Lathosterolosis: A Disorder of Cholesterol Biosynthesis Resembling Smith-Lemli-Opitz Syndrome

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Abstract Lathosterolosis is an inborn error of cholesterol biosynthesis due to deficiency of the enzyme 3-beta-hydroxysteroid-delta-5-desaturase (or sterol-C5-desaturase or SC5D). This leads to a block in conversion of lathosterol into 7-dehydrocholesterol. Only three patients with lathosterolosis have been reported in literature, of which one survived. We report a patient with dysmorphism, multiple congenital anomalies, and developmental delay, initially suspected to have Smith-Lemli-Opitz syndrome, who was later found to have elevated levels of lathosterol in both plasma and fibroblasts. Genetic study confirmed a compound heterozygous mutation in the sterol-C5-desaturase-like (*SC5DL*) gene on chromosome 11q23. Simvastatin was started as a treatment therapy and it resulted in normalization of blood lathosterol level and improvement in the neurodevelopmental profile. However, additional patients are needed for better delineation of the clinical spectrum, genotype-phenotype correlation, and potential efficacy of simvastatin treatment in this rare disorder. If the presence of distinctive facial features and limb anomalies raise the suspicion of a

cholesterol biosynthesis defect, testing of full sterol profile is warranted as normal cholesterol or 7-dehydrocholesterol levels cannot rule out the diagnosis of cholesterol synthesis defect like lathosterolosis.

Introduction

Lathosterolosis (OMIM 607330) is an inborn error of cholesterol biosynthesis due to deficiency of the enzyme 3-beta-hydroxysteroid-delta-5-desaturase (or sterol-C5-desaturase or SC5D). This results in a defect in conversion of lathosterol into 7-dehydrocholesterol. Lathosterolosis was first reported by Brunetti-Pierri et al. in 2002 (Brunetti-Pierri et al. 2002). There were three reported cases in literature so far, of which only one patient survived. From the reported cases, patients with lathosterolosis were characterized by multiple congenital anomalies, learning disability, and liver involvement. We report a child with lathosterolosis confirmed both biochemically and genetically. Simvastatin was started as treatment with clinical response and normalization of blood lathosterol level.

Case History

The proband is the first child of a non-consanguineous Caucasian couple. His parents were healthy and family history was unremarkable for any neurodevelopmental or neurometabolic disorder. The antenatal period was uneventful. He was born at 39 weeks of gestation by vaginal delivery with a birth weight of 3.3 kg and normal Apgar scores. He was noted to have dysmorphic features (bitemporal narrowing, broad nasal tip without anteverted nostrils, and micrognathia) after birth. Physical examination

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also revealed microcephaly (his head circumference dropped from third percentile at birth to 2 cm below third percentile at the age of 18 months and grew along this centile line afterwards), central hypotonia, single umbilical artery, bilateral postaxial hexadactyly of feet, and bilateral soft tissue syndactyly between the second and third toes, for which he subsequently received a corrective operation at 20 months. He did not have any ptosis, cleft palate, or abnormal genitalia. He was noted to have developmental delay without regression since early childhood. Assessment using Griffiths Mental Developmental Scales performed at 20 months of age demonstrated global developmental delay with an overall mental age of 11 months and a developmental quotient of 55 adjusted for chronological age. The mental age of motor, speech, and performance domains were 11.5 months, 10 months, and 7.5 months, respectively. Practical reasoning could not be assessed due to the young age of the patient. Magnetic resonance imaging (MRI) brain performed at 18 months was normal.

The proband was suspected to have Smith-Lemli-Opitz syndrome in view of the dysmorphism, limb anomalies, and developmental delay. Plasma sterol profile was checked at the age of 22 months. Instead of an increased 7-dehydrocholesterol level as typically found in Smith-Lemli-Opitz syndrome, the analysis showed marked elevation of lathosterol [81.6 $\mu\text{mol/L}$ (normal level <18 $\mu\text{mol/L}$)]. The levels of both 7-dehydrocholesterol [0.21 $\mu\text{mol/L}$ (normal level <0.65 $\mu\text{mol/L}$)] and cholesterol (4.1 mmol/L) were normal. This profile was biochemically compatible with the diagnosis of lathosterolosis. Moreover, the patient's skin fibroblasts were sent to the Metabolic Centre of the University Children's Hospital in Heidelberg, Germany, for analysis before commencement of simvastatin. Concentration of lathosterol was elevated (1.48% of total sterol), which was in accordance with the diagnosis of lathosterolosis. Genetic study demonstrated a novel compound heterozygous mutation of sterol-C5-desaturase-like (*SC5DL*) gene.

