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OPEN PEER REVIEW

Pituitary Gland Morphology: A Novel Diagnostic Marker for Differentiating Growth Hormone Deficiency from Idiopathic Short Stature in Children

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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

3 comments · 19 Mar 2024 – 8 Apr 2024

Reza Tavakolizadeh Reviewer

MINOR REVISION 19 Mar 2024

Hello and thank you for your valuable effort to prepare this article.

I will present a few things to improve the article.
 Please mention the ethical code of the study accurately and preferably in the form of a valid link.
 Which standard test is used to diagnose growth hormone deficiency? I mean, which growth hormone stimulation test is used? Please specify the test.
 Please mention what criterion is used to determine bone age.
 In Tables 1 and 3, a term that needs further explanation is used. Despite the proposed explanation (chronological age minus bone age), "Time of growth failure" is not well known. To compare "bone age" with "chronological age", tables and charts are used, based on which the delay in bone age is defined and expressed with a standard deviation.

Referee 1 Reviewer

MINOR REVISION 7 Apr 2024

I appreciate the efforts you have put into the study. Overall, the manuscript presents valuable findings; however, there are some points that need to be addressed for further improvement:

Abstract
1. Lack of clear objectives: Although the abstract mentions the objective of finding differences in pituitary gland morphology for differentiation between GHD and ISS, it does not explicitly state why it is important to differentiate between the two conditions or how this differentiation can impact patient management or treatment decisions.
2. Insufficient details about methods: The abstract lacks important details about the study design, patient selection criteria, specific measurements taken during the assessments, and statistical analysis.

Introduction
3. Lack of a clear rationale for the study: The introduction does not clearly explain why investigating the correlation between pituitary gland morphology and GH levels in children with GHD or ISS is important. It would be useful to highlight the potential benefits of identifying a noninvasive and convenient method for distinguishing between GHD and ISS, such as improving diagnostic accuracy and reducing the need for invasive tests.

Methods
4. Lack of information on sample size calculation: The methods state that 205 patients were enrolled, including 83 with ISS and 122 with GHD, but there is no explanation or justification provided for this sample size. It is important to include information on how the sample size was determined or whether any power analysis was conducted.
5. Potential Confounding Variables: The study does not provide information about potential confounding variables that may influence the results. Factors such as age, sex, pubertal stage, and underlying medical conditions could affect pituitary gland morphology and should be considered as potential confounders.
6. Lack of Blinding: It is not mentioned whether the researchers who assessed the pituitary gland morphology were blinded to the diagnosis of the patients. Lack of blinding introduces the possibility of observer bias, where the knowledge of the patient's diagnosis could influence the interpretation of the imaging results.

7. Insufficient information on the ethics approval and informed consent: The methods mention that the study was approved by the Hospital Ethics Committee, but no details are provided on the specific approval number or the ethical considerations addressed.
8. Statistical analysis
a. Insufficient reporting of quantitative data: The methods mention that quantitative data were expressed as mean ± standard deviation (SD). However, important details such as the specific variables analyzed and the units of measurement are missing.
b. Incomplete description of t-test usage: The methods state that t-tests were used for comparison between two groups. However, no information is provided on the type of t-test used (e.g., independent samples t-test, paired t-test) or the assumptions underlying the tests (e.g., normality, equal variances).
c. Incomplete explanation of correlation analysis: The methods state that Pearson's linear correlation was used for analyzing the correlation between PG features and GH levels. However, no information is provided regarding the interpretation of the correlation coefficients (e.g., strength, direction).
d. Insufficient reporting of ROC curve analysis: The methods mention the use of ROC curves to evaluate the sensitivity and specificity of PG features in the diagnosis of ISS and GHD. However, no information is provided on how the cutoff values for sensitivity and specificity were determined or the thresholds used to define ISS and GHD. Additionally, the methods mention the use of the area under the ROC curve (AUC) to measure accuracy, but no specific AUC values or their interpretation are provided.

