STATINS TREATMENT AND ORO-DENTAL ASPECTS IN A CASE OF HEREDITARY HYPERCHOLESTEROLEMIA IN A CHILD UNDER 6 YEARS

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Abstract

Familial hypercholesterolemia (FH) is a genetic disease with autosomal dominant transmission, characterised by high blood cholesterol levels. The evolution of this disease leads to primary atherosclerosis and cardiovascular disease. Patients with HF develop atherosclerosis by the age of 20 and usually do not survive past the age of 30. We present the case and oro-dental aspects of a preschooler that was diagnosed at the age of 4 with FH, compound heterozygote (mutation/genotype1 LDLR: C20IX, exon 4; mutation/genotype2 LDLR: G571E, exon 12) and the experience of our clinic in the management of this patient that received off-label treatment with statins. When diagnosed, his cholesterol level was 932 mg/dL and his LDL-cholesterol level was 792 mg/dL. Treatment with rosuvastatin and ezetimibe was prescribed. Both substances (rosuvastatin and ezetimibe) are not approved for children under the age of 6 in Europe. Taking into considerations the diagnosis and prognosis for unfavorable evolution, treatment with statins was started at the age of 5 years.

Key words: hereditary hypercholesterolemia, statins, dental eruption retard.

INTRODUCTION

Familial hypercholesterolemia (FH) is a genetic disease with autosomal dominant transmission, although there has been described a rare autosomal-recessive form, characterized by high blood cholesterol levels. High level of low density lipids (LDL-cholesterol) facilitate cholesterol deposits in teguments (xanthelasma), tendons (xanthoma) and coronary arteries which leads, in evolution, to primary atherosclerosis and cardiovascular disease (1, 2).

The prevalence of the heterozygous form of this disease (HeFH) was considered to be 1:500 individuals but recent studies suggest that it might

be more frequent, affecting 1:200-300 individuals. A study published in 2018 estimates the prevalence of FH in Romania to be 1:213 individuals (3). The homozygous form of FH (HoFH) is a rare disease with low prevalence of 1:160.000 – 300.000 persons and it is characterized by a phenotype with extreme LDL-cholesterol values (>500mg/dL) (4). Patients with HoFH develop atherosclerosis by the age of 20 and usually do not survive past the age of 30. The youngest death due to HoFH was a child aged 4 who had a myocardial infarction (5). In male patients with FH coronary atherosclerosis was detected starting with 17 years and in female patients from 25 years (4, 6-8).

FH diagnosis can be confirmed using several scales, such as Dutch Lipid Clinic Network (DLCN), Make Early Diagnosis to Prevent Early Deaths (MEDPED) and Simon Broom Criteria, that take into consideration information regarding LDL-cholesterol values, personal and family medical history for cardiovascular disease, clinical signs of hypercholesterolemia and genetic diagnosis (4). Genetic diagnosis identifies mutations in the LDL receptor (LDLR), apolipoprotein B (apoB), protein convertase subtilisin kexin 9 (PCSK9) and in adaptor protein (LDLRAP) genes (9).

The accumulation of LDL-cholesterol determines cardiovascular disease by being internalized by macrophages in the arterial wall, transforming them into foam cells (components of atherogenic plaques), affecting the arterial response to vasodilator stimuli and other vascular functions, and leading to tissue ischemia (10).

Most FH guidelines recommend target LDL-cholesterol values of <135 mg/dL for pediatric patients, <100 mg/dL for adult patients and <70 mg/dL for patients with comorbidities (diabetes, coronary disease). These target values can be hard to achieve, especially

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in patients with HoFH (4). Some studies show that only a small proportion of the patients suffering from FH was able to reduce their LDL-cholesterol level to half or less of the initial value. Starting treatment with lipid-lowering agents would reduce the relative risk for coronary heart disease with 76% (11).

Pharmacologic treatment is based on LDL-cholesterol levels and should be started as soon as possible, along with lifestyle changes such as hypolipemiant diet, physical exercise and when applicable smoking cessations (12). In what concerns treatment with statins in pediatric patients, there are few studies and guidelines recommend starting treatment at the age of 8-10 years, after 6-12 months of diet. In patients with HoFH, with extreme levels of LDL-cholesterol, pharmacologic treatment should be applied as soon as possible (7, 13).

