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Case report

Weight Loss during Topiramate Treatment in a Severely Obese Adolescent with Congenital Adrenal Hyperplasia and Migraine

Seagroves et al. Weight Loss during Topiramate Treatment in CAH Adolescent

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What is already known?
Youth with classical congenital adrenal hyperplasia (CAH) exhibit earlier adiposity rebound, increased obesity and abdominal adiposity compared to unaffected youth. There is evidence that topiramate therapy is effective in appetite suppression resulting in BMI reduction in obese adults and adolescents. Little is known about the efficacy of topiramate in treating severe obesity associated with CAH.

What does this study add?
Topiramate produced a clinically meaningful and significant weight loss and reduced central adiposity in an adolescent with classical CAH and severe obesity. Topiramate was used safely without an increase in frequency of adrenal crises or glucocorticoid requirement. Topiramate therapy may be especially effective in patients with CAH given their increased visceral adiposity.

Abstract
Youth with classical congenital adrenal hyperplasia (CAH) due to 21-hydroxylase deficiency exhibit an increased prevalence of obesity, early adiposity rebound, and increased abdominal adiposity compared to unaffected youth. Current obesity management in CAH largely focuses on lifestyle modifications. There is evidence that topiramate therapy is effective in reducing BMI, as well as visceral adipose tissue, in unaffected adolescents with exogenous obesity. However, little is known about the efficacy of topiramate in patients with classical CAH. We report a 17-year-old female with severe obesity and salt-wasting CAH due to 21-hydroxylase deficiency, who demonstrated reductions in BMI, as well as abdominal visceral and subcutaneous adipose tissue on topiramate therapy. The patient was diagnosed with classical CAH as a newborn with a 17-hydroxyprogesterone 11,000 ng/dL. She had a BMI > 95th percentile at 3 years old, followed by unremitting obesity. At 17 years old, she was started on topiramate to treat chronic migraines. Following three years of topiramate therapy, her BMI z-score decreased from +2.6 to +2.1. After four years of therapy, her waist circumference decreased from 110 to 101 cm, abdominal visceral adipose tissue decreased substantially by 34.2%, and abdominal subcutaneous adipose tissue decreased by 25.6%. Topiramate therapy was associated with effective weight loss and reduced central adiposity in an adolescent with classical CAH and severe obesity, without side effects. Further study is warranted regarding topiramate therapy in obese youth with classical CAH and increased central adiposity, who are at higher risk for significant morbidity.
Keywords: congenital adrenal hyperplasia, topiramate, obesity, body composition, body fat percentage, adolescent, 21-Hydroxylase deficiency

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Introduction
Youth with classical congenital adrenal hyperplasia (CAH) due to 21-hydroxylase deficiency are at increased risk of earlier adiposity rebound, obesity, and increased abdominal adiposity compared to unaffected youth [1]. These factors could lead to increased risk of cardiovascular disease, hypertension, and diabetes [2]. However, current obesity management in CAH largely focuses on lifestyle modifications. Management guidelines for children with exogenous obesity recommend an intensive, in-clinic, multi-disciplinary intervention, involving 26 contact hours over a six-month period [3]. This may not be feasible in all

clinic settings, and weight loss can be difficult to achieve through these modifications alone. Pediatric guidelines also suggest early, intensive intervention with lifestyle modification, with consideration of anti-obesity pharmacotherapy after failure of lifestyle modifications [4]. Youth with CAH and concomitant severe obesity are a high-risk cohort and require earlier consideration of anti-obesity pharmacotherapies. In addition, adolescents and young adults with classical CAH can have increased abdominal visceral adipose tissue (VAT) which is associated with inflammation, cardiovascular disease, and risk for metabolic syndrome [1]. Thus, patients with CAH could also benefit from therapeutic options which specifically reduce VAT. Topiramate is an FDA-approved drug utilized for the treatment of epilepsy and migraines in children. It is a GABA receptor modulator that reduces glutamate release by blocking voltage-gated Na channels. There is also evidence that topiramate therapy is effective in appetite suppression resulting in BMI reduction in obese adolescents and adults [5], with a side effect profile that can include paresthesias, cognitive slowing, and taste impairment [6]. Little is known about the efficacy of topiramate in the treatment of severe obesity associated with chronic conditions such as CAH. However, as topiramate has been shown to reduce visceral adipose tissue more than placebo in randomized control trials, it may be particularly helpful in conditions like CAH with fat distribution that involves increased visceral adipose tissue [7, 8].

We report an adolescent case of severe obesity associated with classical CAH due to 21-hydroxylase deficiency in which sustained BMI reduction and decreased central adiposity were achieved on topiramate therapy.

