DOI: https://doi.org/10.2298/SARH230316048S
UDC: 616.34-007-085-053.2

CASE REPORT / ПРИКАЗ БОЛЕСНИКА

Teduglutide therapy in a child with short bowel syndrome

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SUMMARY

Introduction Short bowel syndrome (SBS) in children is a rare disease. One of the most common etiological factors for the development of SBS in children is atresia of the small intestine. After surgical correction of the congenital anomaly, the remaining intestine attempts to increase absorption to restore homeostasis, and the process of intestinal adaptation begins. This process of adaptation can be assisted with analogues of endogenous growth factors of the intestine, such as teduglutide.

Case outline This report presents a girl, aged two years and eight months, who had an estimated 20 cm of small intestine after surgical correction of congenital small bowel atresia and clinical signs of SBS. She was repeatedly hospitalized due to frequent need for parenteral correction of fluid, electrolyte, and nutrient imbalances. Stagnation in body weight and slow growth in body height were accompanied by weakened gross motor strength and slowed psychophysical development. After exploit conservative treatment measures, stimulation of intestinal adaptation was initiated with the drug teduglutide. After six months of drug therapy, progress was observed in body parameters, as well as an increase in intelligence quotient and motor abilities.

Conclusion SBS is a challenging entity for every clinician, and its previous therapy has mainly consisted of parenteral substitution of nutrients, fluids, and electrolytes. Surgical treatment carries the risk of loss of the remaining bowel and lifelong immunosuppression. The pharmacological possibilities of promoting intestinal adaptation using drugs such as teduglutide represent a light at the end of the tunnel for patients with SBS.

Keywords: short bowel syndrome; child; teduglutide; glucagon-like peptide-2

INTRODUCTION

Short bowel syndrome (SBS) is defined as a total functional small bowel length less than 200 cm in adult patients who require substitution of food and/or fluids [1]. In pediatric population, SBS does not have such a pragmatic definition in terms of functional bowel length expressed in centimeters, as the length of the bowel increases with growth in children [2]. The North American Society for Pediatric Gastroenterology, Hepatology and Nutrition defines SBS in children as the need for parenteral nutrition (PN) for more than 60 days after bowel resection or a bowel length less than 25% of the expected length [3].

The incidence of SBS in infants is 24.5 per 100,000 live births [4]. There are two types of SBS: primary (as a result of prenatal pathological conditions such as atresia of the small intestine) and secondary (as a result of postnatal pathological conditions) [5].

Small bowel atresia is a rare congenital defect of the small intestine characterized by a disruption in the normal continuity of the small intestine, leading to obstruction of the bowel [6].

The first phase of treatment involves decompression of the intestine through a nasogastric tube, fluid replacement, and antibiotic therapy as a bridge to surgical correction. The second phase of treatment aims to provide adequate function of the remaining part of the digestive tract, often requiring prolonged PN. To reduce the need for PN, surgical procedures for lengthening the intestine and small bowel transplantation can be performed. Surgical treatment options carry the risk of loss of the remaining bowel and lifelong immunosuppression. An alternative to high-risk surgical treatment of SBS is the use of drugs that stimulate intestinal adaptation, such as teduglutide [7].

After an event, such as small bowel atresia, leading to SBS, the rest of the gut attempts to increase absorption to restore homeostasis and the process of intestinal adaptation begins. Numerous growth factors are involved in this process. Glucagon-like peptide-2 (GLP-2) is an endogenous growth factor strongly associated with intestinal growth and post-resection intestinal adaptation. GLP-2 therapy improves intestinal function in children with SBS by increasing intestinal absorption through increased blood flow to and from the intestine, slowing the rate at which food passes through, and reducing stomach acid secretion that can interfere with absorption in the intestine. Teduglutide is a GLP-2 analog and can be an effective and safe therapeutic option for treating SBS in adults and children over one year of age [7].

Received • Примљено: March 16, 2023
Revised • Ревизија: April 30, 2023
Accepted • Прихваћено: May 3, 2023
Online first: May 8, 2023

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The drug is administered as a subcutaneous injection into the abdominal skin at the recommended daily dose of 0.05 mg per kilogram of body weight [7]. The treatment effect should be evaluated after six months of treatment, and in children under the age of two, this can be done after 12 weeks [8, 9].

CASE REPORT

A girl aged two years and eight months was hospitalized, due to frequent, unformed stools, and dehydration. On admission, parameters indicating malnutrition were recorded: body weight of 11.5 kg (eighth percentile), body length of 90 cm (48th percentile) and body mass index of 13.9 kg/m² (third percentile). During the examination, reduced adipose tissue was observed in all predilection sites and inability to walk independently. Laboratory tests showed negative acute-phase reactants, normal blood counts, and biochemical parameters of the liver, pancreas, and kidney function, negative microbiological stool test, and normal urine test.

