Sitosterolaemia: a case of rare hypercholesterolaemia in FH patient’s cohort

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AIMS

Familial Hyperpercholesterolaemia (FH) is the most common of all genetic hypercholesterolaemias. However there are other rare disorders presenting the same phenotype (phenocopies). Sitosterolaemia is one of those rare recessive disorders in which patients can present high levels of LDL-C but, most importantly, they present vegetal fat accumulation in tendons and arteries, leading also to increased cardiovascular risk. The defect in this case is in transporter genes responsible for the intestinal and biliary transport of plant sterols (ABCG5/ABCG8). AIMS: to identify the genetic cause of hypercholesterolaemia in a clinical FH patient presenting a severe phenotype.

Methods

A 4 years child was referred to the Portuguese FH Study, as having a clinical diagnosis of FH, with a total and LDL-C of 455 mg/dl and 391 mg/dl (table 1), xanthomas (figure 1) and a family history of hypercholesterolaemia from her mother’s side. The screening diagnosis of FH was performed in 3 phases: 1) includes the screening for the most common APOB mutations (fragments of exons 26 and 29) and the molecular study of the promoter, splicing and coding regions of the LDLR gene; 2) includes the study of large rearrangements by Multiplex Ligation-dependent Probe Amplification (MLPA) technique; 3) includes the study of the promoter, splicing and coding regions of the PCSK9 gene. Targeted sequencing was performed for LDLR, APOB, PCSK9, LIPA, APOE and ABCG8 genes. Sterol analysis chromatogram was also performed.

Results

- The results of genetic diagnosis of FH turned out to be negative and the clinician asked for sterols chromatography (Figure 2). The high values of sitosterol changed the diagnosis of the child to sitosterolaemia.

- We performed targeted sequencing revealed that the child was homozygous for a known stop mutation in ABCG8 gene: [c.[1974C>G];[1974C>G]] p.[(Tyr658*)];[(Tyr658*)]] (Figure 3A).

- The surprising discovery was that her mother was also homozygous for the same mutation and co-sanguieny was established. This explained the mother’s hypercholesterolaemia and why this child was wrongly diagnosed with FH (Figure 3B).

- Aditionally, the analysis of targeted sequencing also identified a variant in the APOB gene: c.11477C>T, p.(Thr3826Met) (Figure 3C) whose pathogenicity has been proven by functional studies.

CONCLUSIONS

We characterized the complex phenotype in a child with severe dyslipidaemia: the patient has sitosterolaemia and FH. The correct identification of the several causes of hypercholesterolaemia is important to establish the correct treatment for the best patient prognosis. Dietary and pharmacological interventions for the prevention of atherosclerosis can be markedly different within the several genetic dyslipidaemias.