with PHS have been reported with similar response, and some of them with hyperventilation episodes were on treatment with valproate for epilepsy [1]. However, as valproate is a histone deacetylase inhibitor, it may act as a promoter of transcriptional activation and may compensate for the haploinsufficiency of the *TCF4* product [4], thus explaining some of the response to valproate in this patient. Also, as dynamic regulation of histone modifications is involved in long-term memory formation, we believe that specific studies regarding the use of valproate or other histone deacetylases inhibitors as modifiers of memory deficits and breathing dysfunction in PTHS are needed. A synergic effect of valproate and acetazolamide may also be possible and requires further exploration. As epilepsy is frequent in PTHS and to date, no specific antiepileptic drug has proved to be more effective than others in PTHS, more information about valproate effects in this syndrome may be useful [5]. Interestingly, 2 antiepileptic drugs, topiramate and zonisamide, are also carbonic anhydrase inhibitors, so they may be useful in patients with breathing anomalies and epilepsy. To the best of our knowledge, there are not yet reports of response of PTHS to these medications.

In the human brain, *TCF4* is expressed in both neurons, and oligodendrocytes, and is especially important in the development of the noradrenergic system and the maturation of oligodendrocyte progenitors. In early human development, *TCF4* is highly expressed in the central and enteric nervous system, the sclerotome, the parabronchial and kidney mesenchyme, and the genital bud [6]. The highest levels of expression are neocortex, hippocampus, striatum, thalamus and cerebellum [7]. Magnetic resonance (MR) imaging in PTHS may show anomalies in half of the patients, such as ventricular asymmetry, bulging of the caudate nuclei, agenesis or dysgenesis of the corpus callosum, atrophy of the frontal and parietal cortex, arachnoid cysts or mega cisterna magna [5,8]. The 2 main findings in our patient brain MR, ectopic neurohypophysis and colloid cyst of the 3rd ventricle have not been previously reported in PTHS. The physical features in our patient are typical of PTHS, although diagnosis was not reached until she developed hyperventilation. Refractive errors are frequent in PTHS and myopia has been reported in 19% p [9]. Most of patients show a happy and placid personality, with stereotypic movements in 30 % of patients.

Although constipation is frequent, present in about 70-80% of patients with PTHS, our patient did not have constipation. Breathing anomalies are present in about 40-60% of patients, with age of onset from few months to teenagers [5,9]. Both null mutations and missense mutations located in the bHLH domain of *TCF4* impair its interaction *in vitro* with ASCL1, from the PHOX-RET pathway. Interestingly, mutations in components within this pathway have been involved in Hirschprung disease and Ondine hypoventilation syndrome, so the typical findings of severe constipation and/or breathing anomalies in PTHS might be related to an impaired interaction of *TCF4* with components of this pathway [8].

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