Liver cirrhosis and liver failure had previously been reported in a patient with lathosterolosis. We have performed regular ultrasound monitoring of the liver for our patient from three months of starting simvastatin onwards. Serial ultrasound scans showed mild, nonprogressive increase in liver heterogeneity, signifying liver parenchymal disease. Two MRI scans performed 2 years apart demonstrated a normal sized liver with nonprogressive mild T2 hyperintensities along the subcapsular region of the right anterior lobe, which could represent early changes of fibrosis. However, the liver function was normal all along. Over a period of more than 3 years, the level of aspartate aminotransferase (AST) ranged from 43 to 57 U/L (normal level <60 U/L), while that of alanine aminotransferase (ALT) ranged from 10 to 38 U/L (normal level <53

U/L). The highest level of bilirubin and ammonia was 11 $\mu\text{mol/L}$ and 19 $\mu\text{mol/L}$, respectively. The level of bile acid was 1.7 $\mu\text{mol/L}$ (normal level: 1–10 $\mu\text{mol/L}$). Regular ophthalmological evaluation was performed after the diagnosis was confirmed. The initial examination was unremarkable. However, subsequent examination at the age of 4 years showed small dot opacity of each lens with no visual significance. Patient's father was also found to have bilateral small dot lens opacity, which did not affect his vision.

At the age of 23 months, we prescribed simvastatin [3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor] as a therapeutic intervention, with the aim of normalizing the lathosterol level. It was started at a dose of 0.2 mg/kg/day and was gradually stepped up to 1 mg/kg/day. The level of lathosterol normalized 4 weeks after starting the treatment. The highest lathosterol level after starting simvastatin was 18.3 $\mu\text{mol/L}$, which decreased to 7.2 $\mu\text{mol/L}$ after optimizing the dose. Liver function and creatine kinase were all along normal. The level of creatine kinase ranged from 115 U/L to 215 U/L after starting simvastatin treatment (Normal <365 U/L). Developmental assessment using Griffiths Mental Developmental Scales was repeated at the chronological age of 45 months with an overall mental age of 29 months. The mental age of motor, speech, performance, and practical reasoning domains were 25 months, 36 months, 22.7 months, and 36.5 months respectively. The finding was still compatible with global developmental delay, but the overall developmental quotient increased from 55 in the first assessment to 64. It is worth noting that the practical reasoning domain, which was an indicator of patient's cognitive performance, had a standard quotient of 9 and a z score of -1.341 , which fell into the low normal range.

Method

Cholesterol was measured with automated enzymatic method in Roche-Hitachi system. The analysis of sterols was performed by the clinical biochemist. 200 μL of plasma was mixed with 20 μL of 200 $\mu\text{g/mL}$ 5 α -cholestane (internal standard) and was saponified in 1 mL of 4% (w/v) KOH in 90% ethanol at 80°C for 60 min. After saponification, the samples were mixed with 1 mL of water and were extracted two times with 2 mL of hexane. The pooled hexane extracts were dried under nitrogen. The trimethylsilyl ethers of sterols were obtained by derivatizing the residues with 100 μL DMF Sil-Prep™ (Grace, IL, USA) at 60°C for 30 min. Two microliters of derivative mixture was injected at a split ratio of 1:10 into an Agilent 6890/5973 Gas Chromatograph-Mass Selective Detector system installed with a Supelco SAC-5 capillary column (30 m $\times$ 0.25 mm I.D., film thickness 0.25 μm). The carrier gas was helium at a

Table 1 In silico analysis of effect of mutations by PolyPhen-2^a and SIFT^b softwares

Mutations ^c	PolyPhen-2 (prediction score)	SIFT	Reference
c.442A>G; p.K148E	<i>Possibly damaging</i> (0.764)	Affect protein function	Novel
c.630C>A; p.D210E	<i>Probably damaging</i> (0.995)	Affect protein function	Novel
c.86G>A; p.R29Q	<i>Probably damaging</i> (0.996)	Affect protein function	1
c.137A>C; p.Y46S	<i>Probably damaging</i> (0.999)	Affect protein function	5
c.632G>A; p.G211D	<i>Probably damaging</i> (1.000)	Affect protein function	1

^a <http://genetics.bwh.harvard.edu/pph2/index.shtml>

^b <http://sift.jcvi.org>

^c Mutation numbering is based on NCBI reference sequence NM_006918.4 & NP_008849.2

linear rate of 1 mL/min. The oven temperature was 60°C at the beginning and was raised at a rate of 50°C/min up to 280°C and was held for 20 min. The injector temperature and detector temperature were 300°C. Measurements were done in the electron impact mode at 70 eV with an ion source temperature of 230°C. The quadrupole temperature was 150°C. Mass spectrometric acquisition was performed in the SIM (single ion monitoring) mode at $m/z = 357$ for 5 α -cholestane, $m/z = 325$ for 7-dehydrocholesterol, and $m/z = 458$ for lathosterol. The quantification of sterol levels was linear at least up to 50 $\mu\text{mol/L}$. The proband's result was confirmed by twofold dilution. The Mayo Clinic reference range was adopted in this case as the proband is a non-Chinese. Our established normal range for local Chinese is <6 $\mu\text{mol/L}$.

