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CASE REPORT

Fatal Myocardial Infarction at 4.5 Years in a Case of Homozygous Familial Hypercholesterolaemia

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Abstract Management of homozygous familial hypercholesterolaemia is notoriously difficult. For these patients, LDL apheresis is considered the treatment of choice. Treatment initiation is advocated generally from the age of seven years onwards (Thompson et al., Atherosclerosis 198:247–255, 2008). Here, we present the case of a young girl from a large inbred family of Turkish descent with homozygous familial hypercholesterolaemia and fatal outcome at the early age of 4½ years.

In conclusion, this case suggests that management of homozygous familial hypercholesterolaemia may require earlier and more aggressive treatment, including LDL apheresis before the age of seven years.

Introduction

Familial hypercholesterolaemia (FH) is the most common autosomal dominant condition. It is due to defective LDL receptor protein giving rise to increased plasma cholesterol and leading to premature cardiovascular morbidity. In order to allow early detection and treatment of the condition, current guidelines recommend lipid screening in children, although no consensus exists regarding the best screening schedule (Daniels et al. 2008; Koletzko et al. 2007).

The homozygous form of FH (HFH) is rare and manifests early in life with severe hypercholesterolaemia and typical skin lesions. If untreated, it leads to early atherosclerosis and cardiovascular death typically in the second to third decade. The disease is notoriously difficult to manage. The medical treatment combining several cholesterol-lowering drugs, usually a statin with the intestinal cholesterol-absorption inhibitor ezetimibe, does not result in satisfactory reductions of either total or LDL-cholesterol levels. Several other therapeutic approaches have been proposed such as liver transplantation and more recently several pharmacological approaches, such as MTP inhibition, as well as gene therapy, all still being experimental. For the last 30 years or so, LDL apheresis has been used and progressively become a mainstay in the management of HFH.

Case Presentation

The patient (born in 1996) was the first child of consanguineous parents (first-degree cousins), both with known hypercholesterolaemia (cholesterol levels not known) from a widespread and repeatedly inbred family, originating from Turkey and with an extensive history of premature cardiovascular morbidity and mortality as early as the third and fourth decades of life. Several family members have homozygous hypercholesterolaemia with pretreatment levels of total cholesterol above 20 mmol/L. A year before our patient's birth, the parents had received genetic counseling regarding the risk of heterozygous and homozygous transmission of FH.

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Pregnancy and birth – at term with normal birth weight – had been uneventful, a right club-foot had been operated successfully at 9 months, otherwise no past history of note.

The girl was referred to our department at the age of two years by her paediatrician for investigation of multiple xanthomas at her wrists, elbows and right knee. At presentation, she had no corneal arcus lipoides and, apart from the xanthomas, clinical examination was normal. Her total cholesterol was 29.2 mmol/L (1,124 mg/dl; normal range: 2.9–5.2), HDL-cholesterol was 0.70 mmol/L (normal: >1.20), the total to HDL cholesterol ratio was 42, and triglycerides were marginally increased at 1.8 mmol/L (normal <1.55).

The clinical and biochemical picture suggested a homozygous genotype of FH and the patient was put on a restrictive diet without red meat, chocolate and butter, instead olive oil and skimmed milk. So far, no medical treatment was prescribed and it was decided to defer initiation of LDL apheresis because of the invasive nature of the treatment and the young age of the patient. While on dietary treatment only, her total cholesterol decreased to levels around 25 mmol/L.

At 3 years of age, she had normal growth and BMI, as well as psychomotor development, and her parents reported no symptoms suggestive of cardiovascular disease (CVD). She had, however, developed an arcus lipoides corneae and the xanthomas had extended further to the areas of both axillae and the left Achilles tendon. While under dietary measures only, her total cholesterol had decreased to 25 mmol/L, HDL cholesterol 0.80 mmol/L and liver enzymes were normal. Lipoptrotein (a) was within the normal range (<300 mg/L). Echocardiography and ECG at rest were normal.

At each follow-up visit at our out-patient clinics, the xanthomas extended progressively over limbs to the hands and calves, buttocks and the head. Total cholesterol was always between 25 and 26 mmol/L, HDL cholesterol $\leq$ 0.8 mmol/L and triglycerides $\geq$ 2.50 mmol/L. A 24-h ECG was normal.