She is the first child conceived by in vitro fertilization. At 32 weeks of gestation, the mother notices weaker fetal movements. During a gynecological examination fetal tachycardia and deceleration were recorded, and ultrasonographically, ascites and hydroaeric levels were described in the fetal abdomen with a dilated stomach and lower bowel. The emergency caesarean section was indicated.

The child was born in perinatal asphyxia (Apgar score 3/7) with hypotonia, but with eutrophic body parameters: birth weight of 1890 g (50th percentile), birth length of 45 cm (75th percentile), and head circumference of 31 cm (50th percentile). Dilated bowel loops and free fluid in the abdomen were observed on ultrasound. The newborn with a picture of ileus and signs of pneumoperitoneum was operated, when a part of the small intestine was resected. After the resection of the twisted part of the intestine, a distal atretic segment of the ileum was observed; the total remaining length of the small intestine is approximately 26 cm. PN was initiated on the second postoperative day. After one week, due to re-development of the clinical picture of acute abdomen, a resection of a portion of gangrenous distal jejunum in the area of the stoma was performed, along with a T-T jejunoileal anastomosis (the remaining small intestine segment estimated to be 20 cm). Postoperative PN continued until the 19th day of life. From the 15th day of life, intestinal passage was established, and the intake of breast milk and amino acid formula was gradually increased. The child was first fed through a nasogastric tube, and from the 40th day of life, was fed from a bottle.

In laboratory tests, from birth, unconjugated hyperbilirubinemia with elevated gamma glutamyl transferase (GGT) predominated in liver function, until the 10th day of life when a normal GGT was recorded. After that, there was a deterioration in liver function and conversion to conjugated hyperbilirubinemia from the 13th day of life during PN. Conjugated hyperbilirubinemia continued to increase over the next few days, reaching 60% of the total bilirubin value. Signs of cholestasis were maintained with normal values of transaminases and GGT. Ursodeoxycholic acid was introduced on the 18th day of treatment. Stools were spontaneously golden yellow in color with negative bilirubin in stool. It was most likely a case of intestinal failure associated with cholestatic liver disease (IFALD).

On the 54th day of life, the patient was discharged with the following physical parameters: body weight 2140 g (below the third percentile), body length 46.5 cm (10th percentile), head circumference 32 cm (10th percentile).

At the age of three months, she was hospitalized at the University Children's Hospital in Belgrade due to subicterus and malnutrition, where an intraoperative cholangiography with liver biopsy was performed, which showed regular arborization of the bile ducts, and the pathohistology report of the liver biopsy showed preserved structure with moderately expressed cellular and canalicular cholestasis with rare focal necroses in the parenchyma. In the laboratory findings, the following values were elevated: inflammation marker C-reactive protein, ammonia, conjugated hyperbilirubinemia, transaminase and GGT. Lactulose and oral vancomycin were introduced due to hyperammonemia. The patient was fed with an adapted milk formula based on milk proteins, but due to formula intolerance, it was first replaced with an extensively hydrolyzed milk and then with an amino acid-based formula.

The child was regularly monitored at our Institute. The use of vancomycin and lactulose was discontinued from the fourth month with normalization of ammonia levels. Oral therapy with ursodeoxycholic acid was continued until GGT normalized at the age of one year. Supplementation with fat-soluble vitamins continued as regular therapy until the writing of this paper. Over time, there was an improvement in digestive function, the child tolerated a larger amount of food per meal, began to gain weight, and had less frequent stools that were not formed. Mixed non-milk diet was introduced, but inadequate weight gain persisted. The child was hospitalized multiple times due to the need for intravenous fluid replacement and correction of the internal environment.

Given that the patient with SBS and intestinal insufficiency experienced a halt in growth and significant delay in development, failing to achieve three out of six major motor milestones for the age despite all exploit treatment measures, intestinal adaptation was stimulated by starting the use of the drug teduglutide. Teduglutide was administered once a day by subcutaneous injections at a dose of 0.05 mg/kg/day.

After six months of teduglutide treatment, a clinical evaluation and assessment of psychophysical abilities were performed. Although the physical parameters expressed in percentiles for age and gender remained the same, progress was observed in physical parameters: body weight 12.2 kg (+ 700 g in six months, after 18 months of stagnation in body weight, i.e., eighth percentile), and body height 95 cm (+ 5 cm in six months, i.e., 46th percentile) and body mass index 13.51 kg/m² (third percentile).

During teduglutide therapy, the girl began to walk independently. As part of monitoring gross motor development,

a functional motor assessment [gross motor function measure (GMFM)] was performed, and an increase in GMFM score was observed, which was 69.08% before the therapy and 72.79% after six months of treatment with the GLP-2 analogue.

