Lathosterolosis: A Relatively Mild Case with Cataracts and Learning Difficulties

R. Anderson • S. Rust • J. Ashworth •
J. Clayton-Smith • R. L. Taylor • P. T. Clayton •
A. A. M. Morris

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Abstract Lathosterolosis is a rare defect of cholesterol synthesis. Only four previous cases have been reported, two of whom were siblings. We report a fifth patient, with a relatively mild phenotype. He presented at 5 years of age with bilateral posterior cataracts, which were managed with lensectomies and intraocular lens implants. He also had learning difficulties, with a full-scale IQ of 64 at 11 years of age. His head circumference is between the 0.4th and 2nd centiles, and he has mild hypotonia and subtle dysmorphism (a high-arched palate, anteverted nostrils, long philtrum and clinodactyly of toes). The diagnosis was established after sequencing a panel of genes associated

with cataracts, which revealed compound heterozygous *SC5D* mutations: c.479C>G p.(Pro160Arg) and c.630C>A p.(Asp210Glu). The plasma lathosterol concentration was markedly raised at 219.8 µmol/L (control range 0.53–16.0), confirming the diagnosis. The c.630C>A p.(Asp210Glu) mutation has been reported in one previous patient, who also had a relatively mild phenotype (Ho et al., JIMD Rep 12:129–134, 2014). The mutation leads to a relatively conservative amino acid substitution, consistent with some residual enzyme activity. Our patient's family did not notice any benefit from treatment with simvastatin. In summary, milder patients with lathosterolosis may present with learning difficulties, cataracts and very subtle dysmorphism. The diagnosis will be missed unless plasma sterols are analysed or relevant genes sequenced.

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R. Anderson • A. A. M. Morris (✉)
Willink Metabolic Unit, Manchester Academic Health Sciences
Centre, Manchester University Hospitals NHS Foundation Trust,
Manchester, UK
e-mail: andrew.morris@mft.nhs.uk

S. Rust
Paediatric Psychosocial Service, Manchester Academic Health
Sciences Centre, Manchester University Hospitals NHS Foundation
Trust, Manchester, UK

J. Ashworth
Paediatric Ophthalmology Department, Manchester Academic Health
Sciences Centre, Manchester University Hospitals NHS Foundation
Trust, Manchester, UK

J. Clayton-Smith
Genomic Medicine, Manchester Academic Health Sciences Centre,
Manchester University Hospitals NHS Foundation Trust, Manchester,
UK

J. Clayton-Smith • R. L. Taylor • A. A. M. Morris
Division of Evolution and Genomic Sciences, Faculty of Biology,
Medicine and Health, University of Manchester, Manchester, UK

P. T. Clayton
Centre for Translational Omics, Genetics and Genomic Medicine,
UCL Institute of Child Health, London, UK

Introduction

The importance of cholesterol in the human body has long been recognised (Herman 2003). Among other roles, cholesterol is needed for the structure of cell membranes and myelin, for the synthesis of multiple hormones and bile acids and for signalling within the developing embryo, where cholesterol serves to modify hedgehog protein maturation (Herman 2003; Merkens et al. 2009). Furthermore, precursors within the cholesterol synthesis pathway may serve important roles in their own right, for instance, 7-dehydrocholesterol is the immediate precursor for vitamin D synthesis (Herman 2003). More recently, the phenotypes of defects in several stages of cholesterol biosynthesis have been identified (Herman 2003; Waterham 2006), with Smith-Lemli-Opitz syndrome being the most common and well described (Herman 2003; Merkens et al. 2009). It is

not yet clear to what extent these diseases are caused by the reduction in cholesterol function, as opposed to the effects of accumulation of precursors and by-products (Waterham 2006).

