SITOSTEROLEMIA
RARE CAUSE OF HYPERCHOLESTEROLEMIA IN CHILD

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Abstract: Sitosterolemia is a rare disorder of lipid metabolism, caused by pathogenic variants in either of two genes, ABCG5 and ABCG8. We report a sitosterolemia case of a little girl with severe hypercholesterolemia at the age of 11 months. The occurence of the some linear xanthoms at the level of the Achilles tendon, bilaterally and the extremely high cholesterol (total cholesterol: 949.6 mg%, LDL-cholesterol: 837 mg%) have constituted the starting point for subsequent investigations. Cardiac and abdominal ultrasound does not have pointed out the changes. No family history of hypercholesterolemia has been reported. Completing genetic tests confirmed the diagnosis of sitosterolemia. By sequencing the entire genome two mutations were detected in the ABCG5 gene (Q16X and R446X). We present this clinical case due to the rarity and particularity of the disease. Genetic tests play the most important role in diagnosing the disease and in an appropriate therapeutic approach for the child patient. Proper diet and family responsibility is the key to dispensing the case and to avoiding complications.

INTRODUCTION

Sitosterolemia is a rare autosomal-recessive disorder characterized by increased plant sterol levels, xanthomas and increased risk of premature atherosclerosis. The disease is caused by mutations in ABCG5 or ABCG8 (ABCG5 and ABCG8 sterol-transporter are defectives), leading to increased intestinal absorption and to a diminution of the biliary excretion of plant sterols (sitosterol, campesterol, stigmasterol) and cholesterol. The diagnosis of this disease is based on up to 50-fold increased plasma levels of sterols from plants, which are normally very low (<1 mg/dl). Vegetal sterols are very structurally similar to cholesterol, but differ in the presence of an ethyl or methyl group (sitosterol or campesterol) or a double bond (stigmasterol) (Eun, 2016). Sitosterol is the most commonly found vegetable sterol in the diet and the predominant form found in patients with sitosterol. In addition to plant sterols, their saturated derivatives - stanols are also present at high levels (Ajagbe et al., 2015). The cholesterol level is variable compared to other genetic hyperlipidemias. Patients with sitosterolemia exhibit extreme phenotypic heterogeneity, ranging from near asymptomatic individuals to those with severe hypercholesterolemia, which leads to accelerated atherosclerosis and premature cardiac death. High levels of cholesterol (up to 1000 mg/dl) have been reported, especially in children, because the immature child's intestine can absorb higher amounts of cholesterol than adults. The aim of the article is to highlight the diagnostic value of genetic tests and sitosterols dosing in a case of sitosterolemia with severe hypercholesterolemia in a child, without which a final diagnosis of homozygous familial hypercholesterolemia would have been wrong.

MATERIALS AND METHODS

A 11 month-old girl presented with severe hypercholesterolaemia. The presentation to the doctor was determined by the appearance of some linear orange lesions, arranged at Achilles tendon level, bilaterally (possibly xanthomas), difficult to observe because of very well represented subcutaneous cellular tissue. At the clinical exam, I did not detect anything pathologically. We specify that the diet was exclusively natural up to 6 months, after which it was diversified according to the recommendations, with the maintenance of breast milk. The weight index and nutritional index were in the normal range. Initial detection of extremely high cholesterol (total cholesterol: 949.6 mg%, LDL-cholesterol: 837 mg%) was the starting point for further investigations. The girl was dermatological, cardiological, ophthalmological, pediatric (St. Maria Iasi Hospital, IOMC Bucharest) tested, the results being normal. Also, the lipid profile in the dynamics was studied, keeping high values. During 6 weeks, the values were as it follows: total cholesterol 949, 1023, 756 (mg/dl), LDL-cholesterol 837, 945, 667 (mg/dl), HDL cholesterol 48, 54, 40.7 (mg/dl) and triglycerides 215, 120, 241 (mg/dl). Laboratory investigations performed by parents revealed normal levels of cholesterol and triglycerides. Although no family history of

hypercholesterolaemia has been reported so, the young age, the presence of xanthomes and the extremely high LDL-cholesterol level (> 600 mg/dl) were considered arguments to be homozygous familial hypercholesterolaemia. The next step was a transfer to Fundeni hospital, the recommended therapeutic solution being hepatic transplant.
After two months, the parents decided to go to a specialist clinic in Belgium, where the paraclinical investigation protocol started again and, very important, blood samples were sent to the USA for genetic testing. For the first time, the sitosterols were dosed, the calculated value being 2.37 mg%, above the normal limit (0.2-1 mg%). The lipid profile was comparable to the previous ones, the values being high (cholesterol-total: 752 mg%, LDL-cholesterol: 678 mg%, HDL-cholesterol: 42 mg%, triglycerides: 159 mg%). Treatment with ezetimibe 20 mg/day and atorvastatin 20 mg/day was initiated, so that, acute toxic drug hepatitis with severe hepatic cytolysis (TGP = 3610 IU/l, TGO = 2760 IU/l) was reported in 1 week. Hepatic function normalized in 4 weeks after discontinuation of treatment. The first results of genetic testing have excluded the known causes of severe hypercholesterolemia by sequencing the responsible genes (LDLRAP, LDLR, PCSK9, APOE and APOB) so that, liver transplantation was no longer considered an emergency.
Therefore, at the age of 1 year and 5 months, treatment with ezetimibe at the initial dose of 2.5 mg/day is gradually resumed, with a gradual increase to 7.5 mg/day. After 2 months, atorvastatin is combined at a dose of 2.5 mg/day. After 6 months of ezetimibe and atorvastatin, the lipid profile looks encouraging (total cholesterol: 203 mg%, LDL-cholesterol: 147 mg%). After 18 months of combined therapy, at 3 years and 1 month age, high cholesterol values (total cholesterol: 309 mg%, LDL-cholesterol: 249 mg%) and high sitosterol values were found (sitosterol: 7 mg%). That is because of giving up medication for specific periods and calling for alternative medicine, as well as addressing a diversified diet, restricted only to animal fats. The treatment with ezetimibe at the dose of 3.3 mg/day was resumed.
After 2 years and 6 months of expectations and uncertainties, sequencing of the entire genome confirms the diagnosis of sitosterolemia, by detecting two mutations in the ABCG5 gene (Q16X and R446X). She continued the treatment with ezetimibe alone, with a gradual increase in the dose up to 10 mg/day, the actual recommended dose. In recent years, total cholesterol ranged between 179-216 mg%, LDL-cholesterol between 121-169.6 mg% and beta-cholestanol between 6.9-10.9 μg/mL vs. normal (1.6- 6.2 μg/mL).
In terms of diet, the little girl also benefits from sustained and individualized counseling, based on observing basic principles, the diet being poor in plant sterols (nuts, seeds, olives, avocados, vegetable oils, margarine and chocolate) and in animal fats.
As the family chose to leave the country, access to the girl's personal data is limited.

