Le syndrome de Smith-Lemli-Opitz : aspects cliniques et biochimiques chez un nourrisson Tunisien

Smith-Lemli-Opitz syndrome: Clinical and biochemical features in a Tunisian infant

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Résumé :

Introduction : Le syndrome de Smith-Lemli-Opitz (SLOS) est caractérisé par un déficit intellectuel, une dysmorphie faciale, un retard de croissance intra-utérin et un large spectre de malformations congénitales. Il est dû à un déficit en 7-déhydrocholestérol réductase, suite à des mutations au niveau du gène 7DHCR.

Observation : Nous décrivons le premier cas Tunisien de SLOS confirmé biologiquement. Le diagnostic a été suspecté devant une dysmorphie faciale caractéristique (racine du nez large, narines antéversées, rétrognathisme, fente palatine postérieure), une syndactylie bilatérale des deuxièmes et troisièmes orteils, et des anomalies des organes génitaux externes. Il a été confirmé par une diminution du cholestérol et une augmentation du 7-déhydrocholestérol dans le sang. Le score de sévérité était modéré et il corrélait avec le taux bas de cholestérol ainsi qu'avec la fraction élevée du déhydrocholestérol. Une hypothyroïdie était également découverte chez ce patient.

Conclusion : Le SLOS doit être suspecté devant des signes cliniques caractéristiques. L'étude moléculaire du gène 7DHCR n'est pas nécessaire au diagnostic positif, mais peut être très utile dans le diagnostic prénatal.

Abstract :

Background : Smith-Lemli-Opitz syndrome (SLOS) is a genetic disorder characterized by development delay, intrauterine growth retardation and a wild spectrum of congenital malformations. It is caused by mutations in the 7-dehydrocholesterol reductase (7DHCR) gene which results in abnormality of cholesterol metabolism.

Case presentation : We report the first case of a Tunisian patient with SLOS. The diagnosis was suspected by the dysmorphic features (wide nasal bridge, anteverted nares, retrognatia, posterior cleft palate), the bilateral syndactyly of 2nd and 3rd toes and the abnormal genitalia. It was confirmed by a high serum level of 7-dehydrocholesterol and low level of cholesterol. The patient had a moderate severity score that matches with the cholesterol level and the dehydrocholesterol fraction. A hypothyroidism, which is not frequent in SLOS, was present.

Conclusion : SLOS is a severe congenital disorder which has a major phenotypic heterogeneity. It should be suspected when striking features are found. Molecular study of the 7DHCR gene is not essential for diagnosis but can be very useful for prenatal diagnosis.

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Key words: Smith-Lemli-Opitz syndrome, 7DHCR gene, pyloric stenosis.

Introduction

Smith-Lemli-Opitz syndrome (SLOS) (OMIM 270400) is an autosomal recessive disorder characterized by a large spectrum of congenital malformations associated with intellectual disability and developmental delay [1]. The disorder is caused by deficient activity of 7-dehydrocholesterol reductase (DHCR7) which is encoded by the DHCR7 gene localized to chromosome 11q12-13 [1]. We report clinical and biochemical features of SLOS in a Tunisian infant.

Case report:

The patient was the second child of healthy, non consanguineous parents. Prenatal ultrasound showed a fetus with female genitalia and normal growth parameters. No visceral malformations were noted. He was born by cesarean section at 41 gestatinal weeks after an uncomplicated pregnancy with a birth weight of 3200 g. Clinical examination showed dysmorphic features with flattened face, high forehead, palpebral edema, hypertelorism, wide nasal bridge, bulbous nose with anteverted nares, retrognatia, low set ears with abnormal helix, short neck and posterior cleft palate. He had proximally set thumbs and bilateral syndactyly of the 2nd and 3rd toes (figure 1 et 2)

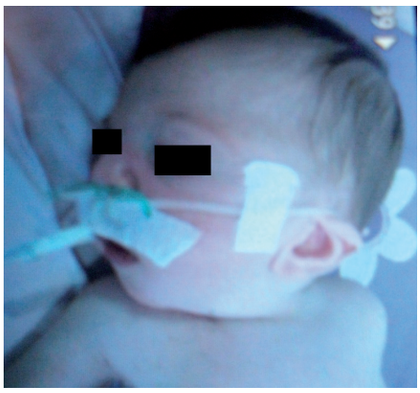

Figure 1 : Dysmorphic features (low set ears, abnormal helix, retrognatia)

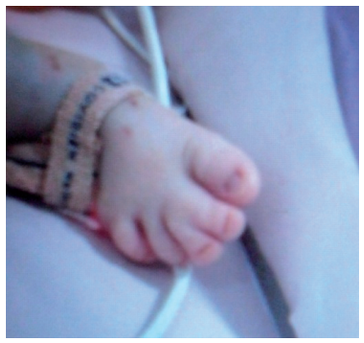

Figure 2 : syndactyly of the 2nd and 3rd toes

He had hypogenitalism with anterior hypospadias, bifid scrotum and ectopic testicles.

