Sitosterolemia: An Atypical Case of Compound Heterozygous Mutation in ABCG5 in a Young Puerto Rican Male

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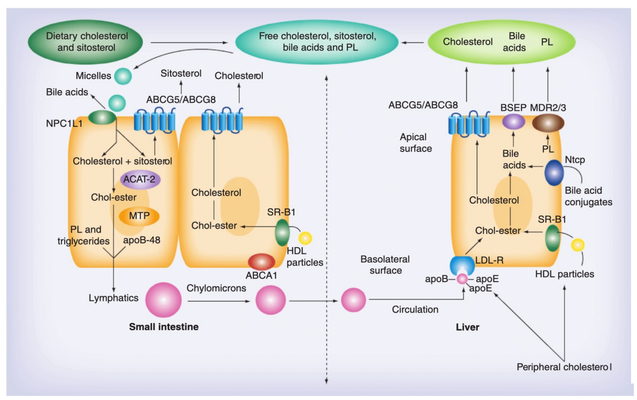
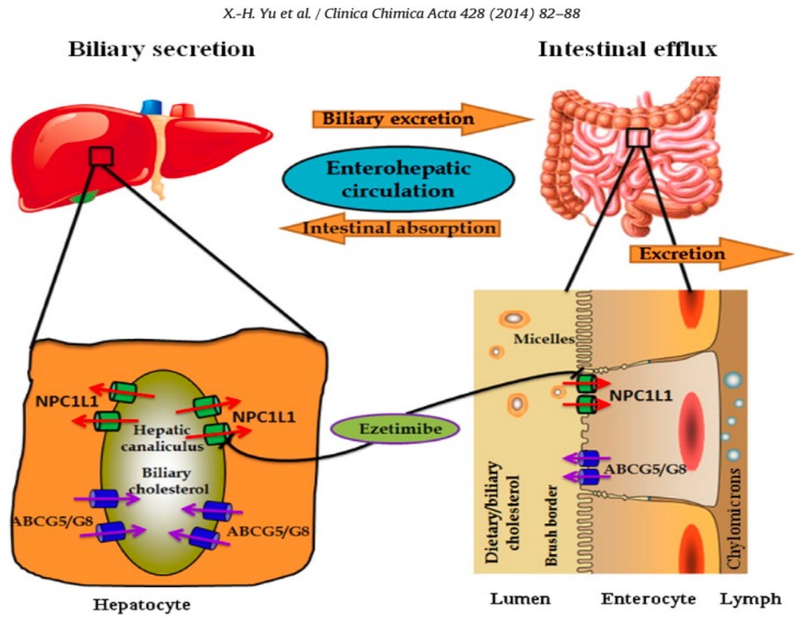
Introduction

Sitosterolemia, is a rare disorder of lipid metabolism, caused by loss of function mutations in the "ATP-binding cassette subfamily G" (ABCG5 and ABCG8) genes located in a head-to-head human chromosome 2p21, as autosomal recessive[1]. This condition is more prevalent in Middle Eastern population and can be inherited as a homozygous or compound heterozygous pattern. Regarding pathophysiology, this condition is characterized by increased intestinal absorption and decreased biliary excretion of dietary sterols, hypercholesterolemia and premature coronary atherosclerosis[2]. As a result of this disorder in lipoprotein metabolism, patients with this condition can have phenotypical variations regarding the presence of tuberous xanthomas, elevated plasma cholesterol and phytosterol levels, thrombocytopenia and hemolytic anemia[3]. These previously mentioned manifestations can vary diversely leading to medical misdiagnosis. It is important to recognize this rare lipid metabolism disorder so early intervention can be started.

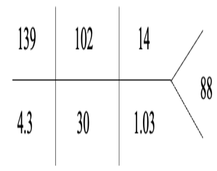


Case

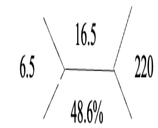
This case report involves a 21-year-old Puerto Rican young man who presents to our endocrinology and lipidology clinic with elevated LDL-C levels since late childhood. He referred having no prior genetic testing or medical treatment. Patient denied chest pain, shortness of breath, palpitations or history of cardiovascular events. Physical examination was unremarkable and there was no presence of corneal arcus or tendinous xanthomas. Family history pertinent for hypercholesterolemia in his father but no early cardiovascular events. Genetic panel was performed, resulting in a compound heterozygous mutation for (c.914C>G, p.(Thr305Arg) in ABCG5 resulting in diagnosis of sitosterolemia. Low cholesterol/low plant sterol diet was recommended[4] and ezetimibe was started[5,6]. Although this ABCG5 mutation is more prevalent in the Middle Eastern population[7], this reported case has been found to be one of the 8 individuals heterozygous for this variant. These heterozygous mutations on ATP-binding cassettes play an important role in the absorption of dietary and biliary sterols in the liver and mediate their excretion from the liver to the bile[8]. Accumulated plant sterols in hepatocytes inactivate SREBP-2, which results in the downregulation of hepatic LDLR expression and consequently in the decreased uptake of serum LDL-C leading to a poor response to statin[9]. Follow up appointment 12 weeks later after therapy, showed lipid profile of total cholesterol 231 mg/dL, LDL-C 164 mg/dL, triglycerides 104 mg/dL and HDL-C 59 mg/dL. Despite the underlying genetic condition, ezetimibe was able to reduce LDL-C by 24%, demonstrating its role in cholesterol management even in cases complicated by rare genetic disorders.



Laboratories



Lipid Profile:
Total Cholesterol: 290 mg/dL
LDL-C: 217 mg/dL
Triglycerides: 69 mg/dL
HDL-C: 65 mg/dL
Non-HDL: 225 mg/dL



TSH: 1.96 uIU/mL
ALT: 23 U/L
AST: 16 U/L
Lp(a): 9.1 mg/dL

Campesterol: 19 mg/L
(normal range: <= 8 mg/L)
Cholestanol: 8.2 mg/L
(normal range: <= 6 mg/L)

Conclusion

This case report highlights the importance of genetic testing and comprehensive evaluation for an accurate diagnosis, as other pathologies like Familial Hypercholesterolemia can present similarly but differs in management. While more common in Middle Eastern populations, this case also highlights sitosterolemia's presence in Hispanic individuals, emphasizing the need for increased awareness and understanding in diverse populations. Based on this case findings genetic testing should be part of the workup performed for proper diagnosis of rare lipid disorders.

References

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