Discussion
9. Insufficient explanation of the significance of correlations: Although the discussion states that PG height and volume are positively correlated with GH peak levels, it does not expand upon the significance of these correlations. Further elaboration on the physiological implications and potential mechanisms underlying these correlations would provide a more thorough discussion.
10. Lack of interpretation of findings in the context of the research question: The discussion does not explicitly link the findings back to the research question or objectives stated in the introduction. It would be helpful to explicitly discuss how the identified markers (PG height, volume, and morphology) address the need for a noninvasive method of differentiating ISS from GHD.
11. Absence of future research directions: The discussion does not provide insights into potential future research directions or avenues for further investigation. Including suggestions for future studies, such as exploring additional markers or conducting longitudinal studies, would enhance the completeness of the discussion.

By addressing these points in the revision of your manuscript, you will improve the clarity, completeness, and impact of your research. I look forward to reviewing the revised version.

Editor-in-Chief MINOR REVISION 8 Apr 2024

Dear authors,
Your article needs Minor Revision.
Regards

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.

Reviewer 1:

Have confounding factors such as age been considered in the analysis of the morphology difference of the PG between the two groups?

The shape and volume of the pituitary gland has a certain correlation with age and this change is more pronounced in the middle and late stages of puberty. Therefore, children aged 3-14 years were included in this study to reduce the influence of age on this study. At the data analysis stage, this study also attempted to perform subgroup analysis on age, but due to the small sample size, no significant positive results were found.

Reviewer 2:

1 Please mention the ethical code of the study, accurately and preferably in the form of a valid link.

This study was approved by the hospital ethics committee (No: 2023-136-01). All participants in this study were informed of the examination procedures and precautions prior to the MRI examination, and signed an informed consent form for the MRI examination.

2 Which standard test is used to diagnose growth hormone deficiency? I mean, which growth hormone stimulation test is used? Please mention specifically.

In this study, GHSTs were conducted according to previously reported methods [17]. (Reference: Chesover AD and Dattani MT (2016), Evaluation of growth hormone stimulation testing in children. Clin Endocrinol (Oxf). 84(5): 708-14. DOI: 10.1111/cen.13035.)

As follows: two stimulating drugs, insulin and levodopa, were used for growth hormone stimulation tests. Blood levels of growth hormone were measured before injection, and 30, 60, 90 and 120 minutes after injection

3 Please mention what criterion is used to determine bone age.

Determine bone age by observing the morphology, size, and degree of development of the ossification centres in the left metacarpophalangeal bone, wrist bone, and lower end of the radius and ulna on X-ray examination of the left wrist.

4 In Tables 1 and 3, a term that needs further explanation is used. Despite the

proposed explanation: chronological age minus bone age, "Time of growth failure" is not well known. To compare "bone age" with "chronological age", tables and charts are used, based on which, the delay of bone age is defined and expressed with a standard deviation.

The meaning of " time of growth failure " is that the abnormal bone age refers to chronological age minus the bone age and -1 to 1 indicates normal bone age, >1 indicates delayed bone age, and <-1 indicates advanced bone age.

. We have replaced the “time of growth failure” with the “abnormal bone age” in the article.

Reviewer 3:

1. Lack of clear objectives: Although the abstract mentions the objective of finding differences in pituitary gland morphology for differentiation between GHD and ISS, it does not explicitly state why it is important to differentiate between the two conditions or how this differentiation can impact patient management or treatment decisions.

Growth hormone and insulin-like growth factor-I are the best therapeutic drugs for treating growth hormone deficiency (GHD), but whether suitable for idiopathic short stature (ISS) is still controversial. So, distinguish these two conditions from short stature remains very important. But now, the diagnosis of GHD depends on growth hormone stimulation tests (GHSTs), while the diagnosis of ISS achieved via exclusion, which is invasive. So, a noninvasive and convenient method to distinguish GHD from ISS would be of great importance.

2. Insufficient details about methods: The abstract lacks important details about the study design, patient selection criteria, specific measurements taken during the assessments, and statistical analysis.

