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## Rare cause of post-squalene disorder of cholesterol biosynthesis

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**Abstract** Errors of cholesterol biosynthesis represent a heterogeneous group of metabolic disorders. The aim of the authors of this article is to present a case of a patient with typical symptoms of a rare post-squalene disorder of cholesterol biosynthesis, its diagnostics and progress in neonatal period. The differential diagnosis of a typical findings on the skin with spontaneous regression ichthyosiform erythroderma, craniofacial dysmorphic features, anomalies of organs or skeletal abnormalities in a newborn may also be the result of a disorder of cholesterol biosynthesis. The final diagnosis is definitely confirmed by DNA analysis. Prognosis depends on the different enzyme defects of cholesterol biosynthesis pathway, but typically on the post-squalene pathway.

Cholesterol is an important substance that plays a significant role in membrane structure, as well as being the precursor for the synthesis of the steroid hormones and bile acids. Cholesterol synthesis occurs in the cytoplasm and microsomes from the two-carbon acetate group of acetyl coenzyme A (acetyl-CoA).<sup>1</sup> The biosynthesis of cholesterol consists of several reactions.

Acetyl-CoA units are converted to mevalonate by a series of reactions. Mevalonate is formed on squalene and then lanosterol. Lanosterol is converted by two different pathways, either with the creation of 7-dehydrocholesterol, or desmosterol with the creation of cholesterol.<sup>2</sup>

Errors of cholesterol biosynthesis represent a heterogeneous group of metabolic disorders that is characterized by multiple dysmorphic features underlining an important role for cholesterol in human embryogenesis and development.<sup>3</sup>

The differential diagnosis of atypical findings on the skin in newborn may be the result of disorder of cholesterol biosynthesis. It may be also associated with various dysmorphic features or anomalies including multiple anomalies of congenital and internal organs and skeletal abnormalities. Some of the post-squalene disorders may point to atypical findings on the skin in the form of psoriatic eruptions, psychomotoric delay or laboratory findings as hypocholesterolemia.<sup>4</sup>

**Key words:** newborn; hypocholesterolemia; stigma; chondrodysplasia punctata; ichthyosiform erythroderma

### Case report

The authors present the case of a female newborn with pathological findings. Growth retardation of long bones and polyhydramnion in the 32<sup>nd</sup> week of gestation were found during pregnancy. The patient

was born by caesarean section in the 39<sup>th</sup> week of gestation. Birth weight was 3360 grams and birth length was 41 centimeters (corresponding to the 3<sup>rd</sup> percentile). Apgar score was 10/10.

Her parents were healthy. In childhood, mother was treated with Pavlik stirrups for dysplasia

coxae congenita. Mother's height in adulthood was 158 centimeters. Her 3-year-old elder sister was healthy.

At birth, short stature, asymmetrical shortening of the femora and humeri, flat face, saddle nose, coarse and sparse hair, wide neck with marked torticollis, transversal lines on the palms with marked ulnar deviation and right talipes equinovarus were all noted. Large hyperkeratotic irregular linear scales on erythrodermic background were found on skin (Fig 1). Cutaneous lesion reminded of a collodion baby.

Fig 1



Newborn with typical skin lesions of Conradi Hünemann

Radiography showed asymmetric shortening of the long bones and expanded metaphyseal femur, tibia and epiphyseal stippling of long bones (Fig 2) and the cartilage of ribs.

Fig 2



Radiographic image of epiphyseal stippling of long bones

Orthopedic examination confirmed right talipes equinovarus with good mobility and right hip with limited abduction, with possible dysplastic changes and tendency for right torticollis.

Ultrasonography detected mild dilatation of renal pelvis of the left side. Echocardiography confirmed small ventricular septal defect and foramen ovale appertum. Ophthalmologic examination excluded cataract and auditory emissions were without pathological findings. Neurological examination and ultrasonography of the brain were negative.

Laboratory tests revealed reduced total cholesterol at 1,87 mmol/l [normal value 2,30 - 4,8 mmol/l] on the second day of life. The level of HDL cholesterol was 0,26 mmol/l [normal value < 1,68 mmol/l], LDL

cholesterol 0.66 mmol/l [Normal value < 3.4 mmol/l], apolipoprotein A-I 0.69 g/l [normal value 1.08 - 2.25 g/l] and apolipoprotein B 0.47 g/l [normal value 0.50 - 1.30 g/l]. After first week of life total cholesterol was at the level of 4.55 mmol/l. However, a mild and isolated hypertriacylglycerolaemia persists in the lipid profile at 1.85 mmol/l [normal value < 1,30 mmol/l]. Complete blood count and CRP were within normal levels.

UV spectrometry and gas chromatography/mass spectrometry (GC/MS) were negative. Cytogenetic examination confirmed female karyotype, 46, XX. Molecular genetic examination detected heterozygous mutation *p.Trp129Term* (c.386G>A) in the EBP gene (EBP - emopamil-binding protein) encoding delta (8)-delta(7) sterol isomerase, thereby confirming the diagnosis of chondrodysplasia punctata type 2 (CDPX2).

## Discussion

Skeletal dysplasias form a heterogeneous group of inherited diseases of the skeleton. They may arise from disorders of metabolism of cartilage, bone or ligament.

According to the international classification of osteochondrodysplasias they are divided into three main groups, including 1. defects of long and flat bones or axial skeleton, 2. pathological development of cartilage and fibrous components of the skeleton, and 3. idiopathic osteolysis.<sup>5</sup>

Chondrodysplasia punctata type 2 (CDPX2) belongs to the first group and is a clinically and genetically heterogeneous disorder.<sup>6</sup> It is characterized by punctiform calcification of the bones.<sup>7</sup> It is an X-linked dominant genetic disorder also known as Conradi-Hünemann-Happle syndrome. Brachytelephalangic form of chondrodysplasia punctata was described by Sheffield in 1976. It is X-linked recessive form, which is caused by mutation in arylsulfatase E gene (ARSE). Zizka et al., 1998, reported two cases of rhizomelic chondrodysplasia punctata with distinctive phenotype and autosomal recessive type of inheritance.

