CLINICAL QUIZ (p116) ANSWER

What is the diagnosis?

The clinical photos show xanthoma over wrists, heels and back of knees and thighs. Blood test showed markedly raised cholesterol with sky high LDL-C. Complete blood count, liver and renal function, CK, lipase, HbA1c and thyroid function were normal. Vitamin D profile, clotting function were also normal. There was no family history of sudden cardiac death, early onset atherosclerotic disease, or early onset ischaemic stroke. Parents are non-consanguineous. Father had history of hyperlipidemia on health screen, which normalised later with dietary modification. His elder brother 5 years old is healthy. Ethan had no intake of over-the-counter drugs and his dietary history was unremarkable. Phytosterol profile as described below showed markedly elevated beta-sitosterol, cholestanol, campesterol and stigmasterol. Genetic workup was done and revealed compound heterozygous mutation c.1166G>A and c.1336C>T of ABCG5. The diagnosis of sitosterolemia 2 (or phytosterolemia) is confirmed in this patient.

Table 1 Lipid profile and phytosterol profile of patient on diagnosis and after starting dietary restriction of plant sterols and cholestyramine

	12/5/2020	20/5/2020	10/6/2020	15/7/2020
Total cholesterol (N: <5.2 mmol/L)	**>15**	**11.7**	3.1	3.7
Triglyceride (N: <1.7 mmol/L)	1.2	1.1	0.7	0.4
HDL-C (N: > 1 mmol/L)	1	0.9	1.5	1.3
LDL-C (N: <4.1 mmol/L)	**16.2**	**10.4**	1.3	2.2
ApoA1 (1.1-1.8 g/L)	1.14	/	/	/
ApoB (0.49-1.15 g/L)	**4.13**	/	/	/
Lp(a) (N: <300 mg/L)	148	/	/	/
Cholestanol (N: <13 umol/L)	**351**	/	/	**22.8**
Campesterol (N: <17.5 umol/L)	**295**	/	/	**77.7**
Stigmasterol (N: <3.5 umol/L)	**22.2**	/	/	**3.7**
Beta-sitosterol (N: 12 umol/L)	**498**	/	/	**123**

What is phytosterolemia?

Phytosterolemia is an autosomal recessively inherited lipid disorder due to increased plant sterols absorption. Biallelic mutations in either ABCG5 or ABCG8 accounts for 42% and 58% of pathogenic variants respectively.[1] They encode for sterol efflux transporters and mutation would lead to increased intestinal absorption and decreased biliary excretion of sterols. Clinical presentation can range from asymptomatic to severe hypercholesterolemia with extensive xanthomas, accelerated atherosclerosis and premature cardiac death. Atypical presentation includes abnormal haematological finding such as haemolytic anaemia with stomatocytosis or macrothrombocytopenia, arthritis, splenomegaly and idiopathic liver disease.[2]

What is the management?

Patients with phytosterolemia are advised to restrict dietary intake of food rich in plant sterols for example vegetable oils, margarine, nuts, seeds and avocados.[3] Dietary advice is important as it contradicts with usual recommendations for hypercholesterolemia, where plant sterols can lower cholesterol absorption by competitive transport pathways. Patients with phytosterolemia typically show excellent response to dietary plant sterols restriction alone and bile acid sequestrants. Sterol absorption inhibitor, Ezetimibe can also be used to control hyperlipidemia. Early recognition of xanthomas and timely diagnosis is essential since delayed diagnosis may lead to poorer prognosis with atherosclerotic cardiovascular disease. Xanthomas typically resolve after a period of treatment. Family carrier screening should be carried out for at-risk family members.

Ethan was started on cholestyramine after preliminary blood tests. Dietitian was consulted and he was advised on low plant sterols diet. He was also supplemented with polyvisol, folic acid, vitamin K1 and ferrum hausmann. Complication screening including ultrasound of abdomen showed no fatty liver, Ultrasound doppler carotid arteries showed no evidence of significant carotid artery stenosis. Ethan was tolerating cholestyramine well with no diarrhoea. He had good response to dietary modification and cholestyramine with normalisation of lipid profile after 4 weeks of treatment. His elder brother was arranged family screening and showed mild elevation of LDL (4.3 mmol/L) with increase in phytosterols as well.

References

1. Myrie SB, Steiner RD, Mymin D. Sitosterolemia. Gene Reviews 2013;Apr 4 [Updated 2020 Jul 16].
2. Yoo EG. Sitosterolemia: a review and update of pathophysiology, clinical spectrum, diagnosis, and management. Ann Pediatr Endocrinol Metab 2016;21:7-14.
3. Izar MC, Tegani DM, Kasmas SH, Fonseca FA. Phytosterols and phytosterolemia: gene-diet interactions. Genes Nutr 2011;6:17-26.