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Utilization of Topiramate as an Adjunct to Lifestyle Intervention for Weight Loss in Pediatric Nonalcoholic Fatty Liver Disease

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Abstract: Nonalcoholic fatty liver disease is the most common chronic liver disease in children and has become the leading indication for liver transplantation in adults. The primary treatment modality is lifestyle modification to promote weight loss, which is challenging to achieve and maintain. Adjunctive weight loss medications, such as topiramate, are commonly used off-label in adults and children with obesity and found to be safe and effective. We report an adolescent male with severe obesity and nonalcoholic steatohepatitis refractory to aggressive lifestyle intervention. He was safely treated with topiramate with resultant weight loss, reduction in body mass index z-score, improvement in liver enzymes, and resolution of hepatic steatosis. This is the first report of using topiramate in a pediatric patient with obesity and nonalcoholic steatohepatitis. Topiramate should be considered in pediatric nonalcoholic fatty liver disease to help curb emotional eating and promote satiety in cases refractory to lifestyle intervention alone.

Key Words: pediatric obesity, pediatric nonalcoholic fatty liver disease, topiramate

INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) is the most common cause of chronic liver disease in children affecting 10% of the population with increased prevalence in obesity (1). A quarter of children have a more progressive subtype called nonalcoholic steatohepatitis (NASH) and 7%–10% develop cirrhosis and end-stage liver disease (2). There is a strong association between NAFLD, obesity, and insulin resistance (3). Increased adiposity and insulin resistance contribute to increased levels of free fatty acids and carbohydrates leading to hepatic lipid accumulation, cell injury, inflammation, and fibrosis (3). Having type 2 diabetes mellitus or obstructive sleep apnea is associated with increased NAFLD severity (4). Aggressive lifestyle modification to promote weight loss is the first line treatment for pediatric NAFLD and is effective when executed appropriately but is difficult to achieve and maintain in practice (5). No medications are approved by the FDA for pediatric NAFLD.

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The authors report no conflicts of interest.

The parents/guardian of the child in question is aware of this case report and have given their consent.

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Case Report

Informed consent was obtained from the parents for publication of the case details. The patient is a 17-year-old male with a history of severe obesity, hypertension, hypertriglyceridemia, low high-density lipoprotein, obstructive sleep apnea, seizures, attention deficit hyperactivity disorder, anxiety, and depression, who presented to the Gastroenterology outpatient clinic in July 2016 with elevated liver enzymes since 2012. His presenting weight was 108.9 kg (greater than 99th percentile), body mass index (BMI) z-score of 2.57, alanine aminotransferase of 159, and aspartate aminotransferase of 100. Evaluation was negative for other chronic liver diseases. Right upper quadrant ultrasound demonstrated hepatic steatosis (Fig. 1). Lifestyle intervention was recommended, and the patient was referred to the multidisciplinary NAFLD program, where he met with a pediatric gastroenterologist with obesity medicine training, a dietician, and a physical activity specialist. Due to persistently elevated liver enzymes and continued weight gain, he underwent a core needle liver biopsy to confirm NAFLD diagnosis and stage disease given his increased risk of NASH and/or advanced fibrosis. Histopathology revealed steatosis (macrovesicular steatosis occupying 20%), mild lobular inflammation, and minimal fibrosis, consistent with NASH, with NAFLD Activity Score (6) of 3/8 (steatosis 1/3 + lobular inflammation 1/3 + hepatocyte ballooning 1/2) and Fibrosis score (6) of 1a (Fig. 1). Despite 3 months of aggressive lifestyle intervention with the NAFLD program, the patient gained an additional 2.9 kg. Therefore, therapy was escalated, and he was started on topiramate 25 mg at bedtime and increased after 1 week to 25 mg twice daily. Topiramate was uptitrated to 50 mg twice daily over a year based on BMI z-score, liver enzymes, and subjective hunger scale (a non-validated scoring system based on a scale of 0 to 10, in which 0 = lowest subjective hunger and 10 = highest subjective hunger). Fourteen months after initiation of topiramate in conjunction with lifestyle management, the patient had a total weight loss of 9.1 kg with improvement in BMI z-score of 0.25. Aspartate aminotransferase normalized and alanine aminotransferase significantly improved (Table 1). Hepatic magnetic resonance elastography (MRE) performed at this time as noninvasive disease surveillance demonstrated a normal fat signal fraction of 4.3% (standard deviation 5.9%) (Fig. 2) suggesting resolution of hepatic steatosis and mildly elevated liver stiffness of 2.97 kPa (normal < 2.9 kPa) consistent with previous histopathology (Fig. 3). The patient reported no side effects from topiramate.