Chondrodysplasia punctata type 2 is rare form of skeletal dysplasia. Its incidence and also prevalence is unknown. In all, approximately 50 cases have been reported in literature.<sup>10</sup>

Molecular analysis can confirm the diagnosis. To date, there have been descriptions in literature which described 46 various mutations.<sup>11</sup> In our case, the mutation of *p.Trp 129Term* (c.386G>A) in the EBP gene encoding delta(8)-delta(7) sterol izomerase was detected in heterozygous state.

Confirmed mutation leads to a premature stop codon of amino acid chain and then to a formation of truncated protein EBP with altered function confirming the diagnosis of CDPX2. Due to the of the gene's mutation, a defect of delta (8) - delta (7) sterol isomerase is formed, which is an enzyme that plays an important role in the last steps of post-squalene pathway of cholesterol biosynthesis. In this case it was an isolated occurrence in the family.

Dysmorphic features represent skin defects including linear or whorled atrophic and pigmentary lesions, striated hyperkeratosis, coarse lusterless hair and alopecia, cataract and craniofacial defects.<sup>12</sup> On admission of the patient in our case, large hyperkeratotic irregular linear scales dominated on the skin. Skin findings improved spontaneously in the neonatal period. Currently, the 1-year-old girl's dry skin and follicular atrophoderma especially on the head persist.

The baby in our case was born at term but Rakheja et al., 2007, reported the case of a premature female newborn with rhizomesoacromelic limb shortening of upper and lower extremities and craniofacial dysmorphism. Diagnosis of CDPX2 was made based on elevated cholest-8(9)-en-3 $\beta$ -ol in serum and tissues. Skin changes, compared with our patient, were not present.

Chondrodysplasia punctata type 2 is one of the six post-squalene disorders of cholesterol biosynthesis. Herman et al., 2003 described other disorders: the Smith-Lemli-Opitz syndrome (SLOS), Desmosterolosis, CHILD (congenital hemidysplasia with ichthyosiform erythroderma and limb defects (syndrome) syndrome, Lathosterolosis and HEM (hydrops-ectopic calcification-moth-eaten skeletal dysplasia) syndrome. Among the most common disorders of cholesterol biosynthesis in the care of some European metabolologists is SLOS.<sup>4</sup>

Gas chromatography/mass spectrometry (GC/MS) analysis revealed markedly elevated levels of 8-cholest-8(9)-en-3 $\beta$ -ol and helped to identify somatic mosaicism in a clinically unaffected men.<sup>15</sup>

Sutphen et al., 1995, reported of a male patient with X-linked dominant chondrodysplasia punctata and with a 47, XXY karyotype, who died at the age of 31 years due to restricted pulmonary disease secondary to severe kyphoscoliosis. Derry et al., 1999, suggested that the presence of toxic sterol intermediates may be associated with lethality in boys and assumed that some features of CDPX2 phenotype form direct defect of abnormal cholesterol biosynthesis. The exact mechanism by which the disrupted enzyme function leads to impaired morphogenesis in skin, eye and bone is unknown.<sup>17</sup>

Published cases in the literature have mostly been females, but X-linked dominant chondrodysplasia punctata may be inherited as a lethal form in hemizygous males.<sup>18</sup>

Other EBP mutations have been reported with no evidence of correlation between phenotype of patients with CDPX2.<sup>7</sup> There are even some studies that present marked variation in expressivity within the same mutation and the same family means, which signals that the phenotypic effect of a given mutation cannot be predicted, even within a family. This strong intra-familial variation is of paramount importance when predicting the prognosis of a particular CDPX2 patient and providing genetic counseling to CDPX2 families.<sup>19</sup> After a complete investigation of the patient's mother, it was found in our case that it was an isolated occurrence of mutation.

Prenatal diagnosis is available by finding mutations on amniocentesis or chorionic villus sampling.<sup>2</sup> Kelley in 1999 found growth retardation, asymmetry of bone and polyhydramnios in fetuses in the second and third trimesters of gestations. In our case a significant growth retardation of long bones and polyhydramnios was detected prenatally in our patient by ultrasonography in the 32<sup>nd</sup> week of gestation.

Chondrodysplasia punctata type 2, known as Conradi-Hünemann-Happle syndrome, is an X chromosomal dominant disorder of cholesterol biosynthesis. In neonatal age, it is necessary to think about this post-squalene disorder of cholesterol biosynthesis within the differential diagnosis of atypical findings on the skin, craniofacial dysmorphic features and asymmetric shortening of extremities or skeletal abnormalities and organ anomalies.

In affected patients, the analysis of sterols in plasma can lead to the detection of accumulation of 8-dehydrocholesterol or cholest-8(9)-enol. Radiographic changes show typical epiphyseal stippling of long bones, which can lead to diagnosis, but it is definitely confirmed by molecular genetic analysis.

Clinical findings were dominated by reversible skin lesions with spontaneous regression ichthyosiform Erythroderma, with the creation of systematic skin atrophy in infancy. The prognosis of patients with Conradi-Hünemann-Happle syndrome is good. Psychomotor development is usually normal, sometimes with mild retardation. Patients need dermatologic care and regular application of emollients. Limb asymmetry and scoliosis can lead to premature arthritis, which would require the cooperation with orthopedists.

Prenatal detection of significant shortening of long bones is an indication for postnatal complete genetic testing.

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