Background

Familial hyperlipidemia is defined by abnormal levels of the following: low density lipoprotein cholesterol (LDL-C); high density lipoprotein cholesterol (HDL); triglycerides (TAG); or any combination of the three. Furthermore, while the disease is of a polygenic nature and at current time is poorly understood, it has been noted that the proteins apoB (needed for the LDL receptor and to aid in the removal of LDL from circulation) and apoE (which aids in the clearance of chylomicrons and very low density lipoprotein) present abnormalities in this illness [1]. With respect to apoB abnormalities, a Mendelian inheritance pattern has been observed in a number of cases despite the fact that familial hyperlipidemia is determined by interaction of multiple genes [2,3] and occurs in only 1–2% of the general population [4].

Anemia itself has numerous forms and causes, but the one that this paper will be focusing on will be iron deficiency anemia. As this is a pediatric case, the thresholds will be for children 6 months to < 5 years of age, and are the same as those used by the World Health Organization: hemoglobin under 11g/dL and Ferritin <12 micrograms/L [5]. Iron deficiency anemia is the most common form of anemia on the planet, ranging as high as 1 in 3 children less than 5 years of age [6].

Case Presentation

A 4 year old African American female presented to her primary care physician complaining of numerous indurated yellow papules on her extremities, where she began several topical formulations including empiric treatment for molluscum contagiousum without any relief. She was referred to dermatology where biopsies of the lesions showed that the lesions were xanthomas.

Past medical history

The patient was full term, born via spontaneous vaginal delivery. The pregnancy was unremarkable as was the perinatal period, with no supplemental oxygen, antibiotics, or phototherapy needed; nor were there hospitalizations, surgeries, or concerns with growth and development.

Family history

Patient’s mother has hypercholesterolemia diagnosed at the age of 5. Her total cholesterol at that time was 500 and was treated with statins since. Patient’s father was absent and his medical history is therefore unknown.

Physical examination

General: no acute distress.

Vital Signs: blood pressure (94/56), weight of 17.3Kg, length 96cm. Heart rate of 118, and oxygen saturation of 100% on room air.

Heent: normocephalic atraumatic, extraocular muscles intact, anicteric sclera, conjunctiva not injective, no evidence of corneal arcus, ocular exudates, or rhinorrhea. Tympanic membranes grey bilaterally, oropharynx clear, neck supple without lymphadenopathy, buccal mucosa without plaque or ulceration.

Cardiovascular: Normal rate and rhythm, no murmurs, good pulses that are equal in all extremities. No edema, dorsal pedalas 2+ bilaterally.

Respiratory: no rhonchi, rales or wheezing, non-laboured breathing, breath sounds equal, and symmetrical chest wall expansions. Gastrointestinal: soft, non-tender, non-distended with normal bowel sounds.

Musculoskeletal: normal range of motion, no swelling.

Neurological: alert and oriented, 5/5 bilateral upper and lower extremities.

Derm: numerous yellow papules and plaques in linear distribution on all extremities, most prominently bilaterally on posterior thighs, patellar surfaces, and creases of arms and legs.
Lipid panel: total cholesterol 899, triglycerides (TAG) 128, HDL 23, LDL 850. CBC: Hemoglobin 7.2, MCV, 64.2, RDW 15.3, MCHC 32.1, platelet 327, reticulocyte count 1.9%, Haptoglobin 145 mg/dL, serum iron 10.1, serum TIBC 98.5, serum ferritin 10, transferrin levels at 8.9, hypochromia and microcytosis with occasional acanthocytes and elliptocytes. 64-slice CT with angiography was negative for early lesions of coronary atherosclerosis. As her cholesterol panel was well above the upper limits of elevated and the presence of xanthomas was noted, no studies on lipid electrophoresis or Apo studies were done.