At around 3½ years, a treatment with atorvastatin 5 mg daily (= 0.25 mg/kg/d) was started. This treatment slowed down the apparent progression of the skin lesions and was paralleled by a consistent decrease of total cholesterol from 25 to around 20 mmol/L, as well as HDL cholesterol to 0.6 mmol/L at the following visits. Liver and muscle enzymes remained normal. At age 4.3 years (1½ months before death), a newly appeared systolic heart murmur was found to be due to mitral regurgitation with left heart dilation. On echocardiography, the main trunk of the left coronary artery was well visualized and appeared normal. No abnormality of the aortic valve or root was noted. It was nevertheless decided to start LDL apheresis treatment as soon as possible and the surgical insertion of a dialysis catheter was scheduled, which, for non-medical reasons, was again postponed for some six months. Around that time, the patient began to complain about recurring abdominal pain. Microhaematuria prompted emergency consultation with the nephrologist, who, faced with a child in reduced general condition, with abdominal pain and dyspnoea, suspected (inferior) myocardial infarction. The diagnosis was confirmed by repeated elevation of cardiac enzymes (troponin-I up to 11.5 mg/L [Normal <0.6] and CK-MB up to 20.7 mg/L [<4.0]). The ECG showed left ventricular (LV) hypertrophy and deep Q-waves in derivations III and aVF. The angiography of the coronary arteries showed a severe three-vessel disease with extensive complete and sub-complete stenoses involving the peripheral segments (Fig. 1).

On the following day, the patient developed ventricular flutter that rapidly progressed to refractory asystolic cardiac arrest and exitus lethalis despite immediate intensive care and full medical treatment. The parents declined post-mortem examination. Genetic analysis showed the homozygous mutation c.1849delA (p.Val597Tyrfs45X). The mutation has not been described so far; it presumably leads to reading frame shift creating a premature stop codon and thus to a truncated protein (Laboratoire de génétique moléculaire, CHU de Liège, Belgium).

Discussion

Patients with homozygous hypercholesterolaemia develop clinical CVD considerably earlier than heterozygous patients, with first symptoms generally appearing during second and third decades of life. Children with manifest CVD before 10 years of age are the exceptions, and in one cohort, no abnormalities in either coronary angiography or non-invasive test results were found in children younger than 6 years (Kolansky et al. 2008). Very few cases of fatal cases before age 10 years have been published (see Table 1 for review of the published cases). The patient presented here reminds us of the importance of adapting the general therapeutic approach to individual patients with more severe disease.

Current treatment guidelines consider LDL apheresis as the treatment of choice for HFH. They stipulate treatment initiation at around 7 years of age (Thompson et al. 2008). Our patient showed a very severe course of disease and fatal outcome at the early age of 4½ years, suggesting that in her case, more aggressive management would have been warranted and the AHA recommendation that “treatment should be instituted as soon as possible” should have been followed by the letter (Kavey et al. 2006), including statin and apheresis treatment. Importantly, her total cholesterol level at diagnosis was close to 30 mmol/L and remained

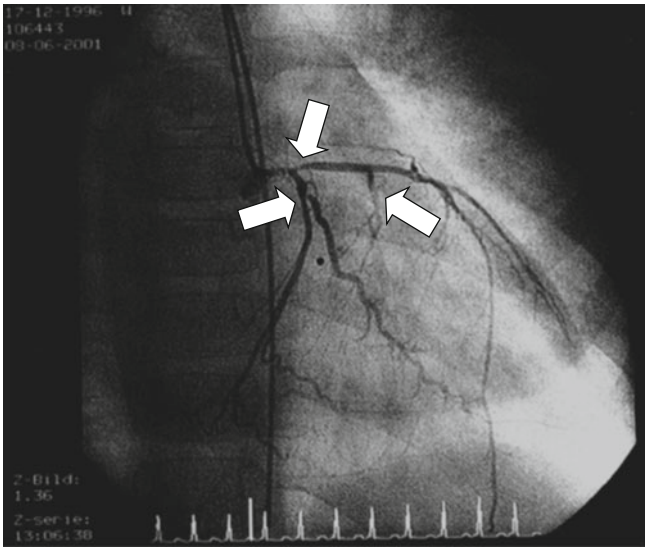

Fig. 1 Coronography showing three-vessel disease (*arrows* point to stenoses)

elevated above 20 mmol/L despite drug treatment, leading to *"fulminant"* coronary artery disease. In the first place, aggressive medical treatment is certainly warranted. In our case, this strategy was hampered by the parents' reluctance to administer an off-label drug to their child.

