

Name of journal: World Journal of Clinical Cases

Manuscript NO: 39481

Manuscript Type: Review

Dear Editor and reviewers,

On behalf of my co-authors, we would like to appreciate Editor and reviewers for the critical comments and suggestions regarding our manuscript. We have studied the comments of Editor and reviewers carefully and have made the necessary revisions. The comments and suggestions help us improve our manuscript remarkably. Our point-by-point responses to the comments of reviewers have been listed in the following pages.

Additionally, the manuscript has been reviewed by a professional English editor from the biomedical editing company of Nature Publishing Group. The grammatical and spelling errors have been corrected and language polishing has been provided.

Thank you again for publishing our manuscript in the *World Journal of Clinical Cases*.

Sincerely yours,

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Responses to Reviewers' Comments

1 Reviewer's code: 04021299

Comments to authors: A nicely written manuscript with a few suggestions: Word count is too high. Reduce the word count to 3000 words

Response: Thank you for your comments and suggestions. Following your advices, we have reduced the text and references to a great extent.

Comments to authors: Reframe few sentences (Highlighted in the text) and remove the grammatical errors

Response: Thank you so much for your careful review of our manuscript. We have corrected the grammatical errors accordingly. And we have received language editing and polishing service from the biomedical editing company of Nature Publishing Group.

Comments to authors: Provide the dermoscopic pictures.

Response: Thank you for your suggestions. A dermoscopic picture of our LHS patient (Figure 2) has been supplemented in the revised version.

2 Reviewer's code: 02520549

Comments to authors: Dear Editor, thank you very much for the invitation to review this interesting manuscript that is dedicated to Laugier-Hunziker syndrome.

Response: Thank you for your comments and interests.

Comments to authors: The manuscript is very wide and i do not know if it corresponds to the pages allowed by your journal to each paper. I suggest to reduce the Whole manuscript and the number of references (154). I would suggest to reduce the historical parts and to improve the biomolecular and genetic aspects.

Response: Thank you for your comments and suggestions. Following your advices, we have removed the historical parts and reduced the text and references to a great

extent.

Comments to authors: I think that the Readers could get lost in the wideness of the manuscript. The work has many technical and scientific aspects of high level. I would suggest to change the title to : Clinical, dermoscopic and pathological aspects of Laugier-Hunziker syndrome: modern complications.

Response: Thank you for your comments and suggestions. LHS shares some features of labial, oral and nail pigmentation with a variety of conditions ranging from normal variation to a sign of an underlying life-threatening abnormality. Our first aim is to extensively review typical and atypical features of LHS. More importantly, however, labial and oral melanotic macules could be the first sign of some severe systemic diseases or syndromes. Therefore, more important significance of the review is conducive to facilitate differential diagnosis, to promote early recognition of underlying diseases including malignancies and to prevent severe complications. In our review, the word "mystery" implies five meanings: Firstly, multiple labial and oral melanotic macules could be worrisome and affected individuals could feel fearful and anxious. Secondly, LHS is uncommon and most clinicians are unfamiliar with the disorder. Thirdly, the etiology of LHS remains completely unknown and no significant advancement of basal study or pathogenesis has been obtained to date. Fourthly, although labial and oral melanotic macules might appear trivial and insignificant, undiscovered underlying diseases could be malignancies or bring about severe complications. Finally, the conditions associated with labial and oral melanotic macules are numerous and a wide differential diagnosis is very complicated and challenging. After careful thought, we decide to maintain the previous title.

3 Reviewer's code: 00646569

Comments to authors: The manuscript discuss characteristics and differential diagnosis of Laugier-Hunziker syndrome. The manuscript in general is interesting and well written but badly organized.

Response: Thank you for your comments and interests.

Comments to authors: There are some minor English language grammatical and some letter mistakes, please revise them. (like "A extensive", "There is also no a systemic abnormality" "Involved locations distribution" "patents with LHS occur longitudinal melanonychia" "malanocytic" "sliver" "Hunzker" "scanty and body hair" "resulting in copious melanin Production" "causative drug ceasing" "incontinent pigmentation" "most exogenous brown to black pigmentation - lack verb- due to dirt,..." "exogenous pigmentation dose - does- not manifest"

Response: Thank you so much for your careful review of our manuscript. We have corrected the grammatical and spelling mistakes accordingly. And we have received language editing and polishing service from the biomedical editing company of Nature Publishing Group.