DISCUSSION

Lifestyle intervention to promote weight loss, the treatment of choice for pediatric NAFLD, is difficult to achieve and maintain. Therefore, adjunctive weight loss medications, such as topiramate, should be considered in children and adolescents with obesity and NAFLD, who are refractory to lifestyle changes, especially in those with increased disease severity (ie, NASH and/or fibrosis). Topiramate is a FDA approved anticonvulsant drug used for the treatment of epilepsy (2 years and older) and migraines (12 years and older), but it has been associated with weight loss (7). Topiramate has been used off-label for weight loss in both adults and children and used

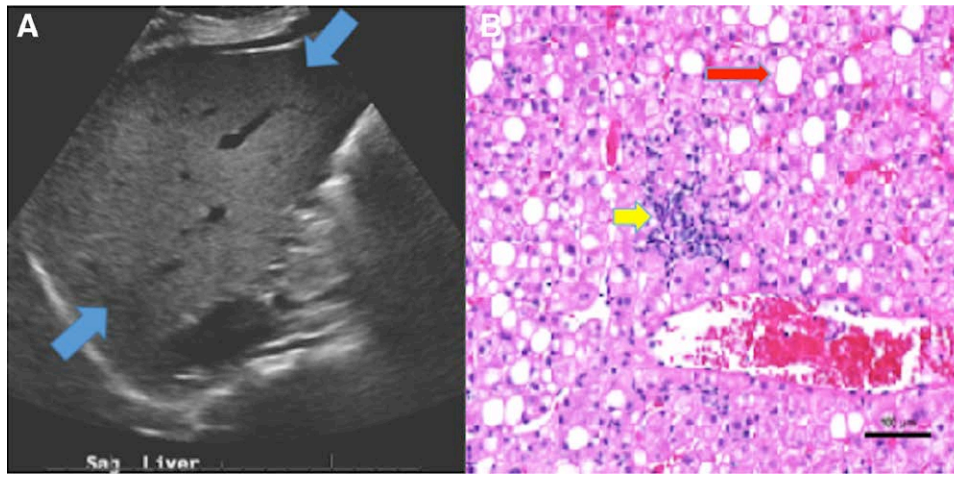

FIGURE 1. Hepatic imaging and histopathology of described patient. A) Right upper quadrant ultrasound showing diffuse increased echogenicity of the liver in keeping with hepatic steatosis (arrows). B) High-power H&E showing pericentral fat (red arrow) and a focus of lobulitis (yellow arrow). NAFLD activity score of 3/8 (range 0–8) and Fibrosis score of 1a (range 0–4). NAFLD = nonalcoholic fatty liver disease.

TABLE 1. Comparison of weight, BMI z-score, and liver enzymes at described patient time points

	Baseline at GI NPV	Start of NAFLD program	3 months post NAFLD program	Topiramate 25 mg QHS	Topiramate 25 mg AM; 50 mg QHS	Topiramate 50 mg BID	14 months post Topiramate
Weight (kg)	108.9	111.5	112.8	115.7	111.2	111.8	106.6
BMI z-score	2.57	2.58	2.59	2.63	2.51	2.52	2.38
ALT (U/L)	159	78	69	69	49	47	45
AST (U/L)	100	49	43	43	40	36	38

BID = twice daily; BMI = body mass index; GI = gastroenterology; NAFLD = nonalcoholic fatty liver disease; NPV = new patient visit; QHS = bedtime.

as an adjunct in binge eating disorders and for weight regain after bariatric surgery (7–9). Studies have shown that topiramate-treated adults lost at least 5%–10% of baseline weight, and it was well tolerated (10, 11). The use of topiramate to promote weight loss in children has been reported in psychiatric patients with antipsychotic medication induced weight gain (12, 13). It has also been studied in children with obesity ranging from case reports, retrospective studies, and randomized controlled trials (14–17).

The mechanisms by which topiramate promotes weight loss are not completely understood. One possibility is by inhibition of carbonic anhydrase, an enzyme involved in lipogenesis (18). In rodents, topiramate was shown to affect lipoprotein lipase in adipose tissue and muscle (19, 20). Topiramate also modulates various neurotransmitters, and in animal models was shown to act centrally to reduce food intake and promote satiety (21). This has been applied to its use in the management of patients with obesity and disordered eating

