Living with inborn errors of cholesterol biosynthesis: lessons from adult patients


In the last decades, nine inherited errors of the distal part of cholesterol biosynthesis have been recognized. Affected patients present complex malformation syndromes involving different organs and systems with variable degrees of severity. We report on the phenotype evolution of three patients with enzymatic defects at three distinct steps of such pathway: Smith–Lemli–Opitz syndrome, X-linked dominant chondrodysplasia punctata type 2 and congenital hemidysplasia with ichthyosiform erythroderma and limb defects syndrome. The patients’ natural history, from childhood to adulthood, is thoroughly described in order to contribute for a better knowledge of these diseases. Our ultimate goals are to contribute for a better characterization of the long-term course of these metabolic disorders and for the recognition of such diseases in older patients.

Conflict of interest

There are no conflicts of interest associated with this publication and there was no external financial support for this work.

Introduction

So far, nine inborn errors of the distal part of cholesterol biosynthesis (IECB) pathway have been recognized (Table 1) (1, 2).

Among them, Smith–Lemli–Opitz syndrome (SLOS), X-linked dominant chondrodysplasia punctata type 2 (CDPX2) and congenital hemidysplasia with ichthyosiform erythroderma and limb defects (CHILD) syndrome are the most frequent and are usually diagnosed in childhood. Nevertheless, milder presentations can escape early diagnosis and should be recognized later. The establishment of such diagnosis has become more pertinent since the phenotype improves with high cholesterol intake, compensating the cholesterol deficiency on peripheral tissues (3), though the central nervous system remains dependent of its own cholesterol synthesis (4).

There are only a few descriptions of these diseases in adults, making the recognition of late-specific clinical features more difficult. Here, we report on the phenotype evolution from childhood to adulthood, of three patients with IECB, dissecting the specificities...
Table 1. Inborn errors of cholesterol biosynthesis

<table>
<thead>
<tr>
<th>Disease</th>
<th>MIM</th>
<th>Gene</th>
<th>Human chromosome</th>
<th>Inheritance</th>
<th>Enzyme</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smith–Lemli–Opitz syndrome</td>
<td>270400</td>
<td>DHCR7</td>
<td>11q12-13</td>
<td>AR</td>
<td>3β-Hydroxysterol Δ7-reductase</td>
</tr>
<tr>
<td>CDPX2</td>
<td>302960</td>
<td>EBP</td>
<td>Xp11.22-11.23</td>
<td>XD</td>
<td>Δ5-Δ7-Sterol isomerase</td>
</tr>
<tr>
<td>CHILD syndrome</td>
<td>308050</td>
<td>NSDHL</td>
<td>Xq28</td>
<td>XD</td>
<td>C4-sterol dehydrogenase</td>
</tr>
<tr>
<td>CK syndrome</td>
<td>300831</td>
<td>NSDHL</td>
<td>Xq28</td>
<td>XR</td>
<td>C4-sterol dehydrogenase</td>
</tr>
<tr>
<td>Greenberg dysplasia</td>
<td>215140</td>
<td>LBR</td>
<td>1q42.1</td>
<td>AR</td>
<td>Δ14-Sterol reductase</td>
</tr>
<tr>
<td>Antley–Bixler syndrome with ambiguous genitalia and disordered steroidogenesis</td>
<td>201750</td>
<td>POR</td>
<td>7q11.2</td>
<td>AR</td>
<td>P450 oxidoreductase</td>
</tr>
<tr>
<td>Desmosteroliosis</td>
<td>602398</td>
<td>DHCR24</td>
<td>1p31.1-p3.3</td>
<td>AR</td>
<td>3β-Hydroxysterol Δ24-reductase</td>
</tr>
<tr>
<td>Lathosteroliosis</td>
<td>607330</td>
<td>SC5D</td>
<td>1q23.3</td>
<td>AR</td>
<td>3β-Hydroxysterol Δ5-desaturase</td>
</tr>
<tr>
<td>Sterol-C4-methyloxidase-like deficiency</td>
<td>607545</td>
<td>SC4MOL</td>
<td>4q32-q34</td>
<td>AR</td>
<td>Sterol-C4-methyloxidase</td>
</tr>
</tbody>
</table>

AR, autosomal recessive; CDPX2, X-linked dominant chondrodysplasia punctata type 2 or Conradi–Hunermann syndrome; CHILD syndrome, congenital hemidysplasia with ichthyosiform erythroderma and limb defects syndrome; XD, X-linked dominant; XR, X-linked recessive.