Because of the word limit, the method is very simple. We enrolled patients (3-14 years) who presented with SS and underwent GHSTs and PG MRI in our hospital from January, 2020 to October, 2022. Finally, 205 patients were enrolled in total, comprising 83 patients with ISS, and 122 with GHD, and GHD patients were divided into two

groups according to the peak GH level in GHSTs. All patients underwent routine physical examinations, GHSTs, PG MRI, and X-rays of the left wrist. Two authors recorded the features (PG height, length, width, volume, pituitary stalk diameter, pituitary stalk length, and pituitary morphology) separately. The morphology of the PG can be divided into three types: convex, flat and concave. Bone age was estimated from X-rays of the left wrist that were read by an experienced radiologist.

Introduction

3. Lack of a clear rationale for the study: The introduction does not clearly explain why investigating the correlation between pituitary gland morphology and GH levels in children with GHD or ISS is important. It would be useful to highlight the potential benefits of identifying a noninvasive and convenient method for distinguishing between GHD and ISS, such as improving diagnostic accuracy and reducing the need for invasive tests.

Pituitary gland morphology in children is closely related to GH secretion, which is closely related to the aetiology of SS. Investigating changes in pituitary gland morphology in children may indirectly reflect GH secretion. MRI is a non-invasive examination that can clearly show changes in the morphology of the pituitary gland in children. It can not only improve the accuracy of the aetiological diagnosis in children with SS, but also reduce the number of invasive examinations and procedures.

Methods

4. Lack of information on sample size calculation: The methods state that 205 patients were enrolled, including 83 with ISS and 122 with GHD, but there is no explanation or justification provided for this sample size. It is important to include information on how the sample size was determined or whether any power analysis was conducted.

According to Chinese and WHO growth references, the age-standardized and age-gender-standardized prevalence of SS in China were as high as 3.70% and 2.69% in 7–

18 year-old school children, respectively. Using the formula $N = \frac{Z^2 * P * (1-P)}{D^2}$, where N is the sample size, Z is the 95% confidence level, set at 1.96, P is the prevalence of SS, and D is the margin of error (<5%), set at 0.05. Finally, the sample size was increased based on a 20% dropout rate, and the final sample sizes were determined to be 69 and 50, which is smaller than the sample size in this study.

5. Potential Confounding Variables: The study does not provide information about potential confounding variables that may influence the results. Factors such as age, sex, pubertal stage, and underlying medical conditions could affect pituitary gland morphology and should be considered as potential confounders.

The shape and volume of the pituitary gland has a certain correlation with age and this change is more pronounced in the middle and late stages of puberty. Therefore, children aged 3-14 years were included in this study to reduce the influence of age on this study. At the data analysis stage, this study also attempted to perform subgroup analysis on age and sex, but due to the small sample size, no significant positive results were found.

6. Lack of Blinding: It is not mentioned whether the researchers who assessed the pituitary gland morphology were blinded to the diagnosis of the patients. Lack of blinding introduces the possibility of observer bias, where the knowledge of the patient's diagnosis could influence the interpretation of the imaging results.

The researchers assessing the morphology of the pituitary gland retrieve the patient's MRI images directly from our PACS system for measurement and assessment. The researchers are not allowed to view the patient's MR scan report prior to measurement and completion. All morphological parameters are measured independently by two researchers. At the same time, there is no description of relevant pituitary morphological parameters in our diagnostic reporting system.

7. Insufficient information on the ethics approval and informed consent: The methods mention that the study was approved by the Hospital Ethics Committee,

but no details are provided on the specific approval number or the ethical considerations addressed.

This study was approved by the hospital ethics committee (number: 2023-136-01). All participants in this study were informed of the examination procedures and precautions prior to the MRI examination and signed an informed consent form for the MRI examination.

8. Statistical analysis

a. Insufficient reporting of quantitative data: The methods mention that quantitative data were expressed as mean ± standard deviation (SD). However, important details such as the specific variables analyzed and the units of measurement are missing.

