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Case report

Improvement in metabolic indices including thyroid hormones via enhanced absorption of nutrients by Teduglutide in short bowel syndrome

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ABSTRACT

Introduction and importance: Short bowel syndrome is characterized by maldigestion and malabsorption resulting in deficiencies of multiple nutrients including vitamins and minerals. Most subjects required parental elimination for survival. GLP-2 RA Teduglutide was recently approved for treatment of short bowel syndrome especially for those requiring parenteral support. Our intent in reporting this subject is to demonstrate the utility of Teduglutide in improving multiple metabolic indices in presence of short bowel syndrome.

Case presentation and clinical discussion: 66-year-old Caucasian female presented with a history of short bowel syndrome and associated vitamin deficiencies, hypothyroidism requiring large dose (300 μg) of levothyroxine, diarrhea and liver cirrhosis. Upon starting teduglutide the subject saw improvement in her symptoms. Moreover, daily dose of Levothyroxine required a gradual decrease to maintain desirable serum concentrations of Free T4, Free T3 and TSH. Serum levels of several vitamins attained greater than therapeutic concentrations requiring dosage reductions. Also notable was the improvement in her liver function tests, remission from ascites and episodes of hepatic encephalopathy and regeneration of liver nodules.

Conclusion: Following administration of GLP2 therapy, an adult subject with short bowel syndrome with concurrent hypothyroidism and multiple vitamin deficiencies, demonstrated a marked improvement in her metabolic parameters resulting in reduction in daily medication doses along with improvement in manifestations of liver cirrhosis.

1. Introduction

Subcutaneous Teduglutide is an analog of glucagon-like peptide 2 (GLP-2) which regulates growth, proliferation and maintenance of cells lining the gastrointestinal tract [1–3]. Teduglutide has been approved for the treatment of patients with short bowel syndrome (SBS) who need parenteral support [1]. Short bowel syndrome is the consequence of a loss of bowel mass due to extensive surgical resection, congenital defects or other rare disorders [4,5]. Teduglutide improves intestinal rehabilitation by promoting mucosal growth and possibly by inhibiting gastric emptying and secretion which in turn reduces intestinal losses and promotes intestinal absorption [1,2]. Most studies have focused on the utility of teduglutide on reducing the need for parenteral support for patients with SBS-Intestinal failure [3,6,7]. We report an adult subject with short bowel syndrome with consequential hepatic cirrhosis with several episodes of encephalopathy and concurrent hypothyroidism as well as multiple nutritional and vitamin deficiencies. Administration of Teduglutide normalized metabolic abnormalities, requiring reduction or discontinuation in daily dose of multiple nutritional supplements, along with normalization of liver function tests and remission from hepatic cirrhosis, ascites and hepatic encephalopathy.

2. Case report

66 year-old female was referred to endocrinology clinic because her serum TSH concentration remained elevated despite appropriate administration of levothyroxine over 250 μg (2.8 μg/kg body weight) taken daily by itself in the morning on an empty stomach with water approximately 1 h prior to breakfast. On further inquiry, she reported a history of short bowel syndrome, a sequela resulting from an extensive

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small bowel resection in 2002. She complained of persistent diarrhea occurring 4–5 times a day with abdominal cramping. She was receiving multiple nutritional supplements including several vitamins and minerals including monthly injections of vitamin B12 as well as infusions of iron. She had received several frequent bouts of parenteral hyperalimentation. She was also being treated by a hepatologist for liver cirrhosis with ascites and encephalopathy. Liver cirrhosis was attributed to the prolonged nutritional deficiencies due to maldigestion and malabsorption as a complication of short bowel syndrome. Past medical history included anxiety, depression, cervial disc disorder and gastroesophageal reflux disease. Past surgical history included bilateral salpingo oophorectomy, cholecystecotmy, appendectomy, total knee replacement in addition to bowel resection. Review of systems was negative for chest pain, palpitations, shortness of breat, edema, headache, vision changes, blood in tools, dysuria, hematuria etc.

Reported therapy consisted of administration of nutritional supplements including vitamin D2 (ergocalciferol) 50,000 units weekly, daily vitamins including B1, B6, A and E. A proton pump inhibitor omeprazole 40 mg daily and dicyclomine 10 mg three times daily, were also administered for treatment of GERD and abdominal cramps respectively. Rifaximin 550 mg twice daily and lactulose 2–3 tablespoons daily as needed to have 2–3 bowel movements were used to prevent onset of hepatic encephalopathy. Other medications included sertraline 150 mg daily for depression, amlodipine 10 mg daily for hypertension and pregablin 25 mg daily as well as oxycodone 10 mg as needed for pain relief.