Case Presentation – Methods and Results

Our female patient was diagnosed with classical, salt-wasting CAH shortly after birth. She presented with virilized external genitalia at birth, and an elevated serum 17-hydroxyprogesterone of 11,000 ng/dL (normal < 78 ng/dL). She was treated with hydrocortisone, fludrocortisone, and salt supplementation. Molecular genetic assessment of *CYP21A2* showed the presence of compound heterozygous mutations (G110del8nt and Q318X) consistent with 21-hydroxylase deficiency. She also had metopic craniosynostosis and developed generalized tonic-clonic seizures at 3 months old, requiring phenobarbital treatment for 4 years. By 3 years old, her BMI was 110 percent of the 95th percentile, and remained > 95th percentile thereafter. She developed chronic migraine headaches and was started on a topiramate dose of 50 mg daily by her neurologist at 17 years old. The topiramate dose was titrated to 100 mg daily over 2 years. At the time of topiramate initiation, lifestyle modifications had already been recommended as treatment for obesity, including routine exercise and nutrition counseling (*e.g.*, reduction of sugar-sweetened beverage intake and increase in fruit and vegetable consumption) at clinic visits. She had only implemented participation in physical exercise at school and neighborhood team soccer and these efforts did not result in notable weight loss. She was on 15 mg/m^2/day of glucocorticoid treatment and had good hormonal control with 17-hydroxyprogesterone 59 ng/dL, androstenedione 91 ng/dL, and testosterone 28 ng/dL. She was not receiving other medications that would have had an impact on her weight. Her growth plates were fused. During the 4-year course of topiramate treatment, she continued her previous lifestyle interventions and did not start any intensive lifestyle modification programs, new therapies, prescriptive dietary regimens or major lifestyle changes. At the time of the 4-year assessment, her total daily dose of glucocorticoid had remained unchanged. Hormone analytes showed: 17-hydroxyprogesterone 221 ng/dL, androstenedione 84 ng/dL, and testosterone 50 ng/dL. She did not have any adrenal crises while on topiramate.

Anthropometric measures

Measures were obtained at clinic visits and during two research studies [protocols were approved by the Children's Hospital Los Angeles (CHLA) institutional review board (CCI-09-00261, CHLA-14-00191). Written informed consent and assent were obtained from a parent and the patient respectively. BMI was calculated, and BMI z-score was reported up to 20 years old. Waist circumference was measured, and waist-to-height ratio was calculated.

At initiation of topiramate treatment, her BMI was 48.5 kg/m^2 (weight 100.2 kg). Following 2.4 years of treatment, her BMI z-score decreased from +2.6 to +2.1 (Figure 1). She had the greatest BMI reduction of 100 mg daily, with a nadir of 35.1 kg/m^2. Although she had a slight rebound increase in BMI of 12% during the third treatment year, she experienced a total BMI reduction of 23% after 4.2 years of topiramate treatment. She also had a decrease in waist circumference [110 cm (90-95th percentile) to 101 cm (50-75th percentile)] and in waist-to-height ratio (0.76 to 0.70).

Body Composition and Adiposity

Body fat was measured using multiple modalities over time as part of a research protocol examining body composition and adiposity distribution in patients with classical CAH. The subject had study visits at 12 and 21 years of age.

Whole body dual energy x-ray absorptiometry (DEXA; Hologic Delphi®/Horizon®, Marlborough, MA) was utilized to examine body composition by measuring total body fat and trunk fat. Prior to topiramate treatment, the subject exhibited high total fat mass of 48.8 kg, total fat percent of 51.9%, and trunk fat of 45.8%. After 4 years of treatment with topiramate, she exhibited a decrease in total fat mass to 36.7 kg, total fat percent to 45.9%, and trunk fat to 40%.

To analyze abdominal adiposity, including VAT and subcutaneous adipose tissue (SAT), single-slice computed tomography (CT) imaging (HiLight Advantage CT, GE, Chicago, IL) was utilized at the time of the patient's initial study visit, prior to topiramate treatment. The CT abdominal axial slice corresponded to the level of the umbilicus and the L4 vertebra. The patient exhibited high amounts of abdominal adipose tissue, as can be seen in adolescents and young adults with classical CAH [9]: VAT was 84.5 cm^2 and SAT was 654.5 cm^2. The imaging modality had subsequently changed to magnetic resonance imaging (MRI) on a 3-Tesla human platform (Achieva, R5.3, Phillips Healthcare, Cleveland, OH) employing a chemical-shift sequence, at the time of her next study visit four years post-initiation of topiramate therapy. For comparison across pre- and post-treatment time points, an MRI abdominal axial slice taken at the second study visit was selected at the level of the L4 vertebra using anatomic landmarks of the musculature and orientation of the intestines to best match the initial CT single-slice (Figure 2). Adipose tissue was segmented (Synapse 3D Fujifilm, Stamford, CT) on quantitative fat fraction images [9]. VAT was observed to be substantially decreased by 34.2% (55.6 cm^2) and SAT was decreased by 25.6% (486.8 cm^2) on the MR image. Although ideally, the