After six months of teduglutide therapy, an assessment of intelligence was performed using the Binet–Simon scale, which showed an increase in the intelligence quotient, indicating normal intellectual ability in the average category.

We confirm that we have read the journal's statement on issues involving ethical publishing and confirm that this work is in accordance with those guidelines, as well as with the ethical standards of the Institute and the Helsinki Declaration of 1964 and its later amendments or comparable ethical standards. Written consent to publish all presented material was obtained from the patient's parents.

DISCUSSION

Modern pharmacotherapy, surgical techniques, and improved hygiene have led to the SBS becoming a clinical entity with an increasing incidence and a reduction in mortality [10]. These epidemiological data have contributed to the stimulation of intestinal adaptation using analogs of intestinal growth factors, such as teduglutide.

Tompson believes that patients with SBS require preventive cholecystectomy due to an increased risk of developing cholelithiasis, especially in cases of need for long-term PN [11]. In our patient, preventive cholecystectomy was not performed, and she had signs of cholestatic syndrome in the first year of life, which we attributed to the first phase of IFALD development. Previous studies and meta-analyses suggest that the main reason for IFALD development is the type of intravenous lipid emulsion for PN. Avoidance of soy-based emulsions is recommended, while fish oil-based emulsions are emphasized as desirable [12].

According to the proposed algorithm for patients with SBS, which is based on the length of residual intestine and the presence of the ileocecal valve and colon, published by Spanish authors, our patient (with residual intestine less than 40 cm and the presence of the ileocecal valve and colon) is a candidate for surgical procedures to lengthen the intestine [12]. According to these authors, with the help of this surgical procedure, sufficient intestinal adaptation will be achieved so that most patients will not have further need for PN or intestinal transplantation [13]. However, new drugs such as teduglutide require a revision of these algorithms. Intestinal hormone analogs may not be a solution for everyone in terms of eliminating the need for PN, but they will allow such patients to achieve better preoperative conditioning and maximum intestinal adaptation.

After six months of treatment, our patient did not require PN anymore, but had one upper respiratory tract infection. The adverse effects of teduglutide have been described in several studies. Ramos Boluda et al. [14] and Kocoshis et al. [15] did not report any adverse effects that required discontinuation of teduglutide. The most commonly reported adverse effects are gastrointestinal in nature, up to 77%: vomiting, abdominal pain, stoma hypertrophy, and cholecystitis, while severe adverse events occur in up to 30% of patients: catheter-related sepsis, heart failure and respiratory diseases [14–17].

This is the first study that used an assessment of gross motor strength and psychological assessment of development to monitor the effect of therapy. The efficacy of teduglutide has mainly been evaluated through the parameter of reducing the amount of fluid needed for parenteral replacement [14–17].

This is the first use of teduglutide in pediatric patients in Serbia. We believe that a treatment guideline for SBS and the use of teduglutide is needed, as it exists in other countries [9].

Conflict of interest: None declared.

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Терапија тедуглутидом код детета са синдромом кратког црева

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САЖЕТАК

Увод Синдром кратког црева код деце је ретка болест. Један од најчешћих етиолошких фактора за развој синдрома кратког црева код деце је атрезија танког црева. После хируршке корекције урођене аномалије остатак црева покушава да повећа апсорпцију како би се повратила хомеостаза и почиње процес интестиналне адаптације. Процес адаптације се може помоћи аналозима ендогених фактора раста црева, као што је тедуглутид.

Приказ болесника У овом раду приказано је женско дете узраста две године и осам месеци које је после хируршке корекције урођене атрезије танког црева имало процењених 20 *cm* танког црева и клиничке знакове синдрома кратког црева. Вишеструко је хоспитализована због честе потребе за парентералном корекцијом баланса течности, електролита и хранљивих материја. Стагнација у телесној тежини и успорено напредовање у телесној висини праћени су ослабљеном грубом моторичком снагом и успореним психофизичким развојем. Након што су исцрпљене конзервативне мере лечења, започето је подстицање интестиналне адаптације применом лека тедуглутид. После шест месеци примене лека уочен је напредак у телесним параметрима, а забележен је и пораст коефицијента интелигенције и моторичких способности.

Закључак Синдром кратког црева је за сваког клиничара изазован ентитет, а његова досадашња терапија углавном се састојала у парентералној супституцији хранљивих материја, течности и електролита. Хируршко лечење носи ризик од губитка преосталог црева и доживотне имуносупресије. Фармаколошке могућности подстицања интестиналне адаптације применом лекова као што је тедуглутид представљају светло на крају тунела за пацијенте са синдромом кратког црева.

Кључне речи: синдром кратког црева; дете; тедуглутид; глукагону сличан пептид 2