Dear Editor

Please find enclosed the edited manuscript in word format (file name: 69094-Review.doc)

Title: Full recovery from chronic headache and hypopituitarism caused by lymphocytic hypophysitis：a case report

Author: Yang, Maoguang, Cai, hanqing, Wang, Sisi, liu, lin, Wang, Chunmei

Name of Journal: World Journal of Clinical Cases

Manuscript NO: 69094

The manuscript has been improved according to the suggestions of reviewer:

- Format has been updated,
- Revision has been made according to the suggestions of the reviewer:

1. There are insufficient descriptions, including incorrect citations, in the introduction and discussion, which need to be revised significantly.

Answer: Yes, I agree with your comment and have corrected the irrelevant references, and the introduction and discussion have been revised.

2. No description regarding MRI findings of other types of hypophysitis or how to narrow down the differentiation, which is often challenging and important in daily practice.

Answer: Yes, I agree with your comment and make the corresponding modification. We reanalyzed the differential diagnosis of different types of PAH and added the corresponding content and references. [treatment (line 149-151)] Thereafter, pulse therapy was continued for 1 month and finally discontinued; the headache was

significantly relieved, and the visual field returned to normal suggesting LYH rather than pituitary adenoma. [Discussion (line 231-235)] A lingual suprasellar and retrosellar extension of the saddle mass in contact with the basal hypothalamus and even infiltration of the basal hypothalamus is a relatively typical finding in granulomatous pituitary inflammation [Honegger J, Fahlbusch R, Bornemann A, Hensen J, Buchfelder M, Müller M, Nomikos P. Lymphocytic and granulomatous hypophysitis: experience with nine cases. Neurosurgery 1997; 40:713-722; discussion 722-713], a feature did not present in our patient. [Discussion (line 244-257)] Our patient's score was -8, favoring a diagnosis of LYH, although granulomatous hypophysitis could also present with similar sellar infiltration; however, it is very rare and often found by autopsy [Rivera JA. Lymphocytic hypophysitis: disease spectrum and approach to diagnosis and therapy. Pituitary 2006; 9:35-45 [PMID: 16703407 DOI: 10.1007/s11102-006-6598-z]; Cheung CC, Ezzat S, Smyth HS, Asa SL. The spectrum and significance of primary hypophysitis. J Clin Endocrinol Metab 2001; 86:1048-1053 [PMID: 11238484 DOI: 10.1210/jcem.86.3.7265]]. IgG4-related hypophysitis was not considered based on a negative serum IGG4 test because elevated serum levels of IgG4 are an important diagnostic indicator of IgG4-related hypophysitis [Gu WJ, Zhang Q, Zhu J, Li J, Wei SH, Mu YM. Rituximab was used to treat recurrent IgG4-related hypophysitis with ophthalmopathy as the initial presentation: A case report and literature review. Medicine (Baltimore) 2017; 96:e6934 [PMID: 28614220 DOI: 10.1097/md.0000000000006934]]. Necrotizing hypophysitis present with lack of contrast enhancement, and sudden-onset hypopituitarism [Gutenberg A, Caturegli P,

Metz I, Martinez R, Mohr A, Brück W, Rohde V. Necrotizing infundibulo-hypophysitis: an entity too rare to be true? Pituitary 2012; 15:202-208 [PMID: 21479815 DOI: 10.1007/s11102-011-0307-2]; Ćaćić M, Marinković J, Kruljac I, Perić B, Čerina V, Stipić D, Pažanin L, Pećina HI, Vrkljan M. ISCHEMIC PITUITARY APOPLEXY, HYPOPITUITARISM AND DIABETES INSIPIDUS: A TRIAD UNIQUE TO NECROTIZING HYPOPHYSITIS. Acta Clin Croat 2018; 57:768-771 [PMID: 31168215 DOI: 10.20471/acc.2018.57.04.20]], diabetes insipidus and radiologic findings of ischemic pituitary are three characteristics of necrotizing hypophysitis [Ćaćić M, Marinković J, Kruljac I, Perić B, Čerina V, Stipić D, Pažanin L, Pećina HI, Vrkljan M. ISCHEMIC PITUITARY APOPLEXY, HYPOPITUITARISM AND DIABETES INSIPIDUS: A TRIAD UNIQUE TO NECROTIZING HYPOPHYSITIS. Acta Clin Croat 2018; 57:768-771 [PMID: 31168215 DOI: 10.20471/acc.2018.57.04.20]]. Our patient presented with marked homogeneous anterior pituitary enhancement without ischemic manifestations. Xanthomatous hypophysitis commonly reveal cystic enlargement and peripheral ring enhancement after contrast [Hanna B, Li YM, Beutler T, Goyal P, Hall WA. Xanthomatous hypophysitis. J Clin Neurosci 2015; 22:1091-1097 [PMID: 25957783 DOI: 10.1016/j.jocn.2015.01.019]; Lin W, Gao L, Guo X, Wang W, Xing B. Xanthomatous Hypophysitis Presenting with Diabetes Insipidus Completely Cured Through Transsphenoidal Surgery: Case Report and Literature Review. World Neurosurg 2017; 104:1051.e1057-1051.e1013 [PMID: 28583458 DOI: 10.1016/j.wneu.2017.05.156]], and is rarely known to improve in response to glucocorticoid therapies [Joung JY, Jeong