Physical examination showed an obese Caucasian woman in no acute distress. Vital signs were unremarkable including regular pulse with a rate 66/min, blood pressure 113/67 mmHg and body weight, 210 lbs. HEENT examination was unremarkable as well. Examination of the neck revealed a palpable non tender firm thyroid gland without nodules or enlargement, mobile on swallowing. No cervical lymphadenopathy was noted. Heart examination revealed normal sounds without a murmur. Examination of lungs was unremarkable with normal vesicular breathing without adventitious sounds. Abdomen appeared distended but non tender with active bowel sounds and no abdominal bruit. Hepatosplenomegaly and ascites were present. Neurological examination showed alert, oriented, appropriately expressive woman with no distress or asterixes without a focal deficit or tremors. Sensations as well as both sensor and motor reflexes were intact. Bilateral lower extremity edema was present. No cyanosis of the nails or clubbing of fingers was evident and radial and pedal pulses were well palpated.

Extensive laboratory testing documented microcytic hypochromic anemia and elevated liver enzymes, alpha fetoprotein, ammonia as well as prothrombin time (INR). Total protein, albumin, free T4 and TSH concentrations as well as vitamin levels and other chemistries including creatinine, urea nitrogen, electrolytes as well as calcium, phosphorus and magnesium levels were all in the normal range. She was started on pancreatic enzyme Creon, pharma 1 capsule four times a day before meals to assist with digestion.

At the follow-up visit a month later, the subject reported that diarrhea had improved and stools had firmed up. A month later her levothyroxine was reduced to 250 μg daily because of subnormal serum TSH level. 6 weeks lateradministration of GLP-2 analog teduglutide was initiated following its availability after approval by FDA. For a couple of weeks after initiation, the patient experienced mild abdominal cramps but denied any other side effects. During the follow up visit at 3 months after starting teduglutide, the subject reported improvement in appetite and a change from frequent diarrhea to formed, soft chalky stools 2–3/day. She continued to experience palpitations attributed to iatrogenic hyperthyroidism prompting a gradual reduction in levothyroxine dose to 150 μg daily to attain and maintain desirable Free T4 and TSH concentrations [Tables 1 and 2]. Continued administration of teduglutide resulted in remission of both ascites and episodes of altered mental status ascribed to hepatic encephalopathy. Laboratory tests showed persistent normalization of serum ammonia, alpha fetoprotein and Liver enzymes even after discontinuation of Rifaximin and Lactulose indicating reversal of cirrhosis induced by malnutrition induced by SBS. Moreover, serum levels of several vitamins attained toxic or supratherapeutic concentrations requiring reduction or withdrawal [Tables 1 and 2].

3. Discussion

Short bowel syndrome is characterized by an “inability to maintain protein-energy, fluid, electrolyte, or micronutrient balances when on a conventional, normal diet.” [5]. A subset of these patients have ‘intestinal failure’ resulting in deficiency of multiple vitamins and minerals induced by maldigestion and malabsorption [5]. Intermittent parenteral hyperalimentation has been the mainstay to meet daily nutritional needs. However, painstaking attempts are also undertaken to administer orally mega doses of fat soluble vitamins to attain and maintain normal concentrations with some success [4,5]. In patients receiving parenteral nutrition vitamin D still needs to be replaced orally due to lack of availability of IV formulation [4,5].

Glucagon-like peptide 2 (GLP-2) is a gastrointestinal peptide secreted by L-cells of the intestinal mucosa in response to luminal contact with unabsorbed nutrients. It promotes mucosal growth, enhances release of intestinal enzymes and delays gastric transit time to promote absorption of nutrients by slowing entry of food into the short bowel [1,2].

Teduglutide, an analog of GLP 2, is approved as the first long-term medical therapy for treatment of adults with SBS dependent on

Table 1
Persistent Improvement in Metabolic Abnormalities over 3 year period following administration of Teduglutide.