Hospital course

The patient presented to her pediatrician with numerous yellow plaques and papules all over her body that caused her mother some concern. Trials of numerous treatments were started, including a course of empiric treatment for mullocsum contagiousum, as well as a referral to dermatology where they took a biopsy and found the lesions to be xanthomas. The patient then had a lipid panel done, confirming the diagnosis of familial hyperlipidemia. She was then referred to a lipid specialist and surgery where she was to get a pheresis catheter put in the superior vena cava (SVC). On the first attempt of placing the catheter, the procedure was halted due to an occlusion of the SVC. A re-attempt was made where the SVC was described as severely stenosed, but not entirely occluded. She was then put on lovenox due to the stenosis, where a confusion of dosing occurred and she had bleeding at the site of the catheter. She stayed overnight at a hospital where the dosing issue was subsequently fixed and she began treatment for her familial hyperlipidemia.

The first few treatments of LDL apheresis were successful and well tolerated. The patient’s lipid panel showed marked improvements; cholesterol went from 899 to 152, with the xanthomas clearing up almost entirely. Her LDL apheresis had to be discontinued due complications including hypotension and abdominal pain. A blood test was then run and showed evidence of iron deficiency anemia. This is a common finding with people on apheresis treatment, and usually the culprit is a mechanical shearing of the red blood cells. However, this was not the case as there was no evidence of such on the CBC; instead, there seemed to be evidence from previous lab results that this patient has been suffering with iron deficiency anemia without a known cause. This ended her apheresis treatment; the catheter was removed and she is being followed by her primary care physician for her lipid levels.

Discussion

We present the case of a 4 year old female who presented to her pediatrician with numerous skin lesions which revealed underlying familial hyperlipidemia. Her treatment course was complicated due to late discovery and the apheresis was delayed due to concerns over severe stenosis, followed by cutting down the number of apheresis due to iron deficiency anemia. Currently she is being medically managed with 30 mg of ferrous sulfate and 10 mg atorvastatin, and is followed carefully by her pediatrician and lipid specialists.

Her familial hyperlipidemia is likely a homozygous type, and is presenting more severely than in her mother. The patient’s paternal side is unknown, but it is likely that he too has some sort of hyperlipidemia given that the patient presented with a grossly elevated lipid panel. This falls in line with the current understanding of familial hyperlipidemia, as it is relatively common and accounts for the many comorbidities associated with familial hyperlipidemia: premature heart disease, obesity, impaired glucose tolerance, etc [7,4].

As for treatment of hyperlipidemia in a child so young, this was a challenge in more ways than one. As per the current guidelines, children under the age of 10 should not be subjected to pharmacotherapy; however, that is levied with the potential risks of hyperlipidemia, including but not limited to: cardiovascular disease, strokes, insulin resistance etc. [8]. The side effects of statins in pediatrics are not well defined, but it is obvious that it is dose dependent and that since it is a cytochrome P450 dependent medication, special care needs to be taken before it can be prescribed [9,10]. As this case showed, the lipid profile placed the patient in the “very high risk” category. Given that one of the major vessels had nearly been occluded, it is reasonable to surmise that statin therapy would not have been able to lower her lipid profile quick enough to prevent cardiovascular events, as generally homozygous familial hyperlipidemia responds poorly to statin therapy [11]. The only remaining option was to get the patient prepped for a course of apheresis therapy, which, after the difficulties of preparation for this treatment, was initially tolerated well and without issue. However, the iron deficiency anemia is quite noteworthy in this case.

Apheresis for hyperlipidemia is not unlike dialysis for kidney failure, and presents many of the same issues. One such issue common is anemia, particularly iron deficiency anemia. While classically the patient undergoing dialysis suffers from an iron deficiency anemia due to hemolysis, in this patient the haptoglobin is within normal range. This signifies that it is unlikely that the red blood cells are being destroyed in a hemolytic manner. In one of the progress notes for this patient, it is noted that there has always been an underlying anemia that presented itself most severely on the day the patient complained of stomach pains and fatigue. At this time, the patient’s hemoglobin was 7.2 g/dL and transfusion was undertaken. Upon further research, a possibility is that iron deficiency anemia is to be expected of other patients in a similar situation. A study had been done on rats where they were diet-induced into a high-fat state; what the researchers noted was that their iron requirements were higher than normal [12]. It is interesting to note that in that experiment the iron requirements were not dependent on inflammation, hepocidin, or intestinal iron absorption.

