Agammaglobulinemia in a Patient with Smith-Lemli-Opitz Syndrome: Case Report

Agamaglobulinemi ile Seyreden Smith-Lemli-Opitz Sendromu: Olgu Sunumu

Smith-Lemli-Opitz Sendromu ve Agamaglobulinemi / Smith-Lemli-Opitz Syndrome and Agammaglobulinemia

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Özet

Smith-Lemli-Opitz sendromu (SLO) otozomal resesif kalıtımla geçen multipl kaonjenital anomaliler, mikrosefali, müsküler hipotoni ve ağır gelişimsel gerilikle seyreden kalıtsal bir hastalıktır. Bu sendroma 7-dehidrokolesterol redüktaz enzimindeki eksiklik neden olur. SLO hastaları müsküler hipotonisitenin neden olduğu azalmış motilite ve solunum eforundan kaynaklanan tekrarlayan solunum yolu enfeksiyonları gösterirler. Bu çalışmada tekrarlayan üriner sistem enfeksiyonları gösteren, kronik diyaresi olan ve rektal sürüntü kültürlerinde Klepsiella pnomonia pozitifliği saptanan 1 yaşında bir erkek hastada sunulmuştur. Hasta aynı zaman da immunglobulin G (IgG) değerleri 50-100 mg/dL arasında olacak şekilde belirgin agamaglobulinemiye sahipti. Hastanın takiplerinde intavenöz immünoglobulin replasmanı ile belirgin klinik iyileşme gözlendi. Bu çalışma ile SLO hastalarında tekrarlayan enfeksiyonların görülmesi ile altta yatan bir immün yetmezliğin olabileceği akılda tutulması gerektiği vurgulanmak istenmiştir.

Anahtar Kelimeler

X Geçişli Agamaglobulinemi; Smith-Lemli-Opitz Sendromu; Rekürrent Enfeksiyonlar

Abstract

Smith-Lemli-Opitz syndrome (SLO) is a rare autosomal recessive (AR) inherited genetic disorder characterized by multiple congenital anomalies, microcephaly, muscular hypotonia, and severe developmental delay. The deficiency of 7-dehydrocholesterol reductase enzyme leads to this syndrome. Patients with SLO display recurrent respiratory infections due to secondary muscular hypotonia which leads to decreased motility and respiratory effort. In this study, we report a 1-year-old boy with SLO presented with recurrent urinary infections and chronic diarrhea with Klebsiella pneumonia positivity in the rectal swabs. The patient had also markedly decreased immunoglobulin G (IgG) between 50-100 mg/dL. In follow-up of patient, markedly clinical improvement was observed with intravenous immunoglobulin (IVIG) replacement. With this study, we would like to draw attention; recurrent infections may indicate primary immunodeficiencies such as agammaglobulinemia in patients with SLO.

Keywords

X Linked Agammaglobulinemia; Smith-Lemli-Opitz Syndrome; Recurrent Infections

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Introduction

SLO is an AR inherited genetic disorder caused by 7-dehydrocholesterol (7-DHC) reductase enzyme deficiency in the cholesterol biosynthesis. The incidence of SLO syndrome is estimated as 1/20000-1/70000 [1]. Patients with SLO are characterized by characteristic face appearance with microcephaly, ptosis, anteverted nares and micrognathia, severe developmental delay, and skeletal abnormities such as syndactyly, postaxial polydactyly. Patients with SLO have markedly decreased cholesterol and markedly elevated 7-DHC levels. 7-DHC levels are also used as a biomarker in diagnosis of patients with SLO [1-2]. The DHCR7 gene is located on chromosome 11q12-13 identified as causative gene [3].These patients present with recurrent respiratory infections due to secondary to muscular hypotonia which leads to decreased respiratory effort. Primary immunodeficiencies have been rarely reported in the SLO patients [4]. Herein, we reported a 1-year-old boy with SLO presented with recurrent urinary infections and chronic diarrhea with K. pneumonia positivity in the rectal swaps. The patient had also agammaglobulinemia.

Case Report

A 1-year-old boy was born as a first child of unconsanguineous parents. The pregnancy was normal in term of fetal movements. The patient was born as a preterm and small for gestational age (SGA) baby with weight: 1730 gram (< 3p), length: 39 cm (< 3p), and head circumference: 29 cm (<3p) at the 35 weeks of gestation age. At the 3 months of age, he was referred to our clinic for diagnostic purposes. Physical examination revealed hypotonia, bitemporal narrowing, ptosis, prominent eyes, short nose, bilateral low-seated ears, very high upper palate, microretrognathia, anteverted nares, bilateral partial syndactylia between the 2nd and 3rd toes, and scrotal hypoplasia (Fig.1). In his laboratory investigation, serum cholesterol and 7-DHC levels were found as 10 (140-200 mg/dl) and 6.6 (normal range, 0.10 ± 0.05 mg/dl) respectively. Clinical manifestations and markedly decreased cholesterol levels as well as markedly increased 7-DHC levels indicated SLO in the presented patient. Cranial MRI (magnetic resonance imaging) showed partial corpus callosum agenesia. At the 4 months of age, the percutaneous endoscopic gastrostomy was performed due to oral feeding difficulty. In his follow-up, recurrent urinary infections were seen and he was hospitalized 3 times by one year. Abdominal ultrasound and voiding cysto-urethrography were normal. Also he had chronic diarrhea, several times K. pneumonia was cultured in the rectal swabs. At one year of age, immunologic evaluation was found as follows; absolute neutrophil count (ANC): 2060/mm^3 (1500-400), absolute lymphocyte count (ALC): 4500/mm^3 (2200-8100), CD3: 3900/mm^3 (1300-6000), CD4: 2600/mm^3 (700-4500), CD8: 1270/mm^3 (400-3200), CD19: 100/mm^3 (500-3600), NK: 530/mm^3 (200-1300), IgG: 56 mg/dL (642-788), IgA: 6.2 mg/dL (43-53), IgM: 12 mg/dL (79-110), IgE: 4.2iu/mL (0-50). Genetic test revealed compound heterozygous mutations (c.278 C>T and IVS7+1 G>A) in exon 9 in the 7-DHC reductase (DHCR7) gene (Table 1). However, we couldn't confirm agammaglobulinemia with genetic test. Immunologic and clinical manifestations indicated x-linked agammaglobulinemia in the presented patient. Also, the older brother of mother had recurrent pneumonia and he had been interned 3 times which was consistent with agammaglobulinemia.