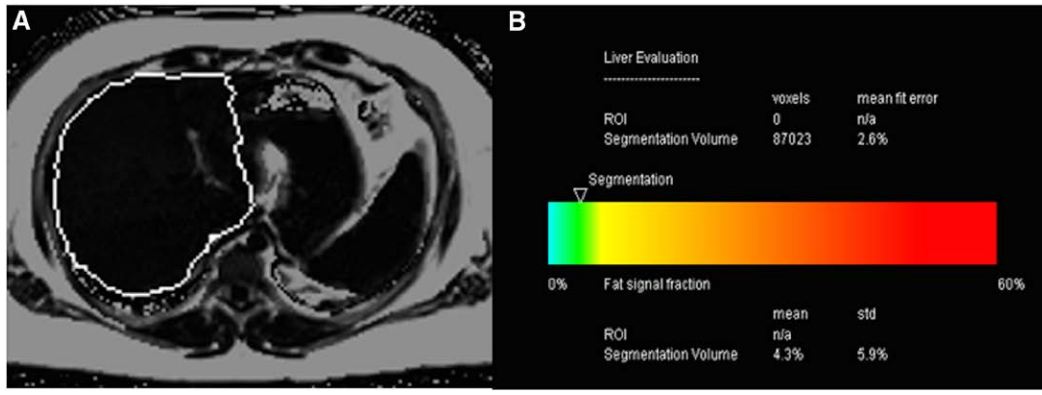

FIGURE 2. Representative images of fat measured using proton density fat fraction. A) Automated liver segmented fat fraction image. B) Color scale shows segmented liver volume fat fraction is 4.3% (SD: 5.9%). Tiny arrow indicates fat fraction of segmented liver volume is in "normal" range (green color). Fat fraction <6% is normal.

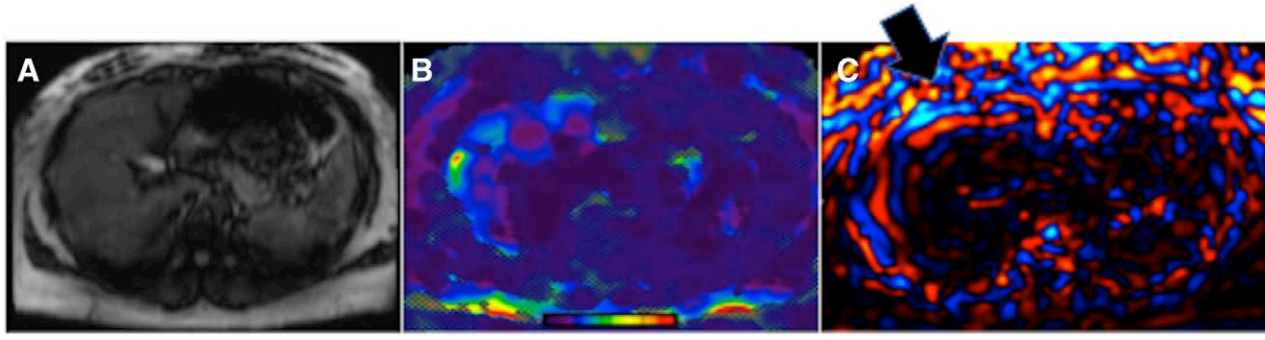

FIGURE 3. Representative images of magnetic resonance elastography (MRE) derived liver stiffness. Mean liver stiffness = 2.97 kPa. Increased liver stiffness is defined as >2.90 kPa. A) Magnitude image. B) Elastogram with color scale ranging from 0 (purple) to 8 kPa (red). C) Wave image. Arrow indicates in red and blue wave pattern on the liver region.

behaviors (2, 3). To our knowledge, no current literature reports the use of topiramate as a weight reduction medication to improve liver enzymes in children and adolescents with obesity and NAFLD. This case report highlights that using topiramate for this purpose should be considered. Topiramate with lifestyle intervention helped promote and maintain weight loss in an adolescent patient with severe obesity, NASH, and psychiatric comorbidities, leading to improvement in liver enzymes and apparent resolution of hepatic steatosis based on hepatic MRE derived fat fraction which has high diagnostic accuracy to classify and predict histologic steatosis grade (22–24), avoiding more invasive options such as metabolic and bariatric surgery.

In conclusion, lifestyle modification to promote weight loss remains the primary treatment for pediatric NAFLD. In refractory cases wherein a patient does not qualify for metabolic and bariatric surgery due to age or who is not interested in surgery, topiramate should be considered. Its role in targeting emotional eating, as demonstrated in pediatric patients with antipsychotic medication induced weight gain, makes it a valuable adjunct to lifestyle intervention, together with enhancing satiety to help achieve and maintain weight loss leading to possible improvement of NAFLD. Studies investigating the safety and efficacy of topiramate for pediatric NAFLD are needed.

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