H, Cho YY, Huh K, Suh YL, Kim KW, Bae JC. Steroid responsive xanthomatous hypophysitis associated with autoimmune thyroiditis: a case report. Endocrinol Metab (Seoul) 2013; 28:65-69 [PMID: 24396654 DOI: 10.3803/EnM.2013.28.1.65]], This is inconsistent with our patient's findings, so necrotizing hypophysitis and xanthomatous hypophysitis was not considered.

3. Throughout this manuscript, the language needs to be significantly improved; the authors should do some additional proofreading on it. This must be crucial.

Answer: I agree with your comment and re-submitted my application to American Journal Experts (AJE) in English language editing with the feedback of the questions, expecting the language to be improved and finally to get a new editing certificate .

4. [Introduction (line 40-41)] "accounting for approximately 70% of all causes of PAH" should be inserted in the previous sentence.

Answer: I agree with your comment and make the corresponding modification. [Introduction (line 66-6)] Histologically, lymphocytic hypophysitis (LYH) is the most common type of primary autoimmune hypophysitis (PAH), accounting for approximately 70% of all causes of PAH, and LYH is characterized by extensive lymphocytic and plasma cell infiltration in the pituitary gland, with varying degrees of pituitary dysfunction.

5. [Introduction (line 43-44)] "a clinical or pathological diagnosis may lead to an underestimation of…" seems odd (underestimation is not introduced by the diagnosis itself, but the counting method).

Answer: I agree with your comment and make the corresponding modification. I

have adjusted the order of words and improving sentencesand to avoid ambiguity. [Introduction (line 70-73)] However, the prevalence of LYH is related to the means by which the diagnosis is made and improper calculation of the incidence of LYH due to different clinical or pathological diagnostic bases.

6. [Introduction (line 44-45)] according to the cited article [5], the frequency was not noted as 60%.

Answer: I agree with your comment and have corrected the irrelevant reference. [6] Hashimoto K, Takao T, Makino S. Lymphocytic adenohypophysitis and lymphocytic infundibuloneurohypophysitis. Endocr J 1997; 44:1-10 [PMID: 9152609 DOI: 10.1507/endocrj.44.1]

7. [Introduction (line 46)] “sellar region tumors” Since it is stated in the plural, please give other examples.

Answer: I agree with your comment and make the corresponding modification. [Introduction (line 64-66)] Given its presence as a pituitary adenoma on the radiographic image, LYH is misdiagnosed as pituitary adenoma in approximately 40% of patients.

8. [Introduction (line 48-52)] this sentence is quite similar to the previous one.

Answer: I agree with your comment and make the corresponding modification. I deleted the possible duplicate content.

9. [Introduction (line 56-58)] the cited article here [11] is a case report of xanthomatous hypophysitis, and there is no description of clinical manifestations of LYH. The authors should not confuse the symptoms caused by inflammation with those

caused by the mass effect.

Answer: I agree with your comment and have corrected the irrelevant reference. [12] Thodou E, Asa SL, Kontogeorgos G, Kovacs K, Horvath E, Ezzat S. Clinical case seminar: lymphocytic hypophysitis: clinicopathological findings. J Clin Endocrinol Metab 1995; 80:2302-2311 [PMID: 7629223 DOI: 10.1210/jcem.80.8.7629223].

