INTER COLLEGAS, VOL. 3, No. 2 (2016)
ISSN 2409-9988

PEDIATRICS

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FAMILIAL HYPERCHOLESTEROLAEMIA IN PEDIATRIC PRACTICE: CURRENT GUIDELINES & CLINICAL CASE

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Abstract: High risk for the population health due to hypercholesterolemia demands routine screening for the children from hyperlipidaemic parents and/or with acute cardiovascular events in family history. The article provides current European Atherosclerosis Society guidelines concerning diagnosis and management of patients with familial hypercholesterolaemia. A case of familial hypercholesterolaemia in a five-year-old girl is presented. Phenotypic presentation together with lipids and genetic analysis are common for the problem diagnosed.

KeyWords: children, familial hypercholesterolaemia, cardiovascular risk

INTRODUCTION

Coronary heart disease (CHD) is one of the leading causes of premature death of adults [1]. Despite the extremely rare clinical presentation of CHD in children and adolescents, Framingham Heart Study shows that high relative risk at a young age will likely be transformed into high absolute risk later in life [2].

In 2006, as soon as risk factors and risk behaviors that accelerate the development of atherosclerosis began in childhood, the Director of the National Heart, Lung, and Blood Institute (NHLBI), Dr. Elizabeth Nabel, appointed an Expert Panel to develop cardiovascular (CV) health guidelines for pediatric care providers. The final report of Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents was published in 2012 [3]. High population coronary risk is also linked to the fact of underdiagnosis and undertreatment of familial hypercholesterolaemia [4].

Familial hypercholesterolaemia (FH) was recognized as a common genetic cause of CHD. FH in vast majority of cases is an autosomal dominant disorder.

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FH is most often caused by mutations in the LDLR gene, resulting in absent or dysfunctional receptors on the surface of hepatocytes, identifying the liver as the principal site of LDL catabolism. More than 1700 mutations in the LDLR gene on chromosome 19 have been identified, of which 79% are probably expressed as a hypercholesterolaemic phenotype [5]. Defects in the genes encoding apolipoprotein B (APOB) and proprotein convertase subtilisin/kexin type 9 (PCSK9) account for 5% and 0,1% of FH cases, respectively. The LDL receptor adaptor protein (LDLRAP1) gene is a very rare recessive form of FH [6].

However, 5–30% of cases of phenotypic FH may arise from mutations in unidentified genes, or have a polygenic cause [7]. All of the monogenic defects result in reduced efficiency of LDL uptake and clearance in hepatocytes and increased circulating total cholesterol and LDL-C concentration. Many individuals considered homozygous have two different genetic defects related to LDLR (i.e. compound HeFH), with mutations in APOB or PCSK9 genes, as well as an LDLR mutation [8].Both homozygous and heterozygous FH result in markedly reduced hepatic capacity to clear atherogenic cholesterol-rich low density lipoproteins (LDLs) from the circulation, with consequent accumulation of LDL cholesterol (LDL-C)

[9]. Circulating LDL penetrate and then accumulate in the artery wall, become oxidatively modified, and subsequently initiate an inflammatory response, which results in vascular injury and formation of atherosclerotic plaque [10]. Additional alterations in the lipoprotein profile in FH may involve elevated levels of lipoprotein(a) [Lp(a)] and triglyceride-rich lipoprotein remnants, together with low levels of dysfunctional high-density lipoproteins (HDLs), which collectively may contribute to accelerated atherosclerosis and CHD [11].

The calculation of risks during elaborating Risk Scores shows that every 0.25 mmol/L (10 mg/dL) increment in non-HDL-C is associated with an increase in atherosclerotic burden equivalent to 1 year of aging [12].

At the same time just children with FH display a variety of changes reflecting both the lipid and the inflammatory arm of atherosclerosis, as well as early atherosclerotic development [13].