Genomic DNA was extracted from peripheral blood samples according to the manufacturer's standard procedure using the QIAamp DNA Blood Mini Kit (Qiagen). All four coding exons of SC5DL gene and their flanking intronic sequences were amplified from the genomic DNA by polymerase chain reaction (PCR) as previously described (Krakowiak et al. 2003). The PCR product was purified using ExoSAP-IT (GE Healthcare) and direct sequencing was performed on both strands with the PCR primers and the Big Dye terminator 3.1 cycle sequencing kit (Applied Biosystems) using an ABI-3730XL genetic analyzer.

Correlation between the position of missense mutation, level of residual enzyme activity (if any), and severity of the clinical phenotype is always difficult to predict, whereas the pathogenicity of nonsense or frameshift mutation is much easier to conclude as truncated protein is usually produced. Testing the effect of the variants in a functional assay of the protein should confirm the pathogenicity of the missense mutation, which is not available in this patient.

Results

Genetic study demonstrated a novel compound heterozygous mutation of sterol-C5-desaturase-like (*SC5DL*) gene. Two novel missense mutations were found in the proband's DNA, p.K148E, and p.D210E. Each parent was heterozygous for one of the two mutations (K148E in mother and D210E in father). Bioinformatics softwares were used for in silico prediction of effect of mutations on the structure and function of protein and the data were summarized in Table 1. These two variants were not listed in the NCBI dbSNP database and were also absent in 150 normal controls.

The patient's skin fibroblasts were sent to the Metabolic Centre of the University Children's Hospital in Heidelberg, Germany, for analysis before commencement of simvastatin. Fibroblasts were cultivated on lipid-depleted medium for 10 days in order to stimulate cholesterol biosynthesis. Sterols were then quantified by gas chromatography/mass spectroscopy (GC/MS). Concentration of lathosterol was elevated (1.48% of total sterols) and was in accordance with the diagnosis of lathosterolosis. Concentration of 8,9-cholestenol was elevated as well (17.53% of total sterols). This was mentioned in the case reported by Brunetti-Pierri et al. (2002), though the level of lathosterol was higher than that of 8,9-cholestenol in Brunetti-Pierri's case. Plant sterols were not increased when compared with controls. Beta-sitosterol and stigmasterol were both 0.01%. The sterol profile is presented in Table 2. The patient's sterol profile in skin fibroblasts after simvastatin treatment is not available. Filipin staining performed in the Institute of Human Genetics, Heidelberg, Germany, showed a "variant" cholesterol storage pattern. Perinuclear cholesterol content was moderately elevated when compared to reference fibroblasts. This finding was also described by

Table 2 Quantification of sterols in fibroblasts

Cholesterol	97%
Lathosterol	1.48%
7-Dehydrocholesterol	0.11%
8-Dehydrocholesterol	0.18%
Desmosterol	0.02%
Lanosterol	0.05%
8,9-Cholestenol	17.53%
Beta-sitosterol	0.01%
Stigmastanol	0.01%

Each sterol is given in percent of total sterols

Krakowiak and colleagues (2003) and supported the diagnosis of lathosterolosis. Electronic microscopic study of the fibroblasts was not performed.

Discussion

Cholesterol is an essential lipid which has multiple crucial functions in the human body. Apart from being a structural lipid in membranes and myelin, cholesterol also acts as the precursor for bile acid, steroid hormone, neuroactive steroid, and oxysterol synthesis. In addition, cholesterol is also necessary for maturation and function of the hedgehog morphogens during embryonic development (Porter 2003). Defects in cholesterol synthesis result in various human malformation syndromes. Smith-Lemli-Opitz syndrome (OMIM 270400) is the most common one and is caused by mutation of the 7-dehydrocholesterol reductase (*DHCR7*) gene. 7-dehydrocholesterol reductase catalyzes the reduction of 7-dehydrocholesterol to cholesterol in the final step of the Kandutsch-Russel cholesterol synthetic pathway. On the other hand, lathosterolosis (OMIM 607330) is a recently recognized defect of cholesterol synthesis, which is due to mutations of the sterol-C5-desaturase-like (*SC5DL*) gene on chromosome 11q23. This leads to deficiency of the enzyme 3-beta-hydroxysteroid-delta-5-desaturase (or sterol-C5-desaturase), which catalyzes the conversion of lathosterol to 7-dehydrocholesterol. Inheritance of both Smith-Lemli-Opitz syndrome and lathosterolosis is autosomal recessive.