comparison would have been made using images from the same modality, given the accuracy of both single-slice CT and MR (mDixon) imaging techniques to quantify adipose tissue, our method of comparison incorporating these modalities is supported by current standards of imaging analyses [10].

Discussion

In our patient with classical CAH and severe obesity, topiramate therapy initiated for migraines produced a reasonably sustained BMI reduction over 4 years, along with reductions in total body fat and central adiposity. The BMI z-score reduction of 0.5 (23%) that she experienced has been associated with improvements in systolic blood pressure, high-density lipoprotein cholesterol, and triglycerides in youth [11]. Her dramatic reduction in VAT by over 50%, along with improvements in markers of abdominal adiposity, carry additional implications for the lowering of ectopic fat accumulation, inflammation, insulin resistance, and cardiovascular disease risk [1, 12].

Topiramate has been demonstrated in some studies to be associated with BMI reduction in adolescents and adults with obesity that is not associated with CAH [5, 13]. However, data to support a new indication (i.e. from the U.S. Food and Drug Administration) for pediatric obesity, or guidelines supporting its off-label use, are lacking. Nonetheless, its clinical utilization by pediatric obesity specialists has continued to increase [14]. As well, more research is needed to understand topiramate stand-along therapy vs combination therapy with phentermine [15] and off-label use of this medication.

Study Limitations

There are several limitations to our report. First, our patient was prescribed topiramate for chronic migraines, with BMI reduction being an incidental outcome. Second, an expanded study is needed of topiramate use in a larger number of patients with classical CAH and severe obesity. Importantly, topiramate did not produce adverse events in our patient, including any increase in frequency of adrenal crises or glucocorticoid requirement, even though a report of topiramate-induced hypoadrenalism exists in an adult with CAH [16]. Our case suggests that topiramate could be a safe pharmacological option for adolescents with CAH and obesity that merits further study.

Conclusion

We conclude that topiramate was associated with substantial weight loss and reduced central adiposity in an adolescent with classical CAH and severe obesity. Topiramate may be especially effective in patients with CAH given their increased visceral adiposity. Topiramate may be especially effective in patients with CAH given their increased visceral adiposity. It is evident from our case and other wider applications of topiramate therapy that more research is needed in obese youth with and without CAH. Further study is warranted of the safety and efficacy of topiramate as adjunctive treatment in obese youth with classical CAH and increased central adiposity, who are at higher risk for significant morbidity.

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Figure 1. BMI z-score pre- and post-topiramate initiation in a female adolescent with classical CAH and severe obesity. Over the course of 2.4 years from initiation of topiramate, the BMI z-score decreased from 2.6 to 1.9 at its lowest point, suggesting topiramate therapy resulted in a substantial and sustained weight loss over a short period of time

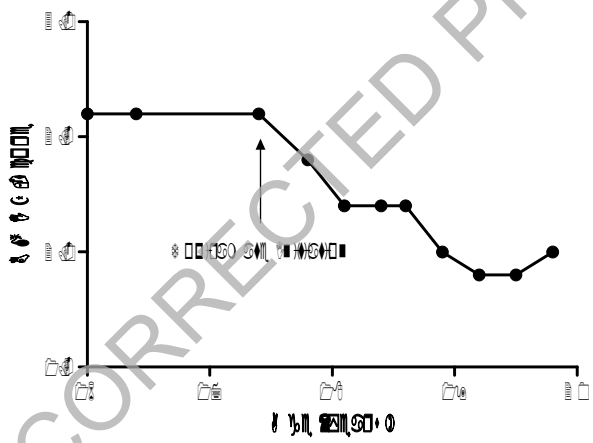

Figure 2. Abdominal adipose tissue imaging of a female adolescent with classical CAH to quantify visceral and subcutaneous adipose tissue. Single-slice images in the axial view, at the L4 vertebra. (A) Single-slice CT image was acquired at 12 years of age, prior to initiation of topiramate treatment. (B) Magnetic resonance image was acquired at 21 years of age, four years following initiation of topiramate treatment