He was hospitalized at the age of 16 days for weak sucking and poor weight gain. Physical exam showed, in addition to the described anomalies at birth, a weight of 3000g, generalized hypotonia, weak sucking, lack of eye tracking and very slow pupillary reflex. The cardiopulmonary examination was normal.

Cerebral MRI was normal. Abdominal ultrasound revealed the presence of a pelvic left kidney and testicles located in the inguinal canals with no evidence of female reproductive organs. Cardiac ultrasound showed no anomalies. The karyotype was 46,XY. A peripheral hypothyroidism was diagnosed (FT4 = 22,8pmol/l, TSH =10 UI l/ ml).

He required enteral feeding with nasal gastric tube. Treatment with L-Thyroxine was started. At 33 days of age, he presented with vomiting and dehydration; pyloric stenosis was diagnosed and the patient underwent pyloroplasty.

SLOS was suspected. The plasma sterol profile showed cholesterol level at 978 mol/l (Normal range: 1110 – 7095 mol/l) and 7 dehydrocholesterol (7-DHC) level at 827 mol/l (Normal level < 3 mol/l) associated to the abnormal presence of 8-dehydrocholesterol (8-DHC) at a level of 895 mol/l. These anomalies confirmed SLOS.

The patient was discharged with enteral feeding. At two years' follow-up, he has failure to thrive, microcephaly and developmental delay.

Discussion :

In this report, the diagnosis of SLOS was suspected by the presence of typical craniofacial dysmorphy, syndactyly of the 2nd and 3rd toes, and disorders of sex development. It was confirmed by high level of serum 7DHC.

Patients with this syndrome are characterized by a revised severity score in which malformations in ten embryologically distinct areas are scored which distinguish three degrees of severity (mild, mode-

rate and severe) [2]. This score does not consider the severity of intellectual disability, behavioral disturbances, or feeding difficulties. Our patient had a severity score of 30 ranking him to a moderate category of SLOS.

In mild SLOS forms, few patients were born with normal birth parameters and poor weight gain and microcephaly were developed later [3] like in our patient.

Infants with SLOS frequently have feeding problems secondary to hypotonia, oral-motor incoordination and gastrointestinal dysmotility. In general, infants with the more severe phenotype have more feeding problems [4]. Pyloric stenosis has been reported in at least 10% of SLOS patients. It is now uncommon in SLOS patients treated with supplementary cholesterol starting shortly after birth [2].

The genitalia in male SLOS patients range from normal to the appearance of complete sex reversal. The high frequency of hypogenitalism in SLOS is not sufficient evidence to implicate inadequate steroid production in utero. The persistence of Mullerian remnants in some SLOS patients [5] suggests defective genital morphogenesis unrelated to steroid hormone levels. It is possibly mediated through sterol related dysfunction of Desert hedgehog in genital tissues [2].

The occurrence of hypothyroidism in association with SLOS is very rare. It had been described with hypercorticism and adrenal dysfunction [6].

Approximately, 10% of SLOS patients have normal cholesterol level due to cross-react of 7DHC and 8DHC as cholesterol in the cholesterol oxidase assay methods [2]. In SLOS, there is an inverse correlation between serum concentration of cholesterol and clinical severity. Mortality is particularly high in patients with the lowest cholesterol concentrations (<7 mg/dl) [7]. DHC fraction (sum of 7- and 8-DHC/ sum of 7- DHC, 8-DHC and cholesterol) in plasma appears to have the best predictive value for clinical severity of patients. Mildly affected patients exhibit DHC fractions < 0.4 while moderately and severely affected patients have DHC fractions ranging from 0.44 to 0.8 [8]. Our patient had a moderate form with a DHC fraction of 0.64.

Treatment with cholesterol reduces irritability, hyperactivity, self-injury and autistic behaviors. It also improves somatic growth and reduces infection frequency [9].

Identification of DHCR7 mutations is not essential for diagnosis but it allows precocious prenatal diagnosis on chorionic villus samples. Prenatal diagnosis of SLOS can also be performed by the dosage of 7DHC and 8DHC levels in amniotic fluid [10].

Conclusion:

To the best of our knowledge, this is the first Tunisian case report of SLOS in Tunisia. We need more series of patients to determine the incidence and the mutational spectrum in Tunisia and to establish genotype-phenotype correlations.

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