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OPEN PEER REVIEW

Introduction of a Novel Cut-off in Newborn Screening of Galactosemia; A Cohort Study

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About this report

This open peer review (OPR) report shows the public comments made on this article during peer review, by the reviewers, the associate editor and the editor-in-chief, for every revision round, together with the authors' replies. Comments appear only with the consent of the people who wrote them. Reviewers who chose to sign their report are named; the others are shown as "Referee". Comments are edited for language only, and confidential remarks to the editors are not included.

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1 Original submission

1 comment · 27 Jul 2024

Referee 1 Reviewer

MAJOR REVISION 27 Jul 2024

Dear author
2 important points must be mentioned:
1- confirmatory test
2- the method of screening in other parts of the world
The manuscript should be edited by a native English speaker.

2

Revision 1

AUTHORS' RESPONSE TO REVIEWERS

Authors' reply to reviewers

The next pages contain the authors' point-by-point reply to the comments of this revision round, as submitted with the revised manuscript. It is published as the authors wrote it.

8/12/2024

Editor-in-Chief

Iranian Journal of Pediatrics

Dear Editor:

Subject: Submission of revised paper our manuscript entitled **"Introduction of a Novel Cut-off in Newborn Screening of Galactosemi**" manuscript ID: 142691.

Thank you for your email dated [29 July 2024] enclosing the reviewers' comments. We have carefully reviewed the comments and have revised the manuscript accordingly. Our responses are given in a point-by-point manner below. Changes to the manuscript are shown in underline/red/bold.

We hope the revised version is now suitable for publication and look forward to hearing from you in due course.

Sincerely,

Prof. B G

Professor of Pathology

Shiraz Transplant Research Center,

Shiraz University of Medical Sciences

Reviewers' Comments:

- **Reviewer 1:**

1. Confirmatory test

Author's response: We would like to thank the honorable reviewer for their time and comments and raising an important point here. We should note that the gold standard for laboratory confirmation of galactosemia diagnosis is by a genetic test, however we have mentioned through the manuscript that not all reported patients with galactosemia were confirmed with DNA exome sequencing due to remarkably unbearable financial burden. Newborns who were labeled as positive cases in our study, were confirmed on the basis of either DNA or clinical features which were confirmed by responding to galactose restricted diet which was feasible in the clinic.

We acknowledged this limitation (We had added these limitations to the manuscript for future studies) and recommended that future studies could address these aspects.

2. the method of screening in other parts of the world

Author's response: We appreciate the reviewer's feedback; we have added related references of other screening methods for galactosemia in clinical practice per the honorable reviewers comment and we have also added a paragraph to the introduction in this regard.

3. native English edition should be done

Author's response: We went through the entire manuscript to correct possible grammatical and English errors as requested.

- Reviewer 2:

1. Overall, this study makes a meaningful contribution to optimizing newborn screening for galactosemia and the findings appear to be clinically relevant. The methods are sound and the conclusions are well-supported by the data presented. With some major revisions, this paper would likely be suitable for publication.

Author's response: We appreciate the honorable reviewer attention to detail.

2. More details on the confirmatory testing methods used for diagnosis could be helpful.

Author's response: The authors appreciate your comments. We revised and mentioned that confirmatory test on the basis of either DNA or clinical features. It was confirmed by responding to galactose restricted diet which was feasible in the clinic.

3. Further discussion of the clinical implications and potential cost savings of the proposed new protocol.

Author's response: Thank you for bringing this to our attention. We added a paragraph to discussion section in this regard.

4. Clarification on how false negatives were identified.

Author's response: The authors are thankful for your reminder. The false-negatives associated with TGAL in the range of our screening are not common, and such patients are likely to present clinically. However, our recent experience with missed cases is nevertheless concerning. During follow-up evaluations, we identified instances of false negative results in patients with classical galactosemia. Despite initial negative test outcomes, these patients exhibited clinical features consistent with the disorder, such as liver dysfunction, susceptibility to infections, and failure to thrive. This discrepancy underscores the importance of comprehensive clinical assessments in conjunction with laboratory tests to ensure accurate diagnosis and effective management of classical galactosemia. Further work is required to establish the optimum screening strategy, to maximize the early detection of CG without excess false-positives.

