BJMG 24 (1), 2021 • 99-102
DOI: 10.2478/bjmg-2021-0002
sciendo

CASE REPORT

SMITH-LEMLI-OPITZ SYNDROME: BOSNIAN AND HERZEGOVINIAN EXPERIENCE

Begic N[1,*], Begic Z[1], Begic E[2,3]

[*]**Corresponding Author:** Nedim Begic, M.D., M.A., Department of Cardiology, Paediatric Clinic, Clinical Centre University of Sarajevo, Patriotske Lige 81, Sarajevo, Bosnia and Herzegovina. E-mail: nedim_begic91@hot mail. com

ABSTRACT

The aim of this paper is to present a patient with the Smith-Lemli-Opitz syndrome (SLOS), with an overview of the modality of diagnosis, and the treatment of the patient. Exome analysis showed two variants in exon 6 of the 7-dehydrocholesterol reductase (*DHCR7*) gene have been determined: missense variant *1)* NM_001360.2: c.470T>C (p.Leu157Pro) and *2)* nonsense variant c.452G>A (W151*). Therefore the *DHCR7* genotype of the patient is NM_001360.2: c.[470T>C; c.452G>A]. The proband, aged 6 years, has global developmental retardation with missing contact gaze and lacking motor development for her age and with peripheral spastic-enhanced muscle tone, and is under the supervision of children neurologists, gastroenterologists, nephrologists and cardiologists.

Keywords: Cholesterol; 7-dehydrocholesterol reductase (*DHCR7*) gene; Metabolism; Smith-Lemli-Opitz syndrome (SLOS); Treatment.

INTRODUCTION

Smith-Lemli-Opitz syndrome (SLOS) is caused by mutations in the 7-dehydrocholesterol reductase (*DHCR7*) gene that leads to deficiency of DHCR7 activity [1,2]. It represents autosomal recessive metabolic disorder characterized by varying congenital malformations, facial dysmorphism, and mental retardation. The aim of this case report is to present a patient with the SLOS, with an overview of the modality of diagnosis, and the treatment of the patient.

CASE PRESENTATION

The patient, who was born by Cesarean section at full term in June 2012, who was the second child of a fourth pregnancy, is described. The child did not immediately cry, was resuscitated, weighed 2770 g, length 47 cm, Apgar score 3/6, amniotic fluid was green. After birth multiple abnormalities were observed, postnatal retardation in response (to severe mental retardation), hexadactyly of the right foot, accessory finger on the fifth finger of the left hand, syndactyly ИИИ of both feet, palatoschisis, microcephaly, micrognathism, broad nasal bridge and base, short nasal root, anteverted nares, complete atrioventricular septal defect, weakened to disappearing swelling reflex, right renal agenesis, central hypothyroidism. The limiting abduction of both hips (Figures 1 and 2). The cranial ultrasound verified narrowed lateral ventricles, corpus callosum attenuated, interhemispherical suture was narrower. Sucking reflex was not developed. The pregnancy was not monitored, and in pregnancy the mother smoked cigarettes. Mother was blood type O, Rh positive.

There were no significant pathological events in the family history. Slow progression in weight, nasogastric probe was placed at birth and percutaneous endoscopic gastrostomy (PEG) was inserted at 3.5 years of age. At the age of 4 years and 10 months, the body weight of the patient was recorded as being 8750 g. At 6 years of age, her body weight was recorded as being 9450 g. The magnetic resonance imaging (MRI) finding on the right frontal and occipital part in the area of the border zone, showed narrowed sulcuses with the expanded cortical border, on the left supraventricular hypointense focal point. An atrio-

[1] Department of Cardiology, Paediatric Clinic, Clinical Centre University of Sarajevo, Sarajevo, Bosnia and Herzegovina

[2] Department of Cardiology, General Hospital "Prim. Dr. Abdulah Nakas," Sarajevo, Bosnia and Herzegovina

[3] Department of Pharmacology, Sarajevo Medical School, Sarajevo School of Science and Technology, Sarajevo, Bosnia and Herzegovina

Figure 1. Patient characteristics.

Figure 2. Patient characteristics, syndactyly II/III of both feet.

ventricular septal defect (AVSD) repair was completed at the age of three [ventricular septal defect (VSD) suture plus Gore-Tex Patch]. Kidney scintigraphy verified function of the left kidney was 92.5%, and of right 7.49%. Human All Exon Kit (50MbV5; Agilent Technologies, Santa Clara, CA, USA) and then sequenced on HiSeq2500 (Illumina Inc., San Diego, CA, USA), averaging more than 153-layer coverage as 100 bp "pairs and reads." Less than 97.0% of the target sequences were at least 20-fold covered.

When analyzing the assumed autosomal recessive inheritance, in the second step, genetic variants were searched. Exome analysis showed two variants in exon 6 of the *DHCR7* gene: missense variant NM_001360.2: c.470T>C (p.Leu157Pro) and nonsense variant c.452G>A (W151*) in a compound heterozygous state (variation in *DHCR7* gene deficiency of DHCR7. Therefore, the *DHCR7* genotype of the patient is NM_001360.2: c.[470 T>C; c.452G>A] (https://www.ncbi.nlm.nih.gov/clinvar/).

