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Hepatic Veno-Occlusive Disease with Immunodeficiency (VODI): A Case Report and Review of Literature

İmmün Yetmezlik ile Birlikte Hepatik Veno-Oklüziv Hastalık (VODI): Bir Vaka Sunumu ve Literatür İncelemesi

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Abstract

Hepatic veno occlusive disease with immunodeficiency syndrome (VODI) is an autosomal recessive primary immunodeficiency associated with hepatic vascular occlusion and fibrosis. The immunodeficiency is characterized by severe hypogammaglobulinemia, combined T and B cell immunodeficiency, absent lymph node germinal centers, and absence of tissue plasma cells. VODI was first described in 1976 in an Australian Lebanese population. In our patient who came to the emergency department with septic shock, all immunoglobulins were too low to count. In the blood analysis of the patient, it was observed that there was no antibody response. Lymphocyte subgroups were almost normal. According to the whole exome sequence (WES) analysis, it was observed that he had a VODI gene defect. There was an increase in intermittent liver function tests and ursodeoxycholic-acid (UDCA) was started. However, hepatic fibrosis has not yet been detected by radiological methods. During the follow-up of our patient, there was serious weight loss due to chronic (prolonged) norovirus infection. The patient is preparing for a bone marrow transplant. The VODI gene defect should be considered in the differential diagnosis in patients with sepsis, invasive infection, and hypogammaglobulinemia, especially in the early stages of life. With early detection of the disease, patients are monitored regularly with intravenous immunoglobulin (IVIG) prophylactic treatments. In this way, patients can be caught before hepatic fibrosis develops and the development of irreversible damage can be prevented, such as failure of the liver.

Keywords: Immunodeficiency, Hepatic fibrosis, Sepsis, Cytomegalovirus, Norovirus, Autosomal recessive.

Özet

İmmün yetmezlik sendromlu hepatik veno oklüziv hastalık (VODI), hepatik vasküler oklüzyon ve fibrozis ile ilişkili otozomal resesif bir primer immün yetmezliktir. İmmün yetmezlik durumu şiddetli hipogamaglobulinemi, kombine T ve B hücre immün yetmezliği, lenf nodlarında germinal merkez yokluğu ve doku plazma hücrelerinin bulunmaması gibi sendromik özellikler ile karakterizedir. VODI ilk kez 1976 yılında Avustralya'daki Lübnanlı bir ailede keşfedildi. Acil servise septik şokla gelen hastamızda tüm immünglobülinler ölçülemeyecek kadar düşüktü. Hastanın kan analizinde antikor yanıtının olmadığı görüldü. Lenfosit alt grupları neredeyse normaldi. Tüm ekzom dizi (*whole exome sequence*, WES) analizine göre VODI geninde bozukluk olduğu görüldü. Aralıklı karaciğer fonksiyon testlerinde artış oldu ve ursodeoksikolik asit (UDCA) başlandı.

Ancak hepatik fibrozis radyolojik yöntemlerle henüz tespit edilmedi. Hastamızın takibinde kronik (uzamış) norovirus enfeksiyonuna bağlı ciddi kilo kaybı mevcuttu. Hastamız kemik iliği nakline hazırlanıyor. Özellikle yaşamın erken evrelerinde invazif enfeksiyonu veya sepsisi olan hastalarda hipogamaglobulinemi tespit edilirse ayırıcı tanıda VODI gen defekti de akla gelmelidir. Hastalığın erken tespiti ile hastalar düzenli olarak ve intravenöz immünoglobulin (IVIG) profilaktik tedavileri ile takip edilmektedir. Bu sayede hastalar hepatik fibrozis gelişmeden yakalanabilir ve karaciğer yetmezliği gibi geri dönüşü olmayan hasarların gelişmesi önlenebilir.

Anahtar Kelimeler: İmmün yetmezlik, Hepatik fibroz, Sepsis, Sitomegalovirus, Norovirus, Otozomal resesif.

Introduction

Hepatic veno occlusive disease with immunodeficiency syndrome (VODI) is an autosomal recessive primary immunodeficiency associated with hepatic vascular occlusion and fibrosis. The immunodeficiency is characterized by severe hypogammaglobulinemia, combined T and B cell immunodeficiency, absence of lymph node germinal centers, and absence of tissue plasma cells [1]. It is in the group of combined immunodeficiencies with syndromic features. The expected findings from the disease are hepatic veno-occlusive disease, *Pneumocystis jirovecii* pneumonia, enteroviral or cytomegalovirus (CMV) infections, predisposition to candida infections, thrombocytopenia, hepatosplenomegaly, and cerebrospinal leukodystrophy [2].