Quantitative data such as Birth weight (kg), Birth height (cm), Bone age (y), Time of growth failure (y), GH peak (ng/mL), Pituitary stalk diameter (mm), Pituitary stalk length (mm), PG length (mm), PG width (mm), PG height (mm), PG volume (mm^3), Tuberculum sellae (mm), Dorsum sellae (mm), Cavernous sinus width (mm), Optic chiasma height (mm) and Optic chiasma width (mm), were expressed as mean ± standard deviation (SD), and t-tests were used for comparison between two groups. Categorical data such as Age (y), Male (n, %), Full-term (n, %), Natural birth (n, %), Intrauterine hypoxia (n, %) and Morphology type (n, %) were expressed as n (%), and chi-squared (c2) tests were used for comparison between groups.

b. Incomplete description of t-test usage: The methods state that t-tests were used for comparison between two groups. However, no information is provided on the type of t-test used (e.g., independent samples t-test, paired t-test) or the assumptions underlying the tests (e.g., normality, equal variances).

Quantitative data were expressed as mean ± standard deviation (SD), and two independent samples t-test were used for comparison between two groups.

c. Incomplete explanation of correlation analysis: The methods state that Pearson's linear correlation was used for analyzing the correlation between PG

features and GH levels. However, no information is provided regarding the interpretation of the correlation coefficients (e.g., strength, direction).

Pearson correlation analysis is represented by r, which ranges from -1 to 1. -1 represents a perfect negative correlation, +1 represents a perfect positive correlation, and 0 represents no linear correlation. The closer r is to -1 or +1, the stronger the linear relationship between the two variables.

d. Insufficient reporting of ROC curve analysis: The methods mention the use of ROC curves to evaluate the sensitivity and specificity of PG features in the diagnosis of ISS and GHD. However, no information is provided on how the cutoff values for sensitivity and specificity were determined or the thresholds used to define ISS and GHD. Additionally, the methods mention the use of the area under the ROC curve (AUC) to measure accuracy, but no specific AUC values or their interpretation are provided.

The area under the ROC curve lies between 0 and 1, and the higher the value, the more accurate the prediction. The cut-off value is obtained by calculating the Jordan index (sensitivity+specificity-1), where the diagnostic threshold with the highest Jordan index is the optimal cut-off value, and the sensitivity and specificity of the optimal cut-off value are optimal.

Discussion

9. Insufficient explanation of the significance of correlations: Although the discussion states that PG height and volume are positively correlated with GH peak levels, it does not expand upon the significance of these correlations. Further elaboration on the physiological implications and potential mechanisms underlying these correlations would provide a more thorough discussion.

When blood levels of GH are below normal, the synthesis and secretion of GH can be increased by negative feedback regulation. Long-term insufficient secretion of GH can, to some extent, lead to reactive hyperplasia and hypertrophy of the PG. The height and volume of the PG are therefore closely related to the synthesis and secretion of GH.

Excessive secretion of GH can lead to pituitary hyperplasia or tumours, while insufficient secretion can lead to SS.

10. Lack of interpretation of findings in the context of the research question: The discussion does not explicitly link the findings back to the research question or objectives stated in the introduction. It would be helpful to explicitly discuss how the identified markers (PG height, volume, and morphology) address the need for a noninvasive method of differentiating ISS from GHD.

In summary, the volume, height and shape of the pituitary gland are closely related to the secretion of GH and the aetiology of SS. If the height of the PG is greater than 5.55 mm, the volume is greater than 276.74 mm^3, and the morphology of the pituitary gland is flat type or convex type, we need to consider the ISS more than GHD.

11. Absence of future research directions: The discussion does not provide insights into potential future research directions or avenues for further investigation. Including suggestions for future studies, such as exploring additional markers or conducting longitudinal studies, would enhance the completeness of the discussion.

With the advancement and development of MRI structural imaging and artificial intelligence, we will use high-resolution 3D structural imaging and big data analysis to further explore the morphological differences of the PG in patients with GHD and ISS, providing a potential non-invasive biomarker for the diagnosis and differential diagnosis of the two types of children in clinical practice.

2 Revision 1

4 comments · 30 Apr 2024 – 7 Jul 2024

Referee 1 Reviewer

MINOR REVISION 30 Apr 2024

I would like to express my appreciation for the effort you have made in revising your manuscript based on the initial comments. You have made some appropriate changes that have significantly improved the overall quality of the paper. However, there are a few points that I believe were not adequately addressed and should be taken into account for future revisions.