*aHypomorphic temperature-sensitive alleles.*

of each disorder in order to contribute for a better knowledge of these diseases.

**Case reports**

**Patient 1 – SLOS**

First child of a healthy and non-consanguineous couple (Fig. 1a–c). Pregnancy was uneventful and the patient was born at term (birth weight 3800 g). During labor, fetal distress was detected. Resuscitation and hospitalization were required due to neonatal sepsis. On clinical examination, the patient also presented: bifid uvula, submucous cleft palate and bilateral syndactyly of the second and third toes.

At the age of five, mild developmental delay was diagnosed: weight was on the 75th centile, height on 10–25th centile and microcephaly was detected. Brain magnetic resonance imaging and cardiac, otolaryngology and ophthalmology observations were normal, as well as abdominal and renal ultrasounds. Karyotype, fragile X syndrome test, and first line metabolic investigation – including amino acids, urinary organic acids, lactate and very long-chain fatty acids were normal.

At 11 years old (yo), total cholesterol levels were slightly decreased (143 mg/dl), whereas plasma concentration of 7-dehydrocholesterol (a cholesterol precursor) was significantly increased (18 mg/l vs <0.2 mg/l in controls) suggesting a defect of the last enzyme of cholesterol biosynthesis pathway. DHCR7 sequencing showed compound heterozygosity for two mild missense mutations H301R/W182L, confirming the diagnosis (5). The patient was put on a cholesterol rich diet (to compensate the endogenous deficit) and simvastatin (to decrease cholesterol precursors). Genetic counseling was provided to the family.

By 14 yo, he presented both weight and height below the fifth centile and puberty delay. Later, he caught up and presently his weight is on the 50th centile and his height is on 10–25th centile.

He attended school for 9 years (with special learning support), but he did not accomplish the skills needed to obtain a driver’s license or enough autonomy to shop alone. Currently, he is a 22 yo young man, unemployed, with several limitations in social interaction.

**Remarks:** SLOS is an intellectual disability/malformation disorder caused by deficiency of 7-dehydrocholesterol reductase which leads to a decreased synthesis of all body cholesterol.

Most metabolic disorders belong to the intoxication type, meaning that the clinical situation worsens with the buildup of the toxic compound. On the contrary, patients with SLOS improve with a diet enriched in cholesterol (6).

The survival rate is unknown. However, decreased cholesterol availability has major consequences for organogenesis and life expectancy is largely dependent on the severity of the internal malformations (7). Our patient does not have pulmonary, cardiovascular, ophthalmological, renal or gastrointestinal abnormalities and thus present a mild phenotype. On the basis of these data, a long-term survival is expected. Nevertheless, some epidemiological studies showed an association between low levels of serum cholesterol and an increased risk of hemorrhagic cerebral strokes in adulthood (8). Nowadays the doubt remains on whether SLOS patients should be considered at risk for cerebral strokes.

**Patient 2 – CDPX2**

Female patient with CDPX2 has been in follow-up since infancy (Fig. 1d–e).

Her parents were young, healthy and non-consanguineous. On the third trimester of pregnancy, hydramnios and short femurs were detected. Delivery occurred at term and required forceps; Apgar index was 8/9.