	Normal range	Aug 18	Jan 19	Jun 19	Dec 19	Apr 20	Nov 20	Feb 21	Dec 21
Free T4	0.89–1.76 ng/dl	1.53	1.68	1.21		1.22	1.16	1.53	1.48
TSH	0.55–4.78 mcIU/ml	0.286	0.011	4.318	3.343	2.561	3.969	3.228	1.953
Calcium	8.7–10.4 mg/dl	9.7	9	9.5	10	9.4	9.3		8.9
Vitamin D	30–80 ng/ml				21.1	41.7	43.8		61.7
Vitamin A	32.5–78 μg/dl			42.7	59.4	49.1	55.7		54.9
Iron	50–175 ug/dl			68	74		75	72	81
Vitamin E	5.5–17 mg/L		23	29		29	28	21	18
Vitamin B12	211–911 pg/ml				390	273	>2000	>2000	>2000
INR	0.9–1.1 ratio					1.1	1.2		
TIBC	250–450 ug/dl		252	297	319		298	323	272
Ferritin	10–291 ng/ml		640	569	517		760.7	861.3	823.3
AST	0–40 U/L		26	31	32	21	31	31	25
ALT	10–49 U/L		27	37	44	24	37	41	28
Alkaline phos	45–129 U/L		76	88	108	93	87		71
Ammonia	11–35 umol/L		13			32	24	18	34
Alpha Fetoprotein	<8.1 ng.ml			10.3	8.8	7.4	8.3		5.2

Table 2
Requirement for dose reduction or discontinuation for several dietary supplements over 3 year period following administration of Teduglutide.

Dose	August 2018	January 2019	June 2019	December 2019	April 2020	November 2020	February 2021	December 2021
Vitamin D	50,000 units weekly	50,000 units weekly	50,000 units weekly	50,000 units weekly	50,000 units weekly	50,000 units weekly	50,000 units every 2 weeks	50,000 units every 2 weeks
Vitamin A	8000 units Daily	8000 units Daily	8000 units Daily	Discontinued				
Levothyroxine	250 μg Daily	150 μg Daily	150 μg Daily	150 μg Daily	150 μg Daily	150 μg Daily	150 μg Daily	150 μg Daily
Vitamin E	1000 units Daily	1000 units QOD	1000 units Q 3 days	Discontinued				
Vitamin B12	1000 units Monthly	1000 units Monthly	1000 units Monthly	Discontinued				
Iron	300 mg IV Monthly	300 mg IV Monthly	300 mg IV Monthly	300 mg IV Monthly	300 mg IV Monthly	300 mg IV Monthly	300 mg IV Monthly	150 mg IV Monthly
Lactulose						10 g Daily PRN	10 g Daily PRN	10 g Daily PRN
Rifaximin	550 mg BID	550 mg BID	550 mg BID	550 mg BID	550 mg BID	550 mg BID	550 mg BID	Discontinued

parenteral support [1]. Teduglutide has been shown to be safe and well-tolerated by patients. It promotes "restoration of structural and functional integrity of the remaining intestine with significant intestinotrophic and pro-absorptive effects, facilitating a reduction in diarrhea as well as frequency of parenteral support in patients with SBS and consequential 'intestinal failure'" [1,4,5].

Hepatocellular injury has been documented in patients with short bowel syndrome/intestinal failure and is attributed to lack of nutrient supply to liver by decrease in nutrients in the spared gut due to maldigestion and malabsorption [9,10]. Long-term parenteral support has been thought to delay onset of liver disorder by supplementation of nutrients directly to the liver through systemic circulation [3,5,8]. A recent study suggests that liver damage ensues as a "consequence of the disrupted enterohepatic circulation following intestinal resection, leading to biliary hypersecretion, bile acid dysmetabolism, and microbial dysbiosis" [11].

Apparently, this is the first report of reversal of cirrhosis with administration of teduglutide as evidenced by remission from hepatic encephalopathy, ascites and normalization of liver enzymes. This finding is consistent with a recent study which showed that low dose GLP-2 administration improves hepatic steatosis in parenterally fed rat model of short bowel syndrome [9]. Reversal in hepatic steatosis is attributed to increased splanchnic blood flow and improvement in cholestasis [11,12]. We attribute reversal of cirrhosis and its complications in our patient to the transport to the liver via portal vein of nutrients in the intestinal lumen induced by enhanced digestion and absorption of ingested food on administration of Teduglutide.

The work is reported in line with the SCARE criteria [13].

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Ethical approval

Exempt for a case report.

Consent

Written informed consent was obtained from the patient for publication of the case report (13]no images in the report). A copy of the written consent is available for review by the Editor in Chief of this journal on request.

Research registration

NA.

Guarantor

All authors are guarantors.

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CRediT authorship contribution statement

All three authors contributed to management of the patient and contributed in preparation of manuscript.

Declaration of competing interest

None.

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