Lathosterolosis is a defect of cholesterol synthesis caused by deficiency of 3-beta-hydrocholesterol-delta-5-desaturase (*SC5D*), thereby preventing conversion of lathosterol to 7-dehydrocholesterol (Brunetti-Pierri et al. 2002). Only four affected individuals have been reported (Brunetti-Pierri et al. 2002; Krakowiak et al. 2003; Rossi et al. 2007; Ho et al. 2014), of whom one was a foetus aborted at 21 weeks' gestation and one died at 18 weeks of age. The four patients all had microcephaly, postaxial polydactyly, syndactyly and variable hepatic involvement. The live-born patients all had facial dysmorphism and cataracts, and those surviving beyond 6 months also displayed central hypotonia and a degree of global developmental delay.

We describe a fifth case of lathosterolosis, confirmed by both genetic and biochemical analyses, with a relatively mild phenotype. The patient has been mentioned briefly in papers on the use of the next-generation sequencing in children with cataracts (Gillespie et al. 2014, 2016).

Case Report

The proband is the second child of healthy non-consanguineous white English parents; his older sister is healthy with normal development. He was born at term following an uneventful antenatal course. There were no significant perinatal concerns, but the patient did have laryngomalacia and neonatal jaundice necessitating phototherapy within the first 72 h of life, with a maximum serum bilirubin level of 299 $\mu\text{mol/L}$.

The patient has always had good physical health, but his developmental milestones were delayed, and he did not walk or talk until 3 years of age. He attended mainstream primary education with some additional support, but from 11 years of age, he has attended a secondary school for children with special needs. His clinical presentation is consistent with an autistic spectrum disorder. He has deficits in social communication, with particular impairment in reciprocity, poor eye contact and difficulties matching his emotional responses to those around him. These difficulties severely affect his social functioning. He also demonstrates a restricted range of interests, and these deficits have been present from a very young age.

His parents describe poor visual attention from an early age, and he failed a routine school vision test when aged 5 years. He was found to have bilateral posterior lens opacities, as well as astigmatism and myopia. The following year, the proband underwent bilateral lensectomies and intraocular lens implants. YAG capsulotomies

were performed for posterior capsular opacification when the proband was 7 years old. The patient's current vision is stable at 0.5 right and 0.3 left LogMar.

In view of the cataracts and the developmental delay, the proband was referred to the Manchester Centre for Genomic Medicine when he was 8 years old. Subtle dysmorphic features were noted (Fig. 1), including a broad forehead, prominent ears, a high-arched palate with crowding of teeth, anteversion of the nostrils, a long philtrum and clinodactyly of toes. At 11 years of age, his height was 143.8 cm (between 25th and 50th centiles), weight 34.9 kg (25th to 50th centiles) and occipitofrontal head circumference 51.1 cm (0.4th to 2nd centiles). Mild hypotonia and joint hyper-extensibility were present.

Initial investigations were unremarkable, including array comparative genomic hybridization. When the patient was 10 years old, next-generation sequencing was undertaken on a panel of 115 genes associated with congenital or childhood cataracts (Gillespie et al. 2014). This identified two heterozygous mutations in the *SC5D* gene: c.479C>G p.(Pro160Arg) and c.630C>A p.(Asp210Glu). The latter mutation has been reported in a previous patient

Fig. 1 Facial appearance of patient aged 11 years

(Ho et al. 2014). The parents were each heterozygous for one mutation.

The diagnosis of lathosterolosis was confirmed by plasma sterol analysis by GC-MS, which revealed a markedly elevated plasma lathosterol concentration of 219.8 $\mu\text{mol/L}$ (control range 0.5–16.0 $\mu\text{mol/L}$). There was also a raised concentration of 8(9)-cholestenol, the immediate precursor of lathosterol, but other intermediates of cholesterol synthesis were normal (Table 1). The total plasma cholesterol concentration was 3.4 mmol/L (reference range 1.2–4.0 mmol/L).