5. Consider including a table summarizing key characteristics of true positive vs. false positive cases.

Author's response: Thank you for bringing this to our attention. We added a table in this regard.

6. References are too old.

Author's response: We appreciate your comment. We revised some references.

Abstract section:

7. ABSTRACT should be modified as Structured ABSTRACT.

Author's response: Thank you for pointing this out. We revised the abstract section into structured.

8. The abstract could be more concise. Some sentences could be shortened or combined.

Author's response: Thank you for your comment. We corrected and revised.

9. The specificity for the 7.35 mg/dl cut-off is listed as 49.2% in the abstract but 95.7% in the results. This discrepancy should be corrected.

Author's response: Thank you for bringing this discrepancy to our attention. We revised the generally.

10. Consider adding a brief conclusion statement at the end.

Author's response: Thank you for your valuable note. We have incorporated your suggestion and added a paragraph as a conclusion in the abstract.

Introduction section:

11. providing more specific data on false positive rates from other studies

Author's response: The authors appreciate your attention to detail. Upon reviewing your comment, we would like to point out that in second paragraph of introduction section the authors discussed different multiple tests which had been reported universally, with different rationales and mechanisms of action (such as: microbiological, fluorometric, colorimetric, tandem mass spectrometric, and a quantitative measurement of total galactose). Plus, we have mentioned that yet false-negative and false-positive results are encountered, and hence the tests are non-specific.

12. Briefly discussing the consequences of false positives (e.g., unnecessary stress, costs)

Author's response: Thank you for the feedback. We added a paragraph explaining how high rates of false positive cases in newborn screening can have several significant consequences.

13. Explaining more clearly why total galactose (TGAL) was chosen as the screening method

Author's response: There has been discussion about newborn screening for classic galactosemia for a long time, but there is still no agreement in place. There is no universal agreement on galactosaemia NBS, highlighting the uncertainties regarding the balance between effectiveness, cost-effectiveness and accuracy of existing screening methods. Currently, there are different screening methods for galactosemia, and the most common of which measure quantifying the activity of GALT enzyme or quantifying total blood galactose (TGAL), which represents the sum of galactose and Gal-1-P on a dry blood spot (DBS) using a fluorometric assay. However, a common practice among screening centers is to solely rely on the TGAL test as the initial screening test which is suitable for mass screening, but it carries high false-positive and false-negative results.

Method section:

14. More details on how false negatives were identified and confirmed

Author's response: During follow-up evaluations, we identified instances of false negative results. We added more details on how false negatives were identified and confirmed in the method section.

15. Clarification on the criteria used for clinical diagnosis in cases without genetic confirmation

Author's response: the authors are grateful for the reviewer's kind reminder. We have clarified the inclusion criteria in the manuscript as requested.

16. If it is part of a national study, it should be mentioned in the method section.

Author's response: we have added a sentence upon honorable reviewer suggestion that every child with galactosemia born in Fars province, Southern west Iran will have a diagnosis and be on treatment within the first week of life.

17. Information on ethical approval and consent procedures

Author's response: we had added the ethical approval code in the method section**. "**Patients' data including TGAL level, hospital admission, and number of true positive cases for assessing the most effective cut-off value of the used screening method were provided by the department of non-communicable diseases research center, Shiraz University of Medical Sciences, Shiraz, Iran. All protocols in this study have received approval from the Ethics Committee of the Shiraz University of Medical Science, as indicated by the ethical code: **IR.SUMS.MED.REC.1401.539.** Moreover, the study was conducted in strict adherence to the applicable guidelines, regulations, and the principles outlined in the Declaration of Helsinki. To ensure privacy and confidentiality, patient information was anonymized prior to analysis, and the researcher took necessary measures to maintain data confidentiality".