Exogenous DNA fragments were enriched by Sure Select (Agilent Technologies). Psychomotor development was slowed, with cerebral cramps from the 8 months, with episodes of generalized tonic-clonic attack (initially combination of phenobarbitone and levetiracetam in therapy, now only levetiracetam suspension 100 mg 2 × 1.3 mL in therapy) with a quadriplegic spastic form at the lower extremities. Patient in therapy has vitamin D3 500 IU per day, omeprazole 10 mg per day, levothyroxine 12.5 mcg per day and cholesterol supplementation through emulsion for infusion. Laboratory findings in August 2018 were as follows: AST 113.0 IU/L, ALT 125.0 IU/L, LDH 218.0 IU/L, total cholesterol 4.3 mmol/L, total triglycerides 1.2 mmol/L.

The patient has a risk of the gastrointestinal, respiratory and urinary tract infections, together with large number of past infection and performed prophylaxis. Patient aged 6 years has global developmental retardation with missing contact gaze and lacking motor development for her age and with peripheral spastic-enhanced muscle tone, and is under the supervision of children's neurologists, gastroenterologists, nephrologists and cardiologists.

DISCUSSION

Classic craniofacial features of SLOS include microcephaly, bitemporal narrowing, ptosis, short nasal root, anteverted nares and micrognathia. In addition, the majority of patients have 2/3 toes syndactyly [3]. Initially, two phenotypes of the SLOS were described, the milder form or type I, and the more severe-form or type II. Following the characterization of the biochemical defect, it was found that they are the same disorder [3]. Currently, over 140 *DHCR7* mutations are associated with SLOS [4]. The severe SLOS phenotype was reported in patients who were homozygous carriers of the two functional null alleles NM_001360.2: c.832-1G>C and NM_001360.2: c.453 G>A (p.Trp151Ter), and for the pathogenic missense variant NM_004826.4: c.1249C>T (p.Arg404Cys) [2]. A detailed evaluation of 207 subjects with SLOS showed that the most severe phenotypes were noticed in subjects with two null variants or with two variants in loop 8-9, while those with one or two pathogenic variants in loop 1-2 or one pathogenic variant in the N-terminus, have the milder phenotypes [5].

Diagnosis and treatment of SLOS patients require a long-lasting and multidisciplinary approach. There is currently no consensus on optimal therapy for individuals with SLOS, partly because of the rare and still poorly studied nature of the condition. However, based on the underlying biochemistry and empirical data, cholesterol supplementation is the usual treatment, but with limited benefits due to the inability of cholesterol to cross the blood-brain

barrier. Moreover, supplemental antioxidants, fat-soluble vitamins and coenzyme Q10 are given to these patients [6]. Statins, pharmacological inhibitors of enzyme 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, are potentially promising candidates for therapy of SLOS, but data are still insufficient. Some of the articles describe that an early liver transplant might be the treatment option in order to prevent neurological deterioration [7]. Additional investigations to better understand the range of cognitive function in SLOS and the factors that modify the clinical phenotype are necessary [8].

Conclusions. It would be useful to consider characterization of SLOS genotypes during the prenatal stage based on the prevalence in certain populations. Future treatment of genetic diseases is gene therapy, but for most patients it is still far from every day clinical practice.

Declaration of Patient Consent. The authors certify that they obtained a signed patient consent form. In the form, the patient's parents gave consent for images and other clinical information on the patient to be reported in the Journal. They understand that the patient's name and initials would not be published and every effort will be made to conceal her identity, but anonymity cannot be guaranteed.

Acknowledgments. Part of this case report was presented at the 87th European Atherosclerosis Society Congress, held at Maastricht, The Netherlands, on 26 May 2020.

Declaration of Interest. The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

REFERENCES

1. Bianconi SE, Cross JL, Wassif CA, Porter FD. Pathogenesis, epidemiology, diagnosis and clinical aspects of Smith-Lemli-Opitz syndrome. Expert Opin Orphan Drugs. 2015; 3(3): 267-280.
2. Witsch-Baumgartner M, Löffler J, Utermann G. Mutations in the human DHCR7 gene. Hum Mutat. 2001; 17(3): 172-182.
3. DeBarber AE, Eroglu Y, Merkens LS, Pappu AS, Steiner RD. Smith-Lemli-Opitz syndrome. Expert Rev Mol Med. 2011; 13: e24.
4. Svoboda MD, Christie JM, Eroglu Y, Freeman KA, Steiner RD. Treatment of Smith-Lemli-Opitz syndrome and other sterol disorders. Am J Med Genet C Semin Med Genet. 2012; 160C(4): 285-294.
5. Waterham HR, Hennekam RCM. Mutational spectum of Smith-Lemli-Opitz syndrome. Am J Med Genet C Semin Med Genet. 2012; 160C(4): 263-284.
6. Ballout RA, Bianconi S, Livinski A, Fu Y-P, Remaley AT, Porter FD. Statins for Smith-Lemli-Opitz syndrome. Cochrane Libr. 2020; 2020(1): CD013521.
7. Ertugrul G, Yankol Y, Mecit N, Kirimlioglu H, Kanmaz T, Acarli K, *et al.* Liver transplant and improvements in cholesterol biosynthesis defects: A case report of Smith-Lemli-Opitz syndrome. Exp Clin Transplant. 2019 Jan 21. doi: 10.6002/ect.2018.0131. Online ahead of print.
8. Eroglu Y, Nguyen-Driver M, Steiner RD, Merkens L, Merkens M, Roullet J-B, *et al.* Normal IQ is possible in Smith-Lemli-Opitz syndrome. Am J Med Genet A. 2017; 173(8): 2097-2100.