Conclusion

Familial hyperlipidemia is a fairly common disease and has multiple presentations depending on gene expression,
environmental factors and genotype. Its severity governs the course of treatment: for mild cases lifestyle modifications prove sufficient; moderate severity dictates pharmacotherapy as the best option (with some caveats); and in severe cases, treatment may go as far as lipid apheresis [12,13]. As lipid apheresis is relatively uncommon, the anemia that preceded the initial wave of treatment could not fully be explained given the lab data taken directly after the patient’s initial symptoms.

The treatment course will be based entirely on her lipid profile in future visits. The current guidelines state that a borderline hyperlipidemia patient is to undergo a lifestyle modification with exercise and low fat diet, the moderate severity patient is to undergo a trial of statin therapy unless under the age of 10, in which case careful consideration must be taken to assess the risk of cardiovascular disease. The severe cases undergo a trial of statin therapy and, if resistant to the therapy, are given a course of lipid apheresis [9]. The anemia is to be treated in a similar manner, where hemoglobin levels under 7 require transfusions and levels under 11 are given a course of ferrous sulfate to try and correct the iron deficiency [5].

As of now, there appears to be an understanding that having iron deficiency anemia may result in hyperlipidemia, but the link to show the opposite in humans still remains; see table 1 for a summary of all the different sources noted on the study of iron deficiency anemia and lipids. One study showed that the opposite phenomenon occurs in women aged 15–50: as the iron profile decreases the lipid profile follows, potentially giving some insight into why there are fewer cardiovascular incidents in the female population [14–16]. However, the issue is that there may be a confounding bias in terms of estrogen, as this will not be present in the patient discussed in this paper. Furthermore, the remaining sources show that when rat pups are subjected to similar lipid levels they also follow a pattern not unlike that of the patient here.

As there may be a relationship between hyperlipidemia and iron levels in the blood, further investigation may be warranted in plotting lipid panels and iron deficiency anemia in the pediatric population. In presenting this patient we bring attention to an unusual treatment course of an otherwise well documented disease, and a possible link between familial hyperlipidemia and iron deficiency anemia.

Acknowledgments

We thank Pediatrics and Adolescent Medicine for their support of this paper.

References

1. Grundy SM (1991) George Lyman Duff Memorial Lecture. Multifactorial etiology of hypercholesterolemia. Implications for prevention of coronary heart disease. Arterioscler Thromb 11: 1619-1635. Link: https://goo.gl/To45Fv

2. Venkatesan S, Cullen P, Pacy P, Halliday D, Scott J (1993) Stable isopes show a direct relation between VLDL apoB overproduction and serum triglyceride levels and indicate a metabolically and biochemically coherent basis for familial combined hyperlipidemia. Arterioscler Thromb 13: 1110-1118. Link: https://goo.gl/PPRksKV

3. Jarvik GP, Brunzell JD, Austin MA, Krauss RM, Motulsky AG, et al. (1994) Genetic predictors of FCHL in four large pedigrees. Influence of ApoB level major locus predicted genotype and LDL subclass phenotype. Arterioscler Thromb 14: 1687-1694. Link: https://goo.gl/5Hx7a

4. Williams RR, Hopkins PN, Hunt SC, Wu LL, Hasstedt SJ, et al. (1990) Population-based frequency of dyslipidemia syndromes in coronary-prone families in Utah. Arch Intern Med 150: 562-568. Link: https://goo.gl/Njt6NC

5. Bruno de Benoist, Erin McLean, Ines Egli, Mary Cogswell (2008). WHO global database on anemia. Retrieved 07 11, 2017, from Worldwide prevalence of anemia 1993-2005: Link: https://goo.gl/Cjr4zV

6. Kassebaum NJ, Jasrasaria R, Naghavi M, Wulf SK, Johns N, et al. (2014) A systematic analysis of global anemia burden from 1990 to 2010. Blood 123: 615-624. Link: https://goo.gl/JK0Tun

7. Özdemir A, Sevinç C, Selamet U, Türkmen F (2007) the use of statins in pediatrics: knowledge base, limitations, and future directions. Pediatrics 119: 370-380. Link: https://goo.gl/zznM2w

