CASE REPORT

Early severe coronary artery disease and aortic coarctation in a child with familial hypercholesterolaemia

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SUMMARY

An 11-year-old boy presented with easy fatigability, multiple xanthomas, and absent pedal pulsations. Laboratory workup showed severe hypercholesterolaemia and non-invasive imaging revealed 'normally functioning' bicuspid aortic valve and tight aortic coarctation. Coronary angiography showed severe right coronary artery (RCA) stenosis. Medical treatment resulted in significant improvement of dyslipidaemia. We successfully performed balloon dilation and stenting of his coarctation, as well as percutaneous coronary intervention for RCA lesion.

BACKGROUND

Homozygous familial hypercholesterolaemia (HoFH) is a rare genetic disorder characterised by early onset of coronary artery disease (CAD). Bicuspid aortic valve (BAV) is the most common congenital abnormality, with a prevalence of 0.5–2% of the population,¹ and is frequently associated with aortic coarctation (CoA). We report an unusual case of HoFH, severe CAD, and BAV-associated coarctation.

CASE PRESENTATION

An 11-year-old boy reported—according to his parents—easy fatigability, recurrent headaches, and multiple skin swellings over the knees, ankles, elbows and fingers. He had no history of dyspnoea, cyanosis or chest pain. The boy's available pedigree is shown in [figure 1](#). Of note, his father, mother, and one of his siblings have heterozygous familial hypercholesterolaemia (FH). Family history is significant for premature CAD and sudden cardiac death in his paternal grandfather.

Clinical examination revealed a height of 123 cm, weight of 25 kg, with a calculated body surface area of 0.92 m². The supine blood pressure was 160/92 mm Hg in the right arm, 150/90 mm Hg in the left arm, and could not be measured in the lower limbs. The pulse was 80/min, regular and equal bilaterally. Pedal and popliteal pulsations were absent bilaterally, with weak femoral pulsations and radiofemoral delay. The skin was remarkable for tendinous xanthomas of the Achilles tendons and tuberous xanthomas over the knees and elbows ([figure 2](#)). The jugular veins showed normal pressure and waveform. Head, neck, abdomen, and chest examination was unremarkable.

Cardiac examination showed a normally positioned apex of left ventricular character. No other

pulsations or thrills were present over the precordium. Auscultation showed a normal S1, loud A2, and normal P2. A grade II/VI, soft, ejection systolic murmur was heard best over the second right intercostal space and left sternal border.

INVESTIGATIONS

The presence of xanthomas mandated a lipid profile, which revealed a total cholesterol (TC) of 474 mg/dL, triglycerides (TG) of 80 mg/dL, low-density lipoprotein cholesterol (LDL-C) of 404 mg/dL, and an high-density lipoprotein cholesterol (HDL-C) of 33 mg/dL. Routine laboratory workup showed mild hypochromic, microcytic anaemia of 112 g/L, with normal liver and kidney functions—alanine transaminase 17 U/L, aspartate transaminase 27 U/L, and serum creatinine level 61.9 µmol/L.

An ECG showed respiratory sinus arrhythmia and inverted-biphasic T waves in leads V1–V6 and III ([figure 3](#)). A transthoracic echocardiogram showed mild left ventricular hypertrophy, with normal global and regional systolic function. The aortic valve was bicuspid, with fusion of the right and left coronary cusps, mild leaflet thickening and calcification, and adequate excursion. There was no significant aortic regurgitation or stenosis, and no other significant valvular disease. Suprasternal view showed a CoA with a peak systolic gradient of 70 mm Hg ([figure 4](#)). Subcostal view showed damping of flow in the abdominal aorta ([figure 5](#)). A tiny patent ductus arteriosus was also noted.

CT of the aorta clearly revealed the congenital CoA of a discrete nature and amenable to intervention ([figure 6](#)).

TREATMENT

Management of this patient included lipid-lowering therapy and intervention for his CoA. Given his FH and functional limitation due to the CoA, we had to rule out the possibility of CAD, despite being asymptomatic.

He was put on 40 mg of atorvastatin, in addition to dietary modification, which resulted in suboptimal lowering of LDL-C; accordingly we titrated the dose to 80 mg and added 10 mg of ezetimibe. Follow-up of the patient's lipid profile revealed a TC of 233 mg/dL, TG 105 mg/dL, LDL-C 167 mg/dL, and HDL-C 35 mg/dL. We added cholestyramine to which he was intolerant due to gastrointestinal upset. Bisoprolol 2.5 mg daily was added as an antihypertensive.