At birth, weight and occipitofrontal circumference (OFC) were within normal range but length was below...
Fig. 1. Phenotypic features. Patient 1 (a) at diagnosis presented mildly coarse facial features with high forehead, epicanthic folds, low nasal bridge, broad nasal tip, full cheeks, large mouth with full lips and (b) bifid uvula (a feature present in several Smith–Lemli–Opitz syndrome patients). In addition, anterior thoracic deformities and scoliosis were also recognized. (c) Currently, with 22 years old (yo), the patient’s face is longer and presents high forehead, large nose with bulbous tip, full cheeks and full lips. Patient 2 (d) at young age had a mildly coarse face with high forehead, epicanthic folds, broad nose, full cheeks, full lips, short neck and asymmetry of upper and lower limbs [radiographic evaluations confirmed the asymmetrical shortening of long bones (more severe on the left lower limb) and punctuate calcification of the epiphyseal regions of long bones, patella and tarsal bones]. (e) The same patient as a young adult (20 yo). The dysmorphic facial features have softened over time. Patient 3 presents (f) an extensive, ill-defined, relatively stable, yellowish scaly plaque affecting the left lower limb, more noticeable at the groin and thigh. The left foot presents pseudosyndactyly. The right foot presents discrete linear hyperqueratotic band over the dorsal surface of the third and fifth toes. (g) On the left buttock, there is a persistent erythematous plaque with large desquamation. (h) Other findings: left hand (and left foot) have severely dystrophic nails. Left hand: multiple finger deformity. Right hand: nail pterygium on the first, third and fourth fingers.

the 5th centile. She was diagnosed with CDPX2 on the neonatal period based on a typical facies, ichthyosiform erythroderma, kyphoscoliosis, congenital (left) hip dislocation and asymmetric shortening of the lower limbs with limitation of extension. Observation by ophthalmology and abdominal, cardiac and transfontanellar ultrasound was normal.

Throughout time the patient always presented normal development and was a successful student; dermatological manifestations became milder (except for alopecia); weight and OFC were adequate but height was below the 5th centile.

The most significant health problems were ophthalmological and orthopedic. She was diagnosed with bilateral cataracts around 3 yo and was submitted to surgery twice. She also needed multiple orthopedic interventions.

Menses started at 11 yo. Karyotype, first line metabolic investigation and thyroid function were normal. The serum cholesterol concentration of patient and both parents was normal, however, plasma levels of 8-dehydrocholesterol and cholest-8(9)-en-3-β-ol were significantly increased in the patient’s sample suggesting a defect in the 3β-hydroxysteroid-Δ8-Δ7sterol isomerase and prompted sequencing of the EBP gene. A novel 41 bp heterozygous deletion was detected. This deletion is predicted to introduce a premature stop codon that gives rise to a truncated protein with less 132 amino acids than the wild type.

Currently the patient is 20 yo and has a normal lifestyle. Regarding some physical activities and sports, she has some limitations due to the orthopedic problems. Concerning education, she has been admitted to college and is completing her course plan successfully. She is fully aware of her disorder, what can be offered in terms of prenatal diagnosis and she has been coping well with it, never having required psychological support.

Remarks: CDPX2 is a rare X-linked disorder with skeletal, skin and ocular manifestations and presumed high male lethality caused by mutations in EBP gene,
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which encodes the 3β-hydroxysteroid-Δ^8-Δ^7 sterol isomerase (1).

So far, more than 70 different mutations have been identified in the EBP gene (9). Our case confirms and extends the high degree of molecular heterogeneity found in CDPX2. Clear genotype–phenotype correlation has not yet been shown, probably because random X-inactivation plays an important role in the clinical severity (1). However, a distinction can be made between classical patients with truncating mutations (like our patient) and atypical patients with missense mutations (10).

Patient 3 – CHILD syndrome

Female patient initially reported by Poiares Baptista and Cortesão as being affected by a new disorder (11). Later, the delineation of CHILD syndrome (12) enabled accurate diagnosis, which was confirmed by NSDHL sequencing that revealed a missense mutation (c.314 C→T; p.A105V) (13).

Prenatal history and delivery were uneventful. At birth, she presented discrete left hemiatrophy of the limbs. Cutaneous manifestations started around 2 months of age, with an extensive erythematous-plaque affecting the left side of the pubic and perineal area, the left buttock and the inner surface of the left thigh, with a sharp limit at the midline of the pubis; there was also another lesion in the left heel and paronychia affecting the left hand and foot. Initially, Candida albicans was detected in skin samples and she markedly improved with topical antifungal therapy. Later, she experienced several inflammatory flares of her dermatosis, always at the same locations, with increased erythema, infiltration and desquamation. The condition was refractory to most treatments. Sometimes, relief was achieved using topical and/or systemic ketoconazole, despite cultures being seldom positive.

