

Response to the Reviewer's Comments

To all reviewers,

We appreciate your comments. Based on your comments, our manuscript is improved the scientific quality and enriched. We can reinforce the manuscript by adding more data and references. However, there were also problems that could not be practically solved. We commented on the reasons why and our opinions about them added in this letter. Thank you for using your precious time for us.

Below is the response to your comments.

Reviewer #1

Specific Comments to Authors:

- Major issue.
1. In this case study, the patient suffered from Bell's palsy for seven years before being treated with uncultured UC-MSC transplantation. I want the authors to provide a careful medical history of the patient before treatment, including the possible etiology of Bell's palsy. Complete head and neck, otological examination, and radiologic studies are paramount, which can help in clinically determining whether the palsy of the facial nerve is due to central causes like stroke or is peripheral. I hope the authors will also provide it.

Response

- After being diagnosed with Bell's palsy, the patient was treated with steroids, but to no avail. We requested the patient's medical records including imaging data at the time, but the patient's data could not be obtained due to the hospital's closure.

However, based on the patient's medical history, we speculate that the patient has facial paralysis of peripheral causes. This is because the patient has no history of a disease with a central cause that could cause facial paralysis, such as stroke.

2. There were no photos of this patient's face before MSC treatment, and although the authors mention in the article that the patient was reluctant to provide them, this is an essential issue in a case report.

Response

- We agree with you. In this case report, the patient's pre-treatment image will be the baseline for post-treatment changes. Unfortunately, the patient was not allowed to take pre-treatment pictures. The reason is that the patient did not get a significant effect from steroid treatment, meridian massage, acupuncture, herbal medicine, etc. The patient had fewer hopes for stem cell treatment, and she was reluctant to keep a record of her distorted face.

3. The photos provided by the author after the patient received the treatment did work well, 'Left eye closure and eyebrow location' and 'the patient's asymmetrical lips' were taken only after three months and 22 months, which are the exact times, the rest of the photos are not consistent in time. I would like to know why.

Response

- Unlike the correction of asymmetric eyes and eyebrows, the correction of asymmetric lips required a longer time. We decided to single out the appropriate images to show the progress of each area in order to convey only the necessary information to our readers. It will help the reader understand the data while showing that the two data are independent of each other.

- Minor issue.

1. In this case study, the authors state, "We injected the injection solution evenly over the left side of the patient's face. 0.25 mL (a total of 16 injections were performed). " Although the authors mention evenly over the left side of the patient's face, I would have preferred a facial diagram indicating the exact injection site. The depth of injection should also be indicated.

Response

- We have included text and an additional figure in the text.

2. Please add whether the patient experienced a short-term local facial reaction and a systemic reaction after receiving the injection treatment, for example, within 1 hour or one day.

Response

- We have added content to the text.

3. I would like the authors to provide photos of uncultured UC-MSCs injections

Response

- No separate images were taken of injecting uncultured UC-MSCs. Instead, an image showing the injection site was added to the text.

4. Here is an additional review. I would like the authors to add to the discussion section to elaborate on why uncultured cells should be used. What are the advantages and disadvantages of each of the uncultured and passaged cells? It would make the discussion section more comprehensive if these were added.

Response

- We added content to the discussion section.

Reviewer #2

This is an interesting case that reported an effective and safe treatment for a middle female patient with Bell's palsy by uncultured umbilical cord-derived mesenchymal stem cells. It has some certain clinical promotion significance in the future. However, it has some limitations below:

Specific Comments to Authors:

1. As a new clinical treatment trial for the patient, it should be carried out by the approval of the hospital's ethics committee, not just the patient's therapy consent.

Response

- At the time of treatment, this treatment method was a treatment method that did not require obtaining an IRB under domestic law. Accordingly, we did not need an IRB, and we forwarded this information to the BPG team.

2. As an allogeneic injection, is it possible to cause allergic reactions in patients and

how to prevent it?

Response

- Recently, research results have been reported that mesenchymal stem cells can treat various allergic reactions by regulating the immune response. Therefore, transplantation of mesenchymal stem cells is unlikely to induce an allergic reaction. Nevertheless, in case of an allergic reaction, we have allergy medications in our hospitals, such as steroid injections. Fortunately, to date, none of the patients treated at our hospital have reported allergic reactions.

3. Did this patient receive this treatment alone, without other ones or medications?

Response

- Yes

4. Whether the Bell's palsy in this patient was caused by immune system diseases, such as systemic lupus erythematosus?

Response

- We determine that the cause of the patient's Bell's palsy is not due to a disease of the immune system. According to the patient's report, there were no special symptoms that could be inferred as the cause of Bell's palsy until just before the onset. According to the pre-treatment consultation record, the patient did not have any health problems at the time of onset and at the time of admission and did not take any special medications. Diseases mentioned in the consultation include Hypertension, Heart disease, Pneumonia, Diabetes, Hyperlipidemia, Cerebral

vascular disease, Lung disease, Kidney disease, Fractures or break, Cutaneous basal cell carcinoma or in situ carcinoma, Cancer or tumor, Inflammatory disease, Infectious disease, Any skin lesions, Diarrhea, Arthritis, and Others.

5. It is suggested that the discussion part start with the treatment of this patient and discuss it combined with the treatment of her.

Response

- We added content to the discussion section.

Reviewer #3

The present case report shows undoubtedly an interesting and potential promising treatment for patients suffering from facial nerve paralysis. The authors report a 7-year lasting Bell's Palsy completely recovered after treatment using uncultured umbilical cord-derived mesenchymal stem cell transplant.

