Author’s response to reviews

Title: Case Report of One month and 15 days old baby with Type V Hyperlipoproteinemia

Authors:

Dr. Shabnam dildar (shabnam.dildar@yahoo.com)

Tahir Shamsi (t.shamsi.62@gmail.com)

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Editor-in-Chief

Dr. Aldo Ferreira Hermosillo,

Subject: BEND-D-19-00409R1

Title: Case Report of One month and 15 days old baby with Type V Hyperlipoproteinemia

Dear Dr. Aldo Ferreira,

Thank you so much Sir, for your valuable comments for this case report. All comments and suggestion have been incorporated. All changes made are mentioned below

EDITORCOMMENTS:

1) Comment: In the first version of your manuscript, you cited the use of a Familial Chylomicronemia Syndrome score higher than 10 that indicates a very likely diagnosis. Furthermore, you previously detected a high TG/TC ratio that indicates elevation of chylomicrons and VLDL. Why did you change your initial diagnosis?
1) Response:

a) We delete FCS score because of change in diagnosis, as per expert panel recommendations in 2018 by Philippe Moulin et al. Proposal on FCS score for Identification and diagnosis of patients with familial chylomicronemia syndrome. (J Atherosclerosis 2018; (275): 265-72). The diagnostic performances of the FCS score low in LPL-deficient FCS patients due to a milder phenotype. On comparison they found lower sensitivity of this score in European patients than in Canadian LPL-deficient patients. According to them general applicability of this scoring system in different geographical ancestries and ethnic backgrounds needs additional studies. Furthermore, they stated that this score was based on an initial cohort of 29 patients with an established diagnosis of FCS. However, further validation in additional larger cohorts of patients with FCS from various countries with a different spectrum of loss of function mutations will be needed. This score is also not validated on Pakistani FCS patients.

b) Lipoprotein electrophoresis report showed increase Pre-beta lipoproteins or VLDL 51.5 % (RR 5-22 %) and Chylomicrons 4.7 % (RR 0-2 %) both increased in type 5 HLP.

c) A high TG/TC ratio indicates elevation of Chylomicrons and VLDL, which is important feature of type 5 hyperlipoproteinemia, we did not delete it is present discussion and conclusion section, line no 189-191.

2) Comment: The time of the lab testing is confounding. There is a basal lipid profile then in the previous version you showed labs at 2 and 3 months (these last ones after treatment). Now, in the current version you show an electrophoresis performed at 2 months with 16 days. Why you didn't show it in the previous version?

2) Response: Patient was diagnosed as Hyperlipidemia at age of 1 month and 15 days and he was started Cholesystramine (Questran sachet) powder at dose of 100 mg/kg on t.i.d basis with NAN-1 formula milk at the age of 1 month and 15 days, his labs done during treatment. His lipoprotein electrophoresis was done at age of 2 month 16 days, on follow up visit he did not show that report to us, may be due to that test was suggested by other endocrinologist on second opinion, we saw that report after some days of follow up, at that time we already submitted the case to your journal.

3) Comment: With respect on the electrophoresis: did it was performed with the patient in treatment (due you state that treatment was initiated at one month with 15 days)? What does this imply? Are we observing a decreased chylomicron levels due treatment effect?
3) Response: Yes, he was started Cholestramine therapy at the age of 1 month and 15 days and lipid electrophoresis done at the age of 2 month 16 days during treatment, decreased Chylomicrons levels due treatment effect.

4) Comment: You state that the treatment consisted in advising the parents to wean him at 3 months and cook his food with olive oil. Is this sentence correct? Why do the physicians decided to wean him at so younger age? What was the specific dietetic treatment?

4) Response: This sentence is not correct, we did not ask mother to start weaning at 3 months of age, as his next follow-up was planned after 3 months and child will have been enter in weaning period so, on mother request proper weaning advices were given.

5) Comment: The authors state that they couldn’t perform a genetic testing. This difficult the proper diagnosis of type V hyperlipoproteinemia. Furthermore, this doesn’t allow us to identify the etiological factors underlying it. The type V hyperlipoproteinemia could be related to genetic factors and acquired or environmental factors (i.e. diabetes, drinking, hormonal therapy, certain drugs, myeloma, SLE, lymphoma, etc). What was the possible explanation for dyslipidemia development in this case? Please revise the manuscript by Gotoda T et al. Diagnosis and management of type 1 and type V hyperlipoproteinemia. (J Atherosclerosis Thromb 2012; 19(1): 1-12).

5) Response:

a) Our limitation was that we did not perform genetic testing because of unavailability of these tests in our country, and patients’ parents were not agreeing to do from any other country due to financial limitation and he is doing with Cholestyramine therapy. We have reviewed the manuscript by Gotoda T et al. Diagnosis and management of type 1 and type V hyperlipoproteinemia. Environmental factors such diabetes, drinking, hormonal therapy, drugs, myeloma, SLE and lymphoma were not present in our patient, and the underlying cause might be genetic. As per Gotoda T et al, Patients with type 5 hyperlipoproteinemia, the presence of underlying diseases or contributing factors such as diabetes, drinking in about 2/3 but not in the remaining 1/3, in our case environmental factors not involved in dyslipidemia development. (added in discussion and conclusion section, line no 206-213)

b) As per Gotoda T et al, the possibility of LPL deficiency is high if the serum TG level is 1,500 mg/dl or high, and if serum total cholesterol level is about 1/10 the serum TG level or lower, Our patient had total cholesterol lower than 1/10 of TG level, the most probable cause of dyslipidemia development is genetic due to LPL deficiency, because he was diagnosed at very
young age (1 month and 15 days), there was no any environmental factor involved, furthermore his TC was lower than 1/10 of serum TG, which gives the possibility of LPL deficiency. The Endocrine Society does not recommend routine measurements of these tests for diagnosis of type HLP. (added discussion and conclusion section, line no 216-225)

6) Comment: Why do the authors didn't evaluate an LPL activity test or quantitative LPL determination?

6) Response: These both tests are not available in our laboratory even not in our country. As per Gotoda T et al, the possibility of LPL deficiency is high if the serum TG level is 1,500 mg/dl or high, and if serum total cholesterol level is about 1/10 the serum TG level or lower. Our patient had total cholesterol lower than 1/10 of TG level, the most probable cause of dyslipidemia development is genetic due to LPL deficiency, because he was diagnosed at very young age (1 month and 15 days), there was no any environmental factor involved, furthermore his TC was lower than 1/10 of serum TG, which gives the possibility of LPL deficiency. (added discussion and conclusion section, line no 216-225)

7) Comment: The manuscript requires a full grammar edition.

7) Response: Grammar correction done

REVIEWER 1 COMMENTS:

1) Comment: The revised manuscript has been appropriately amended, although it is unfortunate the author did not measurement of detail lipid marker such as Apolipoproteins.

So, I have no further comments to this manuscript.

1) Response: Apolipoproteins test and other genetic tests are currently not available in our laboratory even not in our country.

REVIEWER 2 COMMENTS:

1) Comment: The article has the appropriate changes, with the analysis included and the treatment achieved a good control of blood lipids.

1) Response: We changed our diagnosis and done some changes in background and discussion section.