10. [Introduction (line 61)] What does “homogeneous headache” mean?

Answer: I agree with your comment, and the “homogeneous headache” means the headache of the patient is of the same character each time it recurs and worsens, and I have modified the ambiguous terms. [Introduction (line 87)] We herein report a case of a rare recurrence of headache during a significant reduction in pituitary volume accompanied by partial recovery to complete remission of hypopituitarism.

11. [Case report (line 92-94)] How were the other types of hypophysitis ruled out? (Or did the patient receive an empirical treatment before reaching a definitive diagnosis?) Please describe any other laboratory and radiological findings the authors used to differentiate.

Answer: I agree with your comment and make the corresponding modification. Same as the second revision, [treatment (line 149-151)] Thereafter, pulse therapy was continued for 1 month and finally discontinued; the headache was significantly relieved, and the visual field returned to normal suggesting LYH rather than pituitary adenoma. [Discussion (line 231-235)] A lingual suprasellar and retrosellar extension of the saddle mass in contact with the basal hypothalamus and even infiltration of the basal hypothalamus is a relatively typical finding in granulomatous pituitary inflammation

[Honegger J, Fahlbusch R, Bornemann A, Hensen J, Buchfelder M, Müller M, Nomikos P. Lymphocytic and granulomatous hypophysitis: experience with nine cases. Neurosurgery 1997; 40:713-722; discussion 722-713], a feature did not present in our patient. [Discussion (line 244-257)] Our patient's score was -8, favoring a diagnosis of LYH, although granulomatous hypophysitis could also present with similar sellar infiltration; however, it is very rare and often found by autopsy [Rivera JA. Lymphocytic hypophysitis: disease spectrum and approach to diagnosis and therapy. Pituitary 2006; 9:35-45 [PMID: 16703407 DOI: 10.1007/s11102-006-6598-z]; Cheung CC, Ezzat S, Smyth HS, Asa SL. The spectrum and significance of primary hypophysitis. J Clin Endocrinol Metab 2001; 86:1048-1053 [PMID: 11238484 DOI: 10.1210/jcem.86.3.7265]]. IgG4-related hypophysitis was not considered based on a negative serum IGG4 test because elevated serum levels of IgG4 are an important diagnostic indicator of IgG4-related hypophysitis [Gu WJ, Zhang Q, Zhu J, Li J, Wei SH, Mu YM. Rituximab was used to treat recurrent IgG4-related hypophysitis with ophthalmopathy as the initial presentation: A case report and literature review. Medicine (Baltimore) 2017; 96:e6934 [PMID: 28614220 DOI: 10.1097/md.0000000000006934]]. Necrotizing hypophysitis present with lack of contrast enhancement, and sudden-onset hypopituitarism [Gutenberg A, Caturegli P, Metz I, Martinez R, Mohr A, Brück W, Rohde V. Necrotizing infundibulo-hypophysitis: an entity too rare to be true? Pituitary 2012; 15:202-208 [PMID: 21479815 DOI: 10.1007/s11102-011-0307-2]; Ćaćić M, Marinković J, Kruljac I, Perić B, Čerina V, Stipić D, Pažanin L, Pećina HI, Vrkljan M. ISCHEMIC PITUITARY APOPLEXY,