8. Guthrie HA, Froozani M, Sherman AR, Barron GP (1974) Hyperlipidemia in Offspring of Iron-deficient Rats. The Journal of Nutrition 104: 1273-1278. Link: https://goo.gl/SedMeR

9. Belas B, Belamarich PF, Tom-Rezvon C (2007) the use of statins in pediatrics: knowledge base, limitations, and future directions. Pediatrics 119: 370-380. Link: https://goo.gl/zznM2w

10. Bertinato J, Aroche C, Plouffe LJ, Lee M, Murtaza Z (2014) Diet-induced obese rats have higher iron requirements and are more vulnerable to iron deficiency. Eur J Nutr 53: 885-895. Link: https://goo.gl/ga5Mbcu

Table 1: A summary of some of the different studies on the subject of iron deficiency anemia and hyperlipidemia. The overall trend with these papers show that anemia and lipid profiles are linked in some capacity. The majority of these papers show that as the iron is removed from the subject the lipid panel worsens. The exception to this is the study on premenopausal women who have a fall in iron and corresponding fall in lipids, and correcting that iron deficiency seems to affect the lipid panel negatively. This was included to bring to attention that the women in this case were older than 15, and the study failed to account for the effects of estrogen.

| Source | Summary |
|--------|---------|
| (Zulak, 1972) | Three groups of rat pups separated by iron levels: very low, low, and normal. The very low group had elevated serum triglycerides, cholesterol and phospholipids. |
| (Barron, 1974) | Two groups of rat pups, one given a diet of 307 ppm of iron or 5 ppm from gestation to lactation. The group fed 5 ppm developed elevated serum triglycerides, cholesterol, and phospholipids. |
| (Moussa NDONG, 2007) | Two groups of rats, both fed low iron diets, were given morina oleifera at different concentrations to see if the hyperlipidemia could be treated. While this resulted in an improvement in the hyperlipidemia, the iron deficiency anemia remained. |
| (Ali Özdemir, 2007) | A study on premenopausal women with respect to iron deficiency anemia and why it may be so prevalent. The report states that the lipids actually decrease with iron levels, giving older women slight protection against cardiovascular diseases. |
| (Sherman, 1979) | This study brought rat pups to a point of hyperlipidemia via deficient diets and noted iron deficiency anemia. Upon supplementing the diet with iron alone, both the lipids and anemia improved. |
| (Bertinato J1, 2014) | This study explored the iron requirements in rats and found that obese rats had a higher iron requirement than the control group. |
11. Gordon BR, Stein E, Jones P, Illingworth DR (1994) Indications for low-density lipoprotein apheresis. Am J Cardiol 74: 1109-1112. Link: https://goo.gl/Sf6LHw

12. Haney EM, Huffman LH, Bougatsos C, Freeman M, Steiner RD, et al. (2007) Screening and treatment for lipid disorders in children and adolescents: systematic evidence review for the US Preventive Services Task Force. Pediatrics 120: 189-214. Link: https://goo.gl/oF6CeY

13. Kwiterovich PO Jr, Coresh J, Bachorik PS (1993) Prevalence of hyperapobetalipoproteinemia and other lipoprotein phenotypes in men (aged<or = 50 years) and women (<or = 60 years) with coronary artery disease. Am J Cardiol 71: 631-639 Link: https://goo.gl/9fM8UV

14. Ndong M, Uehara M, Katsumata S, Sato S, Suzuki K (2007) Preventive Effects of Moringa oleifera (Lam) on Hyperlipidemia and Hepatocyte Ultrastructural Changes in Iron Deficient Rats. Biosci Biotech Biochem 71: 1826-1833. Link: https://goo.gl/zdyFu3

15. Sherman AR (1979) Serum lipids in suckling and post-weanling iron-deficient rats. Lipids 14: 888-892. Link: https://goo.gl/ki3An

16. Sherman AR, Guthrie HA, Wolinsky I, Zulak IM (1978) Iron Deficiency Hyperlipidemia in 18-Day-Old Rat Pups: Effects of Milk Lipids, Lipoprotein Lipase, and Triglyceride Synthesis. J Nutr 108: 152-162. Link: https://goo.gl/AjXdz3