Firstly, I kindly suggest editing the title as follows: "Pituitary Gland Morphology: A Novel Diagnostic Marker for Differentiating Growth Hormone Deficiency from Idiopathic Short Stature in Children." This revised title accurately reflects the focus of your study and will attract the attention of readers.
Secondly, it is important to mention in both the abstract and the full-text methods that the study design is cross-sectional.
Additionally, I recommend briefly mentioning the names of the statistical tests used in the abstract methods section.
Furthermore, it would be valuable to include information regarding how the sample size was determined or whether any power analysis was conducted in the full-text methods.
Moreover, I noticed that there is no information provided regarding the interpretation of the correlation coefficient values (e.g., strength and direction) in the statistical analysis section.
Lastly, while the methods mention the use of ROC curves to evaluate the sensitivity and specificity of Pituitary Gland (PG) features in the diagnosis of Idiopathic Short Stature (ISS) and Growth Hormone Deficiency (GHD), no information is provided on how the cutoff values for sensitivity and specificity were determined for ISS and GHD.

I look forward to reviewing the revised version of your paper.

Reza Tavakolizadeh Reviewer

MAJOR REVISION 26 May 2024

Thank you for your effort.

Associate Editor

MINOR REVISION 7 Jul 2024

Thanks for the partial revision of your manuscript. Please follow and respond to all of the reviewers' comments.

Editor-in-Chief

MINOR REVISION 7 Jul 2024

Dear authors,
Your article needs Minor Revision.
Regards

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.

Reviewer 1:

1. Firstly, I kindly suggest editing the title as follows: "Pituitary Gland Morphology: A Novel Diagnostic Marker for Differentiating Growth Hormone Deficiency from Idiopathic Short Stature in Children." This revised title accurately reflects the focus of your study and will attract the attention of readers.

We have changed the original title to "Pituitary Gland Morphology: A Novel Diagnostic Marker for Differentiating Growth Hormone Deficiency from Idiopathic Short Stature in Children".

2. Secondly, it is important to mention in both the abstract and the full-text methods that the study design is cross-sectional.

It was clearly stated that the study design was cross-sectional, both in the abstract and in the full text.

3. Additionally, I recommend briefly mentioning the names of the statistical tests used in the abstract methods section.

Statistical tests have been briefly mentioned in the abstract methods section

4. Furthermore, it would be valuable to include information regarding how the sample size was determined or whether any power analysis was conducted in the full-text methods.

In the full-text methods, the sample size calculation method has been added.

Estimating sample sizes

According to Chinese and WHO growth references, the age-standardized and age-gender-standardized prevalence of SS in China were as high as 3.70% and 2.69% in 7–18 year-old school children, respectively. Using the formula $N = \frac{Z^2 * P * (1-P)}{D^2}$, where N is the sample size, Z is the 95% confidence level, set at 1.96, P is the prevalence of SS, and D is the margin of error (<5%), set at 0.05. Finally, the sample size was increased based on a 20% dropout rate, and the final sample sizes were determined to be 69 and 50, which is smaller than the sample size in this study.

5. Moreover, I noticed that there is no information provided regarding the interpretation of the correlation coefficient values (e.g., strength and direction) in the statistical analysis section.

The interpretation of correlation coefficient values has been added to the statistical analysis section

Pearson correlation analysis is represented by R, which ranges from -1 to 1. -1 represents a perfect negative correlation, +1 represents a perfect positive correlation, and 0 represents no linear correlation. The closer r is to -1 or +1, the stronger the linear relationship between the two variables.

6. Lastly, while the methods mention the use of ROC curves to evaluate the sensitivity and specificity of Pituitary Gland (PG) features in the diagnosis of Idiopathic Short Stature (ISS) and Growth Hormone Deficiency (GHD), no information is provided on how the cutoff values for sensitivity and specificity were determined for ISS and GHD.

Added information on cut-off values for sensitivity and specificity for ISS and GHD as follows.