HYPOPITUITARISM AND DIABETES INSIPIDUS: A TRIAD UNIQUE TO NECROTIZING HYPOPHYSITIS. Acta Clin Croat 2018; 57:768-771 [PMID: 31168215 DOI: 10.20471/acc.2018.57.04.20]], diabetes insipidus and radiologic findings of ischemic pituitary are three characteristics of necrotizing hypophysitis [Ćaćić M, Marinković J, Kruljac I, Perić B, Čerina V, Stipić D, Pažanin L, Pećina HI, Vrkljan M. ISCHEMIC PITUITARY APOPLEXY, HYPOPITUITARISM AND DIABETES INSIPIDUS: A TRIAD UNIQUE TO NECROTIZING HYPOPHYSITIS. Acta Clin Croat 2018; 57:768-771 [PMID: 31168215 DOI: 10.20471/acc.2018.57.04.20]]. Our patient presented with marked homogeneous anterior pituitary enhancement without ischemic manifestations. Xanthomatous hypophysitis commonly reveal cystic enlargement and peripheral ring enhancement after contrast [Hanna B, Li YM, Beutler T, Goyal P, Hall WA. Xanthomatous hypophysitis. J Clin Neurosci 2015; 22:1091-1097 [PMID: 25957783 DOI: 10.1016/j.jocn.2015.01.019]; Lin W, Gao L, Guo X, Wang W, Xing B. Xanthomatous Hypophysitis Presenting with Diabetes Insipidus Completely Cured Through Transsphenoidal Surgery: Case Report and Literature Review. World Neurosurg 2017; 104:1051.e1057-1051.e1013 [PMID: 28583458 DOI: 10.1016/j.wneu.2017.05.156]], and is rarely known to improve in response to glucocorticoid therapies [Joung JY, Jeong H, Cho YY, Huh K, Suh YL, Kim KW, Bae JC. Steroid responsive xanthomatous hypophysitis associated with autoimmune thyroiditis: a case report. Endocrinol Metab (Seoul) 2013; 28:65-69 [PMID: 24396654 DOI: 10.3803/EnM.2013.28.1.65]], This is inconsistent with our patient's findings, so necrotizing hypophysitis and xanthomatous

hypophysitis was not considered.

12. [Case report (line 101-103)] Were these test results obtained before or after the treatment described above? If they were done before the treatment, these results should be moved above.

Answer: I agree with your comment and make the corresponding modification, and have moved the test results to the appropriate location. [Laboratory examinations (line 108-111)] The patient was negative for antinuclear antibody, immunoglobulin G, immunoglobulin M, immunoglobulin A, and immunoglobulin G4, which did not support immunoglobulin G4 (IgG4)-related hypophysitis, and no antithyroid antibodies were detected. The remainder of the biochemical and coagulation test results were unremarkable.

13. [Case report (line 108-109)] “thinning and centering of the pituitary stalk” is in contradiction with the description above in line 80, where the pituitary stalk did not deviate on the initial MRI.

Answer: I agree with your comment. My intention was to use the word "centering" to convey the meaning of "not deviate", which caused ambiguity, and I have corrected it. [OUTCOME AND FOLLOW-UP (line 153-155)] Repeat pituitary MRI showed a decreased size of the suprasellar mass with homogeneous enhancement, thinning and not deviated of the pituitary stalk, no elevation of the chiasm, and no abnormal signal in the cavernous sinus.

14. [Discussion (line 146-147)] “Headache is also the most common complaint in the first neurosurgical consultation with an incidence of 89% [10].” There is no

corresponding data supporting this sentence in the cited article [10].

Answer: I agree with your comment and have corrected the irrelevant reference. [18] Kyriacou A, Gnanalingham K, Kearney T. Lymphocytic hypophysitis: modern day management with limited role for surgery. Pituitary 2017; 20:241-250 [PMID: 27778295 DOI: 10.1007/s11102-016-0769-3].

15. [Discussion (line 152)] “DPIDH” -> CPIDH.

Answer: I agree with your comment and make the corresponding modification. [Discussion (line 198)].

16. [Discussion (line 169-170)] ”Secondary adrenal hypofunction is the most common endocrine disorder in LYH (60%) followed by TSH, gonadotropins and prolactin” -> Please correct this sentence. TSH, gonadotropins, and prolactin do not follow the secondary adrenal hypofunction, but their endocrine deficiencies do.

Answer: I agree with your comment and make the corresponding modification. [Discussion (line 216-217)]

17. [Discussion (line 181-184)] The authors should state how the LYH can (or cannot) be differentiated from other types of hypophysitis. The following are some examples of the relevant references to consider in terms of MRI findings of hypophysitis: [PMID: 32763900, 20651017, 26181544, 24165017].