However, before considering it for publication major revisions are required.

Specific Comments to Authors:

1. A brief sentence about the patient's psycho-social aspect related to the facial nerve paralysis should be written in introduction or discussion section.

Response

- We added content to the discussion section.

2. The case report description lacks some relevant information.

2-1. Firstly, the House Brackmann grading of the initial presentation of the paralysis in 2006 is missing.

Response

- We added content to the history of present illness section.

2-2. Although the authors recognize lack of pre-treatment images due to the refusal of the patient, I believe that this case presentation could not be accepted without images of the paralysis before the treatment.

Response

- We are fully aware of this issue. Although there are no pre-treatment images due to the patient's refusal, we thought that the images submitted can show the improvement of the patient's symptoms over time.

2-3. Additionally, they do not report if the patient underwent any imaging study for the paralysis. Diagnosis of Bell's Palsy is an exclusion diagnosis. MRI is generally mandatory for the diagnostic work-up of facial nerve paralysis.

Response

- The patient reported having had imaging examinations at the time of onset. We asked the patient for the results of the imaging examinations, but we did not receive them. Because the hospital was closed, the patient could not get data.

2-4. An electromyography would also be of interest.

Response

- For the same reasons as above, EMG results could not be obtained either.

2-5. Was the patient proposed any surgical procedures (decompression, graft, muscle transposition, etc...) during the 7 years before?

Response

- After receiving steroid treatment at the hospital where the patient was diagnosed with Bell's palsy, the patient reported receiving meridian massage, acupuncture, and herbal medicine, etc. During this period, the patient's symptoms did not improve, and 7 years after the onset, the patient received stem cell treatment at our clinic and was cured.

2-6. I suggest to better describe the treatment modality. Does each treatment consist of 16 injections? Which site were specifically injected? A figure/scheme representing the face illustrating the sites of injection would be useful.

Response

- We added the image and descriptions.

2-7. Did the patient undergo any physiotherapy or speech and language exercise postoperatively?

Response

- After stem cell treatment, the patient did not undergo any additional treatments at our hospital. Also, we did not receive any reports from the patient receiving any additional treatment.

3. Discussion section must be improved.

3-1. A brief illustration of the rehabilitative surgical procedures for facial nerve paralysis (static and dynamic procedure) can be added.

Response

- The patient did not receive any other rehabilitation treatment other than stem cell transplantation.

3-2. What is the hypothetical mechanism of tissue regeneration (nervous, muscle) of the stem cells in this pathology should be discussed.

Response

- We added content to the discussion section.

Reviewer #4

In this article, the authors used uncultured mesenchymal stem cells to treat a patient with facial paralysis. Although the author has done a lot of work on the content of the article, I would like to make some important suggestions on some key issues to help the author improve the quality of the current manuscript.

Specific Comments to Authors:

- 1 . About the section of 'Isolation and quality evaluation of UC-MSCs'. Make sure that you are using mesenchymal stem cells or mixed cell components dominated by mesenchymal stem cells for clinical treatment.

Response

- We performed flow cytometry analysis to confirm the purity of the isolated UC-MSCs. And the cells used for treatment were only cells that met the following criteria based on the results of flow cytometry analysis: CD73 $\geq$ 70%, CD90 $\geq$ 90%, and CD105 $\geq$ 90%. These three markers were specific to MSCs and were discarded if the isolated cells did not meet these criteria.

2. Please provide details of the preparation process of MSC.

Response

- We have modified the contents of the Treatment section.

3. Please provide additional flow analysis results for identification of mesenchymal stem cells.

Response

- As mentioned above, we analyzed flow cytometry whenever we isolated UC-MSCs, and only cells that met the criteria were used for treatment. In this case report, the patient received a total of 8 treatments. The cells used in 1 treatment were from the same umbilical cord, but not all 8 treatments were from the same umbilical cord. Therefore, it was decided not to present the data because it was judged that it could not be expressed in one data. However, we have previously presented flow cytometry data of isolated UC-MSCs in our other case reports using uncultured UC-MSCs. Related data can be found in the two papers below.

Case report for alopecia

<https://www.wjgnet.com/2307-8960/full/v9/i15/3741.htm>

Case report for stroke

<https://www.wjgnet.com/1948-0210/full/v13/i8/1151.htm>

Reviewer #5

Specific Comments to Authors:

1. Elaborate the following sentence in the introduction section-"long term side effects of Bell's palsy can be *fatal".

Response

· Our choice of words is wrong. The proper word for what we mean is 'devastating', not 'fatal'. The content has been corrected. Long-term side effects of Bell's palsy experienced by our patient have been added to the Discussion section.

2. Also mention the tissue depth at which these injections of uncultured UC-MSCs were given to the patient.

Response

· We have added the contents in the Treatment section.

3. However, the authors have very nicely managed the case with the concept of using uncultured UC-MSC in view of their reduced capacity for regeneration after being cultured in-vitro; but, extreme caution is required as there is a risk of transmission of infections.

Response

· I agree with you. We tested thoroughly to overcome the risk of infection.

4. Further large sample, multi centric, population studies are required to confirm reproducibility of results in various ethnic groups.

Response

· I agree with you. Large-scale trials and studies are needed to confirm the reproducibility of the results. We believe this case study will serve as a springboard for the development of treatment for Bell's palsy.