Lathosterolosis is a very rare disease. It was first reported by Brunetti-Pierri in 2002 (Brunetti-Pierri et al. 2002). The second case was reported initially as apparent Smith-Lemli-Opitz syndrome by Parnes in 1990 (Parnes et al. 1990), but was subsequently diagnosed to have lathosterolosis by postmortem examination by Krakowiak et al. in 2003 (Krakowiak et al. 2003). The third case was reported by Rossi in 2007 who followed up on the first case reported by Brunetti-Pierri and described her affected

sibling who was a stillborn (Rossi et al. 2007). Our patient contributed to the fourth reported case of lathosterolosis in the literature. Features of our patient were compared with those of the other three cases (Table 3).

Lathosterolosis appears to have features overlapping with those of Smith-Lemli-Opitz syndrome. However, there may be ascertainment bias as all cases of lathosterolosis were diagnosed after excluding Smith-Lemli-Opitz syndrome. Therefore, additional patients are needed to delineate the definite clinical features of this rare disorder and to know if there is a true phenotypic overlap between two cholesterol synthesis disorders. Smith-Lemli-Opitz syndrome is characterized by distinctive facial appearance (microcephaly, ptosis, small upturned nose, and micrognathia), limb anomalies (polydactyly, 2–3 toe syndactyly), cleft palate, hypospadias, and variable degrees of learning disabilities (Porter 2003). Apart from the fetus who was aborted at 21 weeks of gestation, all three reported cases of lathosterolosis had microcephaly, dysmorphic features, developmental delay/learning disabilities, and appendicular anomalies, namely, postaxial polydactyly and toe syndactyly. However, cleft palate was not detected in all four reported cases of lathosterolosis. The similar phenotypic findings in both Smith-Lemli-Opitz syndrome and lathosterolosis could be due to decreased cholesterol/functional sterol and/or toxic effects of increased sterol precursors. This may in turn have an effect on the different hedgehog functions. The appendicular anomalies may be explained by the impaired Sonic hedgehog function in cholesterol synthesis defect, which plays a role in limb development (Porter 2003). Both Smith-Lemli-Opitz syndrome and lathosterolosis serve as good illustrations that inborn errors of metabolism can merely present with dysmorphic features and developmental delay/learning disability, without any acute or progressive clinical deterioration as in other neurometabolic diseases. If the presence of distinctive facial features and limb anomalies raises the suspicion of cholesterol synthesis defect, testing of full sterol profile is of utmost importance as normal cholesterol or 7-dehydrocholesterol levels cannot rule out the diagnosis of cholesterol synthesis defect, as in our patient with lathosterolosis.

Treatment of Smith-Lemli-Opitz syndrome includes cholesterol supplementation and reduction of the sterol precursor, 7-dehydrocholesterol (Porter 2003). HMG-CoA reductase catalyzes the conversion of HMG-CoA into mevalonic acid in the cholesterol synthesis pathway. Simvastatin, a HMG-CoA reductase inhibitor, is therefore theoretically useful in decreasing the level of sterol precursors in patients with cholesterol synthesis defect. To our knowledge, our patient is the first lathosterolosis patient receiving a therapeutic trial of simvastatin. This drug was started at a low dose (0.2 mg/kg/day) and was