Further assessment showed a mild iron deficiency anaemia (haemoglobin 105 g/L), normal plasma electrolytes, urea and creatinine, bilirubin, albumin, alanine transaminase and alkaline phosphatase, with a minimally deranged coagulation profile (PT 12.6 s, reference range 9.9–11.8 s; APTT 21.6 s, reference range 23.0–31.9 s). There was vitamin D deficiency (plasma total 25-hydroxy, vitamin D concentration 16.4 nmol/L, reference range >50 nmol/L), but other fat-soluble vitamins were normal. An abdominal ultrasound scan at 13 years of age showed no abnormalities of the liver and also excluded malformations of the renal tract.

Cognitive assessment was undertaken using the Wechsler Intelligence Scale for Children, 4th UK Edition (WISC-IV), and the “word reading” and “pseudoword

decoding” subtests of the Wechsler Individual Achievement Tests, 2nd UK Edition (WIAT-II). The patient scored within the *extremely low* range of the WISC-IV (standard score = 64 = first centile), indicating developmental delay in cognitive ability. He scored within the *borderline* ranges of perceptual reasoning and processing speed indices of the WISC-IV, the “pseudoword decoding” subtest of the WIAT-II, and the *extremely low* range of ability on the “word reading” subtest. The patient demonstrated greater aptitude for tasks involving concrete visual stimuli, with marked weakness in language comprehension (Table 2).

A trial of treatment was commenced with simvastatin 40 mg daily and cholesterol 1.75 g daily. In a previous patient, treatment with simvastatin normalised the plasma lathosterol concentration and was associated with an increase in developmental quotient from 55 to 64 (Ho et al. 2014). We planned to repeat the sterol measurements and cognitive assessment after 6 months’ treatment, but we found that the patient’s family had discontinued treatment after 4 months, having observed no benefit, particularly in terms of behaviour.

Discussion

The main clinical features reported in lathosterolosis have been multiple malformations, learning disability, cataracts

Table 1 Plasma sterol analysis by GC-MS

	Patient sample ($\mu\text{mol/L}$)	Control range ($\mu\text{mol/L}$)
8-Dehydrocholesterol	0.53	<2.0
7-Dehydrocholesterol	0.93	0.70–1.96
Desmosterol	0.23	2.65–9.22
8(9) Cholestenol	21.61	<4.0
Lathosterol	219.79	0.53–15.98
Cholestanol	6.95	3.87–18.04
Lanosterol	0.26	0.00–1.53

Table 2 Psychometric assessment

Standard and scaled scores (Percentile)		
<i>Wechsler Intelligence Scale for Children, 4th UK Edition</i>		
Full-scale IQ	–	64 (1st)
Verbal comprehension index	–	69 (2nd)
Perceptual reasoning index	–	73rd (4th)
Working memory index	–	68 (2nd)
Processing speed index		73 (4th)
<i>Wechsler Individual Achievement Test, 2nd UK Edition</i>		
Word reading		63 (1st)
Pseudoword decoding		72 (3rd)

and liver involvement (see Table 3). Many features resemble those of Smith-Lemli-Opitz syndrome, the commonest defect of cholesterol synthesis. Smith-Lemli-Opitz syndrome is known to have a wide range of severity, from cases that are lethal in utero to others with minimal learning difficulties or dysmorphism. Lathosterolosis has generally been considered a very severe condition: of the four previous cases, one died aged 18 weeks with intractable myoclonus and respiratory failure (Krakowiak et al. 2003; Parnes et al. 1990), and one was aborted at 21 weeks' gestation due to multiple malformations (Rossi et al. 2007). All previous cases have been diagnosed by sterol analysis, undertaken because Smith-Lemli-Opitz syndrome was suspected; this may have introduced an ascertainment bias, and it is possible that a number of patients with milder forms of the condition have been missed. The patient reported here had learning difficulties and bilateral cataracts

but only a few minor malformations and no liver involvement.