RESULTS AND DISCUSSIONS

Although no family history of hypercholesterolaemia has been reported, the extremely high LDL-cholesterol level and the occurrence, at a very young age, of xanthomies could have been criteria for supporting the diagnosis of homozygous familial hypercholesterolaemia (Turgeon et al., 2016). Once the genetic tests have been completed, any diagnostic hypothesis has been removed, sitosterolemia being the diagnosis of certainty. It should be underlined that genetic diagnosis, although being the most relevant, are not at all accessible, both because of high costs and other factors. In our case, the family has overcome any barrier. A proper diagnosis is followed by adequate therapeutic behavior, benefits for the patient being huge.
Linear xanthomas were quite relevant to the case assessment and possible, in their absence, the disease would remain undiagnosed for a certain period of time. The true prevalence of sitosterolism cannot be explained precisely because of underdiagnosis and is probably more common than previously thought (Kidambi et al., 2008).
The first dosing of sitosterols revealed slightly high values (2.37 mg%), but much below the values observed in sitosterolemia (14-65 mg%) due to the fact that the girl at 1 year and 1 month was still breast-fed. Since vegetal sterols come entirely from the diet, the baby was exposed to much lower sitosterolytes during breastfeeding, as the heterozygous mother's plasma sitosterol should only be slightly increased. With the interruption of breast milk and the introduction of fruit and vegetables in the diet, the level of vegetable sterol increased (Park et al., 2014). Also, in the case of our baby, before finding out the genetic diagnosis and diet change, the sitosterolemia was 7 mg%. We need to keep in mind that a normal individual absorbs less than 5% of vegetal sterols, while the patient with sitosterolemia absorbs 15-60% of the ingested sitosterol.

The initial extremly high cholesterol levels are in agreement with the underlying disease. However, we note that cholesterol intake can be increased at a breast fed infant due to high cholesterol content in human milk (90-150 mg/liter), but also that the infant's intestinal mucosa can absorb higher amounts of cholesterol compared to that of an adult (Kamelska et al., 2012).
Diet is essential and must be strictly followed, although in pediatric age it is very difficult to achieve this goal. Dietary restriction of both cholesterol and vegetable sterols (vegetable oils, margarine, nuts, seeds, avocado and chocolate) is required. Also some crustaceans (shells, oysters) should be avoided (Gregg et al., 1986). A diet without sterols is almost impossible, because plant sterols are found in almost all herbal foods and the low diet of plant sterols led to just a 30% reduction in sterol levels (Izar et al., 2011). There are authors who claim that a diet low in cholesterol and plant sterols in infants and children would be safe and effective (Simell et al., 2000).
Ezetimibe remains the first choice as a drug therapy, being an inhibitor of intestinal sterol absorption (Othman et al., 2017). Specialty literature shyly supports, with observational studies, treatment with ezetrol under the age of 10 years (Niu et al., 2010; Tsubakio-Yamamoto et al., 2010). In our patient, initiation of treatment with ezetimibe has come with extremely severe cholesterol levels. Despite the hepatic impairment at the initial dose of a very high dose for a child patient (2 mg/kg body weight) subsequently, at lower doses, 1 mg/kg body weight, it has been shown to be safe and well tolerated. If we analyze the levels in the dynamics of LDL-cholesterol (minimum 121 mg% - maximum 169.6 mg% and vegetal sterols - beta-cholestanol (minimum 6.9 µg/ml - maximum 10.9 µg/ml), we notice that cholesterol levels are significantly reduced, only plant sterols remain at slightly higher levels than the reference ones. No beta-cholestanol has been dosed before initiation treatment with ezetimibe in order to make a more accurate comparison. So the efficacy of ezetimibe therapy is clear, especially if we take into consideration that in sitosterolemia, the levels of sitosterol can be increased up to 50 times.
Starting from the fact that in sitosterolemia there is an increased risk of premature atherosclerosis, by the accumulation of plant sterols and/or plasma stanols, we underline once again the important role of an early and accurate diagnosis of the disease (Othman et al., 2013). Our patient has no cardiac complications so far. Appropriate case management significantly improves prognosis and contributes to reducing the morbidity and mortality associated with this disease.

CONCLUSIONS

Genetic tests play the most important role in diagnosing the disease and in an appropriate therapeutic approach for the child patient. Proper diet and family responsibility is the key to dispensing the case and to avoiding complications.

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