Comments to authors: Introduction: You arranged your first 87 references according to year in increasing order but it is better you organize them in the order of mentioning in the subsequent text. like 1-4 for 20,39,56,71 and 5-9 for 49,55,64,80,87. They seem haphazardly organized.

Response: Thank you for your comments and suggestions. We have reorganized the references and modified their order in the subsequent text accordingly.

Comments to authors: There is an additional ref for LHS numbered 103.

Response: Thank you for your reminding. The reference No.103 is a review paper and no case has been reported in the paper. In the revised version, we have rearranged the reference as No.2.

Comments to authors: It would be marvelous to present dermoscopic and pathological photographs of your own patient in fig 1.

Response: Thank you for your suggestion. Dermoscopic and pathological photographs of the LHS patient (Figure 2 and Figure 3) have been supplemented in the revised

version.

Comments to authors: You arranged discussion of differential diagnosis of mucocutaneous pigmentation in a chaotic order. It will be better you arrange this section in the order of table 3 and figure 2 (like you arranged the section of differential diagnosis of melanonychia)

Response: Thank you for your comments and suggestions. We have reorganized the contents on differential diagnosis of mucocutaneous pigmentation and modified the order accordingly.

Comments to authors: You discussed carcinogenicity in PJS very well. But you did not mention which cancers occur in McCune-Albright syndrome and Neurofibromatosis type 1.

Response: Thank you for your comments and suggestions. We have supplemented the texts on malignancies potentials occurring in McCune-Albright syndrome and Neurofibromatosis type 1 accordingly.

Comments to authors: You give full title of genes in other sections but not in LEOPARD syndrome, give full names for PTPN11, RAF1, BRAF and MAP2K1 genes.

Response: Thank you for your comments and suggestions. We have supplemented full names for PTPN11, RAF1, BRAF and MAP2K1 genes in the revised version.

4 Reviewer's code: 00505467

Comments to authors: First of all this is an extensive manuscript on Laugier-Hunziker syndrome that the title does not reflect the hypothesis proposed. In detail the title should omit the word "mystery" more appropriate for Hollywood movies and consider words like educational review (since this is definitely NOT a systematic review just by considering the lack of criteria), and it is being presented more in educational manner.

Response: Thank you for your comments and suggestions. In fact, the word "mystery" has been commonly used in titles of basal or clinical papers (Examples of references were list below). In our review, the word "mystery" implies five meanings: Firstly, multiple labial and oral melanotic macules could be worrisome and affected individuals may feel fearful and anxious. Secondly, LHS is uncommon and most clinicians are unfamiliar with the disorder. Thirdly, the etiology of LHS is completely unknown and no significant advancement of basal study or pathogenesis has been obtained to date. Fourthly, although labial and oral melanotic macules might appear trivial and insignificant, undiscovered underlying diseases could be malignancies or bring about severe complications. Finally, the conditions associated with labial and oral melanotic macules are numerous and a wide differential diagnosis is very complicated and challenging. After careful thought, we decide to maintain the previous title.

Examples of references:

1. De Souza RA. **Mystery behind** Bowen-Conradi syndrome solved: a novel ribosome biogenesis defect. Clin Genet,2010,77(2):116-8.
2. Abdul Rahman MZ, Salleh AB, Abdul Rahman RN, Abdul Rahman MB, Basri M, Leow TC. Unlocking the **mystery behind** the activation phenomenon of T1 lipase: a molecular dynamics simulations approach. Protein Sci, 2012,21(8):1210-21.
3. Singh H, Tripathi A, Kar SK. The Girl Shedding Glass Pieces from Her Body Parts: Unfolding the **Mystery Behind** Dermatitis Artefacta. Indian J Dermatol, 2016,61(2):193-5.
4. Ji P, Manupipatpong S, Xie N, Li Y. Induced Pluripotent Stem Cells: Generation Strategy and Epigenetic **Mystery behind** Reprogramming. Stem Cells Int,2016:8415010.
5. Bwire G, Mwesawina M, Baluku Y, Kanyanda SS, Orach CG. Cross-Border Cholera Outbreaks in Sub-Saharan Africa, the **Mystery behind** the Silent Illness: What Needs to Be Done? PLoS One,2016,11(6):e0156674.
6. Hajjar KA. Central venous catheter thrombosis and the fibrin sleeve: unraveling the **mystery**. Eur J Haematol. 2017, 98(4):318-319.
7. Clark D, Febbraio M, Levin L. Aggressive periodontitis: The unsolved **mystery**. Quintessence Int, 2017;48(2):103-111.
8. Charlier P, Deo S. The Anna O. **mystery**: Hysteria or neuro-tuberculosis? J Neurol Sci. 2017 Oct 15;381:19.
9. Lamotte G. Author response: **Mystery** Case: A case of fulminant encephalopathy in a 69-year-old woman. Neurology, 2018, 90(15):714.
10. Marafioti V, Turri G, Carbone V, Monaco S. Association of prolonged QTc

