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SMITH-LEMLI-OPITZ SYNDROME WITH SEVERE INVOLVEMENT OF THE ORAL CAVITY IN A TEENAGER

Smaranda Diaconescu[1], Elena Traci, Nicoleta Gimiga[1], Maria Bolat[1]*, Ana Maria Fătu Vascu[1], Claudia Olaru[1], Cristina Iordache[1], Georgeta Sinitchi[2], Daniel Olteanu[3], Carmina Cuciuc[3], Laura Trandafir[1]

1. "Gr. T. Popa" University of Medicine and Pharmacy, Iasi, Romania
2. "Atopia" Medical Center, Iasi, Romania
3. Orthodontics trainee, "Gr. T. Popa" University of Medicine and Pharmacy, Iasi, Romania

Corresponding author*: **Maria Bolat, maria.bolat@yahoo.com

ABSTRACT

The Smith-Lemli-Opitz syndrome (SLOS) is a plurimalformative syndrome transmitted by autosomal recessive inheritance. SLOS is caused by the deficiency in the enzyme 7-dehydrocholesterol-delta-reductase (DHCR7) resulting in cholesterol metabolism disorders, more precisely the incapacity to transform dehydrocholesterol into cholesterol. The syndrome is marked by characteristic facial dysmorphism, multiple malformations and intellectual disability. We are reporting the case of a 15 year old patient diagnosed postnatally with bilateral hands and feet polydactyly, and clinodactyly in the 5th toe of the right foot which was surgically treated when the patient was 6 months old. The association with suggestive modifications of the oral cavity (dental impactions, palatoschisis, enlarged alveolar ridges and uvula bifida) that required complex orthodontic therapy and the genetic consult establish the diagnosis of Smith-Lemli-Opitz syndrome.

INTRODUCTION

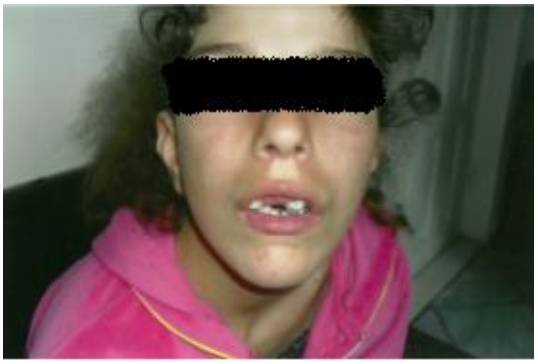
The Smith-Lemli-Opitz syndrome (SLOS) is an affection transmitted by autosomal recessive inheritance that associates multiple malformations and cognitive disorders, with its etiology including an inborn metabolic defect, namely the reduced activity of the enzyme 7-dehydrocholesterol-delta-reductase (DHCR7). SLOS was first described in a serial case study by Smith, Lemli and Opitz in 1964. (1)

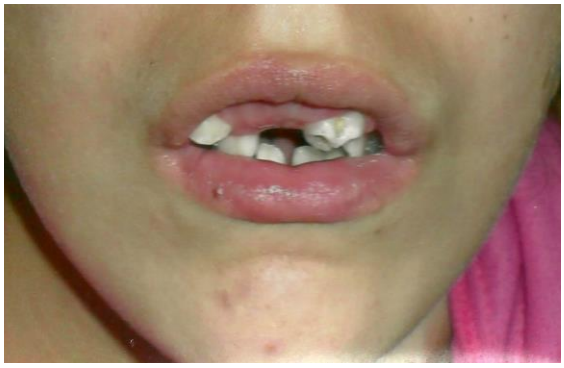
In 1993, Irons et al. noted an abnormal profile of plasma sterols in SLOS patients: low cholesterol levels and increased levels of 7-dehydrocholesterol (7-DHC). (2) The frequency of patients with evident clinical manifestations seems to be higher among Caucasian people, especially in the north of Europe, where it goes up to 1–2% (3). The typical craniofacial features include microcephaly with bitemporal narrowing, short snub nose with anteverted nares, unilateral or bilateral blepharoptosis, epicanthus and retrognathia. The patients frequently have a flat facial profile and low-set ears. More severe cases can also present with hands and feet postaxial polydactyly and cutaneous syndactyly of 2/3 toes, although this is also very frequently encountered in other disorders, which can in its turn lead to diagnostic errors. The oral features can include dental impactions, enlarged alveolar ridges, palatoschisis and uvula bifida. The classic facial appearance does change with time, and some features become less visible with aging. The depth of the impact of SLOS depends on the level of cholesterol.