Other members of the same extended family with clinical homozygous hypercholesterolaemia – presumably carrying the same mutation– had LDL apheresis started at later ages, without clinical signs of CVD, despite pretreatment levels of total cholesterol above 20 mmol/L for some of them. This remarkable clinical heterogeneity within a large inbred family carrying the same mutation has been repeatedly recognized (Ferrières et al. 1995; Heiberg and Slack 1977) and is presumably due to the considerable impact of genetic modifiers (e.g., Abifadel et al. 2009; Koeijvoets et al. 2009) rather than the chronically acting risk factors of the adult patient. In our patient, no additional risk factors were found. There were repeated measures of normal blood pressure, fasting glucose, Lp (a) and renal function (normal plasma creatinine and urea, no proteinuria). Post-mortem analysis revealed a heterozygous carrier state of the thermo-labile C677T-variant of the MTHFR gene. Although a heterozygous state is usually not associated with an increased homocysteine and thrombotic risk, one cannot exclude a contribution to the dismal course in this patient. Unfortunately, homocysteine was never measured.

In the literature, several cases of very early initiation of LDL apheresis have been reported. National registries from the USA (Hudgins et al. 2008), France (Palcoux et al. 2008) and Italy (Stefanutti et al. 2001) list in their cohorts patients as young as 3 years of age at treatment initiation. Coker et al. (2009) from Turkey started apheresis even in a 2 years old patient. Difficulty with acceptance of the invasive nature of the treatment has contributed to postpone apheresis in our patient, as well as in others (Awan et al. 2008). Interestingly, however, in most of the small children mentioned, vascular access was achieved with a peripheral venous cannula, and not with a surgically inserted central line.

Other, equally invasive approaches, such as liver transplantation (Moyle and Tate 2004), or portocaval shunt, have been proposed, but have not found general acceptance.

Less invasive alternatives are not available, yet: Recently, one promising approach among others (for review see Lilly and Rader 2007), inhibition of microsomal triglyceride transfer protein, has been shown to be effective in reducing LDL cholesterol levels, but also leads to serious side effects that preclude its clinical use (Cuchel et al. 2007). Gene therapy is still experimental.

The homozygous mutation c.1849delA (p.Val597-Tyrfs45X), found in our patient, has not been described before. The deletion of one base pair leads to a frameshift. A study investigating genotype–phenotype correlation has found that frameshift mutations were associated with higher levels of LDL-cholesterol than those found in missense mutations (Graham et al. 1999). As the biochemical features and the clinical course make a receptor-negative phenotype in our case most likely, we have not performed functional studies of the mutated LDL receptor.

The considerable clinical heterogeneity has prompted a search for markers that predict severity of cardiovascular involvement. Awan et al. (2008) examined a patient diagnosed with phenotypic homozygous familial hypercholesterolaemia who had similar cholesterol levels as our patient: his pretreatment total cholesterol was 30.2 mmol/L and decreased to 24.0 under medication only treatment without evidence of vascular disease or coronary artery

Table 1 Cases of early death (<10 years) from CVD in hoFH reported in literature

Reference	Type of report	Case documentation	Receptor function	LDL-R gene mutation	Gender	Age-at-death (years)	Tot chol (mmol/L)	Country/ethnic origin	Additional CV risk factors
Widhalm et al. (2011)	Clinical image	A	n.d.	W556R[a]	M	4	21.66	Austria/Turkish	n.k.
Naoumova et al. (2004)	Review	B	neg/null	E387K[a]	F	3	24.4	UK/?	n.d.
Al-Shaikh et al. (2002)	Case series	C, B, G	neg/null	Fr-Canadian I[a]	M	3.1	24.57	Canada/French	n.d.
Rose et al. (1982)	Case report	C, B, A	n.d.	n.d.	M	3	24.65	Canada/?	n.k.
Seftel et al. (1980)	Case series	B	n.d.	n.d.	M	6	18.5	South Africa/ Afrikaner	n.d.
Seftel et al. (1980)	Case series	C, B	n.d.	n.d.	F	6	18.7	South Africa/ Afrikaner	n.d.
Kawahara et al. (1973)	Case report	A	n.d.	n.d.	F	4	24.9	Japan	n.d.
Fredrickson and Levy (1972)	Book Chapter	No details	n.d.	n.d.	?	1.5	?	South Africa/ Caucasian	n.d.
Watanabe et al. (1968)	Case report	A	n.d.	n.d.	M	4	22.8	Japan	n.d.
Bloom et al. (1942)	Case series	C (history)	n.d.	n.d.	F	6.5	n.d.	USA/Syrian	n.k.