Table 3 Comparison of clinical features of reported lathosterolosis cases

	Case 1 (Fetus) (Rossi et al. 2007)	Case 2 (Brunetti-Pierri et al. 2002) (Rossi et al. 2007)	Case 3 (Krakowiak et al. 2003) (Parnes et al. 1990)	Case 4 Our patient
Gender	Female	Female	Male	Male
Ethnic origin	Not available	Not available	French Canadian	Caucasian
Age at diagnosis	N/A	7 years	N/A	22 months
Dysmorphism	N/A	Neonatal period: ptosis, prominent nose with bulbous nasal tip, and micrognathia with protruding upper lip At 7 years old: bitemporal narrowing, epicanthic folds, ptosis, small nose with anteverted nares, small chin, puffy cheeks, and a long philtrum	Ptosis, short nose, micrognathia, prominent alveolar ridges	Bitemporal narrowing, broad nasal tip without anteverted nostrils, micrognathia
Microcephaly	Yes	Yes	Yes	Yes
Limb anomalies	Postaxial hexadactyly of upper and lower limbs Bilateral club feet	Postaxial hexadactyly of left foot Bilateral syndactyly between the 2nd and 4th toes Syndactyly between the 5th toe and the extra digit of the left foot	Bilateral postaxial hexadactyly of feet Bilateral syndactyly between the 2nd and 3rd toes	Bilateral postaxial hexadactyly of feet Bilateral syndactyly between the 2nd and 3rd toes
CNS abnormalities	Type II Arnold-Chiari malformation Lumbosacral meningocele	No	Refractory myoclonic jerks	No
Developmental delay/learning disability	N/A	Yes (unknown severity)	Yes (unknown severity)	Yes (moderate severity)
Liver dysfunction	N/A	Progressive intrahepatic cholestasis resulting in liver failure at 7 years old	Progressive hepatosplenomegaly	USG and MRI showed mild nonprogressive liver parenchymal disease. Normal liver function
Other anomalies	No	Horseshoe kidneys Right cataract Conductive hearing loss Cleft of 8th thoracic vertebra	Bilateral cataract Ambiguous genitalia	Bilateral small dot cataract
Outcome	Aborted at 21 weeks due to multiple malformations	Alive	Died at 18 weeks	Alive
Mutation	<i>SC5DL</i> gene [p.R29Q and p.G211D]	<i>SC5DL</i> gene [p.R29Q and p.G211D]	<i>SC5DL</i> gene [homozygous for p.Y46S]	<i>SC5DL</i> gene [p.K148E and p.D210E]
Parental genetic analysis	Heterozygote carriers	Heterozygote carriers	Heterozygote carriers	Heterozygote carriers

gradually stepped up to 1 mg/kg/day. The level of lathosterol successfully decreased from 81.6 $\mu\text{mol/L}$ to 15.1 $\mu\text{mol/L}$ within 4 weeks time (normal level: $<18 \mu\text{mol/L}$) and remained at a relatively low level afterwards. The highest lathosterol level after starting treatment was 18.3 $\mu\text{mol/L}$, which normalized after optimizing the dose of simvastatin. As rhabdomyolysis is a known adverse effect of statin treatment, creatine kinase level had been monitored regularly and was normal. Since serum cholesterol level was consistently normal in our patient, cholesterol supplementation was not given.

The patient's condition was stable during the follow-up period. He was noted to have developmental progress from a mental age of 11 months to 29 months within a period of 24 months, that is, a gain of 9 points in the overall developmental quotient. The mild, nonprogressive liver parenchymal disease shown by serial ultrasound and MRI scans could be hepatic involvement of the disease. It might already be present before commencement of treatment. Liver diseases were also reported in the other two lathosterolosis patients (Brunetti-Pierri et al. 2002; Rossi et al. 2005, 2007; Krakowiak et al. 2003). Although there are some adult studies suggesting cataract as an adverse effect of statin (Hippisley-Cox and Coupland 2010), the causal relationship between cataract and statin use has not been fully established. The bilateral small dot cataract with no visual significance could also be a manifestation of the disease. Except the stillborn, the other two lathosterolosis patients also had either unilateral or bilateral cataract (Rossi et al. 2007; Krakowiak et al. 2003). Furthermore, hereditary factor could not be completely ruled out as the patient's father also had bilateral small dot opacity without any visual significance. We are still monitoring the long-term outcome to document the efficacy and adverse effects of this therapeutic trial. Apparently, our patient might have a milder phenotype as compared to the other three patients with lathosterolosis. The relative attribution of this milder phenotype to the different underlying genetic mutations or simvastatin treatment is not known. We postulated that the severity of phenotype might be related to the level of lathosterol. The patient reported by Krakowiak had the most severe phenotype. Lathosterol accounted for 35% of total sterols in fibroblasts after 6 days in culture (Krakowiak et al. 2003). On the other hand, the patient reported by Brunetti-Pierri had an intermediate phenotype among the three cases. The level of lathosterol in fibroblasts

was 12.5% of total sterols after 15 days in culture (Brunetti-Pierri et al. 2002). While in our case, the level of lathosterol in fibroblasts was 1.48% of total sterols after 10 days in culture. Additional patients are required to delineate the genotype-phenotype correlation.

Conclusion

Lathosterolosis is a recently recognized autosomal recessive cholesterol synthesis defect which shares certain phenotypic features with Smith-Lemli-Opitz syndrome. Simvastatin was started as treatment in our patient and normalization of lathosterol level had been clearly demonstrated. Additional patients are required for better delineation of the clinical spectrum of this disorder and the effect of statin treatment.

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