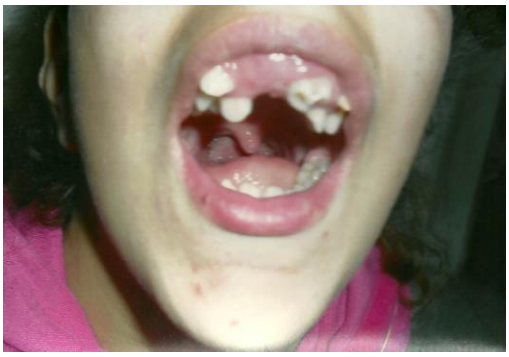
CASE PRESENTATION

We are presenting the case of a 15 year old teenage girl, coming from a rural area, who was admitted to the pediatric gastroenterology department with abdominal pain predominantly in the right upper quadrant and

lumbar region. From a clinical point of view, upon admission the patient had a relatively good general status, presenting with facial dysmorphia, afebrile, juvenile acne, auscultation revealed normal breath sounds, grade I/II systolic heart murmur at the apex, soft, depressible abdomen with respiration-induced movements, presenting with pain in the right upper quadrant and lumbar region, normal bowel movement and micturition, no signs of meningeal irritation. (Fig 1) Paraclinical findings: normal complete blood count, no inflammatory syndrome, normal renal and liver function, total cholesterol 158mg/dl (VN=100-200mg/dl). Case history revealed that the patient was diagnosed postnatally with congenital anomalies, bilateral hands and feet polydactyly, clinodactyly in the 5th toe of the right foot and subumbilical hemangioma. When the patient was about 6 months old, the bilateral hand 5th finger and right foot digitiform appendages were surgically removed, the subumbilical hemangioma was treated with electrocauterization, and one year later she underwent the excision of the supernumerary left foot toe and treatment of the bilateral foot clinodactyly in the 5th toes.







The genetic consult led to recording a phenotype that was suggestive of the Smith-Lemli-Opitz syndrome. At the age of 7, the clinical-biological and growth rate assessment showed a normal morphogram (T=130 cm; G=24kg), bone age was consistent with chronological age, normal growth hormone (Gh=3.5ng/ml), normal euthyroid state, age appropriate mental development (IQ=102, average level intelligence), hypercholesterolemia (total cholesterol – 229 mg/dl, VN 100-200 mg/dl), 42 macrodontia, being referred to the oral-maxillofacial surgical clinic for dental extraction 42. She underwent subsequent orthodontic treatment for dental impactions and supernumerary teeth 11, 12. Upon admission into our clinic, the patient underwent electrocardiogram examination (normal morphology), thoracic teleradiology examination (chest x-ray showed accentuated bilateral hilar and basal markings, clear costodiaphragmatic sinuses, normal cardiomediastinal contours), as well as echocardiography examination that showed no

changes. The psychological examination revealed psychoemotional immaturity. The genetic examination revealed facial dysmorphia, micro-retrognathism, hypodontia, dental malimplantation treated orthodontically, scarring on the cubital side of the hand and scarring on the ulnar side of the foot (surgically treated postaxial polydactyly). The fundus of the eye is normal bilaterally. Abdominal and pelvic echography revealed polycystosis in both ovaries, without any other changes. The examination of the oral cavity showed labial incompetence, everted lower lip, hypertrophy of the mentalis muscles, deep chin groove, modified shape (omega) of the upper dental arcade, high-arched palate, upper jawbone proalveolodontia, inferior arch: mandibular micro-retrognathia, lateral mandibular deviation, dento-alveolar disharmony with crowding, trapeze-shaped arcade, impacted 12 year old molars, class II/I malocclusion (as per Angle's classification) with upper jawbone proalveolodontia, retroalveolar mandibular teeth with 15 mm overjet, 5 mm lateral deviation, deep overbite occlusion 2/3, chronic generalized gingivitis and gingival hyperplasia. (Fig 2, 3) The patient was treated symptomatically (with antispasmodic and prokinetic medication) and showed an improved status upon discharge, with the recommendation to continue orthodontic treatment and to get an endocrinology consult for the subjacent pathology (micropolycystic ovaries and juvenile acne).