interval with Takotsubo cardiomyopathy: A neurocardiac syndrome inside the mystery of the insula of Reil. Clin Cardiol, 2018,41(4):551-555.

Comments to authors: Additionally, since it is NOT a chapter of a book 28 pages (and about 7000 words) are extremely analytic even for an educational review, the authors should consider being more laconic, and sections like "NOMENCLATURE" which is more like an historic review, should be omitted.

Response: Thank you for your comments and suggestions. Following your advices, we have omitted the "NOMENCLATURE" section and reduced the text and references to a great extent. Now the manuscript appears more laconic. We hope the revised version is fit for publication.

Comments to authors: On the other hand, figures are missing; such a descriptive review that considers many observational criteria for a clinical entity should comprise more pictures (figures) of the described clinical observations, especially in the "CLINICAL CHARACTERISTICS", "DERMOSCOPIC FEATURES", "PATHOLOGICAL CHARACTERISTICS", and "DIFFERENTIAL DIAGNOSIS" sections.

Response: Thank you for your suggestions. Dermoscopic and pathological photographs of the LHS patient (Figure 2 and Figure 3) have been supplemented in the revised version. Additionally, too much figures seem no be suitable for a review, but a book. Moreover, you and other reviewers intensively concern that the length of our article. So we would like to further discuss the differential diagnosis of mucocutaneous pigmentation in the future.

Comments to authors: Furthermore, sections like “discussion” about the necessity of such a review manuscript, which aspects of this syndrome should be enlightened, what this manuscript offers in science, which are the future perspectives, are totally absent.

Response: Thank you for your comments and suggestions. Firstly, LHS is uncommon for most clinicians so far. The etiology of LHS is completely unknown and no

significant advancement of basal study or pathogenesis has been obtained to date. There is few literatures on etiology, pathogenesis and management of LHS. We do our best to search and review the literatures. We really want to present some highlights in science, enlightening and perspectives of the syndrome, but we are sorry that we can not express some opinions without any reliable evidence. Certainly, we would like to discuss any advancement on the syndrome in the future.

Comments to authors: Especially the "DIFFERENTIAL DIAGNOSIS" section, should NOT be so descriptive of other clinical entities (15 pages on that section is more like a section of a chapter of a classical medical handbook), but rather be more focused on how to achieve differential diagnosis with tables and algorithms (possibly an algorithmic figure unfolding the differential diagnosis steps would be the most suitable).

Response: Thank you for your comments and suggestions. Following your advices, we have and reduced the text of the section to a great extent. Actually, several tables and an algorithmic figure using tree diagram method aim to facilitate differential diagnosis. A great number of conditions associated with labial, oral and nail pigmentation need a wide differential diagnosis involving various specialties, including Departments of Oral Medicine, Dermatology, Gastroenterology, Gynecology, Endocrinology Cardiology, Orthopaedics, Oncology, etc. A flow chart of differential diagnosis seems not to be fit for various specialties and conditions. In CONCLUSION section, we summarized an universal differential diagnosis steps, which may be suitable for most clinicians of various specialties. In detail, each specialist may have their own guideline and key experiences for differential diagnosis in their specialty. Moreover, you and other reviewers intensively concern that the length of our article. So we would like to further discuss the differential diagnosis of mucocutaneous pigmentation in the future.

Comments to authors: Grammatical, spelling and syntax errors should be corrected. References are updated and adequate.

Response: Thank you for your suggestions. We have received language editing and polishing service from the biomedical editing company of Nature Publishing Group. We have corrected the grammatical, spelling and syntax errors accordingly.

Comments to authors: Abbreviations like "LHS" should be explained first time met in the text, and used thereafter.

Response: Thank you for your suggestions. "LHS" has been explained in the INTRODUCTION section when it first appeared in the text.