VODI has an estimated frequency of 1:2500 live births in the Lebanese population of Sydney, Australia, with 19 cases identified over a period of 30 years. Including these cases, 25 cases were identified in the literature [1,3]. VODI is associated with an 85% mortality rate if unrecognized and untreated with intravenous immunoglobulin (IVIG) and *Pneumocystis jirovecii* prophylaxis [1]. Stem cell transplant preparation regimen may not be successful as it can exacerbate hepatic veno-occlusive.

Case Report

A 45-day-old boy applied to the emergency department with the complaints of fever reaching 40 degrees, respiratory distress, and bruising. There were present exfoliative rash on the body, neck, and face and the heart rate was 220 per minute. The patient was considered to be in septic shock. Fluid deficiency was replaced, meropenem and vancomycin was given to the patient with sepsis dose. The patient was admitted to the ward to be screened for immunodeficiency.

Table 1. Demographic findings.

Patient information and family history	Explanations
Admission age	45-day-old
Sex	Male
Admission findings	Exfoliative rash, pneumonia, septic shock.
Age at diagnosis	70-day-old
Kinship between mother and father	No
Unexpected death at an early age	Yes, his brother died 4-month-old and his father' five siblings died in the first six months of their life.

Prenatal/natal and family history; he was born prematurely, 33 weeks gestation, 1400 gr. His mother's one kidney is agenesic and she had pre-eclampsia during her pregnancy. Due to prematurity and respiratory distress, he was treated in the neonatal intensive care unit (NICU) for 40 days, 25 of which he was intubated. The patient's demographic data is indicated in Table 1.

The result of the patient's hemogram and lenfosit subset is mentioned in Table 2.

Liver function tests and coagulation parameters were within the reference range. There was no growth in blood and urine cultures. Treatment with fluconazole, acyclovir and trimethoprim-sulfamethoxazole was started at prophylactic dose.

Table 2. Hemogram and lymphocyte subset.

	Value	Unit	Reference Range
WBC	4.66	10^9/L	6-13.2
ANC	0.36	10^9/L	0.97-7.2
ALC	3.46	10^9/L	2.14-8.99
CD3	78	%	51-79
CD4	51.8	%	33-55
CD8	32.8	%	11-33
CD19	18.2	%	14-44
CD3- CD16+56+	6.1	%	5-23
CD45RA+	71.3	%	72-93
CD45RO+	27.7	%	9-31
CD4+ CD31+45RA+	31.1	%	57-94
IgG	<0.33	g/L	2.94-11.6
IgA	<0.01	g/L	0.13-0.72
IgM	<0.01	g/L	0.33-1.54
IgE	<0.2	g/L	<15

WBC; white blood cell. ANC; absolute neutrophil count. ALC; absolute lymphocyte count. CD45; common leukocyte antigen. CD3; total T lymphocyte. CD4; helper T lymphocyte. CD8; cytotoxic T lymphocyte. CD19; total B lymphocyte.CD16+56+; natural killer cells. CD45RA; naive lymphocyte. CD45RO; memory lymphocyte.

The number of copies of CMV-DNA was found to be high, which was routinely checked weekly. The prophylactic acyclovir he was taking was discontinued and ganciclovir was started at 15 mg/kg/day. Although the patient received ganciclovir, the CMV-DNA increased to 180000 IU/ml. 10 doses of IVIG replacement therapy (0.5 gr/kg/dose) every other day were added to the patient's treatment. In the follow-up, CMV-DNA gradually regressed. After seeing two negative CMV-DNA results, the patient's ganciclovir was also discontinued, and acyclovir prophylactic dose was started.

The result of the whole exome sequence (WES) panel was seen as a VODI gene homozygous [sp110 c.80dup(p.His28Thrfs*8)] mutation. Our patient's family were not genetically screened. Therefore, the abdomen ultrasonography (USG) and portal venous doppler of the patient was done. Abdomen USG result was that; liver parenchyma echogenicity is heterogeneous, and it may be liver parenchymal disease. Portal Doppler USG result was that; there is a flow pattern showing hepatopetal and respiratory phasicity in the portal system. Portal flow rate is physiological (>11 cm/sec). This USG result is not compatible with veno-occlusive disease. However, our patient will continue to be followed with USG for any veno-occlusive disease that may develop.