n.d. not done/determined, *n.k.* none known (clinical exam), *A* Autopsy, *B* Biochemistry, *C* Clinical work up, *G* Genetic data

[a] Homozygous

disease by the age of 10 years. His cholesterol-year score was estimated at 156 mmol-year/L. This score correlates with calcific atherosclerosis and was proposed by Schmidt et al. (1996) as a simple means to quantify the risk of atherosclerosis. In their cohort, calcific atherosclerosis was not observed until the cholesterol-year score exceeded 260 mmol-year/L. The score of our patient amounts to around 120 mmol-year/L, which is well below the proposed limit of 260. The cholesterol-year-score may be used in heterozygous FH, but does not apply to the homozygous patient, as already stated by Rallidis et al. (1998). They also observed that atherosclerotic lesions almost always involve the aortic root in the homozygote as opposed to heterozygous patients. This specific pathology of homozygous hypercholesterolaemia "appears to be related to the early exposure to high cholesterol levels, and not to the overall burden of cholesterol exposure" (Koh 2005). The relationship between actual levels of plasma cholesterol and progression of coronary artery disease is not clear (see e.g., Sprecher et al. 1985 or Moorjani et al. 1989).

On clinical examination, the high cholesterol levels were mirrored by extensive xanthomatous skin lesions. Increased Achilles tendon thickness and corneal arcus both due to tissue cholesterol deposition are correlated with severity of calcific atherosclerosis (Zech and Hoeg 2008). The appearance of a significant systolic heart murmur due to mitral regurgitation and ventricular dilatation heralded the progressive ischaemia of the myocardium. The murmur was a strong sign of the clinically otherwise silent ongoing myocardial infarction implicating the posterior pillar of the mitral valve. The ensuing mitral regurgitation may well have worsened coronary insufficiency and precipitated the progression of myocardial infarction. Several autopsy studies of hoFH patients who had died in their first or second decade report extensive subendocardial scarring testifying to chronic ischaemia prior to the lethal event (Rose et al. 1982; Sprecher et al. 1985). The diffuse three-vessel type of CAD in our patient therefore may have predisposed her for subendocardial infarction; additional risk factors, namely LV hypertrophy, LV dilation and mitral regurgitation were brought about by papillary muscle infarction (Davies 1977).

Homozygous FH patients typically develop cholesterol deposits on the aortic valve and osteal stenosis of the coronary arteries. In our patient, no aortic valvular or supravalvular abnormality was found on echocardiography, either at the age of 3 or at almost 4½ years. At that latter time, however, the newly appeared mitral regurgitation was prominent. Kolansky and coworkers found poor concordance between evidence of CVD from coronary angiography and results from non-invasive tests. Only the presence of mild-to-moderate aortic valve regurgitation

on echocardiography was significantly associated with angiographic coronary stenosis (Kolansky et al. 2008, see also Kawaguchi et al. 1999). This poses the question of adequate follow-up investigations, as both electro- and echocardiography can miss early signs of CVD, even in experienced hands. Conventional coronary angiography, on the other hand, is an invasive procedure with its own inherent risk, as reported by Marais et al. (1990) in another fatal case of homozygous FH, and should be reserved for the investigation of symptomatic CVD. In our case, death from intractable ventricular fibrillation appeared unrelated to angiography, as it occurred several hours later, after uneventful extubation on the ICU ward. Santos et al. (2008) have suggested CT angiography as a reliable non-invasive method. Even though it is not designed for children below 10 years, it might prove a valid procedure in the future for older patients.

Conclusion

The rapid progression of coronary artery disease and fatal outcome at the early age of 4.5 years in our patient with homozygous familial hypercholesterolaemia suggest that treatment should be initiated as soon as possible after diagnosis. Early initiation of LDL apheresis, in conjunction with high dose medical treatment combining a statin and ezetimibe, is advocated, in order to rapidly achieve the therapeutic goal of total (mean) cholesterol < 9 mmol/L (Thompson et al. 2010). This treatment approach has proved to be safe and highly efficient, including in small children.