Table 1. Immunologic findings of patient

	Patient	Normal range
ANC (mm^3)	2060	1500-400
ALC(mm^3)	4500	2200-8100
CD3 (mm^3)	3900	1300-6000
CD4 (mm^3)	2600	700-4500
CD8 (mm^3)	1270	400-3200
CD19 (mm^3)	100	500-3600
NK (mm^3)	530	200-1300
IgG (mg/dL)	56	642-788
IgA (mg/dL)	6.2	43-53
IgM (mg/dL)	9.2	79-110
IgE (iu/ml)	12	0-50

ANC: Absolute neutrophil count, ALC: Absolute lymphocyte count, NK: Natural killer cell

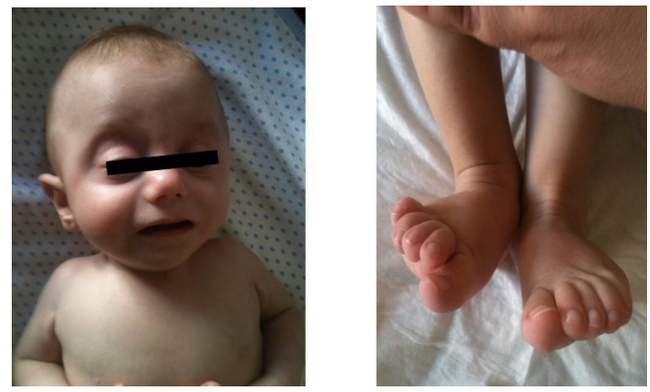

Figure 1. At the age of 1 year. The appearance of patient was consistent with SLO characteristic microcephaly, bitemporal narrowing, microretrognathia, prominent eyes, ptosis, anteverted nares, bilateral low-seated ears, and bilateral partial syndactylia between the 2nd and 3rd toes.

Oral cholesterol supplementation was initiated as 50 mg/kg/day and gradually increased to 100 mg/kg/day in one month. Also, intravenous immunoglobulin (IVIG) replacement was started as monthly infusion. After the IVIG replacement therapy K. pneumonia positivity and recurrent urinary infections were not observed in follow-up of the patient.

Discussion

Cholesterol is a basic cellular membrane lipid molecule. It is highly important membrane permeability and intracellular signaling. Cholesterol is also involved in the synthesis of bile acids, steroid hormones, and vitamin D. In patient with SLO, it is thought that pathogenesis of multisystem manifestations may due to cholesterol deficiency, toxic effects of 7-DHC and its compounds or a combination all of these factors. The diagnosis of SLO based on clinical manifestations and serum cholesterol and 7-DHC levels. Although patients with SLO usually have markedly decreased cholesterol, sometimes mild phenotypic SLO patients may have normal cholesterol levels [1-2]. Some genetic syndromes such as x-linked chondrodysplasia punctata, CHILD syndrome, SC4MOL deficiency, Antley-Bixler syndrome, and HEM dysplasia are involved in cholesterol deficiency which characterized by multisystem malformations. These disorders have quite different manifestations and unique accumulation of biochemical metabolites which are important the pathogenesis

of these disorders. In contrast to these disorders, patients with SLO have markedly elevated 7-DHC levels. Elevated 7-DHC levels are more specific to the patients with SLO than the others [2, 5]. Patients with SLO have an increased number of infections including otitis media, skin and lower respiratory infections due to secondary muscular hypotonia in childhood period. Although patients with SLO often have gastro-esophageal reflux and hypotonia, aspiration pneumonia is rarely seen in their follow-up due to excessive gag reflex [6].

In the medical literature, two articles were reported associated with primary immunodeficiencies in patients with SLO. In the first article, defective monocyte oxidative metabolism was described in a patient presented with recurrent wheezing and atopic dermatitis in 1992 [7]. In the second article, selective antibody immune deficiency against to the polysaccharide antigens was reported in a patient presented with recurrent upper respiratory infection in 2005 [5]. Actually, patients with SLO present with recurrent respiratory tract infections due to secondary to muscular hypotonia which causes decreased respiratory effort. To our knowledge, the presented case is the first agammaglobulinemic patient with SLO.

In conclusion, primary immunodeficiencies have been rarely reported in patients with SLO in the medical literature. In the presented case report, the association of SLO and agammaglobulinemia may be coincidental. However, this case indicates once again that detailed immunologic evaluation is required in patients with SLO who presented with recurrent infections.

Conflict of interest

The authors declare that they have no conflict of interest

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