We used receiver operating characteristic (ROC) curves to evaluate the sensitivity and specificity of PG features in the diagnosis of ISS and GHD and the cut-off value is obtained by calculating the Jordan index (sensitivity+specificity-1), where the diagnostic threshold with the highest Jordan index is the optimal cut-off value. The area under the receiver operating characteristic curve (AUC) was used to measure the accuracy and the area under the ROC curve lies between 0 and 1, and the higher the value, the more accurate the prediction.

3 Revision 2

2 comments · 21 Jul 2024 – 4 Aug 2024

Referee 1 Reviewer

ACCEPT 21 Jul 2024

Dear Authors,

Thank you for your diligent efforts in addressing the comments from the previous round of review. Your revisions have significantly enhanced the clarity and quality of the manuscript, and it is now well-prepared for publication.

I would like to point out a minor error: the term "Youden index" is incorrectly referred to as "Jordan index" in a few instances. Please correct this before the final submission.

Congratulations on your work, and I look forward to seeing it published!

Best regards,

Editor-in-Chief

MINOR REVISION 4 Aug 2024

Dear authors,
Your article needs Minor Revision.
Regards

4

Revision 3

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.

Reply to Reviewers

Reviewer 1:

1. I would like to point out a minor error: the term "Youden index" is incorrectly referred to as "Jordan index" in a few instances. Please correct this before the final submission.

The “Jordan index” in the paper has been changed to “Youden index”.

Associate Editor 2

1. please change title Objective in abstract to Objectives.

The title “Objective” in abstract has been changed to “Objectives”.

2. line 10 abstract, Please correct as: “but whether they are suitable for ISS is still controversial”.

The phrase of “but whether suitable for ISS is still controversial” in line 10 abstract has been changed to “but whether they are suitable for ISS is still controversial”.

3. line 11 abstract, I think distinguishing is better. In addition, I think this sentence is misleading. Correct version could be as follows: “So, distinguishing these two etiologies of SS remains very important”.

The phrase of “So, distinguish these two conditions from SS remains very important” in line 11 abstract has been changed to “So, distinguishing these two etiologies of SS remains very important”.

4. Please add full term of all abbreviations in first time of their usage; for example, PG in abstract, WHO, T1WI, TR, TE, …..

The full term of all abbreviations in first time of their usage have been added.

5. This sentence does not have verb: “Comparison between two groups using two independent samples t-tests or chi-squared tests.”

The phrase of “Comparison between two groups using two independent samples t-tests or chi-squared tests” in the original texts has been changed to “Comparison between two groups used two independent samples t-test or chi-square (χ^2) test”.

6. in lines 34 ands 35, you have used R that I think it is correlation coefficient. It is better to be written as r or rho. [in addition line 143 and other instances in paper]

The correlation coefficient “R” in the paper has been changed to “r”.

7. please change methods title to Patients and Methods in abstract and paper.

The titles of “methods” in abstract and paper has been changed to “Patients and Methods”.

8. please add objective part to paper according to journal format. Please change introduction title to background.

The objective part has been added to the paper according to journal format, and the “introduction” has also been changed to “background”.

9. please correct in line 59: “……. auxology, biochemistry, and imaging evaluations”

The phrase of "auxology, biochemistry, and imaging" in line 59 has been changed to "auxology, biochemistry, and imaging evaluations".

10. in line 62, I don’t understand the word unless. I think it should be replaced with when [Therefore, GHD can only be diagnosed when two GHSTs are positive]

The phrase of " Therefore, GHD can only be diagnosed unless two GHSTs are positive" in line 62 has been changed to " Therefore, GHD can only be diagnosed when two GHSTs are positive".

11. in line 70, please capitalize m [Magnetic]

We have capitalized the m [Magnetic] in line 70.

12. please change aetiology to etiology

The word of “aetiology” in the original text has been changed to “etiology”.

13. you mentioned the study is cross sectional [in abstract and method] and retrospective [in line 81]. Please harmonize this point in paper.

We have harmonized the research methods in abstract and method and line 81.