Microcephaly has been a universal finding in all reported cases of lathosterolosis. Our patient has learning difficulties with a full scale IQ of 64. The two previous patients who survived beyond infancy also had cognitive impairment (Brunetti-Pierri et al. 2002; Rossi et al. 2007; Ho et al. 2014). The patient described by Ho et al. had a developmental quotient of 64 at the age of 3 years 9 months (Griffiths Mental Developmental Scales), suggesting that the degree of cognitive impairment was similar to our patient's. Developmental assessments were not reported for the other patient (Brunetti-Pierri et al. 2002; Rossi et al. 2007). Our patient has autistic features, but this is not specifically mentioned in previous reports.

Cataracts were a prominent feature in our patient and were the clue that led to the diagnosis. Cataracts were also

Table 3 Summary of the current and previously reported patients

	Brunetti-Pierri et al. (2002) and Rossi et al. (2007)	Rossi et al. (2007)	Krakowiak et al. (2003) and Parnes et al. (1990)	Ho et al. (2014)	Current patient
<i>SC5D</i> mutations	p.R29Q & p.G211D	p.R29Q & p.G211D	homozygous p.Y46S	p.K148E & p.D210E	p.P160R & p.D210E
Lathosterol plasma level	338 $\mu\text{mol/l}$	N/A	N/A	81.6 $\mu\text{mol/l}$	219.8 $\mu\text{mol/l}$
Cholesterol level	Normal	N/A	N/A	Normal	Normal
Age at diagnosis	2 years	Postmortem (21 weeks' gestation)	Postmortem (aged 18 weeks)	22 months	10 years
Cognition	Impaired	N/A	N/A	DQ 64 at 3.8 years	IQ 64 at 11 years
Microcephaly	Yes	Yes	Yes	Yes	Yes
Cataracts	Bilateral from 6 years	–	Bilateral from birth	Bilateral dot cataracts from 4 years	Bilateral from 5 years
Liver	Liver failure & portal hypertension with abnormal biochemistry; cholestasis & cholangiolitis on histology	Extramedullary haematopoiesis & atrophy of hepatocytic laminae on histology	Hepatosplenomegaly with abnormal biochemistry; cirrhosis and vacuolated cells on histology	Normal biochemistry; mildly increased heterogeneity on ultrasound	Normal biochemistry & imaging
Dysmorphism	Epicanthus, broad nasal bridge, anteverted nares, long philtrum, micrognathia, high palate	N/A	Ptosis, short nose, micrognathia	Micrognathia, bitemporal narrowing, broad nasal tip	High palate, very mild ptosis, anteverted nares & long philtrum
Limbs	Hexadactyly & syndactyly of left foot	Hexadactyly of both hands and feet, bilateral talipes	Hexadactyly & syndactyly of both feet	Hexadactyly & syndactyly of both feet	Clinodactyly of both feet
Other malformations	Bilobed gall bladder, T8 butterfly vertebra	Lumbosacral myelomeningocele, Arnold-Chiari type 2 malformation	Ambiguous genitalia	Single umbilical artery	

N/A not available

noted in all previous patients except the aborted foetus. The cataracts were present at birth in one patient (Parnes et al. 1990; Krakowiak et al. 2003) and in the others were first noted at the age of 4 years (Ho et al. 2014), 5 years (our patient) and 6 years (Brunetti-Pierri et al. 2002) (Table 3). The cataracts were bilateral in all cases but asymmetrical in one case, only requiring extraction in one eye. One patient only had small dot cataracts at 4 years with normal vision (Ho et al. 2014).

Abnormalities of the digits have been the commonest malformations in previous patients with lathosterolosis, possibly due to the role of hedgehog signalling in limb development. All four previous patients have had postaxial polydactyly (on feet $\pm$ hands) and syndactyly of the toes, but our patient has neither feature, demonstrating that these are not always present in lathosterolosis. The only limb abnormality in our patient was clinodactyly of the toes.

