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Case Report / Olgu Sunumu

Microvillus Inclusion Disease: Can Mesenchymal Stem Cells Be a Potential Treatment Option?

Mikrovillus İnkluzyon Hastalığı'nda Mezenkimal Kök Hücreler Bir Tedavi Seçeneği Olabilir mi?

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Abstract

Microvillus inclusion disease (MVID; MIM #251850), is a rare life-threatening secretory and malabsorptive diarrhea of infancy due to mutations in the MYO5B gene. A 6-day-old male patient was referred to our neonatal intensive care unit for profuse diarrhea beginning on the 2nd day of life causing 17% weight loss, metabolic acidosis and hyponatremia. Our patient had a homozygous mutation in the MYO5B gene. On 110th day of life, mesenchymal stem cell treatment (1x106 cells trans duodenal and 2x106 cells intravenous) was administered. Although fluid and electrolyte requirements did not decrease after stem cell therapy, the rate of blood stream infections was reduced. Small bowel transplantation using cadaveric intestine was performed at the age of 20 months. Unfortunately, the infant died of sepsis one month after transplantation. In this case report, results of stem cell therapy in a newborn infant with MVID were presented and discussed with the relevant literature.

Keywords: Newborn; microvillus inclusion disease; mesenchymal stem cell; treatment

Özet

Mikrovillus inklüzyon hastalığı (MİH), Miyosin 5B genindeki mutasyonlara bağlı oluşan sekretuvar ve osmotik diyare ile seyreden hayatı tehdit edici bir hastalıktır. Mezenkimal kök hücre (MKH) tedavisi intestinal yetmezlikte sınırlı sayıda olguda uygulanmıştır ancak MİH'de sadece hayvan çalışmaları bulunmaktadır. Altı günlük erkek bebek postnatal 2. günde başlayan, ishal, metabolik asidoz ve hiponatremi nedeniyle yenidoğan yoğun bakım ünitemize kabul edildi. 36 hafta 4 günlük, 2960 g olarak doğan bebeğin diyareye bağlı iki kardeş ölüm öyküsü vardı. Olgumuzda MYO5B geninde homozigot mutasyon tespit edildi. Enteral beslenme kesilerek total parenteral beslenme başlandı. Bebeğin yüksek sıvı (350 cc/kg/gün), sodyum (20-25 meq/kg/gün) ve bikarbonat (12-18 meq/kg/gün) ihtiyacı mevcuttu. Postnatal 110. gününde hastaya MKH tedavisi (1x106 Ü transduodenal ve 2x106 Ü IV) uygulandı. Kök hücre tedavisi sonrası her ne kadar sıvı ve elektrolit gereksinimleri azalmasa da sepsis sıklığında azalma gözlendi. Bebek 20 aylıkken kadavradan ince barsak nakli yapıldı, ancak nakilden bir ay sonra sepsis nedeniyle eksitus oldu.

Anahtar Kelimeler: Yenidoğan; mikrovillus inkluzyon hastalığı; mezenkimal kök hücre; tedavi

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1. Introduction

Microvillus inclusion disease (MVID; MIM #251850) is a rare, life-threatening secretory and malabsorptive diarrhea of infancy. Mutations in MYO5B gene which encodes actin-based motor protein Myosin 5B are responsible from the disease state. Myosin 5B is involved in the structure of microvilli cytoskeleton and is required for the regulation of polarized epithelial cells and eventually transport of brush border components. In electron microscopic evaluation accumulation of ‘‘inclusions’’ of microvilli in the cytoplasm of small-bowel biopsy specimens is characteristic finding (1,2). Typical presentation is abundant watery diarrhea starting early in the neonatal period even in the first hours of life. Some cases are defined as “later-onset” but never extend beyond the first 2-3 months of life. Mortality rate has been reported 80% by 18 months of age despite total parenteral nutrition (TPN) which is obligatory for survival (3). Whole organ allogeneic transplantation has improved the survival but most of the patients die before achieving the opportunity of bowel transplantation due to electrolytes and renal tubular function disturbances and complications of parenteral nutrition. Bowel transplantation is also associated with a high risk for morbidity and mortality. In a large case series of MVID, survival rates of children were 63% without small bowel transplantation (SBTx) and 77% with SBTx with a mean follow up period of 3 months to 14 years after bowel transplantation (3).

Recently, trials demonstrating potential regenerating capacity of stem cells in the field of many degenerating disease even in the patients with monogenic and polygenic forms of intestinal failure encourage us to introduce pluripotent stem cells to our patient (4,5). Mesenchymal stem cell treatment was used to improve epithelium regeneration in this life-threatening disease. Results of mesenchymal stem cell (MSC) therapy in this MVID case were presented discussing with the relevant literature.