A Cochrane analysis conducted in 2010, in which there were identified 26 eligible studies, from which 9 were randomized placebo-controlled studies, concludes that treatment with statins is efficient for lowering cholesterol levels in patients with FH, and it seems to be safe on short term but there is not sufficient data to evaluate long term safety (14).

Other therapeutic options that help lowering the cholesterol level as much as possible in patients with HoHF are: PCSK9 inhibitors – could reduce LDL-cholesterol levels by 55-70%, approved in Germany at the age of 12 years for HoHF(15,16); lomitapide (selective inhibitor of microsomal triglyceride transfer protein) – reduces LDL-cholesterol independent of the LDLR and was approved by the European Medicine Agency, Food and Drug Administration (FDA), but due to the fact that long-term safety and efficacy data are not available yet as well as the high cost, experts recommend to use this drug with caution, in patients who maintain high LDL-cholesterol values and elevated cardiovascular risk despite classic management (17); mipomersen (antisense oligonucleotide) – approved by FDA since 2013, reduces the production of human apolipoprotein B-100 (18), but it has adverse reactions at the site of injection and patients experienced flu-like symptoms (19); apheresis – it is usually used when the patient still has an extremely high cholesterol level despite respecting the diet and receiving maximal pharmacological treatment (12, 20).

CASE PRESENTATION

We present the case of a male patient who, at the age of 4, was diagnosed with essential

hypercholesterolemia, with the following values of his lipids profile: total cholesterol 932 mg/dL (normal value ≤ 200 mg/dL (21)), LDL-cholesterol 792 mg/dL (normal value ≤ 130 mg/dL), high density lipids (HDL-cholesterol) 20mg/dL (normal value ≥ 40 mg/dL), total lipids 2286 mg/dL. The patient was examined in an academic centre in Holland where genetic cascade diagnosis was made (both parents and the child were genetically tested): FH compound heterozygous (mutation/genotype 1 LDLR:C20IX, exon 4; mutation/genotype 2 LDLR:G571E, exon 12), having inherited one mutation from each parent. He received recommendation for pharmacologic treatment with statins (rosuvastatin) and ezetimibe. It has to be mentioned that both substances (rosuvastatin and ezetimibe) are not approved for children under the age of 6 in Europe.

His first presentation in our clinic was at the beginning of the year 2016, at the age of 5, with very good general appearance, bilateral xanthomas on the elbow, knee and Achilles tendon. At that time, with hypolipemiant diet alone, the values of his lipid profile were already half of the ones from the moment of the diagnosis (Total cholesterol 453 mg/dL, LDL-cholesterol 401 mg/dL). The disease is still severe, with an LDL-cholesterol value far from the target value of less than 135 mg/dL, this being the reason why, after 4 months of no further improvement, in agreement with his parents, we decide to start off-label treatment with rosuvastatin, in progressive increased dosing. Treatment was started with 2.5 mg/day, after 4 months the dose was increased to 5 mg/day and at present he receives 10 mg/day. Recently, ezetimibe was added to his treatment plan.

In June 2016, at the age of 5 years and 6 months, the patient started off-label treatment with rosuvastatin, 2.5mg/day. In the first month we obtained a decrease of lipid profile values, 20.17% for total cholesterol (from 538 mg/dL to 431 mg/dL) and 35.83% for LDL-cholesterol (from 466 mg/dL to 372 mg/dL), compared with the values from his first evaluation in our clinic. The best outcome in 2 years and 6 months of treatment for total cholesterol lowering was of 36.4% and 42.39% for LDL-cholesterol, when the initial dose of rosuvastatin was first doubled (5 mg/day). Since, in time, the values of his lipid profile reached a plateau level and then even rose again, we decided to add ezetimibe to his treatment plan.

The patient was reassessed initially on a monthly basis, then at 4 and 6 months intervals. During each visit he was reassessed by clinical examination,

at which we noticed involution and then remission of xanthomas from the elbow, knee and Achilean tendons (Figs 3-5), he underwent ophthalmologic evaluation, and laboratory tests (blood count, renal and hepatic function, creatine kinase levels (CK), urine analysis).