The current patient has a high-arched palate, mildly anteverted nostrils and a long philtrum, as have two previous patients (Brunetti-Pierri et al. 2002; Krakowiak et al. 2003). He does not, however, have the other reported dysmorphic features, namely, bitemporal narrowing, epicanthic folds, a broad nasal tip, micrognathia and small chin. Malformations in previous patients have also included ambiguous genitalia (Krakowiak et al. 2003), horseshoe kidneys (Rossi et al. 2007), bilobed gall bladder (Brunetti-Pierri et al. 2002), T8 butterfly vertebra (Brunetti-Pierri et al. 2002), lumbosacral meningomyelocele and Arnold-Chiari type 2 malformation (Rossi et al. 2007) (Table 3). None of these have been found in our patient but he has not had a skeletal survey.

Variable hepatic involvement has been reported in previous cases of lathosterolosis. For the foetus aborted at 21 weeks' gestation, liver histology showed extramedullary haematopoiesis and atrophy of hepatocytic laminae (Rossi et al. 2007). Two other patients had persistently raised plasma levels of bilirubin, transaminases and alkaline phosphatase. One of these developed liver failure and portal hypertension at 7 years of age, with cholestasis and cholangiolitis on histology (Rossi et al. 2007); the other had hepatosplenomegaly, and histology showed cirrhosis and vacuolation, especially of histiocytes, with storage of lipids and mucopolysaccharides (Parnes et al. 1990). The final patient had normal plasma bilirubin, transaminases and alkaline phosphatase levels and no hepatic symptoms, but ultrasound showed mildly increased heterogeneity (Ho et al. 2014). Our patient had neonatal jaundice but no subsequent symptoms or biochemical evidence of liver disease, and liver ultrasound was normal. Though we

found no evidence of liver disease, we plan to continue monitoring for cholestasis, particularly in view of the vitamin D deficiency and very mildly prolonged prothrombin time.

Like all previous cases, our patient has two missense mutations in *SC5D*. Both affect highly conserved amino acids, are predicted damaging in silico (Gillespie et al. 2014) and are extremely rare according to the reference datasets, GnomAD and ExAC. The p.(Asp210Glu) variant has previously been associated with lathosterolosis in an unrelated patient who also had a relatively mild phenotype (Ho et al. 2014), and it is possible that this mutation leaves some residual enzyme activity, accounting for the milder phenotype. It has been suggested that the phenotypic severity may correlate with the lathosterol level in cultured fibroblasts (Ho et al. 2014), but as our patient declined a skin biopsy, this analysis was not performed. His plasma lathosterol concentration was over 2.5 times that in the previous mild patient (Ho et al. 2014), but this may be influenced by the greater age of our patient. The plasma cholesterol concentration has been normal in all patients in whom it has been measured, in contrast to the mouse model (Krakowiak et al. 2003).

In conclusion, this patient displays a milder phenotype than previously described in lathosterolosis, with bilateral cataracts, microcephaly and learning difficulties as the main features. Of particular note, the polydactyly and liver involvement seen in the other cases were absent. There may be a number of patients like this, with cataracts and learning difficulties, who will only be diagnosed if plasma sterol analysis or sequencing of relevant genes is undertaken.

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Contributions of Individual Authors

Drs. Anderson and Morris managed the patient and wrote the case report. Dr. Taylor undertook the next-generation sequencing, and Professors Clayton-Smith and Clayton confirmed the diagnosis clinically and by sterol analysis, respectively. Drs Rust and Ashworth undertook psychological assessment and ophthalmological management, respectively. All authors critically reviewed the manuscript.

Dr. Andrew Morris is the corresponding author and serves as guarantor.

Competing Interest Statement

Drs. Anderson, Rust, Ashworth, Taylor and Morris and Professors Clayton-Smith and Clayton declare that they have no conflict of interest.

Consent

The patient's parents have given written consent for publication. Ethical Committee approval is not needed for this case report.

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