Familial hypercholesterolaemia is diagnosed either on phenotypic criteria, involving an elevated LDL-C level plus a family history of elevated LDL-C, premature CHD, and/or genetic diagnosis, or with genetic testing. As soon as the clinical presentation in childhood is rare, the systematic screening strategies are recommended [14].

Diagnosis of familial hypercholesterolaemia in children and adolescents [15]

- Family history of premature CHD + high LDL-C levels are the two key selective screening criteria
- Cholesterol testing should be used to make a phenotypic diagnosis.
- An LDL-C level ≥ 5 mmol/L (190 mg/dL) on two successive occasions after 3 months diet indicates a high probability of FH.
- A family history of premature CHD in close relative(s) and/or baseline high cholesterol in one parent, together with an LDL-C ≥ 4 mmol/L (160 mg/dL) indicates a high probability of FH. If the parent has a genetic diagnosis, an LDL-C ≥3.5 mmol/L (130 mg/dL) suggests FH in the child.
- Secondary causes of hypercholesterolaemia should be ruled out.
- DNA testing establishes the diagnosis. If a pathogenic LDLR mutation is identified in a first-degree relative, children may also be genetically tested.
- If a parent died from CHD, a child even with moderate hypercholesterolaemia should be tested genetically for FH and inherited elevation in Lp (a).

Clinical management of FH in children and adolescents (by European Atherosclerosis Society Consensus Panel [15])

- Early identification of children with FH ensures that adherence with lifestyle intervention is already established before puberty.
- Children with HeFH should be treated with a fat-modified, heart-healthy diet at diagnosis, and begin statins at age 8–10 years.
- In HeFH, pharmacologic treatment should start at diagnosis: statins are the cornerstone of FH management; in the case of homozygous FH combination with ezetimibe must be started at diagnosis and , if available, lipoprotein apheresis should be started as soon as technically possible.
- Early initiation of lifestyle is essential for ensuring long-term adherence.
- Children diagnosed with FH should have lipoprotein(a) [Lp(a)] measured for risk stratification.
- Boys and girls should start treatment at similar ages.
- For children aged 8–10 years, the Panel recommends that LDL-C is ideally reduced by 50% from pre-

treatment levels.

- For children aged ≥10 years, especially if there are additional cardiovascular risk factors, including elevated Lp (a), the target LDL-C should be 3.5 mmol/L (130 mg/dL).
- The benefits of LDL-C reduction should be balanced against the long-term risk of treatment side effects.
- Adherence should be checked if HeFH children fail to achieve LDL-C targets with combination lipid-lowering treatment. If patients are non-adherent, consider referral to a dedicated, multidisciplinary clinic.
- Children with HeFH should be referred to and cared for at a specialised centre.

As soon as early diagnosis of FH and treatment this category of children is under the priority from the point of potential ongoing early atherosclerosis in young adults, we providing case history of the pediatric patient with FH.

CASE STUDY

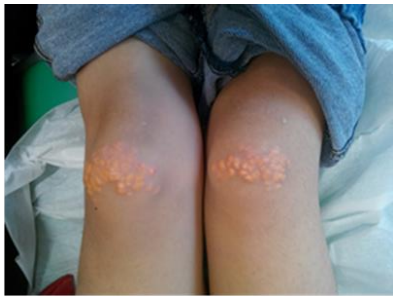
Presentation & medical history:

Otherwise healthy 5 y.o. middle-east origin girl attended the clinic for the assessment due to hyperlipidemia in the siblings. The only complaint is the presence of skin problems on both of her elbows and both knees.

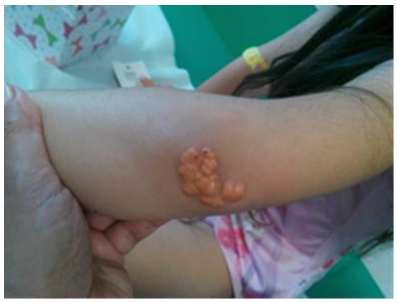
Her parents are known to be affected by hyperlipidaemia a swell as 4 of their 5 children. Her elder brother (21 y.o) suffers from severe hyperlipidemia and had the same skin problems in childhood and has been taking antihyperlipidemic medication together with lipid apheresis for years.

