Sitosterolemia Masquerading as Familial Hypercholesterolemia

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Introduction

- Sitosterolemia is a rare genetic disorder whose clinical manifestations are similar to those of Familial Hypercholesterolemia (FH).
- Affected individuals are at significant risk for premature CVD disease and death.
- Treatment for Sitosterolemia differs significantly from treatment for FH.

Case Reports

#1 - Susan (pseudonym)

- 31 year old Hutterite woman
- Xanthelasma and total cholesterol of 8.98 mmol/L.
- Possibility of FH?
- Neither parent had hypercholesterolemia or CVD. This would not occur with a diagnosis of FH.
- Statin therapy had little effect on serum cholesterol level.
- Plasma sitosterol level was 21.3mg/dL (normal is ≤ 1 mg/dL), confirming diagnosis of Sitosterolemia.
- Other symptoms included lifelong anemia and macrothrombocytopenia, highly characteristic of Sitosterolemia.
- CT angiography revealed aortic and non-occlusive coronary atherosclerosis.

#2 - Kathy (pseudonym)

- Susan's 39 year old sister, Kathy, had a similar history of life-long anemia.
- Kathy had the following findings:
  - xanthelasma
  - total serum cholesterol level of 8.16 mmol/L
  - platelet and erythrocyte abnormalities on blood smear
  - aortic calcification on x-ray
  - sitosterol level of 24.6mg/dL

Diagnostic comparisons –
Sitosterolemia vs. Familial Hypercholesterolemia

	Sitosterolemia	Familial Hypercholesterolemia
Xanthomas	√	√
Premature Atherosclerosis	√	√
Hypercholesterolemia	Variable	√
Response to statin therapy	Minimal	√
Parent affected	Rare	√
Hemolytic anemia	√	-
RBC abnormalities *	√	-
Arthritis	√	-
Platelet abnormalities**	√	-
Prevalence	<1:1,000,000	1:200 to 1:500

*target cells **macrothrombocytes; thrombocytopenia

Sitosterolemia

- Sitosterolemia is a rare autosomal recessive disorder due to mutations in the ABCG5 or ABCG8 genes. It is characterized by raised plasma levels of phystosterols.
- The principal sterol is sitosterol, hence the name. This disease, however, is more appropriately termed Phytosterolemia since all sterols are affected.
- When the ABCG5 orABCG8 is mutated, excessive amounts of sterol are absorbed and retained in blood and tissues.
- As sterols are an important component of cell membranes and organelles, cell physiology is significantly affected and thus RBC and thrombocyte abnormalities may occur.
- These abnormalities may be the initial presentation or the sole clinical feature of this disorder.

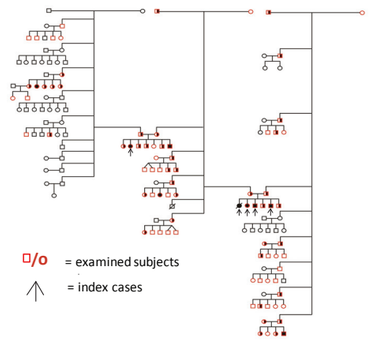
Discussion: What is a Plant Sterol (Phytosterol)?

- Very similar in chemical structure to cholesterol.
- Humans can synthesize cholesterol, but phytosterols are only obtained from diet.
- Sitosterol and campesterol are the most abundant phytosterols. More than 20 have been identified.
- Originate in plants; contained in oily vegetables, nuts and seeds.
- Are part of a normal diet, but unlike cholesterol, are poorly absorbed. Very small amounts are normally detected in the blood.

Genetics

- Isolated communities, such as Hutterite, have a high prevalence of consanguineous relationships which favours the emergence of autosomal recessive disorders, as illustrated below.

Pedigree of 1st, 2nd and 3rd degree relatives of Phytosterolemia cases in two Hutterite colonies



Diagnosis

Can be confirmed by:

- Elevated plasma phytosterol levels (sitosterol or campesterol).
  - Only done in specialized laboratories by gas liquid chromatography (GLC).
- Genetic testing for ABCG5 or G8 mutations (In our kindred ABCG8-S107X).
  - Saliva sample tested by polymerase chain reaction (PCR) methodology.

Dietary Treatment

Sterols are lipid soluble therefore lifelong restriction of lipids high in phytosterols is necessary:

- All vegetable oil and vegetable fats
- Seeds, nuts, including peanut butter
- Chocolate, olives, avocado
- Foods or supplements with added plant sterols
- Shellfish (though not a plant, are high in non-cholesterol sterols)

Fats low in plant sterols (e.g. butter) may be used.

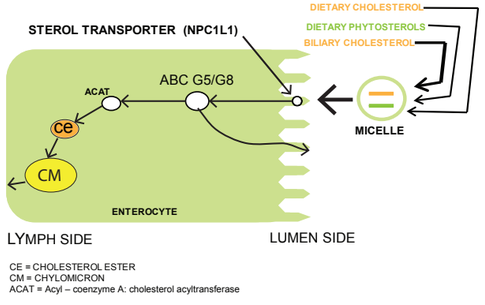
Phytosterol Content of Foods

Food	Serving size	Phytosterol content (mg)
Wheat germ	½ cup	197
Canola oil	1 tbsp	92
Peanuts	1 ounce	62
Rye bread	2 slices	33
Becel ProActiv Margarine	2 tsp	800
Average North American intake is 200-300mg/day.		

Pharmacological Treatment

- Ezetimibe (sterol absorption inhibitor).
  - inhibits the NP1L1 transporter in the intestine.
  - Lowers sitosterol levels by up to 50%.
- Bile acid binding resins
  - cause bile acid malabsorption.

Sterol Absorption



CE = CHOLESTEROL ESTER
CM = CHYLOMICRON
ACAT = Acyl – coenzyme A: cholesterol acyltransferase

Sterol Response to 3 Months Diet and Ezetimibe Therapy

All measurements done by GLC, and are reported in **mg/dL**

Susan	Total Sterols*	Cholesterol	Sitosterol	Campesterol
Pre- Treatment	349.2 (8.98 mmol/L)	310.5 (8.04 mmol/L)	21.3	17.4
Post- Treatment	142.0 (3.65 mmol/L)	129.3 (3.35 mmol/L)	7.2	5.6
Kathy				
Pre- Treatment	317.8 (8.16 mmol/L)	275.5 (7.13 mmol/L)	24.6	18.0
Post- Treatment	205.5 (5.26 mmol/L)	178.8 (4.63 mmol/L)	15.3	11.0

* Equivalent to "Total Cholesterol" by enzymatic method

Conclusion

- Both Sitosterolemia and FH are genetic conditions that cause premature CVD.
- Sitosterolemia has clinical findings similar to FH, however, FH responds to statin therapy and Sitosterolemia does not.
- Treatment for Sitosterolemia requires avoidance of foods usually considered to be heart healthy.
- Ezetimibe, the current pharmacological treatment of choice, lowers all sterol levels (including sitosterol and cholesterol), reducing the risk for premature CVD.

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