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Figure 1 Pedigree of our patient (indicated with an asterisk) and his family. Men are represented by squares and women by circles. Deceased persons are indicated by an X mark. CAD, coronary artery disease; SCD, sudden cardiac death; TC, total cholesterol.

The management options for his CoA included balloon dilation with stenting or operative repair. Stent placement is a suitable option in children who can receive a stent that can be expanded to an adult size (minimum of 2 cm in diameter).² Children with aortic stent placement are more likely to require a planned reintervention, as the stent often needs to be dilated as the child grows. The risks associated with repeat percutaneous interventions need to be balanced against the more invasive surgical repair. Since our patient's aortic size and CoA anatomy were favourable, we opted for the percutaneous option. We also favoured invasive evaluation of his coronary artery anatomy versus non-invasive assessment since diagnostic coronary angiography can be performed in the same sitting as CoA intervention. Additionally, we felt that a definite diagnosis of CAD might influence our management decision for CoA.

Diagnostic coronary angiogram revealed mild (20%) stenosis of mid left main trunk and subtotal proximal right coronary artery (RCA) occlusion (video 1). Given the patient's single-vessel disease with favourable anatomy, we decided to proceed with CoA intervention under general anaesthesia, and to perform percutaneous intervention (PCI) to RCA at a different sitting. We successfully deployed a Cordis Genesis 29 mm stent

Figure 2 Tuberous xanthomas over the knee.

over a NuMED balloon at the site of CoA, with resulting minimal waist and no residual pressure gradient (figure 7 and video 2 show the coarctation before and after intervention, respectively). Aspirin 75 mg and clopidogrel 75 mg daily were added to the drug regimen. One month later, PCI to RCA was performed using a drug-eluting Xience V stent 3.5×28 mm. Although it was a very difficult lesion to dilate, we eventually succeeded using different short non-compliant balloons after deployment of the stent. The final result was excellent with thrombolysis in myocardial infarction (TIMI) 3 flow (video 3).

OUTCOME AND FOLLOW-UP

The patient started playing normally with his peers and using his bicycle without problems. His blood pressure was adequately controlled even after stopping bisoprolol. He achieved significant but still suboptimal reduction of LDL-C level to 167 mg/dL on high-dose atorvastatin plus ezetimibe. He continued to tolerate statins without major side effects. We are currently considering LDL apheresis to achieve target LDL-C level. Of note, carotid artery ultrasound performed 1 year after stabilisation of blood cholesterol level revealed diffuse intimal thickening, with a mean carotid intima-media thickness of 0.61 mm bilaterally and multiple non-flow limiting atheromatous plaques, with surface ulcerations (figure 8).

About 8 months following PCI to RCA, the patient underwent repeat diagnostic coronary and aortic angiography. This revealed stable left main trunk stenosis and an RCA in-stent restenosis of doubtful severity. Fortunately, fractional flow reserve was 0.89, denoting insignificant stenosis. The aortic stent was patent with no significant gradient across. We plan another follow-up angiogram after 1 year. We will arrange for annual echocardiography and MR aortography for early detection of valvular aortic stenosis and/or regurgitation, supra-aortic stenosis, and BAV-associated aortopathy (aneurysm and/or dissection). Finally, we will arrange for cerebral MR angiography to rule out intracranial aneurysms—a common association with CoA.

DISCUSSION

We report a case of FH with 'normally functioning' BAV, CoA, and early severe CAD in an 11-year-old child.

FH is an inherited, mostly autosomal dominant disorder, of lipid metabolism characterised by a high LDL-C level and premature atherosclerosis. LDL receptor genetic defects account for most cases, followed by PCSK9 gene mutations, and mutations in genes encoding for apolipoprotein B (apoB).³ There are two phenotypes: the more severe homozygous form, affecting 1 in 1 000 000 births; and the milder heterozygous form affecting 1 in every 200–500. Untreated, most patients with HoFH develop overt atherosclerosis before the age of 20 years, and generally do not survive past 30 years.

Diagnosis of HoFH can be made on the basis of genetic or clinical criteria, which include an untreated LDL-C>13 mmol/L (500 mg/dL) or treated LDL-C≥8 mmol/L (300 mg/dL), together with either:

- ▶ Cutaneous or tendon xanthomas before age 10 years, or
- ▶ Untreated elevated LDL-C levels consistent with heterozygous FH in both parents.

The European Atherosclerosis Society (EAS) 2014 guidelines state that these LDL-C levels are only indicative, and lower levels, especially in children or in treated patients, do not exclude the diagnosis.⁴ Therefore, we diagnosed our patient as a case of HoFH although he had lower levels of LDL-C than stated in the guidelines.