Physical examination:

- Height – 101 cm, weight – 18,75 kg, BMI = 18,67 kg/m2 (body composition – asthenic, adipose tissue distribution – normal)
- HENT – normal;
- Eyes – circumferential extent of arcus in the peripheral cornea is detected (arcus corneae)
- Lungs – normal
- Cardiovascular system – normal
- Abdomen – normal
- Musculoskeletal system – normal
- CNS - normal
- Lymph nodes – normal
- Skin – regular color, no problems with nails and hair. On the extension surface of both elbows and knees the multiple yellowish papulae were found. No underlying lesions. No pain or itching. Typical presentation of Xanthomas (fig.1).



(a)



(b)

Figure 1. Xanthomas on the skin of knees (a) and elbows (b) in a 5 y.o. girl

Laboratory data are pesented in Table 1.

Table 1.

Laboratory data of patient with FH

Parameter	*UNIT*	*RESULT*
CALCIUM total	MMOL/L	2,5
PHOSPHORUS INORGANIC	MMOL/L	1.67
SODIUM	MMOL/L	138
POTASSIUM	MMOL/L	4,95
CHLORIDE	MMOL/L	102
CHOLESTEROL TOTAL	MG/DL	> 650
TG	MG/DL	206
HDL-Cholesterol	MG/DL	22
LDL-Cholesterol	MG/DL	very high (out of measure)
ALAT	U/L	22
ASAT	U/L	29
GGT	U/L	<10
ALKALINE PHOSPHATASE	U/L	143
CHOLINESTERASE	kU/L	7.0
LIPASE	U/L	69
ALPHA-AMYLASE	U/L	79
BILIRUBIN, TOTAL	MG/DL	0.98
PROTEIN, TOTAL SERUM	G/L	71
ALBUMIN	G/L	44
GLUCOSE	MG/DL	97
CREATININE ENZ, SER	MMOL/L	0.45
Apolopoprotein A1	MG/DL	61
Apolopoprotein B	MG/DL	> 400

- Cardiac ultrasound: normal
- Duplexsonography of carotid vessels: A.carotis communis intima-media thickness (IMT) dextra = 0,38; sinistra = 0,32 mm – normal. A. carotis interna, A. carotis externa, A. vertebralis – normal structure and speed of blood flow

Genetics:

LDLR: E12: c.1729T>C, p. Trp577Arg (FH Marburg) homozygous

Clinical diagnosis: Homozygous familial hypercholesterolemia (LDLR - mutation)

Genetics of family members:

- Mother, Father, 1 brother, 1 sister - LDLR: E12: c.1729T>C, p. Trp577Arg heterozygous
- 1 brother - LDLR: E12: c.1729T>C, p. Trp577Arg homozygous (the similar course of disease, takes statins + lomitapide together with lipid apheresis)
- 1 brother – no mutations detected

Final diagnosis: E78.0 – Familial hypercholesterolemia (Pure hypercholesterolemia)

Diet: heart-healthy, fat-modified - 30% of calories from total fat, 7% of calories from saturated fat, and 200 mg of cholesterol/day

Medication: Patient takes treatment by simvastatin (current dosage 30 mg) in combination with ezetimibe 10 mg. Because the therapy does not completely improve the lipid profile in the patient, the procedure of lipoprotein apheresis should be started as soon as technically possible.

4 CONCLUSIONS

The discussed above clinical case demonstrates strong necessity of examination of the children from families with dyslipidaemia. Presentation seen is the common one for the patients with familial hypercholestherolemia as well as the form of genetic mutation.

High risk for the population health due to hypercholesterolemia demands routine screening for the children from hyperlipidaemic parents and/or with acute cardiovascular events in family history.

CONFLICT OF INTERESTS

There is no conflict of interests.

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Received: 01-Apr. – 2016
Accepted: 20-May. - 2016