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Figure 4. Bilateral knee xanthomas, before starting treatment with rosuvastatin (a. left), 8 months after starting treatment (b. right). Notice the involution. Tendinous xanthomas are considered pathognomonic for HF but they can be associated with rare diseases such as cerebrotendinous xanthomatosis and sitosterolemia [29].

Figure 5. Bilateral Achilles tendon xanthomas, before starting treatment with rosuvastatin (a. left). HF is the most common disease associated with Achilles tendon xanthomas. Xanthomas usually appear on the extensor tendons. This kind of tendons consist of high levels of total and free cholesterol [30]. 8 months after starting treatment (b. right). Notice the involution.

mucosal tissues. Tongue is normal in volume and color of mucosa. He also had dry lips with discreet white angular eschar / desquamation. The opening of the oral cavity can be done only within the mean limits - caused by xerostomia of the lip mucosa. (Figs 2 a-c).

At the moment he did not require odontological and periodontal treatment. He remains under observation for the possibility of an orthodontic treatment. The dentist considered that the malpositions can be remedied after the lateral group eruption. He received recommendations for maintaining an adequate oral hygiene and will have a dental follow-up in a year.

DISCUSSION

The patient tolerated the treatment well, without any adverse effect mentioned in the product's

characteristics. He did not experience constipation, nausea, abdominal pain. Transaminases have had transient increased values that did not require treatment cessation. Urine analysis did not suggest hematuria or proteinuria at any time. The patient did not suffer from myalgia, myopathy during the course of his treatment and CK levels stayed within normal range.

Since it is considered that the risk factors for cardiovascular disease are also risk factors for periodontal disease and patients (22), our patient will also be monitored from a stomatological point of view to ensure that he maintains appropriate oral hygiene and recovers the dental age delay.

The burden of cardiovascular disease is high for patients with FH. A study carried out in France, published in 2018, showed that half of the patients diagnosed with the milder heterozygote form were not receiving statins

treatment at a mean age of 47 years when their first cardiovascular event occurred (23). By starting statins early we aimed to reduce the risk of cardiovascular disease and events such as myocardial infarction which can occur as early as 4.5 years of age (24).

In the last 30 years there were conducted a multitude of studies (mainly on adult patients) in order to evaluate the efficiency of different statins, of which rosuvastatin proved to be the most efficient (25). At pediatric age (especially for children with HoFH), therapeutic resources are limited, statins being approved above the age of 6 years and other options such as lomitapide, mipomersen, evolocumab being approved only for adults or from adolescence (7). Protein aphaeresis is recommended as adjuvant therapy (along with diet and pharmacologic treatment) in HoFH but, as far as we know, it is not available in Romania. Therefore starting treatment off-label with rosuvastation was the only option.

In Japan in 2016, treatment with statins was initiated in a pair of 4 years old twins with compound heterozygote FH, resulting in a decrease of LDL-cholesterol of 50%, concluding that statins could be an acceptable therapeutic option for patients with compound heterozygote FH, before the initiation of aphaeresis (26, 27).

In our patients' case, the best outcome was a decrease with 42.39% of LDL-cholesterol. Compared with the LDL-cholesterol values from the time of the diagnosis, there is a 70.83% decrease using both diet and pharmacologic treatment with statins. Despite all this he maintains lipid profile values above the recommended ones of less than 135 mg/dL and thus the cardiovascular disease risk. At the last evaluation, cholesterol levels tend to approach the ones from the beginning of rosuvastatin treatment, which may be explained rather than by the failure of pharmacologic treatment, by the fact that the child reached school age and the control the parents have on his diet has decreased.

In conclusion, the results we have in our clinic with the management of this patient are consistent with the ones at international level and support the hypothesis that, on short term, statins do not seem to have major adverse affects. It is necessary to evaluate statins safety on long-term because patients with FH will most likely follow statin treatment lifelong. Our experience strengthens the need for extensive statins treatment studies on pediatric patients and the approval of this medication category for younger ages as well as the development of new drugs available for this special category of patients.

Conflict of interest

The authors declare that they have no conflict of interest.

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