Figure 3 Resting ECG. **Figure 4** Continuous wave Doppler across the descending thoracic aorta, showing a peak systolic gradient of 70 mm Hg. **Figure 5** Pulsed-wave Doppler at the abdominal aorta, showing damped monophasic waveform. **Figure 6** Three-dimensional volume rendered reconstruction of CT thoracic aortogram showing discrete aortic coarctation (red arrow).

Although not exclusively associated with HoFH, the presence of cutaneous or tuberous xanthomas in children is highly suggestive of diagnosis. Clinicians should be alert to suspect the diagnosis of FH in children presenting with xanthomas, as this would warrant early initiation of lipid-lowering therapy to reduce the risk of CAD. Xanthomas were early noted in our patient but did not alert his primary care providers, and he was finally diagnosed after developing severe CAD.

Once the diagnosis of HoFH is made, lipid-lowering therapy should be started as early as possible, based on evidence that

Video 1 Coronary angiography showing subtotal occlusion of proximal right coronary artery.

Video 3 Coronary angiography after successful dilation and stenting of proximal right coronary artery with TIMI flow 3.

Figure 7 Aortography showing aortic coarctation before intervention.

Video 2 Aortography showing deployed stent at the site of coarctation.

Figure 8 Carotid ultrasound of the right common carotid artery (RCCA) showing a non-flow limiting atheromatous plaque (arrow) with surface ulceration (asterisk).

treatment can delay the onset of clinically evident CAD.⁴ The LDL-C targets are <3.5 mmol/L (<135 mg/dL) in children.⁵ Statins have proven efficacy as the mainstay of treatment in HoFH. Addition of ezetimibe—a cholesterol absorption inhibitor—further lowers LDL-C levels, with minimal adverse events and relative low costs. In cases with suboptimal response, combinations of statins with bile acid sequestrants can be considered, although their use may be limited by tolerability, as happened with our patient.

Non-pharmacological options are indicated if optimal LDL-C targets are not reached. The National Lipid Association Expert Panel on Familial Hypercholesterolaemia and the 2014 EAS Consensus Panel on Familial Hypercholesterolaemia recommends that lipoprotein apheresis be considered in patients with HoFH and that treatment should be started as soon as possible, ideally by age 5 and not later than 8 years.⁴ This option, despite being very effective in lowering LDL-C levels, is expensive, is not readily available in all centres, and requires venous access. Liver transplantation is a successful therapeutic alternative, however it has the disadvantages of the high risk of post-transplantation surgical complications and mortality and the need for life-long immunosuppressive therapy. In our case, the parents were clearly against this option.

Novel pharmacological drugs include lomitapide and mipomersen; both affect the production and secretion of

apoB-containing lipoproteins through different pathways.⁶ Monoclonal antibody therapy targeting PCSK9 is another promising option.⁷ Finally, gene replacement therapy may decrease LDL-C levels, as well as make patients with HoFH more responsive to existing or novel therapeutics.⁸ Unfortunately, all these options are not available for our patient.

To date, only two case reports of FH associated with CoA have been published. One described a 6-year-old female with FH, BAV, and diffuse coarctation of the descending aorta, plus left renal artery stenosis. Her coronary anatomy was not evaluated and she was lost to follow-up.⁹ The other reported a 14-year-old female presenting with exertional chest pain, and discovered to have FH, impaired left ventricular systolic function, moderate valvular aortic stenosis, mild-to-moderate CoA, and severe proximal left anterior descending and RCA stenoses. She underwent surgical bypass grafting of both coronaries, with deferred intervention for the CoA as it was believed to be mild-to-moderate in severity.¹⁰

The association of FH and CoA in our patient and the previous two case reports is interesting. We hypothesize that the three patients had some degree of CoA that was aggravated by the dyslipidaemia. It is well known that BAV and CoA are commonly associated. Few case reports described ‘acquired’ CoA in patients with atherosclerotic risk factors—namely age, smoking, and hypertension. These patients were above the age of 50 and were noted to have significant calcification of their CoA.^{11 12}

Learning points

- ▶ Clinicians should be aware to suspect familial hypercholesterolaemia (FH) in children presenting with xanthomas.
- ▶ FH requires careful attention for coronary artery disease (CAD) diagnosis, even if asymptomatic.
- ▶ Management of CAD in FH has medical and interventional aspects, both are equally important.
- ▶ High blood pressure in a child, especially with weak/absent pedal pulsations, should always raise the suspicion of aortic coarctation.
- ▶ The association of FH with aortic coarctation is very rare.

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