18. Explanation of why DNA analysis was not performed for all cases.

Author's response: During the study, genetic testing was not conducted for all cases due to the significant financial burden, a practice consistent with other studies that did not utilize genetic methods. Furthermore, some cases were clinically distinguishable without the need for genetic analysis, showing symptoms of galactosemia clearly. Consequently, genetic analysis, which can be expensive, was not performed in these instances.

19. More details on the statistical analysis, particularly the ROC curve methodology

Author's response: Thank you for raising this point. We added further details on how ROC curve methodology works.

Results section:

20. The discrepancy in specificity values for the 7.35 mg/dl cut-off between abstract and results

Author's response: Thank you for bringing this discrepancy to our attention. We revised the generally.

21. Lack of demographic data or characteristics of true positive vs false positive cases

Author's response: The lack of demographic data or differentiation between true positive and false positive cases can be attributed to the fact that the original data collection began in 2006, and not all patient documents were accessible for the assessment of demographic information. This limitation has been acknowledged in the study's limitation section.

22. No information on the clinical outcomes of the identified cases

Author's response: The authors are grateful for the reviewer's kind reminder. However, another limitation was that the initiation of conducting original data collection was in 2006 and not all patients' documents were available for assessing follow up laboratory data.

23. Limited data presented on false negative cases

Author's response: the authors are grateful for the reviewer's kind reminder. However, another limitation was that we only had access quantitative measurement of total blood galactose and no further information.

Discussion section:

24. Provide more in-depth comparison with other studies' cut-off values and screening protocols

Author's response: We appreciate your comment. We revised Discussion section thoroughly. We hope it meets your expectations.

25. Discuss potential clinical and economic impacts of implementing the proposed new cut-offs

Author's response: we appreciate the honorable reviewer for pointing out this note. We accordingly added further details

26. Address limitations more thoroughly, including the lack of genetic confirmation for all cases

Author's response: The authors are thankful for your reminder. We have mentioned in the last paragraphs of our discussion one of the most important limitations of our study was that not all reported patients with galactosemia were confirmed with DNA exome sequencing due to remarkably unbearable financial burden.

27. Suggest specific next steps for validating and implementing the proposed screening protocol

Author's response: Thank you for your comment. We discussed more.

References section:

28. Some are quite old (e.g., from the 1940s and 1960s). While these may be seminal papers, it would be beneficial to include more recent literature, particularly on current screening practices and outcomes. Consider adding references from the past 5 years to ensure the most up-to-date information is included.

Author's response: We appreciate your comment. We revised the old references with new one.

2 Revision 1

0 comments

No public comments in this round.

3

Revision 2

AUTHORS' RESPONSE TO REVIEWERS

Authors' reply to reviewers

The next pages contain the authors' point-by-point reply to the comments of this revision round, as submitted with the revised manuscript. It is published as the authors wrote it.

9/02/2024

Editor-in-Chief

Iranian Journal of Pediatrics

Dear Editor:

Subject: Submission of revised paper our manuscript entitled **"Introduction of a Novel Cut-off in Newborn Screening of Galactosemi**" manuscript ID: 142691.

Thank you for your email dated [1 September 2024] enclosing the reviewers' comments. We have carefully reviewed the comments and have revised the manuscript accordingly. Our responses are given in a point-by-point manner below. Changes to the manuscript are shown in highlighted lines/paragraphs.

We hope the revised version is now suitable for publication and look forward to hearing from you in due course.

Sincerely,

Prof. B G

Professor of Pathology

Reviewers' Comments:

- **Reviewer 1:**

    1. I reviewed the second revision of the article. All the requested changes applied, and the paper also upgraded in the whole sighting. I have no more comments.

Authors' response: The authors are grateful for the reviewer positive feedback and kind encouragements.

- **Reviewer 2:**

2. Thank you for revising your manuscript, now it is more suitable for publication but I think that you should emphasis that " we use this method because of limitation of resources ", in line 195 adept is better to replace with powerful.

Authors' response: we appreciate the honorable reviewer attention to details and kind thoughtful reminder. We revised and clarified as you suggested.

3 Revision 2

0 comments

No public comments in this round.