

Response to reviewer comments:

Reviewer #1: The main scope of the review of Singh et al. was to offer to the reader a comprehensive “understanding” of the disease. They debated: epidemiology, genetics, pathogenesis, clinical features, evaluation (diagnosis), treatment, controversies in management and prognosis.

The manuscript mostly reports what is known in the literature without providing an appropriate list of supporting references; moreover, the authors added a personal contribution only in the paragraph discussing the controversies in the management of the disease.

GENERAL COMMENTS

The title reflects the main subject/hypothesis of the manuscript. The abstract summarizes and reflects the work described in the manuscript, and the same do the key words. A specific comment of the background, methods, and results, and discussion does not apply. Figures are of good quality while the table should be more detailed. The manuscript lacks of appropriate references in the introduction and other sections. The quality and organization of manuscript is good.

Response: Thank you for your valuable opinion. We have elaborated the table 1, added the appropriate references wherever required.

Specific comments:

ABSTRACT

Line 5: change “transaminasemia” with “increase of transaminase”

Response: Changed accordingly

Line 6: rephrase “and even liver failure rarely” as follows “and rarely liver failure”

Response: Modified as suggested

CORE TIP

Line 1: remove “that occurs”

Response: Removed

Line 5: change “same” with “disease”

Response: Changed as suggested

INTRODUCTION

Lines 5-10: sentences are not supported by any references.

Response: Adequate references cited for the sentences from line 5-10 (ref 3 and 4)

GENETICS

Lines 1-10: the entire first part of the paragraph lacks of appropriate references

Response: Lines 1-10 are now supported by references 6-8

Line 5: explain what “in silico tools” are and add a reference.

Response: In silico tools explained from line 5-8 with references 7 and 8.

PATHOGENESIS

Line 1: eliminate “is expressed in the liver, kidney and small intestine” since it is a repetition.

Response: Removed

Line 5-7: you report the presence of aldolase isoenzymes. Explain their physiological role and/or their involvement in the disease and add references.

Response: Physiological role of Aldolase A and C is explained from line 8-11 with ref 14-16.

CLINICAL FEATURES

The entire paragraph should be restructured. At the beginning it should made clear that there is not a genotype-phenotype correlation, and then you should describe the classical presentation in infants with the liver failure variant, and the presentation in adults.

Response: The paragraph has been restructured as suggested with addition of some more information on clinical features along with references.

The reference 15 should be used also in the introduction.

Response: Ref 15 is used in introduction and with revised ref no. 4.

EVALUATION

Line 2-3: you should explain in details “the bedside screening test”. What are the non-glucose-reducing substances?

Response: We have explained in details about the non-glucose reducing sugars and their implication as a bedside screening test from line 16-19. In addition, we have also discussed the pitfalls in diagnosis of HFI from line 2-15 with proper references.

Line 9: at the end of the sentence it is necessary to add a reference.

Response: reference added, no.33

TREATMENT

Table 1 is too generic.

Response: Table 1 elaborated.

At the end of the paragraph add more detail on vitamins and nutritional deficiencies (references)

Response: details on vitamin def added with ref no 34.

CONTROVERSIES IN MANAGEMENT

This is the only paragraph that contains comments and suggestions from the authors. This is the only personal contribution of the authors to the review.

Response: We have added on few lines on liver histology controversies with ref 43. Also, controversies regarding vaccination is included with ref 44-46.

PROGNOSIS

It is partially in contrast with what previously described. Support your conclusions with longitudinal studies (references).

Response: In lack of longitudinal studies, we have modified our prognosis part supported by adequate references 19,20 and 26.

Editorial Office's comments

Science Editor: Specific Comments To Authors: This manuscript provided an overview of hereditary fructose intolerance.

1) Table 1 needs more detail; -

Response: Table 1 has been elaborated

2) please add aldolase isoenzymes' hysiological role and/or their involvement in the disease;

Response: Physiological role of Aldolase A and C is explained from line 8-11 with ref 14-16

3) CLINICAL FEATURES section please reorganize;

Response: Reorganized.

4) please add more details on vitamin and nutrient deficiencies;

Response: adequate details added with references

5) in the manuscript, in the Introduction and some other sentences lack necessary references, please add them.

Response: Appropriate references added wherever required.