As she grew older, inflammatory flares became less frequent. No abnormalities were identified on neurological or ophthalmological examination. Chest X-ray, electrocardiogram, echocardiogram, abdominal and pelvic ultrasound were normal. Basic laboratory evaluation, including lipid profile (total cholesterol 174 mg/dl; high-density lipoprotein cholesterol 73 mg/dl; triglycerides 62 mg/dl) was also normal. Growth was significantly impaired, but intellectual development remained normal.

Presently, she is 47 yo, with 141 cm of height and 45 kg of weight. Skin complaints are mild and sporadic and usually consist of paronychia and inflammation of the left buttock skin (Fig. 1f–h) which improves with ketoconazole cream.

Remarks: CHILD syndrome is a complex multi-system genetic disorder, caused by mutations in the NSDHL gene and characterized by a distinctive skin lesion, the CHILD nevus (12, 13). Clinically, this is an inflammatory lesion with erythema and waxy scaling that presents a particular distribution following a lateralization pattern (more often right-sided), with sharp demarcation at the midline and predilection for the body folds (ptychotropism) (1). Musculoskeletal anomalies are also common, such as extremity hypoplasia (ranging from mild asymmetry to complete absence of a limb). Other possible manifestations include central nervous system anomalies and visceral malformations.

Regarding our patient, her nevus was notoriously ptychotropic affecting the left groin and, despite being predominantly left-sided, she did not have visceral defects. Her phenotype became progressively milder over time, as it happens with the other IECB. Skin complaints were responsible for most of the morbidity. The most effective treatment has been ketoconazole, both orally and topically. C. albicans was sometimes detected in skin samples, thus confirming secondary infection and providing evidence for its role at least in some of the inflammatory flares. Interestingly, ketoconazole inhibits the cholesterol biosynthesis pathway, upstream of the step catalyzed by the enzyme encoded by the NSDHL gene (2), so it is tempting to speculate if ketoconazole interference with this pathway could result in some therapeutic benefit.

Discussion

Hereditary metabolic diseases have traditionally been viewed as pediatric pathologies due to the early onset of clinical manifestations and to the presence of life threatening episodes. Probably, the early pediatric presentation (and especially neonatal ones) is a consequence of such cases being in the more severe spectrum of the disease and therefore with more exuberant clinical manifestations (14). Furthermore, newborns and young children are unable to verbalize and communicate clearly how they feel and pediatricians usually proceed to a systematic clinical examination and exhaustive investigation which in many cases culminates with the diagnosis of these situations. On the contrary, it is uncommon to diagnose these diseases in older patients. The late onset forms are usually associated with a variant of the enzyme with significant residual activity, producing milder phenotypes which are more difficult to recognize. However, nowadays, this situation is changing as there is an increasing number of pediatric patients that reach adulthood because they were offered appropriate treatment, and description of milder presentations makes the identification of such patients easier. Therefore, in several countries, specialized consultations for the diagnosis and treatment of inborn errors of metabolism in adolescent and adult patients are being implemented (15). Furthermore, updated text books are starting to include additional chapters focusing on inborn errors affecting adults and clinical presentation of such diseases in older age range (16).

Here, we presented the evolution of three patients affected with IECB since their young life till adulthood. The differences on their clinical manifestations depended on several factors: the specific step in cholesterol synthesis that is blocked, the type of genetic mutation present and its impact in the structure and function of the enzyme and the amount of exogenous cholesterol.
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which the affected subject received either via placenta during embryonic development or later by oral intake.

None of our patients showed life threatening episodes and their phenotypes actually improved over time. It should also be taken into account the fact that the western adult diet became progressively enriched in cholesterol (due to the increased amount of animal products ingested), which may partially compensate for the deficiency after birth.

In our opinion, most patients with IECB can be diagnosed at young age, but if their clinical features are mild or mixed with other perinatal distress factors they can be underdiagnosed and require recognition later in life. We hope that the thorough description of our patients contributes for a better characterization of the long-term natural course of SLOS, CDPX2 and CHILD syndrome and for an increased awareness and recognition of such diseases in older patients.

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