2. Case

A 6-day-old male patient was referred to our neonatal intensive care unit for profuse diarrhea beginning on the 2nd day of life causing 17% weight loss, metabolic acidosis and hyponatremia. He was born at 36+4 weeks of gestational age and body weight of 2960 g with a prenatal history of polyhydramnios and dilated bowel loops. He was the fourth child of nonconsanguineous parents. Second and third siblings died at 2 and 3,5 months due to complications of intractable diarrhea beginning in the first few days of life. Third child’s exome sequencing identified a homozygous, disease-causing nonsense variant C.4399C>T (p.Gin1467*) in the MYO5B gene. Both parents were found heterozygous for this mutation and did not accept prenatal test for our patient. With the knowledge of the family history, total parenteral nutrition was started immediately and maximum effort was directed to maintain fluid and electrolyte equilibrium. Patient had high fluid (350 ml/kg/day), sodium (20-25meq/kg/day) and bicarbonate requirements (12-18 mEq/kg/day). Sequencing by Illumina-Miseq revealed that he was homozygous for c.4399c>T (p.Q1467*)(p.Gin1467*). So, he was also affected by homozygous mutation in MYO5B gene. On 110th day of life, MSC treatment (1x106 cells trans duodenal and 2x106 cells intravenous) was administered. Although fluid and electrolyte requirements did not decrease after stem cell therapy, the rate of blood stream infections was reduced. Until transferring to a transplantation center at the age of 9 months and weighing 9120 g, he was dependent on TPN via central venous catheterization but free off cholestatic liver disease. Fluid requirement was 220 ml /kg/day and electrolyte equilibrium were maintained with 17 mEq/kg/day Na and 8 mEq//kg/day bicarbonate. Small bowel transplantation using cadaveric intestine was performed at the age of 20 months. Unfortunately, the infant died of sepsis one month after transplantation. Informed consent has been obtained from the parents to share the clinical details of their child.

3. Discussion

In MVID, mutations in the MYO5B gene which encodes a protein called myosin Vb contribute to the dysfunction of enterocytes (1). Survival rate is less than 25% at the age of 9 months. Parenteral nutrition and modification of electrolytes according to the needs of patients are the mainstay of therapy after the diagnosis. Life threatening catheter related infections, central venous thrombosis, and TPN associated liver disease are main complications of long-term parenteral nutrition. Recently genetic susceptibility to liver disease in conjunction with mutations in MYO5B gene was defined that result in aberrant expression of apical/canalicular membrane transporters preventing the normal secretion of bile salts and causing cholestatic liver disease (6).

Patients who survive beyond one year of age achieve the chance for allogeneic intestinal transplantation. More than half of the patients die while waiting for transplantation, and the 5-year survival of patients undergoing transplantation is approximately 60%. Halac et al. (3) described 24 patients with MVID from France, 9 of them were Turkish origin. Thirteen children (54%) underwent SBTx, at a median age of 3.5 years (range 1–12 years), after a mean waiting time of 1.5 years (1 month–2.5 years). Seven transplanted children (54%) are living with a functional graft and have been weaned off TPN. One-fourth (6/24) of children experienced several episodes of intrahepatic cholestasis.

To prevent from allograft rejection, lifelong potent immunomodulatory agents are required which predispose patients to severe recurrent infections and the risk for various post-transplant malignancies. Considering the waiting period for transplantation and the complications that may develop afterwards, it is obvious that treatment methods that will provide early enteral nutrition and eliminate fecal losses are needed in patients with MIVD.

Stem cell transplantation is a promising therapy for the devastating neonatal disorders such as intraventricular hemorrhage, bronchopulmonary dysplasia and hypoxic ischemic encephalopathy and many of the phase 1 clinical studies on the safety and feasibility were conducted. Systemically transplanted MSCs migrate and localize toward injured tissue under chemotactic guidance (7). Recently, stem cell therapy was presented as a promising alternative strategy for overcoming the current limitations of intestinal failure treatment. Hong et al.(5) stated that autologous intestinal stem cells (ISCs) transplantation will be a potential therapeutic strategy if modified ISCs can successfully engraft into the ablated small intestinal niche of intestinal failure patients. Although rodent models have established the feasibility of ISC-based therapies, various challenges must be overcome before these therapies may be used clinically, notably for MVID. And, many of the findings from rodent studies are not always applicable to human systems.

We concluded that the rapid turnover of gut epithelial cells and the absence of receptive surface resulting by the genetic defect were the reasons why our patient did not benefit from treatment. Also, the number of stem cells required to repopulate the immense surface area of the small bowel has not been determined, yet. With the permission of our country's ministry of health, we were allowed to provide this promising treatment once. If we had the opportunity to administer it in multiple doses, it might have an influence on tissue regeneration. Another explanation for the lack of response to MSC treatment was that there was no injured tissue to attract stem cells to the area via signaling. Furthermore, using modified ISCs instead of MSCs may be more beneficial.

In our patient, decreased incidence of infection with probable immunomodulatory effects of stem cells was the secondary gain. Although their mechanisms of action are not completely understood, MSCs have been shown to stimulate significant changes in immune responses and a reduction in inflammation through direct interactions with inflammatory cells, as well as through the release of cytokines (7). We wanted to give this opportunity to our patient. Despite the

fact that a single administration of pluripotent MSC did not appear to be effective in this case, we believe it is a worthwhile experience to share.

In this genetically originated disease, replacement of diseased epithelium by gene corrected epithelium with gene editing technique or the use of human leukocyte antigen-matched allogenic ISCs are seen as promising treatments for the future (8). The use of clustered regularly interspaced short palindromic repeats (CRISPR) to correct the monogenic disease, could increase the chances of success of autologous ISC transplantation. Also, enriching for subtypes of ISCs, such as those isolated from different areas of the gut or from different developmental ages, is necessary because they may respond differently to signaling cues, affecting their expandability (5).

Intestinal failure is a rare but potentially fatal condition caused by an inability to maintain growth and development with nutrition obtained through the enteral route. Recent advances in human intestinal stem cell expansion techniques have enabled the in vitro reconstitution of complex cellular structures that mimic the native bowel. Although the dose and route of administration are still being determined, replacing damaged epithelium with corrected epithelium derived from gene editing of autologous stem cells appears to be a viable therapeutic option in the future.

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