Synopsis

Clinical and biochemical diagnosis of homozygous familial hypercholesterolaemia should prompt treatment initiation, including both pharmacological and LDL apheresis therapy, at any age as soon as possible in order to reach rapidly the treatment goals (Total cholesterol < 9 mmol/L).

References

Abifadel M, Rabès JP, Jambart S, Halaby G, Gannagé-Yared MH, Sarkis A, Beaino G, Varret M, Salem N, Corbani S, Aydénian H, Junien C, Munnich A, Boileau C (2009) The molecular basis of familial hypercholesterolemia in Lebanon: Spectrum of *LDLR* mutations and role of *PCSK9* as a modifier gene. Hum Mutat 30: E682–E691

Al-Shaikh AM, Abdullah MH, Barclay A et al (2002) Impact of the characteristics of patients and their clinical management on outcomes in children with homozygous familial hypercholesterolemia. Cardiol Young 12:105–112

Awan Z, Alrasadi K, Francis GA et al (2008) Vasuclar calcifications in homozygote familial hypercholesterolemia. Arterioscler Thromb Vasc Biol 28:777–785

Bloom D, Kaufman SR, Stevens RA (1942) Hereditary xanthomatosis – familial incidence of xanthoma tuberosum associated with hypercholesteremia and cardiovascular involvment, with report of several cases of sudden death. Arch Dermat Syph 45(1):1–18

Coker M, Ucar SK, Simsek DG, Darcan S, Bak M, Can S (2009) Low density lipoprotein apheresis in pediatric patients with homozygous familial hypercholesterolemia. Ther Apher Dial 13(2):121–128

Cuchel M, Bloedon LT, Szapary PO et al (2007) Inhibition of microsomal triglyceride transfer protein in familial hypercholesterolemia. N Engl J Med 356:148–156

Daniels SR, Greer FR, and the Committee on Nutrition (2008) Lipid screening and cardiovascular health in childhood. Pediatrics 122:198–208

Davies MJ (1977) The pathology of myocardial infarction. J Clin Pathol Suppl 11:45–52

Ferrières J, Lambert J, Lussier-Cacan S, Davignon J (1995) Coronary artery disease in heterozygous familial hypercholesterolemia patients with the same LDL receptor gene mutation. Circulation 92:290–295

Fredrickson DS, Levy RI (1972) Familial hyperlipoproteinemia. In: Stanbury JJ, Wyngaarden JJ, Fredrickson DS (eds) The metabolic basis of inherited disease, 3rd edn. McGraw-Hill Book Co., New York, pp 545–614, see p 574

Graham CA, McClean E, Ward AJ et al (1999) Mutation screening and genotype:phenotype correlation in familial hypercholesterolaemia. Atherosclerosis 147:309–316

Heiberg A, Slack J (1977) Family similarities in the age at coronary death in familial hypercholesterolaemia. Br Med J 2:493–495

Hudgins LC, Keinman B, Scheuer A, White S, Gordon BR (2008) Long-term safety and efficacy of low-density lipoprotein apheresis in childhood for homozygous familial hypercholesterolemia. Am J Cardiol 102:1199–1204

Kavey RE, Allada V, Daniels SR et al (2006) Cardiovascular risk reduction in high-risk pediatric patients (AHA scientific statement). Circulation 114:2710–2738

Kawaguchi A, Miyatake K, Yutani C et al (1999) Characteristic cardiovascular manifestation in homozygous and heterozygous familial hypercholesterolemia. Am Heart J 137:410–418

Kawahara K, Tsukada N, Kawahara N et al (1973) An autopsy case of a child with familial hyperlipidemia. Trans Soc Path Jpn 62:114, quoted from Mabuchi H et al (1978) Am J Med 65:290–297

Koeijvoets KC, Mooijaart SP, Dallinga-Thie GM, Defesche JC, Steyerberg EW, Westendorp RG, Kastelein JJ, van Hagen PM, Sijbrands EJ (2009) Complement factor H Y402H decreases cardiovascular disease risk in patients with familial hypercholesterolaemia. Eur Heart J 30:618–623

Koh TW (2005) Aortic root involvement in familial hypercholesterolemia – transesophageal echocardiographic appearances of supravalvular aortic stenosis. Echocardiography 22(10):859–860

Kolansky DM, Cuchel M, Clark BJ et al (2008) Longitudinal evaluation and assessment of cardiovascular disease in patients with homozygous familial hypercholesterolemia. Am J Cardiol 102:1438–1443