DISCUSSIONS

Cholesterol is found in all the cells, being an essential component of all membranes; it has a major influence on the transmission of intercellular signals. Cholesterol is the precursor to steroid hormones, bile acids and oxysterols, and 7-dehydrocholesterol is the precursor to vitamin D. Haldar et al. showed that incorporating 7-DHC or other precursors of cholesterol significantly alters the electrostatic characteristics of biological membranes, which entails the possibility of modifications in the activity of ion-dependent ATPase and ion channels. (4) Intercellular transmission is also disrupted. An SLOS *in vitro* model using a DHCR-7 pharmaceutical inhibitor showed a modification in the lipid layer and proteins' structure. (5) Paila et al. showed that the serotonin receptor 1A, which requires cholesterol in order to function, had a reduced ligand binding, thus reducing signal efficiency in case of high levels of 7-DHC and low levels of cholesterol. (6) In a different study carried out on 21 SLOS patients, the cerebrospinal fluid analysis showed the reduction in 5-hydroxyindoleacetic acid levels, a serotonin metabolite. (7) In addition to the enzymatic production of oxysterols, cholesterol can also be oxidized non-enzymatically and produce biologically active oxysterols. Based on clinical suspicions, the recommended screening for SLOS is measuring 7-DHC in plasma using chromatography or spectrometry. Values exceeding 2 mcg/ml are considered abnormal. Plasma cholesterol is usually low, but it can also be normal. A normal level of plasma cholesterol does not rule out SLOS. Plasma 7-DHC is a sensitive marker for detecting SLOS, but false-positive increases were noticed when administering some psychoactive drugs, including aripiprazole and trazodone, which are DHCR7 inhibitors. (8) Other psychoactive agents, such as haloperidol, can lead to the increase of 7-DHC levels by boosting cholesterol synthesis. (9) Molecular testing of DHCR7 is recommended in these cases; sequence analysis can detect up to 96% of mutations. In case no mutation or just one mutation is found, quantitative testing such as PCR with analysis of chromosomal microarrays with coverage of DHCR7 and the flanking region is recommended, since several exon deletions have been described. (10) If fetal ultrasound shows intrauterine growth restriction or multiple congenital anomalies, it is possible to carry out an amniocentesis in order to test the amniotic fluid for abnormal levels of 7-DHC using spectrometry or chromatography. There are currently around 20 different panels available on the market, including massively parallel sequencing

techniques and include the DHCR7 gene in their analysis. (11) The clinical indications range from autism to developmental delays, to cholestatic syndromes and epilepsy. Besides, SLOS associates various clinical manifestations such as microcephaly, palatoschisis, micrognathia, syndactyly, impaired weight gain, polydactyly, heart malformations. Treatment includes a diet based on high cholesterol foods (egg yolk) or administering supplements such as crystalline cholesterol suspended in oil or prepared as microencapsulated cholesterol powder. There is a series of factors that limit the effectiveness of the diet. In vitro studies indicate that intracellular cholesterol transport is affected, which suggests a possible defect in the cells' capacity to adequately use exogenous cholesterol. (12, 13) Moreover, cholesterol does not cross the hematoencephalic barrier significantly, the central nervous system being dependent on endogenous synthesis. (14) Other therapeutic options include bile acid analogs (liver cholestasis can occur in severe cases), fresh frozen plasma (rich in lipoproteins such as LDL-low-density lipoprotein), simvastatin (the study by Chan et al. showed that administering simvastatin in 3 patients with high cholesterol diets can generate a reduction of 7-DHC levels and can maintain the levels of total cholesterol). (15) Although all the initial developmental defects leading to structural anomalies can be prevented, biochemical anomalies will remain at the central nervous system level because the hematoencephalic barrier prevents the transfer of cholesterol which plays a part in its development. The majority of SLOS patients with mild to classic phenotypes express a DHCR7 allele with residual enzymatic function. (15) The increased expression of DHCR7 mutant allele or stabilization of the mutant DHCR7 protein could have therapeutic potential. In fact, simvastatin was proved to lead to an increase in the level of cholesterol by increasing the expression of mutant DHCR7 protein with residual enzymatic activity. (12, 15)

CONCLUSIONS

SLOS is a unique disorder due to the fact that it is a malformation, as well as a congenital metabolism error. Thus, the clinical aspects highlighted in SLOS can occur as development defects or can be a consequence of the altered biochemistry of the sterols. Developmental defects occur during intrauterine life, therefore they are not susceptible to be subjected to therapeutic interventions. However, early interventions could be considered in case of pregnancies with such risks. In children with associated suggestive clinical modifications (microcephaly, micrognathia, palatoschisis, polydactyly, blepharoptosis, mental retardation), genetic consult is compulsory; dental and orthodontic interventions initiated early on can in time ensure the adequate esthetics and functionality of the oral cavity.

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