14. please add sequential numbers to titles and sub-titles: 1.Background, 2-Objectives, 3-Patients and Methods, 3.1. Participants and groups, ……

We have added sequential numbers to titles and sub-titles.

15. in line 92, please correct as “space-occupying lesions”

The “space occupying” in line 92 has been changed to “space occupying locations”.

16. please change centre to center

The “centre” in the paper has been changed to “center”.

17. in figure 1 legend, please correct: “A: Convex type” and “The morphology and assessment of the pituitary gland (PG)”

We have corrected the figure 1 legend.

18. please add SPSS manufacturer data based on IBM site address. [https://www.ibm.com/support/pages/how-cite-ibm-spss-statistics-or-earlier-versions-spss]

SPSS manufacturer data has been added.

19. in lines 137 and 138, it is better to be written "statistical analyses"

The "Statistical analysis" in lines 137 and 138 in the paper has been changed to "statistical analyses".

20. I think in line 138, it is better to be mentioned " ….. and two independent samples t-test were used ….." in addition, in line 141, please correct as: "and chi-square (χ 2) test were"

The content of lines 138 and 141 has been modified.

21. in line 149 line, Jordan index is wrong. [Youden index]

The incorrect "Jordan index" has been changed to "Youden index".

22. in line 153, the sentence seems grammatically wrong. [sentence about P value]. Please get a language consult for whole paper. There are some English writing errors in the paper.

This paper has been polished in English by AiMi Academic Services (www.aimieditor. com).

23. what is the meaning of natural birth? Do you mean normal vaginal delivery? Please clarify in text and table 1 and table 3.

It has been clarified in text, table 1 and table 3 that natural birth means vaginal delivery.

24. this sentence is unclear: "However, the GH peak in GHST patients was significantly lower in the GHD group than in the ISS group (P<0.05)" [may be: However, the GH peak in GHST was significantly lower in the GHD group than in the ISS group (P<0.05)].

The expression of the sentence "However, the GH peak in GHST was significantly lower in the GHD group than in the ISS group (P<0.05)" is correct.

25. in figure 2 legend please correct: ISS: idiopathic short stature.

We have corrected the figure 2 legend.

26. please correct table 2 legend as: "Morphological Differences in PG and Pituitary Stalk Between GHD and ISS Groups" [please capitalize first character of words in table legends].

We have corrected the table 2 legend.

27. in line 192, please correct: N=40 and N=82.

We have corrected the: "N=40 and N=82".

28. please add full term of all abbreviations in table footnote for example PG in table 4.

The full term of all abbreviations has been added in table footnote.

29. the part in lines 103-110 that is rational of sample size calculation is better to be deleted. This part is for convincing of referee, so, please delete part Estimating sample sizes [lines 103-110].

Lines 103-110 have been deleted.

30. please add all full terms of abbreviations in tables footnotes, for example, GHD: growth hormone deficiency in table 3 and 4.

The full term of all abbreviations in table 3 and 4 have been added.

31. parts in lines 237-9 could be integrated in the previous sentences and these lines could be deleted [sensitivities and specificities are repetitive and could be deleted] We can write this part as: "Specifically, PG height (in the cut-off value of 5.55 mm) had a sensitivity of 66.3%, a specificity of 85.2%, a positive predictive value of 81.75 %, and a negative predictive value of 71.66 % (AUC= 0.827 [95% CI: 0.770–0.884], P < 0.001). Similarly, PG volume (in the cut-off value of 276.74mm3) had a sensitivity of 84.3%, a specificity of 77.9%, a positive predictive value of 79.23 %, and a negative predictive value of 83.23 % (AUC= 0.886 [95% CI: 0.0.839–0.933], P < 0.001)." Then, data in lines 237-239 could be deleted.

We have made modifications as requested.

32. it is better to explain the MRI sequence and view in figure 1 legend.

The MRI sequence and view have been explained in the figure 1 legend.

4 Revision 3

1 comment · 10 Aug 2024

Editor-in-Chief

ACCEPT 10 Aug 2024

Dear authors,
Your article is acceptable for publication in IJR.
Regards