Koletzko B, Broekaert I, Kreuder J, Cremer P, Schwab O (2007) Leitlinien zur Diagnostik und Therapie von Hyperlipidämien bei Kindern und Jugendlichen Retrieved at: http://www.aps-med.de/documents/hyperlipid-22-12-2007.pdf on 30/12/10

Lilly SM, Rader DJ (2007) New targets and emerging therapies for reducing LDL cholesterol. Curr Opin Lipidol 18(6):650–655

Mabuchi H, Tatami R, Toshihiro H et al (1978) Homozygous familial hypercholesterolemia in Japan. Am J Med 65:290–297

Marais AD, Firth JC, Rose AG, Berger GM (1990) Fatal outcome of homozygous familial hypercholesterolaemia in a black patient. S Afr Med J 77:588–590

Moorjani S, Roy M, Gagné C et al (1989) Homozygous familial hypercholesterolemia among French Canadians in Québec Province. Arteriosclerosis 9:211–216

Moyle M, Tate B (2004) Homozygous familial hypercholesterolemia presenting with cutaneous xanthomas: response to liver transplantation. Australas J Dermatol 45:226–228

Naoumova RP, Thompson GR, Soutar AK (2004) Current management of severe homozygous hypercholesterolaemias. Curr Opin Lipidol 15:413–422

Palcoux JB, Atassi-Dumont M, Lefevre P et al (2008) Low-density lipoprotein apheresis in children with familial hypercholesterolemia: follow-up to 21 years. Ther Apher Dial 12(3):195–201

Rallidis L, Naoumova RP, Thompson GR, Nihoyannopoulos P (1998) Extent and severity of atherosclerotic involvement of the aortic valve and root in familial hypercholesterolaemia. Heart 80:583–590

Rose V, Wilson G, Steiner G (1982) Familial hypercholesterolemia: report of coronary death at age 3 in a homozygous child and prenatal diagnosis in a heterozygous sibling. J Pediatr 100 (5):757–760

Santos RD, Miname MH, Martinez LR et al (2008) Non-invasive detection of aortic and coronary atherosclerosis in homozygous familial hypercholesterolemia by 64 slice multi-detector row computed tomography angiography. Atherosclerosis 197:910–915

Schmidt HH, Hill S, Makariou EV, Feuerstein IM, Dugi KA, Hoeg JM (1996) Relation of cholesterol-year score to severity of calcific atherosclerosis and tissue deposition in homozygous familial hypercholesterolemia. Am J Cardiol 77:575–580

Seftel HC, Baker SG, Sandler MP et al (1980) A host of hypercholesterolaemic homozygotes in South Africa. BMJ 281:633–636

Sprecher DL, Hoeg JM, Schaefer EJ et al (1985) The association of LDL receptor activity, LDL cholesterol level, and clinical course in homozygous familial hypercholesterolemia. Metabolism 34(3):294–299

Stefanutti C, Di Giacomo S, Vivenzio A, Colloridi V, Bosco G, Berni A, Rabbone I, Cerutti F, Bertolini S (2001) Low-density lipoprotein apheresis in a patient aged 3.5 years. Acta paediatr 90:694–701

Thompson GR, HEART-UK LDL Apheresis Working Group (2008) Recommendations for the use of LDL apheresis. Atherosclerosis 198:247–255

Thompson GR, Barbir M, Davies D et al (2010) Efficacy criteria and cholesterol targets for LDL apheresis. Atherosclerosis 208:317–321

Watanabe T, Tanaka K, Yanai N (1968) Essential familial hypercholesterolemic xanthomatosis – an autopsy case with special reference to the pathogenesis of its cardiovascular lipidosis. Acta Pathol Jpn 18:319, quoted from Mabuchi H et al (1978) Am J Med 65:290–297

Widhalm K, Binder CB, Kreissl A et al (2011) Sudden death in a 4-year-old boy: a near-complete occlusion of the coronary artery caused by an aggressive low-density lipoprotein receptor mutation (W556R) in homozygous familial hypercholesterolemia. J Pediatr 158(1):167

Zech LA, Hoeg JM (2008) Correlating corneal arcus with atherosclerosis in familial hypercholesterolemia. Lipids in Health and Disease 7:7. (Available at: http://www.lipidworld.com/content/7/1/7, retrieved on 30/12/10)