Answer: I agree with your comment and Thank you for providing the PMID of the article. I have re-stated the differential diagnosis of LYH and emphasized the differentiation of LYH from granulomatous hypophysitis and IgG4-related hypophysitis in the discussion section. [Discussion (line 244-257)] A lingual suprasellar

and retrosellar extension of the saddle mass in contact with the basal hypothalamus and even infiltration of the basal hypothalamus is a relatively typical finding in granulomatous pituitary inflammation [23], a feature did not present in our patient. [Discussion (line 244-257)] Our patient's score was -8, favoring a diagnosis of LYH, although granulomatous hypophysitis could also present with similar sellar infiltration; however, it is very rare and often found by autopsy [17, 36]. IgG4-related hypophysitis was not considered based on a negative serum IGG4 test because elevated serum levels of IgG4 are an important diagnostic indicator of IgG4-related hypophysitis [37]. Necrotizing hypophysitis present with lack of contrast enhancement, and sudden-onset hypopituitarism [38, 39], diabetes insipidus and radiologic findings of ischemic pituitary are three characteristics of necrotizing hypophysitis [39]. Our patient presented with marked homogeneous anterior pituitary enhancement without ischemic manifestations. Xanthomatous hypophysitis commonly reveal cystic enlargement and peripheral ring enhancement after contrast [40, 41], and is rarely known to improve in response to glucocorticoid therapies [42], This is inconsistent with our patient's findings, so necrotizing hypophysitis and xanthomatous hypophysitis was not considered.

18. [Discussion (line 192-193)] “Our patient's score was -8, favoring a diagnosis of hypophysitis LYH.” This should be stated in the Results before adding any discussion on it.

Answer: I agree with your comment and make the corresponding modification. [Imaging examinations (line 133-134)] According to the scoring system of Gutenberg, our patient was -8, strongly suggesting the diagnosis of LH.

19. [Discussion (line 206-208)] “Surgical treatment may contribute to permanent relief of headache, whereas headache and visual field defects usually improve shortly after treatment” This sentence is confusing. Does the latter “treatment” indicate a nonsurgical one?

Answer: I agree with your comment and make the corresponding modification. The latter “treatment” here means surgery according to the cited articles.[Discussion (line 268)]

20. [Discussion (line 208-213)] This sentence does not make any sense.

Answer: I agree with your comment and I have removed this sentence and adjusted it for context.

21. [Figure 1] optical cross -> optic chiasm; tail arrow & arrow tail -> arrow; triangular arrowheads -> arrowhead [Figure 1D] The arrowhead is not pointing to the pituitary gland but bone. [Figure 1E] The arrowhead is overlaying the pituitary gland.

Answer: I agree with your comment and make the corresponding modification.

22. [Figure 2] dural caudal sign -> dural tail sign; “Pretreatment postgadolinium-enhanced coronal MRI shows the cavernous sinus (arrow) (B) with no significant changes after treatment compared to pretreatment (arrow) (D).” Do the arrows indicate the LYH involvement of the cavernous sinus? If so, please revise the sentence correctly.

Answer: I agree with your comment and make the corresponding modification.

Manuscript NO: 69094

The manuscript has been improved according to the suggestions of re-reviewer#1: I don't see any Discussion this time. Was the Discussion removed? Why?

Answer: The manuscript has add the discussion.

The manuscript has been improved according to the suggestions of re-reviewer#2:

The manuscript is weel handled for language and vocabulary . except word "bother" , the sentence "the headache did not bother the patient because the headache was tolerable" can be re-written.

Answer: I agree with your comment. The sentence has been re-written “the patient did not complain about headache”.

Another comment is about exclusion of IgG3 hypophyisits. Solely normal IgG4 or IgG levels not sufficient to exclude it. Biopsy confirmation is also essential. Other organs as parotis, pancreas (HISORt criteria), etc. had to be checked for IgG4 diseases. A literature recommendaton: by Bando et al. thank you for your effort.

Answer: Yes, I agree with your comment and thank you for sharing the excellent literature, I have read it and the other related literature carefully. The patient did not agree to biopsy of the pituitary gland and pancreas, and case reports of IGg4-related diseases suggest that the pituitary gland is the least involved. This is the regrettable part of this case. Although it cannot be excluded, it cannot be diagnosed as IGg4-related hypophysitis temporarily according to the corresponding diagnostic criteria. In comparison to the more rare IGg4, lymphocytic pituitaryitis is more likely.

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

Sincerely yours,

Wang, Chunmei, Master Degree,

Department of Radiology, The First Hospital of Jilin University,

1 Xinmin Avenue, 130021, Changchun, Jilin.

Wangcm5413@jlu.edu.cn.