The patient was consulted to pediatric gastroenterology after both liver enzymes aspartate aminotransferase (AST) and alanine aminotransferase (ALT) values of the patient were observed to increase gradually in the blood tests. The patient was started with ursodeoxycholic acid (UDCA) at 20 mg/kg twice a day. Liver function tests improved, so liver biopsy was not recommended.

When the patient was 13 months old, the patient was admitted to the emergency department due to vomiting and diarrhea. There was acidosis in the blood gas. It was seen that he dropped from 8.5 kg to 5.2 kg. There is no growth in the bacterial stool culture. No parasites were detected in the stool samples. The stool microbiological panel was positive for enteropathogenic *Escherichia coli* (EPEC) and norovirus. The patient's nutrition was arranged in consultation with the gastroenterology department. Zinc and vitamin A (for 5 days) were added to his treatment.

During hospitalization, the patient developed severe pancytopenia during febrile episodes, requiring multiple erythrocyte and platelet transfusions. *Klebsiella sp.* growth was observed

in blood cultures. Parainfluenza virus type 3 was then detected as positive in the respiratory virus panel, which was checked at various times due to fever.

Our patient is preparing for a bone marrow transplant.

Discussion

Patients with VODI gene defects have been found to have combined immunodeficiency, hepatic veno-occlusive disease or liver failure, and various neurological disorders. Cases diagnosed and followed up with VODI are very rare in Türkiye. There is a patient who was diagnosed with hepatic veno-occlusive disease and immunodeficiency due to homozygous SP110 mutation and suffered from chronic suppurative infections at the age of 18 years in Ankara City Hospital. Two siblings of this patient were diagnosed with abdominal distension. They died of cirrhosis of the liver at the age of about two years. He (18 years old) is under regular treatment with IVIG and UDCA with mild sclerosing cholangitis findings in liver biopsy. His general condition is good and he has been followed for 13 years [4]. In the USA, two siblings of Hispanic origin with a homozygous VODI gene defect developed rapid hepatic veno-occlusion and liver failure, and one of them died at the age of 3 months [6]. Another case in literature; 3-month-old male of Pakistani origin. A homozygous mutation in the SP110 gene was found. He developed recurrent ascites, hypoalbuminemia, and deterioration of liver enzymes. Abdominal ultrasound showed a slightly enlarged liver and moderate ascites. Liver biopsy showed sinusoidal obstructive syndrome (veno-occlusive disease), portal and lobular eosinophils and non-caseating granulomas [8]. Our patient was diagnosed at the age of 5 months and liver fibrosis has not developed yet. Our patient has been monitored with the pediatric gastroenterology department and it was planned to monitor with liver function tests and portal Doppler and abdominal ultrasound with 3-month intervals.

Although severe gastroenteritis and therefore malnutrition were not seen in the literature review, they were seen in our case. However, previous studies show that norovirus causes chronic diarrhea with villous atrophy in patient with common variable immunodeficiency (CVID) [5].

Historically, the prognosis for affected individuals was poor, with 100% mortality in the first year of life if unrecognized and untreated with IVIG and *Pneumocystis jirovecii* prophylaxis [6]. Although our patient was diagnosed early and receiving regular IVIG replacement and prophylaxis, he frequently falls into the state of viral sepsis. And therefore, these patients need to have long-term hospitalization. In sepsis, our patient develops severe leukopenia, lymphopenia, and long-lasting thrombocytopenia. There are studies that VODI gene defect causes thrombocytopenia [7]. However, this patient only had persistent thrombocytopenia during sepsis.

It has been shown that neurological problems (such as cerebral necrosis and cerebral leukodystrophy) in 30% of patients with VODI gene defects [8]. The mentioned neurological defects are not present in our patient, but there is significant hypotonicity in our patient. At sixteen months he has no walking or sitting skills without support. The patient will be monitored every six months for possible neurological disease.

T-Cell receptor excision circle (TREC) screening in the neonatal period may not provide effective results for all immunodeficiencies (such as syndromic immunodeficiencies and combined immunodeficiencies) [6]. However, it was observed that our patient had a low TREC value at the age of 45 days. There is no newborn screening for immunodeficiencies in Türkiye. If there is a screening test programme for all recognisable immunodeficiencies that increases the detection in newborns, it will contribute to the life expectancy and quality of life of our patients.

Conclusion

It is important that physicians have a high awareness, suspicion, and knowledge for this disease, in patients presenting early in life with a picture of combined immune deficiency and deranged liver function, as the earlier the diagnosis and treatment, the better the prognosis. Until the day comes when immunodeficiencies are screened during pregnancy, early diagnosis is the best way to avoid the devastating complications.

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